Esophageal Cancer

Neoadjuvant chemoradiotherapy
and surgery

Slokdarmcarcinoom

Neoadjuvante chemoradiotherapie en chirurgie

Bo Jan Noordman

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Voor mijn moeder

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Introduction

Chapter 1

General introduction and outline of the thesis

Esophageal cancer is a highly lethal malignancy, as reflected by an overall 5-year survival of 17%.[1] In the Netherlands, the incidence of esophageal cancer resembles the growing trend in Western countries, with an incidence of 15/100,000 for men and 6/100,000 for women, and more than 2,600 new cases annually.[2] Two main histological subtypes can be distinguished, *i.e.* esophageal adenocarcinoma (AC) and esophageal squamous cell carcinoma (SCC). Globally, SCC is the most common subtype, especially in areas with high incidence such as eastern and southern Africa and eastern Asia. However, in most Western countries, the incidence of esophageal and esophogastric-junctional (EGJ) AC has surpassed that of SCC.

At the time of diagnosis, only 50% of all patients are potentially curable. Surgical resection has long been considered the primary curative treatment modality for esophageal and junctional cancer. Historically, the Ivor-Lewis procedure has been widely applied, including a thoracotomy with limited lymphadenectomy and thoracic anastomosis.[3] Ever since, two main surgical techniques have evolved. First, the extended *en bloc* transthoracic esophagectomy (TTE) was developed, with extensive two-field lymphadenectomy (upper abdomen and posterior mediastinum). This technique attempts to increase locoregional tumor control by enhancing the radicality of resection.[4-8] It is well established that extensive lymphadenectomy provides the benefit of more accurate staging, but its beneficial effect on survival is still unclear.[9-12] Second, the limited transhiatal esophagectomy (THE) was introduced, which focused on minimization of postoperative morbidity and mortality by preventing a formal thoracotomy. The optimal surgical approach for the treatment of patients with esophageal cancer is still topic of debate.

In the literature reported 5-year survival rates for patients treated with primary surgical resection range from six to 50%, but rarely exceed 35% in Western countries.[13-17] To improve long-term survival, many trials investigated the added value of neoadjuvant chemo- and/or radiotherapy.[18-24]

In most countries, two neoadjuvant approaches have been adopted as standard of care. The first is neoadjuvant chemoradiotherapy (nCRT), now generally based on the CROSS regimen, which resulted in a 5-year overall survival benefit of 14%, compared to surgery alone.[22, 23] An alternative option is perioperative or preoperative chemotherapy using the OEO2, MAGIC or FLOT protocol, which showed an absolute risk reduction of 6%, 13% and 16% at 5-years, respectively.[19, 24, 25] Except partly in Japan and China, it is widely accepted that chemoradiotherapy is the neoadjuvant treatment of choice for patients with squamous cell carcinoma.[26] For patients with adenocarcinoma the optimal multimodality regimen is still topic of debate.[27-29]

The ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) was a multicenter, randomized phase-III trial, comparing neoadjuvant chemoradiotherapy followed by surgery with surgery alone.[22] The study included and analyzed 366 patients from five academic and two non-academic high-volume teaching hospitals

in The Netherlands during a five-year period. Most patients (75%) had an adenocarcinoma and most tumors were located at the EGJ (24%) or in the distal esophagus (58%). Results from the CROSS-trial showed that the addition of nCRT (carboplatin, paclitaxel and 41.4 Gy of concurrent RT) to surgery significantly increases survival as compared to surgery alone in patients with potentially curable SCC or AC of the esophagus or EGJ. Neoadjuvant treatment was well tolerated, with >90% of all patients receiving full treatment. Therefore, neoadjuvant CRT plus surgery is now considered the therapy of first choice in the Netherlands and several other countries for potentially curable esophageal cancer (cT2-3N0-1M0 and cT1N1M0) in patients fit to undergo this treatment.

Application of nCRT prior to surgery has important implications for prognostication and surgical treatment. Most of the conventional prognostic factors identified in the era of primary esophagectomy lose their prognostic value in patients treated with nCRT plus surgery.[30] After nCRT, only the number of clinically suspected metastatic regional lymph nodes (cN-stage) prior to treatment and the number of metastatic regional lymph nodes in the resection specimen (ypN-stage) are independently associated with survival after application of nCRT plus surgery. A model using these parameters to determine prognosis showed only limited prognostic strength. This emphasizes the need for new prognostic parameters. One such parameter is the pretreatment p-TNM staging. This novel staging system aims to determine the pretreatment tumor extent based on the extent of tumor fibrosis, the location of residual tumor cells and regressional changes of lymph nodes in the resection specimen after nCRT. Previously, this staging system has been shown reproducible.[31] Furthermore, it was demonstrated that especially the number of pretreatment metastatic lymph nodes is an important and independent prognostic parameter. Patients with pre-treatment metastastic lymph nodes, which became negative for disease thanks to nCRT, have worse prognosis than patients without pretreatment nodal involvement.[31]

Neoadjuvant CRT downstages both the primary tumor and the regional lymph nodes. The first leads to an increase in the radical resection rate, whereas the latter questions the necessity of extended lymphadenectomy. Some studies have shown previously that the number of resected lymph nodes has prognostic impact on survival, and probably even therapeutic impact in patients after surgery alone.[32] However, after nCRT the number of resected nodes has been shown unrelated to survival.[33] These data question the necessity for maximization of lymphadenectomy after nCRT as can be performed during TTE.

Furthermore, the effects of nCRT on health-related quality of life (HRQOL) are largely unknown. Esophagectomy has a profound and lasting impact on patients' HRQOL.[34] Patients who undergo nCRT might experience a deterioration in HRQOL after nCRT, which might impact postoperative recovery.[35] Furthermore, long-term

effects of especially radiotherapy on heart and lungs have insufficiently been investigated and might have an impact on long-term HRQOL.

In subsequent analyses of secondary endpoints in the CROSS-trial it was found that nearly a third of the patients had a pathologically complete response (pCR) in the resection specimen. A pCR after nCRT was seen in 49% of patients with SCC and 23% of patients with AC. In the OEO2 and MAGIC trials this was substantially less, *i.e.* 4% and 5%, respectively.[22, 36] This observation raises the question whether a surgical resection is of benefit to patients in whom no vital tumor cells can be detected in the resection specimen. Theoretically, an organ sparing approach might be feasible since, intuitively, an esophagectomy in patients with no residual viable tumor cells in the resection specimen has probably no effect on clinical outcome. This imposes an ethical imperative to reconsider the necessity of standard esophagectomy in patients after nCRT. An individualized approach to surgery after nCRT needs to be studied and defined; a new treatment algorithm in which not every patient with potentially curable esophageal cancer needs a resection after completion of nCRT to achieve long-term survival. In an active surveillance approach, patients will be subjected to frequent clinical investigations after nCRT. Esophagectomy will be offered only to those with a proven locoregional recurrence, in the absence of distant metastases. An active surveillance approach could have great advantages given the high postoperative morbidity and substantial mortality, and the impact of surgery on quality of life.[22, 37, 38] However, an active surveillance approach would be justified only if oncological outcome is non-inferior to standard surgery. In order to select patients for active surveillance, the disease should be re-staged after nCRT by means of meticulous clinical response evaluation (CRE). CREs need to accurately categorize patients as clinically complete responders (cCR) or clinically incomplete responders. Such an active surveillance strategy is currently applied in selected patients who refuse surgery or are medically unfit for major surgery after completion of nCRT.[39-42] Explorative retrospective studies in such patients show promising results, with comparable long-term survival for active surveillance (*i.e.* postponed esophagectomy only in patients who develop a locoregional regrowth in the absence of distant metastases) *vs* immediate standard surgery.[39-42]

Outline of the thesis

This thesis consists of two parts. In part I the implications of neoadjuvant chemoradiotherapy on surgical treatment of esophageal cancer are described. Part II is focused on the feasibility of an active surveillance approach instead of standard esophagectomy in clinically complete responders after nCRT.

PART I. Implications of neoadjuvant chemoradiotherapy on surgical treatment

Since the publication of the CROSS-trial, nCRT followed by surgery is the standard of care in several countries, including the Netherlands. Overviews of nCRT and surgery are provided in **chapters 3 and 4**, respectively. In some other countries, perioperative chemotherapy is applied in patients with esophageal adenocarcinoma. The optimal multimodality treatment for these patients remains undetermined. **In chapter 5**, the CROSS nCRT-regimen is retrospectively compared with perioperative chemotherapy regimens in terms of survival, tumor down-staging and effect of lymphadenectomy on survival.

Earlier studies have shown that nCRT leads to substantial down staging of both primary tumor and regional lymph nodes. This questions the need for extended lymphadenectomy. In **chapter 6-8**, the role of lymphadenectomy after application of nCRT is critically appraised and further explored.

In **chapter 9-11**, we investigate the effect of nCRT as standard treatment on health-related quality of life early after completion of neoadjuvant treatment, in the postoperative phase and in the long-term.

In **chapter 12**, we aim to externally validate a previously introduced pre-treatment pathological staging system in the resection specimen after nCRT.

PART II. Active surveillance after neoadjuvant chemoradiotherapy

The high pathologically complete response rate after nCRT provides the rationale to explore an organ-sparing active surveillance approach after nCRT. In order to select patients who might benefit from active surveillance, the disease should be re-staged after nCRT by means of clinical response evaluation (CRE). CREs need to accurately categorize patients as clinically complete responders (cCR) or clinically incomplete responders. In **chapter 13** a systematic review and meta-analysis of the literature is described on the accuracy of detecting residual disease after neoadjuvant chemoradiotherapy. In **chapter 14,** we describe the study protocol of a diagnostic trial aimed to determine which combination of diagnostic tests is adequate for CRE by determining the accuracy of detecting substantial residual disease after nCRT. The main results of this trial are described in **chapter 15**. **Chapter 16 and 17** report the results of in depth analyses on the accuracy of detecting residual disease using endosonographic measurements and PET-CT, respectively. Active surveillance and standard esophagectomy carry specific risks and benefits. Active surveillance may avoid the risk of postoperative complications and decreased health-related quality of life (HRQOL), but patients need to undergo frequent diagnostic tests and it is unknown if survival is non-inferior compared to nCRT plus standard surgery. In **chapter 18**, we investigated factors that influence patients' preferences, and trade-offs that patients are willing to make in their choice be-

tween surgery and active surveillance after nCRT. This will likely improve shared decision making in the future. In **chapter 19**, we provide an overview of the current literature on active surveillance after nCRT for esophageal cancer. Based on this literature and based on the results of chapter 14 and 15, we have designed the phase-III SANO-trial (Surgical As Needed for Oesophageal cancer), assessing the (cost)effectiveness of active surveillance after nCRT, as compared to standard surgery. The protocol of this multicenter stepped wedge randomized controlled trial is described in **chapter 20**. Finally, in **chapter 21**, we illustrate the possible scenarios of an active surveillance strategy, by describing clinical outcomes of three typical patients who underwent active surveillance after nCRT in the Erasmus MC – University Medical Center – Rotterdam.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer Statistics, 2009. CA: A Cancer Journal for Clinicians. 2009;59(4):225-49.
2. Hoeymans N MJ, Schoemaker CG (red.). . Gezondheid en determinanten. Deelrapport van de Volksgezondheid Toekomst Verkenning 2010 Van gezond naar beter. . Bilthoven: RIVM, 2010 Contract No.: RIVM-rapport nr. 270061006.
3. Lewis I. The surgical treatment of carcinoma of the oesophagus; with special reference to a new operation for growths of the middle third. Br J Surg. 1946;34:18-31.
4. Chu KM, Law SY, Fok M, Wong J. A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. Am J Surg. 1997;174(3):320-4.
5. Goldminc M, Maddern G, Le Prise E, Meunier B, Campion JP, Launois B. Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial. Br J Surg. 1993;80(3):367-70.
6. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. Ann Thorac Surg. 2001;72(1):306-13.
7. Jacobi CA, Zieren HU, Muller JM, Pichlmaier H. Surgical therapy of esophageal carcinoma: the influence of surgical approach and esophageal resection on cardiopulmonary function. Eur J Cardiothorac Surg. 1997;11(1):32-7.
8. Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. Br J Surg. 1990;77(8):845-57.
9. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg. 2002;236(2):177-83.
10. Jamieson GG, Lamb PJ, Thompson SK. The role of lymphadenectomy in esophageal cancer. Ann Surg. 2009;250(2):206-9.
11. Lerut T, Nafteux P, Moons J et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg. 2004;240(6):962-72; discussion 72-4.
12. Tong D, Law S. Extended lymphadenectomy in esophageal cancer is crucial. World J Surg. 2013;37(8):1751-6.
13. Gignoux M, Roussel A, Paillot B et al. The value of preoperative radiotherapy in esophageal cancer: Results of a study of the E.O.R.T.C. World J Surg. 1987;11(4):426-32.
14. Wang M, Gu XZ, Yin WB, Huang GJ, Wang LJ, Zhang DW. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 206 patients. Int J Radiat Oncol Biol Phys. 1989;16(2):325-7.
15. Nygaard K, Hagen S, Hansen HS et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: A randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second scandinavian trial in esophageal cancer. World J Surg. 1992;16(6):1104-9.
16. Arnott SJ, Duncan W, Kerr GR et al. Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. Radiother Oncol. 1992;24(2):108-13.
17. Kelsen DP, Ilson DH. Chemotherapy and combined-modality therapy for esophageal cancer. Chest. 1995;107(6 Suppl):224S-32S.
18. Cooper JS, Guo MD, Herskovic A et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281(17):1623-7.
19. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062-7.

20. Ychou M, Boige V, Pignon JP et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-21.
21. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
22. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
23. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
24. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
25. Al-Batran SE, Hofheinz RD, Pauligk C et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17(12):1697-708.
26. Ando N, Kato H, Igaki H et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol. 2012;19(1):68-74.
27. Markar SR, Noordman BJ, Mackenzie H et al. Multimodality treatment for esophageal adenocaricnoma: multi-center propensity-score matched study. Ann Oncol. 2016.
28. Keegan N, Keane F, Cuffe S et al. Neo-AEGIS: A randomized clinical trial of neoadjuvant and adjuvant chemotherapy (modified MAGIC regimen) versus neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the esophagus and esophagogastric junction. J Clin Oncol. 2014;32(5s):(suppl; abstr TPS4145).
29. Klevebro F, Alexandersson von Dobeln G, Wang N et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016;27(4):660-7.
30. Shapiro J, van Klaveren D, Lagarde SM et al. Prediction of survival in patients with oesophageal or junctional cancer receiving neoadjuvant chemoradiotherapy and surgery. Br J Surg. 2016;103(8):1039-47.
31. Shapiro J, Biermann K, van Klaveren D et al. Prognostic value of pretreatment pathological tumor extent in patients treated with neoadjuvant chemoradiotherapy plus surgery for esophageal or junctional cancer. Ann Surg. 2017;265(2):356-62.
32. Peyre CG, Hagen JA, DeMeester SR et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549-56.
33. Talsma AK, Shapiro J, Looman CW et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. Ann Surg. 2014;260(5):786-93.
34. Scarpa M, Valente S, Alfieri R et al. Systematic review of health-related quality of life after esophagectomy for esophageal cancer. World journal of gastroenterology : WJG. 2011;17(42):4660-74.
35. van Meerten E, van der Gaast A, Looman CW, Tilanus HW, Muller K, Essink-Bot ML. Quality of life during neoadjuvant treatment and after surgery for resectable esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2008;71(1):160-6.
36. Smyth EC, Fassan M, Cunningham D et al. Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial. J Clin Oncol. 2016;34(23):2721-7.

37. Noordman BJ, Verdam MGE, Lagarde SM et al. Effect of neoadjuvant chemoradiotherapy on health-related quality of life in esophageal or junctional cancer: results from the randomized CROSS trial. J Clin Oncol. 2017:JCO2017737718.
38. Noordman BJ, Verdam MGE, Lagarde SM et al. Impact of neoadjuvant chemoradiotherapy on health related quality of life in long-term survivors of esophageal or junctional cancer: results from the randomized CROSS trial. Ann Oncol. 2017.
39. Castoro C, Scarpa M, Cagol M et al. Complete clinical response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic oesophagus: is surgery always necessary? J Gastrointest Surg. 2013;17(8):1375-81.
40. Furlong H, Bass G, Breathnach O, O'Neill B, Leen E, Walsh TN. Targeting therapy for esophageal cancer in patients aged 70 and over. J Geriatr Oncol. 2013;4(2):107-13.
41. Taketa T, Correa AM, Suzuki A et al. Outcome of trimodality-eligible esophagogastric cancer patients who declined surgery after preoperative chemoradiation. Oncology. 2012;83(5):300-4.
42. Taketa T, Xiao L, Sudo K et al. Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology. 2013;85(2):95-9.

PART I

Implications of neoadjuvant chemoradiotherapy on surgical treatment

Chapter 2

Surgical approaches to remove the esophagus: open

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Summary

Changes in the diagnosis, evaluation and pre-, per- and postoperative treatment of cancer of the esophagus and esophagogastric junction have resulted in improved prognosis for patients with this uncommon, but deadly, disease. A tailored approach to the management of these patients can now result in an overall 5-year survival of about 50%, which is a dramatic improvement compared to the dismal results reported in the (recent) past. Nevertheless, the optimal surgical approach remains unclear. The widely applied use of multimodality treatment (especially nCRT) questions the necessity of maximization of surgical lymph node retrieval and the introduction MIE might further decrease postoperative morbidity, with reduction of especially pulmonary complications. However, the lack of high-quality evidence on these topics has led to persistence of substantial differences in treatment approach between individual institutions. These differences underline the ongoing need for well-designed clinical trials on specific topics in the field of esophageal cancer surgery.

Surgical therapy

Surgical resection remains the cornerstone of therapy for patients with resectable cancer of the esophagus in the absence of systemic metastases. Surgery, in current practice most of the times combined with neoadjuvant therapy, offers the highest likelihood of cure for patients with locoregional disease. To obtain the best results, the management of esophageal cancer should be individualized and based on a combination of factors including the physiologic status of the patient, tumor type and location, and stage of disease. In this chapter, we describe the different open surgical approaches to remove the esophagus in patients with esophageal cancer. Although minimally invasive techniques are increasingly applied, the benefits of fully minimally invasive esophagectomy have not yet been proven unequivocally and an open or hybrid esophagectomy remains the standard procedure to remove the esophagus in many leading high-volume centers worldwide.[1] At present, the only strong available evidence comes from preliminary results of the French randomized MIRO trial comparing hybrid transthoracic esophagectomy (TTE, laparoscopic gastric mobilization and open thoracotomy) with fully open TTE. These results suggest that hybrid TTE significantly reduces postoperative complications compared to open TTE (odds ratio [OR] for postoperative morbidity 0.31, 95% CI 0.18–0.55, p=0.0001; percentage of pulmonary complications: 17.7% vs. 30.1%, p =0.037).[2]

Patient assessment

Esophageal cancer is a disease that occurs predominantly in the sixth and seventh decades of life. Advanced age alone should not be considered a contraindication for esophageal resection. Although the risk of mortality is higher in patients older than 70 years of age, this increased risk is due to the higher frequency of medical comorbidities such as heart, liver, and kidney disease in the elderly population rather than age per se.[3] It is important to note that when operative mortality is excluded, long-term survival after resection in the elderly population is similar to that observed in younger patients.[4, 5] As a result, octogenarians and nonagenarians can be considered candidates for potentially curative resection, but particular attention needs to be paid to the preoperative assessment of patients' general condition.

The strong etiologic ties between (squamous cell) cancer of the esophagus and alcohol and tobacco usage make it imperative that patients be carefully screened for the presence of cardiovascular, pulmonary, and hepatic dysfunction regardless of their age. It has been estimated that between 20% and 30% of patients with esophageal cancer will have evidence of cardiovascular disease if carefully screened.[6] This evaluation should at least consist of electrocardiography for all patients. The preoperative evaluation should

also include pulmonary function testing. Patients with significant impairment in the forced expiratory volume at 1 second (FEV_1 < 1 L) and those with chronic obstructive pulmonary disease are at increased risk of respiratory complications following surgery.[7, 8] Cirrhosis of the liver is not uncommon in patients with esophageal cancer, particularly those with squamous cell carcinoma. Well-compensated cirrhosis (Child classification A) alone is not a contraindication to resection of an otherwise curable esophageal cancer, but one should be careful when considering resection in the setting of more advanced stages of cirrhosis, especially in the presence of ascites. Furthermore, patients who are planned to undergo neoadjuvant chemo(radio)therapy should be screened for renal insufficiency.

Extent of resection for locoregional esophageal cancer

For several decades the optimal surgical strategy for the potentially curative treatment of patients with locoregional esophageal cancer is under debate. Historically, the Ivor-Lewis procedure has been widely applied, including a thoracotomy with limited lymphadenectomy and thoracic anastomosis.[9] Ever since, two main surgical techniques have evolved. First, the extended *en bloc* TTE was developed. With extensive two-field lymphadenectomy (upper abdomen and posterior mediastinum), this technique attempts to increase locoregional tumor control by enhancing of the radicality of resection.[10-14] It is established that extensive lymphadenectomy provides the benefit of more accurate staging, but its beneficial effect on survival is still unclear.[15-18] Second, the limited transhiatal esophagectomy (THE) was introduced, which focused on minimization of postoperative morbidity and mortality by preventing a thoracotomy.

Lymphatic dissemination in esophageal cancer occurs early and is unpredictable.[19] Once the tumor has penetrated the submucosal layer, up to one-half of patients will have nodal metastases.[20] More than 80% of patients with invasion of the muscularis propria will have at least one involved lymph node.[21] In the presence of transmural invasion, nodal involvement will be present in more than 85%, and the median number of involved nodes and the proportion of patients with more than four involved nodes increase (Table 1a).[22] Extended lymphadenectomy as performed during TTE increases the chance of removal of all tumor-positive lymph nodes and theoratically improves regional tumor control and perhaps even long-term survival. However, high-quality clinical evidence on the optimal extent of lymphadenectomy is absent, especially in the present era of neoadjuvant treatment. Consequently, individual opinions and institutional preferences currently dominate the choice of surgical technique and extent of lymphadenectomy.

Technique of open en bloc transthoracic esophagectomy

En bloc TTE is performed through a right thoracotomy and a midline laparotomy. The proximal anastomosis is performed either through an extra incision made at the left side of the neck or in the chest (see "anastomosis"). When a cervical anastomosis is performed, the procedure starts with a thoracotomy followed by the abdominal part of the operation, whereas in case of an intrathoracic anastomosis the laparotomy is performed prior to the thoracic phase.

The thoracic dissection includes removal of the azygos vein with its associated nodes, the thoracic duct, and the paratracheal, subcarinal, paraesophageal, and parahiatal nodes in continuity with the resected esophagus. Nodes in the aortopulmonary window are removed separately. The block of tissue removed is bounded laterally on each side by the excised mediastinal pleura, anteriorly by the pericardium and membranous part of the trachea, and posteriorly by the aorta and vertebral bodies.

During the thoracic phase the patient is placed in the left lateral decubitus position, with a posterolateral thoracotomy performed entering the chest through the fifth or sixth intercostal space. The inferior pulmonary ligament is divided to the level of the inferior pulmonary vein. The pleura overlying the right main bronchus is divided taking into account its membranous part. The pleura lying on both sides of the azygos arch is incised and the arch is ligated or closed with a stapling device and subsequently transected. The pleura cranial to the azygos arch is incised and saved to create a pedicled "flap" to cover the subsequent intrathoracic anastomosis. The right paratracheal nodes are removed in between the trachea, superior vena cava and the azygos arch. The right vagal nerve and the bronchial artery are divided. The vagal nerve should not be dived with use of electrocautery to prevent injury to the right recurrent nerve. The pleura overlying the lateral aspect of the vertebral bodies is incised from the level of the azygos arch to the diaphragm and the intercostal veins are divided between ligatures or clips where they enter the azygos vein. A dissection plane is then created following each intact intercostal artery to reach the adventitial plane of the aorta. Dissection continues across the anterior surface of the aorta, until the left mediastinal pleura is reached. Direct branches of the thoracic aorta to the esophagus should be carefully ligated before dividing. One or two communicating veins to the hemiazygos need to be ligated as they pass behind the aorta. The mediastinal tissue posteriorly between the azygos vein and the aorta just above the diaphragm includes the thoracic duct, which should be identified and transected at this stage. A heavy non-resorbable ligature should be placed caudally to prevent the development of a chylothorax. The dissection can be ended at the level of both crura of the diaphragm.

The anterior portion of the dissection is performed along the previously incised inferior pulmonary ligament. Hereby the posterior aspect of the pericardium is freed by

blunt and sharp dissection. The pericardium should only be removed when the tumor is adherent. Once the left mediastinal pleura is reached, the plane can be connected with the previous dissection over the aorta. Sometimes the left pleura is incised. The thoracic esophagus is then encircled with a Penrose drain for traction. The anterior dissection is then continued cephalad along the pericardium until the subcarinal nodes are encountered. Careful dissection along the right main bronchus up to the carina and then distally along the left main bronchus allows for removal of the entire subcarinal node basin in continuity with the resected esophagus. At this point, the anterior dissection is also transitioned to the wall of the esophagus by dividing the left vagal nerve where it crosses the left main bronchus. The esophagus is separated from the membranous part of the trachea. In case of an intrathoracic anastomosis, the esophagus is divided above the level of the azygos arch. In case of a cervical anastomosis the dissection is continued towards the root of the neck. The lymph nodes in the aortopulmonary window can be dissected after identification of the left vagal nerve. The left vagal nerve is divided between ligatures at the level of the left main bronchus. The proximal side is carefully moved upward with use of the same ligature, thus preventing damage to the left recurrent nerve when dissecting the AP window nodes. The proximal thoracic duct is also ligated and cut at the level of the fourth vertebral body where it crosses from right to left.

The abdominal portion of the operation begins with a midline laparotomy and inspection of the peritoneal cavity and liver. Normally segment two and three of the liver are mobilized by incising the left triangular ligament with electrocautery. The flaccid part of the lesser omentum is identified and incised in the direction of the right crus. The right gastric artery is identified and the lesser omentum is further mobilized. Then the gastrocolic omentum is divided, carefully preserving the gastroepiploic arcade. This dissection should begin distally at the level of the pylorus, continuing proximally to include division of the short gastric vessels. The short gastric vessels should be divided as close as possible to the spleen to preserve as many collateral vessels to the fundus as possible. In this fashion also an omental wrap around the future anastomosis can be created.

All of the lymph node–bearing tissue overlying the proximal border of the hepatic artery and portal vein is removed. This dissection is continued proximally along the hepatic artery to its origin from the celiac axis. The retroperitoneal tissue above the pancreas overlying the right crus of the diaphragm is dissected medially and superiorly to remain attached to the esophagectomy specimen. Attention is then turned to the greater curvature of the stomach where the gastrocolic omentum is divided. The gastric fundus is rotated to the right to continue the dissection in the retroperitoneum, removing all of the node-bearing tissue above the splenic artery and overlying the left crus of the diaphragm. The musculature of the diaphragmatic hiatus is then incised (in case of a bulky tumor) to meet the incision made in the diaphragm during the thoracic dissec-

tion. Often the diaphragmatic vein needs to be ligated. Retracting the stomach anteriorly, ample exposure of the celiac axis can be achieved to allow for ligation of the coronary vein (= left gastric vein). After this, the upper abdominal lymphadenectomy around the celiac trunk can be completed. The left gastric artery is dived at its origin. A Kocher maneuver can be performed if needed to allow additional mobility of the stomach.

Reconstruction is preferably performed by creation of a gastric tube after resection of the gastric cardia. The gastric tube is created using a linear stapling device. The staple line should begin on the upper fundus at least 5 cm from the distal limit of the tumor and should continue to a point along the lesser curvature corresponding to the fourth or fifth branch of the right gastric artery, in case of a cervical anastomosis, where more length can be achieved by staying closer to the greater curve (consequently a narrower tube). When an intrathoracic anastomosis is performed, more of the right gastric vessels can be preserved and consequently a wider tube can be created. Finally, the staple line is oversewn.

Technique of transhiatal esophagectomy

The operation begins with an abdominal lymph node dissection and gastric mobilization (see "Technique of open *en bloc* transthoracic esophagectomy"). Next, the tendinous part of the esophageal hiatus is incised anteriorly or the muscular part is incised circumferentially after division of the diaphragmatic vein with ligatures. This ensures removal of any potentially involved parahiatal nodes, but it also enlarges the hiatal opening that facilitates the lower mediastinal dissection. Placement of appropriate retractors through the widened esophageal hiatus allows for *en bloc* dissection of all the fatty tissue and lymph nodes surrounding the lower thoracic esophagus under visual control as far as possible. Under normal circumstances this can be done up to the level of the inferior pulmonary veins. In order not to damage the thoracic duct, care should be taken not to dissect at the right side of the thoracic aorta. Subsequently, the gastric tube is created and the cervical esophagus is exposed (see "cervical anastomosis"). The upper thoracic esophagus is delivered into the cervical wound and it is divided in the neck. A large bore vein stripper is inserted through the cervical esophagus and brought out to the gastric remnant. After a long tape is tied to the distal part of the transected esophagus, it is bluntly stripped from the neck towards the abdomen, whilst the adhesions between the esophagus and surrounding structures are manually freed via the widened hiatus. In the lower mediastinum, the vagal nerve trunks that are separated from the esophagus by this maneuver can be divided below the carina with use of scissors. The right lateral attachments are mobilized by a similar maneuver passing the right hand anterior to the esophagus and using the thumb and index finger to bluntly dissect the right lateral attachments. The tape tied follows the inverting esophagus from the

neck to the abdomen. The esophagus is everted again and the resection specimen is sent for pathological examination. The tape is now sutured onto the top of the gastric tube (which has been created at an earlier stage: see above) . The gastric tube can be wrapped in a bowel bag or laparoscopic camera bag to facilitate atraumatic passage and can be brought up to the neck by pulling gently on the tape and pushing the gastric tube into the mediastinum. Care should be taken to avoid rotation of the gastric tube. A cervical anastomosis can subsequently be performed (see "Cervical Anastomosis").

Reconstruction

In the far majority of patients undergoing resection for esophageal cancer, reconstruction is performed using a gastric conduit, where only a single anastomosis is required.

The major disadvantages of using the stomach include the almost complete lack of peristaltic activity and the tendency for persistent reflux into the remaining cervical esophagus that is directly connected to the acid-secreting stomach. In long-term survivors, this ongoing reflux can result in the development of interstitial metaplasia (Barrett) in the cervical remnant.[23] The need to preserve length may also result in more limited margins, especially for large or very distal tumors that can result in local recurrence. As a result, when there is extensive involvement of the stomach and the esophagus, the use of an antiperistaltic or isoperistaltic left colon interposition is preferred. Also, in cases where creation of a (sufficiently oxygenated) gastric tube is technically not possible (e.g. history of gastric surgery or aberrant blood supply of the stomach), reconstruction is performed using a colonic interposition.

During TTE, the surgeon can choose between an anastomosis at the cervical level or in the chest. In contrast, a THE always requires an anastomosis in the neck. Despite the increased rate of recurrent laryngeal nerve damage, leakage and possible stricture formation, some surgeons prefer a cervical anastomosis during TTE, because of a longer proximal tumor-free margin and a theoretically reduced morbidity in case of an anastomotic leak.[24, 25] The latter is founded on the assumption that a leakage of a cervical anastomosis is more likely to be confined to the neck, instead of leaking into the pleural cavity and mediastinum. However, a meta-analysis on this topic did not show differences in pulmonary complications (OR 0.86, 95% CI 0.13 – 5.59, p=0.87) and tumor recurrence (OR 2.01, 95% CI 0.68 – 5.91, p=0.21), which suggests that a cervical anastomosis after TTE does not decrease the risk of thoracic complications compared to an intrathoracic anastomosis.[26] Interestingly, in two large retrospective studies, it was found that the risk of intrathoracic manifestations due to leakage of a cervical anastomosis is significantly less in patients after THE than in patients who underwent TTE. This is probably explained by the difference in mediastinal dissection and pleural resection. After THE, the bilaterally intact parietal pleura may confine infections, which pre-

vents extension to the pleural cavity and mediastinum.[27, 28] Notably, these studies were performed before the introduction of neoadjuvant therapy. Studies comparing cervical with intrathoracic anastomoses in patients who underwent neoadjuvant therapy are lacking. The CROSS trial comparing neoadjuvant chemoradiotherapy plus surgery with surgery alone, in which most anastomoses were performed at cervical level, showed no significant difference in leakage rate.[29] Nevertheless, preoperative radiotherapy likely affects anastomotic healing, especially if the fundus (i.e. the future tip of the gastric tube) was located within the radiation field. Theoretically, the gastric tube can be shorter in case of an intrathoracic anastomosis, with potentially improved oxygenation of the tip and thus enhanced anastomotic healing. On the contrary, radiation damage on the intrathoracic esophageal remnant might hamper intrathoracic anastomotic healing. This topic is currently subject of investigation in an ongoing Dutch randomized trial comparing cervical with intrathoracic anastomosis after neoadjuvant chemoradiotherapy (ICAN trial, Dutch Trial Registry number: NTR4333).

Cervical anastomosis

When a cervical anastomosis is performed after transthoracic esophagectomy, dissection of the proximal part of the thoracic esophagus should be performed as far as possible into the base of the neck to facilitate the later dissection. Exposure of the cervical esophagus is accomplished through an oblique left neck incision placed along the anterior border of the sternocleidomastoid muscle. This incision should extend from the sternal notch to a point halfway to the ear lobe. The omohyoid, sternohyoid, and sternothyroid muscles are divided laterally and the jugular vein and carotid sheath are lateralized. The middle thyroid vein and inferior thyroid artery are ligated. Dissection is then continued posteriorly to the esophagus, down to the dissection plane with the prevertebral fascia, into the thoracic inlet where the dissection plane performed during the thoracotomy is reached. A dissection plane is then created between the esophagus and the trachea. The esophagus is encircled with a Penrose drain and the upper thoracic esophagus is delivered into the neck. The esophagus is divided at the level of the thoracic inlet and the specimen is removed via the abdomen after tying a tape to the esophagus. The cervical remnant should not be too long, thus preventing that the anastomosis will ultimately retract into the upper chest with a possibly increased risk of intra-thoracic manifestation in case of leakage.

With use of the tape, which is tied to top of the gastric tube, the gastric pull-up can be completed. The previously created gastric tube can be wrapped in a plastic bag to facilitate atraumatic passage to the neck. Care should be taken to avoid excessive tension on the stomach or its gastroepiploic arcade during this maneuver, and to avoid twisting of the stomach. The anastomosis is performed between the remaining cervical esophagus and the gastric tube. We prefer to perform an end-to-end anastomosis with single-

layer running suture. Several nonabsorbable sutures should be placed to normalize the size of the hiatus to prevent visceral herniation into the thorax. A nasogastric decompression tube is then carefully passed as well as a nasojejunal feeding tube. Alternatively, one can choose for a percutaneous jejunal feeding tube.

Intrathoracic anastomosis

In case of an intrathoracic anastomosis, the proximal part of the esophagus is divided just above the arch of the azygos vein. With care to prevent rotation, the cardia together with the gastric tube, is delivered through the hiatus into the thoracic cavity, and the surgical specimen (*i.e.* esophagus and cardia) is removed. After placement of 4-8 sutures around the esophagus (PDS 3.0), a purse string prolene 1.0 is placed and after careful inflation of a 30ml balloon of a catheter the diameter of the circular stapler is estimated and the anvil is placed. Subsequently, the gastrotomy is made at the tip of the gastric tube, the circular stapling device is introduced and an end-to-side anastomosis is created using a 25 mm or 29 mm circular stapling device. The gastrotomy is closed with a linear stapler and the linear staple line is oversewn. A naso-gastric tube is passed into the distal stomach. After completion of the anastomosis, omental tissue is wrapped around the anastomosis (omentoplasty).

Colon interposition

When a colon interposition is performed, the complete stomach is removed with the esophagectomy specimen by dividing the duodenum just distal from the pylorus. There are several alternatives to use the colon for interposition. Frequently the left colon is used in an isoperistaltic position. For this purpose the ascending and descending colon are mobilized completely. The left segment of the colon to be interposed derives its arterial supply from the ascending branch of the left colic artery and usually corresponds to the segment extending from the mid-transverse colon to the proximal descending colon. This segment is mobilized by dissecting the middle colic artery back to its origin from the superior mesenteric artery where it arises as a single trunk in most patients. After the middle colic artery and vein are have temporarily been occluded to ensure adequate collateral flow through the marginal artery, these vessels are ligated and divided.

The apex of the arc portended by the vascular pedicle is then marked with a suture and the distance from this point to the neck is measured with an umbilical tape. This tape is used to measure proximally from the first marking stitch to determine the point of transection of the proximal colon. The divided colon is then passed through the bed of the resected esophagus wrapped in a bowel bag, and a single-layer monofilament running anastomosis is performed to the remaining cervical esophagus. Traction is

gently applied to the colon from within the abdomen to eliminate redundancy and the colon is secured to the left crus of the diaphragm with a non-absorbable suture.

The colon is then divided with a linear stapler 5 to 10 cm below the point where it enters the abdomen. Care should be exercised not to leave too long of an intraabdominal segment of colon as this will result in food retention. The mesentery should be divided immediately adjacent to the wall of the colon to avoid injury to the vascular pedicle. A single-layered anastomosis is then performed between the distally divided colon and the Roux-en-Y jejunal loop, and colon continuity is restored by a colo-colostomy.

Alternatively the left colon can be used in antiperistaltic position, which is based on a vascular pedicle of the middle colic artery and vein. In this way the interposed segment can be longer, by making use not only of the descending colon, but also (part of) the sigmoid colon.

Finally, the right colon can be used including the ileocecal valve in an isoperistaltic position and again based on the middle colic vessels. The advantage of this technique is that the ileocecal valve will act as an antifreflux mechanism at the proximal anastomosis.

We routinely perform a catheter jejunostomy to provide early postoperative enteral feeding, and to avoid the need for parenteral nutrition in the event of postoperative complications such as an anastomotic leak. The jejunostomy catheter is removed when the patient is able to maintain body weight by oral feedings, usually 3 to 4 weeks postoperatively.

Complications

Despite recent improvements in perioperative management, postoperative morbidity and mortality following esophagectomy for cancer remain significant. These are large, technically demanding operations that are often performed on patients with compromised cardiopulmonary function. Nutritional disturbances are also common, because of the combined effects of the cancer itself and the obstructing mass in the esophagus.

Recent audits suggest a hospital mortality rate varying from 3.5 to 9% in the West.[30, 31] Complication rates varying from 17 to 74% are reported in both open and minimally invasive esophagectomy series.[32, 33] This wide range of complication rates can be explained by the variations in definitions of complications and the absence of standardization of time periods defining postoperative deaths.[34, 35] Accurate comparison of outcomes between centers to improve the quality of care requires consistency in definitions and data collection. Therefore, an international system for defining and recording postoperative complications associated with esophagectomy has been developed.[36]

Complications occurring in a randomized trial comparing open TTE with open THE for esophageal adenocarcinoma are summarized in Table 1b.[37] Pulmonary complica-

tions including pneumonia (defined as isolation of a pathogen from a sputum culture and an infiltrate on chest x-ray) and atelectasis (defined as lobar collapse on chest x-ray) are among the most common complications, occurring in 57% and 27% of patients who underwent TTE or THE, respectively. These complications can be minimized by early ambulation and careful attention to adequate pain control. Prevention of aspiration can be achieved by keeping the patient in the semi-upright position at all times, and by meticulous attention to maintaining a functioning nasogastric tube. When necessary, a mini-tracheostomy can provide invaluable assistance in clearing retained secretions.

Cardiac complications occur in approximately 26% and 16% of TTE and THE patients, with the development of atrial fibrillation accounting for the majority of these complications. The shift of body fluids and the extensive mediastinal dissection which causes a systemic inflammatory response likely play a role in the pathogenesis. Although these are generally self-limiting, they do require cardiac monitoring and treatment, which can prolong the ICU stay. Atrial fibrillation can also *e.g.* be caused by anastomotic dehiscence with secondary mediastinitis or by mechanical irritation by a chest tube. For these underlying causes specific measures are needed.

Anastomotic complications occur in 10% to 30% of patients depending on the definition and the type of reconstruction performed.[38] Most of these leaks can be managed with local drainage and antibiotic administration as long as the vascular supply to the reconstruction is adequate. We recommend early endoscopy in any patient who is known or suspected to have a substantial leak to exclude potentially life-threatening conduit ischemia, which can be present in as many as 14% of patients with an anastomotic leak.[39]

Results

Long-term survival following esophagectomy depends on several factors including age, gender, weight loss, histological subtype, depth of tumor invasion, radicality of the resection and the number of involved lymph nodes.[29, 40, 41] The impact of surgical approach on long-term survival remains the subject of debate.

In a retrospective analysis from nine high-volume centers on 2,303 patients (60% adenocarcinoma [AC], 40% squamous cell carcinoma [SCC]) who underwent R_0-resections, it was shown that a high total number of resected nodes is an independent prognostic factor of (favorable) survival after primary surgery. The optimal threshold for survival benefit was removal of 23 nodes, and the operation most likely to achieve this number was found to be an *en bloc* transthoracic resection.[42] These findings are arguments in favor of TTE over THE. In contrast, a non-randomized study by two British high-volume centers showed similar long-term survival after THE and TTE for patients with SCC (12%) or AC (88%), while hospital stay was significantly shorter after

THE.[43] This advantage in short-term recovery after THE over TTE without substantially jeopardizing oncological outcome was confirmed in a recent meta-analysis of 52 studies that included 3,389 TTE patients and 2,516 THE patients (48% SCC, 52% AC). In addition to the significantly shorter hospital stay (4 days less in patients who underwent THE, 95% CI: 1–7, p<0.01), THE was associated with shorter operation time (85 minutes shorter, 95% CI 40–129, p<0.001), less pulmonary complications (17.3% vs. 21.4%, odds ratio [OR] 1.37, 95% CI 1.05–1.79, p=0.02) and lower postoperative mortality (7.2% vs. 10.6%, OR 1.48, 95% CI 1.20– 1.83, p<0.001). On the other hand, anastomotic leaks and recurrent nerve palsies occurred more frequently after THE than after TTE. Moreover, lymph node yield was higher after TTE (mean difference of eight nodes, 95% CI 1–14, p=0.02). The results of this meta-analysis should be interpreted with caution, because both randomized and non-randomized studies were included. This probably introduced a selection bias in favor of the THE group, because patients with more advanced tumors probably have been treated preferentially via the chest.[44] On the other hand, more frail patients may have been offered a THE because of no need for a thoracotomy. Finally, the enhanced short-term recovery after THE could not be confirmed in a large (more than 17,000 patients), multicenter observational study that compared TTE with THE; no differences were found in morbidity and mortality. However, a preference for THE in patients with poor performance status probably resulted in selection bias in favor of patients who underwent TTE.[45]

Proponents of the transhiatal approach explain differences in survival by stage that have been consistently reported as being due to stage migration. This occurs when positive nodes in the extended part of the dissection increase pN-stage in patients with a more favourable prognosis compared to patients with the same number of positive nodes after a limited dissection during THE. In an attempt to address this issue, Altorki *et al.* have reported outcome following *en bloc* TTE and transhiatal resections performed in patients with T3N-positive (stage III) disease.[46] In this group of patients, the effect of stage migration was supposed to be limited because all had locally advanced tumors with lymph node involvement. They reported 4-year survival of 35% after *en bloc* resection, which was significantly better than the 11% survival observed after transhiatal esophagectomy. Ultimately, this debate can only be resolved by the completion of a large randomized controlled trial. To date, only one such large trial (HIVEX) has been reported by Hulscher et al.[37] This trial randomized 220 patients with AC of the mid-to-distal esophagus or the gastric cardia substantially involving the esophagus between THE and TTE. By avoiding a thoracotomy, artificial ventilation time (1 day after THE vs. 2 days after TTE, p<0.001) and hospital stay (15 days after THE vs. 19 days after TTE, p<0.001) were shorter and pulmonary complications were reported less frequently (27% after THE vs. 57% after TTE, p<0.001) after THE than after TTE. Nevertheless, in-hospital mortality was comparable between both groups (2% after THE and 4% after

TTE, p=0.45). Interestingly, the more extended TTE was not associated with a higher percentage of tumor-free resection margins (72% after THE vs. 71% after TTE), whereas the median number of resected lymph nodes was two times higher after TTE than after THE (median 31 vs. 16, p<0.001). This high lymph node yield did not translate into a significantly better five-year overall survival (34% after THE and 36% after TTE (p=0.71)).[47] However, in a subsequent subgroup-analysis of patients with a truly esophageal (Siewert type-1) cancer, and more specifically in patients with a limited number (1–8) of positive lymph nodes, an improved long-term survival was found after TTE, (23% after THE vs. 64% TTE, p=0.02). Given the post-hoc design of this analysis, the effect of stage migration on improved survival of TTE patients cannot be excluded, because more lymph nodes were resected after TTE. Furthermore, the relevance of these results is unclear for patients with SCC (only patients with AC were included). The final conclusion of the HIVEX trial was that in patients with advanced truly esophageal cancer (Siewert type-1) TTE is the preferred technique (especially in case of a limited number of positive nodes), while THE suffices in patients with a tumor located at the EGJ (Siewert type-2) and in patients with a poor performance status (especially in case of pulmonary comorbidities), without clinically suspected nodes at or above the carina.[47]

The role of neoadjuvant therapy

Increasingly, the management of esophageal cancer has focused nowadays on multimodality therapy, with neoadjuvant chemotherapy or chemoradiotherapy being administered to nearly all patients with locally advanced disease in many centers. The concept of neoadjuvant therapy in esophageal cancer was spurred by a general disappointment in the results of primary resections, which resulted in survival of 35% or less at 5 years.[37]

Many studies have been performed to test the additional value of preoperative neoadjuvant therapy to surgical resection. A meta-analysis showed that both neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy improve long-term survival.[48] Furthermore, this meta-analysis showed am (nonsignificant) benefit of neoadjuvant chemoradiotherapy (nCRT) over neoadjuvant chemotherapy (nCT) by comparison of the treatment arms of several trials (HR for overall mortality for nCRT vs. nCT 0.88, 95% CI 0.76-1.01, p=0.07). Unfortunately, direct comparisons are limited, especially for patients with AC.

Since the publication of this meta-analysis, the multicenter randomized CROSS trial was completed, comparing nCRT plus surgery with surgery alone in patients with esophageal or junctional cancer (both SCC and AC).[29, 49] The applied regimen (carboplatin and paclitaxel with 41.4 Gy concurrent radiotherapy) had low toxicity compared to earlier trials that mostly used cisplatin and fluorouracil. Median survival dou-

bled from 24% in the surgery alone group to 49% in the nCRT group (HR 0.68, 95% CI 0.53-0.88, p=0.003), with a 5-year survival advantage of 14% (33% vs. 47%). The superior survival in the surgery alone arm of the CROSS trial compared to that in earlier randomized trials, indicates that the survival benefit can be attributed to improved survival in the multimodality arm, and is not due to poor survival in the surgery alone arm.[50, 51] Based on these results, nCRT according to the CROSS regimen plus surgery is now considered standard of care in many countries.

It should be noted that the favorable results of the CROSS trial were not confirmed in a recently completed French randomized trial (Fédération Francophone de Cancérologie Digestive (FFCD) 9901 trial) comparing nCRT plus surgery with surgery alone in stage I and II esophageal cancer patients. The applied neoadjuvant regimen consisted of cisplatin and fluorouracil with 45 Gy concurrent radiotherapy. No differences in 3-year overall survival rate and radical resection rate were found between both treatment arms.[52]

Based on the FFCD 9901 trial, the standard use of nCRT for early-stage tumors can be debated. Possibly, surgery alone suffices in this subgroup of patients. This is supported by the high rate of radical resections (92%) in the surgery alone arm of the French trial. However, the generalizability of the FFCD 9901 trial is questionable due to the low case volume of most participating centers, the high toxicity of the nCRT regimen with less sophisticated radiation techniques compared to the CROSS trial and a remarkably high postoperative mortality rate (11.1%). Therefore, we caution to conclude that patients with early-stage esophageal cancer should not undergo nCRT. We believe that in the absence of high quality evidence on the specific effect of nCRT on early-stage tumors, the results from the CROSS trial (which also included stage-II-cancers) should be leading.[53]

The CROSS trial as well as the FFCD 9901 trial included both AC and SCC. Although nCRT also significantly improves survival in patients with AC, the maximum benefit of nCRT is observed in SCC, which is known to be more radiosensitive than AC.[29, 49] Three small underpowered randomized trials comprising 119, 75 and 131 patients respectively with esophageal AC did not show significant differences in survival between nCRT followed by surgery and nCT followed by surgery. Nevertheless, higher rates of pCR, R0 and ypN0 were found in the nCRT groups and two of these three trials showed a (non-significant) benefit in favor of nCRT.[54-57] The optimal neoadjuvant treatment for esophageal AC remains undetermined and is currently investigated in the randomized Neo-AEGIS (perioperative MAGIC chemotherapy vs. preoperative CROSS chemoradiotherapy, in adenocarcinoma of the esophagus and esophago-gastric junction) trial which is likely to be reported in 2021.[58]

NCRT has a significant down staging effect on both the primary tumor and the regional lymph nodes. In the nCRT-arm of the CROSS trial, a substantial number of pa-

tients (29% overall, 49% SCC, 23% AC) did not have any vital tumor left in the resection specimen. This observation led to the imperative to reconsider the necessity of standard esophagectomy in all patients who undergo nCRT. Therefore, the feasibility of an active surveillance strategy in patients with a clinically complete response (cCR) after nCRT is currently being explored. In this so called SANO (*i.e.* Surgery As Needed in Oesophageal cancer patients) approach, surgical resection would be offered only to patients in whom residual disease is highly suspected or proven after nCRT. Before SANO can be tested in a prospective clinical trial, we aim to determine the accuracy of clinical detection of residual disease after nCRT in the present preSANO trial.[59] Furthermore, the French phase II/III randomized ESOSTRATE trial comparing standard surgery with surgery on demand in case of recurrence in patients with a clinically complete response after nCRT is currently being initiated (ClinicalTrials.gov identifier: NCT02551458).[60]

As outlined above, the randomized HIVEX trial comparing THE with TTE for subcarinal AC only included patients with primary surgery. In that trial TTE did not improve the rate of tumor-free margins (72% after THE vs.71% after TTE), but roughly doubled the number of resected nodes (median ± standard deviation = 16 ± 9 after THE vs. 31 ± 14 after TTE, $p<0.001$). As discussed above, a retrospective international study has shown that after primary surgery the number of resected nodes is correlated with a favorable long-term survival.[42] However, it has been reported that chemoradiotherapy reduces lymph node yield from within the radiotherapy field.[61-63] Importantly, in the patients after primary surgery from the CROSS trial, the total number of resected nodes and the number of resected positive nodes were positively correlated. However, this positive association completely disappeared in patients who underwent nCRT. Furthermore, after surgery alone the total number of removed nodes was positively correlated with overall survival (hazard ratio (HR) per 10 additionally resected nodes, 0.76; $p=0.007$), which corresponds with the earlier retrospective international study.[42, 64] Interestingly, this positive correlation between the number of resected nodes and survival was absent after nCRT (HR 1.00; $p=0.98$). The randomized design of the CROSS trial renders differences between both treatment groups unlikely as an explanation for the (disappearance of the) association in this post-hoc analysis. These results question the necessity of maximization of surgical lymph node dissection after nCRT, both for prognostication and for therapeutic purposes.

The same phenomenon was identified in a large retrospective comparison of 307 patients who underwent nCRT according to CROSS plus surgery and 301 patients who underwent nCT according to MAGIC followed by surgery. In the nCRT group, the association between lymph node harvest and survival was absent. However, in the nCT group, extent of lymphadenectomy seemed to be positively correlated with progression free survival. Again, these data question the necessity for maximization of surgical lymph node retrieval specifically after nCRT. However, extended lymphadenectomy

seems of importance in patients who undergo nCT followed by surgery (or surgery alone).[65]

These indirect arguments need confirmation in a randomized trial comparing TTE with extended lymphadenectomy and THE with limited lymphadenectomy in patients with (Siewert type-1) esophageal cancer who undergo nCRT. We believe that such trial should focus on truly esophageal cancer, and not on junctional cancer, because it already has been shown that THE suffices in junctional cancer if they undergo primary surgery; let alone in patients with junctional cancer who have been treated with preoperative nCRT.

Salvage surgery

Definitive CRT (dCRT) is frequently applied in patients with SCC of the proximal part of the esophagus (*i.e.* above the carina) and in patients not fit for surgery. Although organ preservation is a considerable advantage in the non-operative strategy of dCRT, this approach is associated with high rates (up to 51%) of recurrence or persistence of locoregional disease.[66] In these patients, salvage esophagectomy is an option after failed dCRT with curative intent. This selective surgery is more demanding than primary esophagectomy. Thanks to centralization of care with improvement in patient selection, in surgical technique and in perioperative management, perioperative morbidity and mortality nowadays have substantially decreased.[67] Furthermore, the increased application of nCRT has familiarized surgeons with surgical resection in an irradiated surgical field.

Results of salvage surgery after failed dCRT were analyzed in a non-randomized phase II trial.[68] Forty-three patients were treated with induction CT (5-FU, cisplatin and paclitaxel) followed by CRT (5-FU and cisplatin with concurrent 50.4 Gy). CT scans of the chest and abdomen, positron emission tomography (PET, optional but encouraged), esophagogastroscopy with biopsies and endoscopic ultrasound (EUS) were performed after completion of CRT and serially thereafter. Twenty patients underwent salvage esophagectomy because of residual or recurrent disease without signs of distant metastases. One-year overall survival was 71% (95% CI 54% - 82%). Nevertheless, a subsequent phase III trial was not initiated, because the intended predefined minimal one-year survival rate of 77.5% was not achieved. This predefined one-year survival rate was deducted from the RTOG database, consisting mainly of SCC patients. The proportion of ACs in this trial was 73%. Moreover, three CRT related deaths were reported. Theoretically, elimination or mitigation of induction CT from the regimen might have reduced treatment-related toxicity and increased the chance of achieving the target one-year survival rate of 77.5%.[68]

Furthermore, a more recent retrospective propensity matched analysis compared patients undergoing salvage esophagectomy (n = 308) with patients who underwent nCRT followed by planned esophagectomy (n = 540). In-hospital mortality was comparable (but high) in both groups (8.4% versus 9.3%). Differences in postoperative complications were found for anastomotic leak (17.2% vs. 10.7%; p=0.007) and wound infection (18.5% vs. 12.3%; p=0.026), which were both more frequent in patients who underwent salvage surgery. At three-year follow-up, groups had comparable overall (43.3% versus 40.1%; p=0.542) and disease-free survival rates (39.2% vs. 32.8%; p=0.232), suggesting that salvage surgery can offer acceptable short- and long-term results in a selected group of patients.[69]

Table 1a. Relationship Between Tumor Depth (T-stage) and Lymph Node Status (N-stage) for Esophageal Adenocarcinoma.[54]

Tumor Depth	Prevalence of Node Metastases (%)*	Number of Involved Nodes [median (IQR)]**	Number With 1-4 Involved Nodes (%)†	Number With >4 Involved Nodes (%)‡
Intramucosal (T1A)	1/16 (6)	2 (n/a)	1/16 (6)	0/16 (0)
Submucosal (T1B)	5/16 (31)	1 (n/a)	4/16 (25)	1/16 (6)
Intramuscular (T2)	10/13 (77)	2 (1-4)	9/13 (69)	1/13 (8)
Transmural (T3)	47/55 (85)	5 (3-13.5)	22/55 (40)	25/55 (45)

*$\chi^2 = 42.0$, $p < 0.0001$ (chi-square test for trend).
**$\chi^2 = 11.02$, $p = 0.0116$ (Kruskal-Wallis; includes only patients with involved nodes).
†$\chi^2 = 13.64$, $p = 0.0035$ (chi-square test for trend).
‡$\chi^2 = 21.38$, $p < 0.0001$ (chi-square test for trend).

Table 1b. Postoperative Complications Occurring in 220 Primary Resections for Esophageal Adenocarcinoma in a Randomized Trial Comparing TTE and THE.[68]

Complication	Transthoracic Esophagectomy (%)	Transhiatal Esophagectomy (%)	P Value
Pulmonary complications*	65 (57)	29 (27)	<0.001
Cardiac complications	30 (26)	17 (16)	0.10
Anastomotic leakage**	18 (16)	15 (14)	0.85
Subclinical	8 (7)	9 (8)	
Clinical	10 (9)	6 (6)	
Vocal-cord paralysis†	24 (21)	14 (13)	0.15
Chylous leakage	11 (10)	2 (2)	0.02
Wound infection	11 (10)	8 (8)	0.53

* Pulmonary complications include pneumonia (indicated by isolation of a pathogen from a sputum culture and an infiltrate on chest x-ray) and atelectasis (indicated by lobar collapse on chest x-ray).
** The definition for subclinical anastomotic leakage was anastomotic leakage seen only on contrast radiography, and clinical anastomotic leakage was defined as anastomotic leakage resulting in a cervical salivary fistula (all patients had cervical anastomoses).
†In most cases, vocal-cord paralysis was temporary.

References

1. Thomas N. With Minimally Invasive Esophagectomy, Thoracic Surgeons Must Avoid Falling into the Same Trap Again! Semin Thorac Cardiovasc Surg. 2015;27(2):216-7.
2. Mariette C, Meunier B, Pezet D et al. Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicenter, open-label, randomized phase III controlled trial, the MIRO trial. J Clin Oncol. 2015;33((suppl 3; abstr 5)).
3. Sugimachi K, Inokuchi K, Ueo H, Matsuura H, Matsuzaki K, Mori M. Surgical treatment for carcinoma of the esophagus in the elderly patient. Surg Gynecol Obstet. 1985;160(4):317-9.
4. Zehetner J, Lipham JC, Ayazi S et al. Esophagectomy for cancer in octogenarians. Dis Esophagus. 2010;23(8):666-9.
5. van Nistelrooij AM, Andrinopoulou ER, van Lanschot JJ, Tilanus HW, Wijnhoven BP. Influence of young age on outcome after esophagectomy for cancer. World J Surg. 2012;36(11):2612-21.
6. Konder H, Ponitz-Pohl E, Roher HD, Lennartz H. [Risk assessment and preliminary treatment in patients with esophageal cancer] Risikoeinschatzung und Vorbehandlung bei Osophaguskarzinom-Patienten. Anasth Intensivther Notfallmed. 1988;23(1):9-13.
7. Giuli R, Sancho-Garnier H. Diagnostic, therapeutic, and prognostic features of cancers of the esophagus: results of the international prospective study conducted by the OESO group (790 patients). Surgery. 1986;99(5):614-22.
8. Chan K, Wong J. Mortality after esophagectomy for carcinoma of the esophagus: An analysis of risk factors. Dis Esophagus. 1990;3(46).
9. Lewis I. The surgical treatment of carcinoma of the oesophagus; with special reference to a new operation for growths of the middle third. Br J Surg. 1946;34:18-31.
10. Chu KM, Law SY, Fok M, Wong J. A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. Am J Surg. 1997;174(3):320-4.
11. Goldminc M, Maddern G, Le Prise E, Meunier B, Campion JP, Launois B. Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial. Br J Surg. 1993;80(3):367-70.
12. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. Ann Thorac Surg. 2001;72(1):306-13.
13. Jacobi CA, Zieren HU, Muller JM, Pichlmaier H. Surgical therapy of esophageal carcinoma: the influence of surgical approach and esophageal resection on cardiopulmonary function. Eur J Cardiothorac Surg. 1997;11(1):32-7.
14. Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. Br J Surg. 1990;77(8):845-57.
15. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg. 2002;236(2):177-83.
16. Jamieson GG, Lamb PJ, Thompson SK. The role of lymphadenectomy in esophageal cancer. Ann Surg. 2009;250(2):206-9.
17. Lerut T, Nafteux P, Moons J et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg. 2004;240(6):962-72; discussion 72-4.
18. Tong D, Law S. Extended lymphadenectomy in esophageal cancer is crucial. World J Surg. 2013;37(8):1751-6.
19. Raja S, Rice TW, Goldblum JR et al. Esophageal submucosa: the watershed for esophageal cancer. J Thorac Cardiovasc Surg. 2011;142(6):1403-11 e1.

20. Stein HJ, Feith M, Bruecher BL, Naehrig J, Sarbia M, Siewert JR. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg. 2005;242(4):566-73; discussion 73-5.
21. Nigro JJ, Hagen JA, DeMeester TR et al. Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined to the wall: implications for therapy. J Thorac Cardiovasc Surg. 1999;117(1):16-23; discussion -5.
22. Hagen JA, DeMeester SR, Peters JH, Chandrasoma P, DeMeester TR. Curative resection for esophageal adenocarcinoma: analysis of 100 en bloc esophagectomies. Ann Surg. 2001;234(4):520-30; discussion 30-1.
23. Oberg S, Johansson J, Wenner J, Walther B. Metaplastic columnar mucosa in the cervical esophagus after esophagectomy. Ann Surg. 2002;235(3):338-45.
24. Markar SR, Arya S, Karthikesalingam A, Hanna GB. Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg Oncol. 2013;20(13):4274-81.
25. Chasseray VM, Kiroff GK, Buard JL, Launois B. Cervical or thoracic anastomosis for esophagectomy for carcinoma. Surg Gynecol Obstet. 1989;169(1):55-62.
26. Biere SS, Maas KW, Cuesta MA, van der Peet DL. Cervical or thoracic anastomosis after esophagectomy for cancer: a systematic review and meta-analysis. Dig Surg. 2011;28(1):29-35.
27. Korst RJ, Port JL, Lee PC, Altorki NK. Intrathoracic manifestations of cervical anastomotic leaks after transthoracic esophagectomy for carcinoma. Ann Thorac Surg. 2005;80(4):1185-90.
28. van Heijl M, van Wijngaarden AK, Lagarde SM, Busch OR, van Lanschot JJ, van Berge Henegouwen MI. Intrathoracic manifestations of cervical anastomotic leaks after transhiatal and transthoracic oesophagectomy. Br J Surg. 2010;97(5):726-31.
29. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
30. Auditing DIfC. Jaarrapport. 2014.
31. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med. 2011;364(22):2128-37.
32. Dunst CM, Swanstrom LL. Minimally invasive esophagectomy. J Gastrointest Surg. 2010;14 Suppl 1:S108-14.
33. Courrech Staal EF, Aleman BM, Boot H, van Velthuysen ML, van Tinteren H, van Sandick JW. Systematic review of the benefits and risks of neoadjuvant chemoradiation for oesophageal cancer. Br J Surg. 2010;97(10):1482-96.
34. Blencowe NS, Strong S, McNair AG et al. Reporting of short-term clinical outcomes after esophagectomy: a systematic review. Ann Surg. 2012;255(4):658-66.
35. Talsma AK, Lingsma HF, Steyerberg EW, Wijnhoven BP, Van Lanschot JJ. The 30-day versus in-hospital and 90-day mortality after esophagectomy as indicators for quality of care. Ann Surg. 2014;260(2):267-73.
36. Low DE, Alderson D, Cecconello I et al. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg. 2015;262(2):286-94.
37. Hulscher JB, van Sandick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662-9.
38. Nederlof N, Tilanus HW, Tran TC, Hop WC, Wijnhoven BP, de Jonge J. End-to-end versus end-to-side esophagogastrostomy after esophageal cancer resection: a prospective randomized study. Ann Surg. 2011;254(2):226-33.
39. Portale G, Hagen JA, Peters JH et al. Modern 5-year survival of resectable esophageal adenocarcinoma: single institution experience with 263 patients. J Am Coll Surg. 2006;202(4):588-96; discussion 96-8.
40. Lagarde SM, ten Kate FJ, Reitsma JB, Busch OR, van Lanschot JJ. Prognostic factors in adenocarcinoma of the esophagus or gastroesophageal junction. J Clin Oncol. 2006;24(26):4347-55.

41. Shapiro J, van Klaveren D, Lagarde SM et al. Prediction of survival in patients with oesophageal or junctional cancer receiving neoadjuvant chemoradiotherapy and surgery. Br J Surg. 2016.
42. Peyre CG, Hagen JA, DeMeester SR et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549-56.
43. Davies AR, Sandhu H, Pillai A et al. Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. Br J Surg. 2014;101(5):511-7.
44. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. Ann Surg. 2011;254(6):894-906.
45. Connors RC, Reuben BC, Neumayer LA, Bull DA. Comparing outcomes after transthoracic and transhiatal esophagectomy: a 5-year prospective cohort of 17,395 patients. J Am Coll Surg. 2007;205(6):735-40.
46. Altorki NK, Girardi L, Skinner DB. En bloc esophagectomy improves survival for stage III esophageal cancer. J Thorac Cardiovasc Surg. 1997;114(6):948-55; discussion 55-6.
47. Omloo JM, Lagarde SM, Hulscher JB et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007;246(6):992-1000; discussion -1.
48. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
49. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
50. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335(7):462-7.
51. Tepper J, Krasna MJ, Niedzwiecki D et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26(7):1086-92.
52. Mariette C, Dahan L, Mornex F et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32(23):2416-22.
53. Shapiro J, van Lanschot JJ, Hulshof MC, van der Gaast A. Effectiveness of neoadjuvant chemoradiotherapy for early-stage esophageal cancer (letter to the editor). J Clin Oncol. 2015;33(3):288-9.
54. Stahl M, Walz MK, Stuschke M et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27(6):851-6.
55. Burmeister BH, Thomas JM, Burmeister EA et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer. 2011;47(3):354-60.
56. Klevebro F, Alexandersson von Dobeln G, Wang N et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016.
57. Stahl M, Riera-Knorrenschild J, Stuschke M et al. Preoperative chemoradiotherapy and the long-term run in curative treatment of locally advanced oesophagogastric junction adenocarcinoma: Update of the POET phase III study. J Clin Oncol. 2016;34:(suppl; abstr 4031).
58. Keegan N, Keane F, Cuffe S et al. Neo-AEGIS: A randomized clinical trial of neoadjuvant and adjuvant chemotherapy (modified MAGIC regimen) versus neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the esophagus and esophagogastric junction. J Clin Oncol. 2014;32(5s):(suppl; abstr TPS4145).

59. Noordman BJ, Wijnhoven BP, van Lanschot JJ. Optimal surgical approach for esophageal cancer in the era of minimally invasive esophagectomy and neoadjuvant therapy. Dis Esophagus. 2015.
60. Putora PM, Bedenne L, Budach W et al. Oesophageal cancer: exploring controversies overview of experts' opinions of Austria, Germany, France, Netherlands and Switzerland. Radiat Oncol. 2015;10:116.
61. Robb WB, Dahan L, Mornex F et al. Impact of neoadjuvant chemoradiation on lymph node status in esophageal cancer: post hoc analysis of a randomized controlled trial. Ann Surg. 2015;261(5):902-8.
62. Taflampas P, Christodoulakis M, Gourtsoyianni S, Leventi K, Melissas J, Tsiftsis DD. The effect of preoperative chemoradiotherapy on lymph node harvest after total mesorectal excision for rectal cancer. Dis Colon Rectum. 2009;52(8):1470-4.
63. Lykke J, Roikjaer O, Jess P, Danish Colorectal Cancer G. Tumour stage and preoperative chemoradiotherapy influence the lymph node yield in stages I-III rectal cancer: results from a prospective nationwide cohort study. Colorectal Dis. 2014;16(4):O144-9.
64. Talsma AK, Shapiro J, Looman CW et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. Ann Surg. 2014;260(5):786-93.
65. Markar SR, Noordman BJ, Mackenzie H et al. Multimodality treatment for esophageal adenocaricnoma: multi-center european comparative study. Accepted, Ann Oncol. 2016.
66. Cooper JS, Guo MD, Herskovic A et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281(17):1623-7.
67. Markar SR, Schmidt H, Kunz S, Bodnar A, Hubka M, Low DE. Evolution of standardized clinical pathways: refining multidisciplinary care and process to improve outcomes of the surgical treatment of esophageal cancer. J Gastrointest Surg. 2014;18(7):1238-46.
68. Swisher SG, Winter KA, Komaki RU et al. A Phase II study of a paclitaxel-based chemoradiation regimen with selective surgical salvage for resectable locoregionally advanced esophageal cancer: initial reporting of RTOG 0246. Int J Radiat Oncol Biol Phys. 2012;82(5):1967-72.
69. Markar S, Gronnier C, Duhamel A et al. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: is it a viable therapeutic option? J Clin Oncol. 2015;33(33):3866-73.

Chapter 3

Chemoradiation in esophagogastric junction cancer

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Introduction

For decades, primary surgery as well as radiotherapy (RT) alone were two treatment options for potentially curable esophageal cancer. Outcomes were poor, with most patients developing recurrent disease with associated morbidity and mortality. Both treatment options evolved over time as a result of better staging[1-3] and improved surgical-[4-6] and radiation techniques.[7, 8] Furthermore, the addition of chemotherapy (CT) to RT and the combination of surgical and nonsurgical approaches were important developments in the treatment of esophageal cancer. However, due to a lack of high-quality evidence, treatment of choice for esophageal cancer still remains controversial. Institutional preferences and clinical opinions still dominate the applied treatments. In this chapter we give an overview of the role of chemoradiotherapy (CRT) in the treatment of adenocarcinomas (AC) of the distal esophagus and esophagogastric junction (EGJ).

Classification of junctional tumors

In 1997, the Siewert classification was introduced for the classification of ACs of the esophagus and EGJ (see chapter 7). Using the Siewert classification, three different tumor entities (esophageal, cardiac and subcardiac) are distinguished, based on specific anatomical landmarks.[9] Because advanced tumors often obscure these landmarks and frequent discrepancy is encountered between endoscopic, radiologic, peroperative and pathologic localization, its usefulness and applicability was shown to be limited.[10] Some studies on neoadjuvant therapies selected patients based on histology type (AC or squamous cell carcinoma (SCC)) irrespective of location, others classified patients according to location of the tumor (*e.g.* lower/upper esophagus, EGJ) irrespective of histology. Most studies included all patients with esophageal or junctional tumors, regardless of the histology type. As a consequence, the majority of studies on esophageal cancer are only to a limited extent applicable for patients with ACs of the EGJ. In this chapter, we focus on studies in patients with ACs originating in a Barrett segment or with cardia carcinomas substantially invading the distal esophagus.

Rationale for combination of chemotherapy and radiotherapy

Studies have tested the safety and efficacy of combining CT and RT. Theoretically, both modalities may be active against different tumor cell populations (additive effect). CT may be effective against distant micrometastases while radiation acts locoregionally (spatial cooperation). Furthermore, CT increases the effect of radiation by inhibiting the repair of sublethal radiation damage, may synchronize cells to a specific cell-cycle phase that has increased sensitivity to RT, may decrease repopulation after RT and, by shrink-

ing the tumor, may enhance reoxygenation, which is advantageous for RT (synergistic effect).[11-13]

Definitive chemoradiotherapy

Definitive chemoradiotherapy vs. *definitive radiotherapy alone*

Earliest references to the treatment of esophageal cancer with RT alone date back to the beginning of the 20th century. Outcomes were generally very disappointing with five-year overall-survival rates ranging from 0 to 5%.[14] With the advent of more potent chemotherapeutic agents, combined CRT became a more effective treatment option. Due to the observed synergistic effect of the combination of CT and RT, definitive CRT in patients with potentially curable esophageal cancer was further explored.

Addition of CT to RT in patients with esophageal cancer was studied in a stratified phase III trial performed by the Radiation Therapy Oncology Group (RTOG 85-01 trial).[15] Patients (n=121) with potentially curable ACs or SCCs of the esophagus were randomized between RT alone (64 Gy in 32 fractions) and CRT (two courses of 5-fluoruracil (5-FU) and cisplatin combined with 50 Gy RT, followed by two courses 5-FU and cisplatin). Interim analysis showed a significant difference in median survival between the RT (8.9 months) and combined therapy group (12.5 months, $p<0.001$). This led to an early closure of the trial. Of all analyzed patients, only fifteen (12%) had ACs and 37 (31%) had a primary tumor located in the lower esophagus. The remaining patients had SCC, mainly located in the mid-esophagus. No subgroup analysis based on histology or location was presented.[15] Therefore, it remains unclear to what extent these results are applicable to ACs of the EGJ. Interestingly, long term results did not show any survival difference related to histology in patients treated with CRT, but separate results based on tumor location were still not presented. In line with the medium term results, five-year overall survival was improved in the combined modality group, as compared to patients treated with RT alone: 26% (95% confidence interval (CI) 15%-37%) vs. 0%, respectively.[16]

Dose of radiotherapy in definitive chemoradiotherapy

Although the combination of CT and RT improved results compared to RT alone, the incidence of locoregional residual or recurrent disease remained high (*e.g.* 47% in the RTOG 85-01 trial).[16] In an attempt to improve locoregional control and overall survival, the subsequent RTOG 94-05 (intergroup 0123) phase III trial intensified RT dose.[17] This trial compared the same CRT regimen as was used in the RTOG 85-01 trial (50 Gy) with a higher dose RT (64.8) combined with the standard CT dose. After interim analysis the

RTOG 94-05 trial was closed prematurely because of a high number of treatment related deaths in the high-dose radiotherapy group, albeit that some of these deaths occurred before the end of study treatment. There was no significant difference in locoregional control or long-term survival between the two arms. This study included 31 (14%) patients with ACs. Patients whose tumors extended to within 2.0 cm of the EGJ were excluded because of the concern that the stomach could not tolerate 64.8 Gy. No subgroup analyses were performed.[17] Hence, these results cannot be translated directly to EGJ tumors, but suggest that higher radiation dose is not favorable. However, recent improvements in RT techniques using conformal multiple field techniques or intensity modulated radiotherapy (IMRT) will reduce doses to the normal tissues (especially heart, anterior mediastinum and lung) and might lead to improved tolerability of increased radiation dose in an attempt to improve locoregional control.

Sequential vs. *concurrent chemoradiotherapy*

The effects of sequential versus concurrent CRT were studied in a Cochrane meta-analysis by Wong *et al.* Eight studies including 857 patients on sequential CRT were analyzed. No clinical benefit in terms of mortality (hazard ratio (HR) 0.87, 95% CI 0.74-1.02) and local control was found, as compared to the RT alone group. Moreover, patients in the sequential CRT group experienced significant toxicities. Concurrent CRT was shown to improve overall survival significantly, compared to RT alone (HR 0.73, 95% CI 0.64-0.84). This analysis on concurrent CRT was based on eleven studies including 998 patients (Table 1). In these meta-analyses patients with AC and SCC were pooled and no subgroup analysis on tumor location was presented.[18]

Due to the superior effects of concurrent CRT over a sequential regimen, subsequent studies mainly focused on concurrent CRT. Taken together, these studies suggest that concurrent CRT should be recommended over RT alone or sequential CRT as a non-surgical therapy for potentially curable ACs of the distal esophagus and EGJ. A high dose of RT (64 vs. 50 Gy) combined with CT increases toxicity rates with no difference in survival, but more sophisticated radiation techniques might change this viewpoint in the future.

Salvage surgery

Although organ preservation is a notable advantage of the non-operative strategy of CRT, this approach is associated with a high rate (up to 40%) of recurrent or persistent locoregional disease.[16] Selective surgical resection is a treatment option in patients after failed definitive CRT with curative intent. This so-called salvage surgery is more demanding than primary esophagectomy. Due to improvements in patient selection, perioperative management, surgical technique and centralization of care perioperative mor-

bidity and mortality are nowadays substantially lower.[19] Furthermore, the increased use of neoadjuvant CRT in addition to surgery for esophageal cancer familiarized surgeons with the resection of an irradiated esophagus.

Results of surgical salvage after failed definitive CRT were presented in a non-randomized phase II trial.[20] Forty-three patients, of whom 41 were eligible for analysis, were treated with definitive CRT. This consisted of induction CT (5-FU, cisplatin and paclitaxel) followed by concurrent CRT (50.4 Gy with 5-FU and cisplatin). Esophagogastroscopy with biopsies, endoscopic ultrasound (EUS), CT scans of the chest and abdomen and positron emission tomography (PET, optional but encouraged) were performed after completion of CRT and serially thereafter. Seventeen patients with residual or recurrent disease, but without distant metastases, underwent salvage esophagectomy. During follow-up, esophageal resection was performed in three additional patients because of clinical suspicion of recurrent disease. Tumor cells were found in all these resected specimens. One-year overall survival rate was 71% (95% CI 54%-82%). However, since the intended predefined one-year survival rate of 77.5% was not achieved, a subsequent phase III trial was not initiated. It should be noted that the preset one-year survival rate of 77.5% is deducted from the RTOG database, which consists mainly of SCC patients, whereas the proportion of patients with ACs in this trial was 73%. Moreover, a total of three CRT related deaths were reported. As suggested by the authors, elimination of induction CT from the regimen might lead to less treatment-related toxicity and perhaps achievement of the target one-year survival rate.[20]

Also in this study, patients with AC were not analyzed separately. Given the high proportion of patients with ACs in the study population and the possibly more positive effect of surgical salvage that might be feasible than was achieved by the authors of the study, salvage surgery in addition to definitive CRT in patients with ACs of the distal esophagus and EGJ is an interesting topic, which remains to be investigated more extensively.

Definitive chemoradiotherapy vs. *surgery alone*

Historically, primary surgical resection was considered as the only curative treatment for esophageal cancer.[21] With more effective and less toxic chemotherapeutic agents and more sophisticated radiotherapeutic techniques, curative treatment of esophageal cancer with definitive CRT is now also potentially feasible. But is definitive CRT preferred over surgery alone? High quality evidence on this subject is absent.

Two randomized trials comparing definitive CRT with curative intent to primary esophagectomy have been conducted. Results of the CURE (Chinese University Research group for Esophageal cancer) trial were reported by Chiu et al in 2005.[22] The CRT regimen consisted of 5-FU and cisplatin CT, combined with concurrent 50-60 Gy

RT. In case of incomplete clinical response or recurrence without systemic disease, salvage surgery was performed. No significant difference in two-year overall survival between the CRT group (n=36) and the surgery group (n=45) was found (relative risk 0.89, 95% CI 0.37-2.17, p=0.45).[22] Given the higher incidence of SCC in the East, this study only included SCC patients, thus results are not necessarily applicable to patients with EGJ cancer. In 2007, results of a the second trial comparing definitive CRT (64 Gy and 3 courses of cisplatin and 5-FU) to surgery alone were published as abstract by Carstens *et al.* Patients (n=91) with both AC (50%) and SCC (50%) were included. There was no significant difference in survival between the two treatment arms. Unfortunately, detailed information about study design and results is not available, because so far the trial has not been published as a full paper.[23]

Neoadjuvant chemo- and/ or radiotherapy plus surgery

Neoadjuvant radiotherapy plus surgery

The earliest reports on neoadjuvant RT plus surgery date back to the early 1970s.[24] These reports all consist of uncontrolled case series from often single institutions. In those days, the majority of esophageal cancers were SCC and treatment consisted of either surgery or RT, depending on patient- and tumor characteristics and individual and institutional preferences. Due to disappointing long-term locoregional control after primary surgery, interest developed in the addition of preoperative RT to surgery as a possible means of downstaging the primary tumor. The rationale was that tumor downstaging might increase the radical resectability rate, thereby reducing locoregional recurrence rate and – possibly – improving long-term survival.

A Cochrane meta-analysis from 2005 by Arnott *et al.* reviewed the effects of the addition of preoperative RT to surgery as compared to surgery alone.[25] This review was based on five randomized controlled trials, published between 1981 and 1992, totaling 1,147 patients (Table 2).[26-30] The majority of patients were men (78%), younger than 65 years (80%) with SCCs (89%). The planned total dose of RT ranged from 20 to 40 Gy given in 10 to 20 fractions over a period of one to four weeks, with the delay from end of RT to surgery ranging from one to four weeks. Median follow-up time was nine years. In patients that received neoadjuvant RT, the risk of death was reduced by 11%, HR of 0.89 (95% CI 0.78-1.01) and absolute survival at two- and five years improved (non-significantly) from 30 to 34% and 15 to 18%, respectively. Radical resectability rates were reported as not significantly different between the groups. A subgroup analysis did not show a difference in benefit from preoperative RT for patients with tumors located at the upper/middle esophagus compared to patients with a tumor of the lower esopha-

gus. Due to the high number of patients with SCC, the authors considered analysis by histology as uninformative.

The authors of this meta-analysis concluded that, based on the existing randomized data, there is no clear evidence that preoperative RT alone improves the survival of patients with potentially resectable esophageal cancer.

Neoadjuvant chemotherapy plus surgery

With the advent of more effective and less toxic chemotherapeutic regimens similar interest developed in the addition of neoadjuvant CT to surgery as a means of reducing locoregional tumor burden, thereby potentially increasing locoregional resectability. Moreover, systemic therapy might be able to eradicate distant micrometastatic disease. It is often concluded that compared to historical controls the outcome improves after treatment with pre-operative CT.[31] In summary, results of the individual trials and a recent update of an earlier published meta-analysis indicate that preoperative CT plus surgery offers a slight survival advantage (HR for all-cause mortality 0.87, 95% CI 0.79–0.96, p=0.005) as compared to surgery alone for resectable thoracic esophageal cancer of any histological type.[32] For detailed information on neoadjuvant CT combined with surgery, we refer to Chapter 18.

Neoadjuvant chemoradiotherapy plus surgery

In their meta-analysis, Sjoquist *et al.*[32] identified 13 randomized trials comparing neoadjuvant CRT plus surgery to surgery alone[30, 33-44], published between 1992 and 2012, totaling 1,932 patients (Table 3). Two trials, by Mariette *et al.* and Van der Gaast *et al.*, were only available as abstracts at the time of this meta-analysis, but have now been completed and fully reported.[45, 46.] The largest of these trials, the CROSS trial[45], will be discussed separately in more detail below.

Sample sizes of included trials ranged from 56 to 364 patients. Seven trials included only SCCs[30, 33-35, 37, 39, 42], five trials included both SCC and ACs[38, 40, 41, 45, 47] and one trial included ACs only.[36] Various CT and RT regimens were used. The pooled HR for all-cause mortality in these included trials, when comparing neoadjuvant CRT plus surgery with surgery alone, was 0.78 (95% CI 0.70–0.88, p<0.0001). This corresponds to an absolute survival benefit of 8.7% at two years. The survival benefit for neoadjuvant CRT was similar for AC and SCC. In AC the HR was 0.75 (95% CI 0.59–0.95, p=0.02) and in SCC the HR was 0.80 (95% CI 0.68–0.93, p=0.004). Assessment of the effects of neoadjuvant CRT on survival by tumor site was not possible, because this information was not provided in most included trials.

The conclusion of this meta-analysis was that there is a significant survival benefit for preoperative CRT in patients with AC or SCC of the esophagus.

CROSS trial

The recently completed CROSS trial was a multicenter, randomized phase III trial.[45] The study included and analyzed 366 patients during a five-year period. It included patients from five academic and two non-academic high-volume teaching hospitals in The Netherlands. Most patients (75%) had an AC and most tumors were located at the EGJ (24%) or in the distal esophagus (58%). The study compared neoadjuvant CRT followed by surgery with surgery alone in patients with potentially curable esophageal cancer (cT2-3N0-1M0 and cT1N1M0), with a planned inclusion of 175 patients per arm. The neoadjuvant regimen consisted of carboplatin (AUC=2) and paclitaxel (50 mg/m^2) given by intravenous infusion on days 1, 8, 15, 22 and 29, combined with concurrent radiation therapy using a multiple field technique. A total dose of 41.4 Gy was given in 23 fractions of 1.8 Gy, five fractions per week, starting on the first day of the first cycle of CT. The aim of this trial was to compare overall survival between patients treated with neoadjuvant CRT followed by surgery and patients treated with surgery alone for potentially curable, esophageal AC or SCC.

Neoadjuvant treatment was well tolerated, with >90% of all patients receiving full treatment. The most common toxic effects in the CRT followed by surgery group were leukopenia (6%), anorexia (5%), fatigue (3%) and neutropenia (2%). One patient died of major bleeding while awaiting surgery, probably due to an esophago-aortic fistula. Median overall survival of patients who received neoadjuvant CRT plus surgery was 49 months, compared to 24 months for those who underwent surgery alone. With a median follow-up of 32 months, 70 patients had died in the neoadjuvant CRT group vs. 97 in the surgery-alone group. Three-year overall survival was superior in the neoadjuvant CRT arm (HR 0.66, 95% CI 0.50-0.87, p=0.003). Patients with an AC had a significant survival advantage (p=0.049). No subgroup analysis based on location of the tumor was provided.

In conclusion, results from the CROSS trial show that the addition of neoadjuvant CRT (carboplatin, paclitaxel and 41.4 Gy of concurrent RT) to surgery significantly increases survival as compared to surgery alone in patients with potentially curable AC and SCC of the esophagus or EGJ. Therefore, neoadjuvant CRT plus surgery is now considered the therapy of first choice in the Netherlands and several other countries for potentially curable esophageal cancer (cT2-3N0-1M0 and cT1N1M0) in patients fit to undergo this treatment.

The improvement of survival after neoadjuvant CRT as found in the CROSS-trial, was not demonstrated in the recent FFCD9901 study by Mariette *et al*. This group randomized 195 patients with stage I or II (cT1-2N0-1M0 and T3N0M0) esophageal cancer between neoadjuvant CRT (45 Gy with concurrent 5-FU and cisplatin) or surgery alone. Of all included patients only 29% had an AC. Tumor location was separated in above

(9%) or below the carina. The difference in outcome as compared to the CROSS trial, might be explained by a more toxic CT regimen and a lower tumor stage in the French trial. A majority of patients in the French trial had middle-third SCC, whereas the CROSS trial consisted of mostly lower-third ACs. Since SCCs tend to be more radiosensitive than ACs, the absence of improvement of survival after neoadjuvant CRT in this study is surprising. Furthermore, a postoperative mortality rate of 11.1% in the multimodality group was reported, vs. 3.4% in the surgery only group. The CROSS study reported an in hospital mortality of 4% in both groups. In the French trial 86% of the neoadjuvant CRT patients underwent surgery compared to 92% in the CROSS study, which could be the result of the more toxic chemotherapy regimen and is expected to have a negative influence on survival. Another important point, is that the 195 included patients were recruited from 30 centers during a period of 9 years, corresponding with less than one inclusion per center per year. It is well known that high volume is associated with improved survival.[48] Despite this limitation, state of the art results were achieved in the surgery alone group. Finally, increased radiation dose as compared to the CROSS trial (45 Gy vs. 41.4 Gy, respectively), or differences in radiation technique (conventional APPA-technique vs. more sophisticated conformal four-field radiation) might be responsible for the relatively high mortality rate.

Neoadjuvant chemotherapy vs. *neoadjuvant chemoradiotherapy*

Although results on neoadjuvant RT or neoadjuvant CT did not show convincing improvement of survival, the additive effect of both modalities led to studies on neoadjuvant CRT. The addition of RT to neoadjuvant CT was compared to neoadjuvant CT alone by Stahl *et al.* and Burmeister *et al.*[49, 50] The first group included 126 patients with locally advanced (T3-4NxM0) EGJ ACs (Siewert type 1-3), of whom 119 eligible patients were randomized in their POET (PreOperative chemotherapy or radiochemotherapy in Esophago-gastric adenocarcinoma Trial) trial. The neoadjuvant CT regimen consisted of cisplatin, 5-FU and leucovorin followed by esophagectomy. Patients in the CRT group received the same induction CT, followed by concurrent CRT (cisplatin and etoposide combined with 30Gy). The trial was closed prematurely due to poor accrual. Although not significantly, preoperative CRT improved three-year survival with 20% (47.4% compared to 27.7% in the neoadjuvant CT group, p=0.07). Furthermore, patients in the CRT arm had a significantly higher probability of showing tumor-free lymph nodes (64.4% vs. 36.7%, p=0.01) and pathologically complete response (15.6% vs. 2.0%, p=0.03) at resection. A few comments can be made. First, postoperative mortality in the CRT group was more than doubled (10.2% vs. 3.8%). Given the low total radiation dose applied, it seems likely that other factors than radiation therapy were responsible for this relatively high mortality rate. If these deaths could have been prevented,

significantly improved three-year survival might have been achieved. For comparison, in the CROSS trial, postoperative mortality in the neoadjuvant CRT group was 3.8%.[45] Second, the low radiation dose might have contributed to a relatively low pathologically complete response (pCR) rate (15.6% vs. 23% in the CROSS trial), but still significantly higher than after CT (2%, p=0.03). Increased radiation dose, as used in the CROSS study, might have led to increased pCR rates, which are known to be associated with increased survival. Third, the trial closed prematurely and was consequently underpowered. Significant results might have been achieved if more patients were included. Taken together, these considerations suggest a more positive conclusion than was made by the authors of the trial and seem to point to superiority of neoadjuvant CRT over neoadjuvant CT.[49]

In 2011 Burmeister *et al.* published the results of a phase II trial that randomized patients with ACs of the esophagus and EGJ to preoperative CT or preoperative CRT. The regimen consisted of cisplatin and 5-FU with or without concurrent radiation therapy (35 Gy). Seventy-five patients were included, of whom 66 proceeded to resection. Median overall survival did not differ significantly between the neoadjuvant CT group and the neoadjuvant CRT group (29 months and 32 months, respectively, p=0.83). Nevertheless, R0 resection rate (100% in the neoadjuvant CRT group, 86% in the neoadjuvant CT group) and histopathological response rate (<10% viable cells, 31% in neoadjuvant CRT group and 8% in the neoadjuvant CT group, p=0.01) favored those receiving neoadjuvant CRT. Toxicity and surgical morbidity were not increased by the addition of RT to neoadjuvant CT. An explanation for the absence of improved survival in the neoadjuvant CRT group, despite improvement of two well-known prognostic indicators, might be the restricted size of the cohort. Furthermore, increased dose of RT might have led to further improvement of survival rates. This study only included patients with ACs, but did not distinguish between patients based on location of the tumor.[47]

A significant advantage of both neoadjuvant CRT and neoadjuvant CT was found in the meta-analysis by Sjoquist *et al.* To quantify the relative survival benefits of neoadjuvant CRT compared to neoadjuvant CT, treatment arms of different trials were compared. This indirect comparison showed a trend in favor of neoadjuvant CRT (HR for all-cause mortality for neoadjuvant CRT vs. neoadjuvant CT 0.88, 95% CI 0.76-1.01, p=0.07).[32] A recent meta-analysis of perioperative mortality and postoperative morbidity in 23 studies on neoadjuvant CT and neoadjuvant CRT in esophageal carcinoma did not find a difference in mortality or morbidity between both modalities. Furthermore, no increase in mortality or morbidity attributable to neoadjuvant therapy as compared to surgery alone was found. Subgroup analysis of neoadjuvant CRT in patients with SCC suggested an increased risk of treatment-related mortality compared with surgery alone (RR 1.95, 95% CI 1.06-3.60, p=0.032)[51], which is in line with the increased postoperative mortality rate as reported in the FFCD9901 study.[46]

Definitive chemoradiotherapy vs. neoadjuvant chemoradiotherapy plus surgery

In recent years two randomized trials were reported in literature comparing definitive CRT to neoadjuvant CRT plus surgery for esophageal cancer. Results of both studies were mainly based on patients with SCC.

The first study, by Stahl *et al.,* included 172 patients from eleven centers.[52] In this trial definitive CRT (without salvage surgery) was compared with neoadjuvant CRT plus surgery for 'locally advanced' (T3-4N0-1M0) SCCs of the upper and mid third of the esophagus. The design of the study is debatable in some points, but this is beyond the scope of this chapter. In summary, no difference in overall survival was found. However, locoregional failure was less common, and treatment-related death was more common in the neoadjuvant CRT plus surgery group.

In 2007, Bedenne *et al.* reported the second randomized trial (FFCD 9102) comparing definitive CRT with neoadjuvant CRT plus surgery.[53] Patients with resectable T3N0-1M0 AC or SCC of the esophagus (SCC >90%) were included. All patients were treated with neoadjuvant CT (5-FU and cisplatin) combined with 30 Gy RT in two split courses or 46 Gy RT given continuously. Subsequently, clinical response was evaluated by abdominal ultrasonography, chest X-ray, esophagography and when possible endoscopic ultrasonography. Of all included patients, 259 (58.3%) showed an objective clinical response after neoadjuvant CRT. These patients were randomized between surgery or definitive CRT (15 Gy or 20 Gy in the split course regimen or the continuous regimen, respectively). Both concurrent and sequential CRT were used in the neoadjuvant CRT and definitive CRT treatment strategies. The authors considered both treatment modalities as equivalent if there would be a difference in two-year survival rate of less than 10% between the two treatment arms. Two-year survival rates for the definitive CRT arm and neoadjuvant CRT plus surgery arm were 39.8% and 33.6%, respectively, leading to the conclusion that both treatment modalities are equivalent (p=0.03, representing the chance that the actual difference is >10%). Conclusions of this trial are limited by a few remarkable results. For example, survival rates are substantially lower as compared to survival rates as reported in other trials.[45] Furthermore, locoregional progression differed significantly between definitive CRT and neoadjuvant CRT plus surgery (64.3% and 40.7%, respectively, p=0.003), but this was not translated in different survival rates. Most importantly, the study included mainly patients with SCCs and therefore applicability for patients with EGJ tumors is questionable.[53]

In conclusion, the role for definitive CRT in patients with ACs of the EGJ remains unclear. However, these studies have addressed an important topic, which is relevant in patients with EGJ cancer. Specifically, whether definitive CRT can replace neoadjuvant CRT plus surgery in patients with a clinical complete response on CRT. Larger studies

comparing definitive CRT versus neoadjuvant CRT plus surgery in this group of patients are needed.

Future perspectives

Classification by location and histology

Currently, most tumors of the esophagus, regardless of location and histology, are staged and treated similarly. However, these different tumor types differ in etiology, biology and radiosensitivity. Therefore, when adopting an evidence based approach for optimal management, it is important to consider the proportions of tumors for anatomical subsite and histological type enrolled in a study. Absence of proper subgroup analyses often complicates applicability of results to specific groups of patients. Consequently, current and future trials should focus more on tumor location and histological subtype. Given the strong association between geographic location and histology - in the West the majority of the patients have AC, while in the East most esophageal cancers are SCC – a current three-arm phase III trial in Japan compares two neoadjuvant CT regimens with neoadjuvant CRT in patients with SCC specifically.[54] In parallel with this Japanese study, the Irish ICORG 10-14 study investigates the effect of neoadjuvant CRT vs. neoadjuvant plus adjuvant CT in patients with AC only. These studies will hopefully lead to a more biology-directed treatment strategy.

Dose escalation in definitive chemoradiotherapy

Definitive concurrent CRT is the treatment of choice for esophageal cancer when a non-surgical approach is preferred. Driven by the high rates of recurrent or persistent locoregional disease, current studies in the field of definitive CRT focus on improvement of locoregional control. Although previous studies showed increased treatment related toxicity and no benefit in terms of locoregional control, recent developments in radiation techniques led to the present Dutch ART DECO (A Randomized Trial of Dose Escalation in definitive Chemoradiotherapy for patients with Oesophageal cancer) study. This study aims to improve locoregional control after definitive CRT for patients with potentially curable esophageal cancer (T1-4N0-3M0 AC or SCC) using a conformal multiple field radiation technique. Patients are randomized between standard definitive CRT (carboplatin and paclitaxel plus concurrent 50.4 Gy) and an escalated radiation dose. Patients in the escalated radiation dose arm receive a daily concomitant boost to the primary tumor leading to a total tumor dose of 61.6 Gy. Overall treatment time and chemotherapy are similar in both arms. Primary endpoints in this study are local recurrence rate, survival and treatment related toxicity.

Surgery as needed approach

By the addition of CT and salvage surgery to definitive RT and the use of neoadjuvant CRT in addition to primary surgery, non-operative and operative treatment modalities have moved closer towards each other. However, the benefits of adding salvage surgery to definitive CRT has never been proven. The high pCR rate in the CROSS study led to the imperative to reconsider the necessity of standard esophagectomy in all patients after neoadjuvant CRT. Therefore, we propose a "surgery as needed" approach after completion of neoadjuvant CRT for patients with potentially curable esophageal cancer. In this approach, patients will undergo close surveillance after completion of neoadjuvant CRT according to CROSS. Surgical resection will be offered only to patients in whom a locoregional recurrence is highly suspected or proven, without signs of distant metastases. Such an organ-preserving strategy would have great advantages, but only if long term survival would be comparable to that of the neoadjuvant chemoradiotherapy followed by standard surgery approach. As a first step towards an organ-preserving strategy, we are currently performing the multicenter phase II feasibility preSANO (Surgery As Needed approach in Oesophageal cancer) study to determine the accuracy by which residual disease after neoadjuvant chemoradiotherapy can be detected. After completion of neoadjuvant CRT, patients will undergo two clinical response evaluations (CRE). The first CRE (CRE-I) consists of endoscopy with (random) conventional mucosal biopsies of the primary tumor site and of any other suspected lesions in the esophagus and radial endo-ultrasonography (EUS) for measurement of tumor thickness and -area. Patients who are found to be clinically complete responders (*i.e.* those patients in whom no locoregional or disseminated disease can be proven by histology) will be offered a postponed surgical resection, which will be scheduled approximately six weeks after CRE-I (*i.e.* approximately 12-14 weeks after completion of neoadjuvant CRT). In the two weeks preceding the postponed surgical resection a second clinical response evaluation (CRE-II) will be planned, which will include a whole body PET-CT, plus the investigations as performed at CRE-I. If this preSANO study shows that residual tumor can be predicted reliably, a trial (SANO trial) comparing neoadjuvant chemoradiotherapy plus standard surgery with neoadjuvant chemoradiotherapy plus 'surgery as needed' will be conducted.*

*results of the preSANO trial are described in chapter 14.

Table 1. Randomized controlled trials – Definitive concurrent CRT vs. definitive RT

First Author	Year	Period	N	Tumor	CRT/RT	Survival, HR (95% CI) (RT vs CRT)
Andersen et al. [55]	1984	1977-1981	82	SCC	CRT: Ble+55Gy RT: 63Gy	0.94 (0.59- 1.50)
Araujo et al. [56]	1991	1982-1985	59	SCC	CRT: 5-FU, Ble, Mit+50Gy RT: 50Gy	0.64 (0.36- 1.14)
Cooper et al. [16]	1999	1985-1990	123	SCC/AC	CRT: 5-FU+50Gy RT: 64Gy	0.59 (0.45- 0.77)
Earle et al. [57]	1980	N/A	77	SCC	CRT: Ble+50-60Gy RT: 50-60Gy	1.43 (0.81- 2.54)
Gao et al. [58]	2002	N/A	81	SCC	CRT: Cis+60Gy RT: 60Gy	0.79 (0.46- 1.37)
Kaneta et al. [59]	1997	1994-1996	24	SCC	CRT: Cis+70-72Gy RT: 70-72Gy	0.75 (0.23- 2.40)
Li et al. [60]	2000	N/A	96	SCC/AC	CRT: Cis, 5-FU+50-60Gy RT: 60-70Gy	0.65 (0.43- 1.00)
Roussel et al. [61]	1994	N/A	221	SCC	CRT: Cis+40Gy RT: 40Gy	0.82 (0.62- 1.09)
Slabber et al. [62]	1998	1991-1995	70	SCC	CRT: Cis, 5-FU+40Gy RT: 40Gy	0.83 (0.50- 1.40)
Zhang et al. [63]	1984	N/A	99	N/A	CRT: Ble+39-73Gy RT: 39-73Gy	0.63 (0.39- 1.01)
Zhu et al. [64]	2000	N/A	66	SCC	CRT: Car+60Gy RT: 60Gy	0.62 (0.36- 1.06)

5-FU: 5-fluorouracil, AC: adenocarcinoma, Ble: bleomycin, Car: carboplatin, CI: confidence interval, Cis: cisplatin, CRT: chemoradiotherapy, Gy: Gray (J/kg), HR: hazard ratio, Mit: mitomycin, N/A: not available, N: number of patients, RT: radiotherapy, SCC: squamous cell carcinoma (reprinted with permission and adapted from Wong et al.[18])

Table 2. Randomized controlled trials – Neoadjuvant RT plus surgery vs. surgery alone

First Author	Year	Period	N	Tumor	RT	Survival (RT + S vs S alone)
Launois et al. [26]	1981	1973- 1976	107	SCC	40Gy/8-12d	1.01 (0.67- 1.53)
Gignoux et al. [27]	1988	1976- 1982	229	SCC	33Gy/10 frc/28d	1.02 (0.78- 1.33)
Wang et al. [28]	1989	1977-1988	418	SCC	40Gy/10 frc/12d	0.81 (0.65- 1.01)
Arnott et al. [29]	1992	1979- 1983	176	SCC/AC	20Gy/10 frc/14d	1.19 (0.87- 1.62)
Nygaard et al. [30]	1992	1983- 1988	108	SCC	35Gy/20 frc/ 28d	0.60 (0.40- 0.91)

AC: adenocarcinoma, d: days, frc: fractions, Gy: Gray (J/kg), N: number of patients, RT: radiotherapy, S: surgery, SCC: squamous cell carcinoma (reprinted with permission and adapted from Arnott et al.[25])

Table 3. Randomized controlled trials – Neoadjuvant CRT plus surgery vs. surgery alone

First Author	Year	Period	N	Tumor	CRT		pCR	Survival, HR (95% CI) (CRT + S vs S)
Walsh et al. [35]	1990	N/A	61	SCC	CT: Cis, 5-FU RT: 40Gy/ 15 frc/ 21d	Con		0.74 (0.46-1.18)
Nygaard et al. [30]	1992	1983-1988	106	SCC	CT: Cis, Ble RT: 35Gy/20 frc/ 28d	Seq		0.76 (0.45– 1.28)
Apinop et al. [33]	1994	1986-1992	69	SCC	CT: Cis, 5-FU RT: 40Gy/20 frc/ 28d	Con		0.80 (0.48– 1.34)
Le Prise et al. [34]	1994	1988-1991	86	SCC	CT: Cis, 5-FU RT: 20Gy/10 frc/ 10d	Seq	9.8%	0.85 (0.50– 1.46)
Walsh et al. [36]	1996	1990-1995	113	AC	CT: Cis, 5-FU RT: 40Gy/ 15 frc/ 21d	Con	25%	0.58 (0.38– 0.88)
Bosset et al. [37]	1997	1989-1995	293	SCC	CT: Cis RT: 37Gy/10 frc/ 14d	Seq	21%	0.96 (0.73– 1.27)
Urba et al. [38]	2001	1989-1994	100	SCC/AC	CT: Cis, 5-FU, Vinb RT: 45Gy/30 frc/ 21d	Con	28%	0.74 (048– 1.12)
Lee et al. [39]	2004	1999-2002	101	SCC/AC	CT: Cis, 5-FU RT: 45.6Gy/38 frc/28d	Con	43%	0.88 (0.48– 1.62)
Burmeister et al. [40]	2005	1994- 2000	256	SCC/AC	CT: Cis, 5-FU RT: 35Gy/15 frc/21d	Con	16%	0.94 (0.70– 1.26)
Tepper et al. [41]	2008	1997-2000	56	SCC	CT: Cis, 5-FU RT: 50.4Gy/28 frc/35d	Con	40%	0.40 (0.18– 0.87)
Lv et al. [42]	2010	2000-2009	160	SCC	CT: Cis, Pac RT: 40Gy/20 frc/28d	Con		0.55 (0.36– 0.84)
Van Hagen et al. [45]	2012	2004-2008	366	SCC/AC	CT: Cis, Pac RT: 41.4Gy/23 frc/35d	Con	29%	0.66 (0.50– 0.87)
Mariette et al. [46]	2014	2000-2009	195	SCC/AC	CT: Cis, 5-FU RT: 45Gy/25 frc/35d	Con	33.3%	0.92 (0.63– 1.34)

5-FU: 5-fluorouracil, AC: adenocarcinoma, Ble: bleomycin, CI: confidence interval, Cis: cisplatin, Con: concurrent, CRT: chemoradiotherapy, CT: chemotherapy, d: days, frc: fractions, Gy: Gray (J/kg), HR: hazard ratio, N: number of patients, Pac: paclitaxel S: surgery, pCR; pathologically complete response, RT: radiotherapy, SCC: squamous cell carcinoma, seq: sequential, Vinb: vinblastine (reprinted with permission and adapted from Sjoquist et al.[32])

References

1. Lightdale CJ. Endoscopic ultrasonography in the diagnosis, staging and follow-up of esophageal and gastric cancer. Endoscopy. 1992;24 Suppl 1:297-303.
2. Block MI, Patterson GA, Sundaresan RS et al. Improvement in staging of esophageal cancer with the addition of positron emission tomography. Ann Thorac Surg. 1997;64(3):770-6; discussion 6-7.
3. Hulscher JB, Nieveen van Dijkum EJ, de Wit LT et al. Laparoscopy and laparoscopic ultrasonography in staging carcinoma of the gastric cardia. Eur J Surg. 2000;166(11):862-5.
4. Skinner DB, Little AG, Ferguson MK, Soriano A, Staszak VM. Selection of operation for esophageal cancer based on staging. Ann Surg. 1986;204(4):391-401.
5. Van Lanschot JJ, Van Blankenstein M, Oei HY, Tilanus HW. Randomized comparison of prevertebral and retrosternal gastric tube reconstruction after resection of oesophageal carcinoma. Br J Surg. 1999;86(1):102-8.
6. Hulscher JBF, van Sandick JW, de Boer AGEM et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662-9.
7. Gaspar LE, Qian C, Kocha WI, Coia LR, Herskovic A, Graham M. A phase I/II study of external beam radiation, brachytherapy and concurrent chemotherapy in localized cancer of the esophagus (RTOG 92-07): preliminary toxicity report. Int J Radiat Oncol Biol Phys. 1997;37(3):593-9.
8. Toita T, Ogawa K, Adachi G et al. Concurrent chemoradiotherapy for squamous cell carcinoma of thoracic esophagus: feasibility and outcome of large regional field and high-dose external beam boost irradiation. Jpn J Clin Oncol. 2001;31(8):375-81.
9. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg. 1998;85(11):1457-9.
10. Grotenhuis BA, Wijnhoven BP, Poley JW et al. Preoperative assessment of tumor location and station-specific lymph node status in patients with adenocarcinoma of the gastroesophageal junction. World J Surg. 2013;37(1):147-55.
11. Tannock IF. Treatment of cancer with radiation and drugs. J Clin Oncol. 1996;14(12):3156-74.
12. Hennequin C, Favaudon V. Biological basis for chemo-radiotherapy interactions. Eur J Cancer. 2002;38(2):223-30.
13. Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm--general principles. Nat Clin Pract Oncol. 2007;4(2):86-100.
14. Earlam R, Cunha-Melo JR. Oesophogeal squamous cell carcinoma: II. A critical view of radiotherapy. Br J Surg. 1980;67(7):457-61.
15. Herskovic A, Martz K, al-Sarraf M et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326(24):1593-8.
16. Cooper JS, Guo MD, Herskovic A et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281(17):1623-7.
17. Minsky BD, Pajak TF, Ginsberg RJ et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20(5):1167-74.
18. Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. Cochrane Database Syst Rev. 2006(1):CD002092.
19. Markar SR, Schmidt H, Kunz S, Bodnar A, Hubka M, Low DE. Evolution of standardized clinical pathways: refining multidisciplinary care and process to improve outcomes of the surgical treatment of esophageal cancer. J Gastrointest Surg. 2014;18(7):1238-46.

20. Swisher SG, Winter KA, Komaki RU et al. A Phase II study of a paclitaxel-based chemoradiation regimen with selective surgical salvage for resectable locoregionally advanced esophageal cancer: initial reporting of RTOG 0246. Int J Radiat Oncol Biol Phys. 2012;82(5):1967-72.
21. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: I. A critical review of surgery. Br J Surg. 1980;67(6):381-90.
22. Chiu PW, Chan AC, Leung SF et al. Multicenter prospective randomized trial comparing standard esophagectomy with chemoradiotherapy for treatment of squamous esophageal cancer: early results from the Chinese University Research Group for Esophageal Cancer (CURE). J Gastrointest Surg. 2005;9(6):794-802.
23. Carstens H, Albertsson M, Friesland S et al. A randomized trial of chemoradiotherapy versus surgery alone in patients with resectable esophageal cancer. J Clin Oncol (Meeting Abstracts). 2007;25(18S (June 20 Supplement)):4530.
24. Gignoux M, Roussel A, Paillot B et al. The value of preoperative radiotherapy in esophageal cancer: Results of a study of the E.O.R.T.C. World J Surg. 1987;11(4):426-32.
25. Arnott SJ, Duncan W, Gignoux M et al. Preoperative radiotherapy for esophageal carcinoma. Cochrane Database Syst Rev. 2005(4):CD001799.
26. Launois B, Delarue D, Campion JP, Kerbaol M. Preoperative radiotherapy for carcinoma of the esophagus. Surg Gynecol Obstet. 1981;153(5):690-2.
27. Gignoux M, Roussel A, Paillot B et al. The value of preoperative radiotherapy in esophageal cancer: results of a study by the EORTC. Recent results in cancer research Fortschritte der Krebsforschung Progres dans les recherches sur le cancer. 1988;110:1-13.
28. Wang M, Gu XZ, Yin WB, Huang GJ, Wang LJ, Zhang DW. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 206 patients. Int J Radiat Oncol Biol Phys. 1989;16(2):325-7.
29. Arnott SJ, Duncan W, Kerr GR et al. Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. Radiother Oncol. 1992;24(2):108-13.
30. Nygaard K, Hagen S, Hansen HS et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: A randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second scandinavian trial in esophageal cancer. World J Surg. 1992;16(6):1104-9.
31. Hilgenberg AD, Carey RW, Wilkins EW, Jr., Choi NC, Mathisen DJ, Grillo HC. Preoperative chemotherapy, surgical resection, and selective postoperative therapy for squamous cell carcinoma of the esophagus. Ann Thorac Surg. 1988;45(4):357-63.
32. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
33. Apinop C, Puttisak P, Preecha N. A prospective study of combined therapy in esophageal cancer. Hepatogastroenterol. 1994;41(4):391-3.
34. Prise EL, Etienne PL, Meunier B et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer. 1994;73(7):1779-84.
35. Walsh TN. The role of multimodality therapy in improving survival: a prospective randomised trial. In: Predicting, defining and improving outcomes for oesophageal carcinoma. Dublin. As cited by: Sjoquist, K.M., et al., Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol, 2011. 12(7): p. 681-692: University of Dublin; 1995.
36. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335(7):462-7.
37. Bosset JF, Gignoux M, Triboulet JP et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med. 1997;337(3):161-7.

38. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol. 2001;19(2):305-13.
39. Lee JL, Park SI, Kim SB et al. A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. Ann Oncol. 2004;15(6):947-54.
40. Burmeister BH, Smithers BM, Gebski V et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol. 2005;6(9):659-68.
41. Tepper J, Krasna MJ, Niedzwiecki D et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26(7):1086-92.
42. Lv J, Cao XF, Zhu B, Ji L, Tao L, Wang DD. Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. World journal of gastroenterology : WJG. 2010;16(13):1649-54.
43. Mariette C, Seitz JF, Maillard E et al. Impact of neoadjuvant chemoradiation in localised oesophageal cancer: results of a randomised controlled phase III trial FFCD 9901. Ann Oncol. 2010;21:250-.
44. Van der Gaast A, Van Hagen P, Hulshof MCCM et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study. ASCO Meeting J Clin Oncol; 2010. p. p. 4004.
45. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
46. Mariette C, Dahan L, Mornex F et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32(23):2416-22.
47. Robb WB, Mariette C, Dahan L et al. Surgery alone vs chemoradiotherapy followed by surgery for stage I and II oesophageal cancer: final analysis of a randomised controlled phase III trial FFCD 9901. Gut. 2012;61:A37-A8.
48. Verhoef C, van de Weyer R, Schaapveld M, Bastiaannet E, Plukker JT. Better survival in patients with esophageal cancer after surgical treatment in university hospitals: a plea for performance by surgical oncologists. Ann Surg Oncol. 2007;14(5):1678-87.
49. Stahl M, Walz MK, Stuschke M et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27(6):851-6.
50. Burmeister BH, Thomas JM, Burmeister EA et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer. 2011;47(3):354-60.
51. Kumagai K, Rouvelas I, Tsai JA et al. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. Br J Surg. 2014;101(4):321-38.
52. Stahl M, Stuschke M, Lehmann N et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005;23(10):2310-7.
53. Bedenne L, Michel P, Bouché O et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol. 2007;25(10):1160-8.
54. Nakamura K, Kato K, Igaki H et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). Jpn J Clin Oncol. 2013;43(7):752-5.
55. Andersen AP, Berdal P, Edsmyr F et al. Irradiation, chemotherapy and surgery in esophageal cancer: a randomized clinical study. The first Scandinavian trial in esophageal cancer. Radiother Oncol. 1984;2(3):179-88.

56. Araujo CM, Souhami L, Gil RA et al. A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. Cancer. 1991;67(9):2258-61.
57. Earle JD, Gelber RD, Moertel CG, Hahn RG. A controlled evaluation of combined radiation and bleomycin therapy for squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys. 1980;6(7):821-6.
58. Gao XS, Qiao XY, Yang XR et al. Late course accelerated hyperfractionation radiotherapy concomitant with cisplatin in patients with esophageal carcinoma. Oncol Rep. 2002;9(4):767-72.
59. Kaneta T, Takai Y, Nemoto K et al. [Effects of combination chemoradiotherapy with daily low-dose CDDP for esophageal cancer--results of a randomized trial]. Gan To Kagaku Ryoho. 1997;24(14):2099-104.
60. Li A, Shu BA, Lin YZ, Hu YH. 48 Patients with advanced esophageal cancer treated with DDP-5-FU combined radiotherapy. . Chinese Journal of Clinical Oncology and Rehabilitation 2000;7(6):2.
61. Roussel A, P. H, B. P, M. G, A. M, Sahmoud T. ea. Results of the EORTC-GTCCT Phase III trial of irradiation vs irradiation and CDDP in inoperable esophageal cancer [abstract]. Proceedings, Annual Meeting of the American Society of Clinical Oncologists. 1994;13(199).
62. Slabber CF, Nel JS, Schoeman L, Burger W, Falkson G, Falkson CI. A randomized study of radiotherapy alone versus radiotherapy plus 5-fluorouracil and platinum in patients with inoperable, locally advanced squamous cancer of the esophagus. Am J Clin Oncol. 1998;21(5):462-5.
63. Zhang ZF. [Radiation combined with bleomycin in esophageal carcinoma--a randomized study of 99 patients]. Zhonghua Zhong Liu Za Zhi. 1984;6(5):372-4.
64. Zhu S, Wan J, Zhou D. Combination of external beam and intracavitary radiation and carboplatin chemotherapy in the treatment of esophageal carcinoma. Chinese Journal of Clinical Oncology and Rehabilitation. 2000;27(1):5-8.

Chapter 4

Multimodality treatment for esophageal adenocarcinoma: multi-center propensity-score matched study

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Abstract

Background

The primary aim of this study was to compare survival from neoadjuvant chemoradiotherapy plus surgery (NCRS) versus neoadjuvant chemotherapy plus surgery (NCS) for the treatment of esophageal or junctional adenocarcinoma. The secondary aims were to compare pathological effects, short-term mortality and morbidity, and to evaluate the effect of lymph node harvest upon survival in both treatment groups.

Methods

Data were collected from 10 European centers from 2001 to 2012. Six hundred and eight patients with stage II or III esophageal or esophago-gastric junctional adenocarcinoma were included; 301 in the NCRS group and 307 in the NCS group. Propensity score matching and Cox regression analyses were used to compensate for differences in baseline characteristics.

Results

NCRS resulted in significant pathological benefits with more ypT0 (26.7% versus 5%; P<0.001), more ypN0 (63.3% versus 32.1%; p<0.001), and reduced R1/2 resection margins (7.7% versus 21.8%; p<0.001). Analysis of short-term outcomes showed no statistically significant differences in 30-day or 90-day mortality, but increased incidence of anastomotic leak (23.1% versus 6.8%; p<0.001) in NCRS patients. There were no statistically significant differences between the groups in 3-year overall survival (57.9% versus 53.4%; hazard ratio [HR]=0.89, 95% CI 0.67-1.17, p=0.391) nor disease-free survival (52.9% versus 48.9%; HR=0.90, 95% CI 0.69-1.18, p=0.443). The pattern of recurrence was also similar (p=0.660). There was a higher lymph node harvest in the NCS group (27 versus 14; p<0.001), which was significantly associated with a lower recurrence rate and improved disease free survival within the NCS group.

Conclusion

The survival differences between NCRS and NCS maybe modest, if present at all, for the treatment of locally advanced esophageal or junctional adenocarcinoma. Future large-scale randomized trials must control and monitor indicators of the quality of surgery, as the extent of lymphadenectomy appears to influence prognosis in patients treated with NCS, from this large multi-center European study.

Introduction

Multimodality treatment of esophageal cancer is the standard of care in Western centers, although surgery remains the primary curative modality. Two neoadjuvant approaches have been adopted. The first is neoadjuvant chemoradiotherapy, based in recent years on the CROSS regimen which resulted in a 5-year survival advantage of 14% in comparison with surgery alone.[1, 2] An alternative option is perioperative or preoperative chemotherapy using the MAGIC or OEO2 protocol, which showed, respectively, 5-year survival improvements of 13% and 6% compared with surgery alone.[3, 4] The maximum benefit in the CROSS-trial was observed in squamous cell carcinoma, with highly significant (hazard ratio [HR] =0.48; 95% CI 0.28–0.83; p=0.009) benefit compared with surgery alone, in comparison with adenocarcinoma, where the benefit was more modest (HR=0.73; 95% CI 0.55–0.98; p=0.037), but the benefit of neoadjuvant chemoradiotherapy was consistent across subgroups, without any significant interaction identified.[1, 2] Moreover, two small underpowered randomized trials comprising 119 and 75 patients with esophageal adenocarcinoma did not show a significant difference in survival between neoadjuvant chemoradiotherapy plus surgery versus neoadjuvant chemotherapy plus surgery.[5, 6] The recently reported NeoRES trial in a mixed cohort of 181 patients with esophageal adenocarcinoma and squamous cell carcinoma, showed pathological benefits without any changes in survival associated with the addition of radiotherapy to neoadjuvant chemotherapy.[7]

Therefore, the optimal multimodality treatment for esophageal adenocarcinoma remains undetermined and is the subject of investigation in the more recently initiated Neo-AEGIS trial, which randomizes patients (n=574) with adenocarcinoma of the esophagus or esophago-gastric junction to the CROSS or MAGIC regimens, and is likely to be reported in 2021.[8]

The primary aim of the present retrospective multicenter European study was to compare survival from neoadjuvant chemoradiotherapy plus surgery (NCRS) versus neoadjuvant chemotherapy plus surgery (NCS) for the treatment of adenocarcinoma of the esophagus or esophago-gastric junction. The secondary aims were to compare pathological effects, short-term mortality and morbidity and to evaluate the effect of lymph node harvest upon survival in both treatment groups. The current retrospective study described herein was aimed to reach a sample size similar to the ongoing Neo-AEGIS trial.[8]

Methods

Datasets

Consecutive patient data were retrieved from 10 prospectively maintained surgical European single-center databases; (i) Erasmus MC—University Medical Centre, Rotterdam, Netherlands; (ii) Academic Medical Centre, Amsterdam, Netherlands; (iii) VU Medical Centre, Amsterdam, Netherlands; (iv) Catharina Hospital, Eindhoven, Netherlands; (v) University Medical Centre, Groningen, Netherlands; (vi) Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; (vii) Rijnstate Hospital, Arnhem, Netherlands; (viii) St James's Hospital, Dublin, Ireland; (ix) Imperial College London, UK; and (x) Oxford University Hospitals, Oxford, UK. The datasets have been externally validated and are maintained as part of their respective countries national cancer audits. All patients with adenocarcinoma of the NCRS-arm within the CROSS-trial were included.[1, 2] Management plans and allocation of neoadjuvant therapy were decided upon at multi-disciplinary tumor boards at all centers participating in this study. The study period was from 2001 to 2012 with patient follow-up until December 2015.

Inclusion criteria

The study included patients with stage II or III esophageal or esophagogastric junctional (Siewert type I and II) adenocarcinoma treated with neoadjuvant chemoradiotherapy plus surgery (CROSS regimen; NCRS group)[1, 2] or peri-/preoperative chemotherapy plus surgery (mainly MAGIC, OEO2 or OEO5 regimens; NCS group) (supplementary Appendix).[3, 4, 9]

Exclusion criteria

The study did not include (i) patients with esophageal squamous cell carcinoma; (ii) patients with Siewert type III adenocarcinoma; and (iii) patients treated with definitive chemoradiotherapy. Furthermore, patients who underwent exploratory surgery but did not undergo surgical resection of the tumor due to tumor progression were excluded, as data were not routinely collected as part of the datasets included.

Clinical staging and follow-up

The approach to clinical pretreatment staging used a combination of endoscopic ultrasound (EUS), computerized tomography (CT) and on demand CT-positron emission tomography (CT-PET). EUS was used in 98.3% of patients in the NCRS group and 90.2% of patients in the NCS group. In all centers, after surgery patients were reviewed every 3 months during the first year. In the second year, follow-up took place every 6

months, and annually thereafter until 5 years. In cases of suspected recurrence, thoraco-abdominal CT, PET-CT, and/or upper gastrointestinal endoscopy were performed. Histological, cytological, or unequivocal radiological proof was required before a diagnosis of recurrence was made. The first site of recurrence was used to define whether loco-regional, distant, or mixed relapse had occurred. Median follow-up was 33.5 months (range 0.03–177.8 months), with 46 patients having follow-up of less than 3 years during the study period; 29 (15.8%) in the NCS group and 17 (11.8%) in the NCRS group.

Outcomes

The primary outcome measure was 3-year overall survival. Secondary outcomes included: 3-year disease-free survival; pattern of recurrence (within 3-years); pathological T-stage and N-stage (TNM7)[10]; tumor regression grade (TRG) as reported by Chirieac et al.[11]; 30-day and 90-day mortality; and 30-day morbidity, specifically anastomotic and chyle leak, pulmonary and cardiac complications, and reoperation. The time for overall survival was defined from date of surgery to date of death or date of last follow-up. The time for disease-free survival was defined from date of surgery and the earliest occurrence of disease progression resulting from loco-regional recurrence or distant dissemination, or death from any cause.[2, 12]

Statistical analysis

Data are presented as prevalence (percentage), median (range), and for survival as median (95% CI). Continuous variables are expressed as mean +/- standard deviation or median (range) and categorical variables as percentage. A Mann–Whitney test was used for intergroup comparisons of continuous variables, whereas a $\chi 2$ test or Fisher's exact test was used to compare categorical data. Overall and disease-free survivals were estimated using the Kaplan–Meier method. The log rank test was used to compare survival curves. Missing data were at random and, therefore, only available data were analyzed, in multivariate regression analysis list wise deletion was used.

Propensity matching

In order to reduce the effects of potential confounding factors in the comparisons of short and mid-term outcomes between groups, a propensity score (PS) was calculated to create well-balanced groups. The PS was estimated using a multivariable logistic regression model, with the treatment groups as the dependent variables and potential confounders as covariates. The following confounders were included in the propensity matching: age≥70 years; male gender; American Society of Anesthesiologists (ASA) grade; clinical tumour (cT) stage; and clinical nodal (cN) positivity or negativity. All

patients in the NCS group were matched 1:1 to patients in the NCRS group according to the propensity score using the global optimum method.[13]

Cox regression analysis

Year of surgery and age as continuous variables were not included in the PS matching, as this would have further reduced the dataset dramatically to maintain a good level of matching (fewer than 10 patients per group, and neither demonstrated multivariate associations with endpoints). Therefore, overall- and disease-free survivals were also compared between groups using a multivariable Cox regression model. In this model, adjustment was performed for the same characteristics as in the PS approach, with the addition of year of surgery and age as continuous variable.[14]

Risk-adjusted cumulative sum (RA-CUSUM) curve analysis for the effect of lymph node harvest on survival

RA-CUSUM analysis was used to determine a lymph node harvest threshold that affected overall survival in each of NCRS and NCS groups.[14] The threshold was defined as the minimum lymph node harvest for an alteration in overall survival relationships. Risk prediction models for overall survival were created using regression models. Potential risk factors included in the models were: age, male gender, ASA grade, and clinical T and N stages. The risk prediction models were used to calculate the predicted probability of survival in each case. For the CUSUM curve, the sum of all events was compared with the expected sum of events according to the risk-adjustment model, using the CUSUM equation $S_i=S_{i-1}+(\Sigma_i-\Sigma_R)$; $S_0=0$: S_i is the cumulative sum, Σ_i the sum of events at procedure number i, and Σ_R the sum of expected events at procedure number i. The clinical impact of the threshold was determined by comparing the survival and recurrence rates before and after the change-point in overall survival. To ascertain whether the change-points observed in the CUSUM curves were reliable, we bootstrapped each curve with 1000 iterations to identify the confidence level (CL) of the change point. We computed the CUSUM values at the change point (n=1000). We hypothesized that a reliable change point would have a CUSUM value that was greater than at least 95% of the simulated CUSUM values (CL>95%).

CUSUM curves were computed using Excel (Excel for Mac 2011, version 14.1.4, Microsoft Corporation, Redmond, WA, USA). For the remaining statistical analysis, SPSS software was used (Statistical Package for the Social Sciences software, Version 22, SPSS, Chicago, IL, USA).

Results

Over the 12-year study period 608 patients were included: 301 in the NCRS group and 307 in the NCS group. The NCRS group consisted of patients from the centers, which participated in the CROSS-trial[1, 2] and St James's Hospital, Dublin, whereas NCS patients were provided by Imperial College in London, Oxford University Hospitals in Oxford and St James's Hospital in Dublin. During the study period, no patients with esophageal adenocarcinoma from Imperial College London or Oxford University hospital received neoadjuvant chemoradiotherapy. Within the Dutch cohort, during the study period, less than 3% of patients could not undergo radiotherapy (e.g. due to history of radiotherapy) or had lymph nodes outside the maximum radiation field, received neoadjuvant chemotherapy, and were excluded from the study. From the NCS group, the number of patients receiving MAGIC/ECF regime was 51 (16.6%), OEO2/CF 138 (45%), OEO5/ECX was 87 (28.3%), EOX 21 (6.8%), and other regimes 10 (3.3%). After propensity matching, 442 patients were included in the analysis; 221 in the NCRS group and 221 in the NCS group.

Comparison of patient demographics and treatment strategies (Table 1)

Analysis of patient demographics before matching, showed a significantly lower median age and greater numbers of patients with ASA I in NCRS versus NCS group. After propensity matching, there were no significant differences between the groups in age, patients aged 70 years or older, distribution of patients by ASA grade, WHO performance status and clinical T- and N-stages. After matching, there were significantly more transhiatal resections (61.5% versus 0.5%; $p<0.001$) and significantly fewer transthoracic resections (36.7% versus 94.6%; $p<0.001$) for NCRS versus NCS.

Comparison of tumor pathology and short-term outcomes (Tables 2 and 3)

Both before and after matching, utilization of chemoradiotherapy was associated with significantly more down-staging. This is reflected in the matched comparison by significantly increased incidence of ypT0 (26.7% versus 5%; $p<0.001$), ypN0 (63.3% versus 32.1%; $p<0.001$) in the NCRS group compared with the NCS group. Neoadjuvant chemoradiotherapy was also associated with a significant reduction in the incidence of R1/2 resection margins (7.7% versus 21.8%; $p<0.001$). The NCRS group had a significantly lower median number of harvested lymph nodes (14 versus 27; $p<0.001$) and positive lymph nodes (0 versus 2; $p<0.001$) in comparison with the NCS group. After matching, analysis of short-term outcomes showed no significant differences in 30-daymortality (4.1% versus 1.4%, $p=0.140$) or 90-day mortality (5.9% versus 2.3%) and

morbidity apart from an increased incidence of anastomotic leak (23.1% versus 6.8%; p<0.001) in the NCRS group.

Comparison of survival and recurrence, propensity matched (Table 3 and Figure 1)

Unmatched survival analysis suggested that NCRS was associated with a small improvement in 3-year overall survival (57.8% versus 49.8%; HR 0.79, 95% CI 0.63–1.00; p=0.052) (Figure 1A: log rank test p=0.047). There was no significant difference in 3-year disease-free survival between unmatched groups (52.8% versus 46.9%; HR 0.85; 95% CI 0.68–1.07; p=0.163). After matching, observed differences between the groups in 3-year overall (57.9% versus 53.4%; HR 0.89, 95% CI 0.67–1.17, p=0.391) (Figure 1B) or disease-free survival (52.9% versus 48.9%; HR 0.90, 95% CI 0.69–1.18, p=0.443) were small and statistically non-significant. Following matching, there were no significant differences between the groups in the pattern of recurrence (p=0.660) (Table 3).

Comparison of survival and recurrence, Cox regression (Table 4)

Cox regression analysis including year of treatment and age, as continuous variables did not show significant differences between NCRS and NCS in 3-year overall (HR 0.86; 95% CI 0.66–1.11; p=0.232) and 3-year disease-free survival (HR 0.91; 95% CI 0.71–1.16; p=0.459) (Table 4).

RA-CUSUM analysis of lymph node harvest (Figure 2)

In the NCRS group, RA-CUSUM analysis showed that lymph node harvest did not affect survival or recurrence with no identifiable change-point in the RA-CUSUM curve (Figure 2A). In the NCS group, lymph node harvest significantly influenced survival and recurrence. The mean change-point in overall survival was seen to lie between 22 and 52 lymph nodes (confidence level 95.4%) (Figure 2B). At a lymph node harvest threshold of 52 lymph nodes, there were significant improvements in disease-free survival (22–36 months; p=0.028), and overall recurrence (47.1%–15.9%; p<0.001). However, the improvement in overall survival remained non-significant (27–38 months; p=0.171).

Discussion

The present study showed no significant differences in overall or disease-free 3-year survival or pattern of recurrence between NCRS and NCS groups after propensity matching and Cox regression analysis. This is despite neoadjuvant chemoradiotherapy conferring significant pathological benefits in terms of tumor and nodal down staging

and tumor regression grade. Lymph node harvest uniquely in the NCS group was shown to be significantly associated with disease-free survival and recurrence with an optimal threshold between 22 and 52 lymph nodes removed. Although the incidence of anastomotic leak was higher in the NCRS group, in-hospital mortality and other major postoperative complications were similar.

This study is the largest available analysis that compares NCRS with NCS for the treatment of esophageal and junctional adenocarcinoma. Despite higher rates of ypT0, ypN0, and R0 in the NCRS group, only small nonsignificant survival differences in overall and disease-free 3-year survival were evident. This might be partially explained by a non-significant increase in postoperative mortality rate in the NCRS group. This apparent paradox of significant down-staging at primary and nodal sites, yet no survival benefit, was also evident in three small underpowered randomized trials.[5-7] Taken together, these results suggest that survival differences between NCRS and NCS may be relatively modest, if present at all, and suggest that a large sample size is required for prospective RCTs that compare these modalities.

One intriguing element of the analysis is that the extent of lymphadenectomy may have impacted on disease-free survival and cancer recurrence exclusively in the NCS group. The absence of an association between lymph node harvest and survival in the NCRS group is consistent with the analysis of patients from the CROSS trial and further non-randomized data, which found that the total number of resected nodes was associated with survival in the surgery-alone group but not in the NCRS group.[15, 16] These results suggest that regional control of esophageal adenocarcinoma is essential and might either be achieved through chemotherapy with radical lymphadenectomy or neoadjuvant chemoradiotherapy with limited lymphadenectomy.

It was not possible to match for surgical technique as only one patient had transhiatal resection in the NCS group. At the centers where both transhiatal and transthoracic esophagectomies were performed, no significant difference in survival between the two techniques has been reported.[17] The difference in technique may be responsible for the observed differences in lymph node harvest between the NCRS and NCS groups, in line with results from randomized controlled trials.[17-19] Moreover, in the CROSS-trial lymph node, retrieval after neoadjuvant chemoradiotherapy appeared to be lower than after surgery alone (14 versus 18 lymph nodes, respectively), even when using the same surgical technique.[16] Other authors have also reported that chemoradiotherapy reduces lymph node harvest from within the radiotherapy field, e.g. in rectal cancer.[20, 21] The median number of lymph nodes retrieved in the NCRS group was 14. Consequently, in the present study, it was not possible to examine the added value of radical lymphadenectomy to neoadjuvant chemoradiotherapy on survival for esophageal adenocarcinoma, and this aspect will be of great interest in future trials such as Neo-AEGIS. The analysis in our study indicates that the quality of surgery, using lymph node retrieval as

a proxy for quality and extent of lymphadenectomy, remains an important prognostic factor affecting the outcome from multimodality treatment of esophageal adenocarcinoma. We have previously shown that assurance of surgical quality within randomized controlled trials for the treatment of esophago-gastric cancer is an important aspect of study design and can affect variation in lymph node harvest and mortalit.[22] Nevertheless, a recent analysis of the MAGIC trial has also shown that the presence of lymph node metastases after chemotherapy is an independent predictor of overall survival, although authors did not include lymph node count in the multivariate analysis.[23]

Analysis of short-term outcomes showed no significant difference between NCRS and NCS apart from an increased incidence of anastomotic leak in the NCRS group. There was a non-significant increase in 30-day (4.1% versus 1.4%; p=0.140) and 90-day mortality (5.9% versus 2.3%; p=0.090) in the NCRS group. The centers involved in this study were high volume units, with all procedures performed by high volume surgeons, thus minimizing the effect of surgeon and hospital volume on short-term outcomes.[24-26] A significantly higher proportion of patients in the NCRS group had transhiatal resection with cervical esophageal anastomosis, which is known to be associated with a higher leak rate than thoracic anastomosis.[27] Theoretically, radiotherapy might affect perfusion of the gastric tube and thus anastomotic healing; this notwithstanding, no differences in anastomotic leak were found between the NCRS and surgery alone groups of the CROSS-trial. This effect is currently being further explored in an ongoing Dutch randomized trial comparing cervical with thoracic anastomosis after neoadjuvant chemoradiation.[28]

There are limitations that must be considered in interpreting the results of this analysis, foremost its design as a retrospective, observational study. The propensity-matched analysis controlled for important factors that can influence long-term survival and cancer recurrence. However, both ASA-classification and cN status are subjective parameters in their clinical application that might have influenced the matching process. There may have been a small degree of selection bias within the Dutch cohort during the study period as less than 3% of patients could not undergo radiotherapy (e.g. due to history of radiotherapy) or had suspected lymph nodes outside the maximum radiation field, therefore, underwent neoadjuvant chemotherapy, and were excluded from the study. However, after matching 84.6% and 68.8% of patients in both groups had cT3 and cN positive staging, respectively, which is representative of the esophageal cancer population in Europe. Nevertheless, it was not possible to examine the benefits of NCS and NCRS separately for early and advanced disease because of the sample size of matched patients. Furthermore, there are inevitably other confounding variables including heterogeneity in surgical approach and type of chemotherapy used in the NCS group that may have varied between the groups. Moreover, the propensity matching reduced the sample size, resulting in less statistical power compared with the recently initiated Neo-

AEGIS trial, and especially impeded correction for year of treatment and age as continuous variables. To overcome this limitation, data were also analyzed using Cox regression analysis. During the study period, there was some variation in the definition of complications, with the international consensus only recently published.[29] However, anastomotic leak was defined similarly in all centers with clinical or radiological evidence of leak and postoperative contrast evaluation of the anastomosis was standard of care in all participating centers. Unfortunately, data on toxicity of chemoradiotherapy and chemotherapy were not available in all participating centers. Patients were selected based on whether they underwent surgical resection (and not on whether they were planned to undergo NCS or NCRS), which impeded an intention-to-treat analysis. Therefore, patients not surgically resected due to disease progression, complete clinical response or patient physiological status were not included in this study. In the CROSS trial, 10% of patients in the multimodality arm did not undergo surgical resection due to toxicity or tumor progression, whereas in the MAGIC trial and OEO2 trial this was 17% and 14%, respectively.[3, 4] Finally, follow-up was not sufficient to compare long-term (≥5-year) survival between NCRS and NCS, further emphasizing the need for publication of the long-term results from the MAGIC-trial.

In conclusion, this multi-center European study suggests that any prognostic differences between neoadjuvant chemoradiotherapy plus surgery and neoadjuvant chemotherapy plus surgery for the treatment of locally advanced esophageal and junctional adenocarcinoma are likely to be small. Our study suggests that loco-regional tumor control is of great importance, and can either be achieved through neoadjuvant chemotherapy with extended lymphadenectomy or concurrent chemoradiotherapy with limited lymphadenectomy. The benefit, if any, of extended lymphadenectomy after neoadjuvant chemoradiotherapy has not been addressed by this study and remains unclear. Therefore, future randomized trials evaluating multimodality treatment of esophageal adenocarcinoma must not only comprise an adequate sample size, but must also control and monitor quality of surgery during the trial. We would like to emphasize that this retrospective study does not provide a definitive answer to the unsolved question of the comparative benefits on NCS and NCRS in esophageal adenocarcinoma but supports the importance of the ongoing NeoAEGIS trial and its surgical quality measures.

Collaborators list

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Table 1. Comparative analysis of patient demographics and surgical techniques from unmatched and propensity matched groups.

	Before Matching			After Matching		
	NCRS (n=301) (%)	NCS (n=307) (%)	p-value	NCRS (n=221) (%)	NCS (n=221) (%)	p-value
Age (median (range))	61.3 (19 – 83)	63.9 (30 – 82)	0.013	62 (19 – 83)	63.3 (30 – 82)	0.936
Age ≥ 70	66 (21.9)	88 (28.7)	0.056	50 (22.6)	50 (22.6)	>0.999
Male	258 (85.7)	252 (82.1)	0.224	192 (86.9)	192 (86.9)	>0.999
ASA*						
I	54 (19.4)	18 (5.9)	<0.001	16 (7.2)	16 (7.2)	>0.999
II	190 (68.1)	214 (69.7)		173 (78.3)	173 (78.3)	
III	35 (12.5)	74 (24.1)		32 (14.5)	32 (14.5)	
IV	0 (0)	1 (0.3)		0 (0)	0 (0)	
WHO performance status*						
0	252 (83.7)	113 (89)	0.293	181 (81.9)	61 (88.4)	0.381
1	47 (15.6)	14 (11)		38 (17.2)	8 (11.6)	
2	2 (0.7)	0 (0)		2 (0.9)	0 (0)	
cT stage*						
1	10 (3.4)	6 (2)	0.120	3 (1.4)	3 (1.4)	>0.999
2	43 (14.4)	36 (11.7)		23 (10.4)	23 (10.4)	
3	236 (79.2)	248 (80.8)		187 (84.6)	187 (84.6)	
4	9 (3)	17 (5.5)		8 (3.6)	8 (3.6)	
cN stage*						
Negative	108 (35.9)	93 (30.3)	0.17	69 (31.2)	69 (31.2)	>0.999
Positive	193 (64.1)	214 (69.7)		152 (68.8)	152 (68.8)	
Operation						
Transhiatal	168 (55.8)	1 (0.3)	<0.0001	136 (61.5)	1 (0.5)	<0.001
Transthoracic	127 (42.2)	284 (92.5)		81 (36.7)	209 (94.6)	
3-Stage	6 (2)	22 (7.2)		4 (1.8)	11 (5)	

NCRS, neoadjuvant chemoradiotherapy and surgery. NCS, neoadjuvant chemotherapy and surgery. ASA, American Society of Anesthesiologists classification. *Missing data

Table 2. Comparative analysis of tumor pathology from unmatched and propensity matched groups.

	Before Matching			After Matching		
	NCRS (n= 301) (%)	NCS (n=307) (%)	p-value	NCRS (n=221) (%)	NCS (n=221) (%)	p-value
Tumour location*						
Proximal	1 (0.3)	0 (0)	0.141	1 (0.5)	0 (0)	0.329
Middle	13 (4.4)	6 (2)		9 (4.1)	5 (2.3)	
Distal / EGJ	284 (95.3)	300 (98)		210 (95.5)	216 (97.7)	
pT stage*						
0	85 (28.2)	16 (5.2)	<0.001	59 (26.7)	11 (5)	<0.001
I	45 (15)	27 (8.8)		32 (14.5)	19 (8.6)	
2	61 (20.3)	76 (24.8)		49 (22.2)	58 (26.2)	
3	108 (35.9)	174 (56.9)		79 (35.7)	125 (56.6)	
4	2 (0.7)	13 (4.2)		2 (0.9)	8 (3.6)	
pN stage						
0	189 (62.8)	98 (31.9)	<0.001	140 (63.3)	71 (32.1)	<0.001
1	82 (27.2)	92 (30)		65 (29.4)	76 (34.4)	
2	21 (7)	57 (18.6)		11 (5)	41 (18.6)	
3	9 (3)	60 (19.5)		5 (2.3)	33 (14.9)	
Mandard TRG*						
1	85 (28.5)	14 (5.4)	<0.001	59 (27.1)	11 (5.6)	<0.001
2	73 (24.5)	19 (7.4)		58 (26.6)	12 (6.1)	
3	80 (26.8)	46 (17.8)		62 (28.4)	32 (16.3)	
4/5	60 (20.1)	178 (68.9)		39 (17.9)	141 (71.9)	
Resection margin*						
R0	278 (92.4)	220 (77.5)	<0.001	204 (92.3)	165 (78.2)	<0.001
R1/2	23 (7.6)	64 (22.5)		17 (7.7)	46 (21.8)	
LN harvest (median (range))						
Total	15 (0 – 53)	31 (0 – 129)	<0.001	14 (0 – 52)	27 (0 – 129)	<0.001
Positive	0 (0 – 28)	2 (0 – 44)	<0.001	0 (0 – 9)	2 (0 – 33)	<0.001

NCRS, neoadjuvant chemoradiotherapy and surgery. NCS, neoadjuvant chemotherapy and surgery. EGJ, esophago-gastric junction. TRG, tumor regression grade. *Missing data

Table 3. Comparative analysis of short-term outcomes and three-year recurrence from unmatched and propensity matched groups.

	Before Matching			After Matching		
	NCRS (n=301) (%)	NCS (n=307) (%)	p-value	NCRS (n=221) (%)	NCS (n=221) (%)	p-value
30-day mortality	9 (3)	5 (1.6)	0.263	9 (4.1)	3 (1.4)	0.140
90-day mortality	15 (5)	7 (2.3)	0.074	13 (5.9)	5 (2.3)	0.090
Anastomotic leak*	61 (20.4)	15 (5.6)	<0.001	51 (23.1)	13 (6.8)	<0.001
Pulmonary complications*	135 (44.9)	103 (38.9)	0.15	101 (45.7)	72 (38.3)	0.134
Cardiac complications*	58 (19.3)	56 (21.1)	0.581	43 (19.5)	36 (19.1)	>0.999
Chyle leak*	22 (7.3)	24 (9.1)	0.448	17 (7.7)	13 (6.9)	0.850
Reoperation	27 (9.1)	20 (6.5)	0.108	22 (10.2)	14 (6.5)	0.050
Recurrence						
Locoregional	15 (5.0)	19 (6.2)	0.542	10 (4.5)	14 (6.3)	0.660
Distant	73 (24.3)	70 (22.8)		56 (25.3)	60 (27.1)	
Mixed	30 (10.0)	22 (7.2)		19 (8.6)	14 (6.3)	

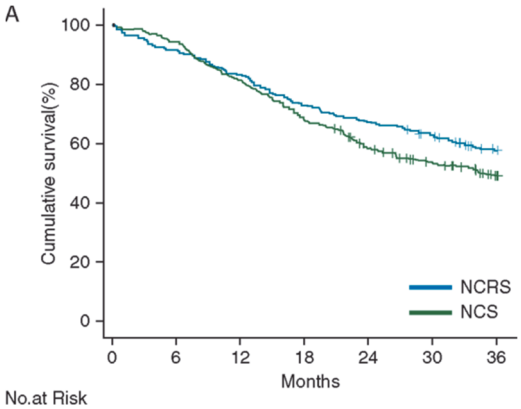
NCRS, neoadjuvant chemoradiotherapy and surgery; NCS, neoadjuvant chemotherapy and surgery. *Missing data

Table 4. Cox regression analysis for overall survival, with correction for year of treatment and age as continuous variables.

		95% Confidence Interval		
	Hazard Ratio	Lower	Upper	*P* value
Neoadjuvant therapy				
NCS	1.00			
NCRS	0.86	0.66	1.11	0.232
Age	1.01	1.00	1.02	0.195
Gender				
Male	1.00			
Female	0.87	0.62	1.21	0.402
ASA				0.013
I	1.00			
II	1.04	0.70	1.56	0.839
III and IV	1.60	1.01	2.53	0.045
cT stage				0.038
1	1.00			
2	0.47	0.21	1.05	0.065
3 and 4	0.80	0.39	1.64	0.541
cN stage				
cN0	1.00			
cNpositive	1.55	1.17	2.05	0.002
Year of surgery	0.98	0.93	1.02	0.306

NCRS, neoadjuvant chemoradiotherapy and surgery; NCS, neoadjuvant chemotherapy and surgery.

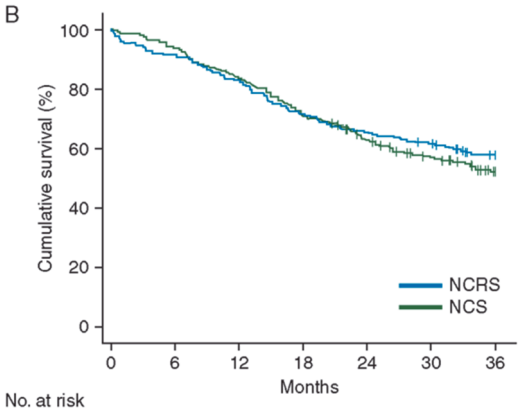
Figure 1a. Unmatched Kaplan-Meier survival analysis showing a significant (p=0.047) improvement in overall survival with neoadjuvant chemoradiotherapy plus surgery (NCRS, n=301) compared with neoadjuvant chemotherapy plus surgery (NCS, n=307) for esophageal adenocarcinoma.



No.at Risk

NCRS	301	274	249	218	201	184	159
NCS	307	287	248	206	172	148	123

Figure 1b. Propensity-matched Kaplan-Meier survival analysis showing no significant difference (p=0.391) in overall survival between neoadjuvant chemoradiotherapy plus surgery (NCRS, n=221) and neoadjuvant chemotherapy plus surgery (NCS, n=221) for esophageal adenocarcinoma.



No. at risk

NCRS	221	201	182	157	144	134	117
NCS	221	206	183	156	132	112	89

Figure 2a. RA-CUSUM analysis of lymph node harvest vs. overall survival in chemoradiotherapy plus surgery group (NCRS); lymph node harvest does not affect survival with no discernable pattern to this CUSUM curve.

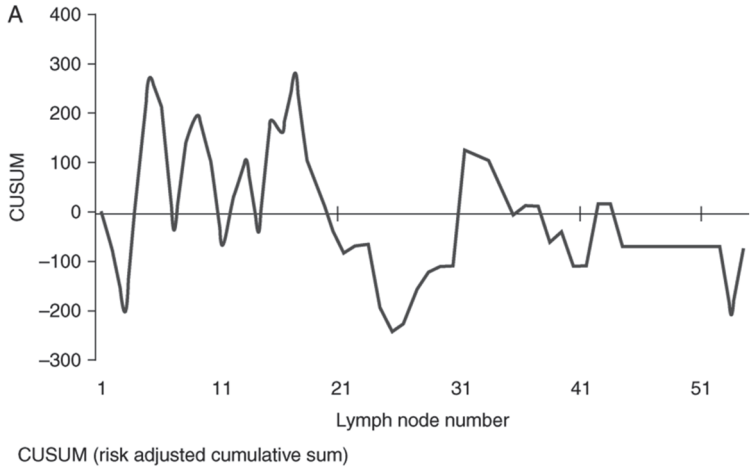
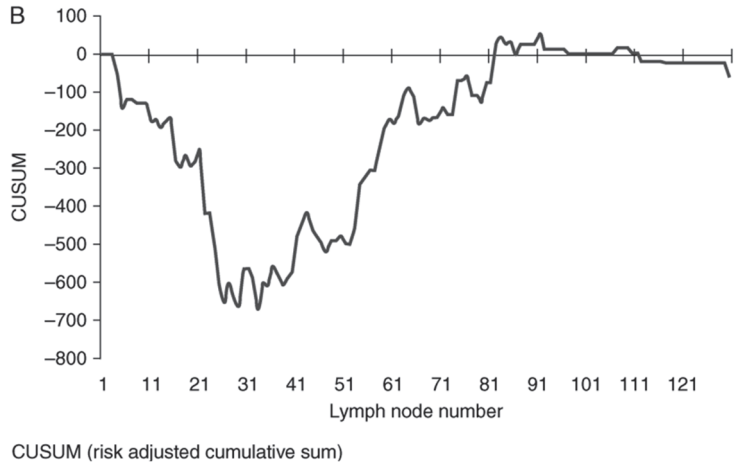


Figure 2b. RA-CUSUM analysis of lymph node harvest vs. overall survival in chemotherapy plus surgery group (NCS); change point as illustrated by the plateau of curve at 22–52 lymph nodes. Above 52 lymph nodes there were significant improvements in disease-free survival (22 to 36 months; p=0.028), and overall recurrence (47.1% to 15.9%; P<0.001) and non-significant improvement in overall survival (27 to 38 months; p=0.171).



Appendix

The NCRS regimen consists of weekly administration of paclitaxel (50 mg/m^2 body-surface area) and carboplatin (area under the curve: 2 mg/ml/min) for five weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week).[22, 23] The MAGIC NCS regimen comprises 3 preoperative and 3 postoperative cycles of intravenous epirubicin (50 mg/m^2 body-surface area) and cisplatin (60 m/m^2 body-surface area) on day 1, and a continuous intravenous infusion of fluorouracil (200 mg/m^2/day) for 21 days.[24] The OEO2 NCS regimen comprises 2 cycles of cisplatin (80mg/m^2 body-surface area) by intravenous infusion on day 1 and fluorouracil (1,000 mg/m^2 body-surface area daily) as a continuous infusion over 96 hours every 3 weeks.[19] The OEO5 NCS regimen comprises four 3-weekly cycles of epirubicin (50 mg/m^2 body-surface area) and cisplatin (60 mg/m^2 body-surface area) given by intravenous infusion on day 1, and capecitabine given orally continuously for 12 weeks at a total daily dose of 1250mg/m^2 body surface area.[9]

References

1. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
2. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
3. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
4. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062-7.
5. Burmeister BH, Thomas JM, Burmeister EA et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer. 2011;47(3):354-60.
6. Stahl M, Walz MK, Stuschke M et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27(6):851-6.
7. Klevebro F, Alexandersson von Dobeln G, Wang N et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016.
8. Reynolds JV, Preston SR, O'Neill B et al. ICORG 10-14: NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study (Neo-AEGIS). BMC Cancer. 2017;17(1):401.
9. Alderson D, Langley RE, Nankivell MG et al. Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072). J Clin Oncol. 2015;33(Abstr 4002).
10. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer., ebrary Inc. TNM classification of malignant tumors. New York: Wiley-Blackwell; 2009. Available from: http://site.ebrary.com/lib/yale/Doc?id=10342913, last accessed: January 29th, 2018.
11. Chirieac LR, Swisher SG, Ajani JA et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer. 2005;103(7):1347-55.
12. Hudis CA, Barlow WE, Costantino JP et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol. 2007;25(15):2127-32.
13. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998;17(19):2265-81.
14. Grigg OA, Farewell VT, Spiegelhalter DJ. Use of risk-adjusted CUSUM and RSPRT charts for monitoring in medical contexts. Stat Methods Med Res. 2003;12(2):147-70.
15. Shapiro J, van Klaveren D, Lagarde SM et al. Prediction of survival in patients with oesophageal or junctional cancer receiving neoadjuvant chemoradiotherapy and surgery. Br J Surg. 2016;103(8):1039-47.
16. Talsma AK, Shapiro J, Looman CW et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. Ann Surg. 2014;260(5):786-93.
17. Omloo JM, Lagarde SM, Hulscher JB et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007;246(6):992-1000; discussion -1.
18. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. Ann Surg. 2011;254(6):894-906.

19. Chu KM, Law SY, Fok M, Wong J. A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. Am J Surg. 1997;174(3):320-4.
20. Lykke J, Roikjaer O, Jess P, Danish Colorectal Cancer G. Tumour stage and preoperative chemoradiotherapy influence the lymph node yield in stages I-III rectal cancer: results from a prospective nationwide cohort study. Colorectal Dis. 2014;16(4):O144-9.
21. Taflampas P, Christodoulakis M, Gourtsoyianni S, Leventi K, Melissas J, Tsiftsis DD. The effect of preoperative chemoradiotherapy on lymph node harvest after total mesorectal excision for rectal cancer. Dis Colon Rectum. 2009;52(8):1470-4.
22. Markar SR, Wiggins T, Ni M et al. Assessment of the quality of surgery within randomised controlled trials for the treatment of gastro-oesophageal cancer: a systematic review. Lancet Oncol. 2015;16(1):e23-31.
23. Smyth EC, Fassan M, Cunningham D et al. Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial. J Clin Oncol. 2016;34(23):2721-7.
24. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med. 2011;364(22):2128-37.
25. Mamidanna R, Ni Z, Anderson O et al. Surgeon Volume and Cancer Esophagectomy, Gastrectomy, and Pancreatectomy: A Population-based Study in England. Ann Surg. 2016;263(4):727-32.
26. Markar SR, Karthikesalingam A, Thrumurthy S, Low DE. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. J Gastrointest Surg. 2012;16(5):1055-63.
27. Markar SR, Arya S, Karthikesalingam A, Hanna GB. Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg Oncol. 2013;20(13):4274-81.
28. van Workum F, Rosman C. Netherlands Trial Register: NTR4333 2013 [Available from: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4333.
29. Low DE, Alderson D, Cecconello I et al. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg. 2015;262(2):286-94.

Chapter 5

Optimal surgical approach for esophageal cancer in the era of MIE and neoadjuvant therapy

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Summary

The optimal surgical technique for the potentially curative treatment of patients with esophageal cancer is still under debate. The transhiatal esophagectomy with limited lymphadenectomy mainly focuses on a decrease of postoperative morbidity and mortality by preventing a formal thoracotomy. The transthoracic esophagectomy (TTE) with extended two-field lymphadenectomy attempts to improve the radicality of the resection and thus to increase locoregional tumor control, but is associated with increased postoperative morbidity. The recent introduction of different minimally invasive techniques probably decreases postoperative morbidity following TTE, with reduction of especially pulmonary complications, but high-quality evidence is still limited. It is widely agreed that extended lymphadenectomy as performed during TTE provides the benefit of more accurate staging, but its effect on improvement of survival is still debated. The literature on this topic is contradictory and the choice of surgical approach is primarily driven by personal opinions and institutional preferences. Moreover, the available evidence is mainly based on patients who underwent surgery alone without neoadjuvant therapy. Results of recent studies suggest that neoadjuvant chemoradiotherapy abolishes any possibly positive effect of extended lymphadenectomy as performed during TTE on survival, but this effect should be confirmed in future research. This review gives an overview and reflects the authors' personal view on the role of TTE and THE in the treatment of potentially curative treatment of patients with locally advanced esophageal cancer in the era of minimally invasive esophagectomy and neoadjuvant treatment and outlines future research perspectives.

Introduction

For several decades it has been debated what is the optimal surgical technique for the potentially curative primary treatment of patients with locally advanced esophageal cancer. Over the years two main different surgical strategies have evolved. On the one hand the limited transhiatal approach (transhiatal esophagectomy, [THE]) was developed, which mainly focused on a decrease of postoperative morbidity and mortality by preventing a formal thoracotomy. On the other hand the extended transthoracic approach (transthoracic esophagectomy, [TTE]) was introduced with two-field lymphadenectomy (posterior mediastinum and upper abdomen) in an attempt to improve the radicality of the resection and thus to increase locoregional tumor control.[1-5] It is widely agreed that extensive lymphadenectomy provides the benefit of more accurate staging, but its effect on improvement of survival is still under debate.[6-9]

In esophageal cancer, lymphatic dissemination occurs early and is unpredictable. It has been shown that 20-40% of all early submucosal (T1b) esophageal tumors have already disseminated to regional lymph nodes.[10-16] Therefore, endoscopic treatment is generally reserved for patients with mucosal (T1a) disease. Moreover, the pattern of lymphatic dissemination is unpredictable with skip metastases at more distant sites while lymph nodes in the direct vicinity of the primary tumor are negative.[17] This is one of the reasons why the sentinel node concept is still considered experimental in the surgical treatment of esophageal cancer patients. Extended lymphadenectomy – as performed during TTE – theoretically increases the chance of radical removal of all positive lymph nodes and thereby improves regional tumor control and long term survival. However, due to a lack of high-quality clinical evidence, especially in the present era of minimally invasive surgery and neoadjuvant treatment, institutional preferences and clinical opinions dominate the choice of surgical approach. In this review, we give an overview of the role of TTE and THE in the treatment of squamous cell carcinomas (SCC) and adenocarcinomas (AC) of the esophagus and esophagogastric junction (EGJ).

Role of lymphadenectomy

In a large retrospective study on 2,303 patients (60% AC, 40% SCC) that underwent R_0 resections from nine high-volume centers around the world it was shown using multivariable analysis that a high total number of resected nodes is an independent prognosticator of (favorable) survival after primary surgical resection of esophageal or junctional cancer. The optimal threshold for this survival benefit was removal of at least 23 nodes and the operation most likely to achieve this threshold was found to be an *en bloc*

resection.[18] These findings are arguments in favor of maximizing the extent of lymphadenectomy and therefore in favor of TTE over THE.

In contrast, a recent nonrandomized study from two British centers showed a similar long-term oncological outcome after THE and TTE for patients with AC (88%) or SCC (12%), while hospital stay was shorter after THE.[19] This advantage of THE over TTE in short-term recovery without substantially jeopardizing long-term oncological outcome was also confirmed in a recent meta-analysis that included 52 studies with 3,389 TTE patients and 2,516 THE patients (52% AC, 48% SCC). In addition to shorter hospital stay (on average 4 days less in patients who underwent THE, 95% confidence interval [CI] 1-7, p<0.01), THE was associated with shorter operative time (THE procedures took a mean of 85 minutes shorter, 95% CI 40-129, p<0.001), less pulmonary complications (17.3% vs. 21.4%, odds ratio [OR] 1.37, 95% CI 1.05-1.79, p=0.02) and lower postoperative mortality (7.2% vs. 10.6%, OR 1.48, 95% CI 1.20-1.83, p<0.001). On the other hand, patients who underwent THE experienced more anastomotic leaks and more recurrent nerve palsies. Furthermore, lymph node retrieval was significantly higher after TTE, with a mean difference of eight nodes (95% CI 1-14, p=0.02). These results must be interpreted with caution, because this analysis included both randomized and non-randomized studies which probably led to a selection bias in favor of the THE group, because more advanced tumors might have been treated preferentially with TTE.[20] Finally, it should be noted that the enhanced short-term recovery after THE was questioned in a large-volume, multicenter observational study in more than 17,000 patients who underwent THE or TTE; no differences were found in overall morbidity and mortality. However, a preference for THE in patients with poor performance status probably led to selection bias in favor of the TTE group.[21]

HIVEX trial

The limited THE and the extended TTE have been compared in a randomized trial (HIVEX trial), which was performed in two high-volume Dutch academic centers. [22] This trial included 220 patients with AC of the mid-to-distal esophagus or AC of the gastric cardia substantially involving the distal esophagus. By preventing a formal thoracotomy postoperative pulmonary complications occurred less frequently (27% after THE vs. 57% after TTE, p<0.001) and artificial ventilation time (1 day after THE vs. 2 days after TTE, p<0.001) and hospital stay (15 days after THE vs. 19 days after TTE, p<0.001) were shorter after THE. However, in-hospital mortality was comparable between the two groups (2% after THE vs. 4% after TTE, p=0.45). Interestingly, the more extended TTE did not lead to a higher percentage of tumor-free resection margins (72% in the THE group vs. 71% in the TTE group) , but the median number of removed

lymph nodes was two times as high after TTE compared to THE (median 31 vs. 16, p<0.001).[22] This improved lymph node retrieval did not translate into a significantly better overall 5-year survival; 34% after THE and 36% after TTE (p=0.71).[23] However, in a subgroup analysis of patients with a truly esophageal (type-1) cancer a better long-term survival was achieved, more specifically in those patients with a limited number (1-8) of positive nodes (23% after THE vs. 64% TTE, p= 0.02). It should be noted that stage migration might have played a role in the improved survival in this TTE group, because the total number of resected lymph nodes was higher after TTE. Furthermore, relevance and level of evidence of these results are questionable for SCC, because only patients with AC were included. The final conclusion of that randomized trial was that in advanced type-1 esophageal cancer patients TTE was the preferred technique, especially in case of a limited number of positive nodes, while THE should be preferred in patients with a type-2 tumor which is located at the EGJ and in patients with a poor general condition without clinically suspected lymph nodes at or above the carina.[23]

Role of minimally invasive esophagectomy

Over the last decade minimally invasive techniques (laparoscopy, thoracoscopy) have been developed and are increasingly applied in esophageal cancer surgery. The potential advantage of minimally invasive esophagectomy (MIE) might be the limitation of surgical trauma, while potentially preserving the radicality of the resection and the extent of lymph node dissection. Several surgical approaches and combinations of techniques have been described, varying from hybrid procedures (thoracoscopy in combination with laparotomy or thoracotomy with laparoscopy) to even completely minimally invasive approaches (thoracoscopy with laparoscopy). So far, only one randomized trial has been published as a full paper, comparing open with minimally invasive TTE.[24] This trial included 115 patients with resectable cancer of the esophagus or EGJ. MIE was shown to have a lower postoperative pulmonary infection rate (relative risk 0.35, 95% CI 0.16–0.78, p=0.005).[24] However, this trial was criticized, mainly because of the subjectivity of the primary endpoint, the limited number of included patients, the short length of follow-up and the high recurrent nerve palsy rate with a (secondary?) high pneumonia rate in the open esophagectomy group.[25-27] It was concluded that larger trials with longer follow-up are needed to establish more definite conclusions concerning the exact role of minimally invasive techniques.[26] Recently, the results of the French MIRO trial have been presented and published in abstract form. This trial randomly assigned 207 patients between open TTE and hybrid MIE (laparoscopic gastric mobilization and open thoracotomy). Both postoperative morbidity (OR 0.31, 95% CI 0.18-0.55, p=0.0001) and pulmonary complications (30.1% vs. 17.7%, p=0.037) were lower in the hybrid arm.[28]

These preliminary results suggest that a hybrid TTE approach using laparoscopy and thoracotomy reduces postoperative complications as compared to open TTE using both laparotomy and thoracotomy. In order to determine whether the complication rate after hybrid TTE can be decreased even more, a trial is needed in which patients are randomized between hybrid MIE and fully minimally invasive MIE.

Thoracoscopic TTE clearly diminishes the surgical trauma to the chest wall in comparison with a conventional thoracotomy, potentially leading to a decreased postoperative pulmonary complication rate.[24] In comparison with a limited transhiatal resection (which completely abolishes the necessity of a thoracotomy/thoracoscopy), however, thoracoscopic TTE still requires a limited trauma to the chest wall (four port sites) and a prolonged (partial) collapse of the right lung throughout the thoracic phase of the operation. It is well established that a lung collapse leads to an increased risk of pulmonary complications.[22] Taking into account the relatively low complication rate after open THE, the impact of this prolonged partial lung collapse in combination with the limited trauma to the chest wall during thoracoscopic TTE needs to be evaluated in a randomized trial, comparing the minimally invasive TTE with a conventional or minimally invasive THE.[29, 30]

Thoracic versus cervical anastomosis

Using the transhiatal technique, an anastomosis between the proximal esophagus and the replacement conduit is required at the cervical level. In contrast, a transthoracic technique allows for a choice between a cervical and a thoracic anastomosis. After TTE, some surgeons favor a cervical anastomosis despite the increased rate of leakage[31], possible stricture formation and recurrent laryngeal nerve damage, because of a longer proximal tumor free margin and a potentially reduced morbidity in case of an anastomotic leak.[32] The latter is based on the assumption that an anastomotic leakage will likely be confined to the neck, instead of leaking into the mediastinum and pleural cavity. However, a recent meta-analysis on this topic did not find significant differences in pulmonary complications (OR 0.86, 95% CI 0.13-5.59, p=0.87) or tumor recurrence (OR 2.01, 95% CI 0.68-5.91, p=0.21).[33] This study included only three small randomized trials with a total of 175 patients, but suggests that performing a cervical anastomosis after TTE does not decrease the risk of intrathoracic complications as compared to a thoracic anastomosis after TTE. Indeed, in two large retrospective cohort studies, the risk of developing intrathoracic manifestations due to leakage of a cervical anastomosis was shown to be significantly less in patients who underwent THE as compared to patients who underwent TTE. This was explained by the difference in pleural dissection. It

was hypothesized, that after THE a bilaterally intact parietal pleura may confine infections and prevent extension into the mediastinum and pleural cavity.[34, 35]

These studies have been performed before the introduction of neoadjuvant therapy and studies comparing cervical with thoracic anastomoses after neoadjuvant therapy are lacking. In the randomized CROSS trial comparing neoadjuvant chemoradiotherapy followed by surgery to surgery alone, almost all anastomoses were performed at the level of the neck and no significant difference was identified in anastomotic leakage rate.[36] However, the effect of radiotherapy on anastomotic healing in the chest might be of significant importance and should be further explored. In case of a thoracic anastomosis the required length of the gastric tube can be shorter with potentially improved oxygenation of the tip and enhanced anastomotic healing. On the other hand, the intrathoracic esophageal remnant might show more radiation damage, which might hamper intrathoracic anastomotic healing.

Impact of neoadjuvant chemoradiotherapy on surgical strategy

It should be underlined, that all above trials comparing different surgical techniques mainly included patients who underwent primary surgical resection without neoadjuvant therapy. But even after careful selection of patients for potentially curative primary surgical resection, 5-year survival rarely exceeds 40% and the majority of patients still dies of recurrent disease.[23] For that reason many studies have been performed worldwide to test the potential value of adding preoperative neoadjuvant therapy to primary surgical resection. The most recent meta-analysis has shown that both neoadjuvant chemotherapy (nCT) and neoadjuvant chemoradiotherapy (nCRT) are able to improve long-term treatment outcome.[37] This meta-analysis showed a trend in favor of nCRT over nCT by comparing treatment arms of different trials (hazard ratio [HR] for all-cause mortality for nCRT vs. nCT 0.88, 95% CI 0.76-1.01, p=0.07), but direct comparisons are limited. Especially for patients with AC, explaining why the Neo-AEGIS trial, that compares nCRT with nCT in patients with AC, is ongoing. Ever since, a Dutch multicenter randomized controlled study (CROSS trial) was completed, comparing nCRT followed by surgery with surgery alone in patients with SCC or AC of the esophagus (type-1) or EGJ (type-2).[36] The applied regimen of five cycles of carboplatin and paclitaxel with 23 fractions of 1.8 Gy concurrent confocal radiotherapy was shown to have low toxicity with >90% of patients tolerating the complete planned regimen. In-hospital mortality after subsequent surgical resection was not influenced (4% in both treatment arms), and also in-hospital morbidity was comparable between the two groups. Interestingly, median survival doubled from 24% in the surgery alone arm to 49% in the combined treatment arm (p=0.003), and 5-year survival improved from 34%

to 47%.[36, 38] The difference in overall survival in the CROSS trial was not due to poor survival in the surgery alone group, but can be attributed to improved survival in the chemoradiotherapy followed by surgery group. This is supported by the superior overall survival in the surgery alone group in the CROSS trial as compared to that reported in earlier randomized trials.[39, 40] Based on these results, nCRT according to CROSS followed by surgery is now considered standard of care in many countries. It should be noted that the survival benefit of nCRT found in the CROSS trial was not supported by a recently published French randomized trial (Fédération Francophone de Cancérologie Digestive (FFCD) 9901 trial) comparing nCRT followed by surgery with surgery alone in patients with stage I and II esophageal cancer. Neoadjuvant therapy consisted of cisplatin and fluorouracil with 45 Gy concurrent radiotherapy. Neither the 3-year overall survival rate nor the microscopically radical resection rate were improved in the nCRT followed by surgery group.[41] Based on these results, the benefit of nCRT for patients with early-stage tumors is debatable. Possibly, treatment with surgery alone is already effective in these patients, which is supported by the high radical resection rate (92%) in the surgery alone group of the French trial. However, the generalizability of the results of the French trial has been questioned due to its low case volume in many of the participating centers, its toxic nCRT regimen with less sophisticated radiation techniques in comparison with the CROSS trial and its remarkably high postoperative mortality rate. Therefore, we caution to conclude that nCRT is not beneficial in early-stage cancer and we believe that, as long as high quality evidence on the effect of nCRT on early-stage tumors is lacking, the results from the CROSS trial (which included stage II cancers) should be considered leading, especially for stage II cancers.[42]

Neoadjuvant treatment according to CROSS has a significant down staging effect both on the primary tumor and on the regional lymph nodes. In the CROSS trial the percentage of patients with (residual) positive lymph nodes in the resection specimen decreased from 76% in the surgery alone group to 32% in the combined treatment group.[36] Moreover, a substantial number of patients (29%) did not have any vital tumor cells left in the resection specimen after nCRT. This high pathologically complete response rate led to the imperative to reconsider the necessity of standard esophagectomy in all patients. Therefore, we hope to propose in the near future a "Surgery As Needed approach in Oesophageal cancer patients (SANO-approach)". In this approach, patients will undergo active surveillance after completion of nCRT. Esophagectomy will be offered only to patients in whom a locoregional recurrence is highly suspected or proven. This organ-preserving strategy would be preferred, but only if long term survival would be comparable to that of the present standard surgery approach. As a first step towards an organ-preserving strategy, we are currently performing the multicenter phase II feasibility preSANO-trial to determine the accuracy by which residual disease after nCRT can be detected.[43] Furthermore, in France, a phase II/III randomized trial comparing

standard surgery with surgery on demand in case of recurrence in clinically complete responders after nCRT is currently being initiated (ESOSTRATE-trial).[44]

As underlined above, the randomized HIVEX trial comparing THE and TTE for subcarinal tumors was performed in patients who did not undergo neoadjuvant therapy. In that trial TTE did not lead to a higher rate of tumor free margins (71% after TTE vs. 72% after THE), but roughly doubled the number of removed nodes (median ± standard deviation = 31 ± 14 after TTE vs. 16 ± 9 after THE, p<0.001). The randomized CROSS trial has shown, however, that in patients after nCRT the total number of resected nodes is significantly lower than in patients after primary surgery.[45] Importantly, in patients after primary surgery in the CROSS trial there was a positive correlation between the total number of resected nodes and the number of resected positive nodes. However, this positive association was not present after nCRT: by resecting more nodes the number of resected positive nodes remained unchanged. Furthermore, after primary surgery the total number of resected nodes had a positive correlation with survival (HR per 10 additionally resected nodes, 0.76; p=0.007), which is in line with an earlier retrospective international study, as discussed above.[18, 45] Interestingly, this positive correlation between the total number of resected nodes and survival was completely absent after nCRT (HR 1.00; p=0.98). After surgery alone a higher number of resected nodes was associated with improved survival, while in a comparable group of patients who were randomly allocated to undergo nCRT plus surgery, this association was lost. The randomization procedure within the CROSS trial renders asymmetry between both treatment arms unlikely as a possible explanation for the (disappearance of the) observed association in this secondary analysis. These data question the necessity of maximization of surgical lymph node retrieval after nCRT, both for diagnostic purposes and for therapeutic reasons.

The same phenomenon was identified in a larger (albeit retrospective) analysis of 391 patients who underwent primary surgery and 626 patients who underwent nCRT according to CROSS followed by surgery.[46] In the surgery alone group, TTE was associated with a significantly more favorable prognosis as compared to THE (HR for TTE vs THE = 0.73, p=0.023), whereas in patients treated with nCRT followed by surgery TTE was associated with a (non-significantly) *less* favorable prognosis (HR TTE vs. THE = 1.18, p=0.246). Again, these data suggest that maximization of surgical lymph node retrieval is probably relevant in patients who undergo surgery alone, but question its necessity after nCRT.

In order to confirm these indirect arguments, a randomized trial is needed comparing TTE and THE in patients with (type-1) esophageal cancer who undergo nCRT according to CROSS. In our opinion, such trial should focus on patients with (type-1) esophageal cancer and not on patients with (type-2) junctional cancer, because the HIVEX trial has already shown sufficiently that in patients with type-2 junctional cancer

THE suffices. Even if they undergo primary surgical resection without preoperative neoadjuvant therapy; let alone in patients with type-2 junctional cancer who undergo nCRT followed by surgery. It should be noted that in the HIVEX trial also type-1 malignancies were included and conclusions regarding the absence of benefit of TTE for type-2 cancer are obtained from a subgroup analysis.

Conclusion and future directions

The optimal surgical strategy (transthoracic or transhiatal resection) for esophageal carcinoma remains unclear. A trend towards an improved 5-year survival after TTE was shown in a randomized trial, but this study was performed before implementation of nCRT and MIE.[22] The extended lymphadenectomy in TTE might decrease the rate of locoregional recurrences and thus increase survival. However, the necessity of maximization of surgical lymph node retrieval after nCRT has recently been questioned.[45, 46] The recent introduction of MIE might decrease postoperative morbidity following TTE, with reduction of especially pulmonary complications, but high-quality evidence is still limited.

Therefore, some important questions remain to be addressed. First, several minimally invasive TTE approaches have been described, but the superiority of one technique over another in terms of postoperative complications and oncological outcome remains unknown. Randomization between the hybrid procedure as performed in the recent MIRO trial[28] versus a fully minimally invasive esophagectomy as described in the TIME trial[24], will reveal possible advantages of thoracoscopy over thoracotomy, both combined with laparoscopic gastric mobilization. A reduction in postoperative (pulmonary) complication rate after thoracoscopic TTE would only be acceptable if this is accompanied by a similar or improved oncological outcome. Furthermore, such trial design would allow for a second randomization procedure within each arm between a thoracic and a cervical anastomosis (4-arm study), to define the optimal location of the anastomosis.

Second, the oncological necessity of extended lymph node dissection in patients with type-1 esophageal AC or SCC (located below the carina) in the era of neoadjuvant therapy should be studied. If a randomized trial comparing TTE with THE shows that THE is adequate after nCRT, this will clearly have advantages in reducing especially pulmonary complications. Moreover, the discussion on thoracoscopy vs. thoracotomy would then be futile.

Finally, direct comparison between minimally invasive THE and open THE will clarify whether the relatively low complication rate of an open THE can be decreased even more. Especially if THE would prove to be sufficient for patients who have been pretreated with nCRT or in the growing elderly population, minimization of surgical trauma and avoidance of postoperative complications is crucial.

References

1. Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. Br J Surg. 1990;77(8):845-57.
2. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. Ann Thorac Surg. 2001;72(1):306-13.
3. Goldminc M, Maddern G, Le Prise E, Meunier B, Campion JP, Launois B. Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial. Br J Surg. 1993;80(3):367-70.
4. Chu KM, Law SY, Fok M, Wong J. A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. Am J Surg. 1997;174(3):320-4.
5. Jacobi CA, Zieren HU, Muller JM, Pichlmaier H. Surgical therapy of esophageal carcinoma: the influence of surgical approach and esophageal resection on cardiopulmonary function. Eur J Cardiothorac Surg. 1997;11(1):32-7.
6. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg. 2002;236(2):177-83.
7. Lerut T, Nafteux P, Moons J et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg. 2004;240(6):962-72; discussion 72-4.
8. Jamieson GG, Lamb PJ, Thompson SK. The role of lymphadenectomy in esophageal cancer. Ann Surg. 2009;250(2):206-9.
9. Tong D, Law S. Extended lymphadenectomy in esophageal cancer is crucial. World J Surg. 2013;37(8):1751-6.
10. Stein HJ, Feith M, Bruecher BL, Naehrig J, Sarbia M, Siewert JR. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg. 2005;242(4):566-73; discussion 73-5.
11. Stein HJ, Feith M, Mueller J, Werner M, Siewert JR. Limited resection for early adenocarcinoma in Barrett's esophagus. Ann Surg. 2000;232(6):733-42.
12. Stein HJ, Feith M, von Rahden BH, Siewert JR. Approach to early Barrett's cancer. World J Surg. 2003;27(9):1040-6.
13. Westerterp M, Koppert LB, Buskens CJ et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch. 2005;446(5):497-504.
14. Holscher AH, Bollschweiler E, Schneider PM, Siewert JR. Prognosis of early esophageal cancer. Comparison between adeno- and squamous cell carcinoma. Cancer. 1995;76(2):178-86.
15. Fujita H, Sueyoshi S, Yamana H et al. Optimum treatment strategy for superficial esophageal cancer: endoscopic mucosal resection versus radical esophagectomy. World J Surg. 2001;25(4):424-31.
16. Ancona E, Guido E, Cutrone C et al. A new endoscopic technique for suspension of esophageal prosthesis for refractory caustic esophageal strictures. Dis Esophagus. 2008;21(3):262-5.
17. Raja S, Rice TW, Goldblum JR et al. Esophageal submucosa: the watershed for esophageal cancer. J Thorac Cardiovasc Surg. 2011;142(6):1403-11 e1.
18. Peyre CG, Hagen JA, DeMeester SR et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549-56.
19. Davies AR, Sandhu H, Pillai A et al. Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. Br J Surg. 2014;101(5):511-7.
20. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. Ann Surg. 2011;254(6):894-906.

21. Connors RC, Reuben BC, Neumayer LA, Bull DA. Comparing outcomes after transthoracic and transhiatal esophagectomy: a 5-year prospective cohort of 17,395 patients. J Am Coll Surg. 2007;205(6):735-40.
22. Hulscher JB, van Sandick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662-9.
23. Omloo JM, Lagarde SM, Hulscher JB et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007;246(6):992-1000; discussion -1.
24. Biere SS, van Berge Henegouwen MI, Maas KW et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet. 2012;379(9829):1887-92.
25. Swisher S, Ajani J, Correa A, Komaki R, Hofstetter W. Minimally invasive versus open oesophagectomy for oesophageal cancer. Lancet. 2012;380(9845):883; author reply 5-6.
26. Law S. Is minimally invasive preferable to open oesophagectomy? Lancet. 2012;379(9829):1856-8.
27. Mariette C, Robb WB. Minimally invasive versus open oesophagectomy for oesophageal cancer. Lancet. 2012;380(9845):883; author reply 5-6.
28. Mariette C, Meunier B, Pezet D et al. Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised phase III controlled trial, the MIRO trial. 2014 Congress of the European Society for the Diseases of the Esophagus. 2014.
29. DePaula AL, Hashiba K, Ferreira EA, de Paula RA, Grecco E. Laparoscopic transhiatal esophagectomy with esophagogastroplasty. Surg Laparosc Endosc. 1995;5(1):1-5.
30. Scheepers JJ, Veenhof AA, van der Peet DL et al. Laparoscopic transhiatal resection for malignancies of the distal esophagus: outcome of the first 50 resected patients. Surgery. 2008;143(2):278-85.
31. Markar SR, Arya S, Karthikesalingam A, Hanna GB. Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg Oncol. 2013;20(13):4274-81.
32. Chasseray VM, Kiroff GK, Buard JL, Launois B. Cervical or thoracic anastomosis for esophagectomy for carcinoma. Surg Gynecol Obstet. 1989;169(1):55-62.
33. Biere SS, Maas KW, Cuesta MA, van der Peet DL. Cervical or thoracic anastomosis after esophagectomy for cancer: a systematic review and meta-analysis. Dig Surg. 2011;28(1):29-35.
34. van Heijl M, van Wijngaarden AK, Lagarde SM, Busch OR, van Lanschot JJ, van Berge Henegouwen MI. Intrathoracic manifestations of cervical anastomotic leaks after transhiatal and transthoracic oesophagectomy. Br J Surg. 2010;97(5):726-31.
35. Korst RJ, Port JL, Lee PC, Altorki NK. Intrathoracic manifestations of cervical anastomotic leaks after transthoracic esophagectomy for carcinoma. Ann Thorac Surg. 2005;80(4):1185-90.
36. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
37. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
38. Nederlof N, Slaman AE, Van Hagen P et al. Using the comprehensive complications index (CCI) to assess the impact of neoadjuvant chemoradiotherapy on postoperative complications after esophagectomy in esophageal cancer patients. Submitted for publication. 2015.
39. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335(7):462-7.
40. Tepper J, Krasna MJ, Niedzwiecki D et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26(7):1086-92.

41. Mariette C, Dahan L, Mornex F et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32(23):2416-22.
42. Shapiro J, van Lanschot JJ, Hulshof MC, van der Gaast A. Effectiveness of neoadjuvant chemoradiotherapy for early-stage esophageal cancer (letter to the editor). J Clin Oncol. 2015;33(3):288-9.
43. Noordman BJ, Shapiro J, Spaander MC et al. Accuracy of detecting residual disease after CROSS neoadjuvant chemoradiotherapy for esophageal cancer (preSANO trial). JMIR Res Protoc. 2015;In press.
44. Putora PM, Bedenne L, Budach W et al. Oesophageal cancer: exploring controversies overview of experts' opinions of Austria, Germany, France, Netherlands and Switzerland. Radiat Oncol. 2015;10:116.
45. Talsma AK, Shapiro J, Looman CW et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. Ann Surg. 2014;260(5):786-93.
46. Shapiro J, Van Klaveren D, Lagarde SM et al. Impact of neoadjuvant chemoradiotherapy on conventional prognostic factors and on prediction of individual survival in patients with esophageal or junctional cancer. Br J Surg. 2016;Accepted for publication.

Chapter 6

Effect of lymphadenectomy on survival in oesophageal cancer

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Refers to M. van der Schaaf et al. Extent of lymph node removal during esophageal cancer surgery and survival. J. Natl Cancer Inst. 107, djv043 (2015)

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In patients with oesophageal cancer, the effect of lymphadenectomy on survival remains unclear. A recent retrospective cohort study suggests that extensive lymphadenectomy does not improve survival and might even hamper it in patients with early T-stage tumours. The available data show conflicting results and the introduction of neoadjuvant chemoradiotherapy might decrease any positive effect of extensive lymphadenectomy on survival.

It is established that extensive lymphadenectomy during oesophagectomy for oesophageal cancer provides the benefit of more-accurate staging, but its effect on survival is still under debate.[1, 2] Extensive lymphadenectomy theoretically increases the probability of radical removal of all tumour-positive lymph nodes, and thereby might improve long-term survival. However, some researchers consider lymph-node metastases only as indicators of systemic disease, and not as governors of survival.[3] In this regard, any suggested therapeutic effect is explained by stage migration, with positive nodes in the extended part of the dissection leading to an increased N-stage, but a more-favourable prognosis compared with patients harbouring the same number of positive nodes after a limited dissection. In this context stage migration leads to biased stage-by-stage comparisons of survival.

In a recently published study, it has been reported that extensive lymphadenectomy during surgery for oesophageal cancer does not improve survival.[4] This nationwide population-based cohort study from Sweden in 1,044 patients with oesophageal cancer who had undergone oesophagectomy analysed the independent effect of lymphadenectomy on long-term survival.[4] The number of lymph nodes resected were analysed both as a continuous variable and as a median and quartile variable. The data were adjusted for age, sex, comorbidities, T-stage, neoadjuvant therapy, surgeon volume and calendar period. No influence of the number of lymph nodes removed on overall 5-year mortality, when analysed as a continuous variable, was found (hazard ratio [HR] for mortality 1.00, 95% CI 0.99– 1.01). Furthermore, no differences in overall 5-year mortality were reported in patients in the third (7–15 nodes) and fourth (16–114 nodes) quartiles as compared to patients in the lowest two quartiles combined (<7 nodes, HR 1.13, 95% CI 0.95– 1.35 and HR 1.17, 95% CI 0.94–1.42, respectively). However, a comparison between the combined quartiles 1 and 2 versus quartiles 3 and 4 showed a significantly increased HR in favour of the lower quartiles (HR 1.21, 95% CI 1.03– 1.42, p=0.02). Moreover, in a subgroup analysis of patients with early T-stage tumours (Tis-T1), an unfavourable HR was found for patients in the combined quartiles 3 and 4 (7–114 nodes) as compared to patients in quartiles 1 and 2 (<7, HR 1.53, 95% CI 1.13– 1.27, p=0.006). These results suggest that maximization of surgical lymph-node retrieval does not improve survival and might hamper survival in patients with early T-stage tumours.[4]

The large sample size and nationwide design of this study with complete follow-up of at least 24 months led to sufficient statistical power and a relatively low risk of selection bias. The homogeneity of the study population is further improved by the use of the same surgical technique (transthoracic oesophagectomy, [TTO]) in 95% of all included patients.[4] Furthermore, the adjustment for a number of well-known prognostic factors, as mentioned above, decreased the possibility of confounding.

The investigators state that it is unfeasible to study the effects of the number of removed nodes in a randomized trial design and conclude that an observational study design remains the best option. However, a randomized trial comparing TTO with extensive lymphadenectomy (with a median number of lymph nodes removed of 31) versus transhiatal oesophagectomy (THO) with limited lymphadenectomy (median number of lymph nodes removed of 16) did not show differences in overall 5-year survival between both arms.[5] A subgroup analysis of patients with Siewert type-1 oesophageal cancer with a limited number (1–8) of positive nodes showed an improved survival in favour of the TTO group;[6] however, this effect might be explained, at least partially, by stage migration.

The retrospective design of the present study[4] necessitates a correction for possible confounding factors owing to a lack of random distribution of patients in terms of the number of lymph nodes removed. While most of the relevant factors have been addressed well, an important prognostic factor that was not considered, but might influence the extent of lymphadenectomy, is the number of suspected regional lymph-node metastases preoperatively and peroperatively (clinical N-stage). Although accuracy of clinical N-staging is poor, patients suspected for a high number of lymph-node metastases are more likely to undergo a more-extensive lymphadenectomy as compared to patients without or with a limited number of suspected regional lymph nodes metastases. Therefore, patients with more-advanced tumours and a less-favourable prognosis might have a higher number of lymph nodes resected. In oesophageal cancer, lymphatic dissemination is chaotic and unpredictable and occurs early in tumorigenesis; thus, adjustment only for T-stage does not properly correct for any differences in clinical N-stage.

Moreover, it should be noted that the median number of removed and identified nodes of seven in the Swedish study is relatively low compared with the available literature on TTO, with means varying from 15 to 34.[5, 7] A large international retrospective study[8] on 2,303 patients showed that a high number of resected nodes is an independent prognostic factor for favourable survival after surgery alone in patients with oesophageal or gastro-oesophageal junction cancer, a result that is in sharp contrast with the results from the Swedish study. The optimal threshold for this survival benefit was shown to be at least 23 nodes removed.[8] A recent meta-analysis that compared TTO with extensive lymphadenectomy versus THO with limited lymphadenectomy in 5,905 patients from

52 studies, showed a similar 5-year survival after TTO or THO, while short-term recovery was more favourable after THO. These results, however, must be interpreted with caution because the analysis included both non-randomized and randomized studies.[7] This limitation probably led to a selection bias in favour of the THO group, since more-advanced tumours might have been treated with TTO.

Finally, after publication of the results of the randomized CROSS II trial comparing neoadjuvant chemoradiotherapy followed by surgery versus surgery alone in patients with oesophageal cancer,[9] this multimodal approach has become standard of care in many countries. The studies we have discussed mainly included patients who did not undergo neoadjuvant therapy. Neoadjuvant chemoradiotherapy has a marked down-staging effect on the primary tumour as well as on the regional lymph nodes. This 'sterilizing' effect on lymph nodes theoretically diminishes the potential positive impact of extensive lymphadenectomy on survival. Therefore, separate analyses of patients who underwent neoadjuvant chemoradiotherapy plus surgery and patients who underwent surgery alone are mandatory. In the CROSS trial, the total number of resected nodes in patients who underwent surgery alone had a positive association with overall survival,[10] which correlates well with the already discussed international retrospective study.[8] Interestingly, this relationship between the total number of resected nodes and overall survival was completely lost in the group receiving neoadjuvant chemoradiotherapy. The same phenomenon has been shown in a larger (albeit retrospective) study on 391 patients who underwent surgery alone and 626 patients who underwent neoadjuvant chemoradiotherapy according to the same scheme as used in the CROSS trial, followed by surgery.[11] These data suggest that maximal lymph-node retrieval is relevant in patients who undergo surgery alone, but question whether such an approach is necessary after neoadjuvant chemoradiotherapy.

In conclusion, the effect of the extent of lymphadenectomy on survival remains controversial. The available literature on this topic shows conflicting results, with personal opinions and institutional preferences continuing to dominate the choice of lymphadenectomy procedure. High-quality evidence is needed to reduce the variations in clinical practice. Future research should distinguish between patients treated with surgery alone and patients who undergo neoadjuvant therapy before surgery. Neoadjuvant therapy has been suggested to abolish any positive effect of extensive lymphadenectomy on survival, but this effect should be further explored, preferably in a randomized setting comparing TTO with THO after neoadjuvant chemoradiotherapy, and focused on truly oesophageal (Siewert type-1) tumours. One such trial is currently being initiated in the Netherlands and its results are eagerly awaited.

References

1. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg. 2002;236(2):177-83.
2. Tong D, Law S. Extended lymphadenectomy in esophageal cancer is crucial. World J Surg. 2013;37(8):1751-6.
3. Cady B. Lymph node metastases. Indicators, but not governors of survival. Arch Surg. 1984;119(9):1067-72.
4. van der Schaaf M, Johar A, Wijnhoven B, Lagergren P, Lagergren J. Extent of lymph node removal during esophageal cancer surgery and survival. J Natl Cancer Inst. 2015;107(5).
5. Hulscher JB, van Sandick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662-9.
6. Omloo JM, Lagarde SM, Hulscher JB et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007;246(6):992-1000; discussion -1.
7. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. Ann Surg. 2011;254(6):894-906.
8. Peyre CG, Hagen JA, DeMeester SR et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549-56.
9. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
10. Talsma AK, Shapiro J, Looman CW et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. Ann Surg. 2014;260(5):786-93.
11. Shapiro J, Van Klaveren D, Lagarde SM et al. Impact of neoadjuvant chemoradiotherapy on conventional prognostic factors and on prediction of individual survival in patients with esophageal or junctional cancer. Br J Surg. 2016;Accepted for publication.

Chapter 7

Chaper 7A
The impact of surgical approach on long-term survival in esophageal adenocarcinoma patients with or without neoadjuvant chemoradiotherapy

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Abstract

Objective

To compare overall survival in patients with esophageal adenocarcinoma who underwent transhiatal esophagectomy with limited lymphadenectomy (THE) or transthoracic esophagectomy with extended lymphadenectomy (TTE) with or without neoadjuvant chemoradiotherapy (nCRT).

Background

The application of neoadjuvant therapy might change the association between the extent of lymphadenectomy and survival in patients with esophageal adenocarcinoma. This may influence the choice of surgical approach in patients treated with nCRT.

Methods

Patients with potentially curable subcarinal esophageal adenocarcinoma treated with surgery alone or nCRT followed by surgery in 7 centers were included. The effect of surgical approach on overall survival, differentiated by the addition or omission of nCRT, was analyzed using a multivariable Cox regression model that included well-known prognostic factors and factors that might have influenced the choice of surgical approach.

Results

In total, 701 patients were included, of whom 318 had TTE with extended lymphadenectomy and 383 had THE with limited lymphadenectomy. TTE had differential effects on survival (p for interaction=0.02), with a more favorable prognostic effect in patients who were treated with surgery alone (hazard ratio [HR]=0.77, 95% confidence interval [CI] 0.58–1.03). This association was statistically significant in a subgroup of patients with 1-8 positive lymph nodes in the resection specimen (HR=0.62, 95% CI 0.43–0.90). The favorable prognostic effect of TTE over THE was absent in the nCRT plus surgery group (HR=1.16, 95% CI 0.80–1.66) and in the subgroup of nCRT-patients with 1 to 8 positive lymph nodes in the resection specimen (HR=1.00, 95% CI 0.61–1.68).

Conclusions

Compared to surgery alone, the addition of nCRT may reduce the need for TTE with extended lymphadenectomy in order to improve long-term survival in patients with esophageal adenocarcinoma.

Introduction

The optimal surgical approach for the treatment of patients with esophageal adenocarcinoma is still under debate. Transhiatal esophagectomy (THE) with limited lymphadenectomy mainly focuses on a decrease of postoperative morbidity and mortality by preventing a formal thoracotomy. The transthoracic esophagectomy (TTE) with extended two-field lymphadenectomy attempts to improve the radicality of the resection and thus to increase locoregional tumor control. TTE is, however, associated with increased postoperative morbidity.[1]

For esophageal carcinoma at or above the level of the carina TTE with a two-field lymph node dissection is mandatory. For adenocarcinomas located below the level of the carina, either TTE or THE can be performed, depending on surgeon's preference and patient characteristics. For adenocarcinomas involving the esophagogastric junction and/or gastric cardia, a survival benefit for TTE over THE is theoretically unlikely and has never been proven.[1]

Neoadjuvant therapy downstages the primary tumor as well as the regional lymph node metastases. The 'sterilizing' effect on lymph nodes theoretically reduces the potential positive impact of extended lymphadenectomy on survival.[2, 3] This may have an impact on the required extent of lymphadenectomy in patients treated with neoadjuvant therapy and thus on the choice of the operative approach.

Therefore, the objective of this study was to assess the effect of surgical approach (TTE with extended lymphadenectomy vs. THE with limited lymphadenectomy) on survival, differentiated by the addition or omission of neoadjuvant chemoradiotherapy (nCRT), in patients with a subcarinal esophageal adenocarcinoma treated with nCRT followed by surgery versus surgery alone. It was hypothesized that TTE is associated with a more favorable prognosis compared to THE in patients who have surgery alone, but that this benefit is absent in patients who receive nCRT before surgery.

Methods

Patients

Patients were included with potentially curable subcarinal esophageal adenocarcinoma (including Siewert type 1). Included patients underwent surgery alone as standard of care in the Erasmus MC, Rotterdam (January 1996–January 2001) and in the Academic Medical Center (AMC), Amsterdam (January 1996-December 2004), nCRT followed by surgery as part of the phase 2 CROSS-I trial in the Erasmus MC[4] (April 2001–March 2004), surgery alone or nCRT followed by surgery as part of the phase 3 multicenter randomized CROSS-II trial in the seven participating centers[5, 6] (June 2004–February

2009), or nCRT followed by surgery as standard of care at the Erasmus MC or the AMC (March 2009–August 2013). Only patients who underwent a transthoracic or transhiatal resection were included. The choice for surgical technique was driven by personal preferences with both techniques performed in all participating centers, but after publication of the long-term results of the HIVEX trial in 2007 there was an overall shift towards TTE.[1] Patients with Siewert type 2 cancers were excluded, because a survival benefit for TTE over THE is theoretically unlikely and has never been proven.[1] Furthermore, patients who did not undergo at least 80% of the planned dose of chemo- and/or radiotherapy, who received a different nCRT regimen, who had signs of distant metastases at the time of surgery or in whom the tumor was not resected during surgery were excluded. The in- and exclusion criteria of the CROSS-II trial were retrospectively applied to all patients of the surgery alone group, *i.e.* all included patients that underwent the complete clinical staging protocol (see below) and had locally advanced disease at clinical staging (cT2-T4a and cT1N+).[5]

Clinical staging

Pretreatment staging procedures consisted of endoscopy with histological biopsy, endoscopic ultrasonography (with fine needle aspiration when indicated), CT scan of the neck, chest and abdomen and external ultrasonography of the neck (when indicated). PET scans were not routinely performed during the study period. Tumor location was determined by pretreatment endoscopy. Clinical T-stage and N-stage were determined by endoscopic ultrasonography and CT-scanning and/or fluorodeoxyglucose-PET-scanning and (re)scored according to the Union for International Cancer Control (UICC) tumor node metastasis classification (TNM) Cancer Staging, 6th edition.[7]

Treatment

The nCRT regimen consisted of weekly administration of paclitaxel (50 mg/m^2 body-surface area) and carboplatin (area under the curve: 2 mg/ml/min) for five weeks and concurrent external beam radiotherapy with a total dose of 41.4 Gy in 23 fractions, 5 days per week. Patients underwent either TTE with extended lymphadenectomy or THE with limited lymphadenectomy. In both the transthoracic and the transhiatal approach, an upper abdominal lymphadenectomy was routinely performed, including removal of nodes along the origin of the left gastric artery, the hepatic artery and the splenic artery (lymph node stations 1-10 and 15-20 according to the American Joint Committee of Cancer 7th edition[8]).

Pathology

All pathological data were collected from prospectively maintained databases. Histological tumor type was determined in the pretreatment biopsy. The definition for a microscopically radical resection (R0) was a tumor-free resection margin ≥ 1 mm. R1 was defined as a microscopically tumor-free resection margin <1 mm, with a macroscopically radical resection. Pathological T-stage and N-stage were (re)scored according to the UICC TNM Cancer Staging, 7th edition[9], N0: no nodes positive; N1: 1-2 lymph nodes positive; N2: 3-6 lymph nodes positive; N3: ≥7 lymph nodes positive.

Follow-up and data collection

All clinical data were taken from prospectively collected institutional databases. Overall survival was determined using municipal registers. Disease free survival was defined as the interval between start of therapy and the earliest occurrence of disease recurrence.

Statistical analysis

Results are presented as frequencies with percentages for categorical variables or as medians with interquartile range in case of continuous variables. The treatment groups were compared using the Student's *t* test or the Mann-Whitney test as adequate to compare continuous variables, whereas χ^2 test or Fisher's exact test was used for comparison of categorical data.

The association between surgical approach and survival was analyzed using a multivariable Cox regression model, including tests for interaction with the addition or omission of nCRT. Besides well-known prognostic factors (age, sex, American Society of Anesthesiologist [ASA] classification, pathological T stage and year of treatment), this model contained factors that might have influenced the preference of surgical approach (pulmonary and cardiovascular comorbidities and clinical N stage). The variables pathological N stage and radicality of resection were not included in the primary model, because these factors were believed to be potentially influenced directly by the type of surgical approach. As a sensitivity analysis, multivariable analysis was also performed after inclusion of these two additional parameters in the model. Statistical significance was set at $p<0.05$.

Results

Patients

A total of 701 patients were included with potentially curable subcarinal esophageal adenocarcinoma, of whom 358 were treated with surgery alone and 343 underwent nCRT followed by surgery. In the surgery alone group 107 patients had TTE and 251 had THE, in the nCRT group this was 221 and 132, resp. Median age at diagnosis was 63 years in the surgery alone group and 61 years in the multimodality group (Table 1a and 1b). The majority of patients were male (85% and 86%, resp.), most often clinically staged as cT3 (72% and 77%, resp.). Statistically significant differences in pretreatment characteristics were observed between the surgery alone group and nCRT plus surgery group for clinical N-stage (47% clinically node positive in the surgery alone group *vs* 69% in the nCRT plus surgery group, $p<0.01$). Furthermore, THE was performed significantly more often in the surgery alone group as compared to the nCRT plus surgery group. Within the surgery alone group patients who underwent TTE were significantly younger (median age 62 vs. 65, $p<0.01$) and had better ASA-classification scores ($p<0.01$). On the other hand, these patients had significantly more advanced tumors, based on clinical T and N staging ($p=0.02$ and $p=0.04$, respectively). In the nCRT group, patients who underwent TTE were also younger and had better ASA-classifications, although these differences were not statistically significant. Also, nCRT patients treated with TTE were more often clinically staged pretreatment as node positive ($p=0.02$).

Lymph node retrieval

The median number (interquartile range) of resected lymph nodes in patients who underwent surgery alone was 26 (18 - 36) in the TTE group and 14 (8 – 18) in the THE group ($p<0.01$). In patients treated with nCRT followed by surgery these numbers were 21 (16 – 28) and 12 (7 – 16), respectively ($p<0.01$).

Overall survival

In multivariable Cox regression analysis including the parameters age, gender, ASA-classification, pathological T stage, pulmonary and cardiovascular comorbidities and clinical N stage, TTE had differential effects on overall survival in patients who underwent surgery alone compared to patients who underwent nCRT plus surgery (p for interaction=0.02). TTE was independently associated with a more favorable prognosis in patients who were treated with surgery alone (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.58 – 1.03, $p=0.08$, Table 2). Results were comparable in a subgroup of patients with clinically suspected lymph node involvement (HR 0.69, 95% CI 0.47 –

1.02, p=0.07), whereas in a subgroup of patients who had surgery alone and 1 to 8 positive lymph nodes in the resection specimen, this association was statistically significant (HR 0.62, 95% CI 0.43 – 0.90, p=0.01). The favorable prognostic effect of TTE over THE after surgery alone was absent in the nCRT followed by surgery group (HR 1.16, 95% CI 0.80 – 1.66, p=0.44, Table 2) and in the subgroups of nCRT patients with clinically suspected lymph node involvement (HR 1.35, 95% CI 0.87 – 2.14, p=0.18) and with 1 to 8 positive lymph nodes in the resection specimen (HR 1.00, 95% CI 0.61 – 1.68, p=0.98).

Addition of pathological N-stage and radicality of resection to the Cox regression models showed comparable results: HR 0.78 in favor of TTE, 95% CI 0.59 – 1.04, p=0.09, for patients in the surgery alone group and HR 0.99, 95% CI 0.69 – 1.43, p=0.97, for patients who underwent nCRT followed by surgery.

Disease free survival

Analysis of disease free survival was performed using the same Cox regression model. TTE had differential effects on disease free survival in the surgery alone group compared to the nCRT plus surgery group (p for interaction=0.03). TTE was associated with a more favorable disease free survival in patients who had surgery alone (HR 0.79, 95% [CI] 0.58 – 1.07, p=0.13, Table 3), whereas this favorable effect was absent and even slightly but not significantly reversed in patients who received nCRT plus surgery (HR 1.27, 95% CI 0.85 – 1.91, p=0.24).

Discussion

The present study shows that the choice of surgical technique has a differential effect on overall survival in patients with subcarinal esophageal adenocarcinoma who underwent surgery alone compared to patients who received nCRT prior to surgery. TTE was independently associated with a more favorable prognosis in patients who underwent surgery alone, especially in patients with a limited number of positive lymph nodes. This benefit was, however, absent in patients who underwent nCRT.

A retrospective analysis of 2,303 patients (60% AC, 40% SCC) who underwent R0-resections, showed that the total number of resected nodes is an independent prognostic factor of (favorable) survival after surgery alone.[10] These findings are indirect arguments in favor of TTE over THE in patients treated without nCRT. In contrast, a non-randomized study by two British high-volume centers showed comparable long-term survival after THE and TTE for patients with SCC (12%) or AC (88%).[11] These results were confirmed in a meta-analysis of 52 studies that included 3,389 TTE patients and 2,516 THE patients (48% SCC, 52% AC).[12] It should be noted that this meta-analysis included both randomized and non-randomized studies. This probably led to a selection

bias in favor of the patients who underwent THE, because the more advanced tumors probably were selected to undergo a thoracotomy. On the other hand, THE might have been the preferred technique in frail patients in order to minimize complications by avoiding a thoracotomy. Hence, due to the unknown effects of these confounding factors, results must be interpreted with caution.

The HIVEX trial randomly assigned 220 patients with esophageal AC located both below the carina (Siewert type-1) and of the gastric cardia (Siewert type-2) to primary TTE or THE (without nCRT). The higher lymph node yield in the TTE group of the HIVEX trial (median 31 vs. 16, resp., p<0.001), treated by surgery without nCRT, did not translate into a significantly increased five-year overall survival rate. However, patients with a truly esophageal adenocarcinoma treated with TTE, and more specifically those with a limited number (1–8) of positive lymph nodes, had a significantly improved 5-year overall survival compared to THE patients (39% after TTE vs. 19% after THE, 95% CI for the difference 3% to 37%, p=0.05), which is confirmed by the current study. The final conclusion of the HIVEX trial was that in patients with advanced truly esophageal adenocarcinoma, especially with a limited number of positive nodes, TTE should be the preferred technique, while THE should be regarded as the preferred technique in patients with a tumor located at the EGJ or in patients with a poor performance status (especially in case of pulmonary comorbidities), in absence of clinically suspected lymph nodes at or above the level of the carina.[1] For that reason, these variables were included in the multivariable Cox regression model of the present study. Based on the long-term results of the HIVEX trial, there was a shift in preferred surgical technique over time for truly esophageal adenocarcinoma from of THE to TTE, which is reflected in the proportions of TTE and THE during the time period of the present study.

It has been reported that nCRT decreases the number of lymph nodes detected in the resection specimen, which is also reflected by the results of the present study.[13-15] Furthermore, in a post-hoc analysis of the CROSS-II trial, the total number of resected nodes was correlated with improved overall survival after surgery alone (HR per 10 additionally resected nodes 0.76, 95% CI 0.61–0.95, p=0.007), which corresponds with the above described retrospective international study.[2, 10] However, this correlation was absent in patients pretreated with nCRT (HR 1.00, 95% CI 0.84–1.25 p=0.98). The randomized design of the CROSS trial excludes selection bias as an explanation for this finding. Therefore, these results question the necessity of extended lymph node dissection in patients treated with nCRT.

The same phenomenon was shown in a recent retrospective propensity matched comparison of 301 patients who underwent perioperative chemotherapy combined with surgery and 307 patients who underwent nCRT followed by surgery. In the nCRT group, total lymph node harvest and survival were not associated. Interestingly, in the perioperative chemotherapy group, the number of resected nodes was positively corre-

lated with progression free survival. These data suggest, that TTE might be beneficial in patients treated with perioperative chemotherapy but not after nCRT.[16] This difference in effect of lymphadenectomy might be explained by the substantial 'sterilizing' effect of radiotherapy on the regional lymph nodes.

If the results of the present analysis can be confirmed in future studies, factors such as the risk for postoperative complications, patient's quality of life and surgeon's preference may determine the choice of surgical approach in patients treated with nCRT, rather than the impact on long-term survival. In the last decade, minimally invasive techniques are increasingly applied in esophageal cancer surgery, with the potential advantage of limitation of surgical trauma, possibly without jeopardizing the potential to perform a radical resection with extensive lymphadenectomy. Although the necessity of the latter is questioned after nCRT by the results of the present and earlier studies, an additional advantage of a thoracic approach is the possibility to perform an intrathoracic anastomosis, instead of the cervical anastomosis that is always required when using the transhiatal technique. Multiple studies have suggested a lower leakage rate after an intrathoracic anastomosis compared to a cervical anastomosis and this is currently being investigated in the Dutch randomized iCAN-trial.[17, 18] Consequently, in the absence of oncological benefit for TTE and if minimally invasive transthoracic techniques can reduce the incidence of postoperative (pulmonary) complications to rates comparable to that of THE, this lower anastomotic leakage rate might be ultimately decisive in the choice of surgical approach after nCRT.

This study has some limitations including its retrospective design. The multivariable Cox regression analysis controlled for important factors that are known to influence the choice of surgical approach and long-term survival. There are probably other confounding factors between the two groups, and both cN status and ASA-classification are subjective parameters. In the surgery-alone group, less patients had clinically suspected lymph nodes and cN stage does not associated with survival, highlighting the limited accuracy of clinical N-staging, particularly in that time period. Nevertheless, addition of cardiovascular and pulmonary comorbidities in the regression model further strengthens the correction for comorbidities, whereas the sensitivity analysis with pN stage (which is more accurate than cN stage) included showed results comparable to the original model. Therefore, we feel that correction for more advanced disease and nodal positivity in the TTE group is adequate. Moreover, the exact location of suspected regional lymph nodes, which may have influenced the choice between TTE and THE, was not available for the included patients. Furthermore, the time period in which these patients were included was relatively long (1996-2013), which might have introduced bias between patients who underwent surgery alone and those who underwent nCRT followed by surgery (*e.g.* improved staging as a result of the introduction of PET-CT, which was performed routinely for cT3 tumors since 2012). To improve homogeneity

between both treatment groups, patients in the surgery alone group were retrospectively selected following the inclusion criteria of CROSS-I and -II trials and year of treatment was included in the Cox regression model.[5, 6, 7]

Conclusion

In conclusion, compared to surgery alone, the addition of nCRT may reduce the need for TTE with extended lymphadenectomy in order to improve long-term survival in patients with subcarinal esophageal adenocarcinoma.

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Table 1a. Pretreatment characteristics in 358 patients with potentially curable subcarinal esophageal adenocarcinoma, treated with surgery alone.

	total		TTE		THE		
	(n= 358)		(n= 107)		(n= 251)		
	1996 – 2009						
	n	(%)*	n	(%)*	n	(%)*	p **
age [years]							<0.01
median (p25 – p75)	63 (56 – 70)		62 (54 – 68)		65 (57 – 72)		
gender							0.49
female	54	(15)	14	(13)	40	(16)	
male	304	(85)	93	(87)	211	(84)	
cT-stage‡							0.02
cT1	4	(2)	1	(1)	3	(1)	
cT2	83	(25)	16	(15)	67	(28)	
cT3	256	(72)	90	(84)	166	(69)	
cT4a	3	(2)	0	(0)	3	(1)	
missing	12		0		12		
cN-stage‡							0.04
cN0	164	(53)	40	(38)	124	(50)	
cN1	188	(47)	65	(62)	123	(50)	
missing	6		2		4		
ASA classification							<0.01
I	66	(16)	29	(28)	37	(15)	
II	233	(66)	66	(64)	167	(67)	
III and IV	52	(17)	8	(8)	44	(18)	
missing	7		4		3		

* Data presented as median (interquartile range) or number (%). Percentages may not add up to 100 due to rounding.

** Data were compared between the surgery alone and nCRT plus surgery groups using Student's t-test for continuous variables and χ^2 test for categorical variables.

‡ Clinical T-stage and N-stage were determined by endoscopic ultrasonography and/or CT-scanning and/or FDG-PET-scanning according to the Union for International Cancer Control (UICC) TNM Cancer Staging, 6th edition.[7]

Table 1b. Pretreatment characteristics in 343 patients with potentially curable subcarinal esophageal adenocarcinoma, treated with neoadjuvant chemoradiotherapy followed by surgery.

	total		TTE		THE		
	(n= 343)		(n= 211)		(n= 132)		
	2001 – 2013						
	n	(%)*	n	(%)*	n	(%)*	p **
age [years]							0.11
median (p25 – p75)	61 (56 – 70)		61 (55 – 69)		64 (56 – 71)		
gender							0.08
female	48	(14)	35	(17)	13	(10)	
male	295	(86)	176	(83)	119	(90)	
cT-stage‡							0.61
cT1	4	(1)	3	(1)	1	(1)	
cT2	69	(21)	42	(21)	27	(21)	
cT3	257	(77)	158	(77)	99	(76)	
cT4a	4	(1)	1	(0)	3	(2)	
missing	9		7		2		
cN-stage‡							0.02
cN0	110	(31)	57	(28)	53	(40)	
cN1	226	(69)	148	(72)	78	(60)	
missing	7		6		1		
ASA classification							0.07
I	70	(21)	50	(24)	20	(15)	
II	210	(63)	126	(62)	84	(64)	
III and IV	56	(17)	29	(14)	27	(21)	
missing	7		6		1		

* Data presented as median (interquartile range) or number (%). Percentages may not add up to 100 due to rounding.

** Data were compared between the surgery alone and nCRT plus surgery groups using Student's t-test for continuous variables and χ^2 test for categorical variables.

‡ Clinical T-stage and N-stage were determined by endoscopic ultrasonography and/or CT-scanning and/or FDG-PET-scanning according to the Union for International Cancer Control (UICC) TNM Cancer Staging, 6th edition.[7]

Table 2. Multivariable Cox regression analysis comparing transthoracic esophagectomy with transhiatal esophagectomy in patients who underwent surgery alone or neoadjuvant chemoradiotherapy (nCRT) followed by surgery including the variables age, gender, ASA-classification, pulmonary and cardiovascular comorbidities, clinical N stage (cN) and pathological T stage (pT).

	surgery alone (n=358) 1996 – 2009			nCRT plus surgery (n=343) 2001 – 2013		
	HR	95% CI	p	HR	95% CI	p
surgical approach						
transhiatal approach	1 (ref)	–	–	1 (ref)	–	–
transthoracic approach	0.77	(0.58 – 1.03)	0.08	1.16	(0.80 – 1.66)	0.44
age	1.01	(1.00 – 1.03)	0.09	1.01	(0.99 – 1.03)	0.32
gender						
male	1 (ref)	–	–	1 (ref)	–	–
female	0.94	(0.66 – 1.33)	0.72	0.86	(0.55 – 1.32)	0.48
ASA						
I	1 (ref)	–	–	1 (ref)	–	–
II	1.00	(0.71 – 1.40)	0.99	1.03	(0.70 – 1.54)	0.86
III and IV	1.12	(0.69 – 1.80)	0.65	1.57	(0.93 – 2.63)	0.09
pulmonary comorbidities						
no	1 (ref)	–	–	1 (ref)	–	–
yes	1.34	(0.93 – 1.92)	0.12	1.25	(0.86 – 1.81)	0.19
cardiovascular comorbidities						
no	1 (ref)	–	–	1 (ref)	–	–
yes	0.88	(0.67 – 1.17)	0.39	1.00	(0.74 – 1.38)	0.97
cN-stage						
cN0	1 (ref)	–	–	1 (ref)	–	–
cN-positive	1.13	(0.88 – 1.47)	0.34	1.50	(1.08 – 2.08)	0.02
(y)pT-stage						
ypT0	–	–	–	1 (ref)	–	–
(y)pT1	1 (ref)	–	–	1.34	(0.81 – 2.20)	0.26
(y)pT2	1.58	(0.87 – 2.89)	0.14	1.36	(0.83 – 2.22)	0.22
(y)pT3/4	4.85	(2.85 – 8.24)	<0.01	1.89	(1.27 – 2.81)	0.02
Year of treatment	0.95	(0.92 – 0.99)	0.01	0.98	(0.93 – 1.04)	0.58

HR: hazard ratio, CI: confidence interval

Table 3. Multivariable Cox regression analysis for disease free survival comparing transthoracic esophagectomy with transhiatal esophagectomy in patients who underwent surgery alone or neoadjuvant chemoradiotherapy (nCRT) followed by surgery including the variables age, gender, ASA-classification, pulmonary and cardiovascular comorbidities, clinical N stage (cN) and pathological T stage (pT).

	surgery alone (n=332*) 1996 – 2009			nCRT plus surgery (n=321*) 2001 – 2013		
	HR	95% CI	p	HR	95% CI	p
surgical approach						
transhiatal approach	1 (ref)	–	–	1 (ref)	–	–
transthoracic approach	0.79	(0.58 – 1.07)	0.13	1.27	(0.85 – 1.91)	0.24
age	1.01	(0.99 – 1.02)	0.41	1.00	(0.98 – 1.02)	0.72
gender						
male	1 (ref)	–	–	1 (ref)	–	–
female	0.93	(0.65 – 1.35)	0.71	0.79	(0.48 – 1.30)	0.35
ASA						
I	1 (ref)	–	–	1 (ref)	–	–
II	0.92	(0.64 – 1.30)	0.62	1.04	(0.67 – 1.60)	0.86
III and IV	1.04	(0.63 – 1.70)	0.89	1.07	(0.58 – 1.99)	0.83
pulmonary comorbidities						
no	1 (ref)	–	–	1 (ref)	–	–
yes	1.25	(0.84 – 1.85)	0.28	1.05	(0.65 – 1.77)	0.82
cardiovascular comorbidities						
no	1 (ref)	–	–	1 (ref)	–	–
yes	0.92	(0.68 – 1.24)	0.57	0.86	(0.60 – 1.22)	0.39
cN-stage						
cN0	1 (ref)	–	–	1 (ref)	–	–
cN-positive	1.05	(0.80 – 1.39)	0.71	1.79	(1.22 – 2.64)	<0.01
(y)pT-stage						
ypT0	–	–	–	1 (ref)	–	–
(y)pT1	1 (ref)	–	–	1.38	(0.67 – 2.52)	0.29
(y)pT2	2.87	(1.23 – 6.71)	0.02	1.54	(0.87 – 2.74)	0.14
(y)pT3/4	7.81	(3.63 – 16.82)	<0.01	2.34	(1.47 – 3.72)	<0.01
Year of treatment	0.96	(0.92 – 1.00)	0.03	0.99	(0.93 – 1.05)	0.68

HR: hazard ratio, CI: confidence interval *26 patients in the surgery alone group and 22 patients in the nCRT group had missing data regarding disease free survival.

References

1. Omloo JM, Lagarde SM, Hulscher JB et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007;246(6):992-1000; discussion -1.
2. Talsma AK, Shapiro J, Looman CW et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. Ann Surg. 2014;260(5):786-93.
3. Shapiro J, van Klaveren D, Lagarde SM et al. Prediction of survival in patients with oesophageal or junctional cancer receiving neoadjuvant chemoradiotherapy and surgery. Br J Surg. 2016;103(8):1039-47.
4. van Meerten E, Muller K, Tilanus HW et al. Neoadjuvant concurrent chemoradiation with weekly paclitaxel and carboplatin for patients with oesophageal cancer: a phase II study. Br J Cancer. 2006;94(10):1389-94.
5. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
6. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
7. Sobin LH, Wittekind C, et al. TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss; 2002.
8. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual (7th ed). New York, NY: Springer; 2010.
9. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer., ebrary Inc. TNM classification of malignant tumors. New York: Wiley-Blackwell; 2009. Available from: http://site.ebrary.com/lib/yale/Doc?id=10342913, last accessed: January 29th, 2018.
10. Peyre CG, Hagen JA, DeMeester SR et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549-56.
11. Davies AR, Sandhu H, Pillai A et al. Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. Br J Surg. 2014;101(5):511-7.
12. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. Ann Surg. 2011;254(6):894-906.
13. Robb WB, Dahan L, Mornex F et al. Impact of neoadjuvant chemoradiation on lymph node status in esophageal cancer: post hoc analysis of a randomized controlled trial. Ann Surg. 2015;261(5):902-8.
14. Taflampas P, Christodoulakis M, Gourtsoyianni S, Leventi K, Melissas J, Tsiftsis DD. The effect of preoperative chemoradiotherapy on lymph node harvest after total mesorectal excision for rectal cancer. Dis Colon Rectum. 2009;52(8):1470-4.
15. Lykke J, Roikjaer O, Jess P, Danish Colorectal Cancer G. Tumour stage and preoperative chemoradiotherapy influence the lymph node yield in stages I-III rectal cancer: results from a prospective nationwide cohort study. Colorectal Dis. 2014;16(4):O144-9.
16. Markar SR, Noordman BJ, Mackenzie H et al. Multimodality treatment for esophageal adenocaricnoma: multi-center european comparative study. Accepted, Ann Oncol. 2016.
17. Biere SS, Maas KW, Cuesta MA, van der Peet DL. Cervical or thoracic anastomosis after esophagectomy for cancer: a systematic review and meta-analysis. Dig Surg. 2011;28(1):29-35.
18. van Workum F, Rosman C. Netherlands Trial Register: NTR4333 2013 [Available from: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4333.

19. Noordman BJ, van Klaveren D, van Berge Henegouwen MI et al. Impact of Surgical Approach on Long-term Survival in Esophageal Adenocarcinoma Patients With or Without Neoadjuvant Chemoradiotherapy. Ann Surg. 2018;267(5):892-7.
20. Macdonald JS, Smalley SR, Benedetti J et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725-30.
21. Lee J, Lim DH, Kim S et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol. 2012;30(3):268-73.
22. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
23. Al-Batran SE, Hofheinz RD, Pauligk C et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17(12):1697-708.

Chapter 8

Effect of neoadjuvant chemoradiotherapy on health-related quality of life in esophageal or junctional cancer: results from the randomized CROSS trial

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Abstract

Purpose

To compare pre-agreed health-related quality of life (HRQOL) domains in patients with esophageal or junctional cancer who received neoadjuvant chemoradiotherapy (nCRT) followed by surgery or surgery alone. Secondary aims were to examine the effect of nCRT on HRQOL before surgery and the effect of surgery on HRQOL.

Patients and Methods

Patients were randomly assigned to nCRT (carboplatin plus paclitaxel with concurrent 41.4-Gy radiotherapy) followed by surgery or surgery alone. HRQOL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (QLQC30) and –Oesophageal Cancer Module (QLQ-OES24) questionnaires pretreatment and at 3, 6, 9, and 12 months postoperatively. The nCRT group also received preoperative questionnaires. Physical functioning (PF; QLQ-C30) and eating problems (EA; QLQ-OES24) were chosen as predefined primary end points. Predefined secondary end points were global QOL (GQOL; QLQ-C30), fatigue (FA; QLQ-C30), and emotional problems (EM; QLQ-OES24).

Results

A total of 363 patients were analyzed. No statistically significant differences in postoperative HRQOL were found between treatment groups. In the nCRT group, PF, EA, GQOL, FA, and EM scores deteriorated 1 week after nCRT (Cohen's d -0.93, $p<0.001$; 0.47, $p<0.001$; -0.84, $p<0.001$; 1.45, $p<0.001$ and 0.32, $p=0.001$, respectively). In both treatment groups, all end points declined 3 months postoperatively compared with baseline (Cohen's d -1.00; 0.33; -0.47; -0.34 and 0.33, resp., all $p<0.001$), followed by a continuous gradual improvement. EA, GQOL, and EM were restored to baseline levels during follow-up, whereas PF and FA remained impaired 1 year postoperatively (Cohen's d 0.52 and -0.53, respectively, both $p<0.001$).

Conclusion

Although HRQOL declined during nCRT, no effect of nCRT was apparent on postoperative HRQOL compared with surgery alone. In addition to the improvement in survival, these findings support the view that nCRT according to the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study–regimen can be regarded as a standard of care.

Introduction

Esophageal cancer is characterized by high recurrence rates and poor 5-year survival after primary surgical resection.[1] To improve the radicality of surgery and long-term survival, many trials on the added value of neoadjuvant therapy have been undertaken.[2-8]

One of the largest and most recent trials is the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study (CROSS). The randomized CROSS trial compared carboplatin plus paclitaxel– based neoadjuvant concurrent chemoradiotherapy (nCRT) regimen plus surgery with surgery alone in patients with esophageal or esophagogastric junctional cancer from eight centers in the Netherlands. Long-term results showed a statistically significant and clinically relevant increase in survival for both squamous cell and adenocarcinoma subtypes, with acceptable toxicity.[9, 10] On the basis of these results, the CROSS regimen is now standard treatment in many countries.

The enhanced emphasis on health-related quality of life (HRQOL) and other patient-reported outcome measures assumes a more prominent role for these factors as end points in clinical cancer trials.[11] An esophagectomy is a major operation with substantial morbidity and mortality and may have a profound effect on patients' QOL.[12-14] However, in the field of esophageal cancer, only limited high-quality data on HRQOL are available. So far, HRQOL data have been reported in two randomized esophageal cancer trials, which compared transthoracic versus transhiatal esophagectomy in patients who underwent primary surgery without neoadjuvant therapy and primary surgery versus definitive CRT.[15, 16] Results from randomized trials in patients with esophageal cancer investigating the effect of combined neoadjuvant therapy and surgery on HRQOL have not yet been published. The available evidence comes from two small observational studies. Both studies suggested that the addition of nCRT to surgery had no influence on postoperative HRQOL, but they were likely influenced by selection bias and lacked statistical power.[17, 18]

The primary aim of this substudy of the CROSS trial, with HRQOL as a secondary end point, was to compare HRQOL in patients with esophageal or junctional cancer who received nCRT plus surgery or surgery alone. Furthermore, the effect of nCRT on HRQOL before surgery and the effect of surgery on HRQOL were examined over time. It was hypothesized that nCRT impairs HRQOL before surgery but does not affect postoperative recovery in terms of HRQOL.

Patients and methods

Details of this randomized trial have been reported previously and are summarized in the Appendix Trial Design (online only).[9, 10, 19]

HRQOL measurement

The self-report questionnaires were mailed after random assignment and 3, 6, 9, and 12 months postoperatively. Postoperative HRQOL was compared between both groups using date of surgery as reference point. Patients who were randomly assigned to the nCRT group also received questionnaires 1 week after nCRT (ie, 3 to 5 weeks before surgery). Cancer-specific HRQOL was measured with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), a validated self-report questionnaire for patients with cancer.[20] Tumor-specific HRQOL was measured by the EORTC QLQ–Oesophageal Cancer Module (QLQ-OES24), because the currently used derivative QLQ-OES18 was not yet available.[21] End points were predefined by consensus discussion with experienced upper-GI surgical oncologists, medical oncologists, and nurse practitioners before analysis of the data. End points were selected based on clinical relevance and hypothesized association with nCRT. This led to the primary end points of physical functioning (PF; QLQ-C30) and eating problems (EA; QLQ-OES24). Secondary end points were defined as global QOL (GQOL; QLQ-C30), fatigue (FA; QLQ-C30), and emotional problems (EM; QLQ-OES24).

Statistical analysis

Data were analyzed on an intention-to-treat basis, with comparison of HRQOL as primary objective. Pretreatment characteristics were compared using the Mann-Whitney or Student's t test for continuous variables and the x2 or Fisher's exact test for categorical data. Questionnaire scores were computed according to EORTC guidelines.[22] Baseline HRQOL scores were compared using the Student's t test. Differential effects over time between treatment groups and longitudinal comparison of the baseline scores and scores from follow-up measurements (3, 6, 9, and 12 months postoperatively) were performed using mixed modeling. If there were no statistically significant differences over time between both groups, baseline scores and scores from the postoperative measurements of both groups were combined to analyze longitudinal HRQOL. Use of mixed modeling enabled the analysis of all data, because it allowed for inclusion of questionnaire scores from patients with different numbers of completed measurements.[23] Therefore, the statistical analyses included data from patients who were unable to complete the questionnaires on one or more occasions and from those who dropped out during the trial. Mean differences over time and differential effects over time between treatment groups were described for statistically significant outcomes. Cohen's d (CD) effect sizes were calculated to give an indication of the clinical relevance of effects and to enable standardized comparison between results from different outcome variables. CD effect sizes were derived from the beta estimates in the mixed modeling procedure through

standardization of both outcome and predictor variables. CD values of 0.2, 0.5, and 0.8 indicate small, medium, and large effects, respectively.[24] Values ≥0.5 were considered clinically relevant.[25] In a separate analysis, recurrence of disease and death in the subsequent time period were included as control variables, which enabled the evaluation of possible effect of recurrence of disease and death on the trajectory of HRQOL scores. Recurrence of disease was defined as the earliest occurrence of disease progression resulting in irresectability, locoregional recurrence (after completion of therapy), or distant dissemination (before, during, or after treatment). To correct for multiple testing, statistical significance was set at $p<0.01$ (the main analyses included five comparisons, and thus, a Bonferroni correction of .05/5 was applied), except for baseline comparisons. For those latter analyses, $p<0.05$ was considered significant. All reported P values are two sided. Statistical analysis was performed using Statistical Package for the Social Sciences software, version 21.0 (SPSS, Chicago, IL).

Results

Of the 368 randomly assigned patients, 363 were included in the HRQOL analysis. Two withdrew consent, two were enrolled in the trial before the HRQOL study started, and one center (which included one patient) did not participate in the HRQOL study (Fig 1). There were no clinically relevant differences in pretreatment characteristics between groups (Table 1). Because of an administrative error, 89 patients did not receive baseline questionnaires (nCRT group, n = 58; surgery-alone group, n = 31). These patients were not excluded, because their baseline characteristics did not differ significantly from the study population (data not shown), and follow-up questionnaires were correctly completed.

Overall response rates at the different measurement points were 54% to 76% and were lower in the surgery-alone group than in the nCRT group (Table 2). At each measurement point, pretreatment characteristics (age, sex, tumor location, cT stage, cN stage, and WHO performance status) of patients who completed the questionnaires were not statistically different between the two groups (data not shown). In the nCRT group, the median time to surgery calculated from the day of last radiation treatment was 46 days (interquartile range, 40 to 55 days). Mean scores of HRQOL domains that were not predefined end points are listed in Table 3.

Predefined primary end points

PF. As shown in Figure 2A, baseline PF levels and all changes over time were comparable between groups ($p=0.60$ and $p=0.18$, respectively). PF declined at 3months postoperatively (-18, $p<0.001$; CD -1.00, 95% CI -1.14 – -0.86) and improved from 3 to 6

months postoperatively (+5, p<0.001; CD 0.30, 95% CI 0.18 – 0.41). From then, the improvement was no longer statistically significant (9 vs. 6 months, p=0.07; 12 vs. 9 months, p=0.27), and baseline levels were not reached during follow-up (-8, p<0.001, CD -0.53, 95% CI -0.67 – -0.39). In the nCRT group, PF declined 1 week after nCRT (-17, p<0.001; CD -0.93, 95% CI -1.12 – -0.74).

EA. As shown in Figure 2B, no statistically significant differences in EA were found at baseline (p=0.20), and changes over time were comparable between groups (p=0.45). Three months postoperatively, EA had worsened in both groups (+8, p<0.001; CD 0.32, 95% CI 0.15 – 0.50) and thereafter improved from 3 to 6 months (-9, p<0.001; CD -0.32, 95% CI -0.44 – -0.20) and from 6 to 9 months (+5, p=0.001; CD -0.22, 95% CI -0.34 – -0.09). In both groups, 6 months postoperatively, EA levels returned to baseline (p=0.98), and no further improvement was found after 12months of follow-up compared with baseline levels (p=0.01). The nCRT group reported a deterioration in EA 1 week after completion of nCRT (+12, p=0.001; CD 0.47, 95% CI 0.21 – 0.72).

Predefined secondary end points.

GQOL. As shown in Figure 2C, baseline GQOL scores and all changes in GQOL over time were comparable between groups (p=0.53 and p=0.76, respectively). GQOL scores significantly declined 3 months postoperatively (-10, P = 0.002; CD -0.47, 95% CI -0.62 – -0.31), improved between 3 and 6 months postoperatively (+4, p=0.001; CD 0.24, 95% CI 0.10 – 0.37), reached baseline levels 9 months postoperatively (p=0.31), and stabilized subsequently (p=0.34). Compared with baseline, patients in the nCRT group reported significantly worse GQOL 1 week after nCRT (-17, p<0.001; CD -0.84, 95% CI -1.08 – -0.60).

FA. As shown in Figure 2D, baseline FA levels were comparable between groups (p=0.42), and there were no statistically significant differences in changes over time (p=.30). Postoperatively, FA levels worsened (+24, p<0.001; CD 1.01, 95% CI 0.86 – 1.16) but subsequently improved in the periods from 3 to 6 months (-8, p<0.001; CD -0.34, 95% CI -0.46 – -0.22). Thereafter, FA levels remained stable from 6 to 9 months (p=0.04) and from 9 to 12 months (p=0.58) but did not return to baseline levels (+10, p<0.001; CD 0.52, 95% CI 0.38 – 0.65). In the nCRT group, a significant deterioration was reported 1 week after nCRT (+34, p<0.001, CD 1.45, 95% CI 1.23 – 1.66).

EM. As shown in Figure 2E, baseline EM scores were comparable between groups (p=0.26), and both groups reported comparable changes over time (p=0.75). Three months postoperatively, EMworsened (+8, p<0.001; CD 0.33, 95% CI 0.18 – 0.49) but improved from 3 to 6 months (-6, p<0.001; CD -0.26, 95% CI -0.40 – -0.13) and from 6 to 9 months (-5, p=0.003; CD -0.22, 95% CI -0.36 – -0.08) postoperatively and stabilized thereafter (9 to 12 months, p=0.74). Baseline levels were reached at 6 months (p=0.39)

and stabilized thereafter (p=0.05). Patients in the nCRT group reported a deterioration in EM 1 week after nCRT (+9, p=0.001; CD 0.32, 95% CI 0.14 – 0.50).

Results of the model including randomized grouping for longitudinal effects are shown in Appendix Tables A1 to A5.

Influence of recurrence of disease and death

Inclusion of recurrence of disease and death as control variables did not influence the overall trends in HRQOL trajectories (data not shown). However, the deterioration and restoration of primary and secondary end points during follow-up were worse for patients who developed recurrent disease and for patientswho died in the subsequent time period (data not shown). Patients in the surgery-alone group who died during follow-up showed themost severe deteriorations, especially in the 6- and 9-month follow-up measures.

Influence of missing baseline questionnaires

Availability of a completed baseline questionnaire was included as control variable. Inclusion of this variable did not influence the described overall trends in HRQOL trajectories (data not shown).

Discussion

This randomized trial did not show statistically significant differences in postoperative HRQOL in patients with esophageal or junctional cancer treated with a multimodality regimen based on carboplatin plus paclitaxel with 41.4 Gy of concurrent radiotherapy plus surgery, compared with patients who underwent surgery alone. Patients in the nCRT group experienced deterioration in all HRQOL end points immediately after completion of nCRT, but this did not affect recovery during the first postoperative year in terms of HRQOL.

In both treatment groups, all primary and secondary HRQOL end points declined postoperatively, but most were restored to pretreatment levels within 1 year postoperatively. GQOL, EA, and EM reached baseline levels 6 months (GQOL and EA) and 9 months postoperatively (EM) and stabilized from then. However, PF and FA levels were not restored to pretreatment levels during the first year of follow-up, and corresponding effect sizes were clinically relevant (CD,-0.53 and 0.52, respectively). The scores of these domains stabilized 6 and 9 months postoperatively, which suggests that further spontaneous improvement to be unlikely.

This study is the first clinical trial and the largest available analysis to our knowledge comparing HRQOL in patients with esophageal cancer who underwent neoadjuvant therapy plus surgery or surgery alone. Two small observational studies have suggested that postoperative HRQOL is not affected by addition of nCRT to surgery, but these studies used different nCRT regimens and were criticized because of the potential influence of selection bias and lack of statistical power.[17, 18] The randomized design of our study largely excludes selection bias, and the relatively large sample size increases the power to detect small but clinically relevant differences. Hence, these results demonstrate more reliably that postoperative HRQOL is not affected by nCRT, thereby confirming the results fromthese previous studies. These findings can help clinicians and patients to make more properly informed treatment decisions, especially patients who fear the negative effect of neoadjuvant treatment. Besides the relatively low toxicity and the strong effect on survival after nCRT plus surgery according to CROSS,[9, 10] the comparable effect on postoperative HRQOL with surgery alone confirms that the benefits of this effective regimen outweigh its harms. Nevertheless, it should be noted that the application of nCRT delays surgery and subsequent postoperative recovery by 2 to 3 months. This delay is substantial, especially for patients who turn out to be nonsurvivors. Furthermore, the long-term effects of adding nCRT to surgery on HRQOL are largely unknown and need to be further explored. Although it has been shown that nCRT containing cisplatin and fluorouracil with 66 Gy of concurrent radiotherapy significantly hampers long-term HRQOL, the CROSS regimen theoretically may have fewer negative effects because of the mild toxicity of the applied chemotherapeutic agents and the relatively low radiation dose.[26]

In line with our study, a profound deterioration in HRQOL scores immediately after completion of nCRT has been described in the phase II CROSS-I trial and other observational studies.[17, 18, 27] This decline in all end points 1 week after completion of nCRT is explained by persisting adverse effects of chemotherapy and radiotherapy, such as anorexia, FA, esophagitis, and hematologic toxicity. This emphasizes the need for sufficient time between nCRT and surgery, which allows patients to recover and reach more optimal physical condition before surgery. Earlier studies have suggested that postponement of surgery to at least 12 weeks after nCRT does not jeopardize long-term oncologic outcome and even tends to increase the pathologic complete response rate, which might improve prognostication.[28, 29] Unfortunately, no HRQOL assessment was performed during nCRT or just before surgery. In clinical practice, we have witnessed general improvements in patients' condition in the period between nCRT and surgery. Therefore, we recommend timing of surgery to be guided by patients' condition, and we advocate that surgery should be postponed to up to 12 weeks after completion of nCRT in case of persisting adverse events or bad general condition. To further optimize the timing of surgery, the course of HRQOL in the period between nCRT and surgery

should be monitored more carefully. On the basis of the available literature and our clinical experience, it seems that HRQOL substantially improves over a period of 6 to 12 weeks.[17]

Although some studies have suggested that the effect of esophagectomy onHRQOL is restored within 1 year postoperatively[15] or can be attributed to only a small group of patients,[30] most studies have shown lasting and substantial negative effects.[13, 14, 31] This is confirmed by the results of our study, in which two of the five end points (ie, PF and FA) did not return to baseline levels during the first year follow-up, and none of the end points improved compared with baseline levels (for patients suffering from esophageal cancer). These effects could only partly be explained by recurrence of disease or death in the subsequent study period, emphasizing the adverse effect of esophagectomy on HRQOL. Cognitive behavioral therapy, which was not routinely offered in our study, might be successful in treating patients with lasting FA.[32] Furthermore, new treatment strategies, such as minimally invasive esophagectomy and an active surveillance approach after nCRT (instead of standard surgery), might improve HRQOL in these patients.[33, 34]

Limitations of this study include overall attrition and lower response rates in the surgery-alone group than in the nCRT group. Attrition is inevitable in HRQOL studies with severely ill patients. Nevertheless, at each measurement point, pretreatment prognostic parameters of patients who completed the questionnaires were comparable between the two treatment groups, suggesting the effect of attrition bias to be small. Lower response rates in the surgery-alone group might be explained by primary surgery being standard treatment during the performance of the trial. Consequently, patients in the surgery-alone group could have been less motivated to complete HRQOL questionnaires than patients in the experimental nCRT group. Another possible explanation is the increasing rate of recurrence being more common in the surgeryalone group.

Because of the relatively low number of older patients (patients age ≥76 years were excluded from the trial) and patients with poorer performance status (patients with WHO 2 were also excluded), results from this study cannot be generalized to these specific categories of vulnerable patients. The effect of this treatment regimen on HRQOL will need to be tested for these subgroups of patients in future studies.

Furthermore, it has been pointed out previously that patients who receive neoadjuvant treatment may report better recovery from surgery, as a result of adjustments to toxicity as experienced during neoadjuvant treatment leading to a re-evaluation of internal standards (ie, response shift). In our study, it was not possible to correct for this potential effect.[17]

Finally, although formally validated, sensitivity of HRQOL questionnaires remains uncertain, and these questionnaires might be too crude to detect small but clinically

relevant differences. To optimize precision, both generic and disease-specific questionnaires were used, and together with the large sample size of the current trial, we expect sensitivity to be relatively high compared with that of earlier studies on this topic. Of note, the QLQ-OES24 questionnaire has been refined into the QLQ-OES18, with revision of the hypothesized scales and the removal of two single items. We do not believe this invalidates the results of our study, because the EA scale was retained in its original form. The EM scale showed modest to high correlations within all validation analyses but was deleted because of overlap with the QLQ-C30 questionnaire.[21]

In conclusion, although HRQOL declined immediately after nCRT, no effect of nCRT according to CROSS was apparent on postoperative short-term HRQOL compared with surgery alone. In addition to the earlier described improvement in long-term overall and disease-free survival, these results support the view that nCRT according to this effective regimen should be regarded as a standard of care for patients with locally advanced resectable esophageal or esophagogastric junctional cancer.

Table 1. Baseline characteristics of patients with potentially curable esophageal or esophagogastric junction cancer, according to treatment group.*

Characteristic	nCRT plus surgery (N = 177)	Surgery alone (N = 186)
Age — yr.		
Median	60	60
IQR	55 - 67	54 - 66
Male sex — no. (%)	134 (76)	151 (81)
Tumor type — no. (%)		
Adenocarcinoma	134 (76)	140 (75)
Squamous-cell carcinoma	40 (23)	42 (23)
Large cell undifferentiated	3 (2)	4 (2)
Tumor location — no. (%)†		
Esophagus		
Proximal third	4 (2)	4 (2)
Middle third	24 (14)	23 (12)
Distal third	104 (59)	107 (58)
Esophagogastric junction	39 (22)	48 (26)
Missing data	6 (3)	4 (2)
Clinical T stage — no. (%)‡		
cT1	1 (1)	1 (1)
cT2	26 (15)	35 (19)
cT3	149 (84)	145 (78)
cT4§	0	1 (1)
Could not be determined¶	1 (1)	4 (2)
Clinical N stage — no. (%)‖		
N0	59 (33)	58 (31)
N1	115 (65)	118 (63)
Could not be determined¶	3 (2)	10 (5)
WHO performance status — no. (%)**		
0	144 (81)	161 (87)
1	33 (19)	25 (13)

* Percentages may not add up to 100 because of rounding.

† Tumor length and location were determined by means of endoscopy.

‡ Clinical tumor (cT) stage was assessed by means of endoscopic ultrasonography or computed tomography (CT) and was classified according to the International Union against Cancer (UICC) tumor–node–metastasis (TNM) classification, 6th edition.

§ One patient was originally staged as cT3 stage but revised to cT4 based on central revision of all endoscopy reports.[9]

¶ This category included patients in whom the tumor could not be fully investigated by means of a transducer for endoscopic ultrasonography owing to a stenosis caused by the tumor.

‖ Clinical lymph-node (N) stage was assessed by means of endoscopic ultrasonography, CT, or 18F-fluorodeoxyglucose positron-emission tomography and was classified according to UICC TNM classification, 6th edition.

** WHO performance status scores are on a scale of 0 to 5, with lower numbers indicating better performance status; 0 indicates fully active, and 1 unable to carry out heavy physical work.

IQR, interquartile range; nCRT, neoadjuvant chemoradiotherapy; WHO, World Health Organization.

Table 2. Patients eligible for quality of life assessment, returning the quality of life questionnaire, deceased, not returning the quality of life questionnaire because they were too ill or because of random reasons at each measurement point.

Status	Baseline	Post-nCRT	3 months postop	6 months postop	9 months postop	12 months postop
Eligible	363	177	342	308	285	260
nCRT + surgery	177	177	163	151	145	136
surgery alone	186		179	157	140	124
Returned total (% of eligible)	235 (65)	104 (59)	228 (67)	210 (68)	185 (65)	166 (64)
nCRT + surgery (%)	134 (76)	104 (59)	119 (73)	113 (75)	103 (71)	94 (69)
surgery alone (%)	101 (54)	NA	109 (61)	97 (62)	82 (59)	72 (58)
Deceased	0	0	21	55	78	103
Too ill	0	24	38	27	36	32
Randomly missing / other	128*	49	76	71	64	62

NA, not applicable; nCRT, neoadjuvant chemoradiotherapy.
*(of whom 89 due to administrative error)

Table 3. Mean scores for all domains in the two EORTC questionnaires that were not predefined endpoints according to treatment group.

	baseline		post-nCRT		3 months postop		6 months postop		9 months postop		12 months postop	
	surgery alone	nCRT	surgery alone	nCRT	surgery alone	nCRT	surgery alone	nCRT	surgery alone	nCRT	surgery alone	nCRT
QLQ-C30												
Functional scales												
Role	85(22)	88(24)	NA	57(29)	55(32)	60(30)	68(29)	68(30)	73(26)	76(28)	78(24)	77(27)
Emotional	71(20)	71(21)	NA	74(21)	75(24)	78(21)	76(22)	80(23)	80(18)	82(19)	77(20)	83(20)
Cognitive	89(16)	93(15)	NA	84(21)	82(21)	82(22)	85(18)	85(17)	84(18)	86(17)	84(19)	87(19)
Social	85(20)	87(20)	NA	77(24)	68(27)	69(28)	75(25)	80(21)	78(25)	84(22)	83(23)	85(23)
Symptom scores			NA									
Nausea and vomiting	12(20)	8(14)	NA	22(28)	21(24)	19(23)	13(20)	21(24)	12(18)	13(18)	11(16)	12(19)
Pain	14(20)	14(20)	NA	31(29)	23(28)	17(23)	21(25)	17(24)	15(24)	13(22)	17(20)	11(19)
Dyspnea	10(20)	5(12)	NA	20(26)	26(27)	28(29)	22(27)	24(26)	22(26)	18(23)	16(22)	17(24)
Insomnia	20(28)	23(26)	NA	29(31)	26(31)	22(30)	22(26)	20(28)	26(30)	15(23)	19(26)	17(26)
Loss of appetite	14(24)	13(25)	NA	41(36)	30(33)	34(33)	18(27)	24(33)	13(25)	12(20)	13(22)	14(24)
Constipation	6(15)	8(19)	NA	24(33)	13(26)	9(23)	10(19)	6(17)	9(20)	6(16)	10(22)	9(20)
Diarrhea	5(12)	2(10)	NA	14(26)	21(27)	21(28)	22(26)	20(25)	16(22)	17(23)	17(21)	15(23)
Financial worries	6(17)	9(20)	NA	8(19)	10(20)	12(24)	14(24)	13(21)	9(18)	13(20)	13(24)	12(22)
QLQ-OES24												
Dysphagia	62(34)	64(35)	NA	53(32)	70(31)	74(28)	79(29)	75(30)	75(33)	76(30)	74(34)	77(29)
Deglutition	16(23)	15(24)	NA	14(20)	19(23)	21(23)	15(24)	13(21)	18(26)	15(21)	13(20)	15(23)
Swallowing of saliva	17(30)	18(31)	NA	18(29)	18(31)	18(30)	15(29)	11(26)	17(30)	16(29)	12(22)	15(27)

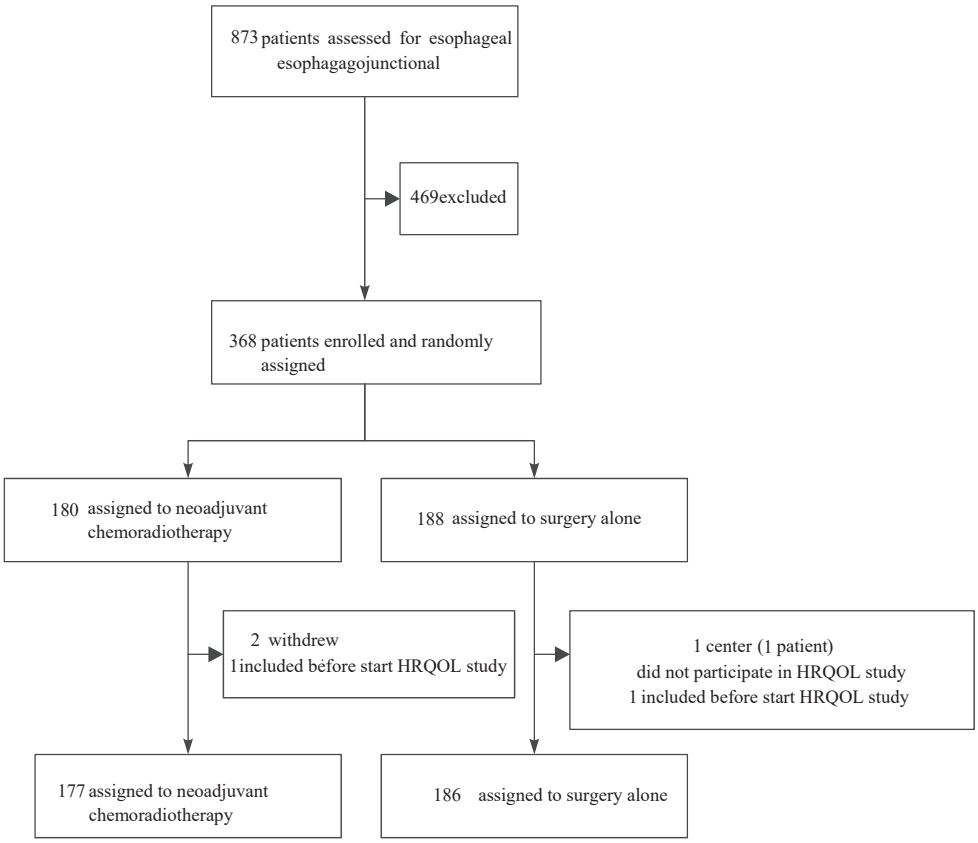
Table 3. continued

	baseline		post-nCRT		3 months postop		6 months postop		9 months postop		12 months postop	
	surgery alone	nCRT	surgery alone	nCRT	surgery alone	nCRT	surgery alone	nCRT	surgery alone	nCRT	surgery alone	nCRT
QLQ-OES24												
Aspiration	13(23)	13(24)	NA	9(19)	19(25)	23(26)	16(25)	15(23)	17(25)	15(21)	14(23)	16(23)
GI symptoms (24)	22(19)	15(15)	NA	21(19)	23(21)	18(18)	22(19)	20(18)	21(21)	21(20)	24(23)	20(21)
GI symptoms (18)	9(19)	7(16)	NA	16(23)	17(26)	12(20)	18(23)	17(22)	18(24)	20(24)	21(25)	18(24)
Pain	23(24)	18(21)	NA	32(25)	12(16)	12(19)	12(18)	11(13)	11(17)	11(19)	12(19)	8(13)
Dry mouth	14(24)	9(20)	NA	25(31)	19(29)	21(30)	13(24)	21(26)	16(25)	20(31)	18(24)	16(24)
Trouble with taste	10(23)	7(21)	NA	37(37)	24(33)	24(33)	13(26)	14(25)	13(24)	11(24)	13(23)	9(21)
Trouble with coughing	16(22)	13(21)	NA	31(31)	37(34)	41(35)	29(29)	25(30)	29(29)	24(27)	22(24)	16(20)
Trouble with speaking	6(17)	4(16)	NA	6(17)	19(28)	18(29)	11(25)	11(25)	13(28)	11(25)	14(28)	11(25)
Hair loss	0(0)	0(0)	NA	24(29)	8(24)	23(34)	24(25)	18(30)	29(37)	26(40)	19(26)	15(29)

Scores are presented as mean. Standard deviations are shown between parentheses.

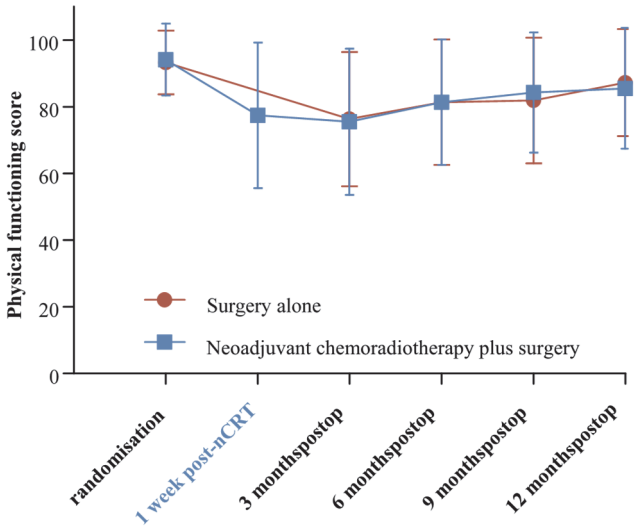
EORTC, European Organisation for Research and Treatment of Cancer; NA, not applicable; nCRT, neoadjuvant chemoradiotherapy; QLQ-C30, Quality of Life Questionnaire–Core 30; QLQ-OES24, Quality of Life Questionnaire–Oesophageal Cancer Module; SD, standard deviation.

Figure 1. CONSORT diagram.

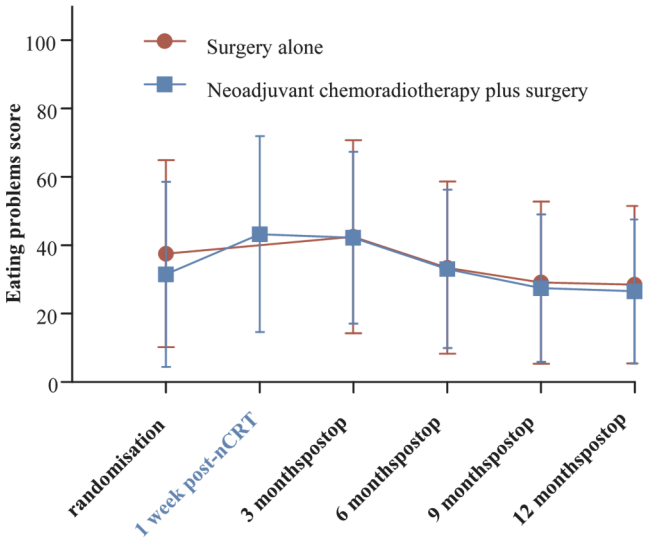


HRQOL, health related quality of life

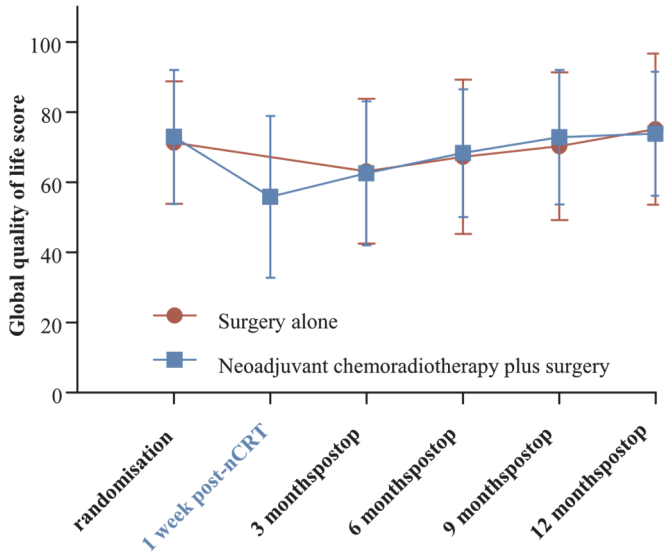
Figure 2. Mean scores with standard deviations for primary endpoints (A) physical functioning, (B) eating problems and secondary endpoints (C) global quality of life, (D) fatigue and (E) emotional problems according to treatment group. nCRT, neoadjuvant chemoradiotherapy



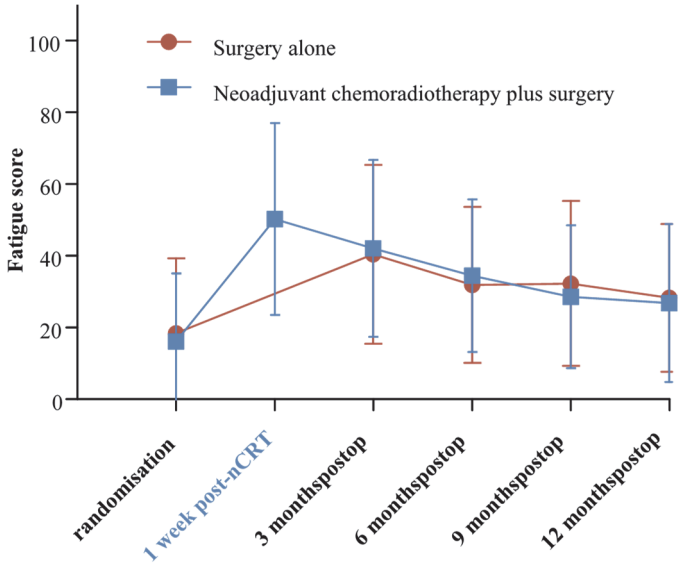
A



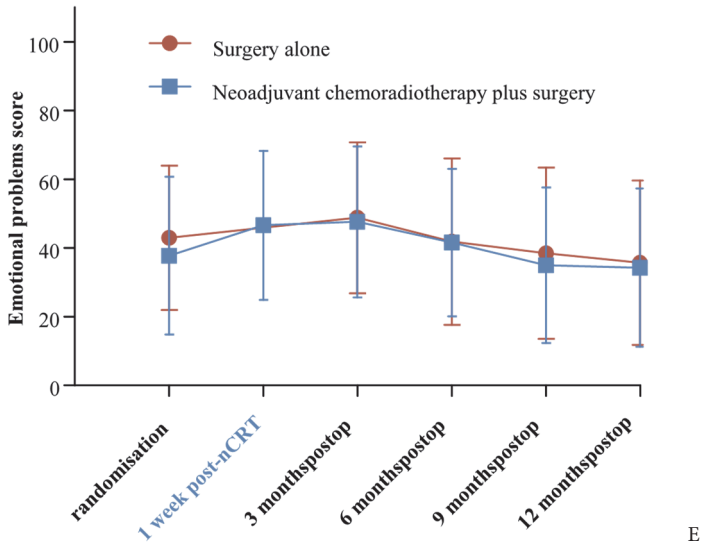
B


Global quality of life score
100
80
60
40
20
0
Surgery alone
Neoadjuvant chemoradiotherapy plus surgery
randomisation
1 week post-nCRT
3 monthspostop
6 monthspostop
9 monthspostop
12 monthspostop

C


Fatigue score
100
80
60
40
20
0
Surgery alone
Neoadjuvant chemoradiotherapy plus surgery
randomisation
1 week post-nCRT
3 monthspostop
6 monthspostop
9 monthspostop
12 monthspostop

D


Surgery alone
Neoadjuvant chemoradiotherapy plus surgery
Emotional problems score
100
80
60
40
20
0
randomisation
1 week post-nCRT
3 monthspostop
6 monthspostop
9 monthspostop
12 monthspostop

E

Appendix

Supplementary Table 1. Mixed modeling analysis including randomized grouping for longitudinal effects on physical functioning.

Parameter	Cohen's d	p-value	95% Confidence Interval
Baseline scores for nCRT group	0.56	<0.001	0.47 to 0.65
Difference for surgery alone	-0.04	0.598	-0.18 to 0.10
Comparison with baseline			
1 week post-nCRT (nCRT)	-0.93	<0.001	-1.12 to -0.74
3 months postop (nCRT)	-1.09	<0.001	-1.29 to -0.90
Difference for surgery alone	0.21	0.157	-0.08 to 0.49
6 months postop (nCRT)	-0.70	<0.001	-0.89 to -0.52
Difference for sugery alone	0.01	0.968	-0.27 to 0.28
9 months postop (nCRT)	-0.53	<0.001	-0.72 to -0.35
Difference for surgery alone	-0.15	0.287	-0.43 to 0.13
12 months postop (nCRT)	-0.51	<0.001	-0.69 to -0.32
Difference for surgery alone	-0.05	0.717	-0.34 to 0.23
Comparison with previous measurement			
3 months postop (nCRT)	-0.16	0.164	-0.38 to 0.07
6 months postop (nCRT)	0.39	<0.001	0.24 to 0.54
Difference for surgery alone	-0.20	0.079	-0.43 to 0.02
9 months postop (nCRT)	0.17	0.022	0.02 to 0.32
Difference for surgery alone	-0.16	0.159	-0.38 to 0.06
12 months postop (nCRT)	0.03	0.730	-0.14 to 0.19
Difference for surgery alone	0.10	0.430	-0.15 to 0.35

*Cohen's D effect-sizes were derived from the beta-estimates in the mixed modelling procedure through standardization of both outcome and predictor variables. Results from different models were combined into one table (per outcome measure) for reasons of conciseness. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as "difference for surgery alone".
nCRT, neoadjuvant chemoradiotherapy

Supplementary Table 2. Mixed modeling analysis including randomized grouping for longitudinal effects on global health status.

Parameter	Cohen's d	p-value	95% Confidence Interval
Baseline scores for nCRT group	0.22	0.004	0.07 to 0.37
Difference for surgery alone	-0.07	0.533	-0.30 to 0.16
Comparison with baseline			
1 week post-nCRT (nCRT)	-0.84	<0.001	-1.08 to -0.60
3 months postop (nCRT)	-0.52	<0.001	-0.72 to -0.31
Difference for surgery alone	0.11	0.467	-0.19 to 0.42
6 months postop (nCRT)	-0.21	0.058	-0.42 to 0.01
Difference for sugery alone	-0.04	0.801	-0.36 to 0.28
9 months postop (nCRT)	-0.06	0.574	-0.29 to 0.16
Difference for surgery alone	-0.05	0.776	-0.39 to 0.29
12 months postop (nCRT)	-0.04	0.729	-0.27 to 0.19
Difference for surgery alone	0.05	0.799	-0.31 to 0.40
Comparison with previous measurement			
3 months postop (nCRT)	0.33	0.008	0.09 to 0.57
6 months postop (nCRT)	0.31	0.001	0.13 to 0.49
Difference for surgery alone	-0.16	0.255	-0.42 to 0.11
9 months postop (nCRT)	0.14	0.145	-0.05 to 0.34
Difference for surgery alone	-0.01	0.958	-0.30 to 0.28
12 months postop (nCRT)	0.02	0.792	-0.15 to 0.20
Difference for surgery alone	0.09	0.491	-0.18 to 0.37

*Cohen's D effect-sizes were derived from the beta-estimates in the mixed modelling procedure through standardization of both outcome and predictor variables. Results from different models were combined into one table (per outcome measure) for reasons of conciseness. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as "difference for surgery alone".

nCRT, neoadjuvant chemoradiotherapy

Supplementary Table 3. Mixed modeling analysis including randomized grouping for longitudinal effects on fatigue.

Parameter	Cohen's d	p-value	95% Confidence Interval
Baseline scores for nCRT group	-0.63	<0.001	-0.76 to -0.49
Difference for surgery alone	0.08	0.421	-0.12 to 0.29
Comparison with baseline			
1 week post-nCRT (nCRT)	1.45	<0.001	1.23 to 1.67
3 months postop (nCRT)	1.12	<0.001	0.91 to 1.32
Difference for surgery alone	-0.23	0.137	-0.53 to 0.07
6 months postop (nCRT)	0.74	<0.001	0.54 to 0.93
Difference for sugery alone	-0.14	0.331	-0.44 to 0.15
9 months postop (nCRT)	0.53	<0.001	0.34 to 0.72
Difference for surgery alone	0.05	0.754	-0.25 to 0.34
12 months postop (nCRT)	0.49	<0.001	0.31 to 0.68
Difference for surgery alone	0.05	0.723	-0.23 to 0.33
Comparison with previous measurement			
3 months postop (nCRT)	-0.33	0.002	-0.54 to 0.12
6 months postop (nCRT)	-0.38	<0.001	-0.54 to -0.22
Difference for surgery alone	0.08	0.487	-0.15 to 0.32
9 months postop (nCRT)	-0.21	0.010	-0.37 to -0.05
Difference for surgery alone	0.19	0.119	-0.05 to 0.43
12 months postop (nCRT)	-0.03	0.656	-0.19 to 0.12
Difference for surgery alone	0.00	0.970	-0.23 to 0.24

*Cohen's D effect-sizes were derived from the beta-estimates in the mixed modelling procedure through standardization of both outcome and predictor variables. Results from different models were combined into one table (per outcome measure) for reasons of conciseness. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as "difference for surgery alone".
nCRT, neoadjuvant chemoradiotherapy

Supplementary Table 4. Mixed modeling analysis including randomized grouping for longitudinal effects on emotional problems.

Parameter	Cohen's d	p-value	95% Confidence Interval
Baseline scores for nCRT group	-0.09	0.262	-0.26 to 0.07
Difference for surgery alone	0.18	0.159	-0.07 to 0.43
Comparison with baseline			
1 week post-nCRT (nCRT)	0.32	0.001	0.14 to 0.50
3 months postop (nCRT)	0.40	<0.001	0.19 to 0.61
Difference for surgery alone	-0.15	0.346	-0.46 to 0.16
6 months postop (nCRT)	0.14	0.215	-0.08 to 0.36
Difference for sugery alone	-0.15	0.362	-0.48 to 0.18
9 months postop (nCRT)	-0.14	0.218	-0.37 to 0.09
Difference for surgery alone	0.00	0.992	-0.35 to 0.35
12 months postop (nCRT)	-0.14	0.210	-0.36 to 0.08
Difference for surgery alone	-0.06	0.712	-0.40 to 0.28
Comparison with previous measurement			
3 months postop (nCRT)	0.08	0.459	-0.13 to 0.28
6 months postop (nCRT)	-0.26	0.006	-0.45 to -0.07
Difference for surgery alone	0.00	0.989	-0.28 to 0.27
9 months postop (nCRT)	-0.28	0.003	-0.47 to -0.10
Difference for surgery alone	0.15	0.295	-0.13 to 0.43
12 months postop (nCRT)	0.00	0.982	-0.19 to 0.19
Difference for surgery alone	-0.06	0.675	-0.36 to 0.23

*Cohen's D effect-sizes were derived from the beta-estimates in the mixed modelling procedure through standardization of both outcome and predictor variables. Results from different models were combined into one table (per outcome measure) for reasons of conciseness. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as "difference for surgery alone".

nCRT, neoadjuvant chemoradiotherapy

Supplementary Table 5. Mixed modeling analysis including randomized grouping for longitudinal effects on eating problems.

Parameter	Cohen's d	p-value	95% Confidence Interval
Baseline scores for nCRT group	-0.10	0.294	-0.28 to 0.09
Difference for surgery alone	0.21	0.136	-0.07 to 0.49
Comparison with baseline			
1 week post-nCRT (nCRT)	0.47	0.001	0.21 to 0.72
3 months postop (nCRT)	0.43	0.001	0.19 to 0.68
Difference for surgery alone	-0.25	0.177	-0.61 to 0.11
6 months postop (nCRT)	0.07	0.582	-0.17 to 0.30
Difference for sugery alone	-0.15	0.403	-0.50 to 0.20
9 months postop (nCRT)	-0.13	0.267	-0.37 to 0.10
Difference for surgery alone	-0.19	0.283	0.55 to 0.16
12 months postop (nCRT)	-0.21	0.086	-0.45 to 0.03
Difference for surgery alone	-0.05	0.774	-0.42 to 0.31
Comparison with previous measurement			
3 months postop (nCRT)	-0.03	0.816	-0.30 to 0.23
6 months postop (nCRT)	-0.37	<0.001	-0.53 to -0.21
Difference for surgery alone	0.10	0.422	-0.14 to 0.33
9 months postop (nCRT)	-0.20	0.022	-0.37 to -0.03
Difference for surgery alone	-0.04	0.741	-0.30 to 0.21
12 months postop (nCRT)	-0.08	0.280	-0.22 to 0.07
Difference for surgery alone	0.14	0.212	-0.08 to 0.36

*Cohen's D effect-sizes were derived from the beta-estimates in the mixed modelling procedure through standardization of both outcome and predictor variables. Results from different models were combined into one table (per outcome measure) for reasons of conciseness. Differences between the two treatment groups at baseline measurement and differences in change between measurements are referred to as "difference for surgery alone".

nCRT, neoadjuvant chemoradiotherapy

References

1. Hulscher JB, van Sandick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662-9.
2. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062-7.
3. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
4. Kelsen DP, Ginsberg R, Pajak TF et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med. 1998;339(27):1979-84.
5. Mariette C, Dahan L, Mornex F et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32(23):2416-22.
6. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
7. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335(7):462-7.
8. Ychou M, Boige V, Pignon JP et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-21.
9. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
10. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
11. Vodicka E, Kim K, Devine EB, Gnanasakthy A, Scoggins JF, Patrick DL. Inclusion of patient-reported outcome measures in registered clinical trials: Evidence from ClinicalTrials.gov (2007-2013). Contemp Clin Trials. 2015;43:1-9.
12. De Boer AG, Genovesi PI, Sprangers MA, Van Sandick JW, Obertop H, Van Lanschot JJ. Quality of life in long-term survivors after curative transhiatal oesophagectomy for oesophageal carcinoma. Br J Surg. 2000;87(12):1716-21.
13. Djarv T, Lagergren J, Blazeby JM, Lagergren P. Long-term health-related quality of life following surgery for oesophageal cancer. Br J Surg. 2008;95(18581441):1121-6.
14. Scarpa M, Valente S, Alfieri R et al. Systematic review of health-related quality of life after esophagectomy for esophageal cancer. World journal of gastroenterology : WJG. 2011;17(42):4660-74.
15. de Boer AG, van Lanschot JJ, van Sandick JW et al. Quality of life after transhiatal compared with extended transthoracic resection for adenocarcinoma of the esophagus. J Clin Oncol. 2004;22(20):4202-8.
16. Teoh AY, Yan Chiu PW, Wong TC, Liu SY, Hung Wong SK, Ng EK. Functional performance and quality of life in patients with squamous esophageal carcinoma receiving surgery or chemoradiation: results from a randomized trial. Ann Surg. 2011;253(1):1-5.
17. Blazeby JM, Sanford E, Falk SJ, Alderson D, Donovan JL. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. Cancer. 2005;103(9):1791-9.
18. Reynolds JV, McLaughlin R, Moore J, Rowley S, Ravi N, Byrne PJ. Prospective evaluation of quality of life in patients with localized oesophageal cancer treated by multimodality therapy or surgery alone. Br J Surg. 2006;93(9):1084-90.

19. van Heijl M, van Lanschot JJ, Koppert LB et al. Neoadjuvant chemoradiation followed by surgery versus surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus (CROSS). BMC Surg. 2008;8:21.
20. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
21. Blazeby JM, Conroy T, Hammerlid E et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. Eur J Cancer. 2003;39(10):1384-94.
22. Fayers PM, Aaronson NK, Bjordal K et al. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
23. Twisk J, de Vente W. Attrition in longitudinal studies. How to deal with missing data. J Clin Epidemiol. 2002;55(4):329-37.
24. Cohen J. Statistical power analysis for the behavorial sciences. 2nd ed. Hillsdale, New Jersey: Erlbaum; 1988.
25. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582-92.
26. Hurmuzlu M, Aarstad HJ, Aarstad AK, Hjermstad MJ, Viste A. Health-related quality of life in long-term survivors after high-dose chemoradiotherapy followed by surgery in esophageal cancer. Dis Esophagus. 2011;24(1):39-47.
27. van Meerten E, van der Gaast A, Looman CW, Tilanus HW, Muller K, Essink-Bot ML. Quality of life during neoadjuvant treatment and after surgery for resectable esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2008;71(1):160-6.
28. Ruol A, Rizzetto C, Castoro C et al. Interval between neoadjuvant chemoradiotherapy and surgery for squamous cell carcinoma of the thoracic esophagus: does delayed surgery have an impact on outcome? Ann Surg. 2010;252(5):788-96.
29. Shapiro J, van Hagen P, Lingsma HF et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. Ann Surg. 2014;260(5):807-14.
30. Derogar M, Lagergren P. Health-related quality of life among 5-year survivors of esophageal cancer surgery: a prospective population-based study. J Clin Oncol. 2012;30(4):413-8.
31. Lagergren P, Avery KN, Hughes R et al. Health-related quality of life among patients cured by surgery for esophageal cancer. Cancer. 2007;110(3):686-93.
32. Gielissen MF, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. J Clin Oncol. 2006;24(30):4882-7.
33. Biere SS, van Berge Henegouwen MI, Maas KW et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet. 2012;379(9829):1887-92.
34. Taketa T, Xiao L, Sudo K et al. Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology. 2013;85(2):95-9.

Chapter 9

Quality of life during and after completion of neoadjuvant chemoradiotherapy for oesophageal and junctional cancer

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Abstract

Background

Knowledge about the course of health-related quality of life (HRQOL) during and after completion of neoadjuvant chemoradiotherapy (nCRT) for oesophageal or junctional carcinoma is needed to optimize the timing of surgery. This study aimed to assess the course of HRQOL in the period from the start of nCRT until standard surgery.

Patients and methods

This was a multicentre prospective cohort study. Patients with locally advanced oesophageal or oesophago-gastric junctional cancer who were planned for nCRT plus oesophagectomy were eligible. HRQOL was measured with the EORTC-QLQ-C30, QLQ-OG25 and QLQ-CIPN20 questionnaires before nCRT, during the last cycle of nCRT, and 2, 4, 6, 8, 10, 12, 14, and 16 weeks after nCRT and before surgery. Endpoints were predefined, based on the hypothesized impact of nCRT. Primary endpoints were physical functioning, odynophagia and sensory symptoms. Secondary endpoints were global quality of life, fatigue, weight loss and motor symptoms. Mixed modelling analysis was used to evaluate changes over-time.

Results

Ninety-six of 106 eligible patients (91%) were included. Returned questionnaires ranged from 94%-99% until week 12 and dropped to 78% in week 16 following nCRT. There was a profound negative impact of nCRT on all HRQOL-endpoints during the last cycle of nCRT (all $p<0.001$) and at two weeks after nCRT (all $p<0.001$). Physical functioning, odynophagia and sensory symptoms were restored to pre-treatment levels at 8, 4 and 6 weeks after nCRT, respectively. Secondary endpoints were restored to baseline levels at 4-6 weeks after nCRT. Odynophagia, fatigue and weight loss improved after nCRT, as compared to baseline levels at 6 ($p<0.001$), 16 ($p=0.001$) and 12 weeks ($p<0.001$), respectively.

Conclusion

HRQOL decreases significantly after completion of nCRT for oesophageal cancer, but all HRQOL endpoints are restored to baseline levels within 8 weeks. Odynophagia, fatigue and weight loss improved after 6-16 weeks following nCRT, compared to baseline levels.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is a standard of care for patients with potentially curable oesophageal or oesophagogastric junctional cancer.[1, 2] Although oesophagectomy has profound impact on both long-term and short-term patients' health related quality of life (HRQOL), addition of nCRT to surgery does not jeopardize HRQOL after surgery, compared to surgery alone.[3, 4] However, immediately after completion of nCRT (prior to surgery), patients show a profound drop in HRQOL compared to baseline levels.[3, 5, 6] This deterioration improves after surgery, suggesting that HRQOL is restored in the period between completion of nCRT and surgery.[3, 5] However, the detailed course of HRQOL during and after completion of nCRT is unknown. Such information might impact the timing of surgery, which is under debate. Traditionally, surgery is planned 4-6 weeks after completion of nCRT. However, it has been shown that a longer time to surgery (up to 12 weeks) does not endanger oncological outcome.[7] Increasing the time to surgery would allow patients to recover from nCRT and optimize their physical condition before surgery. Furthermore, a longer waiting time to surgery has been suggested to increase pathologically complete response (i.e. no viable tumour cells in the resection specimen) rate, which might improve prognostication.[7]

The primary aim of this study was to assess the course of HRQOL in the period from the start of nCRT until surgery in patients with locally advanced oesophageal or junctional carcinoma.

Methods

This was a multicentre prospective cohort study. Patients with locally advanced oesophageal or oesophago-gastric junctional cancer who were planned to undergo nCRT according to the CROSS regimen (weekly administration of carboplatin and paclitaxel plus 41.4 Gy concurrent radiotherapy) were considered eligible.[1] Patients who were considered insufficiently fluent in the Dutch language or cognitively unable to understand the questionnaire were excluded. Consecutive patients were recruited prior to the start of nCRT in the Erasmus MC – University Medical Centre, Rotterdam and in the Elisabeth-Tweesteden Hospital, Tilburg. The study was approved by the ethics committee of the Erasmus MC (MEC-2016-250).

Health-related quality of life measurement

Patients were informed about the study by their own physician. Subsequently, patients were asked to participate by telephone by one of the investigators. Participating patients

received the self-report questionnaires by mail and were asked by telephone to complete questionnaires at baseline (prior to nCRT), at the date of the last cycle of nCRT, and every two weeks thereafter until the date of surgery, with a maximum follow-up of 16 weeks after completion of nCRT. All patients were reminded two times by telephone by one of the investigators during each assessment.

Cancer-related general HRQOL was measured with the EORTC-QLQ-C30, a validated questionnaire for cancer patients.[8] Oesophageal cancer-specific HRQOL was assessed with the EORTC-QLQ-OG25, a validated questionnaire for patients with cancer of the oesophagus, the oesophago-gastric junction and the stomach.[9] Chemotherapy-induced peripheral neuropathy (CIPN) symptoms were assessed using the EORTC-QLQ-CIPN20, a questionnaire designed to elicit patients' experience of symptoms related to CIPN.[10]

Prior to the start of the study, endpoints were defined by individual consensus discussion with upper-GI surgical oncologists, medical oncologists and nurse practitioners. Primary and secondary endpoints from each questionnaire were chosen based on hypothesized impact of nCRT. This led to assignment of physical functioning (EORTC-QLQ-C30), odynophagia (EORTC-QLQ-OG-25) and sensory symptoms (EORTC-QLQ-CIPN20) as primary endpoints; and global quality of life, fatigue (both QLQ-C30), weight loss (EORTC-QLQ-OG25) and motor symptoms (EORTC-QLQ-CIPN20) as secondary endpoints.

Statistical analysis

Data were analysed on intention-to-treat basis. Pre-treatment clinicopathological characteristics were collected and described. Questionnaire scores were transformed into a 0-100 scale according to EORTC-guidelines.[11] Higher scores for functional and global scales (e.g. physical functioning and global quality of life) indicate better HRQOL. Higher scores on symptom scales (e.g. fatigue) indicate worse HRQOL. Over-time changes in the follow-up measurements were analysed using mixed modelling analysis, a technique that enables analysis of all completed questionnaires, by allowing for inclusion of data from patients with different numbers of completed measurements.[12] Mean over-time differences were described. Cohen's d (CD) effect sizes based on the beta-estimates from the mixed modelling analyses were used to allow for standardized comparison between different endpoints and to assess clinical relevance of the found effects. CD values of 0.2, 0.5 and 0.8 indicate small, medium and large effects, respectively.[13] Effect sizes ≥0.5 were defined as clinically relevant.[14]

On an exploratory basis, we investigated the effects of several background variables on the trajectory of HRQOL-scores. As the investigated sample showed variation in timing of surgery, this could have influenced the course of HRQL. Some patients (n=29)

participated in the diagnostic preSANO trial.[15, 16] In that trial, patients underwent a clinical response evaluation 4-6 weeks after nCRT to determine the accuracy of detecting residual disease. Patients with residual disease or no-pass during clinical response evaluation after 4-6 weeks underwent immediate surgical resection, whereas remaining patients had surgery 10-14 weeks after completion of nCRT. Patients with (substantial) residual disease after nCRT might experience worse HRQOL after nCRT, which potentially induces a bias. Furthermore, variations in time to surgery can be attributed to patient-related characteristics, such as comorbidities or general condition. More vulnerable patients could have longer time to surgery intentionally. This might negatively influence HRQOL at longer follow-up measurements, so HRQL may improve more strongly at the later measures if all patients could have been included. Therefore, the presence of residual disease during clinical response evaluation (only for patients who participated in the preSANO trial), comorbidities (Charlson comorbidity index) and ASA-score were included in a separate analysis to investigate their potential effect on the course of HRQL.[17]

As correction for multiple comparisons, $p<0.006$ was considered statistically significant (a Bonferroni correction of 0.05/9 was applied, since the main analyses included nine comparisons (with pre-treatment levels). All p-values are two-sided. Data were analysed using SPSS version 24.0.

Results

Of 106 eligible patients, 96 (91%) were included from May 2016 through June 2017 (10 patients refused participation). Rates of response to the questionnaires were 78% - 99% (Table 1). Median age of patients was 68 (IQR 61-71) and 77 (80%) patients were men. Most patients had cT3 tumour (80%) and suspicious regional lymph nodes (66%, as determined by endoscopic ultrasound, CT and/or PET-CT, Table 2).

Predefined primary endpoints

Physical functioning (Figure 1A)

Over-time changes in physical functioning levels were statistically significant ($p<0.001$). Physical functioning had declined at the last cycle of nCRT (-16, $p<0.001$; CD -0.80, 95% CI -1.00 - -0.59) compared to baseline levels, and remained stable from two weeks after nCRT ($p=0.79$) during follow-up. Physical functioning improved from 2 to 10 weeks after nCRT (4 vs. 2 weeks +6, $p<0.001$; CD 0.30, 95% CI 0.17 – 0.42, 6 vs. 4 weeks +6, $p<0.001$; CD 0.28, 95% CI 0.17 – 0.39, 8 vs. 6 weeks +5, $p<0.001$; CD 0.24, 95% CI 0.15 – 0.32, 10 vs. 8 weeks +3, $p=0.003$; CD 0.15, 95% CI 0.05 – 0.24, resp.). From then on-

wards, the improvement was no longer statistically significant. Baseline levels were reached at 8 weeks (p=0.95), but were not exceeded during follow-up (p>0.006).

Odynophagia (Figure 1B)
There were statistically significant over-time changes in odynophagia levels (p<0.001). Compared to baseline levels, odynophagia levels had worsened at the last cycle of nCRT (14, p<0.001; CD -0.45, 95% CI 0.20 - 0.70), and remained at that level 2 weeks after nCRT (p=0.038). Thereafter, odynophagia levels improved from 2 to 4 weeks (-21, p<0.001; CD -0.69, 95% CI -0.89 - -0.49) and from 4 to 6 weeks (-11, p<0.001; CD -0.37, 95% CI -0.50 - -0.24). From then onwards, improvement was no longer statistically significant, as compared to the previous measurement. Four weeks after nCRT, baseline levels were reached (p=0.68), and from 6 weeks, odynophagia levels had improved compared to baseline levels (6 weeks -15, p<0.001; CD -0.42, 95% CI -0.64 - -0.20, 10 weeks -24, p<0.001; CD -0.77, 95% CI -0.98 - -0.57).

Sensory symptoms (Figure 1C)
Generally, over-time changes in sensory symptoms were not statistically significant (p=0.009). However, the specific comparisons between occasions showed that sensory symptoms had worsened at the last cycle of nCRT as compared to pre-treatment levels, (+4, p<0.001; CD 0.53, 95% CI 0.28 - 0.80). At 6 weeks after nCRT, sensory symptoms had returned to baseline levels (p=0.013). There was no further statistically significant improvement compared to previous measurements.

Predefined secondary endpoints

Global quality of life (Figure 1D)
Global quality of life scores showed statistically significant changes over-time (P<0.001). At the last cycle of nCRT global quality of life scores had declined (-16, p<0.001; CD -0.77, 95% CI -0.96 - -0.57,) and had further worsened 2 weeks thereafter (-6, p=0.002; CD -0.29, 95% CI -0.47 - -0.11). From 2 to 8 weeks after nCRT, global quality of life levels improved, as compared to the previous measurement (4 vs. 2 weeks +11, p<0.001; CD 0.51, 95% CI 0.33 – 0.69, 6 vs. 4 weeks +7, p<0.001; CD 0.34, 95% CI 0.19 – 0.49, 8 vs. 6 weeks +5, p=0.001; CD 0.24, 95% CI 0.10 – 0.39, resp.). From then onwards, improvement was no longer statistically significant. At 6 weeks after nCRT baseline levels were reached (p=0.031). Baseline levels were not exceeded during follow-up.

Fatigue (Figure 1E)
Over time, fatigue levels changed statistically significantly (p<0.001). Compared to baseline, fatigue levels increased at the last cycle of nCRT (+34, p<0.001; CD 1.21, 95% CI

1.04 – 1.39) and remained stable until 2 weeks after nCRT (p=0.32). From then onwards, there was an improvement until 6 weeks, as compared to the previous measurements (4 vs. 2 weeks -15, p<0.001; CD -0.57, 95% CI -0.73 – -0.41, 6 vs. 4 weeks -13, p<0.001; CD -0.46, 95% CI -0.60 – -0.32). Baseline levels were reached at 6 weeks (p=0.007). Thereafter, there was no statistically significant improvement compared to the previous measurement. Compared to baseline levels, there was an improvement at 16 weeks after nCRT (-8, p=0.001; CD -0.28, 95% CI -0.44 – -0.11).

Weight loss (Figure 1F)
Weight loss scores changed statistically significantly over-time (p<0.001). At the last cycle of nCRT weight loss had worsened compared to baseline levels (+10, p=0.002, CD 0.36, 95% CI 0.13 – 0.58), which did not improve at 2 and 4 weeks after nCRT compared to the previous measurement (p=0.263 and p=0.038, resp.). From then onwards, scores returned to baseline levels at 4 weeks after nCRT (p=0.031) and further improved (6 vs. 4 weeks -9, p<0.001; CD -0.31, 95% CI -0.47 – -0.16, 8 vs. 6 weeks -7, p<0.001; CD -0.24, 95% CI -0.37 – -0.12). At 12 weeks after nCRT, weight loss scores had improved compared to baseline levels (-15, p<0.001; CD -0.52, 95% CI -0.79 – -0.26).

Motor symptoms (Figure 1G)
There was a statistically significant over-time change in motor symptoms (p<0.001). Motor symptoms had worsened at the last cycle of nCRT (+4, p<0.001; CD 0.47, 95% CI 0.26 – 0.68). At 4 weeks after nCRT, motor symptoms had returned to baseline levels (p=0.028). There were no further improvements in motor symptoms compared to previous measurements.

Other endpoints
Mean scores of HRQOL domains other than the predefined endpoints are presented in Table 3.

Influence of residual disease, comorbidities and general condition
Inclusion of the presence of residual disease during clinical response evaluation, comorbidities (Charlson comorbidity index) and ASA score as control variables did not impact the reported overall trends in HRQOL-trajectories (data not shown). However, patients with Charlson comorbidity index >4 showed worse physical functioning, global quality of life and fatigue levels, but changes over-time were similar compared to patients with Charlson comorbidity index ≤4. Furthermore, patients with a positive clinical response evaluation at 4-6 weeks after nCRT showed a more profound decrease in global quality of life scores during nCRT, and more severe odynophagia symptoms during all measurement points.

Discussion

This prospective cohort study shows a profound negative, short-term impact of nCRT on all HRQOL-endpoints in oesophageal or junctional cancer patients treated with a multimodality regimen based on carboplatin/paclitaxel combined with 41.4Gy of concurrent radiotherapy. Subsequently, all primary and secondary HRQOL endpoints were restored to baseline levels in 4-10 weeks after completion of nCRT. Odynophagia, fatigue and weight loss even improved after nCRT, as compared to baseline levels at 6, 16 and 12 weeks, respectively.

This is the first study investigating the detailed short-term course of HRQOL after nCRT for oesophageal or junctional cancer. A previous study showed a negative impact of nCRT on HRQOL 12 weeks after the start of neoadjuvant treatment, which was restored to baseline levels 3 weeks prior to surgery.[6] However, this study employed a small sample size (n=34), only two measurements after nCRT with respect to the start of nCRT instead of the end of nCRT, and date of surgery hampering precise assessment of the HRQOL trajectory after nCRT. The HRQOL analysis of the CROSS-trial also showed a profound deterioration one week after completion of nCRT compared to baseline scores in all primary and secondary HRQOL-endpoints (physical functioning, global quality of life, fatigue, eating and emotional functioning). However, this study lacked extra measurements between the end of nCRT and the date of surgery.[3]

The results of the present study underline the value of sufficient recuperation time between completion of nCRT and oesophagectomy to enable patients to undergo surgery in optimal physical condition, potentially improving surgical outcome. It has been suggested that delaying oesophagectomy up to 12 weeks after completion of nCRT does not jeopardize oncological outcome. Moreover, delayed surgery tends to increase the pathologically complete response rate, potentially improving prognosis.[7, 18] We recommend that timing of surgery is guided by patients' condition. It is advocated that surgery should be postponed to up to 12 weeks after completion of nCRT, and even more than that, when patients experience persisting adverse events or are in bad general condition, especially in the absence of residual disease.

Previous studies have shown lasting deterioration of HRQOL after multimodality treatment on HRQOL in patients with oesophageal cancer.[4, 19-21] Given the current results, these negative findings are likely attributable to oesophagectomy and not to chemoradiotherapy per se. Definitive chemoradiotherapy without oesophagectomy circumvents the adverse effects of surgery, however, long-term oncological outcome has been suggested inferior, compared to (nCRT plus) surgery.[22] An active surveillance strategy after completion of nCRT is topic of investigation in the ESOSTRATE and SANO trials.[15, 23] In this novel treatment strategy, patients undergo frequent clinical examinations after completion of nCRT and oesophagectomy is offered only to patients

with a histologically proven or highly suspected locoregional regrowth, without signs of distant dissemination. This active surveillance strategy might reduce the number of patients who need oesophagectomy by 30-40%, reducing the impact of surgery on HRQOL. Results of the present study can be used when informing patients in whom a (future) active surveillance strategy is considered, since the stable HRQOL levels during the last measurements likely reflect HRQOL levels during active surveillance.

Limitations of the current study include the differences in timing of surgery between patients, which introduced different follow-up times between patients. Nevertheless, inclusion for the confounders presence of residual disease during clinical response evaluation (only patients in preSANO trial), comorbidities (Charlson comorbidity index) and ASA score did not influence the overall trends in HRQOL-trajectories.

In conclusion, there was a substantial decrease in HRQOL after completion of nCRT for oesophageal cancer, which was restored to baseline levels for all endpoints within 10 weeks. Odynophagia, fatigue and weight loss had improved within 16 weeks after nCRT, compared to baseline levels. These results support delay of surgery, especially in vulnerable patients, and can be used to inform patients in whom a (future) active surveillance strategy is considered.

Table 1. Patients eligible for quality of life assessment, returning the quality of life questionnaire, underwent surgery, deceased, not returning the quality of life questionnaire because they were too ill or because of random reasons at each measurement point.

Status	Baseline	Last cycle	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	14 weeks	16 weeks
Eligible	96	96	96	96	93	88	56	49	42	32
Returned total (% of eligible)	95 (99)	90 (94)	93 (97)	92 (96)	89 (96)	83 (94)	51 (91)	46 (94)	37 (88)	25 (78)
Surgery	0	0	0	0	3	8	39	46	53	63
Deceased	0	0	0	0	0	0	1	1	1	1
Too ill	0	4	1	1	1	1	1	1	3	4
Randomly missing / other	1	2	2	3	3	4	4	2	2	3

Table 2. Clinicopathological characteristics of the study patients

Characteristic	N=96
Age at randomization — yr.	
Median	68
IQ Range	61 – 71
Male sex — no. (%)	77 (80)
Tumour type — no. (%)	
Squamous-cell carcinoma	18 (19)
Adenocarcinoma	78 (81)
Clinical T stage — no. (%)†	
cT1	1 (1)
cT2	15 (16)
cT3	77 (80)
cT4	3 (3)
Clinical N stage — no. (%)¶	
cN0	33 (34)
cN1	38 (4)
cN2	19 (20)
cN3	6 (6)
ASA classification — no. (%)‖	
1	15 (16)
2	65 (68)
3	14 (15)
Missing	2 (2)

† Clinical tumour (cT) stage was assessed by means of endoscopic ultrasonography or computed tomography (CT) and was classified according to the International Union for Cancer Control (IUCC) tumour–node–metastasis (TNM) classification, 7th edition.

Clinical lymph-node (N) stage was assessed by means of endoscopic ultrasonography, CT, or 18F-fluorodeoxyglucose positron-emission tomography and was classified according to IUCC TNM classification, 7th edition.

‖ ASA classification is on a scale of 0 to 5, with lower numbers indicating better physical status; 1 indicates a normal healthy patient, 2 a patient with mild systemic disease, and 3 a patient with severe systemic disease.

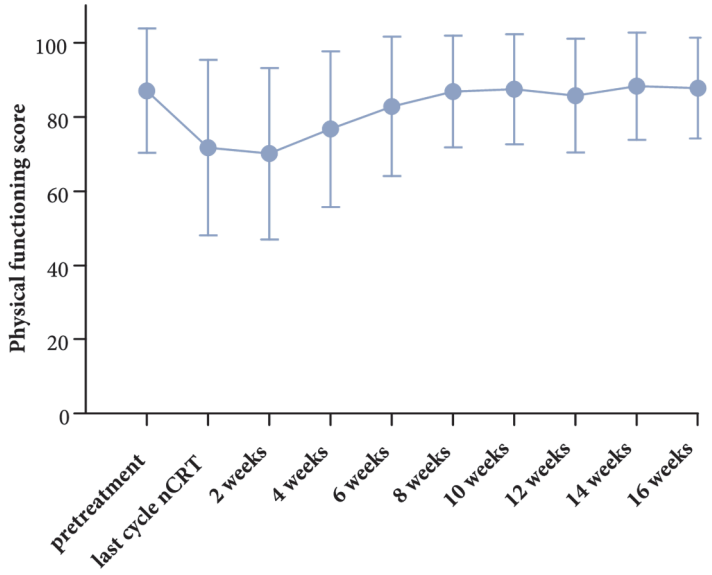
Table 3. Mean scores for all domains in the three EORTC questionnaires that were not predefined endpoints.

Status	Baseline	Last cycle	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	14 weeks	16 weeks
QLQ-C30										
Functional scales										
Role	82 (23)	56 (32)	50 (32)	26 (30)	71 (27)	79 (23)	81 (22)	81 (25)	82 (25)	85 (25)
Emotional	75 (20)	74 (24)	72 (23)	78 (19)	80 (20)	81 (17)	81 (19)	83 (16)	82 (17)	82 (19)
Cognitive	91 (16)	81 (25)	82 (20)	86 (19)	91 (16)	92 (16)	91 (17)	93 (14)	93 (13)	95 (12)
Social	88 (18)	70 (30)	69 (27)	78 (23)	86 (20)	88 (18)	89 (18)	89 (18)	90 (19)	91 (18)
Symptom scores										
Nausea and vomiting	12 (23)	28 (30)	32 (32)	13 (20)	10 (19)	5 (15)	3 (8)	5 (11)	5 (11)	1 (3)
Pain	14 (19)	32 (28)	38 (31)	22 (26)	14 (20)	11 (20)	12 (22)	11 (21)	12 (24)	9 (19)
Dyspnoea	8 (16)	20 (26)	22 (26)	20 (26)	12 (21)	11(21)	11 (21)	13 (19)	11 (19)	8 (15)
Insomnia	27 (30)	35 (33)	33 (34)	24 (31)	20 (25)	16 (24)	18 (24)	17 (26)	14 (20)	12 (25)
Loss of appetite	21 (28)	46 (35)	52 (35)	33 (34)	18 (26)	12 (24)	12 (22)	12 (24)	11 (21)	7 (17)
Constipation	9 (21)	25 (33)	25 (32)	13 (24)	7 (16)	5 (14)	7 (15)	4 (13)	4 (10)	7 (17)
Diarrhoea	6 (17)	16 (26)	15 (26)	5 (16)	4 (12)	5 (13)	7 (13)	3 (9)	4 (13)	5 (12)
Financial worries	3 (12)	8 (22)	6 (18)	5 (14)	5 (17)	5 (16)	4 (16)	4 (13)	4 (10)	4 (11)
QLQ-OG25										
Symptom scores										
Dysphagia	27 (25)	41 (28)	56 (30)	25 (25)	16 (19)	13 (21)	10 (17)	6 (12)	6 (15)	4 (7)
Eating	42 (28)	57 (28)	62 (28)	40 (31)	27 (28)	20 (27)	16 (23)	13 (20)	10 (17)	9 (15)
Reflux	9 (18)	14 (23)	16 (26)	8 (21)	5 (14)	3 (10)	3 (12)	3 (11)	1 (6)	1 (7)
Pain and discomfort	15 (23)	29 (28)	30 (32)	22 (28)	14 (23)	13 (22)	10 (19)	7 (17)	7 (17)	10 (20)
Anxiety	52 (25)	46 (26)	47 (27)	43 (25)	41 (27)	43 (26)	42 (26)	41 (22)	39 (26)	36 (27)
Eating with others	27 (33)	34 (35)	36 (26)	21 (30)	11 (24)	7 (17)	5 (12)	5 (14)	4 (10)	1 (7)
Dry mouth	13 (23)	26 (28)	29 (30)	17 (24)	13 (20)	9 (20)	12 (21)	13 (27)	9 (22)	7 (14)
Trouble with taste	18 (32)	44 (37)	46 (35)	32 (32)	21 (27)	12 (24)	10 (20)	8 (20)	5 (12)	7 (17)
Trouble with swallowing saliva	13 (27)	24 (32)	24 (30)	14 (26)	7 (18)	5 (15)	3 (11)	3 (12)	2 (8)	3 (9)
Choked when swallowing	10 (22)	9 (17)	9 (18)	5 (14)	3 (10)	4 (13)	2 (9)	4 (13)	5 (14)	3 (9)
Trouble with coughing	26 (26)	32 (28)	34 (28)	28 (27)	21 (23)	23 (24)	19 (24)	19 (25)	17 (22)	16 (17)
Trouble talking	6 (18)	10 (19)	13 (24)	8 (18)	3 (10)	3 (11)	5 (13)	4 (13)	4 (10)	4 (11)
Hair loss	10 (25)	22 (29)	19 (26)	21 (29)	19 (31)	16 (26)	14 (28)	14 (31)	17 (36)	5 (13)
QLQ-CIPN20										
Autonomic scale	11 (15)	21 (19)	22 (19)	18 (18)	14 (16)	14 (15)	14 (15)	14 (16)	14 (18)	14 (18)

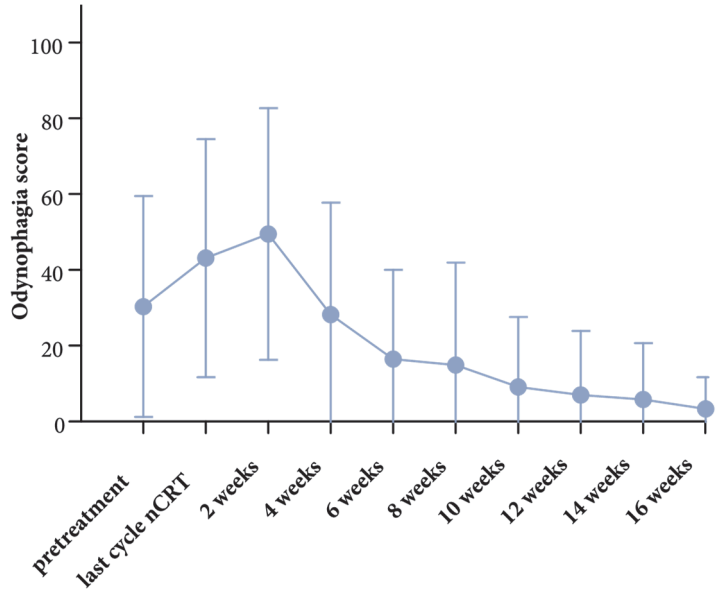
Scores are presented as mean. Standard deviations are shown between parentheses.

EORTC: European organization for research and treatment of cancer.

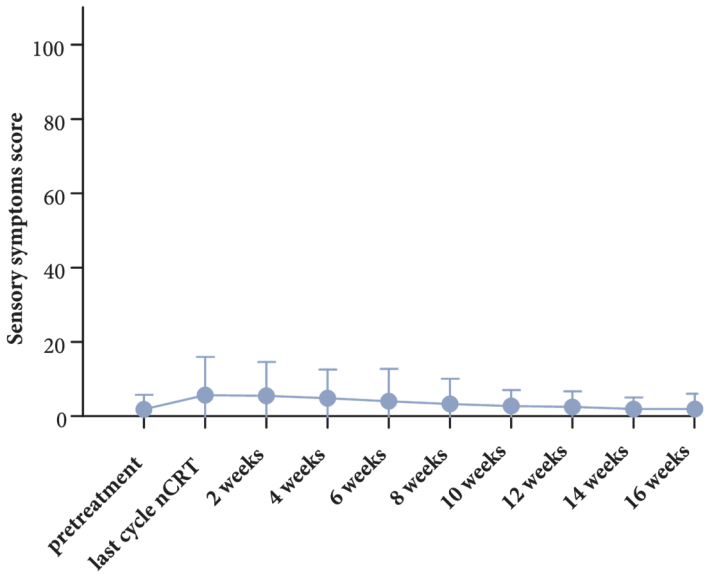
Figure 1. Mean scores with standard deviations for a) physical functioning, b) odynophagia, c) sensory symptoms (primary endpoints), d) global quality of lfie, e) fatigue, f) weight loss and g) motor symptoms (secondary endpoints).



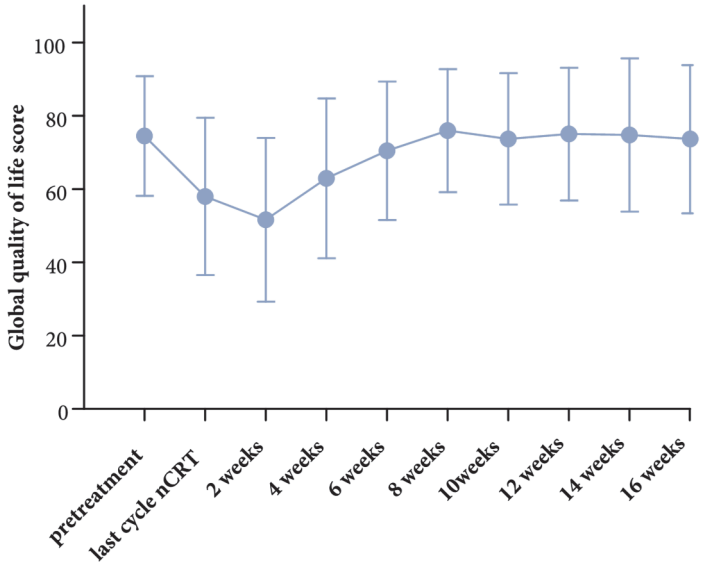
A



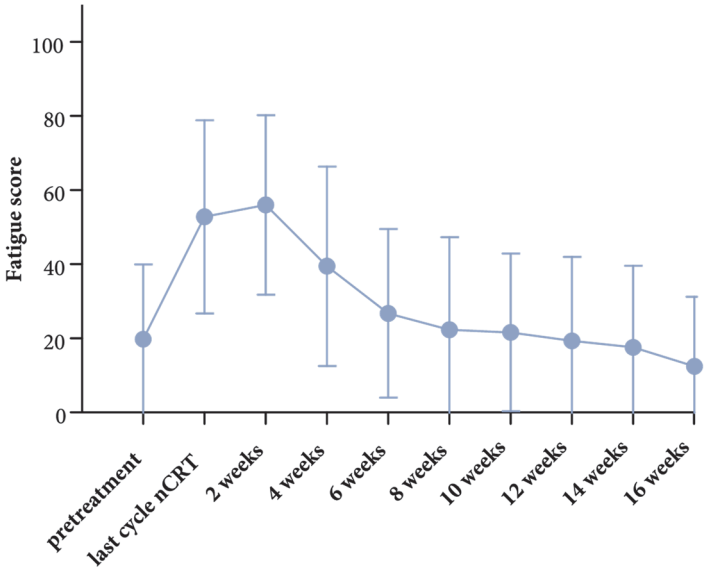
B


Sensory symptoms score
100
80
60
40
20
0
pretreatment
last cycle nCRT
2 weeks
4 weeks
6 weeks
8 weeks
10 weeks
12 weeks
14 weeks
16 weeks

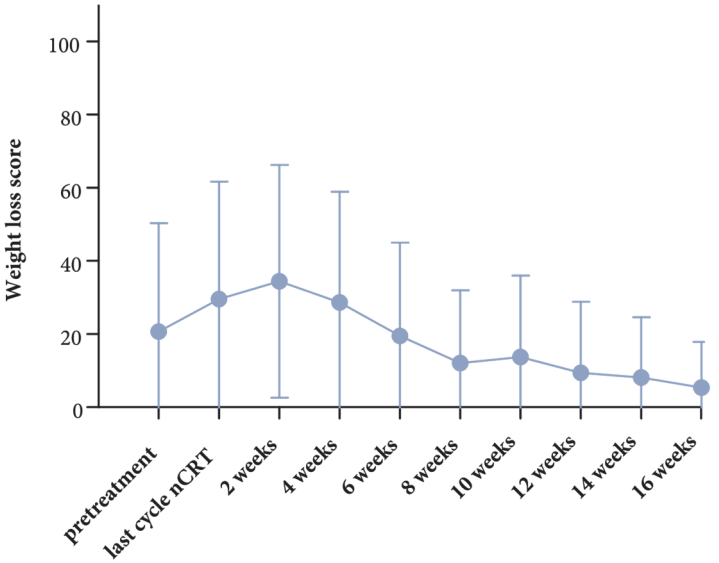
C


Global quality of life score
100
80
60
40
20
0
pretreatment
last cycle nCRT
2 weeks
4 weeks
6 weeks
8 weeks
10weeks
12 weeks
14 weeks
16 weeks

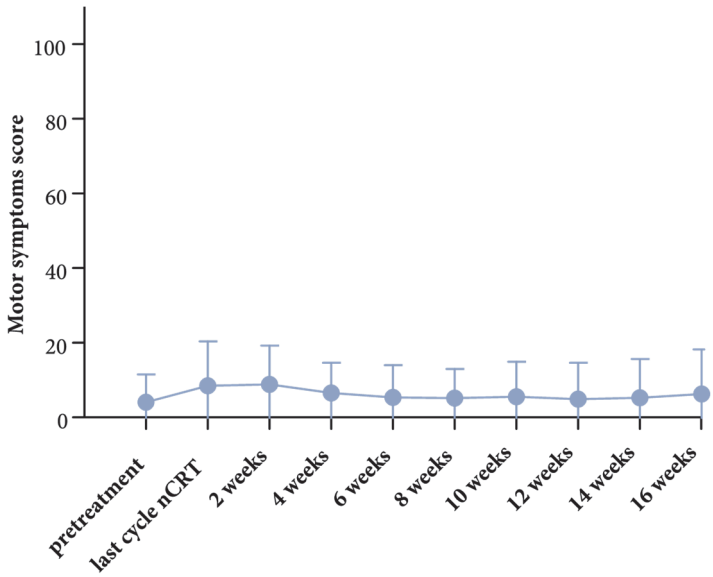
D


Fatigue score
100
80
60
40
20
0
pretreatment
last cycle nCRT
2 weeks
4 weeks
6 weeks
8 weeks
10 weeks
12 weeks
14 weeks
16 weeks

E


Weight loss score
100
80
60
40
20
0
pretreatment
last cycle nCRT
2 weeks
4 weeks
6 weeks
8 weeks
10 weeks
12 weeks
14 weeks
16 weeks

F


Motor symptoms score
100
80
60
40
20
0
pretreatment
last cycle nCRT
2 weeks
4 weeks
6 weeks
8 weeks
10 weeks
12 weeks
14 weeks
16 weeks

G

References

1. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
2. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
3. Noordman BJ, Verdam MGE, Lagarde SM et al. Effect of neoadjuvant chemoradiotherapy on health-related quality of life in esophageal or junctional cancer: results from the randomized CROSS trial. J Clin Oncol. 2017:JCO2017737718.
4. Noordman BJ, Verdam MGE, Lagarde SM et al. Impact of neoadjuvant chemoradiotherapy on health-related quality of life in long-term survivors of esophageal or junctional cancer: results from the randomized CROSS trial. Ann Oncol. 2018;29(2):445-51.
5. van Meerten E, van der Gaast A, Looman CW, Tilanus HW, Muller K, Essink-Bot ML. Quality of life during neoadjuvant treatment and after surgery for resectable esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2008;71(1):160-6.
6. Blazeby JM, Sanford E, Falk SJ, Alderson D, Donovan JL. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. Cancer. 2005;103(9):1791-9.
7. Shapiro J, van Hagen P, Lingsma HF et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. Ann Surg. 2014;260(5):807-14.
8. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
9. Lagergren P, Fayers P, Conroy T et al. Clinical and psychometric validation of a questionnaire module, the EORTC QLQ-OG25, to assess health-related quality of life in patients with cancer of the oesophagus, the oesophago-gastric junction and the stomach. Eur J Cancer. 2007;43(14):2066-73.
10. Postma TJ, Aaronson NK, Heimans JJ et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. Eur J Cancer. 2005;41(8):1135-9.
11. Fayers PM, Aaronson NK, Bjordal K et al. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
12. Twisk J, de Vente W. Attrition in longitudinal studies. How to deal with missing data. J Clin Epidemiol. 2002;55(4):329-37.
13. Cohen J. Statistical power analysis for the behavorial sciences. 2nd ed. Hillsdale, New Jersey: Erlbaum; 1988.
14. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582-92.
15. Noordman BJ, Shapiro J, Spaander MC et al. Accuracy of detecting residual disease after CROSS neoadjuvant chemoradiotherapy for esophageal cancer (preSANO Trial): rationale and protocol. JMIR Res Protoc. 2015;4(2):e79.
16. Noordman BJ, Spaander MC, Wijnhoven BP et al. Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO trial). In press, Lancet Oncol. 2017.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
18. Ruol A, Rizzetto C, Castoro C et al. Interval between neoadjuvant chemoradiotherapy and surgery for squamous cell carcinoma of the thoracic esophagus: does delayed surgery have an impact on outcome? Ann Surg. 2010;252(5):788-96.

19. Derogar M, Lagergren P. Health-related quality of life among 5-year survivors of esophageal cancer surgery: a prospective population-based study. J Clin Oncol. 2012;30(4):413-8.
20. Schandl A, Lagergren J, Johar A, Lagergren P. Health-related quality of life 10 years after oesophageal cancer surgery. Eur J Cancer. 2016;dec(69):43-50.
21. Djarv T, Lagergren J, Blazeby JM, Lagergren P. Long-term health-related quality of life following surgery for oesophageal cancer. Br J Surg. 2008;95(18581441):1121-6.
22. Blum MA, taketa T, Sudo K, Wadhwa R, Skinner DB, Ajani JA. Chemoradiation for esophageal cancer. Thorac Surg Clin. 2016;23(4):551-8.
23. Putora PM, Bedenne L, Budach W et al. Oesophageal cancer: exploring controversies overview of experts' opinions of Austria, Germany, France, Netherlands and Switzerland. Radiat Oncol. 2015;10:116.

Chapter 10

Impact of neoadjuvant chemoradiotherapy on health related quality of life in long-term survivors of esophageal or junctional cancer: results from the randomized CROSS trial

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Department of Surgery[8], University Medical Center Groningen, Groningen, the Netherlands
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Department of Public Health[10], Erasmus MC – University Medical Center – Rotterdam, the Netherlands
Department of Department of Medical Statistics and Bioinformatics[11], Leiden University Medical Center, Leiden, the Netherlands
Department of Medical Oncology[12], Erasmus MC – University Medical Center – Rotterdam, the Netherlands

Abstract

Background

Neoadjuvant chemoradiotherapy (nCRT) plus surgery is a standard of care for patients with esophageal or junctional cancer, but the long-term impact of nCRT on health-related quality of life (HRQOL) is unknown. The purpose of this study is to compare very long-term HRQOL in long-term survivors of esophageal cancer who received nCRT plus surgery or surgery alone.

Patients and methods

Patients were randomly assigned to receive nCRT (carboplatin/paclitaxel with 41.4Gy radiotherapy) plus surgery or surgery alone. HRQOL was measured using EORTC-QLQ-C30, EORTC-QLQ-OES24 and K-BILD questionnaires after a minimum follow-up of 6 years. To allow for examination over time, EORTC-QLQ-C30 and QLQ-OES24 questionnaire scores were compared to pre-treatment and 12-months-postoperative questionnaire scores. Physical functioning (QLQ-C30), eating problems (QLQ-OES24) and respiratory problems (K-BILD) were predefined primary endpoints. Predefined secondary endpoints were global quality of life and fatigue (both QLQ-C30).

Results

After a median follow-up of 105 months, 123/368 included patients (33%) were still alive (70 nCRT plus surgery, 53 surgery alone). No statistically significant or clinically relevant differential effects in HRQOL-endpoints were found between both groups. Compared to one-year postoperative levels, eating problems, physical functioning, global quality of life and fatigue remained at the same level in both groups. Compared to pre-treatment levels, eating problems had improved (Cohen's d -0.37, p=0.011) during long-term follow-up, whereas physical functioning and fatigue were not restored to pre-treatment levels in both groups (Cohen's d -0.56 and 0.51, resp., both p<0.001).

Conclusion(s)

Although physical functioning and fatigue remain reduced after long-term follow-up, no adverse impact of nCRT is apparent on long-term HRQOL compared to patients who were treated with surgery alone. In addition to the earlier reported improvement in survival and the absence of impact on short-term HRQOL, these results support the view that nCRT according to CROSS can be considered as a standard of care.

Clinical trials number

Trial registration number: Netherlands Trial Register NTR487

Introduction

Esophageal cancer is characterized by frequent locoregional and distant recurrence. The 5-year overall survival rate rarely exceeds 40% after primary surgery. In order to improve locoregional control and overall survival, neoadjuvant chemo(radio)therapy has been investigated in many clinical trials.[1]

The ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial compared a carboplatin and paclitaxel based neoadjuvant chemoradiotherapy (nCRT) regimen plus surgery with surgery alone. Eight centers in The Netherlands participated. After a minimum follow up of 5 years, a clinically relevant and statistically significant benefit in overall- and progression free survival rates was shown for the multimodality group. Treatment-related toxicity and postoperative complication rate were acceptable.[2, 3] Based on these results, nCRT followed by surgery according to the CROSS-regimen is a standard care in many countries.[4]

The increasing emphasis on patient-reported outcome measures (PROMs) and health-related quality of life (HRQOL) leads to a more prominent role of these measures as endpoints in clinical trials. Thus far, HRQOL has received limited attention in the field of esophageal cancer, but the wide introduction of nCRT and the associated increased survival emphasize the need for high-quality HRQOL-data from these patients. It is known that esophagectomy has profound and lasting impact on patients' HRQOL.[5, 6] The short-term HRQOL-analysis of the CROSS trial (follow-up ≤1 year) showed that adding nCRT to surgery does not adversely impact postoperative HRQOL[6], which is in line with results from earlier retrospective studies.[7-9] However, follow-up of these studies did not exceed 24 months.[6-9] Importantly, side-effects of radiotherapy can develop years after treatment, with the lungs being the most radiosensitive organ in the chest.[10] Therefore, long-term HRQOL-data from patients treated with nCRT plus surgery are desired.

The aim of this sub-study of the CROSS trial was to compare HRQOL in long-term survivors (>6 years) who received nCRT plus surgery or surgery alone.

Methods

Details of this randomized trial have been reported previously.[2, 3] Briefly, patients with locally advanced (clinical stage T1N1M0 or T2–3N0–1M0, 6th edition of the Union for International Cancer Control TNM cancer staging)[11] esophageal or esophagogastric junctional squamous cell carcinoma or adenocarcinoma were eligible. Patients were randomized between nCRT plus surgery and surgery alone. The study protocol was approved by the ethical committees of the participating centers, and ethical approval for

long-term HRQOL-measurement was provided by the medical ethical committee of the Erasmus MC. All included patients provided written informed consent.

Procedures

Patients assigned to nCRT were treated with carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m2 of body-surface area) for five weekly cycles. Concomitant radiation therapy was given in 23 fractions of 1.8 Gy (41.4 Gy total). Patients assigned to surgery alone were operated as soon as possible, whereas patients in the nCRT group underwent surgery 4–6 weeks after completion of nCRT. Patients with carcinomas at or above the level of the carina underwent a transthoracic esophagectomy with two-field lymphadenectomy, whereas patients with carcinomas below the carina, either had a transthoracic esophagectomy with two-field lymphadenectomy or a transhiatal esophagectomy with upper abdominal and lower mediastinal lymphadenectomy, depending on patient characteristics and local preferences. For patients with carcinomas involving the esophagogastric junction, a transhiatal esophagectomy was recommended.

Health-related quality of life measurement

Cancer-specific HRQOL was assessed using the EORTC-QLQ-C30, a validated self-completed questionnaire designed for cancer patients.[12] Tumor-specific HRQOL was assessed using the EORTC-QLQ-OES24 self-completed questionnaire.[13] The EORTC-QLQ-OES24 was used to allow for comparison with baseline and 12-months postoperative questionnaires, as the currently used derivative, EORTC QLQ-OES18, was not available at that time. During long-term follow-up assessment, the K-BILD questionnaire was added to assess pulmonary effects of radiotherapy. The K-BILD is a self-completed validated questionnaire for interstitial lung disease patients.[14]

The self-completed questionnaires were mailed to all patients who were alive after a minimum follow-up of 6 years after surgery. Patients who had not completed the questionnaires within one month were reminded two times by telephone. To allow for examination of HRQOL over time, questionnaire scores were compared to pretreatment and 12-months-postoperative questionnaire scores from the earlier short-term HRQOL-study (follow-up ≤1 year after surgery).[6] Prior to the analysis, endpoints were predefined by consensus discussion with experienced medical oncologists, upper-GI surgical oncologists and nurse practitioners. Endpoints were defined based on clinical relevance and hypothesized relation with long-term outcome of nCRT. Primary endpoints were physical functioning (QLQ-C30), eating problems (QLQ-OES24) and total respiratory problems (K-BILD). Secondary endpoints were global quality of life and fatigue (both QLQ-C30).

Statistical analysis

Patients who were alive during long-term follow-up assessment (July 2015) were included in the analysis. Pre-treatment patient characteristics were compared using the Student's *t* or Mann-Whitney test for continuous characteristics, whereas χ^2 test or Fisher's exact tests were used for comparison of categorical characteristics.

Questionnaire scale scores were transformed into a 0-100 scale as was described previously.[14, 15] Baseline (questionnaire) scores of the two treatment groups were compared using the Student's *t* test. Over-time differential effects between the treatment groups and longitudinal differences of the follow-up measurements were investigated using mixed modeling analysis. If no statistically significant differential effects were found between both groups, results of the combined groups are reported. Mixed modeling allows for inclusion of questionnaires from subjects with different numbers of completed measurements and thereby enables analysis of all available data.[16] Hence, all available questionnaires were included in the analyses. Mean changes between groups and over time differential effects were described. Cohen's d (CD) effect sizes were calculated to assess clinical relevance of the effects and to enable standardized comparison between different outcome variables. CD effect-sizes were derived from the beta-estimates in the mixed modeling procedure. CD values of 0.2, 0.5 and 0.8 reflect small, medium and large effects, respectively.[17] Values greater than 0.5 indicate clinically relevant effects.[18]

As multiple comparisons correction, $p<0.025$ was considered statistically significant for the mixed models analyses (the main analyses included two comparisons and thus a Bonferroni correction of 0.05/2 was applied), whereas $p<0.05$ was considered statistically significant for clinical characteristics and baseline-score comparisons. All p-values are two-sided. Data were analyzed using SPSS version 21.0.

Results

Of the 368 patients included in the CROSS trial, 123 (33%) were still alive (70 nCRT plus surgery, 53surgery alone). Median follow-up was 105 months. Patients in the nCRT-group were older, but there were no other statistically significant differences in pre-treatment clinicopathological characteristics between the groups (Table 1). The majority of patients was male (76% and 77%, resp.), most patients had an adenocarcinoma (73% and 76%, resp.)and most tumors were clinically staged as cT3 (77% and 76%, resp.). Most patients had suspected locoregional lymph node metastases (54% and 69%, resp.). Due to an administrative error, 32 of the long-term survivors did not receive baseline HRQOL-questionnaires. These patients were not excluded from the analysis, because their pre-treatment characteristics were not significantly different from the

total study group (data not shown) and follow-up questionnaires were correctly mailed and completed.[6]

Overall response rate to the HRQOL-questionnaires in the 123 long-term survivors was 89% (Table 2). In the nCRT-group response rate was 94%, whereas in the surgery alone group this was 83% (p=0.07). Mean scores of all HRQOL-domains of the EORTC-questionnaires and K-BILD-questionnaire are reported in Table 3a and Table 3b, respectively.

Primary endpoints

Pretreatment, there were no statistically significant differences in physical functioning between both groups (p=0.32). Effects over time were comparable in both groups (p=0.46). Physical functioning had declined 12 months after surgery compared to baseline (-6, p<0.001; CD -0.37, 95% CI -0.58– -0.16), and stayed stable during long-term follow-up (-3, p=0.10; CD -0.19, 95% CI -0.42–0.04, Figure 1A).

Baseline eating problems scores and overall changes over time were comparable in both groups (p=0.52, p=0.90, resp.). Twelve months postoperatively, eating problems were comparable to baseline (-4, p=0.24; CD -0.18, 95% CI -0.48–0.12) and remained stable after long-term follow-up (-5, p=0.09; CD -0.20, 95% CI -0.43–0.03). Compared to baseline, a significant improvement was reported after long-term follow-up (-9, p=0.011; CD -0.37, 95% CI -0.66– -0.09, Figure 1B).

After long-time follow-up, there were no statistically significant differences in overall respiratory problems between both groups (p=0.69; CD 0.08, 95% CI -0.32–0.48).

Secondary endpoints

No statistically significant differences in global quality of life were found at baseline (p=0.35), and no differential effects between both groups over time-up were detected (p=0.57). One year after surgery, scores were comparable to baseline (+2, p=0.56; CD 0.08, 95% CI -0.20–0.37) and no statistically significant improvement was found after long-term follow-up compared to 12 months postoperatively (+2, p=0.96; CD 0.01, 95% CI -0.24–0.26).

Baseline fatigue levels were comparable in both groups (p=0.60) and all effects over time were comparable between the groups (p=0.48). One year after surgery, fatigue levels had worsened compared to baseline (+9, p<0.001; CD 0.39, 95% CI 0.16–0.62), and remained stable during long-term follow-up (+2, p=0.24; CD 0.12, 95% CI -0.08–0.31).

Influence of missing baseline questionnaires

In order to investigate the effect of missing baseline questionnaires, the availability of baseline questionnaires was included as control variable in a separate analysis. This did not influence the described trends in HRQOL-trajectory (data not shown).

Discussion

There were no clinically relevant differential effects in HRQOL between long-term survivors of esophageal or esophagogastric junctional cancer treated with nCRT and surgery, compared to surgery alone. In both groups, eating problems improved compared to one-year-postoperative-levels, whereas physical functioning, global HRQOL and fatigue remained at the same level. Physical functioning and fatigue were not restored to pretreatment levels and corresponding effect sizes were clinically relevant (CD -0.56 and 0.51, resp.). These results indicate a lasting impact of surgery, regardless of the use of nCRT.

Earlier studies have shown that adding nCRT to surgery does not adversely impact postoperative HRQOL. However, most of these studies have been criticized by their non-randomized designs and small sample sizes, which make them prone for selection bias and limit their ability to detect small but potentially clinically relevant differences.[7-9] Methodological strengths of the current study include its randomized design and low attrition rate after long-term follow-up, thereby minimizing the risks of selection and attrition bias. Furthermore, the availability of pretreatment and one-year postoperative data enabled investigation of change trajectories. Notably, none of the previous studies focused on long-term follow-up.[7-9] Late side-effects of radiotherapy can develop years after initial treatment, with the lungs being the most radiosensitive organ in the chest. Symptomatic radiotherapy-induced pulmonary fibrosis is reported in up to 10% of patients after thoracic radiotherapy. Its incidence depends on the total radiation dose, the irradiated lung volume and the use of chemotherapy. Especially concurrent chemotherapy is associated with an increased incidence of (chemo-)radiotherapy induced pulmonary fibrosis. Symptoms include dyspnea, chest pain, cough, malaise and weight loss, which may exert profound effects on HRQOL, thereby underlining the relevance of effect studies.[10] The finding that adding nCRT to surgery does not adversely impact postoperative HRQOL, confirms the relatively low toxicity of the CROSS-regimen.[2, 6] Interestingly, an earlier study found a lasting impairment in physical functioning and dyspnea after chemoradiotherapy, compared to surgery alone. These conflicting results can be explained by the higher dose of radiotherapy (66Gy) and the more toxic chemotherapeutic agents that were applied in that study (5-FU /cisplatinum).[19] It should be noted that novel radiotherapy techniques applied in the CROSS trial have likely also

reduced therapy related complications. Besides the improvement in survival, the absent impact on HRQOL is an important argument to apply the CROSS-regimen as regimen of first choice.[3]

Although no impact of nCRT on HRQOL was apparent, both treatment groups experienced long-lasting impact of oesophagectomy on HRQOL. The reported deterioration in physical functioning and fatigue might also be explained by increasing age. However, studies that used a matched reference population also reported reduced long-term HRQOL.[20, 21] Moreover, pretreatment HRQOL-data were obtained after patients had been confronted with the diagnosis of esophageal cancer, when they already were suffering from disease symptoms and were psychologically affected by their recent diagnosis. Consequently, pretreatment HRQOL-levels probably represent an underestimation of patients' HRQOL-levels before diagnosis, thereby further emphasizing the (negative) impact of esophagectomy.

The lasting deterioration in HRQOL is in line with earlier studies.[5, 21, 22] Our short-term analysis on all included patients showed impaired physical functioning and fatigue one year after surgery.[6] The current analysis in long-term survivors shows comparable results, indicating that these symptoms last. This suggests that impairment cannot be attributed to a selected group of patients (e.g. patients with subclinical disease recurrence), as was suggested earlier.[20] A recent study investigated HRQOL in patients who were alive 10 years after surgical treatment. Although these patients underwent primary surgery, results are in line with those of the current study, showing that long-term HRQOL remains substantially impaired.[21] These findings not only call for long-term supportive care including long-lasting rehabilitation such as cognitive behavior therapy for patients with lasting fatigue[23], but also for new treatment strategies with optimal preservation of HRQOL.

Definitive chemoradiotherapy without esophagectomy has been evaluated for patients with squamous cell carcinoma. Locoregional recurrence rates and long-term survival were found to be inferior, as compared to (nCRT followed by) surgery. Therefore, definitive chemoradiotherapy with active surveillance and salvage surgery for non-responders is a treatment option.[4] Furthermore, the effects of minimally invasive and hybrid surgical techniques, and an active surveillance strategy after nCRT (instead of standard esophagectomy) on HRQOL should be investigated.[24, 25]

Limitations of the current study include its relatively small sample size. This is inevitable in long-term follow-up studies investigating diseases with poor survival. The current study provides the largest available dataset on long-term HRQOL after nCRT, and its sample size has sufficient power to detect clinically relevant differences. Nevertheless, the ability of this data set to capture long-term complications that are present in a minority of patients is limited. Patients in the nCRT-group were slightly older than patients in the surgery alone group. However, survivors were selected from randomized

groups with similar baseline characteristics, suggesting that this difference in age is a result of the experimental treatment (nCRT), rather than of selection bias.[2, 3] Moreover, it does not seem plausible that the higher age has positively influenced HRQOL. Furthermore, patients completed questionnaires at one point in time, which introduced different follow-up times between patients who were included at different time points. However, there were no differences in median follow-up time between both groups and it is unlikely that treatment-related-HRQOL still changes substantially after more than 6 years of follow-up. Therefore, we feel that the effect of differences in follow-up duration on HRQOL-outcome is negligible. Since this trial included relatively few patients with poor performance status (patients with WHO>2 were excluded) and high age (patients >75 years were also excluded), the results cannot be extrapolated to other categories of more vulnerable patients. The effect of the CROSS-regimen on (long-term) HRQOL in more vulnerable subgroups of patients remains to be investigated. Finally, the EORTC-QLQ-OES24 has been revised into the EORTC-QLQ-OES18, with refinement of the hypothesized scales and removal of two single items.[13] To allow for comparison with baseline and 12-months postoperative questionnaires, we used the EORTC-QLQ-OES24. We believe that this did not limit the validity of the results, because the eating problems domain was retained in its original form.

In conclusion, no impact of nCRT is apparent on long-term HRQOL compared to surgery alone. In addition to the improvement in long-term survival and the absent impact on postoperative recovery, these results support the view that nCRT can be considered as a standard care for patients with locally advanced esophageal or esophagogastric junctional cancer.

Table 1. Clinicopathological characteristics of patients with potentially curable esophageal or esophagogastric junction cancer, according to treatment allocation.

Characteristic	nCRT plus surgery (N = 70)	Surgery alone (N = 53)	p-value
Follow-up — months			
Median	104	105	0.635
IQ Range	90 – 116	87 – 117	
Age at randomization — yr.			
Median	60	57	0.024
IQ Range	55 - 65	51 - 62	
Male sex — no. (%)	53 (76)	41 (77)	0.832
Tumor type — no. (%)			0.205
Adenocarcinoma	51 (73)	40 (76)	
Squamous-cell carcinoma	19 (27)	11 (21)	
Other	0	2 (4)	
Tumor location — no. (%)†			0.571
Esophagus			
Proximal and middle third	12 (18)	6 (12)	
Distal third	36 (54)	32 (62)	
Esophagogastric junction	19 (28)	14 (27)	
Missing data	3	1	
Clinical T stage — no. (%)‡			0.965
cT1/cT2	16 (23)	12 (24)	
cT3	53 (77)	39 (76)	
Could not be determined§	1	2	
Clinical N stage — no. (%)¶			0.116
N0	31 (46)	16 (31)	
N1	37 (54)	35 (69)	
Could not be determined§	2	2	
WHO performance status — no. (%)‖			0.425
0	57 (81)	46 (87)	
1	13 (19)	7 (13)	

* Percentages may not add up to 100 because of rounding. WHO denotes World Health Organization.

† Tumor length and location were determined by means of endoscopy.

‡ Clinical tumor (cT) stage was assessed by means of endoscopic ultrasonography or computed tomography (CT) and was classified according to the International Union against Cancer (UICC) tumor–node–metastasis (TNM) classification, 6th edition.

§ This category included patients in whom the tumor could not be fully investigated by means of a transducer for endoscopic ultrasonography owing to a stenosis caused by the tumor.

Clinical lymph-node (N) stage was assessed by means of endoscopic ultrasonography, CT, or 18F-fluorodeoxyglucose positron-emission tomography and was classified according to UICC TNM classification, 6th edition.

‖ WHO performance status scores are on a scale of 0 to 5, with lower numbers indicating better performance status; 0 indicates fully active, and 1 unable to carry out heavy physical work.

Table 2. Patients eligible for quality of life assessment, returning the quality of life questionnaire, deceased, not returning the quality of life questionnaire because they were too ill or because of random reasons at each measurement point.

Status	Pre-treatment	12 months postoperatively	Long-term follow-up (>6 years postoperatively)
Eligible	123	123	123
nCRT + surgery	70	70	70
surgery alone	53	53	53
Returned total (% of eligible)	83(67)	79 (64)	110 (89)
nCRT + surgery (%)	57 (81)	49 (70)	66 (94)
surgery alone (%)	26 (49)	30 (57)	44 (83)
Deceased	N/A	N/A	N/A
Too ill	0	1	1
Randomly missing / other	40*	43	12

* (of whom 32 due to administrative error)

Table 3a. Mean scores for all domains in the two EORTC questionnaires according to treatment group.

	Pre-treatment		12 months postoperatively		Long-term follow-up (>6 years postoperatively)	
	nCRT plus surgery	surgery alone	nCRT plus surgery	surgery alone	nCRT plus surgery	surgery alone
QLQ-C30						
Global quality of life	76(19)	73(15)	76(17)	77(22)	76(22)	78(19)
Functional scales						
Physical	96(9)	94(8)	89(16)	91(10)	86(16)	86(20)
Role	88(27)	85(22)	80(25)	78(23)	82(24)	82(25)
Emotional	68(24)	67(18)	86(17)	79(20)	87(18)	84(22)
Cognitive	92(17)	85(19)	88(18)	83(19)	85(19)	84(20)
Social	85(23)	81(21)	90(16)	78(24)	87(20)	80(24)
Symptom scores						
Fatigue	13(17)	16(21)	25(20)	20(15)	27(22)	22(24)
Nausea and vomiting	5(11)	6(12)	11(16)	15(20)	7(14)	10(21)
Pain	12(19)	14(22)	6(11)	18(20)	10(20)	10(17)
Dyspnea	5(12)	2(9)	16(22)	11(18)	19(25)	14(21)
Insomnia	23(26)	20(31)	14(23)	16(25)	20(27)	20(27)
Loss of appetite	10(24)	7(17)	10(19)	10(18)	12(23)	15(28)
Constipation	8(19)	1(6)	8(20)	11(20)	10(17)	5(12)
Diarrhea	2(11)	0(0)	16(24)	18(23)	16(24)	17(26)
Financial worries	7(18)	9(24)	9(19)	13(26)	12(25)	11(28)
QLQ-OES24						
Eating problems	29(27)	33(28)	24(21)	29(27)	20(20)	22(23)
Emotional problems*	36(25)	48(18)	29(20)	33(23)	29(22)	25(24)

Table 3a. Continued

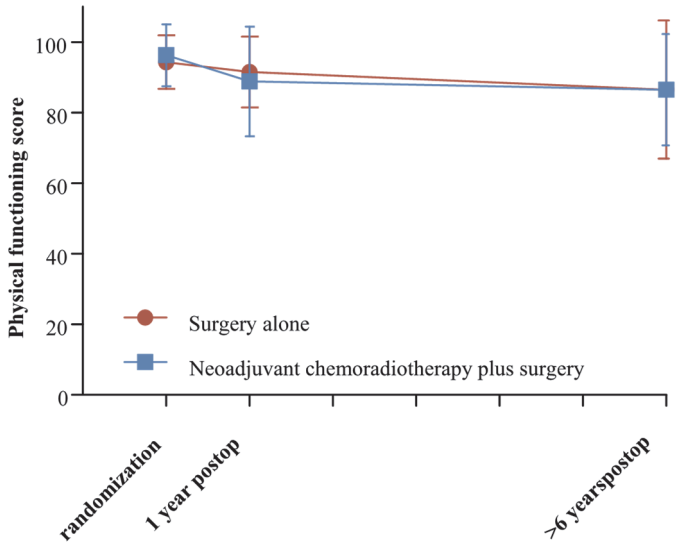
	Pre-treatment		12 months postoperatively		Long-term follow-up (>6 years postoperatively)	
	nCRT plus surgery	surgery alone	nCRT plus surgery	surgery alone	nCRT plus surgery	surgery alone
Dysphagia	74(33)	63(35)	83(28)	69(38)	82(31)	76(36)
Deglutition	16(27)	9(16)	16(26)	13(19)	12(20)	18(22)
Swallowing of saliva	18(34)	11(23)	14(30)	10(22)	10(25)	17(32)
Aspiration	14(27)	7(14)	18(28)	16(23)	13(24)	18(25)
GI symptoms (24)*	16(19)	21(16)	21(22)	25(25)	20(19)	25(30)
GI symptoms (18)	10(20)	7(13)	19(26)	22(27)	19(24)	26(32)
Pain	16(20)	23(27)	8(14)	9(15)	8(16)	7(11)
Dry mouth	8(21)	12(19)	17(25)	14(23)	17(25)	13(24)
Trouble with taste	7(19)	9(24)	9(21)	8(14)	8(20)	8(23)
Trouble with coughing	13(21)	12(21)	17(21)	20(21)	17(24)	18(27)
Trouble with speaking	4(17)	0(0)	12(27)	10(26)	9(22)	11(22)
Hair loss*	0(0)	0(0)	13(17)	33(33)	8(23)	0(0)

Scores are presented as mean. Standard deviations are shown between parentheses.
* Domains were removed after validation and refinement of the QLQ-OES24 into the QLQ-OES18 questionnaire.
EORTC: European organization for research and treatment of cancer.

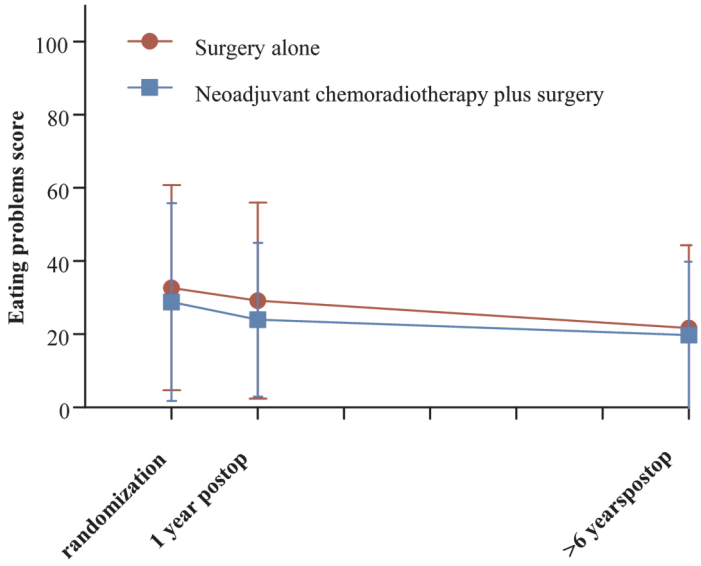
Table 3b. Mean scores for all domains in the K-BILD questionnaire according to treatment group.

	>6 years postoperatively		
	nCRT plus surgery	surgery alone	p-value
Psychological symptoms	86 (19)	87 (17)	0.95
Breathlessness and activity	73 (23)	77(23)	0.41
Chest symptoms	89 (17)	93 (16)	0.24
Total	81 (18)	83 (17)	0.69

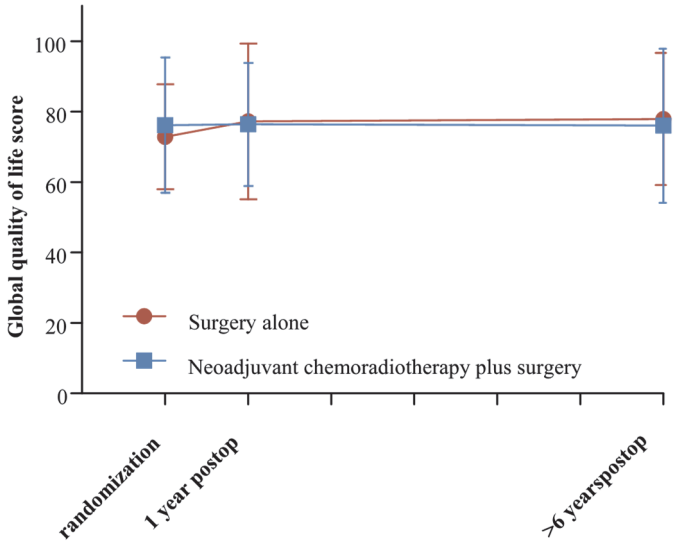
Figure 1. Mean scores with standard deviations for a) physical functioning, b) eating problems (primary endpoints), c) global quality of life and d) fatigue (secondary endpoints) according to treatment allocations.



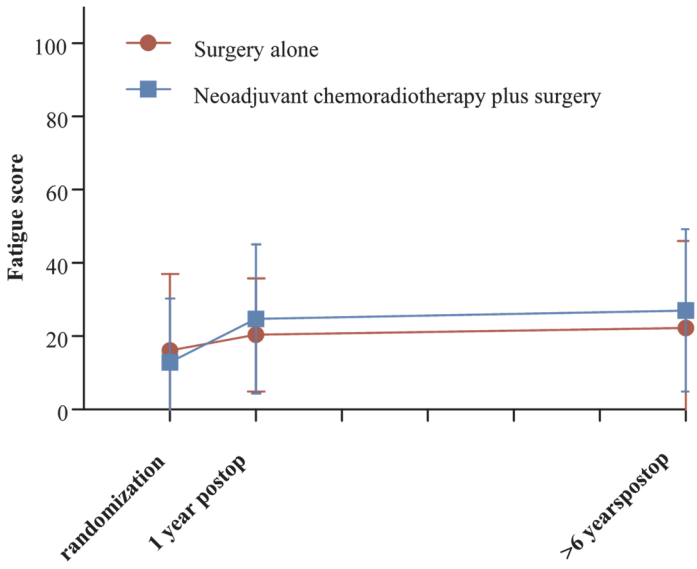
A



B


Global quality of life score
100
80
60
40
20
0
Surgery alone
Neoadjuvant chemoradiotherapy plus surgery
randomization
1 year postop
>6 yearspostop

C


Fatigue score
100
80
60
40
20
0
Surgery alone
Neoadjuvant chemoradiotherapy plus surgery
randomization
1 year postop
>6 yearspostop

D

References

1. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
2. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
3. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
4. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann oncol. 2016(27(suppl 5)):v50-v7.
5. Scarpa M, Valente S, Alfieri R et al. Systematic review of health-related quality of life after esophagectomy for esophageal cancer. World journal of gastroenterology : WJG. 2011;17(42):4660-74.
6. Noordman BJ, Verdam MGE, Lagarde SM et al. Impact of neoadjuvant chemoradiotherapy on health related quality of life in esopageal or junctional cancer: results from the randomized CROSS trial. In press, J Clin Oncol. 2017.
7. Blazeby JM, Sanford E, Falk SJ, Alderson D, Donovan JL. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. Cancer. 2005;103(9):1791-9.
8. Hauser C, Patett C, von Schoenfels W et al. Does neoadjuvant treatment before oncologic esophagectomy affect the postoperative quality of life? A prospective, longitudinal outcome study. Dis Esophagus. 2015;28(7):652-9.
9. Reynolds JV, McLaughlin R, Moore J, Rowley S, Ravi N, Byrne PJ. Prospective evaluation of quality of life in patients with localized oesophageal cancer treated by multimodality therapy or surgery alone. Br J Surg. 2006;93(9):1084-90.
10. Abratt RP, Morgan GW, Silvestri G, Willcox P. Pulmonary complications of radiation therapy. Clin Chest Med. 2004;25(1):167-77.
11. Sobin LH, Wittekind C, et al. TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss; 2002.
12. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
13. Blazeby JM, Conroy T, Hammerlid E et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. Eur J Cancer. 2003;39(10):1384-94.
14. Patel AS, Siegert RJ, Brignall K et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax. 2012;67(9):804-10.
15. Fayers PM, Aaronson NK, Bjordal K et al. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
16. Twisk J, de Vente W. Attrition in longitudinal studies. How to deal with missing data. J Clin Epidemiol. 2002;55(4):329-37.
17. Cohen J. Statistical power analysis for the behavorial sciences. 2nd ed. Hillsdale, New Jersey: Erlbaum; 1988.
18. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582-92.

19. Hurmuzlu M, Aarstad HJ, Aarstad AK, Hjermstad MJ, Viste A. Health-related quality of life in long-term survivors after high-dose chemoradiotherapy followed by surgery in esophageal cancer. Dis Esophagus. 2011;24(1):39-47.
20. Derogar M, Lagergren P. Health-related quality of life among 5-year survivors of esophageal cancer surgery: a prospective population-based study. J Clin Oncol. 2012;30(4):413-8.
21. Schandl A, Lagergren J, Johar A, Lagergren P. Health-related quality of life 10 years after oesophageal cancer surgery. Eur J Cancer. 2016;dec(69):43-50.
22. Lagergren P, Avery KN, Hughes R et al. Health-related quality of life among patients cured by surgery for esophageal cancer. Cancer. 2007;110(3):686-93.
23. Gielissen MF, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. J Clin Oncol. 2006;24(30):4882-7.
24. Putora PM, Bedenne L, Budach W et al. Oesophageal cancer: exploring controversies overview of experts' opinions of Austria, Germany, France, Netherlands and Switzerland. Radiat Oncol. 2015;10:116.
25. Noordman BJ, Shapiro J, Spaander MC et al. Accuracy of detecting residual disease after CROSS neoadjuvant chemoradiotherapy for esophageal cancer (preSANO Trial): rationale and protocol. JMIR Res Protoc. 2015;4(2):e79.

PART II

Active surveillance after neoadjuvant chemoradiotherapy

Chapter 13

Accuracy of detecting residual disease after CROSS neoadjuvant chemoradiotherapy for esophageal cancer (preSANO trial): rationale and protocol

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JMIR Research Protocols 2015;4(2):e79

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Abstract

Background

Results from the recent CROSS trial showed that neoadjuvant chemoradiotherapy (nCRT) significantly increased survival as compared to surgery alone in patients with potentially curable esophageal cancer. Furthermore, in the nCRT arm 49% of patients with a squamous cell carcinoma and 23% of patients with an adenocarcinoma had a pathologically complete response in the resection specimen. These results provide a rationale to reconsider and study the timing and necessity of esophagectomy in (all) patients after application of the CROSS-regimen.

Objective

We propose a *surgery as needed* approach after completion of nCRT. In this approach, patients will undergo active surveillance after completion of nCRT. Surgical resection would be offered only to those patients in whom residual disease or a locoregional recurrence is highly suspected or proven. However, before a *Surgery As Needed approach in Oesophageal cancer patients* (SANO) can be tested in a randomized controlled trial, we aim to determine the accuracy of detecting the presence or absence of residual disease after nCRT (preSANO trial).

Methods

This study is set up as a prospective, single arm, multicenter, diagnostic trial. Operable patients with potentially curable squamous cell- or adenocarcinoma of the esophagus or esophago-gastric junction will be included. Approximately 4-6 weeks after completion of nCRT all included patients will undergo a first clinical response evaluation (CRE-I) including endoscopy with (random) conventional mucosal biopsies of the primary tumor site and of any other suspected lesions in the esophagus and radial endoultrasonography (EUS) for measurement of tumor thickness and -area. Patients in whom no locoregional or disseminated disease can be proven by (cyto)histology will be offered a postponed surgical resection, 6-8 weeks after CRE-I (*i.e.* approximately 12-14 weeks after completion of nCRT). In the week preceding the postponed surgical resection a second clinical response evaluation (CRE-II) will be planned, which will include a whole body PET-CT, followed again by endoscopy with (random) conventional mucosal biopsies of the primary tumor site and any other suspected lesions in the esophagus, radial EUS for measurement of tumor thickness and –area and linear EUS plus fine needle aspiration of PET-positive lesions and/ or suspected lymph nodes. The main study parameter is the correlation between the clinical response assessment during CRE-I and CRE-II and the final pathological response in the resection specimen.

Results

Enrolment began July 23, 2013, results expected January 2016.

Discussion

If this preSANO trial shows that the presence or absence of residual tumor can be predicted reliably 6 or 12 weeks after completion of nCRT, a randomized trial comparing nCRT plus standard surgery versus chemoradiotherapy plus 'surgery as needed' will be conducted (SANO trial).

Registration

Netherlands Trial Register (NTR4834)

Background

Cancer of the esophagus remains a highly lethal malignancy, as reflected by an average overall five-year survival of 17%.[1] In the Netherlands, the incidence of esophageal cancer resembles the growing trend in Western countries, with an estimated incidence of 15/100,000 for men and 6/100,000 for women[2], and more than 2,500 new cases diagnosed nationally each year.

At present, surgical resection is still considered the cornerstone of curative treatment for patients eligible with stage cT1b-4aN0-3M0 disease. The reported five-year survival rate for patients who undergo an esophagectomy ranges from 20 to 50%, but rarely exceeds 35%.[3-7]. Esophagectomy is associated with postoperative mortality rates of 1-5% in high-volume centers, severe postoperative morbidity and a substantial impact on the quality of life.[8-13] In order to improve the radicality of surgical resection and the long term survival after surgical resection many trials have been performed to study the effect of (neo-) adjuvant chemo- and/or radiation therapy.[14-17] One of the largest trials is the recently published CROSS trial. This randomized trial compared neoadjuvant chemoradiotherapy (nCRT) plus surgery to surgery alone.[18] During a five-year period 366 patients from 5 academic and 2 non-academic high-volume teaching hospitals in the Netherlands were included. This study showed that the addition of nCRT (Carboplatin AUC2, Paclitaxel 50 mg/m^2 and 41.4 Gy of concurrent radiotherapy) to surgery significantly increases long term survival as compared to surgery alone. Median overall survival of patients who received nCRT plus surgery was 49 months, compared to 24 months for those who received surgery alone and the 3-year overall survival was superior in the nCRT arm (hazard ratio (HR) = 0.66; 95% confidence interval (CI) 0.50-0.87; p=0.003). Therefore, nCRT plus surgery is now considered the therapy of choice in the Netherlands and several other countries for potentially curable esophageal cancer (cT2-3N0-3M0 and cT1N1-3M0, according to the UICC TNM classification, 7th ed.).[19] In subsequent analyses of secondary endpoints of the CROSS trial an interesting observation was made. In the nCRT arm, 49% of patients with a squamous cell carcinoma (SCC) and 23% of patients with an adenocarcinoma (AC) had a pathologically complete response (pCR) in the resection specimen (*i.e.* no viable tumor cells were found, neither at the site of the primary tumor nor in the resected regional lymph nodes, as determined by conventional histological examination).[18] Therefore, these results provide a rationale to reconsider and study the timing and necessity of standard esophagectomy in (all) patients after application of the CROSS regimen.

We propose a *surgery as needed* approach after completion of nCRT for carcinoma of the esophagus. In this *surgery as needed* approach, patients will undergo active surveillance after completion of nCRT. Surgical resection would be offered only to those patients in whom a locoregional recurrence is highly suspected or proven, in the absence

of any signs of distant dissemination. Such an organ-preserving strategy would clearly have great advantages. Postoperative mortality and severe morbidity (grade ≥3 according to the Clavien-Dindo classification[20]) after esophagectomy in the Netherlands is 5% and 60%, respectively. Thus, a non-surgical treatment strategy in patients with a clinically complete response after nCRT, theoretically saves 5% mortality and 60% severe morbidity in this patient group. Moreover, this approach might improve quality of life and might lead to a reduction in health care costs. However, this *surgery as needed* approach is only favorable if long term survival would be comparable to that of the trimodality approach comprising nCRT followed by standard surgery. Before a *surgery as needed* approach can be tested in a randomized trial, we aim to determine the feasibility of accurate detection of residual disease after chemoradiotherapy.

The aim of this present prospective, multicenter, diagnostic preSANO study trial is to determine the accuracy by which we can detect the presence or absence of residual disease after nCRT. The results of this trial will inform us about the percentage of patients with a clinically complete response after nCRT, and will help to estimate the number of patients needed for a subsequent randomized controlled trial. This future so called SANO-trial (Surgery As Needed in Oesophageal cancer patients) will randomize patients to nCRT plus surgery versus nCRT followed by active surveillance.

Methods

Study design

The preSANO trial is a prospective, multicenter, diagnostic trial including 120 patients, using a single arm. Five high-volume centers in the Netherlands are currently participating in this study (Erasmus Medical Center, Rotterdam; Academic Medical Center, Amsterdam; University Medical Center, Utrecht; Catharina Cancer Center, Eindhoven; Atrium Medical Center, Heerlen). The study has been approved by the medical ethics committee of the Erasmus Medical Center (MEC2013-211) and has been registered in the Netherlands Trial Register (NTR4834).

Study population

We plan to include individuals from a population of operable patients with potentially curable SCC or AC of the esophagus or esophago-gastric junction. All patients who are planned to undergo nCRT according to the CROSS regimen[18], followed by surgical resection are eligible to participate. Patients with dementia or altered mental status prohibiting the understanding and giving of informed consent will be excluded from participation in this study. Patients will undergo conventional pre-treatment selection (in-

cluding at least a "*partial body*" F18-FDG PET-CT to assess the avidity of the primary tumor process; Figure 1 and Table 1).

Study algorithm

Overview

All included patients will receive nCRT according to the CROSS protocol (Carboplatin, Paclitaxel and 41.4 Gy of concurrent radiotherapy).[18] Patients will be reevaluated either once or twice before undergoing surgical resection during *clinical response evaluations* (CRE). The aim of these CREs will be to identify those patients in whom residual and/or disseminated disease is present.

CRE-I

The first CRE (CRE-I) will be performed 4-6 weeks after completion of chemoradiotherapy (Figure 1). During CRE-I, all patients will undergo esophagogastroduodenoscopy (EGD) with registration of endoscopic images for future reference and biopsies of any suspected lesions, including mucosal biopsies at the site of the primary tumor (one regular biopsy per centimeter in each of the 4 quadrants), radial endoscopic ultrasonography (EUS) for measurement of maximal tumor thickness and –area and linear EUS. Patients with (cyto)histological evidence of locoregional residual disease, but without evidence of disseminated disease, will be offered immediate surgical resection. These patients have no clear benefit from postponement of surgical resection and should therefore have no delay according to current recommendations. Patients without (cyto)histological evidence of locoregional residual disease and without disseminated disease will be considered to be *clinically complete responders* and will be offered a postponed surgical resection. In these patients a surgical resection will be postponed for an additional 6-8 weeks, allowing patients more time to reach a better condition for surgery.

CRE-II

In the week preceding the planned postponed surgical resection a second clinical response evaluation (CRE-II) will be scheduled. CRE-II will be performed only in patients who were considered to be clinically complete responders (*i.e.* no viable tumor found) at CRE-I. CRE-II will consist of a PET-CT (standard for all patients at CRE-II and only for tumor positive patients at CRE-I), an EGD with registration of endoscopic images for future reference and biopsies of any suspected lesions, including (random) mucosal biopsies at the site of the primary tumor, radial endoscopic ultrasonography (EUS) for measurement of maximal tumor thickness and -area and linear EUS plus fine needle aspiration (FNA) of PET-positive lesions and/ or suspected lymph nodes.

An important difference between CRE-I and CRE-II will be that during CRE-I clinically complete responders will be offered a postponed surgical resection, whereas after CRE-II both locoregionally complete- and non-complete responders will be advised to undergo a surgical resection (Figure 1). In other words, all patients who are considered clinically complete responders at CRE-I and are therefore allowed to postpone their surgery by an additional 6-8 weeks, will undergo CRE-II followed by the postponed surgical resection, irrespective of the locoregional findings during CRE-II. The diagnostic results from CRE-II will later be compared with results from both CRE-I and the final pathological analysis of the resection specimen. However, patients with (cyto)histological evidence of disseminated disease during CRE-I or CRE-II will be excluded from further curative therapy and will be referred for palliative care.

If after CRE-II the planned operation is postponed for more than 4 weeks (e.g. because the patient has not yet sufficiently recovered from the nCRT), a CRE-III (comparable to CRE-II) will be performed one week before the (further) postponed operation.

Surgery

Surgical resection will be attempted immediately after CRE-I only in those patients who present at CRE-I with (cyto)histologically proven residual disease after completion of nCRT, without any signs of disseminated disease. All other patients will undergo surgical resection after CRE-II in the absence of distant metastases.

A transthoracic esophageal resection or a transhiatal approach can be performed, depending on both patient characteristics and local expertise and preference. Both open and minimally invasive techniques are allowed.

A wide local excision including the regional lymph nodes is carried out in both techniques including a standard dissection of the lymph nodes around the coeliac axis. The continuity of the digestive tract will preferably be restored by a gastric tube reconstruction or if required by a colonic interposition.

At least 15, but preferably 23 or more lymph nodes should be aimed to be removed in every patient, since it has been shown that long-term survival is maximized with the removal of at least 23 nodes.[21] Moreover, the risk of understaging the tumor in these patients should be minimized. If an insufficient number of nodes is removed, the patient might be erroneously staged as ypN0, while in fact ypNpos nodes have been left *in-situ* (stage migration).

Pathology

All resection specimens will be revised centrally by two independent expert pathologists, using a standard protocol. In case of a discordant outcome, the specimens will be reviewed by a third independent expert pathologist. A final diagnosis will be made only if at least two pathologists agree. Also, all the CRE-II biopsies of patients who were con-

sidered negative at CRE-II, but who had >10% residual tumor in their resection specimen will be revised centrally following the same strategy. In these specimens special attention will be given to the effects of the preoperative chemoradiation, *i.e.* tumor reduction and therapy effects. The lymph node dissection should contain at least 15, but preferably 23 or more nodes derived from both mediastinum and upper abdomen which are essential for correct ypTNM staging. The resection margins, especially the circumferential margin, will be evaluated with a 1mm cut-off point for vital tumor. This implies that the tumor-free margin should be >1mm in order to be classified as R_0. If vital tumor is present at ≤1mm from the surgical resection margin it is considered microscopically positive (R_1).

Interim analysis

An interim analysis will be performed by an independent safety committee after a total inclusion of 60 patients in order to carefully monitor serious complications during CRE-I and CRE-II and to assess the achieved radicality of the performed operations.

Main study parameter/endpoint

The main study parameter in this study is the correlation between the clinical response assessment during CRE-I and CRE-II and the final pathological response in the resection specimen, as measured by the modified tumor regression grading (TRG) system of Chirieac[22]; no residual carcinoma (TRG1), 1-10% residual carcinoma (TRG2), 11-50% residual carcinoma (TRG3), 51-100% residual carcinoma (TRG4).

We propose that in this study TRG2 residual tumors may be missed as long as we expect them to be detectable reliably as soon as they have outgrown from TRG2 to TRG3-4 during follow up. The risk that TRG2 residual tumors will lead to irresectability in the short-term is likely to be small/negligible. However, we do propose that TRG3 and TRG4 residual tumors should be detected without further delay in order to prevent short-term loss of resectability and to minimize the risk of long-term distant disease dissemination. The validity of these assumptions can only be determined in a future SANO trial, in which an active surveillance strategy will be compared with standard surgery in all patients after nCRT.

Statistical analysis

Sample size calculation

As was seen in the previous CROSS trial approximately 40% of the included patients will have TRG3 or TRG4 residual tumor in the resection specimen.[18] With a total inclusion of 120 patients, approximately 45 patients will have TRG3 or TRG4 residual tumor. We consider 45 patients a sufficiently large sample for determining the accuracy of individ-

ual and/or combined diagnostic tests. In order to estimate the distribution of 120 patients planned to be included, data were used from the CROSS trial as indicated in Figure 2. Furthermore, several assumptions were made:

- We assume that during the first clinical response evaluation (CRE-I), clinically complete responders will comprise patients with TRG1 or TRG2 (as taken from the pathological response data of the CROSS trial), whereas clinically non-complete responders will be patients with TRG3 or TRG4.

- The percentage of patients with SCC and AC with TRG1 or TRG2 in the CROSS trial was 78% and 57%, respectively. This means that approximately 60% of included patients are expected to have negative (cyto)histology at CRE-I.

- In a trial by Blom *et al* [23] approximately 10% of patients who were re-evaluated by PET-CT after completion of nCRT had newly discovered disseminated disease. We assume less newly found disseminated disease with positive (cyto)histology at CRE-II, because a number of these patients are expected to be discovered during CRE-I.

- We assume that approximately 25% of clinically complete responders will refuse to undergo the postponed resection and choose to undergo an active surveillance strategy if no alarming results are found during CRE-II.

These calculations indicate that approximately 60 patients will show a clinically complete response after combined diagnostic investigations, during CRE-I and CRE-II (including EUS-FNA with tumor thickness measurements and PET-CT). Of these, approximately 15 patients will refuse to undergo surgery and will undergo active surveillance and approximately 30 patients will have a pathologically complete response (TRG1). The 15 remaining patients are expected to have residual disease, of whom approximately 12 patients will have TRG2 residual tumor and approximately 3 patients will have TRG3 or TRG4 residual tumor. As we proposed above, TRG2 residual tumors may be missed. Therefore, we expect that approximately 3 patients with clinically relevant residual disease (TRG3 or TRG4) will be missed.

In case of unexpected aberrant distribution of patients in the preSANO-trial that leads to decreased TRG3 and TRG4 rates, results of the first 120 patients will be analyzed following the present protocol. If these results are promising but do not reach statistical significance, possibly due to a lack of power, inclusion of extra patients will be considered. If inclusion of extra patients is desirable, the protocol will be amended and assessed by the medical ethics committee.

Data analysis

The clinical response evaluation will consist of different diagnostic modalities. Results of each diagnostic modality will be presented as categorical or continuous data, depending on the outcome measure of each diagnostic modality. These results will be correlated to the (categorical) tumor regression grading in the resection specimen, using a chi-square

based test (categorical-categorical) or a one-way ANOVA test (continuous-categorical) with post-hoc testing.

Results

The first patient has been enrolled on July 23, 2013 and results are expected in January 2016.

Discussion

The uniqueness of this study lies in the prospective evaluation of a sufficiently large number of patients, using multiple diagnostic modalities on different time points. Although (cyto)histological assessment of biopsies and / or FNAs is the most objective parameter, several studies have shown that the response to nCRT is reflected by tumor size or volume as assessed by EUS.[24-27] The rationale to include a second clinical response evaluation before a planned surgical resection is to allow for a comparison between multiple measurements and to increase the chance of detecting residual- and/or disseminated disease. It is expected that during CRE-II (due to an extended time period from the end of nCRT) the F18-FDG PET-CT signal will have a more favorable signal-to-noise ratio than has been described previously[28-33], because after 12 weeks the artefacts due to radiation-induced inflammation are expected to have largely dissolved. This allows for identification of suspected lymph nodes to be targeted by FNA during CRE-II.

The reason to include patients with SCC as well as patients with AC in the preSANO trial, is that the CROSS regimen has been shown to be effective in both groups of patients. The pCR rate of 49% in patients with SCC and 23% in patients with AC in the CROSS trial, provide a rationale for a SANO approach in both histological subtypes . Furthermore, together with the low frequency of toxic effects of the CROSS regimen (91% received the full treatment regimen of nCRT), these high pCR rates advocate the use of the relatively low dose of 41.4 Gy radiotherapy.[18]

Although we have not yet clearly shown that we are able to detect a clinically threatening residual cancer 4-6 weeks after nCRT, there are several arguments why it is not deemed necessary to do so before we can further delay the planned surgical resection with an additional 6-8 weeks. Recently, it was shown that prolonged time to surgery after nCRT up to at least 12 weeks had no effect on disease-free- and overall survival (HR=1.00 and HR=1.06 per additional week, p=0.976 and p=0.139, respectively). Moreover, prolonged time to surgery increased the probability of pCR in the resection speci-

men (odds ratio, OR=1.35 per additional week of time to surgery, p=0.0004).[34] Comparable results have been published by other groups.[35, 36]

Postoperative mortality and severe morbidity (grade ≥3 according to the Clavien-Dindo classification[20]) after esophagectomy in the Netherlands is 5% and 60%, respectively. Thus, a non-surgical treatment strategy in patients with a clinically complete response after nCRT, theoretically saves up to 5% mortality and 60% severe morbidity in this patient group. Moreover, this approach might improve quality of life and might lead to a reduction in health care costs. Therefore, we will consider this study as successful when the results of the combined diagnostic modalities lead to a maximum percentage of clinically false-negative TRG3 and TRG4 tumors of twice the postoperative mortality (*i.e.* 10%). If more than 10% of TRG3 or TRG4 tumors will be missed, the SANO trial will be reconsidered.

If the preSANO trial shows that TRG3 and TRG4 residual tumor can be predicted reliably, a randomized trial comparing nCRT plus standard surgery versus chemoradiotherapy plus '*Surgery As Needed in Oesophageal cancer patients*' (the SANO trial) will be conducted. Hopefully, this SANO trial will result in an organ-preserving treatment strategy for a selected group of patients and therefore reduce treatment related morbidity and mortality, improve quality of life and lead to a reduction in health care costs.

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Table 1. Study algorithm

Parameter	Pretreatment	First clinical response evaluation (CRE-I)	Second clinical response evaluation (CRE-II)
History, Physical Examination	X	X	X
Performance status	X	X	X
Haematology[1]	X		
eGFR	X		
Biochemistry[2]	X		
Endoscopy + (random) biopsies	X	X	X
Radial EUS[3]	X	X	X
Linear EUS (+FNA)[4]	X		X
CT of neck, thorax, abdomen and pelvis	X		
PET-CT	X *"partial body"*	X[7] *"whole body"*	X[8] *"whole body"*
Pulmonary function tests	X		
Bronchoscopy[5]	X		
ECG	X		
Toxicity[6]	Baseline		

[1] Hematology: CBC, differential

[2] Biochemistry: serum protein, albumin, magnesium, electrolytes, serum creatinin, bilirubin, alkaline phosphatase, AST, and pregnancy test if indicated at baseline only

[3] Radial EUS: with measurement of maximum tumor thickness and –area

[4] Linear EUS: with fine-needle aspiration (FNA) of any suspected lymph nodes

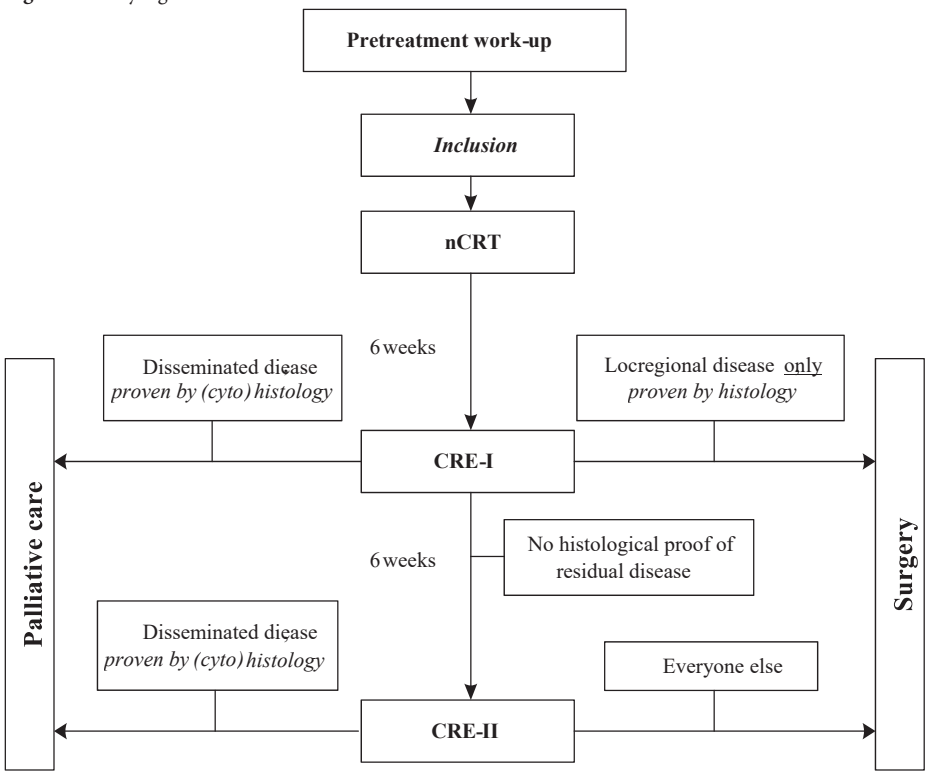
[5] Bronchoscopy: when tumor is located above the carina and when there is suspicion for invasion of the tracheo-bronchial tree

[6] Toxicity: to be evaluated after each cycle (incidence and grade according to CTC toxicity scale)

[7] PET-CT: during CRE-I, after EGD and EUS, only for clinically non-complete responders, to exclude disseminated disease

[8] PET-CT: during CRE-II, prior to EGD and EUS, for all patients (all were clinically complete responders during CRE-I) to guide EGD and EUS in targeting suspected locoregional lesions and to exclude disseminated disease

Figure 1. Study algorithm.



Pretreatment work-up and clinical response evaluations include:

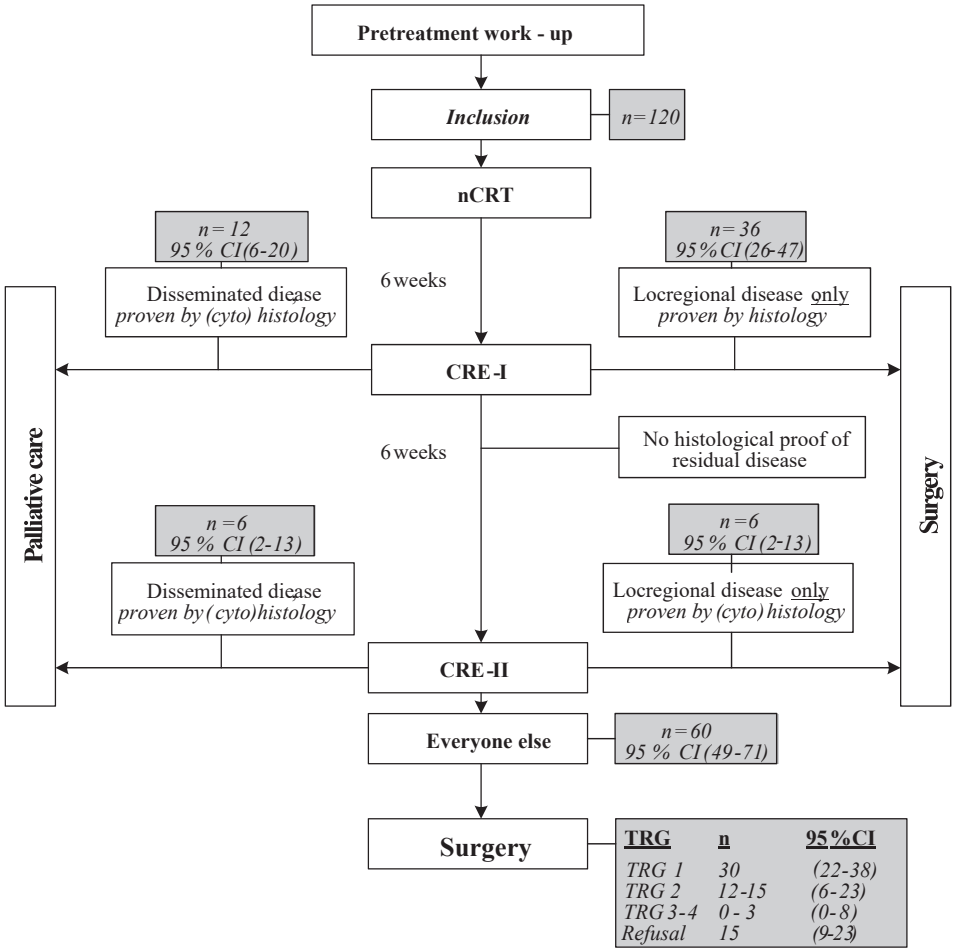
- 'partial body' or 'whole body' ^{18}F-FDG PET-CT[1]
- EGD (with biopsies)
- EUS (with FNA)[2]
- Dedicated CT of neck, thorax, abdomen and pelvis (in pretreatment work-up and on indication)
- Externa US of the neck (in pretreatment work-up and on indication)

[1] During the pretreatment work-up, it suffices when a "*partial body*" F18-FDG PET-CT of the esophagus will be performed (to test for avidity of the primary lesion); if it is preferred to make a "*whole-body*" PET-CT not only after, but also before the neoadjuvant chemoradiotherapy in order to detect distant metastases at an earlier stage, the indication for performing an external US with FNA of the neck can be limited to those patients who have a suspected lymph node on the PET-CT [23]. In the period after neoadjuvant therapy one *whole-body* F18-FDG PET-CT will be performed either at CRE-I (for the clinically non-complete responders) or at CRE-II (for the clinically complete responders at CRE-I).

[2] EUS with FNA of suspected lymph nodes only during CRE-II, not during CRE-I

CRE: clinical response evaluation; CT: computed tomography; EUS: endoscopic ultrasonography; FNA: fine-needle aspiration; nCRT: neoadjuvant chemoradiotherapy; EGD: esophagogastroduodenoscopy; PET: positron-emission tomography; US: ultrasonography.

Figure 2. Expected distribution of patients (based partly on CROSS-trial data)



All numbers are based on an inclusion of 120 patients. CI: confidence interval; CRE: clinical response evaluation; nCRT: neoadjuvant chemoradiotherapy; N: number of patients; TRG: tumor regression grade, as measured by the modified TRG system of Chirieac.[22] Of the 45 patients who will undergo a postponed resection following CRE-II, 15 patients are expected to have a pathologically incomplete response (at least TRG2).

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer Statistics, 2009. CA: A Cancer Journal for Clinicians. 2009;59(4):225-49.
2. Hoeymans N MJ, Schoemaker CG (red.) Gezondheid en determinanten. Deelrapport van de volksgezondheid toekomst verkenning 2010 van gezond naar beter 2010(RIVM-rapport nr. 270061006).
3. Nygaard K, Hagen S, Hansen HS et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: A randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second scandinavian trial in esophageal cancer. World J Surg. 1992;16(6):1104-9.
4. Gignoux M, Roussel A, Paillot B et al. The value of preoperative radiotherapy in esophageal cancer: Results of a study of the E.O.R.T.C. World J Surg. 1987;11(4):426-32.
5. Arnott SJ, Duncan W, Gignoux M et al. Preoperative radiotherapy for esophageal carcinoma. Cochrane Database Syst Rev. 2005(4):CD001799.
6. Kelsen DP, Ginsberg R, Pajak TF et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med. 1998;339(27):1979-84.
7. Wang M, Gu XZ, Yin WB, Huang GJ, Wang LJ, Zhang DW. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 206 patients. Int J Radiat Oncol Biol Phys. 1989;16(2):325-7.
8. Seely AJE, Ivanovic J, Threader J et al. Systematic classification of morbidity and mortality after thoracic surgery. Ann Thorac Surg. 2010;90(20732521):936-42.
9. Bailey SH, Bull DA, Harpole DH et al. Outcomes after esophagectomy: a ten-year prospective cohort. Ann Thorac Surg. 2003;75(12537219):217-22.
10. Donohoe CL, McGillycuddy E, Reynolds JV. Long-term health-related quality of life for disease-free esophageal cancer patients. World J Surg. 2011;35(8):1853-60.
11. Djarv T, Blazeby JM, Lagergren P. Predictors of postoperative quality of life after esophagectomy for cancer. J Clin Oncol. 2009;27(19289614):1963-8.
12. Djarv T, Lagergren J, Blazeby JM, Lagergren P. Long-term health-related quality of life following surgery for oesophageal cancer. Br J Surg. 2008;95(18581441):1121-6.
13. Verhoef C, van de Weyer R, Schaapveld M, Bastiaannet E, Plukker JT. Better survival in patients with esophageal cancer after surgical treatment in university hospitals: a plea for performance by surgical oncologists. Ann Surg Oncol. 2007;14(5):1678-87.
14. Cooper JS, Guo MD, Herskovic A et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281(17):1623-7.
15. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062-7.
16. Ychou M, Boige V, Pignon JP et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-21.
17. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
18. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
19. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer., ebrary Inc. TNM classification of malignant tumors. New York: Wiley-Blackwell; 2009. Available from: http://site.ebrary.com/lib/yale/Doc?id=10342913, last accessed: January 29th, 2018.

20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
21. Vansteenkiste JF, Stroobants SG, De Leyn PR et al. Lymph node staging in non-small-cell lung cancer with FDG-PET scan: a prospective study on 690 lymph node stations from 68 patients. J Clin Oncol. 1998;16(6):2142-9.
22. Chirieac LR, Swisher SG, Ajani JA et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer. 2005;103(7):1347-55.
23. Blom RL, Schreurs WM, Belgers HJ, Oostenbrug LE, Vliegen RF, Sosef MN. The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma. Eur J Surg Oncol. 2011;37(9):774-8.
24. Willis J, Cooper GS, Isenberg G et al. Correlation of EUS measurement with pathologic assessment of neoadjuvant therapy response in esophageal carcinoma. Gastrointest Endosc. 2002;55(6):655-61.
25. Isenberg G, Chak A, Canto MI et al. Endoscopic ultrasound in restaging of esophageal cancer after neoadjuvant chemoradiation. Gastrointest Endosc. 1998;48(2):158-63.
26. Hirata N, Kawamoto K, Ueyama T, Masuda K, Utsunomiya T, Kuwano H. Using endosonography to assess the effects of neoadjuvant therapy in patients with advanced esophageal cancer. AJR Am J Roentgenol. 1997;169(2):485-91.
27. Jost C, Binek J, Schuller JC et al. Endosonographic radial tumor thickness after neoadjuvant chemoradiation therapy to predict response and survival in patients with locally advanced esophageal cancer: a prospective multicenter phase ll study by the Swiss Group for Clinical Cancer Research (SAKK 75/02). Gastrointest Endosc. 2010;71(7):1114-21.
28. Gillham CM, Lucey JA, Keogan M et al. (18)FDG uptake during induction chemoradiation for oesophageal cancer fails to predict histomorphological tumour response. Br J Cancer. 2006;95(9):1174-9.
29. Flamen P, Van Cutsem E, Lerut A et al. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. Ann Oncol. 2002;13(3):361-8.
30. Song SY, Kim JH, Ryu JS et al. FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. Int J Radiat Oncol Biol Phys. 2005;63(4):1053-9.
31. Levine EA, Farmer MR, Clark P et al. Predictive value of 18-fluoro-deoxy-glucose-positron emission tomography (18F-FDG-PET) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. Ann Surg. 2006;243(4):472-8.
32. Arslan N, Miller TR, Dehdashti F, Battafarano RJ, Siegel BA. Evaluation of response to neoadjuvant therapy by quantitative 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography in patients with esophageal cancer. Mol Imaging Biol. 2002;4(4):301-10.
33. McLoughlin JM, Melis M, Siegel EM et al. Are patients with esophageal cancer who become PET negative after neoadjuvant chemoradiation free of cancer? J Am Coll Surg. 2008;206(5):879-86; discussion 86-7.
34. Shapiro J, van Hagen P, Lingsma HF et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. Ann Surg. 2014;260(5):807-14.
35. Kim JY, Correa AM, Vaporciyan AA et al. Does the timing of esophagectomy after chemoradiation affect outcome? Ann Thorac Surg. 2012;93(1):207-13.
36. Ruol A, Rizzetto C, Castoro C et al. Interval Between Neoadjuvant Chemoradiotherapy and Surgery for Squamous Cell Carcinoma of the Thoracic Esophagus. Annals of Surgery. 2010;252(5):788-96.

Chapter 14

Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study

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Summary

Background

After neoadjuvant chemoradiotherapy for oesophageal cancer, roughly half of the patients with squamous cell carcinoma and a quarter of those with adenocarcinoma have a pathological complete response of the primary tumour before surgery. Thus, the necessity of standard oesophagectomy after neoadjuvant chemoradiotherapy should be reconsidered for patients who respond sufficiently to neoadjuvant treatment. In this study, we aimed to establish the accuracy of detection of residual disease after neoadjuvant chemoradiotherapy with different diagnostic approaches, and the optimal combination of diagnostic techniques for clinical response evaluations.

Methods

The preSANO trial was a prospective, multicentre, diagnostic cohort study at six centres in the Netherlands. Eligible patients were aged 18 years or older, had histologically proven, resectable, squamous cell carcinoma or adenocarcinoma of the oesophagus or oesophagogastric junction, and were eligible for potential curative therapy with neoadjuvant chemoradiotherapy (five weekly cycles of carboplatin [area under the curve 2 mg/mL per min] plus paclitaxel [50 mg/m² of body-surface area] combined with 41.4 Gy radiotherapy in 23 fractions) followed by oesophagectomy. 4–6 weeks after completion of neoadjuvant chemoradiotherapy, patients had oesophagogastroduodenoscopy with biopsies and endoscopic ultrasonography with measurement of maximum tumour thickness. Patients with histologically proven locoregional residual disease or no-pass during endoscopy and without distant metastases underwent immediate surgical resection. In the remaining patients a second clinical response evaluation was done (PET–CT, oesophagogastroduodenoscopy with biopsies, endoscopic ultrasonography with measurement of maximum tumour thickness, and fine-needle aspiration of suspicious lymph nodes), followed by surgery 12–14 weeks after completion of neoadjuvant chemoradiotherapy. The primary endpoint was the correlation between clinical response during clinical response evaluations and the final pathological response in resection specimens, as shown by the proportion of tumour regression grade (TRG) 3 or 4 (>10% residual carcinoma in the resection specimen) residual tumours that was missed during clinical response evaluations. This study was registered with the Netherlands Trial Register (NTR4834), and has been completed.

Findings

Between July 22, 2013, and Dec 28, 2016, 219 patients were included, 207 of whom were included in the analyses. Eight of 26 TRG3 or TRG4 tumours (31% [95% CI 17–50]) were missed by endoscopy with regular biopsies and fine-needle aspiration. Four of 41

TRG3 or TRG4 tumours (10% [95% CI 4–23]) were missed with bite-on-bite biopsies and fine-needle aspiration. Endoscopic ultrasonography with maximum tumour thickness measurement missed TRG3 or TRG4 residual tumours in 11 of 39 patients (28% [95% CI 17–44]). PET–CT missed six of 41 TRG3 or TRG4 tumours (15% [95% CI 7–28]). PET–CT detected interval distant histologically proven metastases in 18 (9%) of 190 patients (one squamous cell carcinoma, 17 adenocarcinomas).

Interpretation

After neoadjuvant chemoradiotherapy for oesophageal cancer, clinical response evaluation with endoscopic ultrasonography, bite-on-bite biopsies, and fine-needle aspiration of suspicious lymph nodes was adequate for detection of locoregional residual disease, with PET–CT for detection of interval metastases. Active surveillance with this combination of diagnostic modalities is now being assessed in a phase 3 randomised controlled trial (SANO trial; Netherlands Trial Register NTR6803).

Research in context

Evidence before this study

We did not do a formal search of published work before this trial. The randomised CROSS trial established chemoradiotherapy (weekly administration of carboplatin and paclitaxel plus 41.4 Gy concurrent radiotherapy) followed by surgery as the standard of care for patients with oesophageal cancer, compared with surgery alone. However, after neoadjuvant chemoradiotherapy plus surgery, 29% of treated patients achieve a pathological complete response (as measured by histological examination of resection specimens), which provides a rationale for an active surveillance approach after neoadjuvant chemoradiotherapy with oesophagectomy offered only to patients with proven locoregional recurrence and without evidence of distant metastases. In a systematic review of four small retrospective studies, promising overall survival outcomes were associated with active surveillance after neoadjuvant chemoradiotherapy in patients with oesophageal cancer who had a clinically complete response. Additionally, previous small retrospective studies of single diagnostic modalities (endoscopy plus biopsy, endoscopic ultrasonography, or ^{18}F-fluorodeoxyglucose PET–CT) for detection of residual disease after neoadjuvant chemoradiotherapy have shown poor diagnostic accuracy. So far, the optimal combination of diagnostic tests for detection of residual disease in patients with oesophageal or gastroesophageal junction cancer after neoadjuvant chemoradiotherapy is unknown.

Added value of this study

By contrast with previous studies, in this multicentre, prospective cohort study, all available diagnostic modalities used for pre-treatment staging in clinical practice were applied to detect residual disease during active surveillance. These findings establish the optimal set of diagnostic modalities to accurately detect residual disease after neoadjuvant therapy in patients with oesophageal cancer, allowing the stratification of patients who would benefit from active surveillance versus radical oesophagostomy.

Implications of all the available evidence

Clinical response evaluations after neoadjuvant chemoradiotherapy for oesophageal cancer should consist of endoscopic ultrasonography with bite-on-bite biopsies and fine-needle aspiration of suspicious lymph nodes for detection of locoregional residual disease and PET–CT for detection of interval metastases. The promising diagnostic results of this study provide the rationale for a phase 3, randomised, controlled trial of active surveillance versus standard surgery in patients with oesophageal cancer treated with neoadjuvant chemoradiotherapy. Our results can be used to define the composition of the clinical response evaluations and subsequent surveillance examinations in future trials that could establish a new management protocol for patients with oesophageal cancer.

Introduction

Oesophageal cancer is an aggressive malignancy: the proportion of patients who achieve 5-year survival after primary oesophagectomy rarely exceeds 35%.[1] Overall survival has improved substantially in the past two decades, however, mainly as a result of the widespread use of neoadjuvant chemo-radiotherapy.[2] Five weekly cycles of carboplatin (area under the curve 2 mg/mL per min) plus paclitaxel (50 mg/m² of body-surface area) plus 41.4 Gy radiotherapy in 23 fractions followed by oesophagectomy significantly improved overall survival at 5 years compared with oesophagectomy alone (47% [95% CI 39–54] in the neoadjuvant group *vs* 33% [26–40] in the surgery only group; hazard ratio 0.68 [95% CI 0.53–0.88]; log-rank p=0.003).[3, 4] In 47 (29%) of 161 patients with oesophageal carcinoma (18 [49%] of 37 with squamous cell carcinoma and 28 [23%] of 121 with adenocarcinoma), a pathological complete response was noted after neoadjuvant chemoradiotherapy—ie, no viable tumour cells were detected in the resected specimen during conventional histological examination.[3]

This high frequency of pathological complete response provides a rationale to reconsider the necessity of standard oesophagectomy after neoadjuvant chemoradiotherapy.

Theoretically, active surveillance could be feasible in patients without locoregional or disseminated disease, given that oesophagectomy probably does not affect oncological outcomes in patients with no viable tumour cells. In a pan-active surveillance approach, patients would undergo regular clinical investigations after neoadjuvant chemoradiotherapy, and oesophagectomy would be offered only to those with proven locoregional recurrence and no evidence of distant metastases.[3, 5-7] However, an active surveillance approach would only be justified if the associated oncological outcomes were non-inferior to those achieved with standard surgery. To select patients for active surveillance, disease should be restaged after neoadjuvant chemoradiotherapy by means of clinical response evaluations, which need to accurately classify patients as complete or incomplete responders. We aimed to establish which combination of diagnostic tests for clinical response evaluation most accurately detects residual disease after neoadjuvant chemoradiotherapy in patients with oesophageal cancer.

Methods

Study design and participants

We did a prospective, multicentre, diagnostic cohort study at six centres in the Netherlands (appendix p 6); the study protocol has been previously published.[8] After adjuvant chemoradiotherapy, patients underwent a first clinical response evaluation. Patients found to be complete responders during the first clinical response evaluation (ie, those with no locoregional or disseminated disease proven by cytohistology) were offered postponed surgical resection, and in the week preceding surgery, a second clinical response evaluation was done before patients without distant metastases underwent oesophagectomy. If the planned operation was postponed for more than 4 weeks after the second clinical response evaluation (eg, because the patient had not sufficiently recovered from neoadjuvant chemoradiotherapy), a third clinical response evaluation was recommended a week before surgery.

Eligible patients were aged 18 years or older, had histologically proven, resectable, squamous cell carcinoma or adenocarcinoma of the oesophagus or oesophagogastric junction, and were eligible for potential curative therapy with neoadjuvant chemoradiotherapy followed by oesophagectomy.[3] Patients with a severe stricture (no pass) on initial endoscopic ultrasonographic staging at baseline (ie, pre-treatment) were also included. The study protocol was approved by the medical ethics committee of the Erasmus MC (Rotterdam, MEC-2013-211). All patients provided written informed consent.

Procedures

All patients underwent primary clinical staging at baseline, including oesophagogastroduodenoscopy with biopsies, endoscopic ultrasonography with measurement of maximum tumour thickness,[9] CT of the neck, chest, and upper abdomen, and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET–CT. Most patients were consciously sedated with midazolam during endoscopic ultrasonography; general anaesthesia was not routinely used.

The neoadjuvant chemoradiotherapy regimen consisted of five weekly cycles of carboplatin (area under the curve 2 mg/mL per min) plus paclitaxel (50 mg/m^2 of body-surface area) combined with 41.4 Gy radiotherapy in 23 fractions, as per the CROSS trial recommendations.[3] 4–6 weeks after completion of the last cycle of neoadjuvant chemotherapy, patients underwent a first clinical response evaluation before surgery to identify non-responders. During this clinical response evaluation, all patients underwent oesophagogastroduodenoscopy with biopsies and radial endoscopic ultrasonography with measurement of maximum tumour thickness and area. Patients with a severe stricture at endoscopy (no-pass) or histological evidence of locoregional residual disease underwent PET–CT to exclude distant metastases. If no distant metastases were detected, eligible patients underwent surgery within 2 weeks of the PET–CT assessment. Patients without histological evidence of residual disease during the first clinical response evaluation were offered postponed surgery scheduled approximately 6–8 weeks after the first clinical response evaluation and approximately 12–14 weeks after neoadjuvant chemoradiotherapy (compared with 6–8 weeks after neoadjuvant chemoradiotherapy for those with histological evidence of residual disease). In the week before surgery, we did a second clinical response evaluation to detect any residual disease that had developed or was previously undetected. The second clinical response evaluations comprised PET–CT, followed by oesophagogastroduodenoscopy with biopsies, radial endoscopic ultrasonography for measurement of maximum tumour thickness and area, and linear endoscopic ultrasonography plus fine-needle aspiration of any suspicious lymph nodes or ^{18}F-FDG-avid lesions. After the second clinical response evaluation, all patients without distant metastases underwent oesophagectomy. The third clinical response evaluation (in patients who needed it) was similar to the second.

When we designed the trial, endoscopy with random, conventional mucosal biopsies of the primary tumor site and of any other suspected lesions in the oesophagus were prespecified by protocol as part of the clinical response evaluations,8 because the safety of deep bite-on-bite biopsies after neoadjuvant chemoradiotherapy was unknown. An interim safety analysis was pre-planned after inclusion of 60 patients to monitor serious complications and assess the radicality of the performed operations. On April 20, 2015, after about 95 patients were enrolled and had a regular biopsy, the interim safety analy-

sis showed no biopsy-related adverse events, and the protocol was amended on June 22, 2015, to change the biopsy strategy. Thereafter, bite-on-bite biopsies were done instead of conventional biopsies during clinical response evaluations.[10]

During bite-on-bite biopsies, a second, deep, biopsy sample is taken at the same location as the first to increase the chance of detecting residual disease— especially submucosal—tumours (appendix p 7). Biopsies were taken from at least four different locations from the primary tumour site and from any suspicious lesions in the oesophagus. The regular biopsy procedure consisted of one biopsy of at least four different locations on the site of the primary tumour and from any suspicious lesion. All endoscopy reports and endoscopic ultrasonography images were reviewed by an experienced upper-gastrointestinal gastroenterologist (MCWS), who was blinded to pathological response results in the resected specimen after surgery.

During the second clinical response evaluation, fine-needle aspiration was done on any suspicious lymph nodes (round, hypoechogenic, and greater than 5 mm in diameter), or any lymph nodes adjacent to the primary tumour. Potential contamination from the primary tumour during fine-needle aspiration of adjacent lymph nodes was not an issue because the source of residual disease was not a variable considered in the trial outcome analyses. Maximum tumour thickness was measured as reported previously[9], maximum tumour thickness of 6 mm or greater during the second clinical response evaluation was classified as non-complete response.[9]

Biopsies done at the first clinical response evaluation with uncertain outcome were deemed negative to reduce the risk of false-positive biopsies, whereas those with uncertain outcomes done at the second clinical response evaluation were judged positive to reduce the risk of false-negative biopsies, in light of a future active surveillance strategy in patients with a clinical complete response after second clinical response evaluation.[11, 12] Fine-needle aspirates taken from suspicious lymph nodes with uncertain outcomes or that were not representative (ie, no lymphoid tissue present) were considered positive for residual disease. PET–CT was done according to the European Association of Nuclear Medicine guidelines.[13] All scans were reviewed by an experienced PET–CT radiologist (RV), who was blinded to pathological response results

^{18}F-FDG PET–CT scans were visually assessed, including intensity of uptake and ^{18}F-FDG uptake in the environment (eg, adjacent oesophagus). A qualitative judgment was made, and results were scored from 1 to 5: 1 (benign), 2 (probably benign), 3 (equivocal), 4 (probably malignant), and 5 (malignant). To ensure we did not exclude any tumour residue, we defined all scores of 2 or higher as ^{18}F-FDG positive. For locoregional response assessment, ^{18}F-PET–CT scans from the first clinical response evaluation were analysed, whereas for distant dissemination scans from both clinical response evaluations, if available, were used.

Transthoracic or transhiatal oesophagectomy was done depending on patient characteristics and local preference. A wide excision, including removal of regional lymph nodes and standard dissection of the lymph nodes around the coeliac axis, was done in all patients with the aim of removing at least 15 lymph nodes.

Resected tumours reviewed by an experienced upper gastrointestinal pathologist (KB [an author] and MD [a collaborator]) following a standard protocol, and classified and graded according to the Union for International Cancer Control TNM Cancer Staging (7th edn).[14] We used the Chirieac modified tumour regression grade (TRG) system,[15] the most commonly used system in the Netherlands, to classify pathological response in the resected specimens as no residual carcinoma (TRG1), 1–10% residual carcinoma (TRG2), 11–50% residual carcinoma (TRG3), and greater than 50% residual carcinoma (TRG4).[15] All negative biopsies in patients with TRG3 or TRG4 tumours were re-reviewed by KB and MD.

Serious adverse events, which resulted in death, were life threatening, required hospital admission or prolongation of hospital stay, resulted in persistent or significant disability or incapacity, or were considered serious by the treating physician, were monitored continuously from the first clinical response evaluation until the day that the patient underwent surgery. Participants could leave the study at any time for any reason if they wished to do so, and investigators could withdraw participants from the study for urgent medical reasons.

Outcomes

The primary outcome was to establish the accuracy of residual disease detection after neoadjuvant chemoradiotherapy, as reflected by the proportion of tumours classified as TRG3 or TRG4 that was missed during clinical response evaluations. The secondary outcome was the proportion of patients who had an R0 resection, defined as a resection with no gross or microscopic tumour cells present. Other prespecified outcomes were correlations between individual diagnostic modality (endoscopic examinations, PET–CT, and analysis of cytohistological biopsies) and pathological findings in the resection specimen, and optimal cutoffs with maximal distinction between patients with and without clinically relevant residual disease. Results for R0 resection will be published elsewhere.

Statistical analysis

We hypothesised that TRG3 and TRG4 tumours could be detected reliably with the described clinical response evaluations. The estimated maximum percentage of clinically false-negative TRG3 and TRG4 tumours accounted for was 10%.[8] Initially, we aimed to enroll 120 patients, approximately 45 (38%) of whom were estimated to have TRG3

or TRG4 residual tumours after surgery as per the CROSS trial results.[3] However, because of the change in biopsy strategy as per protocol amendment (June 22, 2015) after about 95 patients were enrolled and had a regular biopsy, the total sample size was increased to 215, to ensure that at least 120 patients would undergone bite-on-bite biopsies during the clinical response evaluations.

Outcomes were analysed separately for both biopsy strategies (regular biopsies *vs* bite-on-bite biopsies). For endoscopic biopsies, results from both clinical response evaluations were combined (if either was positive, the patient was classified as having residual disease). Outcomes of endoscopic ultrasonography with measurement of maximum tumour thickness and PET–CT were analysed in the overall patient population, because these modalities were not amended during the trial. Patients who did not have neoadjuvant chemoradiotherapy or who withdrew consent, and those with missing index tests because of protocol violation or death were excluded from all analyses. Patients with missing reference standard (ie, TRG) were excluded from the primary analysis. Perioperatively irresectable tumours (T4b) confirmed with frozen section analysis were classified as TRG4. 95% CIs were calculated according to the Wilson procedure, without a correction for continuity. Results of PET–CT and endoscopy with biopsies and fine-needle aspiration, and maximum tumour thickness measurement were correlated to TRG with the χ^2 test. An interim safety analysis (the results of which will be published elsewhere) was done to assess the radicality of the performed operations after a total inclusion of 60 patients. The pre-planned stopping rule established that if the proportion of patients with a radical resection was 70% or less in the first 60 patients, the trial would be stopped.

We calculated sensitivity, specificity, positive predictive value, and negative predictive value for TRG2, TRG3, and TRG4 combined versus TRG1. Patients with TRG2 tumours were not excluded from sensitivity, specificity, negative predictive value and positive predictive value analyses because this would bias results. As a secondary sensitivity analysis, we used multiple imputation of TRG for patients who had active surveillance (instead of surgery) after clinical response evaluations to calculate the proportion of TRG3 and TRG4 residual tumours that was missed during clinical response evaluations, and sensitivity, specificity, positive predictive values, and negative predictive values for combined TRG2–4 versus TRG1.[16] We used a significance level of 0.05, based on two-sided tests. All analyses were done in SPSS (version 21.0). This study is registered with the Netherlands Trial Register (NTR4834).

Role of the funding source

The study funder had no role in study design; data collection, analysis, interpretation, or writing of the report. JJBvL had access to all study data and had final responsibility for the decision to submit for publication.

Results

Between July 22, 2013, and Dec 28, 2016, 219 patients were enrolled (Figure 1); 12 (6%) were excluded from further analyses: eight patients withdrew consent and four did not received the complete neoadjuvant chemoradiotherapy regimen (one had neoadjuvant chemotherapy only, two had definitive chemoradiotherapy, and one received palliative chemotherapy). Of 207 patients who underwent clinical response evaluations, 84 (41%) had clinical response evaluations with upper endoscopy and regular biopsies, of whom 61 (73%) were included in the analyses, and 123 (59%) had bite-on-bite biopsies, of whom 115 (93%) were included in the corresponding analyses (Figure 1). Of the 207 patients who underwent clinical response evaluations, 113 (55%) were included in the endoscopic ultrasonographic examination of maximum tumour thickness, and 129 (62%) were included in the PET–CT analysis (Figure 1). Baseline characteristics of all patients who underwent clinical response evaluations are shown in Table 1.

Outcomes of regular biopsies and fine-needle aspiration during clinical response evaluations were significantly associated with the TRG of resected specimens (p=0.0036; Table 2). Eight of 26 patients who had a regular biopsies and fine-needle aspiration, with a passable endoscopy, had negative biopsies despite having a TRG3 or TRG4 tumour (proportion of clinically false-negative cases 31% [95% CI 17–50]). 31 (51%) of 61 patients had positive biopsies, positive fine-needle aspiration, or no-pass. Sensitivity, specificity, negative predictive value, and positive predictive value of TRG2–4 versus TRG1 were 54% (95% CI 38–68; 20 of 37), 69% (42–87; nine of 13), 35% (19–54; nine of 26), and 83% (64–93; 20 of 24), respectively (Table 2). Four patients with TRG1 residual tumours had false-positive results (one had a positive biopsy, one no-pass, one had an uncertain biopsy at the second clinical response evaluation, and one non-representative fine-needle aspiration specimen from suspicious lymph node).

Outcomes of bite-on-bite biopsies and fine-needle aspiration during clinical response evaluations were significantly associated with the TRG of resected specimens (p<0.0001; Table 2). Four of 41 patients who had bite-on-bite biopsies and fine-needle aspiration had negative results despite having TRG3 or TRG4 tumours(proportion of clinically false negative cases 10% [95% CI 4–23]; Table 2). 69 (60%) of 115 patients had positive bite-on- bite biopsies, positive fine-needle aspiration, or nopass at endoscopy. After the first clinical response evaluation 45 (39%) of 115 patients who had bite-on-bite

biopsies had a positive index test. All four of 41 patients with a negative bite-on-bite biopsy (false-negative cases 10%, 95% CI 11–21; Table 2) had TRG3 residual disease—one patient had squamous cell carcinoma and three had adenocarcinomas. Sensitivity, specificity, negative predictive value, and positive predictive value of TRG2–4 versus TRG1 were 77% (95% CI 66–85; 54 of 70), 72% (49–88; 13 of 18), 45% (28–62; 13 of 29), and 92% (82–96; 54 of 59), respectively (Table 2). Of the five patients with TRG1 residual tumours who had false-positive results, four (80%) were no-pass, and one (20%) had a non-representative fine-needle aspiration specimen from a suspicious lymph node.

Of the 69 patients with positive bite-on-bite biopsies, fine-needle aspirate, or no-pass, seven (10%) had positive fine-needle aspirates, but negative biopsies and a passable tumour (ie, seven of the 24 positive second clinical response evaluations were based on positive fine-needle-aspiration results only). On the basis of biopsy results only (ie, without fine-needle aspiration data), eight (31%) of 26 TRG3 or TRG4 tumours were missed with regular biopsies, and seven (17%) of 41 with bite-on-bite biopsies.

95 (84%) of 113 patients included in the endoscopic ultrasonographic examination during the second clinical response evaluation underwent oesophagectomy. Maximum tumour thickness of 6 mm or greater during the second clinical response evaluation was significantly associated with TRG of resection specimens (p=0.035; Table 2). 11 (28%) of 39 patients with TRG3 or TRG4 residual disease had maximum tumour thickness of less than 6 mm at their second or third clinical response evaluation (proportion of clinically false-negative cases 28% [95% CI 17–44]; Table 2). Sensitivity, specificity, negative predictive value, and positive predictive value for TRG2–4 versus TRG1 residual disease were 60% (95% CI 48–71; 41 of 68), 59% (41–75; 16 of 27), 37% (24–52; 16 of 43), and 79% (66–88; 41 of 52), respectively (Table 2).

Outcomes of PET–CT during the second clinical response evaluation were not significantly associated with tumour regression grades (p=0.191; Table 2). Six of 41 patients with TRG3 or TRG4 residual tumours had negative PET–CT results (proportion of clinically false negative cases 15% [95% CI 7–28]; Table 2). 102 (79%) of 129 patients had positive PET–CT results during the second or third clinical response evaluation. The six patients with false-negative PET–CTs comprised two (33%) patients with TRG3 tumours and four (67%) patients with TRG4 tumours. Sensitivity, specificity, negative predictive value, and positive predictive value for TRG2–4 versus TRG1 were 80% (95% CI 70–88; 57 of 71), 37% (22–56; ten of 27), 42% (24–61; ten of 24), and 77% (66–85; 57 of 74), respectively (Table 2).

190 (92%) of 207 patients were included in the analysis of interval distant metastases (17 patients with missing follow-up scans were excluded: one participating centre did not do follow-up scans after a positive first clinical response evaluation). In 38 (20%) of 190 patients, PET–CT identified possible metastases, resulting in 18 (9%) cases of histologically proven metastases (one squamous cell carcinoma, 17 adenocarcinomas). De-

tection of distant metastases was more sensitive with PET–CT than with low-dose CT: ^{18}F-FDG-positive metastases would have been missed by CT in three patients; in another three patients, distant lymph nodes smaller than 6 mm in diameter would probably not have been scored positive without a positive .^{18}F-FDG-PET. In at least two of the remaining 12 patients, the positive findings on PET increased the confidence.

No biopsy-related or fine-needle-aspiration-related serious adverse events were encountered during any clinical response evaluation in any patients included in the analyses. One patient had a mucosal tear during endoscopy, but this event did not have treatment implications. Two patients died during the study (one because of an aorto-oesophageal fistula and one because of pulmonary failure). Neither death was related to clinical response evaluations.

Sensitivity analysis after imputation of the TRG for patients who had active surveillance after clinical response evaluations showed a proportion of false-negative case rates for detection of residual tumour similar to those in the main analysis (Table 3), for endoscopy with regular biopsies and fine-needle aspiration (31% [95% CI 13–49]), endoscopy with bite-on-bite biopsies and fine-needle aspiration (11% [1–21]), endoscopic ultrasonography with maximum tumour thickness at the second clinical response evaluation (29% [15–43]), and PET–CT at the second clinical response evaluation (14% [3–24]). The appendix shows outcomes for patients who were excluded from the analyses (p 2).

Discussion

To our knowledge, our trial is the first prospective study designed to assess the optimal composition of clinical response evaluations and the accuracy of residual disease detection in patients with oesophageal or junctional cancer. Repeated endoscopic ultrasonography with bite-on-bite biopsies and fine-needle aspiration of suspicious lymph nodes was safe, and missed 10% (95% CI 4–23) of TRG3 and TRG4 residual tumours after neoadjuvant chemoradiotherapy for oesophageal or junctional cancer. Endoscopic ultrasonography with regular biopsies and fine-needle aspiration, measurement of maximum tumour thickness, and PET–CT were less accurate to detect locoregional residual disease, as shown by the high proportion of false-negative cases. Results were similar in the sensitivity analyses, which used multiple imputation of TRG for patients who received active surveillance instead of oesophagectomy. PET–CT scans after neoadjuvant chemoradiotherapy detected new interval metastases in 9% (95% CI 6–14) of patients who had a pre-treatment or baseline PET–CT scan. These results provide insight into the optimal composition of clinical response evaluations after neoadjuvant chemoradiotherapy for patients with oesophageal or junctional cancer, and might help to stratify

patients who would benefit from active surveillance and those who should undergo oesophagectomy.

In view of the substantial postoperative morbidity and mortality associated with surgery, and the effect of surgery on quality of life, an active surveillance approach could improve outcomes, not only for patients who do not show signs of disease after neoadjuvant chemoradiotherapy, but also for those with subclinical distant metastases after neoadjuvant chemoradiotherapy.[3, 5-7] All available diagnostic modalities used in clinical practice for pretreatment staging were applied to detect residual disease, and compared to establish the optimal composition of future active surveillance strategies. Previous studies[17-22] of clinical response evaluations were retrospective and examined a single diagnostic modality for residual disease detection. Furthermore, the main objective of diagnostic examinations in previous studies[17-22] was not to detect residual disease to identify patients who might benefit from active surveillance. Therefore, diagnostic accuracy might have not been accurately estimated.

Biopsies were more accurate in our study than reported previously.[17, 22, 23] Possible explanations for this increased accuracy are the timepoints chosen for the first and second clinical response evaluations, and the adherence to a strict, pre-specified protocol in our trial, including random biopsies from the site of the primary tumour and targeted biopsies from any suspicious lesions. Fine-needle aspiration of suspicious lymph nodes also increased the sensitivity of the clinical response evaluation assessments in patients with negative biopsies. The percentage of TRG3 or TRG4 residual tumours that was missed by endoscopy plus regular biopsies and fine-needle aspiration decreased from 31% (95% CI 17–50) to 10% (4–23) after introduction of bite-on-bite biopsies, and the negative predictive value increased from 35% (95% CI 19–54) to 45% (28–62). Residual disease is often located in the oesophageal mucosa, or the deeper submucosa, but can be rarely also present in isolated remnants within the muscle layer or the surrounding stroma (deeper than the submucosa).[10] Bite-on-bite biopsies are thought to increase the chance of detecting residual cancer cells in deeper layers of the oesophagus, such as the submucosa, compared with regular biopsies, which rarely penetrate the submucosa (appendix p 7).

Although the diagnostic accuracy of PET–CT for the detection of locoregional residual disease is poor, PET–CT was useful for detection of interval distant metastases (in 9% [95% CI 6–14] of all patients) during clinical response evaluations. The extended period from the end of neoadjuvant chemoradiotherapy to PET–CT during the second clinical response evaluation supposedly improved the signal-to-noise ratio, because artifacts related to radiation-induced oesophagitis were expected to have diminished. Nevertheless, results were similar to those noted in previous studies.[18, 19, 24] During active surveillance, PET-CT is expected to detect distant metastases, thereby preventing oesophagectomy in patients with initially subclinical distant metastases. In view of the

high frequency of false positivity (63% [95% CI 44–78] of TRG1 tumours) of PET–CT for detection of locoregional disease and the limited additional value as an adjunct to endoscopy with bite-on-bite biopsies and fine-needle aspiration, we propose that PET–CT should primarily be used for detection of distant metastases during response evaluations. However, during active surveillance, serial PET–CT might prove valuable for detection of local regrowths: an increase in ^{18}F-FDG-avidity theoretically suggests disease recurrence, whereas a decrease is more likely to depict recovery from oesophagitis.

Results of measurement of maximum tumour thickness were similar to those from an earlier study.[9] However, diagnostic accuracy of maximum tumour thickness was worse than that of endoscopic ultrasonography with bite-on-bite biopsies and fine-needle aspiration, with 28% (95% CI 17–44) of TRG3 and TRG4 tumours missed and a frequency of false-positive diagnosis of 41% (95% CI 25–59) for TRG1 tumours. Taken together, we recommend that clinical response evaluations after neoadjuvant chemoradiotherapy in patients with oesophageal or gastroesophageal junction cancer should consist of repeated endoscopy with bite-on-bite biopsies and fine-needle aspiration of suspicious lymph nodes for detection of locoregional residual disease and PET–CT for detection of interval metastases.

The minimum diagnostic accuracy for safe active surveillance will continue to be debated until a clinical trial is done to establish it. Even a very small amount of residual disease (eg, TRG2) should ideally not be missed during clinical response evaluations, because patients with residual viable cancer cells do not benefit from an active surveillance strategy and should have oesophagectomy as soon as possible. Conversely, if locoregional residual disease is initially missed, but can be detected during active surveillance while the tumour is still resectable, oncological outcomes should not be worse. Evidence of successful active surveillance strategies in patients with head and neck, rectal, or bladder cancer,[25-27] supports the adoption of active surveillance after neoadjuvant chemoradiotherapy in patients with oesophageal cancer. A systematic review[7] showed that postponed radical resection was associated with good survival outcomes (ie, similar to those with standard surgery; median overall survival 58 months [95% CI 27.7 to not reached]) in most patients with oesophageal cancer who showed locoregional regrowth during active surveillance.[7, 28, 29] This median overall survival in complete responders to neoadjuvant chemoradiotherapy managed with active surveillance is similar to that of patients with a complete clinical response who undergo surgery after neoadjuvant chemoradiotherapy.[28, 29] In these studies, clinical response was assessed by endoscopy with regular biopsies and PET–CT. The use of bite-on-bite biopsies and the addition of fine-needle aspiration from suspicious lymph nodes could increase diagnostic accuracy. The promising results of our study in combination with those of previous publications justify a randomised, controlled, phase 3 trial of active surveillance versus standard surgery.The results of our study could serve to define the composition of the

clinical response evaluations and the subsequent surveillance examinations in such trials.

Investigators of the ongoing, randomised, phase 3 ESOSTRATE and SANO trials are comparing both treatment strategies.[11] Both trials aim to include 300 patients with squamous cell carcinoma or adenocarcinoma of the oesophagus who were clinical complete responders after neoadjuvant chemoradiotherapy. Although pathological complete responses are more likely in patients with squamous cell carcinoma (49%), they are also common in those with adenocarcinoma (23%) after carboplatin and paclitaxel combined with 41.4 Gy radiotherapy with low toxicity.[3] The activity-toxicity ratio in both histological subtypes is the rationale for the use of this regimen in the preSANO and SANO trials, rather than a definitive chemoradiotherapy regimen without surgery.[3] Furthermore, our results show that the risk of false-negative biopsies during clinical response evaluations is not higher in patients with adenocarcinoma than in those with squamous cell carcinoma. The primary endpoint of the ESOSTRATE trial is disease-free survival and overall survival in the SANO trial. On the basis of the results of our study, clinical response evaluations in the SANO trial consist of repeated endoscopic ultrasonography with bite-on-bite biopsies and fine-needle aspiration, plus PET–CT scans for detection of distant metastases. Patients with negative results in the first and second clinical response evaluations after neoadjuvant chemoradiotherapy will be classified as clinical complete responders and allocated to either active surveillance or immediate surgery on the basis of stepped-wedge cluster randomisation.

The diagnostic accuracy of clinical response evaluations is expected to improve, reducing the number of patients who need postponed oesophagectomy or who have irresectable regrowths during active surveillance. Dynamic contrast-enhanced MRI and diffusion-weighted MRI are promising new techniques that will need to be assessed in larger diagnostic trials.[30, 31] Furthermore, the incorporation of liquid biopsies to analyse circulating cell-free tumour DNA derived from blood samples might improve the prediction of response to neoadjuvant chemoradiotherapy and the detection of disease recurrence during active surveillance.

Limitations of our study include the change in the biopsy strategy during the trial. The improved diagnostic accuracy of bite-on-bite biopsies compared with regular biopsies could be explained by a learning-curve effect. The assumption that TRG2 residual disease can be safely missed during initial response evaluation assessments is based on the hypothesis that these tumours can be reliably detected as they progress to stage TRG3 or TRG4, and that surgery will still be a curative option at this point. However, we acknowledge that this assumption can be only formally tested by comparing active surveillance with standard resection in a randomised, controlled, clinical trial. In the SANO trial, strict stopping rules have been prespecified by protocol for timely detection of resectable locoregional regrowth (any T stage <T4b) and the feasibility of achieving

radical resection in the active surveillance arm. Because of the small number of patients with squamous cell carcinoma included in this study, the extent to which our results can be generalised is unclear. However, active surveillance after definitive chemoradiotherapy is a standard of care in many centres for patients with squamous cell carcinoma, and is the recommend standard of care in some guidelines.[32] Nevertheless, if a patient has a clinical complete response based on endoscopy with bite-on-bite biopsies and fine-needle aspiration, the risk that there is any residual disease left seems similar in both subgroups of patients with oesophageal cancer, those with squamous cell carcinoma and those with adenocarcinoma. Repeat CT of the thorax, abdomen, and pelvis was not done as part of the first clinical response evaluation. Furthermore, use of a limited range of diagnostic modalities during the first clinical response evaluation could have reduced the accuracy of residual disease detection in the first clinical response evaluation compared with the second. Additionally, to include any degree of possible tumour residue, we defined all PET–CT scores of 2 (probably benign) as ^{18}F-FDG-positive, and thus probably included some cases with radioisotope uptake due to oesophagitis rather than oesophageal malignancy, resulting in overdiagnosis. For the same reason, fine-needle aspiration specimens taken from suspicious lymph nodes with uncertain outcomes or that were not representative were classified as positive, but should not be considered to be correctly diagnosed. Finally, overall and progression-free survival data according to TRG will be published when follow-up is sufficient.

In conclusion, clinical response evaluation comprising endoscopic ultrasonography with bite-on-bite biopsies and fine-needle aspiration of suspicious lymph nodes for detection of locoregional residual disease in combination with PET–CT for detection of interval metastases after neoadjuvant chemoradiotherapy for oesophageal or gastroesophageal junctional cancer is an adequate strategy for clinical response evaluation. The ongoing, randomised, phase 3 SANO trial (Netherlands Trial Register: NTR6803) has incorporated this diagnostic strategy and will compare active surveillance with standard resection in patients who achieve a complete response after neoadjuvant chemoradiotherapy.

Acknowledgments

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Table 1. Baseline characteristics of patients who underwent clinical response evaluations.*

	Regular biopsies (N=84)	Bite-on-bite biopsies (N=123)	Overall (N=207)
Age — yr.			
Median	65	66	66
IQ Range	60 - 70	60 - 71	60 - 71
Male sex — no. (%)	72 (86)	101 (82)	173 (84)
Tumour type — no. (%)			
Squamous-cell carcinoma	22 (26)	21 (17)	43 (21)
Adenocarcinoma	61 (73)	102 (83)	163 (78)
Adenosquamous cell carcinoma	1 (1)	0 (0)	1 (0)
Clinical T stage — no. (%)*			
cT1	0 (0)	1 (1)	1 (<1)
cT2	14 (17)	26 (21)	40 (19)
cT3	66 (79)	88 (72)	154 (74)
cT4	3 (4)	8 (7)	11 (5)
Missing	1 (1)	0 (0)	1 (<1)
Clinical N stage — no. (%)‖			
N0	21 (25)	42 (34)	63 (30)
N1	32 (38)	48 (39)	80 (39)
N2	29 (35)	28 (23)	57 (28)
N3	1 (1)	5 (4)	6 (3)
Missing	1 (1)	0 (0)	1 (<1)

Data are n (%), unless otherwise specified. Percentages might not total to 100% because of rounding. *Assessed by endoscopic ultrasonography or CT and classified according to the International Union against Cancer's TNM classification (7th edn).

Table 2. Clinical response evaluation outcomes per diagnostic modalities and tumour regression grade in patients who underwent oesophagectomy after neoadjuvant chemoradiotherapy.

	Tumour regression grade				
Outcome diagnostic modality	TRG1	TRG2	TRG3	TRG4	Total
Endoscopy with regular biopsies and fine-needle aspiration*					
positive	4 (31%)	2 (18%)	4 (44%)	14 (82%)	24
negative	9 (69%)	9 (82%)	5 (56%)	3 (18%)	26
Total	13	11	9	17	50
Endoscopy with bite-on-bite biopsies and fine-needle aspiration†					
positive	5 (28%)	17 (59%)	20 (83%)	17 (100%)	59
negative	13 (72%)	12 (41%)	4 (17%)	0	29
Total	18	29	24	17	88
EUS with maximum tumour thickness CRE-II‡					
positive	11 (41%)	13 (45%)	13 (65%)	15 (79%)	52
negative	16 (59%)	16 (55%)	7 (35%)	4 (21%)	43
Total	27	29	20	19	95
PET-CT CRE-II¶					
positive	17 (63%)	22 (73%)	17 (89%)	18 (82%)	74
negative	10 (37%)	8 (27%)	2 (11%)	4 (18%)	24
Total	27	30	19	22	98

* p=0.0036 (chi-square)

† p<0.0001 (chi-square)

‡ p=0.035 (chi-square)

p=0.191(chi-square)

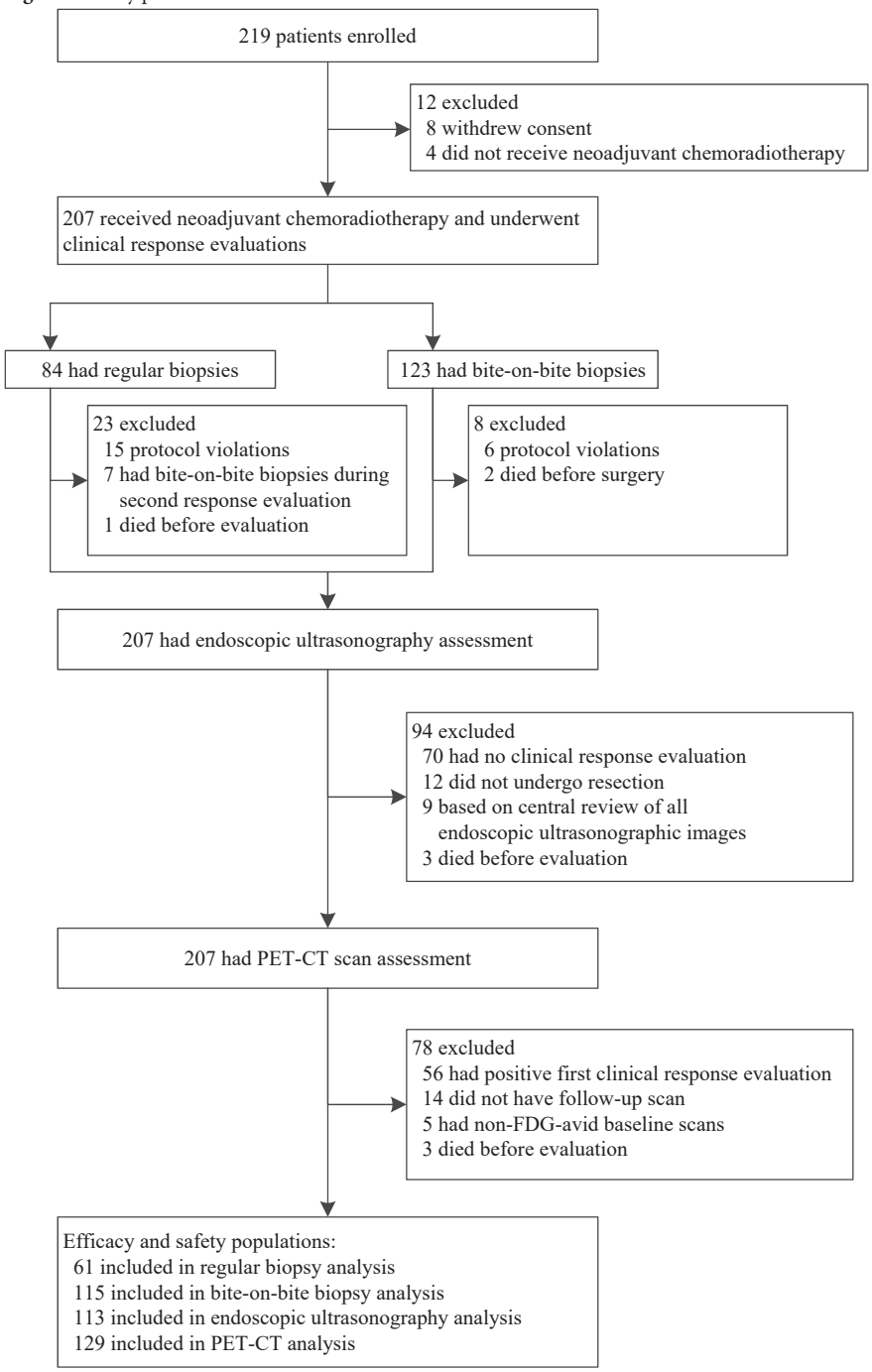
CRE: clinical response evaluation

Table 3. Sensitivity analysis for accuracy of residual tumour detection in clinical response evaluations and predictive value of the tumour regression grades.

	False-negative TRG3-4 (95% CI)	Sensitivity TRG1 vs. TRG2-3-4 (95% CI)	Specificity TRG1 vs. TRG2-3-4 (95% CI)	negative predictive value TRG1 vs. TRG2-3-4 (95% CI)	positive predictive value TRG1 vs. TRG2-3-4 (95% CI)
Endoscopy with regular biopsies and fine-needle aspiration	31% (13%-49%)	54% (38%-70%)	69% (44%-94%)	35% (16%-53%)	83% (68%-98%)
Endoscopy with bite-on-bite biopsies and fine-needle aspiration	11% 1 (1%-21%)	74% (64%-83%)	77% (59%-95%)	45% (29%-62%)	92% (85%-99%)
EUS with maximum tumour thickness CRE-II	29% (15%-43%)	59% (48%-70%)	58% (40%-75%)	38% (25%-52%)	76% (64%-87%)
PET-CT CRE-II	14% (3%-24%)	82% (73%-90%)	38% (21%-55%)	44% 26%-63%)	77% (68%-87%)

Accuracy estimates were calculated as TRG1 vs TRG2–4 after multiple imputation (for age, sex, histology, tumour grading, clinical T stage, clinical tumour stage, clinical lymph-node stage, WHO performance score, number of cycles of chemotherapy, total radiation dose, and results from endoscopic biopsies, fine-needle aspiration, maximum tumour thickness measurement, and PET–CT) per diagnostic modality for patients who had active surveillance instead of surgery after clinical response evaluations. Totals per group cannot be calculated, since this is a multiple imputation analysis. TRG=tumour regression grade. *Calculated as the proportion of TRG3 and TRG4 residual tumours missed during clinical response evaluations per diagnostic modality.

Figure 1. Study profile.



Appendix

Supplementary Table 1. Outcomes of patients who were excluded from analyses.

Outcome diagnostic modality	TRG1	TRG2	TRG3	TRG4	No surgery	Total
Endoscopy with regular biopsies and FNA						
Died before CRE	0	0	0	0	1	1
Regular biopsies CRE-I, bite-on-bite biopsies CRE-II	0	4	1	1	1	7
Surgery with negative biopsies at CRE-I	0	1	0	0	0	1
No biopsies	1	0	0	1	2	4
No FNA of suspicious lymph nodes	3	1	0	1	5	10
Total	4	6	1	3	9	23
Endoscopy with bite-on-bite biopsies and FNA						
Died before CRE	0	0	0	0	2	2
Surgery with negative biopsies at CRE-I	3	1	0	0	0	4
No biopsies	0	0	0	1	0	1
No FNA of suspicious lymph nodes	0	0	1	0	0	1
Total	3	1	1	1	2	8
EUS with maximum tumour thickness CRE-II						
Died before CRE	0	0	0	0	3	3
No CRE-II measurement	9	17	14	13	17	70
Excluded based on revision	2	1	1	4	1	9
No revision performed, because no resection	0	0	0	0	12	12
Total	11	18	15	17	33	94
PET-CT CRE-II						
Died before CRE	0	0	0	0	3	3
Positive CRE-I	6	15	11	12	12	56
No follow-up scan	4	2	4	3	1	14
Non-FDG-avid	1	0	1	1	2	5
Total	11	17	16	16	18	78

TRG: tumour regression grade, FNA: fine-needle aspiration, CRE: clinical response evaluation.

Supplementary Table 2. Outcomes of EUS-FNA from suspicious lymph nodes as determined by PET-CT and/or EUS.

	TRG1	TRG2	TRG3	TRG4	No surgery	Total
Presence tumour FNA						
No tumour	5	5	0	1	3	15
Tumour	0	0	1	3	4	8
Uncertain	2	2	2	2	1	9
Total	7	7	3	6	8	32

EUS: endoscopic ultrasonography, FNA: fine-needle aspiration, TRG: tumour regression grade.

Supplementary Table 3. Clinical response evaluations using different diagnostic modalities in relation to tumour regression grade of the resection specimen (gold standard) in patients with squamous cell carcinoma who underwent oesophagectomy after neoadjuvant chemoradiotherapy.

	Tumour regression grade				
Outcome diagnostic modality	TRG1	TRG2	TRG3	TRG4	Total
Endoscopy with regular biopsies and FNA*					
positive	2	0	1	3	6
negative	5	1	0	0	6
Total	7	1	1	3	12
Endoscopy with bite-on-bite biopsies and FNA†					
positive	2	2	3	3	10
negative	4	1	1	0	6
Total	6	3	4	3	16
EUS with maximum tumour thicknessCRE-II‡					
positive	2	1	0	3	6
negative	10	2	2	0	14
Total	12	3	2	3	20
PET-CT CRE-II¶					
positive	5	2	1	4	12
negative	7	1	1	0	9
Total	12	3	2	4	21

TRG: tumour regression grade, FNA: fine-needle aspiration, CRE: clinical response evaluation.

Supplementary Table 4. Clinical response evaluations using different diagnostic modalities in relation to tumour regression grade of the resection specimen (gold standard) in patients with adenocarcinoma who underwent oesophagectomy after neoadjuvant chemoradiotherapy.

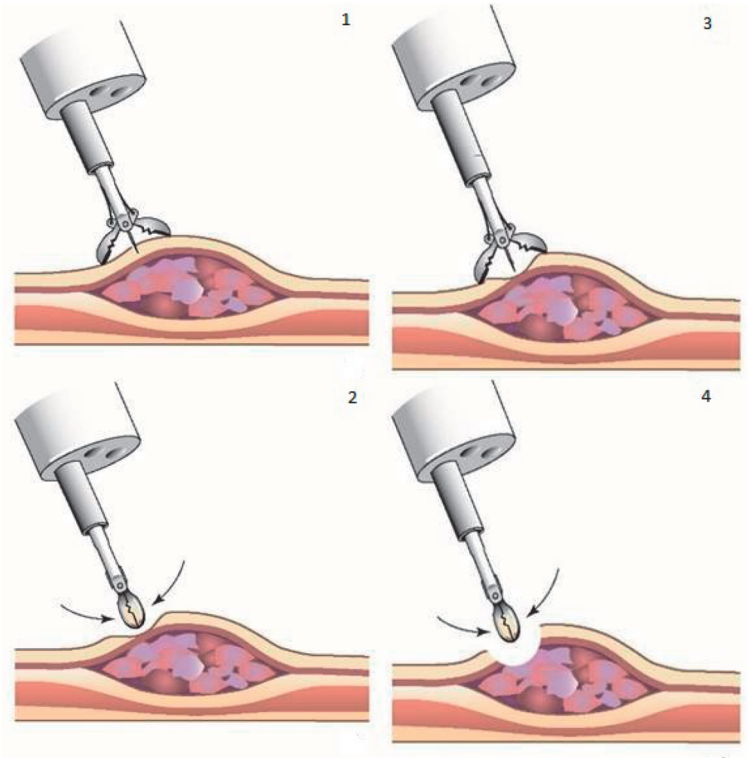
	Tumour regression grade				
Outcome diagnostic modality	TRG1	TRG2	TRG3	TRG4	Total
Endoscopy with regular biopsies and FNA*					
positive	2	2	3	10	17
negative	4	8	5	3	20
Total	6	10	8	13	37
Endoscopy with bite-on-bite biopsies and FNA†					
positive	3	15	17	14	49
negative	9	11	3	0	23
Total	12	26	20	14	72
EUS with maximum tumour thickness CRE-II‡					
positive	9	12	13	12	46
negative	6	14	5	4	26
Total	15	26	18	16	75
PET-CT CRE-II¶					
positive	12	20	16	14	62
negative	3	7	1	4	15
Total	15	27	17	18	77

TRG: tumour regression grade, FNA: fine-needle aspiration, CRE: clinical response evaluation.

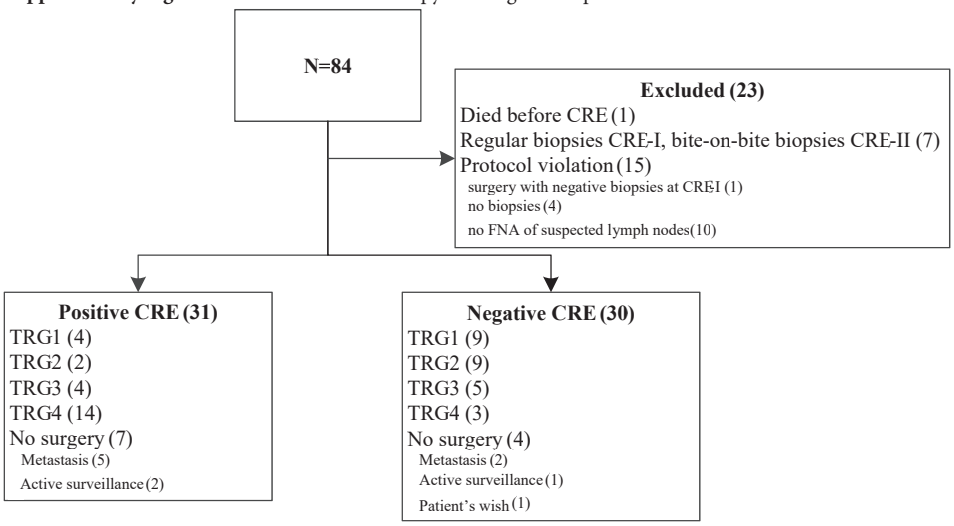
Supplementary Table 5. Sites from which patients were recruited, principle investigator responsible for this site and the number patients which were recruited from that site.

	Principle investigator	Number of patients
Erasmus MC – University Medical Centre Rotterdam	J. Jan B. van Lanschot	106
Academic Medical Centre	Mark I. van Berge Henegouwen	36
Zuyderland Medical Centre	Meindert N. Sosef	28
Catharina Hospital	Grard A.P. Nieuwenhuijzen	28
University Medical Centre Utrecht	Richard van Hillegersberg	18
Radboud University Medical Centre	Peter D. Siersema	3

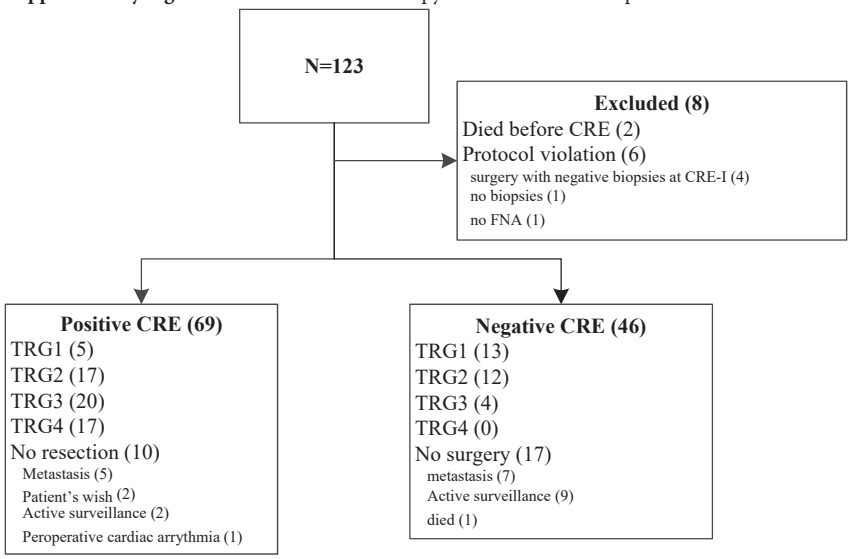
Supplementary Figure 1. Bite-on-bite biopsies (1+2+3+4) supposedly increase the chance of detecting submucosal tumour deposits compared to conventional biopsies (1+2).



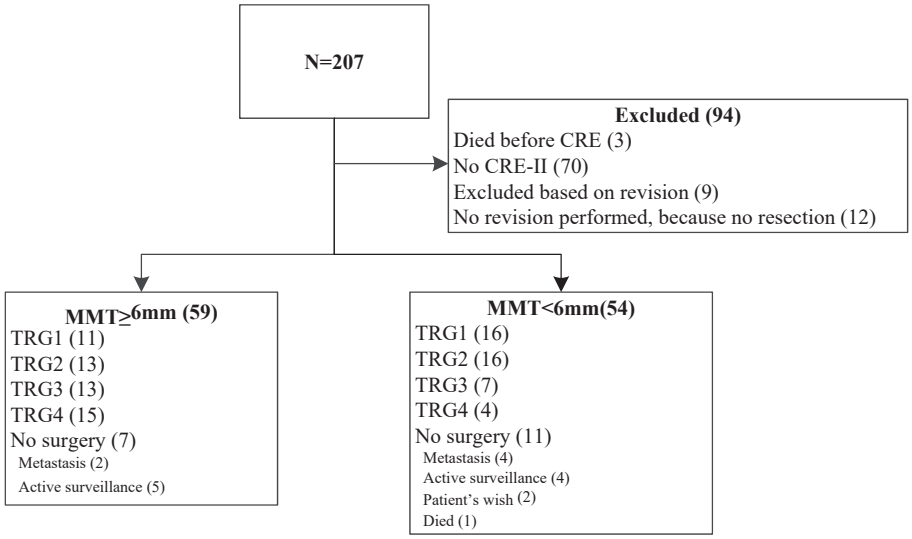
Supplementary Figure 2. Flowchart for endoscopy with regular biopsies and FNA.



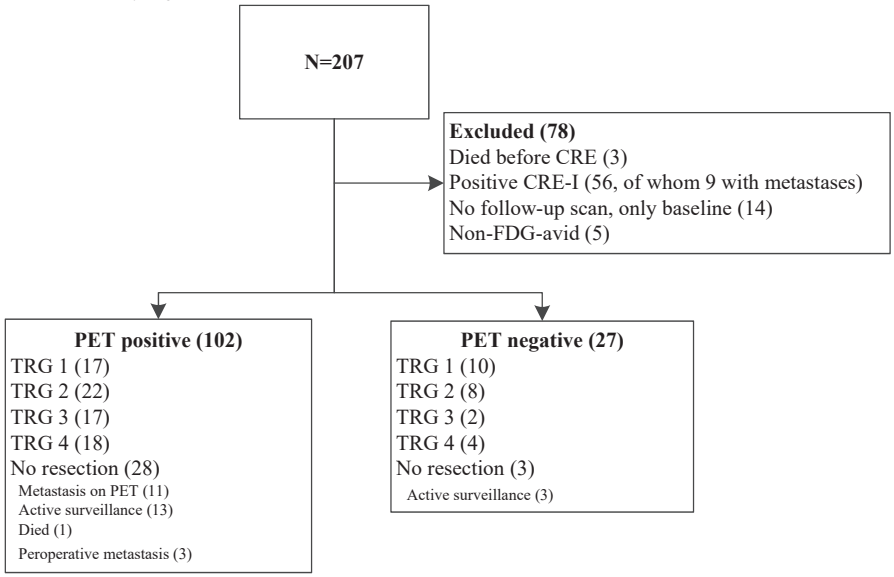
Supplementary Figure 3. Flowchart for endoscopy with bite-on-bite biopsies and FNA.



Supplementary Figure 4. Flowchart for endoscopic ultrasonography with maximum tumour thickness measurement.



Supplementary Figure 5. Flowchart for 18-FDG PET-CT.



References

1. Hulscher JB, van Sandick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662-9.
2. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
3. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
4. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
5. Noordman BJ, Verdam MGE, Lagarde SM et al. Effect of neoadjuvant chemoradiotherapy on health-related quality of life in esophageal or junctional cancer: results from the randomized CROSS trial. J Clin Oncol. 2017:JCO2017737718.
6. Noordman BJ, Verdam MGE, Lagarde SM et al. Impact of neoadjuvant chemoradiotherapy on health related quality of life in long-term survivors of esophageal or junctional cancer: results from the randomized CROSS trial. Ann Oncol. 2017.
7. Noordman BJ, Wijnhoven BPL, Lagarde SM et al. Active surveillance in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal or junctional cancer. Dis Esophagus. 2017;30(12):1-8.
8. Noordman BJ, Shapiro J, Spaander MC et al. Accuracy of detecting residual disease after CROSS neoadjuvant chemoradiotherapy for esophageal cancer (preSANO Trial): rationale and protocol. JMIR Res Protoc. 2015;4(2):e79.
9. Jost C, Binek J, Schuller JC et al. Endosonographic radial tumor thickness after neoadjuvant chemoradiation therapy to predict response and survival in patients with locally advanced esophageal cancer: a prospective multicenter phase ll study by the Swiss Group for Clinical Cancer Research (SAKK 75/02). Gastrointest Endosc. 2010;71(7):1114-21.
10. Shapiro J, ten Kate FJ, van Hagen P, Biermann K, Wijnhoven BP, van Lanschot JJ. Residual esophageal cancer after neoadjuvant chemoradiotherapy frequently involves the mucosa and submucosa. Ann Surg. 2013;258(5):678-88; discussion 88-9.
11. Noordman BJ, Wijnhoven BPL, Lagarde SM et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial. BMC Cancer. 2018;18(1):142.
12. Shapiro J, van Hagen P, Lingsma HF et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. Ann Surg. 2014;260(5):807-13; discussion 13-4.
13. Boellaard R, O'Doherty MJ, Weber WA et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2010;37(1):181-200.
14. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer., ebrary Inc. TNM classification of malignant tumors. New York: Wiley-Blackwell; 2009. Available from: http://site.ebrary.com/lib/yale/Doc?id=10342913, last accessed: January 29th, 2018.
15. Chirieac LR, Swisher SG, Ajani JA et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer. 2005;103(7):1347-55.
16. Naaktgeboren CA, de Groot JA, Rutjes AW, bossuyt PM, Reitsma JB, Moons KG. Anticipating missing reference standard data when planning diagnostic accuracy studies. BMJ. 2016(352):i402.

17. Cheedella NK, Suzuki A, Xiao L et al. Association between clinical complete response and pathological complete response after preoperative chemoradiation in patients with gastroesophageal cancer: analysis in a large cohort. Ann Oncol. 2013;24(5):1262-6.
18. Elliott JA, O'Farrell NJ, King S et al. Value of CT-PET after neoadjuvant chemoradiation in the prediction of histological tumour regression, nodal status and survival in oesophageal adenocarcinoma. Br J Surg. 2014;101(13):1702-11.
19. Heneghan HM, Donohoe C, Elliot J et al. Can CT-PET and Endoscopic Assessment Post-Neoadjuvant Chemoradiotherapy Predict Residual Disease in Esophageal Cancer? Ann Surg. 2016;264(5):831-8.
20. Kim MK, Ryu JS, Kim SB et al. Value of complete metabolic response by (18)F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. Eur J Cancer. 2007;43(9):1385-91.
21. Piessen G, Petyt G, Duhamel A, Mirabel X, Huglo D, Mariette C. Ineffectiveness of (1)(8)F-fluorodeoxyglucose positron emission tomography in the evaluation of tumor response after completion of neoadjuvant chemoradiation in esophageal cancer. Ann Surg. 2013;258(1):66-76.
22. Schneider PM, Metzger R, Schaefer H et al. Response evaluation by endoscopy, rebiopsy, and endoscopic ultrasound does not accurately predict histopathologic regression after neoadjuvant chemoradiation for esophageal cancer. Ann Surg. 2008;248(6):902-8.
23. Sarkaria IS, Rizk NP, Bains MS et al. Post-treatment endoscopic biopsy is a poor-predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. Ann Surg. 2009;249(5):764-7.
24. Blom RL, Schreurs WM, Belgers HJ, Oostenbrug LE, Vliegen RF, Sosef MN. The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma. Eur J Surg Oncol. 2011;37(9):774-8.
25. Mehanna H, Wong WL, McConkey CC et al. PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. N Engl J Med. 2016;374(15):1444-54.
26. Renehan AG, Malcomson L, Emsley R et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol. 2016;17(2):174-83.
27. Rödel C, Wiess C, Sauer R. Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol. 2006;24(35):5536-44.
28. Castoro C, Scarpa M, Cagol M et al. Complete clinical response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic oesophagus: is surgery always necessary? J Gastrointest Surg. 2013;17(8):1375-81.
29. Taketa T, Xiao L, Sudo K et al. Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology. 2013;85(2):95-9.
30. Heethuis SE, van Rossum PS, Lips IM et al. Dynamic contrast-enhanced MRI for treatment response assessment in patients with oesophageal cancer receiving neoadjuvant chemoradiotherapy. Radiother Oncol. 2016;120(1):128-35.
31. van Rossum PS, van Lier AL, van Vulpen M et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. Radiother Oncol. 2015;115(2):163-70.
32. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann oncol. 2016(27(suppl 5)):v50-v7.

Chapter 16

Accuracy of 18F-FDG PET/CT in predicting residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer

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Abstract

Purpose

Aim of the study was to explore optimal evaluation of qualitative and quantitative F-18-FDG-PET/CT in response evaluations 12-14 weeks after neoadjuvant chemoradiotherapy (nCRT) in oesophageal cancer patients.

Methods

This is a side-study of the prospective preSANO trial. Baseline and FDG-PET/CT scans 12-14 weeks after nCRT were qualitatively assessed for presence of tumour. Standardised uptake values normalised for lean body mass for maximum (SULmax,) were measured in all scans. Primary endpoint was the proportion of missed patients with tumour regression grade (TRG) 3-4 (>10% vital residual tumour) in qualitative and quantitative analyses. Receiver Operating Characteristic (ROC) curve analysis for TRG1 vs. TRG3-4 using SULmax, SUL ratio tumour/oesophagus and Δ(%)SULmax was performed to define optimal cut-off values. Secondary endpoints were sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) and these were calculated for TRG1 vs. TRG2-3-4 in both qualitative and quantitative results.

Results

In total, 129 of 219 patients included in preSANO were analysed 12-14 weeks after nCRT. Qualitative FDG-PET/CT was unable to detect TRG3-4 in 15% of patients. Sensitivity, specificity, NPV and PPV in qualitative analysis for detecting TRG1 vs. TRG2-3-4 was 80%, 37%, 42% and 77% respectively. In 18 of 190 patients (9.5%) with follow-up scans after nCRT, FDG-PET/CT identified interval metastases. Quantitative parameters missed TRG3-4 tumour in 27-61% of patients. Optimal cut-off value for detecting TRG1 vs. TRG2-3-4 was seen with SULmax at 2.93.

Conclusions

Qualitative and quantitative analyses of FDG-PET/CT are unable to reliably detect TRG3-4 and to discriminate substantial residual disease from benign FDG-uptake after nCRT. Repeated FDG-PET/CT is useful for the detection of interval metastases.

Introduction

Oesophageal cancer is the eighth most common type of cancer worldwide with an overall 5-year survival of about 35% after primary oesophagectomy.[1] Since the introduction of neoadjuvant chemo(radio)therapy, long term survival rates have increased to 45-50%.[2-4] Neoadjuvant chemoradiotherapy (nCRT) using carboplatin and paclitaxel combined with 41.4 Gy of concurrent radiotherapy induces a pathologically complete response (ypT0N0) in 29% of patients with oesophageal cancer.[5] This has raised the question whether an active surveillance approach can be applied after nCRT. In such an active surveillance approach, patients without signs of residual disease after nCRT are regularly examined in follow-up clinical investigations. Oesophagectomy will then be offered to patients with proven locoregional recurrence only, in the absence of distant metastases. To explore the feasibility of an active surveillance strategy, reliable clinical response evaluations (CREs) are needed to exclude substantial residual disease. For this purpose, a diagnostic multicentre trial has been performed (preSANO trial, NL41732.078.13) comprising endoscopy, (bite-on-bite) biopsies, endoscopic ultrasound (EUS) with fine needle aspiration (FNA) of suspected lymph nodes and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) for response evaluation after nCRT.[6, 7] The optimal way of analysing FDG-PET/CT in response evaluations is topic of debate. In this side-study of the preSANO-trial we further explore the accuracy of FDG-PET/CT parameters in predicting residual disease on a qualitative and quantitative basis.

Patients and methods

Patients

Details of the multicentre prospective diagnostic preSANO trial have been described previously.[6, 7] Briefly, patients with potentially curable adenocarcinoma or squamous cell carcinoma of the oesophagus or oesophagogastric junction, who were planned to undergo nCRT according to the CROSS regimen (five weekly cycles of carboplatin (area under the curve of 2 mg per millilitre per minute) and paclitaxel (50 mg per square meter of body-surface area) combined with 41.4 Gy radiotherapy in 23 fractions) followed by surgical resection were included.[5] Pre-treatment FDG-PET/CT was performed at the time of diagnosis. The first CRE (CRE-1) was performed 4-6 weeks after completion of nCRT. During CRE-1, FDG-PET/CT was performed only in patients with histologically proven residual disease, to detect distant metastases. In the absence of disseminated disease, patients with histologically proven locoregional residual disease were scheduled for surgery. In case of negative endoscopic biopsies at CRE-1, surgery was

postponed for another 4-6 weeks and patients underwent a second CRE (CRE-2). During CRE-2, all patients first underwent FDG-PET/CT, with the objective to assess locoregional response and to detect possible distant metastases. Subsequently, patients underwent endoscopy with (bite-on-bite) biopsies and EUS with FNA of suspected lymph nodes and/or FDG-positive lesions. According to the study protocol, all patients were scheduled for surgery after CRE-2, if no distant metastases were detected. When surgery was further postponed (for example because of patients' preference or poor physical condition) another FDG-PET/CT and endoscopy (CRE-3) were performed preceding planned surgery.[6] The trial was approved by the medical-ethical committee of Erasmus MC Rotterdam (MEC-2013-211). All patients provided written informed consent.

^{18}F-FDG PET/CT acquisition and processing

Pre-treatment ^{18}F-FDG PET/CT was performed to assess FDG avidity of the primary tumour. Scanning was performed according to EANM guidelines version 1.0, with scanning at 60±5 minutes post intravenous injection of 2.3 MBq/kg ^{18}F-FDG.[8] Only attenuation corrected and ordered subset expectation maximization (OSEM) reconstructed images were used in the analyses.

Before scanning, all patients were requested to fast for at least six hours and to prehydrate with 1-2 litres of water. Patient's weight and height were measured. In all patients, blood glucose levels were required to be less than 8.0 mmol/L. Patients had to be in resting condition before scanning. Modern equipment, including multislice CT (16-slice or better) and if possible time-of-flight (TOF) PET, was used. PET/CT scanners were calibrated for quantitative standardized uptake value (SUV) measurements, according to EARL qualifications.[9]

Qualitative assessments

For qualitative analysis, both baseline FDG-PET/CT and the last FDG-PET/CT scan before surgery (CRE-2 or CRE-3) were examined. CRE-1 scans (4-6 weeks after nCRT) were excluded, since it is expected that 4-6 weeks after nCRT the effect of radiation-induced oesophagitis would be still substantial.[10, 11] For assessment of distant dissemination both CRE-1 and CRE-2/-3 scans were used.

If pre-treatment scans (before the start of chemoradiation) did not show a level of tumour FDG-uptake that was clearly above the level of the surrounding oesophagus and other tissues, a follow-up FDG-PET/CT could not be used to accurately assess the effects of the neoadjuvant treatment. These patients were considered as "non-FDG avid" and are described separately (Supplementary Table 1).

Furthermore, patients with missing follow-up FDG-PET/CT scan after nCRT, prior to surgery, were excluded from the qualitative analysis.

Image analysis

The presence of residual tumour, including positive lymph nodes and/or haematogenous metastases, was centrally assessed by an experienced nuclear medicine physician (R.V.), who was blinded for all clinical information except weight, height, injected 18F-FDG activity and time-interval between injection and start of PET. In case of disagreement with the original report, a second nuclear medicine physician (L.H.G.) reviewed the study independently and a consensus agreement between both reviewers was established.

During review, tumour status on follow-up FDG-PET/CT scans was scored as either "no suspect lesions" or "locoregional residual lesions" (including locoregional progression). A lesion was considered FDG-positive, when any uptake in the lesion itself was above the adjacent oesophageal background uptake. For qualitative dichotomous analysis, the FDG-PET/CT scan was classified as "FDG-negative" when no visible uptake was seen. An "FDG-positive" scan included locoregional residual lesions, locoregional progression, presence of haematogenous metastases, or a combination of those.

Confidence scores were assigned for the primary tumour, lymph nodes and haematogenous metastases. The following scoring system was used: 1= benign/no uptake; 2= probably benign/minimal uptake; 3= equivocal; 4= probably malignant; 5= malignant. In this scoring system, a lesion was considered (probably) malignant if any focal abnormal accumulation of FDG was observed, which was not explained by oesophagitis or other benign or physiologic cause. A scan was scored as benign, when the uptake in the lesion did not differ at all from the surrounding normal background uptake. A probably benign lesion was scored in case of diffuse, minimal uptake of FDG above the background. A lesion was scored "equivocal" if a focal accumulation could not be distinguished, but neither could be called "benign". During qualitative analysis using confidence scores, an "FDG-negative" scan included confidence scores "benign" and "probably benign". An "FDG-positive" scan comprised the scores "equivocal", "probably malignant" and "malignant".

Quantitative assessments

For quantitative assessments, global volumes of interest (VOIs) were manually drawn over the primary tumour and visual lymph nodes (Osirix MD, version 6.5.2. Pixmeo, Berne, Switzerland). The same was done for the reference regions of the physiological oesophagus, liver and bloodpool. Standardised uptake values normalised for lean body mass for maximum (SUL_{max}) and mean values (SUL_{mean}) were calculated from the activi-

ty values inside the VOI. Lean body mass was calculated using the James equation[9], which is defined as follows,

$$LBM = (1.1 - G*0.03)*BW - (128 + G*20)*\left(\frac{BW}{H}\right)^2$$

where G stands for gender (female = 1; male = 0), BW = body weight (kg) and H = body height (cm).

In the follow-up FDG-PET/CT scans, the VOI was placed as closely as possible in the same locations, to obtain post-nCRT measurements. As lesions after nCRT could have become (very) small, SUL_{max} parameters were used for lesions, not SUL_{peak}. This was to avoid substantial partial volume effects with (very) small lesions.

The relation between the bloodpool and liver SUV_{mean} and body weight was determined in all available patients with CRE scans. The same was done for the bloodpool and liver SUL_{mean}, as to determine which parameter, SUV or SUL, should be finally used for the quantitative assessments.

Histopathology

The pathology report of the resected oesophagus served as reference (gold standard). Visual and quantitative assessments on FDG-PET/CT scans were compared to pathologic response in the resection specimen according to the tumour regression grading (TRG) system of Chirieac, using four categories: TRG1, no vital residual tumour cells; TRG2, 1-10% vital residual tumour cells; TRG3, 11-50%; and TRG4, >50%.[12] An experienced pathologist centrally revised all pathology results. An arbitrary "TRG4" was assigned to patients who were operated with intent to resect the tumour, but who were deemed irresectable (T4b) during surgery.

Outcomes

The primary outcome was the proportion of TRG3-4 residual tumours that was missed using qualitative assessment of FDG-PET/CT and using the quantitative parameters SUL_{max} at tumour, SUL ratio (the ratio of SUL-tumour/SUL-oesophagus), absolute ΔSUL_{max} and $\Delta\%SUL_{max}$. Minimal residual tumour (TRG2) was considered acceptable to be missed, because it is expected that TRG2 tumour will become timely detectable during follow-up if it has developed in TRG3-4 tumour.[6]

Secondary outcomes comprised sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for detection of TRG1 vs. TRG2-3-4 in qualitative and quantitative analysis of FDG-PET/CT. For correct statistical calculation of secondary endpoints, patients with TRG2 were also included.

Statistical analysis

The calculation of the sample size in the preSANO study has been expounded earlier[6, 7] All patients eligible for analysis in this side-study were included. Chi-square test was used to calculate the association between qualitative PET outcomes and TRG. Receiver Operating Characteristic (ROC) curve analysis was performed for TRG1 versus TRG3-4 for the PET-parameters SUL_{max} at tumour, SUL ratio, absolute ΔSUL_{max} and $\Delta\%SUL_{max}$. Area under the ROC was calculated with a 95% confidence interval. Cut-off points were defined using the Youden index, that calculates the maximum of [sensitivity + specificity -1].[13] For qualitative results and for the quantitative optimal cut-off points, sensitivity, specificity, NPV and PPV were calculated for differentiation between TRG1 versus TRG2-3-4, using standard formulas.
All tests were two-sided. *P*-values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS Statistics version 24.

Results

Patients

Clinicopathological characteristics of the patients are shown in Table 1. Some 219 patients were included, of whom 12 left the study (8 withdrew informed consent, 4 did not have nCRT)[7]. Median age was 66 years (interquartile range 60-71); most patients were male (84%) and most tumours were adenocarcinomas (78%).

At CRE-2/-3, a total of 129 patients were eligible for analysis of FDG-PET/CT at a median time of 11 weeks (interquartile range 10-12) after nCRT (CRE-2: n = 126; CRE-3 n = 3, Figure 1). Of the 78 of 207 patients who were excluded, five had no uptake of FDG that was clearly above the level of the surrounding oesophagus and other tissues in the primary tumour at baseline, and were considered as non-FDG avid. Seventeen of 78 patients did not have a follow-up FDG-PET/CT scan before surgery and only had baseline scans (3 patients died before CRE; 14 patients did not have a follow-up scan, as one institution did not perform FDG-PET/CT after a positive CRE-1). The remaining 56 of 78 patients did not qualify for CRE-2/-3, because of positive biopsies at CRE-1. At CRE-1, FDG-PET/CT was performed at a median time of 7.4 weeks (interquartile range 6.0-8.3) after nCRT.

One patient did not have a baseline FDG-PET/CT. This patient was included in the analyses, since a follow-up scan after nCRT was correctly performed. In 16 patients, surgery was postponed due to poor physical condition or because of patients' preference. One patient died during the study (unrelated to oesophageal cancer). In three

patients, metastases were detected peroperatively and resection was not performed (2 patients with peritoneal metastasis; 1 patient with liver metastasis).

Baseline FDG-PET/CT scans were acquired 61.0±9.1 minutes after injection of 212±64.3 MBq ^{18}F-FDG. For CRE scans (CRE-1/-2/-3), this was 61.9±8.8 minutes with injection of 206±55.8 MBq ^{18}F-FDG. As injection to scan intervals did not influence SUL_{mean} of the bloodpool, patients were not excluded based on the injection to scan intervals (for complete results, see Supplementary Figure 1).

At baseline and at CRE-1/-2/-3, glucose levels were 5.9±1.3 mmol/L and 6.8±1.5 mmol/L, respectively, and were not significantly correlated with the blood pool SUL_{mean} (p=0.08 and p=0.22, respectively). Patients with serum glucose >8 mmol/L (at baseline n=17; at CRE-1/-2/-3 n=19) were therefore also included.

Surgery was performed at a median time of 3.7 weeks (interquartile range 2.1-5.0) after patients' last FDG-PET/CT. For CRE-1, this was 2.0 weeks (interquartile range 1.2-4.0); for CRE-2/-3 this was 4.2 weeks (interquartile range 3.0-5.3). Nineteen patients had surgery >6 weeks after CRE-2/-3 FDG-PET/CT (median 8.0 weeks, interquartile range 6.6-8.7 weeks).

Qualitative FDG-PET/CT analysis

At CRE-2/-3, no stastistically significant association was found between qualitative PET and TRG outcome (p=0.19). Some 6 of 41 patients with TRG3-4 had visually negative FDG-PET/CT (false-negative TRG3-4; 15%), while 17 of 27 patients had TRG1 but a positive FDG-PET/CT (false positives; 63%) (Table 2). Sensitivity, specificity, NPV, PPV of TRG1 vs. TRG2-3-4 were 57/71 (80%), 10/27 (37%), 10/24 (42%) and 57/72 (77%), respectively. Outcomes of patients who were excluded from analyses are shown in Supplementary Table 1.

Since 17 patients did not have a follow-up scan performed, 190 patients were included for analysis of detection of interval metastases on FDG-PET/CT. Some 38 of 190 patients (20%) had suspicion of distant metastases on PET/CT. In 18 of 38 patients metastases were pathologically confirmed (true-positives; 9.5%; squamous cell carcinoma: n = 1; adenocarcinoma: n = 17). At CRE-1, 7 patients with metastases were detected; at CRE-2 this was true for 11 patients.

Adding "confidence scores" to qualitative FDG-PET/CT analyses showed that an overlap appears in TRG for all confidence scores, especially for TRG2 (Figure 2). No statistically significant association with TRG was found (p=0.072). More clinically false-negative patients with TRG3-4 (12/41; 29%) and less false positives for TRG1 (13/27; 48%) were seen compared to the dichotomous method of qualitative analysis. Consequently, the sensitivity, specificity, NPV and PPV of TRG1 vs. TRG2-3-4 were 44/71 (62%), 14/27 (52%), 14/41 (34%) and 44/57 (81%), respectively.

Quantitative FDG-PET/CT analysis

SUV_{max} measurements were corrected for lean body mass, since SUV showed weight dependency (P<0.001 for both SUV_{mean} of the blood pool and liver); which disappeared with SUL (p=0.575 for the blood pool SUL_{mean}; p=0.268 for SUL_{mean} of the liver).

In all patients with TRG outcomes (i.e. availability of surgical resection specimen), CRE SUL_{max}, $\%\Delta SUL_{max}$ and SUL ratio were 3.0±1.1, -57±30 and 1.6±0.56 in patients with TRG1; and for TRG2 these were 3.6±1.4, -46±31 and 1.8±0.78; for TRG3-4 these were 4.2±2.1, -49±21 and 2.1±0.82. Supplementary Figure 2 visualizes the overlap in the parameters CRE SUL_{max}, $\%\Delta SUL_{max}$ and SUL ratio parameters for the different TRG outcomes. Furthermore, there is an overlap in the low ranges of both SUL_{max} and SUL ratio for qualitative FDG-positive and FDG-negative scans, in patients with TRG3 or TRG4 (Supplementary Figure 3).

ROC-curves of CRE-2/-3 SUL_{max}, SUL ratio and $\Delta(\%)SUL_{max}$ are shown in Figure 3 and Table 3. For TRG1 vs. TRG3-4, optimal accuracy is seen using SUL_{max} at a cut-off of 2.93 (area under ROC 0.70; optimal cut-off 2.93; sensitivity 66%, specificity 74%).

Results of implementing the optimal cut-off values for quantitative parameters are displayed in Supplementary Table 3. With an optimal cut-off of SUL_{max} at 2.93, 14 of 41 patients with TRG3-4 were missed (34% false negative). Using this cut-off, sensitivity, specificity, NPV and PPV for TRG1 vs. TRG2-3-4 were 43/71 (61%), 20/27 (74%), 20/48 (42%) and 43/50 (86%), respectively.

An optimal cut-off for SUL ratio of 1.47 missed 11 of 41 TRG3-4 (27%). The sensitivity, specificity, NPV and PPV for TRG1 vs. TRG2-3-4 were 45/71 (63%), 16/27 (59%) 16/42 (38%) and 45/56 (80%), respectively.

For ΔSUL_{max} at an optimal cut-off of 4.03, 23 of 41 (56%) TRG3-4 were missed. The sensitivity, specificity, NPV and PPV for TRG1 vs. TRG2-3-4 were 31/70 (44%), 8/27 (30%), 8/47 (17%) and 31/50 (62%), respectively.

With $\Delta\%SUL_{max}$ at an optimal cut-off of a decrease of 56.31%, 25 of 41 (61%) TRG3-4 tumours were missed. Consequently, the sensitivity, specificity, NPV and PPV for TRG1 vs. TRG2-3-4 were 31/70 (44%), 7/27 (26%), 7/46 (15%) and 31/51 (61%), respectively.

Discussion

The value of FDG-PET/CT at a median time of 11 weeks (interquartile range 10-12) after nCRT for detection of locoregional residual disease in patients with oesophageal cancer is limited, both qualitatively and quantitatively. In this study, qualitative dichotomous analysis of FDG-PET/CT scans missed TRG3-4 tumours in 15% of patients. FDG-PET/CT had a relatively high sensitivity of 80% for detecting TRG2-3-4 versus no

tumour (TRG1), but yielded a specificity of only 37%. Adding "confidence scores" to the visual interpretation of FDG-PET/CT scans did not increase diagnostic accuracy, and showed an overlap in all TRG results for different confidence scores (Figure 2). This illustrates the difficulty of visual response assessment on FDG-PET/CT at this specific time-point after nCRT, where small tumour lesions apparently cannot be distinguished reliably from physiologic oesophageal metabolism or post-radiation oesophagitis.

Quantitative analysis of tumour response only moderately discriminated between TRG1 and TRG3-4, as shown in ROC analyses where areas under the curve did not exceed 0.7. The different post-nCRT FDG-PET/CT parameters missed TRG3-4 tumours in 27-61% of the patients, when using the optimal cut-off points from ROC analysis. Furthermore, for discriminating TRG2-3-4 from TRG1, the optimal cut-off value was SUL_{max} at 2.93 and provided an accuracy of only 64%. Thus, quantitative analysis of FDG-PET/CT alone appears not sufficiently accurate to quantify pathological response in order to select patients for an active surveillance strategy. Also, quantitative assessment cannot be used to identify visually FDG-false negatives (Supplementary Figure 3). Additionally, overlap is seen between qualitative outcomes and quantitative cut-off values in false-positive TRG1 and false-negative TRG3-4 (Supplementary Table 4 and 5). This indicates that to a large extent patients are misqualified by both qualitative and quantitative methods, suggesting that biological factors may be the underlying cause of this misqualification.

To our knowledge, this is the first prospective study that systematically assessed the role of FDG-PET/CT in clinical response evaluation after nCRT for oesophageal cancer. PET/CT for locoregional response evaluation was performed at 12 weeks after nCRT. Immediately after nCRT, a false-positive signal is frequently detected by PET due to radiotherapy-induced inflammation and tumour necrosis. Based on knowledge from other malignancies, such as lymphoma and breast cancer, we hypothesized that PET/CT might be more accurate to guide targeted endoscopic and endosonographic biopsies at 12 weeks after nCRT compared to for example 6 weeks.[8, 14]

The value of FDG-PET/CT in response evaluation after nCRT has been studied before.[10, 15-24] Most FDG-PET/CT scans were performed at shorter time interval after completion of nCRT (during nCRT or within 6 weeks after completion of nCRT). Definitions of pathologically complete response (pCR) varied from TRG1 of the primary tumour to ypT0N0 and ≤10% residual tumour cells. One study, similar to the present study, assessed the association between any visible FDG-uptake (5-7 weeks after nCRT) and any residual tumour cells in the resection specimen, demonstrating a sensitivity, specificity and accuracy of 74%, 22% and 53%, respectively.[11] This is in line with the qualitative analysis of this study, with a sensitivity, specificity and accuracy of 80%, 37% and 68%, respectively. The healing of post radiation oesophagitis may have contributed to the somewhat better performance of FDG-PET/CT at a longer interval after nCRT in

the present study. Furthermore, several studies investigated the association between complete metabolic response (cMR, defined as SUV_{max} <4 and N0) and pCR defined as ypT0N0.[10, 17, 22] Sensitivity, specificity, NPV and PPV ranged from 51-67%, 46%-67%, 63%-82% and 27%-79%, respectively, also demonstrating only a modest diagnostic accuracy of quantitative FDG-PET analysis. With quantitative SUL_{max} in the present study, comparable findings for TRG 1 vs. TRG2-3-4 were found (sensitivity 74%, specificity 60%, NPV 64% and PPV 86%).

It is difficult to speculate on the minimal diagnostic accuracy that is needed to safely postpone surgery in an active surveillance approach for oesophageal cancer. In patients in whom vital tumour initially has been missed, tumour recurrence may be detected in the window of opportunity during systematic rigorous follow-up. However, this window of opportunity is limited and is the topic of current research. The strategy for follow-up includes FDG-PET/CT for detection of suspicious lymph nodes and systemic metastases, and will be combined with endoscopy with bite-on-bite biopsies and endo-ultrasonography with fine needle aspiration of suspicious lymph nodes, as is currently applied in the prospective SANO-trial (Surgery As Needed for Oesophageal cancer; trial NTR 6803).[7, 25] The SANO-trial will compare treatment outcome after nCRT in patients who have a complete clinical response 12 weeks after nCRT, randomising patients for immediate oesophagectomy versus an active surveillance approach.[25]

In serial follow-up, the use of qualitative and quantitative FDG-PET/CT might be more promising (for an example see Figure 4). As is seen in the present study, FDG-PET/CT at a certain time-point at low SUL, no distinction can be made between small, but vital, residual tumour and physiological oesophageal metabolism or surrounding oesophagitis. Over time however, an increase in FDG-signal is expected to reflect tumour recurrence. Decreasing SUL would be compatible with recovery from radiation induced oesophagitis or other phenomena such as Candida infection and gastro-oesophageal reflux disease that otherwise would have caused false-positive FDG-uptake.[26] To be able to detect small FDG changes reliably, we advocate consistent and strict scanning protocols during follow-up.

Apart from being used for response evaluation post-nCRT, FDG-PET/CT is most useful for detection of interval metastases. Other studies, with shorter time to response assessments, all have reported similar numbers of 8% detection of interval metastases.[27-31] FDG-PET/CT has been reported to have a sensitivity of 74% and a specificity of 91% in detecting (interval) metastases, and is considered a cost-effective tool preventing futile surgery.[32] The 9.5% detection of metastases that was found in the present study suggests that a prolonged interval from nCRT to surgery may help to avoid unneccesary surgery.

One of the limitations of this study is that, due to the multicentre character of the trial, not all baseline and follow-up FDG-PET/CT scans were made in the same hospital

using the same scanner. Some variability was encountered in quality of scanning, with five patients who had noisy images. However, this reflects clinical practice and these scans were still adequate for visual analysis. Generally, noisy images deteriorate the confidence of reading and the accuracy of SUL measurements. We would therefore strongly recommend high quality scanning using the same scanner at CRE-2 and later, in order to allow detection of small lesions (lymph nodes, systemic metastases) at these time-points. Some patients had a prolonged interval between the last FDG-PET/CT and surgery (Supplementary Table 2). Therefore, the amount of residual disease at the time of the last scan may not have been representative for TRG in the resection specimen of these patients. We therefore stress the importance of a short interval between the last PET/CT and surgery in diagnostic studies, as to prevent falsely negative results. Furthermore, it is a topic of debate if TRG2 tumours can be safely missed. The main endpoint was the percentage of TRG3-4 tumours that were missed on FDG-PET/CT. According to the preSANO protocol, TRG2 residual tumours were allowed to be missed, because of the assumption that these tumours will become detectable over time, before they have become irresectable. This assumption can only be tested in a large comparative trial, such as the current SANO-trial.[6, 25]

In conclusion, the value of FDG-PET/CT approximately 12 weeks after nCRT for detection of locoregional recurrence of oesophageal cancer is limited, both qualitatively and quantitatively. Distinction of small TRG3-4 tumour from surrounding physiological metabolism or post-radiation oesophagitis is difficult and may cause false-positive and false-negative results. Therefore, a clinically useful cut-off point for detection of residual tumour by SUL cannot be determined. Quantitative measurements might be applicable to support qualitative interpretation as to monitor metabolism during serial follow-up in an active surveillance strategy after nCRT, provided that each follow-up scan is performed on the same scanner and in the same way. Most importantly, qualitative assessment of FDG-PET/CT is useful for the detection of interval metastases (9.5%) at 12 weeks after nCRT. The current SANO-trial will assess the value of FDG-PET/CT and other diagnostic modalities in an active surveillance approach.[7, 25]

Table 1. Baseline characteristics of the study population [7]

Baseline characteristics	N=207
Age — yr.	
Median (interquartile range)	66 (60-71)
Male sex — no. (%)	173 (84)
Tumour type — no. (%)	
Squamous-cell carcinoma	44 (21)
Adenocarcinoma	162 (78)
Adenosquamous cell carcinoma	1 (0)
Clinical T stage — no. (%)‡	
cT1	1 (0)
cT2	40 (19)
cT3	154 (74)
cT4	11 (5)
Missing	1 (0)
Clinical N stage — no. (%)‖	
N0	63 (30)
N1	80 (39)
N2	57 (28)
N3	6 (3)
Missing	1 (0)
Body mass index*	26±4.4
Missing	4 (2)
Lean body mass*	61±9.8
Missing	4 (2)
Glucose (mmol/L)	5.9±1.3
Missing	6 (3)
Injection dose ^{18}F-FDG (Mbq)	212±64.3
Missing	2 (1)
Interval between injection and scanning (min)	61.0±9.1
Missing	5 (2)

Plus-minus values are means ±SD

*The body-mass index (BMI) is the weight in kilograms divided by the square of the height in metres

*The lean body mass (LBM) was calculated according to the James equation[9]

Table 2. Results for qualitative dichotomous FDG-PET/CT analysis at CRE-2/-3.[7]

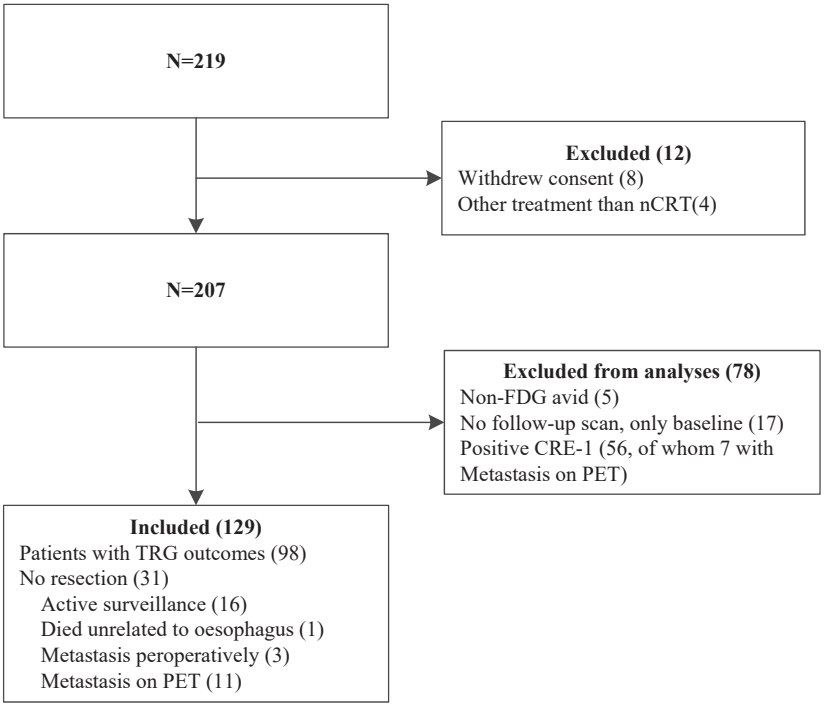
	TRG1	TRG2	TRG3	TRG4	Total
FDG-positive	17	22	17	18	74
FDG-negative	10	8	2	4	24
Total	27	30	19	22	98

p=0.19 (chi-square)

Table 3. Accuracy of FDG-PET/CT in predicting TRG3-4 versus TRG 1 at CRE-2/-3 with optimal cut-off points.

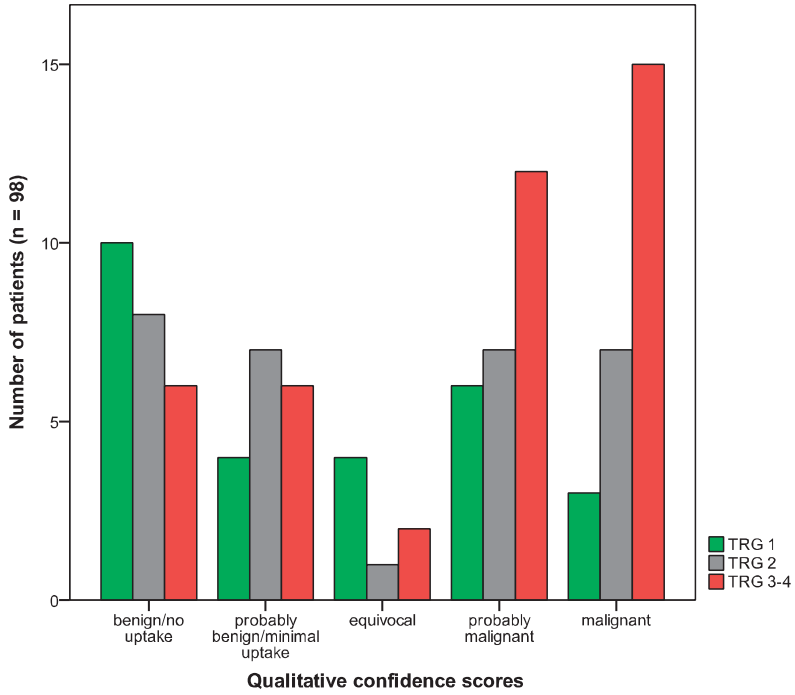
Parameter	AU-ROC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)
SUL_{max} tumour	0.70 (0.57– 0.83)	2.93	66	74
SUL_{max} ratio tumour/oesophagus (SUR)	0.70 (0.56 – 0.83)	1.47	73	63
ΔSUL_{max} (absolute)	0.59 (0.45 – 0.73)	4.03	56	70
ΔSUL_{max} (percentage)	0.64 (0.50 – 0.78)	-56.31	61	74

Figure 1. Flowchart of final inclusion of 129 patients at CRE-2/-3.[7]



nCRT: neoadjuvant chemoradiotherapy; CRE: clinical response evaluation; TRG, tumour regression grade

Figure 2. Confidence scores in 98 patients at CRE-2/-3



p=0.072 (chi-square)

Figure 3a. Receiver operating characteristic curve analysis of SUL_{max} tumour and SUL_{max} ratio tumour/oesophagus at CRE-2/-3 in predicting TRG1 vs. TRG3-4. **3b**. Receiver operating characteristic curve analysis of ΔSUL_{max} (absolute) and ΔSUL_{max} (percentage) at CRE-2/-3 in predicting TRG1 vs. TRG3-4.

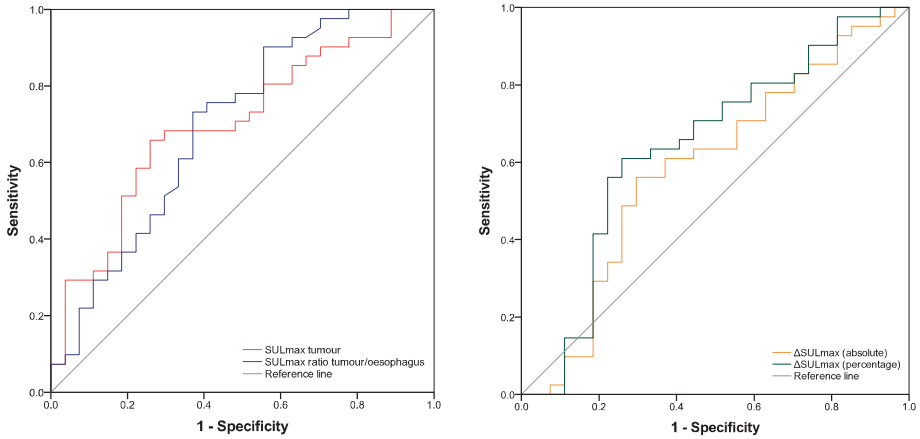
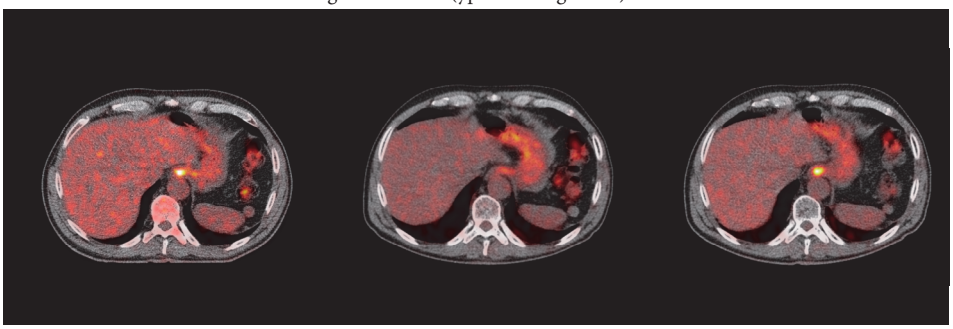


Figure 4. Serial FDG-PET/CT after nCRT shows an increase in FDG-avidity 24 weeks after completion of nCRT (right), after an initially clinically complete response at 12 weeks (middle). Based on these PET/CT findings oesophagectomy was performed and residual tumour was found in the resection specimen. The resection was radical and tumour margins were free (ypT3N1R0 grade 3).



nCRT: neoadjuvant chemoradiotherapy

Appendix

Supplementary Table 1. Outcomes of patients that were excluded from analyses.[7]

Outcome FDG-PET/CT	TRG1	TRG2	TRG3	TRG4	No surgery*	Total
Died before CRE	0	0	0	0	3	3
Positive CRE-I	6	15	11	12	12	56
No follow-up scan	4	2	4	3	1	14
Non-FDG avid	1	0	1	1	2	5
Total	11	17	16	16	18	78

TRG: tumour regression grade; CRE: clinical response evaluation. *No surgery because of death, patient's preference of poor physical condition

Supplementary Table 2. Visual FDG-PET/CT analysis versus TRG for patients with surgery >6 weeks later than FDG-PET/CT for all CREs.

	TRG1	TRG2	TRG3	TRG4	*Total*
FDG-positive	4	7	2	4	17
FDG-negative	1	0	0	1	2
Total	5	7	2	5	19

Supplementary Table 3. Results of quantitative FDG-PET/CT analysis at CRE-2/-3 using optimal cut-off values.

	Tumour regression grade (TRG)				
PET parameter cut-off values	TRG1	TRG2	TRG3	TRG4	Total
SUL_{max} 2.93					
FDG-positive	7	16	10	17	50
FDG-negative	20	14	9	5	48
Total	27	30	19	22	98
SUL_{max} ratio tumour/oesophagus (SUR) 1.47					
FDG-positive	11	15	11	19	56
FDG-negative	16	15	8	3	42
Total	27	30	19	22	98
ΔSUL_{max} (absolute) 4.03					
FDG-positive	19	13	9	9	50
FDG-negative	8	16	10	13	47
Total	27	29	19	22	97
ΔSUL_{max} (percentage) -56.31					
FDG-positive	20	15	9	7	51
FDG-negative	7	14	10	15	46
Total	27	29	19	22	97

TRG: tumour regression grade

Supplementary Table 4. Overlap of missed patients with TRG3-4 tumours in qualitative analysis and in quantitative analysis at CRE-2/-3 using optimal cut-off values.

	Qualitative dichotomous FDG-negative	Qualitative confidence score FDG-negative	SUL_{max} <2.93	SUR <1.47	abs ΔSUL_{max} <4.03	$\Delta\%SUL_{max}$ <56.31 decrease
Qualitative dichotomous FDG-negative	6					
Qualitative confidence score FDG-negative	6	12				
SUL_{max} <2.93	6	8	14			
SUR <1.47	4	7	9	11		
abs ΔSUL_{max} <4.03	2	5	8	6	23	
$\Delta\%SUL_{max}$ <56.31 decrease	2	5	7	5	22	25

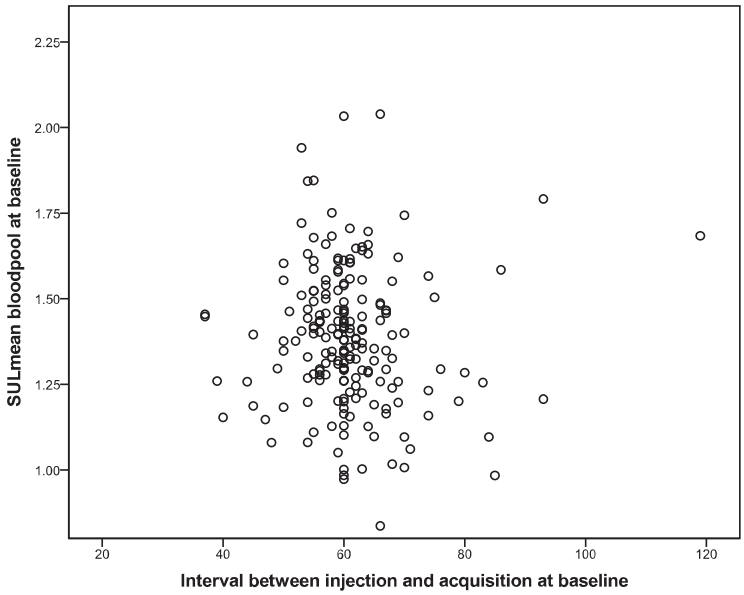
SUR: SUL_{max} ratio tumour/oesophagus; abs: absolute

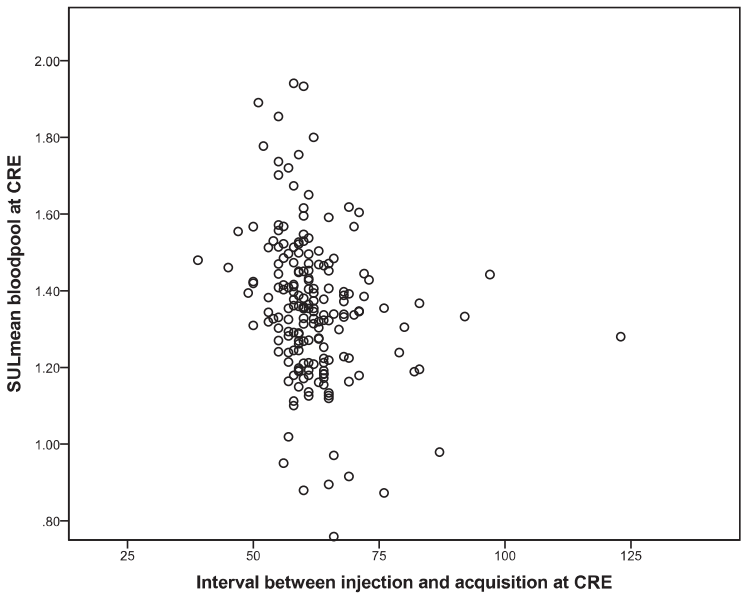
Supplementary Table 5. Overlap of false-positive patients with TRG1 (complete response) in qualitative analysis and quantitative analysis at CRE-2/-3 using optimal cut-off values.

	Qualitative dichotomous FDG-positive	Qualitative confidence score FDG-positive	SUL_{max} >2.93	SUR >1.47	abs ΔSUL_{max} >4.03	$\Delta\%SUL_{max}$ >56.31 increase
Qualitative dichotomous FDG-positive	17					
Qualitative confidence score FDG-positive	13	13				
SUL_{max} >2.93	7	7	7			
SUR >1.47	11	10	6	11		
abs ΔSUL_{max} >4.03	11	7	4	7	19	
$\Delta\%SUL_{max}$ >56.31 increase	11	7	4	7	19	20

SUR: SUL_{max} ratio tumour/oesophagus; abs: absolute

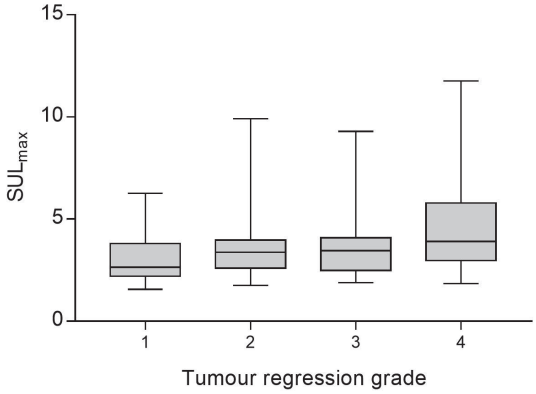
Supplementary Figure 1. SUL_{mean} of the bloodpool at baseline and CRE-1/-2/-3 versus injection time to scanning.

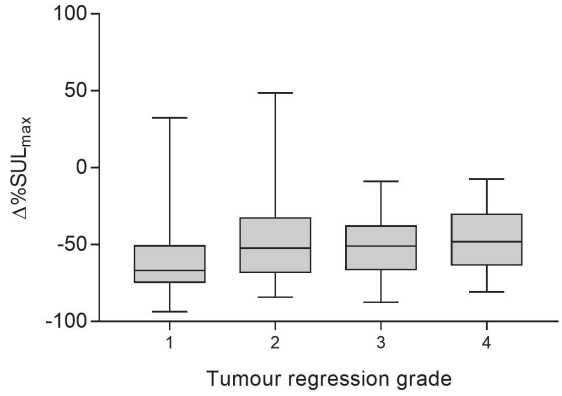


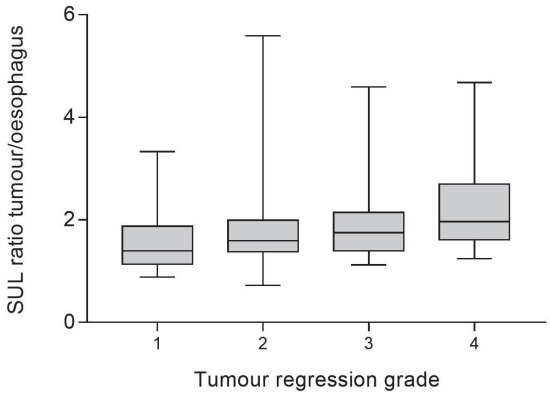


CRE: clinical response evaluation

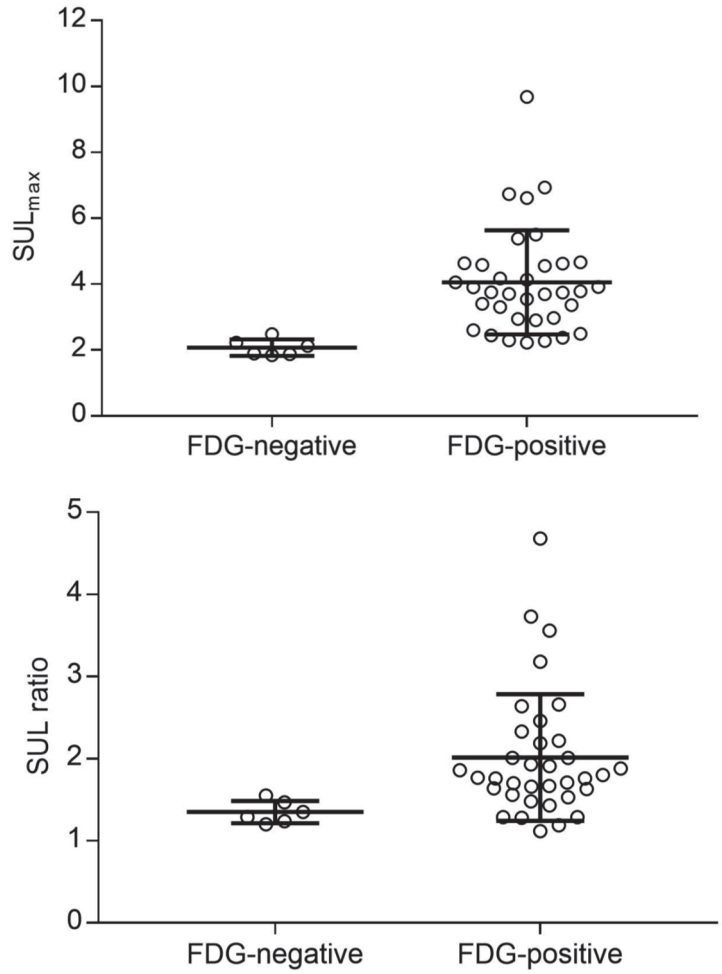
Supplementary Figure 2. SUL_{max}, $\%\Delta SUL_{max}$ and SUL ratio in all patients with various TRG outcomes.







Supplementary Figure 3. SUL_{max} and SUL ratio at CRE-2/-3 for qualitatively FDG-positive and FDG-negative scans, in TRG3-4 tumours.



References

1. Omloo JM, Lagarde SM, Hulscher JB et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007;246(6):992-1000; discussion -1.
2. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062-7.
3. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. The Lancet Oncology. 2011;12(7):681-92.
4. Talsma AK, Damhuis RA, Steyerberg EW, Rosman C, Van Lanschot JJ, wijnhoven BP. Determinants of improved survival after oesophagectomy for cancer. Br J Surg. 2015;102(6):668-75.
5. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
6. Noordman BJ, Shapiro J, Spaander MC et al. Accuracy of detecting residual disease after CROSS neoadjuvant chemoradiotherapy for esophageal cancer (preSANO Trial): rationale and protocol. JMIR Res Protoc. 2015;4(2):e79.
7. Noordman BJ, Spaander MCW, Valkema R et al. Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study. The Lancet Oncology. 2018.
8. Boellaard R, O'Doherty MJ, Weber WA et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2010;37(1):181-200.
9. Aide N, Lasnon C, Veit-Haibach P, Sera T, Sattler B, Boellaard R. EANM/EARL harmonization strategies in PET quantification: from daily practice to multicentre oncological studies. European journal of nuclear medicine and molecular imaging. 2017;44(Suppl 1):17-31.
10. Kim MK, Ryu JS, Kim SB et al. Value of complete metabolic response by (18)F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. Eur J Cancer. 2007;43(9):1385-91.
11. McLoughlin JM, Melis M, Siegel EM et al. Are patients with esophageal cancer who become PET negative after neoadjuvant chemoradiation free of cancer? J Am Coll Surg. 2008;206(5):879-86; discussion 86-7.
12. Chirieac LR, Swisher SG, Ajani JA et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer. 2005;103(7):1347-55.
13. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. Biometrical journal Biometrische Zeitschrift. 2005;47(4):458-72.
14. Juweid ME, Stroobants S, Hoekstra OS et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25(5):571-8.
15. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of 18F FDG PET: a systematic review. Radiology. 2010;254(3):707-17.
16. Chen YM, Pan XF, Tong LJ, Shi YP, Chen T. Can (1)(8)F-fluorodeoxyglucose positron emission tomography predict responses to neoadjuvant therapy in oesophageal cancer patients? A meta-analysis. Nuclear medicine communications. 2011;32(11):1005-10.
17. Elliott JA, O'Farrell NJ, King S et al. Value of CT-PET after neoadjuvant chemoradiation in the prediction of histological tumour regression, nodal status and survival in oesophageal adenocarcinoma. Br J Surg. 2014;101(13):1702-11.

18. Monjazeb AM, Riedlinger G, Aklilu M et al. Outcomes of patients with esophageal cancer staged with [(1)(8)F]fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(31):4714-21.
19. Swisher SG, Erasmus J, Maish M et al. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. Cancer. 2004;101(8):1776-85.
20. Brucher BL, Weber W, Bauer M et al. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Annals of surgery. 2001;233(3):300-9.
21. Goense L, van Rossum PS, Reitsma JB et al. Diagnostic Performance of (1)(8)F-FDG PET and PET/CT for the Detection of Recurrent Esophageal Cancer After Treatment with Curative Intent: A Systematic Review and Meta-Analysis. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2015;56(7):995-1002.
22. Heneghan HM, Donohoe C, Elliot J et al. Can CT-PET and Endoscopic Assessment PostNeoadjuvant Chemoradiotherapy Predict Residual Disease in Esophageal Cancer? Ann Surg. 2016.
23. Klayton T, Li T, Yu JQ et al. The role of qualitative and quantitative analysis of F18-FDG positron emission tomography in predicting pathologic response following chemoradiotherapy in patients with esophageal carcinoma. Journal of gastrointestinal cancer. 2012;43(4):612-8.
24. Wieder HA, Brucher BL, Zimmermann F et al. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004;22(5):900-8.
25. Noordman BJ, Wijnhoven BPL, Lagarde SM et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial. BMC Cancer. 2018;18(1):142.
26. van Rossum PS, van Lier AL, Lips IM et al. Imaging of oesophageal cancer with FDG-PET/CT and MRI. Clinical radiology. 2015;70(1):81-95.
27. Blom RL, Schreurs WM, Belgers HJ, Oostenbrug LE, Vliegen RF, Sosef MN. The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma. Eur J Surg Oncol. 2011;37(9):774-8.
28. Bruzzi JF, Swisher SG, Truong MT et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. Cancer. 2007;109(1):125-34.
29. Stiekema J, Vermeulen D, Vegt E et al. Detecting interval metastases and response assessment using 18F-FDG PET/CT after neoadjuvant chemoradiotherapy for esophageal cancer. Clinical nuclear medicine. 2014;39(10):862-7.
30. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA, Eloubeidi MA. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. J Thorac Cardiovasc Surg. 2005;129(6):1232-41.
31. Goense L, Ruurda JP, Carter BW et al. Prediction and diagnosis of interval metastasis after neoadjuvant chemoradiotherapy for oesophageal cancer using (18)F-FDG PET/CT. European journal of nuclear medicine and molecular imaging. 2018.
32. Anderegg MC, de Groof EJ, Gisbertz SS et al. 18F-FDG PET-CT after Neoadjuvant Chemoradiotherapy in Esophageal Cancer Patients to Optimize Surgical Decision Making. PloS one. 2015;10(11):e0133690.

Chapter 17

Active surveillance in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal or junctional cancer

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Abstract

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is standard of care for locally advanced esophageal cancer in many countries. After nCRT up to one third of all patients have a pathologically complete response in the resection specimen, posing an ethical imperative to reconsider the necessity of standard surgery in all operable patients after nCRT. An active surveillance strategy following nCRT, in which patients are subjected to frequent clinical investigations after the completion of neoadjuvant therapy, has been evaluated in other types of cancer with promising results. In esophageal cancer, both patients who are cured by neoadjuvant therapy alone as well as patients with subclinical disseminated disease at the time of completion of neoadjuvant therapy may benefit from such an organ sparing approach. Active surveillance is currently applied in selected patients with esophageal cancer who refuse surgery or are medically unfit for major surgery after completion of nCRT, but this strategy is not (yet) adopted as an alternative to standard surgery or definitive chemoradiation. The available literature is scarce, but suggests that long-term oncological outcomes after active surveillance are non-inferior compared to standard surgical resection, providing justification for comparison of both treatments in a phase III trial. This review gives an overview of the current knowledge regarding active surveillance after completion of nCRT in esophageal cancer and outlines future research perspectives.

Introduction

Surgical resection has long been considered the primary curative treatment modality for stages cT1b-4aN0-3M0 esophageal or junctional cancer. In the literature reported 5-year survival rates for patients treated with primary surgical resection range from six to 50%, but rarely exceed 35%.[1-5] To improve long-term survival, many trials investigated the added value of neoadjuvant chemo- and/or radiotherapy. [6-12]

In most countries, two neoadjuvant approaches have been adopted as standard of care. The first is neoadjuvant chemoradiotherapy (nCRT), now generally based on the CROSS regimen, which resulted in a 5-year overall survival benefit of 14%, compared to surgery alone.[10, 11] An alternative option is perioperative or preoperative chemotherapy using the OEO2 or the MAGIC protocol, which showed an absolute risk reduction of 6% and 13% at 5-years, respectively.[7, 12] Except for Japan, it is widely accepted that chemoradiotherapy is the neoadjuvant treatment of choice for patients with squamous cell carcinoma. For patients with adenocarcinoma the optimal multimodality regimen is still topic of debate.[13-15] A significant survival benefit of nCRT over nCT has never been proven for patients with adenocarcinoma, but nCRT is associated with a high percentage of pathologically complete response (pCR) for both histological subtypes.[13, 16, 17] A pCR means that no viable tumor cells can be detected at the site of the primary tumor or in the resected regional lymph nodes, as determined by conventional histological examination.

In subsequent analyses of secondary endpoints of the CROSS trial it was found that nearly a third (29%) of the patients had a pathologically complete response (pCR) in the resection specimen. In the CROSS trial, a pCR after nCRT was seen in 49% of patients with a squamous cell carcinoma and 23% of patients with an adenocarcinoma. In the OEO2 and MAGIC trials this was 4% and 5%, respectively.[10, 18] This observation raises the question whether a surgical resection is of benefit for patients who were already cured locoregionally by nCRT alone. Theoretically, an organ sparing approach might be feasible since, intuitively, an esophagectomy in patients with no residual viable tumor cells has no effect on clinical outcome. An esophagectomy is associated with a risk for per- and postoperative mortality and morbidity and reduces quality of life in both the short and long term.[19-24] This imposes an ethical imperative to reconsider the necessity of standard esophagectomy in patients after nCRT. An individualized approach to surgery after nCRT should be studied and defined; a new treatment algorithm in which not every patient with potentially curable esophageal cancer needs a resection after completion of nCRT to achieve long-term survival. Such an active surveillance strategy is currently applied in selected patients who refuse surgery or are medically unfit for major surgery after completion of nCRT.[25-28] In this review, we give an overview of the feasibil-

ity and effectiveness of an active surveillance approach after completion of nCRT for carcinoma of the esophagus.

Rationale for an active surveillance approach

In an active surveillance strategy, patients are subjected to serial clinical investigations after completion of nCRT. Surgical resection will be offered only to patients in whom a locoregional regrowth/residual disease is highly suspected or proven, without signs of distant dissemination.

In other types of cancer including rectal and head and neck cancer, similar approaches have been evaluated with excellent results.[29-32] In a recent study in patients who received nCRT for rectal cancer, 65% of all patients with a clinically complete response (cCR, *i.e.* no residual disease based on clinical diagnostics) did not need surgery. Of the remaining 35%, a successful delayed surgical resection was performed in 90% of patients. Oncological outcome was comparable between both treatment groups.[30] In advanced head and neck cancer active surveillance after chemoradiotherapy is widely accepted nowadays. In a recent randomized controlled trial (RCT) that compared standard neck dissection with PET-CT guided surveillance, survival was similar for both groups, but surveillance resulted in considerably fewer operations and was more cost-effective.[32]

Who will benefit from an active surveillance approach?

An organ-preserving active surveillance strategy in esophageal cancer will not only have advantages for individuals who are already cured by neoadjuvant therapy alone, but also for patients with subclinical disseminated disease (*i.e.* micrometastases) at the time of completion of neoadjuvant therapy. After tumor staging and neoadjuvant treatment, micrometastases may be present but yet undetectable. With time these disseminated tumor cells will become clinically manifest. Distant metastases, which are the main determinants of long-term survival after nCRT plus surgery (especially in patients with a pathologically complete response), are grossly independent of locoregional therapy.[7, 33] Although the biology of distant dissemination is not fully understood, current assumptions hold that the process of spreading and seeding of tumor cells from the primary lesion is an early event. The process of tumor cell dissemination may well have occurred at the time of first clinical presentation and subsequent locoregional treatment (*i.e.* nCRT with and without subsequent surgery).[34] This is reflected by the large number of patients who develop hematogenous metastases within two years after surgery.[10, 11, 35]

Hence, no matter how timely and aggressive locoregional treatment is, it will hardly affect the survival-determining events of distant dissemination. At present, patients with occult distant metastases undergo an esophageal resection which ultimately is of no benefit to them, because distant metastases are still below the detection limit at the first clinical evaluation after nCRT. It should be noted that another theoretical explanation for the high rate of distant dissemination early after esophagectomy is that the depression of the immune system after major surgery might enhance hematogenic diffusion of tumor cells. This phenomenon will not take place if the patient is not operated on.[36] This hypothesis also supports an active surveillance strategy. Hence, it is hypothesized that application of an active surveillance strategy in patients with a clinically complete response after nCRT may reduce the need for an esophagectomy in 30 to 40% of all patients.[10, 11, 25, 27, 28]

An active surveillance approach is only justified if long-term oncological outcome is similar to that after nCRT followed by surgery. Therefore, tumor regrowth after nCRT should be detected at a curable stage, *i.e.* in the period between the *clinical detection limit* and the *resectability limit* and before the potential development of distant dissemination from disease regrowth (Figure 1). Currently, the time span of this period and its variation between patients is unknown. Therefore, an intensive surveillance strategy (or approach) should be applied aiming to detect regrowth of cancer as early as possible before the tumor is irresectable. Since the majority of locoregional regrowths are expected to occur within 12 months after nCRT and nearly all within 24 months, an intensive surveillance strategy should be performed in the first two years.[37]

Clinical response evaluations: identifying and excluding minor- and non-responders

After completion of nCRT, all patients should be re-staged, which is defined as the clinical response evaluation (CRE). After a CRE, patients can be categorized as clinically complete responders or clinically incomplete responders. Only clinically complete responders (*i.e.* patients in whom no locoregional or disseminated disease can be proven) are offered active surveillance. Clinically incomplete responders with locoregional disease in the absence of distant metastases will be referred for immediate surgery, whereas clinically incomplete responders with distant metastases will be referred for palliative care or second line chemotherapy.

Multiple studies have focused on the accuracy of detecting residual disease during clinical response evaluation after nCRT for esophageal cancer. A surgical resection as standard treatment in a potentially curative setting was (almost) always performed. Although the accuracy of endoscopy with standard biopsies is limited (false negative

rate 41%-69%)[38-40], a recent study suggested that endoscopy with deep (bite-on-bite) biopsies is more accurate in detecting residual disease after nCRT. Tumor-negative bite-on-bite biopsies were 85% predictive for a pathologically complete response in the resection specimen (*i.e.* 15% false negative for any residual cancer).[41] Bite-on-bite biopsies increase the chance of detecting residual submucosal tumor deposits compared to conventional biopsies (Figure 2). After nCRT, residual disease is frequently located in the submucosa (and mucosa), and is rarely present as an isolated remnant only in the proper muscle layer, surrounding stroma and/or regional lymph nodes.[42] The use of fine needle aspiration (FNA) to detect lymph node metastases theoretically further increases the diagnostic accuracy, but literature regarding this topic is lacking.

18F-FDG PET-CT can identify non-complete responders with moderate sensitivity (46–88 %) and specificity (56–87 %) during CREs. The substantial false negative (12 – 54%) and false positive rates (13–44 %) of a single PET-CT after nCRT limit its applicability for detection of locoregional residual disease during CRE.[43-48] However, PET-CT is highly valuable in the detection of interval metastases, as development of metastatic disease during the nCRT period can be detected by PET-CT in up to 10% of all patients.[49] Moreover, serial PET-CT during active surveillance might be useful in the detection of local regrowths, as a subtle increase in FDG-avidity may indicate recurrence of malignancy, whereas a decrease in FDG-avidity more likely depicts the recovery from earlier radiotherapy induced esophagitis.

The maximum tumor thickness (MTT) and changes in MTT as determined by endoscopic ultrasound (EUS) are predictive for histopathological response on nCRT, as shown by a Swiss study.[50] However, these findings need validation in an independent cohort.[50]

At present, the Dutch preSANO trial investigates the accuracy of clinical response evaluation and the optimal diagnostic set for detecting residual disease after nCRT for esophageal cancer using a combination of endoscopy with bite-on-bite biopsies, radial EUS for measurement of maximal tumour thickness and –area, lineair EUS-guided FNA of suspected lymph nodes, and 18F-FDG PET-CT.[51] Approximately six weeks after completion of nCRT a first CRE is performed including endoscopy with bite-on-bite biopsies and EUS. Patients in whom no residual disease can be proven by histology will be offered postponed surgery, approximately 12-14 weeks after completion of nCRT. One week before the planned surgical resection, a second clinical response evaluation (CRE-II) is performed with a PET-CT scan followed by endoscopy with bite-on-bite biopsies, EUS and FNA of all suspected lymph nodes and/or PET-positive lesions. The rationale to include this second CRE is to increase the absolute chance of detecting residual disease and to allow for a comparison between serial measurements. The safety of delaying surgery to 12-14 weeks is supported by a recent study suggesting that prolonged time to surgery after nCRT up to at least 12 weeks has no negative effect on dis-

ease-free and overall survival (HR=1.00 and HR=1.06 per additional week). Moreover, prolonged time to surgery increases the probability of a pathologically complete response in the resection specimen (odds ratio=1.35 per additional week of time to surgery, p=.0004).[52] Similar results have been published by other groups.[53-55] The main study parameter of the preSANO trial is the correlation between clinical response during the CREs and pathological response in the resection specimen. Results of the preSANO trial are expected end-2017 and will reveal the optimal combination of diagnostic tests to detect residual disease after nCRT.[51]

Although several studies have investigated the accuracy of detecting residual disease after nCRT, the minimum accuracy needed for testing an active surveillance strategy in a clinical trial is under debate. Intuitively, any residual disease after nCRT may not be missed since these patients do not benefit from active surveillance and should undergo surgery as soon as possible. On the other hand, as long as tumor regrowth after nCRT can be detected at a curable stage during active surveillance (Figure 1), long-term oncological outcome is theoretically not jeopardized and residual disease may be missed during initial CREs. This conception is supported by the available literature on active surveillance after nCRT for rectal or esophageal cancer, which shows that a delayed (radical) resection can be performed successfully in nearly all patients with locoregional regrowth that was detected during active surveillance using endoscopy with (conventional) biopsies and PET-CT (see below).[25, 27, 28, 30] It should be noted that a postponed surgical resection has been suggested to increase the risk of postoperative complications. However, this phenomenon is reported mainly after treatment with high dose of definitive chemoradiotherapy (radiotherapy dose >50 Gy; so called salvage esophagectomy) in low-volume centers and it is unknown whether this also applies after treatment with a lower dose of radiotherapy (CROSS regimen).[56, 57] Taken together, it is felt that the decision to perform a phase III trial that compares active surveillance with standard surgery should not depend on a predefined minimum sensitivity or negative predictive value of response evaluation, but rather on results from (phase I/II) studies that have reported clinical outcomes of an active surveillance strategy in selected patients with a cCR after nCRT. Nevertheless, results from studies on diagnostic accuracy are highly valuable, especially for determination of the optimal composition of a diagnostic set of tests for response and surveillance evaluations.

Outcomes after active surveillance: a systematic review

A systematic review was conducted to provide a complete overview of all literature on clinical outcomes of active surveillance after nCRT.

Methods

A systematic literature search on active surveillance after neoadjuvant chemoradiotherapy for esophageal cancer was performed in Embase, Medline Ovid, Web of Science, Scopus and the Cochrane Library databases from the inception of the databases to August 9th 2016 by using the search terms "esophageal cancer", "active surveillance" and "neoadjuvant chemoradiotherapy" and its synonyms in the title and abstract fields (Table 1). The literature search was performed by an independent specialized literature researcher. Two reviewers independently screened titles and abstracts of the retrieved publications.

Inclusion criteria were; patients had esophageal cancer, underwent nCRT (regimen not specified), had a clinically complete response during response evaluation after neoadjuvant treatment (diagnostic modalities not specified) and were subjected to active surveillance after neoadjuvant treatment. Publications other than systematic reviews, randomized controlled trials, cohort studies, case-control studies or patient series were excluded.

Results

We identified 489 unique records from the database search. A total of 20 articles concerning active surveillance after nCRT for esophageal cancer were identified based on title/abstract screening. Full text screening resulted in the final selection of four articles.

Some 61 patients with squamous cell carcinoma (n=18), adenocarcinoma (n=40) or other cancer type (n=3) from MD Anderson Cancer Center who declined surgery after nCRT had a cCR based on PET-CT and endoscopy with regular biopsies. The 5-year overall survival rate was 58%. Some 12 of 13 patients who developed a locoregional regrowth in the absence of distant metastases during surveillance underwent a radical esophagectomy.[27] In line with rectal cancer, these results suggest that a delayed resection can technically be performed in nearly all patients with residual locoregional disease that has been missed initially during response evaluation.[30] In a subsequent comparative analysis, 36 patients that underwent active surveillance from the same cohort were matched to 36 patients who underwent nCRT followed by standard surgery using the propensity-score method. Estimated median overall survival was non-significantly better in the active surveillance group than in the standard surgery group (58 months, 95% confidence interval [C.I.]: 27.7 to not applicable vs. 51 months, 95% CI: 30.7 to not applicable, respectively, p=0.28). All eleven patients in the active surveillance group with locoregional regrowth in the absence of distant metastases underwent delayed surgery with excellent outcome (median overall survival 58 months). Furthermore, distant dis-

semination rate (the percentage of patients who developed distant metastases) was comparable in both groups (31% in the active surveillance group and 28% in the standard surgery group).[28] These results support the earlier described assumption that dissemination already must have occurred in most patients at time of diagnosis.

A second study from Italy reported on patients that underwent surveillance (n=38) and patients after planned surgery (n=39). All patients had a cCR after nCRT for esophageal squamous cell carcinoma. Clinical response was assessed using endoscopy with regular biopsies and patients in the surveillance group were not operated on because they were considered unfit for surgery or declined surgery. Nevertheless, 5-year overall survival rates were comparable in both groups (57 % in the active surveillance group vs. 50 % in the standard surgery group, p=0.99).[25]

Similar outcomes were described by a small Irish study that analyzed 25 patients who underwent nCRT with or without surgery when a cCR was diagnosed after endoscopy post-nCRT.[26]

Based on the promising results from these explorative (phase I/II) studies, we feel that an active surveillance approach is feasible and can now safely be tested in a phase III trial.

Conclusion and future directions

An active surveillance approach is currently applied only in patients who refuse surgery or are considered unfit for surgery after completion of nCRT. In the near future, an organ preserving strategy may be offered as an alternative treatment to patients with a cCR after completion of nCRT. However, a phase III trial is needed to ascertain that active surveillance does not lead to inferior long-term oncological outcome as compared to standard surgery. At present, two trials, the French ESOSTRATE-trial and the Dutch-SANO trial (Surgery As Needed for Oesophageal cancer), have been initiated to address this important question.[58] Both trials plan to recruit 300 patients each (including adenocarcinoma and squamous cell carcinoma) with a cCR after completion of nCRT. Both trials use different nCRT regimens, with the SANO-trial using the relatively mild CROSS regimen and the ESOSTRATE-trial using higher doses of nCRT. The latter would probably increase pCR rate, but at the cost of an increase in toxicity and postoperative complications, potentially leading to a less beneficial effectivity/toxicity ratio. The primary endpoint of both trials is overall survival. After response evaluation using endoscopy with (bite-on-bite) biopsies, EUS with FNA and 18F-FDG PET-CT, patients with a cCR will be randomized to receive either active surveillance or standard surgery. In both studies, the sample size leads to a non-inferiority margin of 15%. Combining outcomes of both trials will reduce this non-inferiority margin to 10%, which is in line

with other non-inferiority oncological clinical trials comparing active surveillance with standard surgery.[32] Results of both trials are expected in 2023.

It is anticipated that in the next few years the diagnostic accuracy of tests to assess tumor response to nCRT will improve. Promising results have been published using diffusion-weighted MRI and dynamic contrast-enhanced MRI, but its clinical applicability remains to be proven.[59, 60] If residual disease and/or local regrowths can be detected more accurately or at an earlier stage than with the current diagnostic modalities, this may reduce the proportion of patients scheduled for a postponed surgical resection and the proportion of patients with irresectable regrowths during active surveillance. Nevertheless, current diagnostic modalities have proven to be sufficiently accurate in response evaluation and detection of local regrowths during active surveillance to justify testing of this promising treatment strategy as potential standard of care.

Acknowledgements

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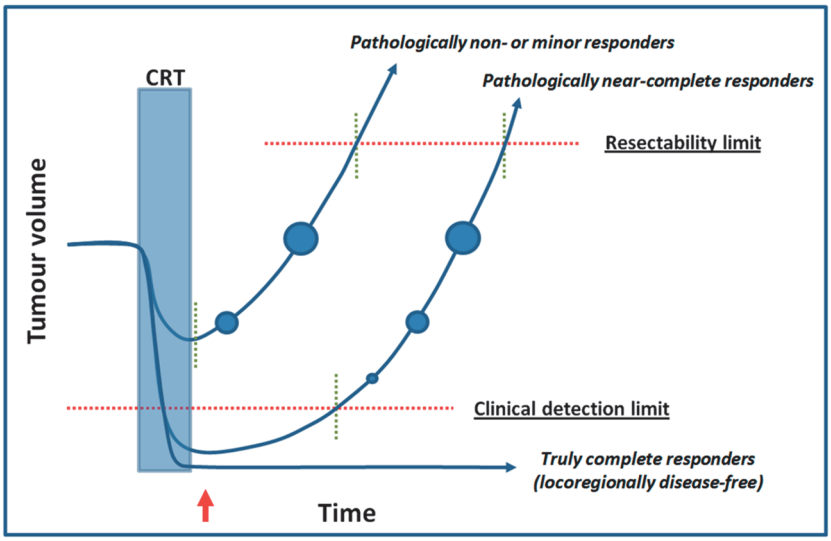
Table 1. Search strategy for systematic review on clinical outcomes after active surveillance.

Database	Search	Hits
Embase	('esophagus cancer'/exp OR 'esophagus tumor'/de OR (((esophag* OR oesophag*) NEAR/6 (cancer* OR neoplas* OR carcino* OR adenocarcino* OR tumor* OR tumour* OR malign*))):ab,ti) AND ('watchful waiting'/de OR (((watch* OR see) NEAR/3 wait*) OR (active* NEAR/3 surveil*) OR ((selective* OR reserv* OR selected* OR needed OR necessar* OR unnecessar* OR declin* OR avoid* OR on-demand) NEAR/6 (resect* OR surg* OR resect* OR esophagectom* OR oesophagectom*))):ab,ti) AND ('chemoradiotherapy'/exp OR (chemoradi* OR radiochemo* OR (chemotherap* NEAR/6 radiotherap*)):ab,ti)	284
Medline Orvid	("Esophageal Neoplasms"/ OR (((esophag* OR oesophag*) ADJ6 (cancer* OR neoplas* OR carcino* OR adenocarcino* OR tumor* OR tumour* OR malign*))).ab,ti.) AND ("Watchful Waiting"/ OR (((watch* OR see) ADJ3 wait*) OR (active* ADJ3 surveil*) OR ((selective* OR needed OR necessar* OR unnecessar* OR declin* OR avoid* OR on-demand) ADJ6 (resect* OR surg* OR resect* OR esophagectom* OR oesophagectom*))).ab,ti.) AND (exp "Chemoradiotherapy"/ OR ("Chemotherapy, Adjuvant"/ AND "Radiotherapy, Adjuvant"/) OR (chemoradi* OR radiochemo* OR (chemotherap* ADJ6 radiotherap*)).ab,ti.)	106
Cochrane	((((esophag* OR oesophag*) NEAR/6 (cancer* OR neoplas* OR carcino* OR adenocarcino* OR tumor* OR tumour* OR malign*))):ab,ti) AND ((((watch* OR see) NEAR/3 wait*) OR (active* NEAR/3 surveil*) OR ((selective* OR needed OR necessar* OR unnecessar* OR declin* OR avoid* OR on-demand) NEAR/6 (resect* OR surg* OR resect* OR esophagectom* OR oesophagectom*))):ab,ti) AND ((chemoradi* OR radiochemo* OR (chemotherap* NEAR/6 radiotherap*)):ab,ti)	110
Web of science	TS=(((((esophag* OR oesophag*) NEAR/5 (cancer* OR neoplas* OR carcino* OR adenocarcino* OR tumor* OR tumour* OR malign*)))) AND ((((watch* OR see) NEAR/2 wait*) OR (active* NEAR/2 surveil*) OR ((selective* OR needed OR necessar* OR unnecessar* OR declin* OR avoid* OR on-demand) NEAR/5 (resect* OR surg* OR resect* OR esophagectom* OR oesophagectom*)))) AND ((chemoradi* OR radiochemo* OR (chemotherap* NEAR/5 radiotherap*))))	248
Scopus	TITLE-ABS-KEY(((((esophag* OR oesophag*) W/5 (cancer* OR neoplas* OR carcino* OR adenocarcino* OR tumor* OR tumour* OR malign*)))) AND ((((watch* OR see) W/2 wait*) OR (active* W/2 surveil*) OR ((selective* OR needed OR necessar* OR unnecessar* OR declin* OR avoid* OR on-demand) W/2 (resect* OR surg* OR resect* OR esophagectom* OR oesophagectom*)))) AND ((chemoradi* OR radiochemo* OR (chemotherap* W/5 radiotherap*))))	5
Total		753

Figure 1. Tumor response after neoadjuvant chemoradiotherapy.



CRT: chemoradiotherapy; Red arrow: time of clinical response evaluation (CRE); Vertical interrupted green lines: boundaries of theoretical time windows. First vertical interrupted green line on each curve refers to the first moment after CRT that a tumor becomes clinically detectable. Second vertical interrupted green line on each curve refers to the moment that a tumor becomes irresectable (T4b). Circles depict progression of locoregional tumor volume. The clinical detection limit is the minimal amount of disease that can be detected by the combination of symptoms, endoscopy with biopsies and imaging modalities.

Figure 2. Bite-on-bite biopsies (1+2+3+4) supposedly increase the chance of detecting submucosal tumour deposits compared to conventional biopsies (1+2).

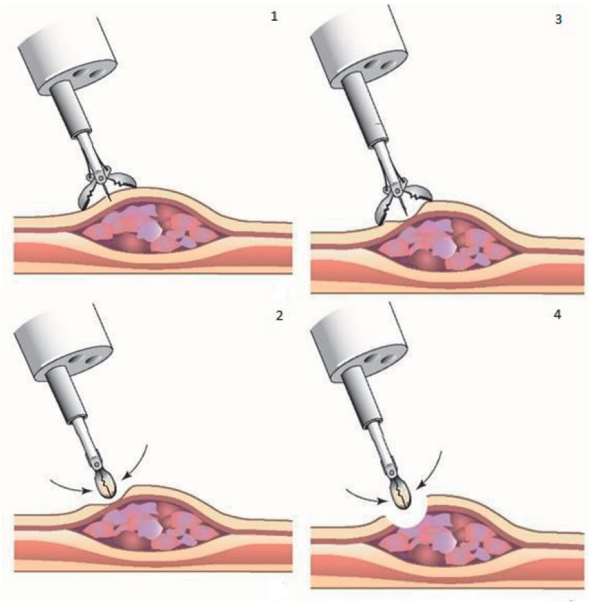
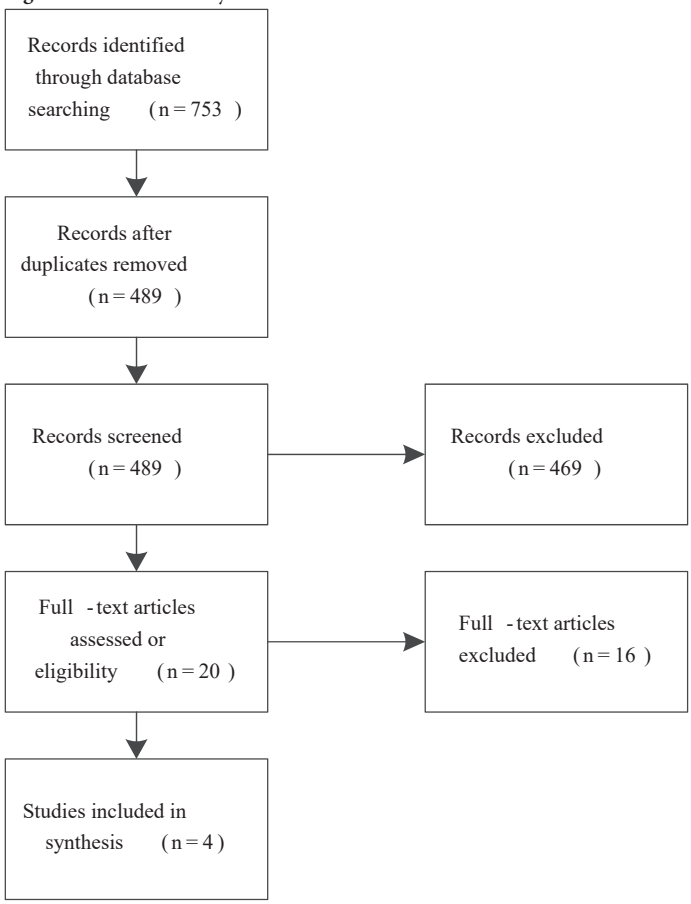


Figure 3. Flowchart for systematic review on clinical outcomes after active surveillance.



References

1. Gignoux M, Roussel A, Paillot B et al. The value of preoperative radiotherapy in esophageal cancer: Results of a study of the E.O.R.T.C. World J Surg. 1987;11(4):426-32.
2. Wang M, Gu XZ, Yin WB, Huang GJ, Wang LJ, Zhang DW. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 206 patients. Int J Radiat Oncol Biol Phys. 1989;16(2):325-7.
3. Nygaard K, Hagen S, Hansen HS et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: A randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second scandinavian trial in esophageal cancer. World J Surg. 1992;16(6):1104-9.
4. Arnott SJ, Duncan W, Kerr GR et al. Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. Radiother Oncol. 1992;24(2):108-13.
5. Kelsen DP, Ilson DH. Chemotherapy and combined-modality therapy for esophageal cancer. Chest. 1995;107(6 Suppl):224S-32S.
6. Cooper JS, Guo MD, Herskovic A et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281(17):1623-7.
7. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062-7.
8. Ychou M, Boige V, Pignon JP et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-21.
9. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
10. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
11. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
12. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
13. Markar SR, Noordman BJ, Mackenzie H et al. Multimodality treatment for esophageal adenocaricnoma: multi-center propensity-score matched study. Ann Oncol. 2016.
14. Keegan N, Keane F, Cuffe S et al. Neo-AEGIS: A randomized clinical trial of neoadjuvant and adjuvant chemotherapy (modified MAGIC regimen) versus neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the esophagus and esophagogastric junction. J Clin Oncol. 2014;32(5s):(suppl; abstr TPS4145).
15. Klevebro F, Alexandersson von Dobeln G, Wang N et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016;27(4):660-7.
16. Burmeister BH, Thomas JM, Burmeister EA et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer. 2011;47(3):354-60.
17. Stahl M, Walz MK, Stuschke M et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27(6):851-6.

18. Smyth EC, Fassan M, Cunningham D et al. Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial. J Clin Oncol. 2016;34(23):2721-7.
19. Seely AJE, Ivanovic J, Threader J et al. Systematic classification of morbidity and mortality after thoracic surgery. Ann Thorac Surg. 2010;90(20732521):936-42.
20. Bailey SH, Bull DA, Harpole DH et al. Outcomes after esophagectomy: a ten-year prospective cohort. Ann Thorac Surg. 2003;75(12537219):217-22.
21. Donohoe CL, McGillycuddy E, Reynolds JV. Long-term health-related quality of life for disease-free esophageal cancer patients. World J Surg. 2011;35(8):1853-60.
22. Djarv T, Lagergren J, Blazeby JM, Lagergren P. Long-term health-related quality of life following surgery for oesophageal cancer. Br J Surg. 2008;95(18581441):1121-6.
23. Djarv T, Blazeby JM, Lagergren P. Predictors of postoperative quality of life after esophagectomy for cancer. J Clin Oncol. 2009;27(19289614):1963-8.
24. Verhoef C, van de Weyer R, Schaapveld M, Bastiaannet E, Plukker JT. Better survival in patients with esophageal cancer after surgical treatment in university hospitals: a plea for performance by surgical oncologists. Ann Surg Oncol. 2007;14(5):1678-87.
25. Castoro C, Scarpa M, Cagol M et al. Complete clinical response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic oesophagus: is surgery always necessary? J Gastrointest Surg. 2013;17(8):1375-81.
26. Furlong H, Bass G, Breathnach O, O'Neill B, Leen E, Walsh TN. Targeting therapy for esophageal cancer in patients aged 70 and over. J Geriatr Oncol. 2013;4(2):107-13.
27. Taketa T, Correa AM, Suzuki A et al. Outcome of trimodality-eligible esophagogastric cancer patients who declined surgery after preoperative chemoradiation. Oncology. 2012;83(5):300-4.
28. Taketa T, Xiao L, Sudo K et al. Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology. 2013;85(2):95-9.
29. Habr-Gama A, Perez RO, Nadalin W et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240(4):711-7; discussion 7-8.
30. Renehan AG, Malcomson L, Emsley R et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol. 2016;17(2):174-83.
31. Maas M, Beets-Tan RG, Lambregts DM et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol. 2011;29(35):4633-40.
32. Mehanna H, Wong WL, McConkey CC et al. PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. N Engl J Med. 2016;374(15):1444-54.
33. Oppedijk V, van der Gaast A, van Lanschot JJ et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol. 2014;32(5):385-91.
34. Chambers AF, Groom AC, MacDonald IC. Metastasis: Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer. 2002;2(8):563-72.
35. Shiozaki H, Sudo K, Xiao L et al. Distribution and timing of distant metastasis after local therapy in a large cohort of patients with esophageal and esophagogastric junction cancer. Oncology. 2014;86(5-6):336-9.
36. Tohme S, Simmons RL, Tsung A. Surgery for cancer: a trigger for metastases. Cancer Res. 2017;77(7):1548 - 52.
37. Versteijne E, van Laarhoven HW, van Hooft JE et al. Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: locoregional recurrence pattern. Dis Esophagus. 2015;28(5):453-9.

38. Sarkaria IS, Rizk NP, Bains MS et al. Post-treatment endoscopic biopsy is a poor-predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. Ann Surg. 2009;249(5):764-7.
39. Schneider PM, Metzger R, Schaefer H et al. Response evaluation by endoscopy, rebiopsy, and endoscopic ultrasound does not accurately predict histopathologic regression after neoadjuvant chemoradiation for esophageal cancer. Ann Surg. 2008;248(6):902-8.
40. Bates BA, Detterbeck FC, Bernard SA, Qaqish BF, Tepper JE. Concurrent radiation therapy and chemotherapy followed by esophagectomy for localized esophageal carcinoma. J Clin Oncol. 1996;14(1):156-63.
41. Walsh TN, Bass GA, Furlong H et al. Clinical complete response to chemo-radiotherapy in esophageal carcinoma: is surgery still required? Submitted for publication. 2015.
42. Shapiro J, ten Kate FJ, van Hagen P, Biermann K, Wijnhoven BP, van Lanschot JJ. Residual esophageal cancer after neoadjuvant chemoradiotherapy frequently involves the mucosa and submucosa. Ann Surg. 2013;258(5):678-88; discussion 88-9.
43. Swisher SG, Maish M, Erasmus JJ et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. Ann Thorac Surg. 2004;78(4):1152-60; discussion -60.
44. Kim MK, Ryu JS, Kim SB et al. Value of complete metabolic response by 18F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. Eur J Cancer. 2007;43(9):1385-91.
45. Heneghan HM, Donohoe C, Elliot J et al. Can CT-PET and Endoscopic Assessment PostNeoadjuvant Chemoradiotherapy Predict Residual Disease in Esophageal Cancer? Ann Surg. 2016.
46. Elliott JA, O'Farrell NJ, King S et al. Value of CT-PET after neoadjuvant chemoradiation in the prediction of histological tumour regression, nodal status and survival in oesophageal adenocarcinoma. Br J Surg. 2014;101(13):1702-11.
47. Dewan A, Sharma S, Dewan A et al. Impact on Radiological and Pathological Response with Neoadjuvant Chemoradiation and Its Effect on Survival in Squamous Cell Carcinoma of Thoracic Esophagus. J Gastrointest Cancer. 2016:1-8.
48. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA, Eloubeidi MA. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. J Thorac Cardiovasc Surg. 2005;129(6):1232-41.
49. Blom RL, Schreurs WMJ, Belgers HJ, Oostenbrug LE, Vliegen RF, Sosef MN. The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma. Eur J Surg Oncol. 2011;37(9):774-8.
50. Jost C, Binek J, Schuller JC et al. Endosonographic radial tumor thickness after neoadjuvant chemoradiation therapy to predict response and survival in patients with locally advanced esophageal cancer: a prospective multicenter phase ll study by the Swiss Group for Clinical Cancer Research (SAKK 75/02). Gastrointest Endosc. 2010;71(7):1114-21.
51. Noordman BJ, Shapiro J, Spaander MC et al. Accuracy of Detecting Residual Disease After CROSS Neoadjuvant Chemoradiotherapy for Esophageal Cancer (preSANO Trial): Rationale and Protocol. JMIR Res Protoc. 2015;4(2):e79.
52. Shapiro J, van Hagen P, Lingsma HF et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. Ann Surg. 2014;260(5):807-14.
53. Kim JY, Correa AM, Vaporciyan AA et al. Does the timing of esophagectomy after chemoradiation affect outcome? Ann Thorac Surg. 2012;93(1):207-12; discussion 12-3.
54. Ruol A, Rizzetto C, Castoro C et al. Interval between neoadjuvant chemoradiotherapy and surgery for squamous cell carcinoma of the thoracic esophagus: does delayed surgery have an impact on outcome? Ann Surg. 2010;252(5):788-96.

55. Kathiravetpillai N, Koeter M, van der Sangen MJ et al. Delaying surgery after neoadjuvant chemoradiotherapy does not significantly influence postoperative morbidity or oncological outcome in patients with oesophageal adenocarcinoma. Eur J Surg Oncol. 2016;42(8):1183-90.
56. Markar S, Gronnier C, Duhamel A et al. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: is it a viable therapeutic option? J Clin Oncol. 2015;33(33):3866-73.
57. Markar SR, Karthikesalingam A, Penna M, Low DE. Assessment of short-term clinical outcomes following salvage esophagectomy for the treatment of esophageal malignancy: systematic review and pooled analysis. Ann Surg Oncol. 2014;21(3):922-31.
58. Putora PM, Bedenne L, Budach W et al. Oesophageal cancer: exploring controversies overview of experts' opinions of Austria, Germany, France, Netherlands and Switzerland. Radiat Oncol. 2015;10:116.
59. Heethuis SE, van Rossum PS, Lips IM et al. Dynamic contrast-enhanced MRI for treatment response assessment in patients with oesophageal cancer receiving neoadjuvant chemoradiotherapy. Radiother Oncol. 2016;120(1):128-35.
60. van Rossum PS, van Lier AL, van Vulpen M et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. Radiother Oncol. 2015;115(2):163-70.

Chapter 18

Patients' preferences for treatment after neoadjuvant chemoradiotherapy for oesophageal cancer

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Abstract

Background

After neoadjuvant chemoradiotherapy (nCRT) plus surgery for oesophageal cancer, 29 per cent of patients have a pathologically complete response in the resection specimen. Active surveillance after nCRT (instead of standard oesophagectomy) may improve health-related quality of life (HRQoL), but patients need to undergo frequent diagnostic tests and it is unknown whether survival is worse than that after standard oesophagectomy. Factors that influence patients' preferences, and trade-offs that patients are willing to make in their choice between surgery and active surveillance were investigated here.

Methods

A prospective discrete-choice experiment was conducted. Patients with oesophageal cancer completed questionnaires 4–6 weeks after nCRT, before surgery. Patients' preferences were quantified using scenarios based on five aspects: 5-year overall survival, short-term HRQoL, long-term HRQoL, the risk that oesophagectomy is still necessary, and the frequency of clinical examinations using endoscopy and PET–CT. Panel latent class analysis was used.

Results

Some 100 of 104 patients (96.2 per cent) responded. All aspects, except the frequency of clinical examinations, influenced patients' preferences. Five-year overall survival, the chance that oesophagectomy is still necessary and long-term HRQoL were the most important attributes. On average, based on calculation of the indifference point between standard surgery and active surveillance, patients were willing to trade off 16 per cent 5-year overall survival to reduce the risk that oesophagectomy is necessary from 100 per cent (standard surgery) to 35 per cent (active surveillance).

Conclusion

Patients are willing to trade off substantial 5-year survival to achieve a reduction in the risk that oesophagectomy is necessary.

Introduction

The widespread introduction of neoadjuvant chemoradiotherapy (nCRT) as a standard of care before resection with curative intent has led to a substantial improvement in survival rates in oesophageal cancer.[1-3] After nCRT plus surgery, about one-third of all patients (49 per cent of patients with squamous cell carcinoma (SCC) and 23 per cent of those with adenocarcinoma) have a pathologically complete response in the resection specimen, meaning that no viable tumour cells can be found.[3] Therefore, an active surveillance approach could be applied in selected patients with both histological subtypes.[4-6] During active surveillance after nCRT, clinical investigations are performed to detect residual or recurrent cancer. Only patients with locoregional tumour after nCRT and without distant metastases undergo surgery. Active surveillance has been tested successfully in head and neck, rectal, prostate and bladder cancer.[7-10]

An active surveillance approach has potential advantages compared with oesophagectomy in all patients after nCRT. Oesophagectomy is associated with postoperative morbidity and mortality, and has a lasting impact on health-related quality of life (HRQoL).[3, 11, 12] On the other hand, active surveillance carries the risk of detecting locoregional residual disease at an unresectable stage, potentially jeopardizing long-term survival. Patients also experience a physical burden from frequent clinical investigations using endoscopy and PET–CT. Moreover, patients may experience increased anxiety and distress owing to the idea of possibly having residual tumour that is not treated radically and the need for oesophagectomy at some time point during follow-up.

To optimize shared decision-making in defining the best treatment for patients with oesophageal cancer, a better understanding of patients' preferences for treatment is needed. Patients' views and beliefs can differ substantially from those of their physician(s).[13-17] The aim of this study was to determine the relative importance of factors that influence patients' preferences for undergoing active surveillance versus oesophagectomy after nCRT for oesophageal cancer, and to investigate the trade-offs patients make in their choice of both treatment alternatives. It was hypothesized that long-term outcomes (especially life expectancy and long-term HRQoL) outweigh short-term outcomes in patients' treatment decisions, and patients are willing to trade off survival to a certain extent to avoid the need for oesophagectomy.

Methods

This was a prospective cohort study. Patients who were treated with nCRT according to the CROSS (ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study) regimen for histologically proven SCC or adenocarcinoma of the oesophagus or oe-

sophagogastric junction were eligible.[3] Patients with altered mental status prohibiting understanding of the questionnaire and those who were insufficiently fluent in the Dutch language were excluded. Consecutive patients were recruited 4–6 weeks after completion of nCRT in the Erasmus MC – University Medical Centre Rotterdam and in Maasstad Hospital, Rotterdam. The study protocol was approved by the medical ethics committee, Erasmus MC – University Medical Centre Rotterdam (MEC-2015-083).

Discrete-choice experiment

In a discrete-choice experiment (DCE) it is assumed that interventions, such as treatment strategies, can be described by their characteristics (attributes; such as 5-year overall survival, short-term HRQoL, long-term HRQoL).[18] It is also assumed that patients' preferences for an intervention are determined by the levels of these attributes (for example, 5-year survival rates of 45, 60 and 75 per cent).[18] The trade-offs that patients make between the attributes can be evaluated by offering a series of choices in treatment alternatives with different combinations of attribute levels.[19]

Attributes and attribute levels

Relevant attributes that might influence the choice of oesophagectomy versus active surveillance after nCRT and the attribute levels were chosen based on information in the literature[1, 4-6, 11, 12], and consensus discussion with two upper gastrointestinal surgeons and five patients who underwent nCRT followed by surgical resection. Attributes were 5-year overall survival, short-term HRQoL (3 months after treatment), long-term HRQoL (more than 1 year after treatment), the risk that oesophagectomy is still necessary, and the average number of surveillance examinations per year involving endoscopy and PET–CT necessary for 5 years of follow-up after treatment (Table 1). The risk that oesophagectomy is still necessary reflects the risk that residual disease is missed during the initial response evaluation, but is detected at a resectable stage during active surveillance. Decreased 5-year overall survival in the active surveillance alternative reflects the risk that a regrowth is detected at an unresectable stage during active surveillance (T4b or distant metastases). HRQoL was presented on a visual analogue scale (VAS) ranging from 0 to 100, where 100 represents the best health status.

Study design and questionnaire

Clinicopathological characteristics (age, sex, ASA fitness grade, tumour histology, clinical tumour and node categories) and other variables, including level of education, household situation and current HRQoL, were collected. HRQoL was measured using the five-level version of the EuroQol Five Dimensions questionnaire (EQ-5D-5L™; EuroQol Group, Rotterdam, the Netherlands).[20]

The combination of five attributes, encompassing three levels, each with two possible active surveillance scenarios, leads to 88 209 ($((3^5 \times (3^5 - 1)/2) \times 3$) hypothetical scenarios for three different surgery scenarios. The three surgery scenarios were based on 5-year overall survival rates of 55, 65 and 75 per cent. As it is not feasible to present all possible scenarios to each patient, a subset of scenarios was generated in such a way that all parameters of interest could be estimated. A Bayesian efficient design was generated by maximizing D-efficiency using NGene software (http://www.choice-metrics.com).[21] This resulted in 18 choice sets per questionnaire. To take statistical efficiency into account as well as task complexity, each choice set consisted of two active surveillance alternatives (active surveillance A and active surveillance B) and one surgery alternative ('opt-out'). Including two active surveillance alternatives in each choice set reduced the total number of choice sets per questionnaire. Patients were asked to consider the three treatment alternatives in each scenario and to choose the alternative that appealed most to them. An example of a choice set is shown in Figure 1.

Each questionnaire started with a detailed description of the treatment alternatives, the attributes and their levels. This included a description of the impact of the treatment alternatives on HRQoL and an explanation of the HRQoL scales. This was followed by an example of a choice task. The main part of the questionnaire consisted of 18 choice sets. The questionnaire also contained a question assessing the difficulty experienced in completing the questionnaire (5-point scale). The validity of the questionnaire was determined in a pilot study including 30 patients. Pilot data were accordingly used for further optimization of efficiency of the choice set.

Patients were asked to fill in the questionnaire 6 weeks after completion of nCRT, before surgery. Before completion of the questionnaire, all patients received a standardized face-to-face explanation of the background and concept of the study, and the potential risks and benefits of both treatment alternatives (active surveillance and standard surgery) from the investigator, including a standardized explanation of potential short- and long-term side-effects of the surgical procedure.

Statistical analysis

Calculation of the sample size for DCEs is complicated as it depends on the true values of the parameters estimated in the choice models.[22] Studies have shown that sample sizes of 40–100 respondents may be sufficient for reliable statistical analyses.[23-25] The aim here was to include 100 respondents.

Several models exist for analysis of discrete-choice data.[26] Taking into account the authors' interest in preference heterogeneity, as well as the sample size, a mixed logit model or a latent class model were alternatives for analysis of the choice observations. A latent class model was selected as it had the best fit for the choice observations (pseudo-

R^2 0.48 versus 0.69 using NLogit software; http://www.limdep.com/).[27] Details of the model are described in Appendix 1 (supporting information).

For the class coefficients, the statistical significance of a coefficient ($p<0.050$) indicates that, conditional on belonging to that class, respondents considered the attribute important in making their choices for oesophageal treatment. The directions of coefficients reflect whether the attributes have a positive or negative effect on utility. It was expected that the attributes 5-year overall survival and one or more levels of short-term HRQoL and long-term HRQoL would have a positive effect.[28, 29] The association between the socio-demographic or clinicopathological parameters (age, HRQoL based on EQ-5D™ VAS score, anxiety/depression based on EQ-5D™ anxiety/depression dimension, sex, ASA grade, educational level, household situation, tumour histology and cancer stage according to the UICC classification[30]) and the probability of belonging to one of the two classes was analysed. In terms of the class assignment parameters, statistically significant parameter estimates indicate that the associated co-variable can be used to help in understanding the different segments. For example, if the 'age older than 65 years' parameter associated with a particular class in the assignment model is positive and significant, this is indicative that people over 65 years of age are more likely to belong to that particular class as given in equation (1) (Appendix 1, supporting information).

Class-specific importance scores were calculated for the active surveillance alternative to visualize the relative importance of a given attribute in that class by dividing the difference in utility between highest and lowest level for a single attribute by the sum of the differences of all attributes for that class.[31] An attribute with an importance score of 1 represents the most important attribute, whereas an attribute with an importance score of 5 represents the least important attribute.

Trade-offs

Willingness to trade off 5-year survival to achieve a reduction in the risk that oesophagectomy is still needed, or to achieve an improvement in long-term HRQoL, was calculated. These values represent how much one is willing to trade off for a 1-unit change in the attribute of interest. The average trade-offs are based on calculation of the indifference point between standard surgery and active surveillance, after adjustment for the risk that oesophagectomy is still necessary of 35% and the long-term HRQoL score of 80 in the 'base case' for active surveillance.

Results

From March 2015 to January 2017, 104 patients were included. The response rate was 100 of 104 (96.2 per cent). Responding patients had a median age of 67 (i.q.r. 61–72)

years and 78 of 100 patients were men. Twenty-five had a high educational level and 32 patients experienced symptoms of anxiety/depression. The majority had a cT3 tumour (76 per cent) and suspected locoregional lymph nodes as determined by endoscopic ultrasonography, CT and PET–CT (62 per cent) (Table 2).

Discrete-choice experiment results

Two classes of patients were identified using a latent class model (Table 3). Patients with a preference for an active surveillance approach had a higher probability of belonging to class 1, whereas patients who preferred surgery had a higher probability of belonging to class 2. The class probabilities within the sample were 0.60 for class 1 and 0.40 for class 2. No sociodemographic or clinicopathological characteristics were associated with the probability of belonging to one of the two classes.

For both latent classes, 5-year overall survival, the risk that oesophagectomy is still necessary and long-term HRQoL significantly influenced patients' preference for oesophageal cancer therapy. The directions of the coefficients corresponded to the predefined hypotheses. The positive coefficient for 5-year overall survival and the increasing coefficients associated with increases in short-term HRQoL and in long-term HRQoL indicate that patients prefer a treatment strategy that generates an increase in these attributes (increased survival and HRQoL). The negative coefficient associated with the risk that surgery is still necessary and the decreasing coefficients associated with an increase in the number of surveillance examinations indicate that these attributes are negatively associated with patients' preferences.

The importance scores in both latent classes were similar, with 5-year overall survival the most important attribute, followe1d by the risk that oesophagectomy is still necessary, long-term HRQoL, short-term HRQoL and frequency of surveillance examinations after completion of therapy. This was irrespective of the 5-year survival rate after surgery (55, 65 or 75 per cent). Seventy-four of the 100 respondents did not find the DCE questions difficult.

Willingness to trade off survival

Based on their preferences, patients' willingness to trade off 5-year overall survival chances to obtain an improvement in one of the other attributes was assessed (Table 4). Keeping other attributes at the median level (short-term HRQoL VAS score 80, long-term HRQoL VAS score 80, 3 surveillance examinations per year), patients were willing to trade off on average a 26, 16 and 10 per cent decrease in 5-year overall survival to achieve a 15, 35 and 55 per cent risk respectively that oesophagectomy is still necessary (compared with 100 per cent). Similarly, to achieve an increase in long-term HRQoL from 70 (after standard surgery) to 80 and 90 (after active surveillance), patients were willing to trade-off 16 and 19 per cent 5-year overall survival respectively.

Discussion

This prospective study showed that 5-year overall survival, long-term HRQoL and the chance that oesophagectomy is still necessary influenced patients' preference for either active surveillance or planned surgery after nCRT for oesophageal cancer. There was a substantial preference heterogeneity and two latent classes were identified. The first consisted of patients with a strong preference for active surveillance and the second comprised patients with a strong preference for standard oesophagectomy. No predisposing factors (such age, HRQoL, ASA grade) could be identified that would enable classification of patients into one of the two classes. On average, patients were willing to trade off 16 per cent 5-year overall survival to reduce the risk of oesophagectomy being necessary from 100 to 35 per cent.

Strengths of this study include its prospective design and the low attrition rate, thereby excluding the risk of selection bias. The low rate of attrition can be explained by the face-to-face setting in which the questionnaires were explained. Furthermore, questionnaires were completed at the most realistic time point, 6 weeks after completion of nCRT and before surgery. This closely matches the moment when a decision regarding active surveillance or oesophagectomy is made in clinical practice. A labelled DCE design was used, in which the treatment alternative is mentioned in each choice option (active surveillance or standard surgery) (Figure *1*), whereas in an unlabelled design the treatment option is presented as option A, B or C and is described by attribute levels in the choice set. The choice between surgical and non-surgical treatments may evoke individual preferences that cannot be described in a questionnaire (such as anxiety about oesophagectomy). Therefore, it is difficult to convey the essential differences between active surveillance and oesophagectomy from a patient's perspective. The use of a labelled design leads to more realistic scenarios and takes into account individual feelings/preferences for a specific treatment, which further increases the validity of the results.[32]

The results of this study indicate that long-term treatment outcomes (survival and long-term HRQoL) outweigh short-term attributes (short-term HRQoL and burden of surveillance examinations with endoscopy and PET–CT). They confirm the results of another DCE, which investigated preoperative preferences of patients towards surgery for oesophagogastric cancer.[17] The latter study found that overall survival rate and long-term HRQoL outweighed short-term outcomes such as postoperative morbidity, hospital type and a surgeon's reputation. These findings underline the need for addressing long-term outcomes of different treatment modalities during counselling, before delving into details of treatment options. This may lead to improvements in meeting patients' treatment expectations.

The higher choice probability (0.60) for active surveillance than for standard surgery (0.40) is in line with the authors' hypothesis and with the findings of other studies.[14, 33]

Nevertheless, a substantial subgroup of patients has a strong preference for standard oesophagectomy, even if long-term survival would be comparable to that achieved with active surveillance. This can be explained by patients who experience fear having residual tumour that is not treated radically. Another possible explanation is that patients have had a bad experience with upper gastrointestinal endoscopy. Moreover, potential external influences, such as the role of the wider family, might influence patients' treatment preferences. Future research should focus on further identification of factors associated with patients' *a priori* choice probability for active surveillance or standard oesophagectomy.

An intriguing finding is that patients were willing to trade off on average 16 per cent 5-year survival chance in order to avoid oesophagectomy. This phenomenon has been described to a lesser extent in patients with prostate cancer.[14, 33] The high postoperative morbidity and mortality rates associated with oesophagectomy, and the lasting impact of such surgery on patients' HRQoL likely underlie the substantial loss of life expectancy that patients are willing to trade off[3,11,12]. For clinicians, who tend to focus on long-term survival outcomes, it is important to realize that patients and physicians may differ in their trade-offs between different treatment options.[14, 15, 17, 26, 34, 35]

The present findings may help patients and clinicians choose between active surveillance and oesophagectomy. Knowledge about the preferences of other patients with oesophageal cancer might help patients to clarify their own thoughts, whereas understanding factors that influence patients' treatment decisions may make physicians more sensitive to individual patient's preferences. This may have positive effects on the quality of shared decision-making.

These findings may be useful in the design of new studies in oesophageal cancer. Although active surveillance is applied in selected patients only, this organ-sparing approach is currently under study. The Dutch SANO (Surgery As Needed for Oesophageal cancer) trial and the French ESOSTRATE trial are prospective studies comparing active surveillance with standard oesophagectomy in patients with a clinically complete response after nCRT.[36, 37] The primary endpoint of both trials is overall survival and results are expected in 2023. The SANO trial has been designed as a non-inferiority trial with a non-inferiority margin of 15 per cent, supported by the results of the present study. As a secondary endpoint, the SANO trial is aiming to design a decision aid, in order to further tailor treatment and help patients in their individual treatment decision.[38]

Figure 1. Example of a choice set.

Treatment 1, 2 en 3 are different. Wich alternative would you choose?

Please imagine that no residual cancer can be found after completion of chemoradiotherapy. Your surgeon tells you that both "active surveillance" and "standard surgery" can be considered as treatment options.

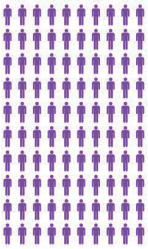
	1. Active surveillance A	2. Active surveillance B	3. Standard surgery
Short-term quality of life (3 months after treatment) on a 0-100 scale, due to pain, fatigue, tube feeding , hospital admission and treatment-related complications.	70	80	60
Long-term quality of life (1 year after treatment) on a 0-100 scale, due to impaired physical functioning, eating problems, sleeping slightly elevated and defecation problems.	70	80	70
Chance that surgery is necessary	 **35%** (35 out of 100 patients)	 **55%** (55 out of 100 patients)	 **100%** (100 out of 100 patients)
Physical burden of … (number) examinations per year with endoscopy and PET-CT-scanning after initial treatment. This accounts for the first 5 years after treatment.	3	2	1
Chance to be alive in 5 years	 **45%** (45 out of 100 patients)	 **45%** (45 out of 100 patients)	 **75%** (75 out of 100 patients)
Wich alternative would you choose?	☐	☐	☐

Table 1. Attributes and attribute levels for active surveillance versus standard oesophagectomy after neoadjuvant chemoradiotherapy for oesophageal cancer.

Attribute	Levels
Active surveillance	
5-year overall survival (%)	45
	60
	75
Short-term HRQoL (VAS 0–100)	70
	80
	90
Long-term HRQoL (VAS 0–100)	70
	80
	90
Risk that surgery is still necessary (%)	15
	35
	55
Average no. of surveillance examinations per year	2
	3
	4
Standard oesophagectomy	
5-year overall survival (%)	55
	65
	75
Short-term HRQoL (VAS 0–100)	70
Long-term HRQoL (VAS 0–100)	70
Risk that surgery is necessary	100
Average no. of examinations per year	1

HRQoL, health-related quality of life; VAS, visual analogue scale.

Table 2. Clinicopathological characteristics of the study patients.

	No. of patients* (n = 100)
Age at randomization (years)†	67 (61–72)
Sex ratio (M : F)	78 : 22
Educational level	
Low	36
Intermediate	38
High	25
Missing	1
Household situation	
With partner/family member	81
Single	19
EQ-5D™ VAS score†	70 (60–80)
Anxiety/depression symptoms‡	32
Tumour type	
Squamous cell carcinoma	26
Adenocarcinoma	74
Clinical T category§	
cT2	20
cT3	76
cT4	4
Clinical N category¶	
cN0	38
cN1	42
cN2	16
cN3	4
ASA fitness grade#	
I	6
II	68
III	25
Missing	1

*Unless indicated otherwise; †values are median (i.q.r.). ‡Based on EQ-5D™ anxiety/depression dimension. §Assessed by endoscopic ultrasonography or CT, and classified according to the UICC TNM classification, seventh edition[30].

Assessed by endoscopic ultrasonography, CT or [^{18}F]fluorodeoxyglucose PET, and classified according to the UICC TNM classification, seventh edition[30]. #Scale of 0 to V, with lower numbers indicating better physical status: I, normal healthy patient; II, patient with mild systemic disease; III, patient with severe systemic disease.

Table 3. Patients' preferences for treatment of oesophageal cancer after neoadjuvant chemoradiotheraopy based on a latent class model with two latent classes (100 patients).

	Latent class 1: preference for active surveillance		Latent class 1: preference for standard surgery	
	Odds ratio*	Importance score	Odds ratio*	Importance score
Constant (standard surgery)	1.23 (1.48, 3.73)†‡		9.99 (7.62, 12.36)†‡	
Alternative 1: active surveillance				
5-year overall survival, active surveillance (per 10%)	3.42 (2.69, 4.39)‡	1	5.37 (3.39, 8.33)‡	1
Short-term HRQoL		4		4
Low	0.73		1.23	
Medium	1.14 (0.96, 1.36)		0.95 (0.66, 1.38)	
High	1.20 (1.00, 1.45)		0.85 (0.58, 1.23)	
Long-term HRQoL		3		3
Low	0.63		0.80	
Medium	1.03 (0.87, 1.23)		0.85 (0.61, 1.20)	
High	1.54 (1.28, 1.84)‡		1.46 (1.03, 2.08)‡	
Risk that surgery is still necessary (per 10%)	0.63 (0.56, 0.69)‡	2	0.76 (0.64, 0.91)‡	2
Annual no. of diagnostic tests				
2	1.06	5	1.09	5
3	1.03 (0.87, 1.23)		0.90 (0.63, 1.26)	
4	0.90 (0.75, 1.09)		1.03 (0.73, 1.45)	
Alternative 2: standard surgery				
5-year overall survival, standard surgery (%)				
55	0.21		0.22	
65	1.79 (0.94, 3.39)		0.80 (0.52, 1.25)	
75	2.66 (1.42, 5.00)‡		5.70 (2.72, 11.94)‡	
Average class probability	0.60		0.40	

Values in parentheses are 95 per cent confidence intervals. *Unless indicated otherwise; †coefficient. ‡Significant at 5 per cent level.

Table 4. Willingness to trade off 5-year survival.

	Willingness to trade off 5-year survival (%)
Risk that oesophagectomy is necessary (%)*	
15	26 (11, 34)
35	16 (4, 28)
55	10 (–3, 22)
Long-term HRQoL (scale 0–100)†	
80	16 (4, 28)
90	19 (7, 31)

Values in parentheses are 95 per cent confidence intervals. *Compared with 100 per cent risk that oesophagectomy is necessary. †Compared with long-term health-related quality of life (HRQoL) score of 70 after standard surgery.

References

1. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
2. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
3. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
4. Castoro C, Scarpa M, Cagol M et al. Complete clinical response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic oesophagus: is surgery always necessary? J Gastrointest Surg. 2013;17(8):1375-81.
5. Furlong H, Bass G, Breathnach O, O'Neill B, Leen E, Walsh TN. Targeting therapy for esophageal cancer in patients aged 70 and over. J Geriatr Oncol. 2013;4(2):107-13.
6. Taketa T, Xiao L, Sudo K et al. Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology. 2013;85(2):95-9.
7. Mehanna H, Wong WL, McConkey CC et al. PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. N Engl J Med. 2016;374(15):1444-54.
8. Renehan AG, Malcomson L, Emsley R et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol. 2016;17(2):174-83.
9. Rödel C, Wiess C, Sauer R. Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol. 2006;24(35):5536-44.
10. Wilt TJ, Brawer MK, Jones KM et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367(3):203-13.
11. Noordman BJ, Verdam MGE, Lagarde SM et al. Effect of neoadjuvant chemoradiotherapy on health-related quality of life in esophageal or junctional cancer: results from the randomized CROSS trial. J Clin Oncol. 2017:JCO2017737718.
12. Noordman BJ, Verdam MGE, Lagarde SM et al. Impact of neoadjuvant chemoradiotherapy on health-related quality of life in long-term survivors of esophageal or junctional cancer: results from the randomized CROSS trial. Ann Oncol. 2018;29(2):445-51.
13. Chewning B, Bylund CL, Shah B, Arora NK, Gueguen JA, Makoul G. Patient preferences for shared decisions: a systematic review. Patient Educ Couns. 2012;86(1):9-18.
14. de Bekker-Grob EW, Bliemer MC, Donkers B et al. Patients' and urologists' preferences for prostate cancer treatment: a discrete choice experiment. Br J Cancer. 2013;109(3):633-40.
15. Emberton M. Medical treatment of benign prostatic hyperplasia: physician and patient preferences and satisfaction. Int J Clin Pract. 2010;64(10):1425-35.
16. Godolphin W. The role of risk communication in shared decision making. Bmj. 2003;327(7417):692-3.
17. Thrumurthy SG, Morris JJ, Mughal MM, Ward JB. Discrete-choice preference comparison between patients and doctors for the surgical management of oesophagogastric cancer. Br J Surg. 2011;98(8):1124-31; discussion 32.
18. Ryan M. Discrete choice experiments in health care. Bmj. 2004;328(7436):360-1.
19. Hensher DA, Rose JM, Greene WH. Applied choice analysis: a primer. Cambridge: Cambridge University Press; 2005.
20. Herdman M, Gudex C, Lloyd A et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

21. Reed Johnson F, Lancsar E, Marshall D et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value Health. 2013;16(1):3-13.
22. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics. 2008;26(8):661-77.
23. Berchi C, Dupuis JM, Launoy G. The reasons of general practitioners for promoting colorectal cancer mass screening in France. Eur J Health Econ. 2006;7(2):91-8.
24. de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, Koes BW, Steyerberg EW. Preferences of GPs and patients for preventive osteoporosis drug treatment: a discrete-choice experiment. Pharmacoeconomics. 2009;27(3):211-9.
25. Salkeld G, Solomon M, Butow P, Short L. Discrete-choice experiment to measure patient preferences for the surgical management of colorectal cancer. Br J Surg. 2005;92(6):742-7.
26. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. Health Econ. 2012;21(2):145-72.
27. Swait JD, Louviere J. The role of the scale parameter in the estimation and comparison of multinomial logit models. J Marketing Res. 1993(30):305-14.
28. Hol L, de Bekker-Grob EW, van Dam L et al. Preferences for colorectal cancer screening strategies: a discrete choice experiment. Br J Cancer. 2010;102(6):972-80.
29. van Dam L, Hol L, de Bekker-Grob EW et al. What determines individuals' preferences for colorectal cancer screening programmes? A discrete choice experiment. Eur J Cancer. 2010;46(1):150-9.
30. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer., ebrary Inc. TNM classification of malignant tumors. New York: Wiley-Blackwell; 2009. Available from: http://site.ebrary.com/lib/yale/Doc?id=10342913, last accessed: January 29th, 2018.
31. Louviere J, Hensher DA, Swait JD. Stated choice methods: analysis and application. Cambridge: Cambridge University Press; 2000.
32. de Bekker-Grob EW, Hol L, Donkers B et al. Labeled versus unlabeled discrete choice experiments in health economics: an application to colorectal cancer screening. Value Health. 2010;13(2):315-23.
33. Sculpher M, Bryan S, Fry P, de Winter P, Payne H, Emberton M. Patients' preferences for the management of non-metastatic prostate cancer: discrete choice experiment. BMJ. 2004;328(7436):382.
34. Bishop AJ, Marteau TM, Armstrong D et al. Women and health care professionals' preferences for Down's Syndrome screening tests: a conjoint analysis study. Bjog. 2004;111(8):775-9.
35. Mantovani LG, Monzini MS, Mannucci PM et al. Differences between patients', physicians' and pharmacists' preferences for treatment products in haemophilia: a discrete choice experiment. Haemophilia. 2005;11(6):589-97.
36. Donohoe CL, Reynolds JV. Neoadjuvant treatment of locally advanced esophageal and junctional cancer: the evidence-base, current key questions and clinical trials. J Thorac Dis. 2017;9(Suppl 8):S697-S704.
37. Noordman BJ, Wijnhoven BPL, Lagarde SM et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial. BMC Cancer. 2018;18(1):142.
38. Ibrahim SA. Decision Aids and Elective Joint Replacement - How Knowledge Affects Utilization. N Engl J Med. 2017;376(26):2509-11.

Chapter 19

Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial.

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Abstract

Background

Neoadjuvant chemoradiotherapy (nCRT) plus surgery is a standard treatment for locally advanced oesophageal cancer. With this treatment, 29% of patients have a pathologically complete response in the resection specimen. This provides the rationale for investigating an active surveillance approach. The aim of this study is to assess the (cost-)effectiveness of active surveillance vs. standard oesophagectomy after nCRT for oesophageal cancer.

Methods

This is a phase-III multi-centre, stepped-wedge cluster randomised controlled trial. A total of 300 patients with clinically complete response (cCR, i.e. no local or disseminated disease proven by histology) after nCRT will be randomised to show non-inferiority of active surveillance to standard oesophagectomy (non-inferiority margin 15%, intra-correlation coefficient 0.02, power 80%, 2-sided α 0.05, 12% drop-out). Patients will undergo a first clinical response evaluation (CRE-I) 4-6 weeks after nCRT, consisting of endoscopy with bite-on-bite biopsies of the primary tumour site and other suspected lesions. Clinically complete responders will undergo a second CRE (CRE-II), 6-8 weeks after CRE-I. CRE-II will include 18F-FDG-PET-CT, followed by endoscopy with bite-on-bite biopsies and ultra-endosonography plus fine needle aspiration of suspected lymph nodes and/or PET-positive lesions. Patients with cCR at CRE-II will be assigned to oesophagectomy (first phase) or active surveillance (second phase of the study). The duration of the first phase is determined randomly over the 12 centres, i.e., stepped-wedge cluster design. Patients in the active surveillance arm will undergo diagnostic evaluations similar to CRE-II at 6/9/12/16/20/24/30/36/48 and 60 months after nCRT. In this arm, oesophagectomy will be offered only to patients in whom locoregional regrowth is highly suspected or proven, without distant dissemination. The main study parameter is overall survival; secondary endpoints include percentage of patients who do not undergo surgery, quality of life, clinical irresectability (cT4b) rate, radical resection rate, postoperative complications, progression-free survival, distant dissemination rate, and cost-effectiveness. We hypothesise that active surveillance leads to non-inferior survival, improved quality of life and a reduction in costs, compared to standard oesophagectomy.

Discussion

If active surveillance and surgery as needed after nCRT leads to non-inferior survival compared to standard oesophagectomy, this organ-sparing approach can be implemented as a standard of care.

Background

Oesophageal cancer is an aggressive disease with poor outcomes after primary surgery.[1] Since the introduction of neoadjuvant chemo(radio)therapy, survival rates have improved substantially.[2] The randomised ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) showed an absolute 5-year overall survival benefit of 14% after neoadjuvant chemoradiotherapy (nCRT) plus surgery, compared to surgery alone.[3, 4] Moreover, after nCRT according to CROSS, 29% of all patients (49% for squamous cell carcinoma [SCC] and 23% for adenocarcinoma [AC]) had a pathologically complete response (pCR) in the resection specimen.[3] This high pCR-rate provides the rationale to explore an organ-sparing active surveillance approach after nCRT since, intuitively, an oesophagectomy in patients with no viable residual tumour does not improve oncological outcome. In this organ-sparing treatment strategy, patients will undergo frequent diagnostic evaluations after nCRT. An oesophagectomy will be performed only in patients with a proven or high suspicion of locoregional regrowth, in the absence of distant metastases. This treatment strategy would have great advantages, especially given the perioperative morbidity and mortality, and the lasting impact on patients' health-related quality of life (HRQOL) that is associated with oesophagectomy.[3, 5-9] An active surveillance approach would not only benefit patients who are cured by nCRT alone, but also patients with undetectable distant metastases (i.e. micrometastases) after completion of nCRT. Currently, patients with occult distant metastases undergo standard oesophagectomy. This theoretically is of no benefit, because distant metastases, which are the main determinants of long-term survival, are below the detection limit at the first clinical evaluation after nCRT. During active surveillance, these occult metastases might become clinically manifest, which will prevent patients from a non-beneficial oesophagectomy.

At present, active surveillance is applied in selected patients who refuse oesophagectomy or who are finally considered unfit for surgery after nCRT.[10-13] Explorative retrospective studies in these patients show promising results, with comparable long-term survival for active surveillance *vs* immediate standard surgery and comparable outcomes of postponed oesophagectomy in patients who develop a locoregional regrowth in the absence of distant metastases.[10-13]

In the recently completed diagnostic preSANO-trial, endoscopy with bite-on-bite biopsies and ultra-endosonography with fine needle aspiration (FNA) of suspected lymph nodes for detection of locoregional residual disease, combined with 18F-FDG PET-CT for detection of interval metastases was adequate for clinical response evaluation after nCRT for oesophageal cancer. Using two rounds of clinical response evaluations (CREs), sensitivity and specificity for differentiation between tumour regression grade (TRG) 3-4 (i.e. >10% vital cells) and TRG 1 (i.e. no vital cells) residual tumour

using endoscopy with bite-on-bite biopsies and FNA were 90% and 72%, respectively. 18F-FDG PET-CT after nCRT detected interval metastases in 10% of patients.[14, 15]

The results of the preSANO-trial in combination with results in the literature on the clinical outcome of active surveillance justify a phase-III trial, comparing active surveillance with standard surgery in patients with a clinically complete response after nCRT.

Objective

The aim of this study is to assess the (cost-)effectiveness (including non-financial costs and survival) of active surveillance after nCRT - as compared to standard surgery - for patients with SCC or AC of the oesophagus or oesophagogastric junction.

Methods

Study design

The SANO-trial is a phase III multi-centre, stepped-wedge, cluster randomised controlled non-inferiority trial. This design involves random sequential switch of clusters of participating institutions from the control arm (standard surgery) to the interventional arm (active surveillance). Randomisation is performed at the institutional level, instead of the individual level (Figure 1 and 2).[16] Twelve high-volume centres in the Netherlands are participating in this study (Erasmus Medical Centre, Rotterdam; Catharina Cancer Institute, Eindhoven; Zuyderland Medical Centre, Heerlen; Radboud University Medical Centre, Nijmegen; Elisabeth Tweesteden Hospital, Tilburg; Gelre Hospital, Apeldoorn; Leiden University Medical Centre, Leiden; Maasstad Hospital, Rotterdam; Zorggroep Twente, Almelo; Netherlands Cancer Institute, Amsterdam; Reinier de Graaf Group, Delft; Medical Centre Leeuwarden). Based on these 12 participating centres, 6 clusters with comparable estimated inclusion rates will be formed, each cluster comprising 2 participating centres. Based on the expected inclusion period of 36 months and the inclusion of 60 clinically complete responders from the preSANO trial (see below; Statistical Analysis; Sample Size Calculation), every 4.5 months one cluster will switch from the control arm to the interventional arm. Clusters will be determined by randomisation, but always consist of a centre with high expected total inclusion (≥45) and a centre with a lower (<30) expected total inclusion.

During the first 4.5 months of the trial, all centres will provide standard immediate surgery and will gain experience in the performance of clinical response (and surveillance) evaluations. After 4.5 months, a cluster of 2 centres (Erasmus MC and Zuyderland Medical Centre) with extensive experience in CREs and a large number of patients included in the preSANO-trial, will start to provide the novel strategy (active surveil-

lance). After the next 4.5 months, another cluster of 2 participating centres will be randomly assigned by the sponsor using a computer-generated number sequence to begin with active surveillance. This procedure will be repeated after 4.5 months until all clusters have crossed over into the active surveillance arm. The final phase of the trial, with all sites including patients in the active surveillance arm, finishes approximately 9 months after the last cluster of two sites have switched from the control arm to the interventional arm (Figure 2).

Patients who prefer the treatment that is not offered as study treatment in that particular centre at that time (e.g. active surveillance in a centre that has not yet crossed over into the active surveillance group) cannot be included in the trial. These patients will still be treated in the same centre, but outside the trial.

Expected numbers of patients included in both study arms during the different time periods and predefined clusters with comparable expected numbers of inclusions are shown in Figure 2. Inclusion rate will be closely monitored during the trial, and time periods will be adjusted if the number of included patients differ substantially from the expectations.

Study population

Operable patients with locally advanced resectable SCC or AC of the oesophagus or oesophagogastric junction who are planned to undergo nCRT according to CROSS followed by surgical resection are eligible for inclusion.[3] Patients with language difficulties, dementia or altered mental status prohibiting the understanding and giving of informed consent and patients with non-FDG-avid tumours at baseline will be excluded from participation in this study. Patients will have conventional pre-treatment work-up (including F18-FDG PET-CT to assess the avidity of the primary tumour).

Study algorithm (Table 1, Figure 1, Figure 3)

All included patients will undergo nCRT according to CROSS (Carboplatin AUC 2 mg/mL per min, Paclitaxel 50 mg/m2 of body-surface area and 41.4 Gy of concurrent radiotherapy in 23 fractions).[3] Patients will be re-staged after nCRT during CREs to select those who may benefit from active surveillance. CREs categorise patients as clinically complete responders or clinically incomplete responders. Only patients in whom no locoregional or disseminated disease is proven (cCR) during CREs, will be included in the comparative part of this trial.

CREs

Approximately 4-6 weeks after completion of nCRT all included patients will undergo a first clinical response evaluation (CRE-I) including oesophagogastroduodenoscopy

(OGD) with at least 8 (random) biopsies, including at least 4 bite-on-bite biopsies of the primary tumour site and of any other suspected lesions. Patients with (cyto)histological evidence of locoregional residual disease during CRE-I will be offered a subsequent 18F-FDG PET-CT to exclude disseminated disease and will be offered immediate surgery (i.e. 6-8 weeks after completion of nCRT). Patients who are found to be cCR will undergo a second CRE (CRE-II) 6-8 weeks after CRE-I (i.e. 10-14 weeks after completion of nCRT). CRE-II will include an 18F-FDG PET-CT, followed by OGD with bite-on-bite biopsies of the primary tumour site and any other suspected lesions, radial EUS and in case of PET-positive lesions and/or suspected lymph nodes, even if these lymph nodes are located directly adjacent to the primary tumour site, linear EUS with FNA. The 18F-FDG PET-CT during CRE-II must be available to guide the endoscopist in taking biopsies and FNA during OGD and EUS. Patients with (cyto)histological evidence of locoregional residual disease or highly suspected locoregional residual disease on 18F-FDG PET-CT, and without distant metastases during CRE-II will undergo surgery immediately after CRE-II (i.e. 10-14 weeks after completion of nCRT). Patients with distant metastases will be referred for palliative care.

Patients without (cyto)histological evidence of residual disease during CRE-II (cCR), in the absence of distant metastases, will be assigned to active surveillance (experimental arm) or standard surgery (control arm), according to the randomisation at the institutional level.

Active surveillance

Patients in the active surveillance arm will undergo active surveillance by 18F-FDG PET-CT, OGD with at least 8 biopsies, including at least 4 bite-on-bite biopsies and EUS plus FNA of all suspected lymph nodes at 6, 9, 12, 16, 20, 24, 30, 36, 48 and 60 months after completion of nCRT or when symptoms or results of any diagnostic test require shorter assessment intervals. Patients with (cyto)histological evidence of disseminated disease during active surveillance will be referred for palliative care (Figure 3).

Surgery

All patients in the control arm without distant metastases will be offered oesophagectomy after CRE-II, whereas patients in the active surveillance arm will be offered surgery only when locoregional regrowth is highly suspected or proven, also without any signs of distant dissemination (Figure 3).

A transthoracic oesophagectomy or a transhiatal oesophagectomy will be performed, depending on both patient characteristics and local expertise and preference. Open, hybrid and completely minimally invasive techniques are allowed. At least 15 lymph nodes should be harvested in every patient. An en-bloc resection of the primary tumour and the regional lymph nodes should be carried out including a standard dissection of

the lymph nodes around the coeliac axis (separately collected for nodes along the left gastric, common hepatic and splenic artery). In the chest, at least the right paratracheal, subcarinal and para-oesophageal lymph nodes should be harvested.

Pathology

All CRE- and surveillance biopsies will be assessed by expert GI pathologists. Initially, all biopsies will be analysed based on the regular HE-slides (which contains two or three levels). If analysis at these levels reveals obvious vital tumour, the biopsy will be classified (diagnosed) as positive. If the assessment of this HE-slide is negative for malignancy (no malignancy), deeper sections will be performed (two or three additional levels, depending on the amount of tissue on the paraffin block). In case of doubt regarding the presence of tumour (cells) after analysis of a biopsy at the aforementioned additional levels, extra dPAS and (pan)keratin staining will be performed. In case of an originally diagnosed signet-ring cell carcinoma or a poorly cohesive carcinoma with mucin production, analysis at three additional (deeper) levels and dPAS and keratin staining will be performed consistently.

Only the CRE- and surveillance biopsies with uncertain outcome will be revised at the Department of Pathology of the Erasmus MC following the same strategy.

The resection specimens will be assessed using the 7th edition of the UICC TNM cancer staging. Microscopically radical resection (R0) will be defined as a tumour-free resection margin (margin >1mm not required). Also, prepTNM staging will be estimated as described earlier.[17] Tumour regression grade (TRG) will be determined according to the modified Mandard classification (TRG 1 to 4).[15]

Centralised multidisciplinary tumour board

During CRE-I and CRE-II, positive (cyto)histology is preferably available when offering a patient surgical resection. However, during active surveillance we do allow a centralised multidisciplinary tumour board (MTB, Erasmus MC) to recommend surgical resection in selected patients who have a high clinical / diagnostic suspicion of tumour regrowth, despite repeatedly negative (cyto)histology. This centralised MTB will monitor and decide on all such suspected patients from all participating centres. The reason for offering surgical resection in patients with a (strong) clinical suspicion of regrowth, but without positive (cyto)histology is to minimise the risk that a difficulty in confirming regrowth by histology causes a delay that will permit a tumour regrowth to expand into an irresectable stage. If for instance the intensity of a hotspot on 18F-FDG PET-CT substantially increases over time during surveillance but positive (cyto)histology cannot be obtained, the MTB can decide to recommend surgery.

Follow-up

Follow-up visits of patients in both study arms will occur at 6, 9, 12, 16, 20, 24, 30, 36, 48 and 60 months after completion of nCRT. Additional visits will be scheduled if complaints will arise before the next visit. In cases of suspected recurrence, thoraco-abdominal CT, PET-CT and/or upper gastrointestinal endoscopy will be performed. In order to accurately compare distant dissemination rates between both treatment arms, 18F-FDG PET-CT scan will be performed in all patients in the standard surgery arm after one and two years of follow-up, after which most (>80% and >90%, resp.) distant metastases will likely have been detected.[18] If a patient in the active surveillance will undergo postponed oesophagectomy due to a locoregional regrowth without distant metastases, follow-up will be performed according to the Dutch Guideline for oesophageal cancer.[19]

Study parameters/endpoints

The main study parameter in this study is overall survival of patients with cCR at CRE-II (*i.e.* 10-14 weeks after completion of nCRT). Secondary study parameters include:

- The percentage of patients in the active surveillance arm who do not undergo surgery (*i.e.* patients who are cured by nCRT or who have occult distant metastases during initial staging, which become manifest during active surveillance);
- HRQOL as measured with EQ-5D[20], QLQ-C30[21], QLC-OG25[22] and Cancer Worry Scale[23] questionnaires;
- Clinical irresectability (cT4b) rate; R_0-resection rate defined as percentage of patients within the entire randomised population who undergo resection, defined as a tumour-free resection margin;
- Postoperative morbidity/complications for all randomised patients with cCR who undergo resection, as defined by the Esophageal Complications Consensus Group[24];
- Postoperative mortality for all patients with cCR who undergo resection, defined as 90 day- and/or in-hospital mortality;
- Progression-free survival, defined as the interval between randomisation and the earliest occurrence of disease progression resulting in primary (or peroperative) irresectability of disease, locoregional regrowth (after completion of therapy);
- Distant dissemination rate;
- Cost-effectiveness.

Safety and stopping rules

Delaying surgical resection in patients in the active surveillance arm should neither lead to a significant reduction in tumour resectability and radical resection rate, nor to a significant increase in postoperative mortality and distant dissemination rate. Therefore, the following parameters are closely monitored;

- Proportion of all patients in the active surveillance arm that present with an irresectable or incurable (T4b or R2) regrowth, in the absence of distant metastases;
- Proportion of all patients in the active surveillance arm that undergo a microscopically non-radical (R1) resection;
- Postoperative morbidity; postoperative in-hospital mortality in all patients in the active surveillance arm, proportion of all patients in the active surveillance arm with hospital stay >60 days or who develop postoperative trachea-neo-oesophageal fistula;
- Proportion of all patients in the active surveillance arm that develop distant dissemination after one and two years of follow-up.

If outcomes of one or more of these parameters in the active surveillance arm significantly exceed the outcomes in the standard surgery arm or in the Dutch Upper-GI Cancer Audit (DUCA) data 2016, all participating centres will be notified immediately and further inclusion will be stopped.[25] Patients who have been already included will be informed and offered the possibility of immediate (high-priority) surgical resection, even in the absence of suspicion of regrowth. Continuation of active surveillance will also still be offered.

Statistical analysis

Sample size calculation

In the present phase-III study, we plan to randomise at institutional level 300 patients with cCR during CRE-II between active surveillance and standard surgical resection. Simulation of trial outcomes with expected equal 3-year overall survival rates of 67% in both trial arms and an intra-correlation coefficient of 0.02 to account for between-institution variation (inter-quartile range for 3-year overall survival rates of 63%-71%) indicates a total sample size of 264 patients to show non-inferiority of surveillance to standard surgery with 80% power.[26] Non-inferiority is defined as a 3-year survival rate that is no more than 15 percentage points below the expected 67% 3-year survival rate among patients in the standard surgery arm (data based on the CROSS-trial).[3, 4] To allow for a 12% drop-out (e.g. patients in the active surveillance-arm who request immediate surgery in the absence of clinically proven or suspected regrowth) 300 patients are required for randomisation. Based on preliminary data from the current preSANO-trial, we expect that 50% of all included patients will have cCR during CRE-II, leading to a total required inclusion of 600 patients.[14]

To reduce the number of newly included patients and to optimally use the data from the preSANO-trial, all recently (≥ May 2015) included patients with cCR during CRE-II from the current preSANO-trial who underwent bite-on-bite biopsies during CRE-I and CRE-II will be included in the control arm (n=60 patients). Assuming a 50% cCR rate,

the total number of required patients to be newly included in the SANO-trial will drop from 600 to 480 patients. Consequently, patients with cCR are randomised at an institutional level in a 3:5 ratio.

No interim analyses are planned for survival outcomes.

Data analysis

The difference in survival over a 3-year horizon between the control arm and the experimental treatment arm will be analysed with a mixed-effects Cox regression model. Use of a mixed regression model – including an institution-level random effect – is required to capture the potential between-institutional variation in survival.[27] To correct for potential selection bias, the treatment effect will be estimated with adjustment for prognostic factors for survival, i.e. age, sex, histologic subtype of tumour, clinical N stage, and WHO performance score. We will also use the mixed-effects Cox regression model to study potential differences in treatment effect between subgroups of patients. Subgroups are predefined according to age, sex, histologic subtype of tumour, clinical N stage, and WHO performance score. HRQOL data will be analysed according to the EuroQol, EORTC and Cancer Worry Scale scoring manuals.[20-23] Repeated measurement analysis will be used to evaluate within and between group differences. Data will be analysed following the intention-to-treat principle, including protocol deviators. A per protocol analysis will be performed as a secondary analysis.

Ethical and regulatory considerations

The study has been approved by the medical ethics committee of the Erasmus MC (MEC2017-392) and has been registered in the Netherlands Trial Register (NTR 6803). The study will be conducted according to the principles of the Declaration of Helsinki (10th version, Fortaleza, 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable guidelines, regulations and Acts. In each participating centre, the local coordinating or principal investigator will be responsible for recruitment, data collection, follow-up of included patients, completion of case report forms and adherence to the study protocol. The supervising physician or any other physician of the multidisciplinary team will inform subjects about the study and ask for their consent using standard information letters and informed consent forms. Both patient information letters and informed consent forms are attached as separate documents.

An independent safety committee will be established to perform on-going safety surveillance and to perform interim analyses to assess the safety data and the stopping rules as described in "safety and stopping rules". Each stopping rule will be repeatedly tested when the first 10, 20, 30 and 50 events for that particular stopping rule have oc-

curred (*i.e.* [ad 1 and 2] detection of locoregional regrowth, [ad 3] the performance of delayed surgery or [ad 4] the detection of distant metastases).

The project leader (JL) is responsible for the study design and conduct of the trial, for the preparation of the protocol and revisions and for preparation of case report forms. Revisions of the study protocol will be communicated to all local chief investigators. The Clinical Trial Centre (CTC) of the Erasmus MC – University Medical Centre Rotterdam is responsible for the data master file, data verification and randomisation. Randomisation will be performed via a computer-generated random numbers sequence. Data will be collected using individual trial case numbers on standardised case report forms collated centrally by the CTC. Patients will not be individually identifiable. The final dataset will be available to all study investigators but will not be analysed per centre. Authorships will be defined following the International Committee of Medical Journal Editors guidelines.[28] Results will be communicated via international conferences, via publications and via the NTR.

Discussion

Trials comparing surgical and non-surgical treatment modalities often fail due to low accrual if randomisation is at the patient level, which might be explained by patient preferences for an intervention.[29-32] Therefore, a stepped-wedge cluster design is applied in the present trial.[33] In a stepped-wedge design, randomisation takes place at the institutional level, and not at the patient level. Consequently, at the moment of inclusion patients know which treatment arm they will be assigned to, thereby overcoming uncertainty about which treatment patients will undergo. We expect that this will improve patients' willingness to participate. When proven successful, the stepped-wedge design might be used as a new standard for comparing surgical with conservative treatments in clinical trials.

We will include both patients with SCC and patients with AC, since SCC and AC both respond to nCRT and no statistically significant differential effects were found in the CROSS-trial. Both patients with SCC and AC have a substantial pCR rate (49% and 23% in CROSS respectively).[3] Moreover, preliminary results of the preSANO-trial suggests that residual disease can be diagnosed with comparable accuracy in patients with both histological subtypes.

Furthermore, in combination with the relatively low frequency of toxicity of the CROSS-regimen (91% completed the full nCRT-regimen), the high pCR-rate supports the use of the relatively low radiation dose of 41.4 Gy.[3] The beneficial effectivity/toxicity ratio is the rationale to apply the CROSS-regimen in the SANO-trial, and not a definitive chemoradiotherapy regimen (≥50 Gy of radiotherapy). The latter could increase the

pCR-rate, but probably at the cost of a substantial increase in toxicity and postoperative complications, leading to a less beneficial effectivity/toxicity ratio. It should be noted that postponement of surgical resection, as will be performed in patients who develop locoregional regrowth in the absence of distant metastases, has been suggested to increase the incidence of postoperative complications. However, this phenomenon has been reported primarily after treatment with high-dose of definitive chemoradiotherapy (so called salvage esophagectomy) in low-volume centres.[34, 35] The SANO-trial will reveal whether this also applies to a lower dose of radiotherapy (CROSS regimen) in high-volume centres.

If the SANO-trial shows that active surveillance after nCRT for oesophageal cancer leads to non-inferior survival compared to standard oesophagectomy, this organ-sparing approach could be implemented as a standard of care. Of note, the French ESOSTRATE-trial is also comparing active surveillance with standard surgery in patients with cCR after nCRT. The ESOSTRATE-trial aims to include a total of 300 patients with SCC or AC with cCR after nCRT.[36] The primary endpoint is overall survival, as in the SANO-trial. Combining results from the ESOSTRATE-trial and the SANO-trial would lead to more certainty. Recently, we have shown that 54% and 61% of all patients are willing to trade-off 15% and 10% overall survival, respectively, to undergo active surveillance instead of standard surgery.[37] Therefore, the statistical power of the SANO-trial is for a non-inferiority margin of 15%; combination with the French ESOSTRATE-trial would reduce this margin to 10%. Hence, the future combination of results with the ESOSTRATE-trial is important to further increase our knowledge of an active surveillance approach beyond what we will learn from the SANO-trial only.

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To be determined	Pathology	

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Dr. J. Nieken	Pathology	Medisch Centrum Leeuwarden
Drs. V. Oppedijk	Radiotherapy	Radiotherapeutisch Instituut Friesland
Prof. dr. J.P.E.N. Pierie	Surgery	Medisch Centrum Leeuwarden
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Table 1. Study algorithm.

	Pretreatment	CRE-I (4-6 weeks after nCRT)	CRE-II (10-14 weeks after nCRT)	Standard surgery arm (6, 9, 12, 16, 20, 24, 30, 36, 48 and 60 months after nCRT)	Active surveillance arm (6, 9, 12, 16, 20, 24, 30, 36, 48 and 60 months after nCRT)
Informed consent	X				
Inclusion			X		
Treatment allocation*			X		
ECOG performance status	X	X	X	X	X
Endoscopy with bite-on-bite biopsies	X	X	X		X
Radial EUS	X		X		X
Linear EUS with FNA of suspected lymph nodes	X		X		X
18F-FDG PET-CT (whole-body)	X	X[1]	X[2]	X[3]	X[2]
Quality of Life (EQ-5D, QLQ-C30, QLC-OG25 en Cancer Worry Scale)	X		X	X[4]	X[4]
Oesophagectomy		X[5]	X[6]	All	At indication[7]

[1] 18F-FDG PET-CT: during CRE-I, after OGD, only for clinically non-complete responders, to exclude disseminated disease.

[2] 18F-FDG PET-CT: during CRE-II and active surveillance, prior to OGD and EUS, for all patients (all were clinically complete responders during CRE-I) to guide endoscopists in taken biopsies / FNA during OGD and EUS and to exclude disseminated disease.

[3] PET-CT in the standard surgery arm will be performed at 12 and 24 months after nCRT only, to exclude disseminated disaese.

[4] Quality of life will be assessed during the first 2 years only.

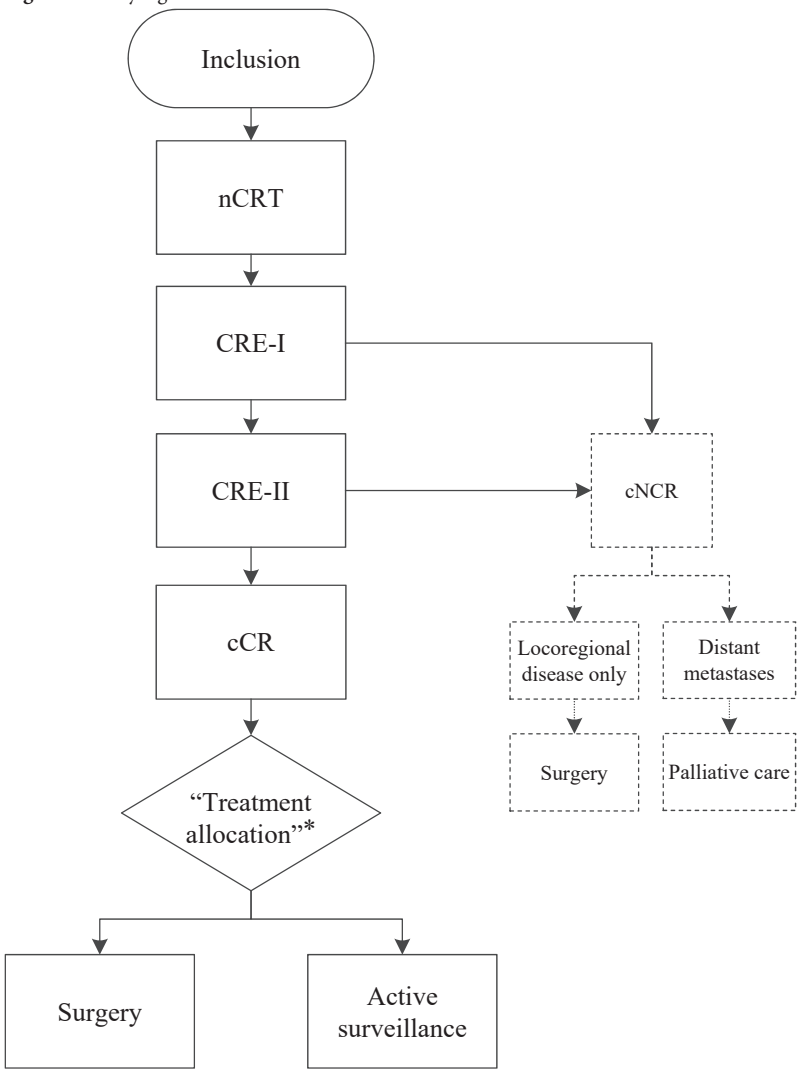
[5] Only for patients with locoregional disease.

[6] After CRE-II: Only for patients with cCR who are allocated to surgery.

[7] Only for patients in whom a locoregional regrowth is highly suspected or proven, without any signs of distant dissemination.

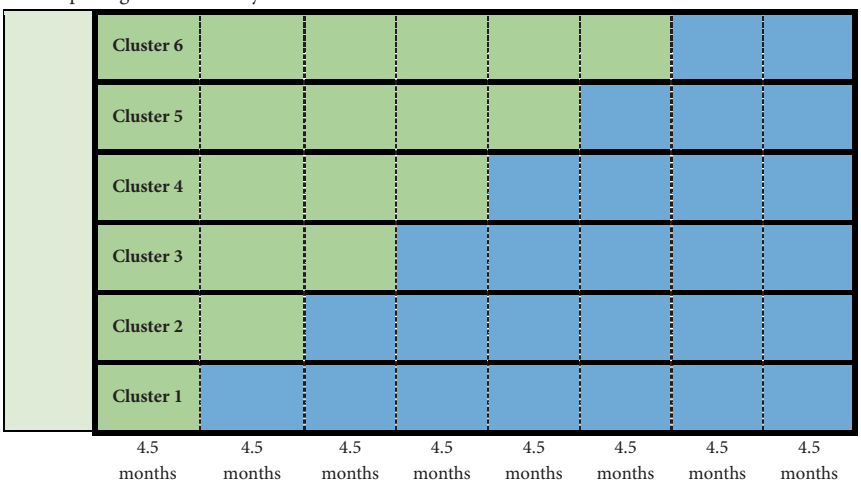
CRE: clinical response evaluation; nCRT: neoadjuvant chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group EUS: endo-ultrasonograpy; FNA: fine needle aspiraton. *At this point the patient will be allocated to one of the two treatment arms, dependent on the institution. Randomisation has already been performed at the institutional level and will be known to the patient at the moment of inclusion

Figure 1. Study algorithm.



nCRT: neoadjuvant chemoradiotherapy; CRE: clinical response evaluation; cNCR: clinically non-complete response; cCR: clinically complete response. *At this point the patient will be allocated to one of the two treatment arms, dependent on the institution in which the actual treatment takes place. Randomisation will be performed at the institutional level. Patients will know their allocated treatment at the moment of inclusion.

Figure 2. Stepped-wedge cluster design with addition of preSANO cCR-patients and sequential cross-over of 6 clusters comprising 2 centres every 4.5 months.



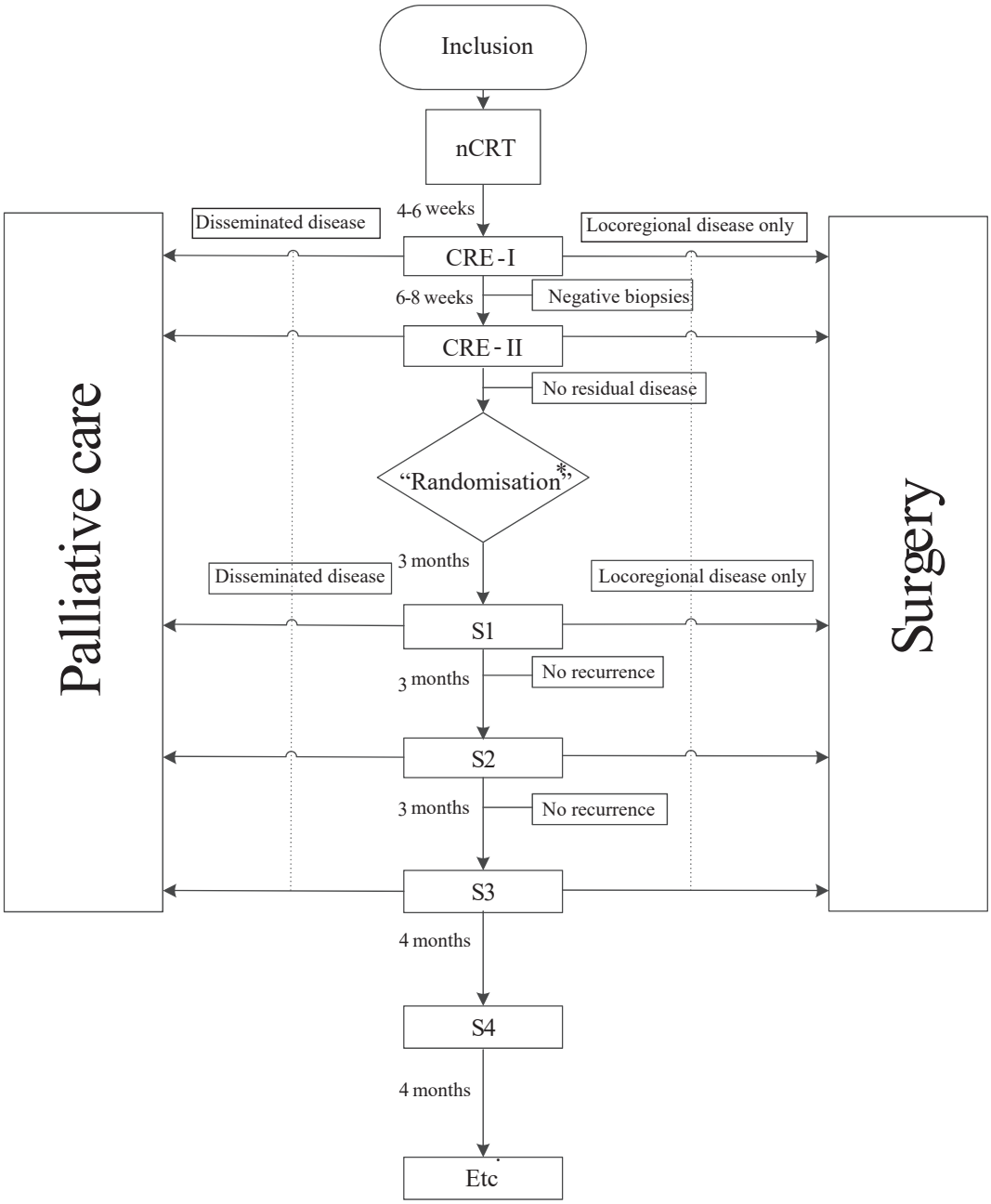
Expected number of patients with cCR included in each treatment arm per time period

	60	25	22	18	13	8	4		N = 150
			5	10	16	22	28	34	35	N = 150
Total	**60**	**25**	**27**	**28**	**29**	**30**	**32**	**34**	**35**	**N = 300**

cCR from preSANO-2 (control)
control arm (standard surgery)
intervention arm (active surveillance)

cCR: clinically complete response (based on results from the preSANO trial, it is expected that 50% of all included patients have a cCR).

Figure 3. Expected distribution of patients.



nCRT: neoadjuvant chemoradiotherapy; CRE: clinical response evaluation; S1: first surveillance evaluation; S2: second surveillance evaluation etc. Treatment allocation*: randomisation will be performed at institutional level and will be known already at the moment of inclusion; immediate surgery arm of randomisation not shown.

References

1. Hulscher JB, van Sandick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662-9.
2. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
3. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
4. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
5. De Boer AG, Genovesi PI, Sprangers MA, Van Sandick JW, Obertop H, Van Lanschot JJ. Quality of life in long-term survivors after curative transhiatal oesophagectomy for oesophageal carcinoma. Br J Surg. 2000;87(12):1716-21.
6. Djarv T, Lagergren J, Blazeby JM, Lagergren P. Long-term health-related quality of life following surgery for oesophageal cancer. Br J Surg. 2008;95(18581441):1121-6.
7. Scarpa M, Valente S, Alfieri R et al. Systematic review of health-related quality of life after esophagectomy for esophageal cancer. World journal of gastroenterology : WJG. 2011;17(42):4660-74.
8. Noordman BJ, Verdam MGE, Lagarde SM et al. Impact of neoadjuvant chemoradiotherapy on health related quality of life in esopageal or junctional cancer: results from the randomized CROSS trial. In press, J Clin Oncol. 2017.
9. Noordman BJ, Verdam MGE, Lagarde SM et al. Impact of neoadjuvant chemoradiotherapy on health related quality of life in long-term survivors of esophageal or junctional cancer: results from the randomized cross trial. Submitted for publication. 2017.
10. Castoro C, Scarpa M, Cagol M et al. Complete clinical response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic oesophagus: is surgery always necessary? J Gastrointest Surg. 2013;17(8):1375-81.
11. Taketa T, Correa AM, Suzuki A et al. Outcome of trimodality-eligible esophagogastric cancer patients who declined surgery after preoperative chemoradiation. Oncology. 2012;83(5):300-4.
12. Taketa T, Xiao L, Sudo K et al. Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology. 2013;85(2):95-9.
13. Furlong H, Bass G, Breathnach O, O'Neill B, Leen E, Walsh TN. Targeting therapy for esophageal cancer in patients aged 70 and over. J Geriatr Oncol. 2013;4(2):107-13.
14. Noordman BJ, Spaander MC, Wijnhoven BP et al. Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO trial). In press, Lancet Oncol. 2017.
15. Chirieac LR, Swisher SG, Ajani JA et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer. 2005;103(7):1347-55.
16. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ. 2015;350:h391.
17. Shapiro J, Biermann K, van Klaveren D et al. Prognostic value of pretreatment pathological tumor extent in patients treated with neoadjuvant chemoradiotherapy plus surgery for esophageal or junctional cancer. Ann Surg. 2017;265(2):356-62.
18. Shiozaki H, Sudo K, Xiao L et al. Distribution and timing of distant metastasis after local therapy in a large cohort of patients with esophageal and esophagogastric junction cancer. Oncology. 2014;86(5-6):336-9.
19. Nederland IK. National guideline oesophageal cancer: Oncoline; 2015 [updated 2015-01-05. Available from: http://www.oncoline.nl/oesofaguscarcinoom.

20. Janssen MF, Pickard AS, Golicki D et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.
21. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
22. Lagergren P, Fayers P, Conroy T et al. Clinical and psychometric validation of a questionnaire module, the EORTC QLQ-OG25, to assess health-related quality of life in patients with cancer of the oesophagus, the oesophago-gastric junction and the stomach. Eur J Cancer. 2007;43(14):2066-73.
23. Custers JA, van den Berg SW, van Laarhoven HW, Bleiker EM, Gielissen MF, Prins JB. The Cancer Worry Scale: detecting fear of recurrence in breast cancer survivors. Cancer Nurs. 2014;37(1):E44-50.
24. Low DE, Alderson D, Cecconello I et al. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg. 2015;262(2):286-94.
25. Auditing DIfC. Jaarrapportage 2016. 2016.
26. Baio G, Copas A, Ambler G, Hargreaves J, Beard E, Omar RZ. Sample size calculation for a stepped wedge trial. Trials. 2015;16:354.
27. Thernau TM, Grambsch PM. Modeling Surivival Data: Extending the Cox Model: Springer-Verlag; 2000.
28. ICoMJ E. Defining the role of authors and contributors. Philadelphia:: ICMJE;; 2014.
29. Blazeby JM, Strong S, Donovan JL et al. Feasibility RCT of definitive chemoradiotherapy or chemotherapy and surgery for oesophageal squamous cell cancer. Br J Cancer. 2014;111(2):234-40.
30. Bonvalot S. Is there a role for surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomised trial. Personal communication.
31. Du CY, Zhou Y, Song C et al. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomised trial in China. Eur J Cancer. 2014;50(10):1772-8.
32. Earlam R. An MRC prospective randomised trial of radiotherapy versus surgery for operable squamous cell carcinoma of the oesophagus. Ann R Coll Surg Engl. 1991;73(1):8-12.
33. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC Med Res Methodol. 2006;6:54.
34. Markar S, Gronnier C, Duhamel A et al. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: is it a viable therapeutic option? J Clin Oncol. 2015;33(33):3866-73.
35. Markar SR, Karthikesalingam A, Penna M, Low DE. Assessment of short-term clinical outcomes following salvage esophagectomy for the treatment of esophageal malignancy: systematic review and pooled analysis. Ann Surg Oncol. 2014;21(3):922-31.
36. [Available from: https://clinicaltrials.gov/ct2/show/NCT02551458.
37. Noordman BJ, De Bekker-Grob EW, Coene PPLO et al. Patients' preferences for treatment after neoadjuvant chemoradiotherapy for esophageal cancer: a discrete choice experiment. In preperation. 2017.

Chapter 20

Organ-sparing treatment in oesophageal cancer: feasible and safe?

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Summary

In many countries, neoadjuvant chemoradiotherapy (nCRT) plus surgery is standard treatment for resectable oesophageal cancer. After nCRT, up to 30% of all patients have no residual disease in the resection specimen. Consequently, an active surveillance approach, in which patients undergo frequent clinical investigations after nCRT instead of standard oesophagectomy, is increasingly applied in selected patients. Here, we describe outcomes for three patients who underwent active surveillance. A 63-year old woman was considered unfit for surgery after nCRT. Four years after completion of nCRT, she still had no signs of disease recurrence. The second patient, a 57-year old woman, refused surgery when no residual disease was detectable after nCRT. One year following treatment, she developed a vertebral metastasis, in the absence of locoregional disease. The third patient concerned a 66-year old man with a clinically complete response after nCRT, who also refused surgery. During active surveillance, he developed a locoregional regrowth and underwent a (postoponed) microscopically radical oesophagectomy.

Introduction

Oesophagectomy has been considered an elementary component of curative treatment for patients with locally advanced oesophageal cancer. Last years, patients undergo chemoradiotherapy prior to surgery. Consequently, 5-year overall survival rates have been improved and in some patients, no vital tumour cells can be found in the resection specimen. This questions the necessity of an oesophagectomy in all patients; perhaps this operation can be postponed or even omitted in a subgroup of these patients.

Thanks to preoperative chemoradiotherapy 5-year overall survival has increased from 35% to 50%. NCRT is highly effective and in about 30% of all cases no malignant cells are present in the resection specimen, as determined by conventional histopathological analysis (so called *pathologically complete response*). Chances on a pathologically complete response differ between histological subtypes, but are substantial in both most common subtypes (about 25% for adenocarcinoma and 50% for squamous cell carcinoma).[1]

Such an organ sparing treatment strategy with active surveillance after nCRT is already applied successfully in patients with bladder carcinoma, rectal carcinoma or head and neck cancer.[2-4] Here, we illustrate the possible scenarios of an active surveillance strategy in oesophageal cancer, by describing clinical outcomes of three typical patients who underwent active surveillance after nCRT at our institute.

Patient A is a 63-year old single woman with no offspring. She has been smoking until 4 years ago. Her history includes severe rheumatoid arthritis and bilateral implantation of hip prostheses. Her rheumatoid arthritis is treated with anakinra and prednisone.

Five years ago she developed progressive dysphagia, resulting in the inability for oral nutrition. She was diagnosed with a locally advanced squamous cell cancer of 14 cm length in the mid- and distal part of the oesophagus (cT3N1M0). The multidisciplinary tumour board advised nCRT (41.4 Gy during 4.5 weeks with weekly cycles of carboplatin and paclitaxel), followed by oesophagectomy. Six weeks after completion of nCRT she underwent clinical investigations. Pathological assessment of endoscopic biopsies suggested a clinically complete response: none of the biopsies contained vital tumour cells. Because of her limited physical condition and the absence of detectable vital tumour, oesophagectomy was provisionally omitted and an active surveillance strategy was conducted.

Currently, four years after completion of nCRT, the patient is doing fairly good. Her body weight is stable without artificial nutrition. During repeated clinical investigations consisting of endoscopy with biopsies and ^{18}FDG PET-CT there is still a clinically complete response. If after 5 years of active surveillance no residual disease is shown, she will

be discharged from further follow-up, since we believe that the risk of recurrence would be negligible.

Patient B is a 57-year old divorced woman with no offspring and no medical history. She visited her general practitioner with feelings of general illness and 6kg unintended weight loss. At haemotological investigation she had anaemia (Hb 7.0 mmol/ml). Gastroscopy was performed, showing a poorly differentiated squamous cell carcinoma of the mid-part of the oesophagus (T1smN1M0).

After diagnostic work-up with ^{18}FDG PET-CT, endoscopy and endo-ultrasonography nCRT followed by oesophagectomy was proposed. She was included in the preSANO trial (pre-Surgery As Needed for Oesophageal cancer).[5, 6] This trial evaluates the tumour response on nCRT by performing clinical response evaluations consisting of endoscopy with biopsies, endo-ultrasonography and ^{18}FDG PET-CT at 6 and 12 weeks after completion of nCRT. No signs of vital residual disease were found and following the study protocol the patient should have underwent oesophagectomy. However, based on extensive conversation with other patients who underwent oesophagectomy, she refused surgery, fearing the potential impact of surgery on health-related quality of life. She preferred active surveillance. One year after completion of nCRT, an ^{18}FDG PET-CT was performed as part of the active surveillance strategy and showed a laesion suspicious for a solitary distant metastasis in the vertebral column at level L4 (Figure 1). After histological confirmation with a biopsy of the laesion, the patient underwent palliative radiotherapy using the so called cyberknife (two times 12Gy). Except for some pain radiating to the left buttock, the patient had no complaints after this treatment.

Currently, more than two years after diagnosis, she still has no complaints. Based on ^{18}FDG PET-CT and endoscopy there is still a clinically complete response. The rapid detection of the distant metastasis suggests that it was already present in an undetectable stage during initial diagnosis. Regardless of the locoregional response to nCRT, this patient would not benefit from oesophagectomy, since her prognosis is determined mainly by the distant metastasis.

Patient C, a 66-year old married man with two daughters and a history of depression, complained about retrosternal pain during intake of food and hot beverages. After extensive clinical investigations using ^{18}FDG PET-CT, endoscopy and endo-ultrasonography, he was diagnosed with a poorly differentiated adenocarcinoma (cT2-3N1M0) of the oesophago-gastric junction. After discussion in the multidisciplinary tumour board the patient was advised to undergo nCRT followed by oesophagectomy.

The patient was included in the preSANO-trial, like patient B.[5, 6] During clinical response evaluations at 6 and 12 weeks after completion of nCRT no signs of vital residual tumour were found (clinically complete response). Based on this outcome, the patient preferred active surveillance instead of standard oesophagectomy. Six months after completion of nCRT, an ^{18}FDG PET-CT showed an increase in FDG-avidity at the loca-

tion of the initial primary tumour (Figure 2). During endoscopy a laesion suspected for regrowth of disease was found, but no biopsies were taken.

Based on ^{18}FDG PET-CT and endoscopy the patient was strongly suspected to have a locoregional regrowth, without distant metastases. Therefore, the tumour board advised oesophagectomy, and the patient agreed. The thorocolaparoscopic operation was performed at 6.5 months after completion of nCRT without any complications. The resection specimen showed a microscopically radically resected tumour (ypT3N1R0G3). Postoperatively, the patient developed a thoracic seroma, which was treated by percutaneous drainage. The patient was discharged on day 10 postoperatively.

Six months after surgery the patient is doing fine and there are no signs of disease recurrence. Follow-up is performed according to the same regimen as patients who undergo immediate surgery following completion of nCRT. This regimen consists of frequent outpatient visits during 5 years after surgery and additional investigations when indicated.

Discussion

In patients with a clinically complete response after nCRT who undergo active surveillance, there are several potential clinical scenarios.

Subclinical micrometastatic disease

The group of patients who benefit from active surveillance not only consists of patients who are cured by nCRT alone, but also of patients with subclinical distant metastases at the time of completion of nCRT. The latter group, as reflected by patient B, would not benefit from oesophagectomy, since micrometastases are already present during initial staging. Over time, these disseminated tumour cells become clinically manifest. Distant metastases are the main determinants for long-term survival after nCRT followed by oesophagectomy, and are not curable with the currently available systemic therapies. Although the biology of distant dissemination is not fully understood, assumptions hold that spreading and seeding of tumour cells from the primary laesion is an early event and has already occurred in many patients at the time of first clinical presentation and subsequent locoregional treatment (*i.e.* nCRT with and without subsequent surgery).[7] This is supported by the large number of patients who develop distant metastases within 2 years after surgery.[1, 8, 9] No matter how timely and aggressive locoregional treatment will be, it will hardly affect the survival-determining events of distant dissemination. At present, patients with occult distant metastases undergo a non-beneficial oesophagectomy because the metastases are below the detection limit at the first clinical evaluation after nCRT.

Active surveillance

It is expected that an active surveillance strategy can reduce the need for oesophagectomy in 30-40% of all patients with locally advanced oesophageal cancer, as a result of either cure after nCRT alone or manifestation of distant dissemination during active surveillance.[8, 10, 11] This is expected to improve health-related quality of life, to reduce treatment-related morbidity and mortality, and to reduce costs.

However, active surveillance is only justified if long-term survival is comparable to nCRT followed by immediate oesophagectomy. Tumour regrowth after nCRT should be detected at a curable stage, and before the development of distant dissemination from disease regrowth. Therefore, an intensive surveillance regimen is necessary (frequent ^{18}FDG PET-CT, endoscopy and endo-ultrasonography with cytological puncture of suspicious lymph nodes), aiming to detect as many regrowths, as early as possible before they become irresectable. In order to reduce the risk of false-negative biopsies, extensive biopsies of the original tumour area should be taken, preferably using a bite-on-bite technique. The optimal set of investigations for detection of residual disease after nCRT was topic of investigation of the preSANO-trial, clinical response evaluation after neoadjuvant chemoradiotherapy is adequate using endoscopy with (bite-on-bite) biopsies and endo-ultrasonography with aspiration of suspicious lymph nodes for detection of locoregional residual disease and ^{18}FDG PET-CT for detection of interval distant metastases.[6]

Patient C is an example of a case in which the regrowth was detected in a curable stage. Although no biopsies were taken to obtain histopathological evidence of locoregional regrowth, the increase in FDG-avidity was so convincing, that the tumour board deemed renewed endoscopy to take biopsies not necessary.

Regrowth in irresectable stage

We are not experienced with locoregional regrowths detected in an irresectable stage (T4b). This is an important risk of active surveillance and is accompanied with a bad prognosis, since there is currently no curative treatment available for these patients. Based on the (scarcely available) literature, nCRT plus active surveillance with frequent investigation using at least ^{18}FDG PET-CT and endoscopy with biopsies leads to similar long-term survival, as compared to nCRT followed by immediate oesophagectomy.[8, 10, 11] This should be carefully examined in a prospective clinical trial. Furthermore, outcomes of active surveillance might improve by the use of new diagnostic modalities during response evaluation, such as MRI and circulating tumour DNA.

Postponed surgery

Next to the risk of detection of a locoregional regrowth in an irresectable stage, literature suggests that late effects of radiotherapy increase the risk of postoperative complications in case of postponed surgery. However, this phenomenon has been described especially in patients who underwent high dose radiotherapy (>50Gy, whereas the Dutch CROSS-regimen consists of 41.4 Gy) and in low-volume centres.[12] It is unknown whether this increased risk of postoperative complications also applies for patients who are treated according to the CROSS-regimen and undergo oesophagectomy in a high-volume centre (>20 oesophagectomies per year). Moreover, the potential increase in postoperative complications in this small group of patients who need postponed surgery is probably counterbalanced by the number of patients who avoid unnecessary surgery as a results of the active surveillance strategy.

Active surveillance in selected patients

Active surveillance is not (yet) a standard of care, but it is applied increasingly in selected patients with a clinically complete response.[10, 11] Although squamous cell carcinoma has a higher probability to achieve a pathologically complete response (50%), this probability is also substantial for adenocarcinoma (25%). Therefore, active surveillance is applied in patients with both histological subtypes. In current practice, this concerns mainly patients who refuse surgery (e.g. patients B and C), or who are medically unfit for surgery (patient A).

Before an active surveillance strategy can be applied as a standard of care, the non-inferiority of this organ-sparing strategy compared to nCRT plus immediate surgery must be tested in a clinical trial. In order to answer this research question, the current SANO-trial (Surgery As Needed for Oesophageal cancer) is comparing both treatment strategies in 12 Dutch high-volume centres.[13]

Ladies and gentlemen, an active surveillance strategy can save selected patients with oesophageal cancer and a clinically complete response after nCRT from a potentially unnecessary oesophagectomy. If this treatment is applied, we recommend frequent clinical investigations using ^{18}FDG PET-CT, endoscopy with (bite-on-bite) biopsies and ultra-endosongraphy with cytological puncture of suspicious lymph nodes.

Before an active surveillance strategy can be applied as a standard of care for patients with a clinically complete response after nCRT, a clinical trial should assess whether this treatment strategy leads to comparable long-term oncological outcome without increase of perioperative morbidity.

Figure 1. CT (left) and FDG PET-CT (right) one year after completion of neoadjuvant chemoradiotherapy showing a lesion suspicious for solitary distant metastasis in the vertebral body of L4.

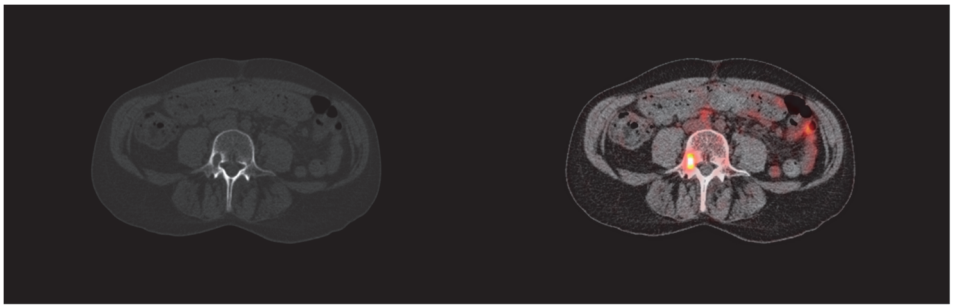
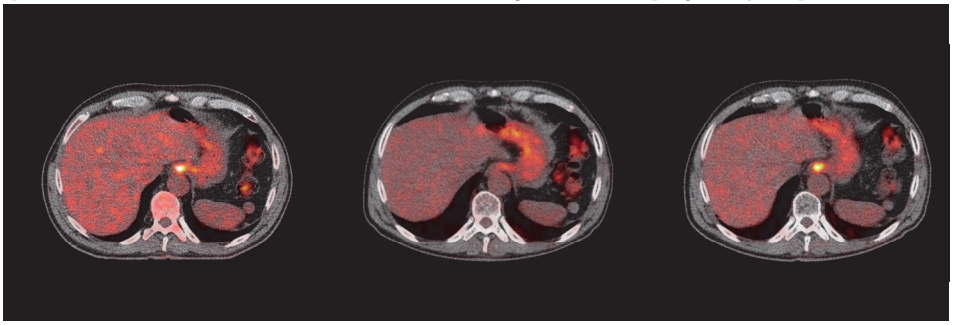


Figure 2. Serial FDG PET-CT after neoadjuvant chemoradiotherapy shows an increase in FDG-avidity 24 weeks after completion of neoadjuvant chemoradiotherapy (right), after an initially clinically complete response at 12 weeks (middle). Based on these PET-CT findings a radical oesophagectomy was performed.



nCRT: neoadjuvant chemoradiotherapy

References

1. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
2. Mehanna H, Wong WL, McConkey CC et al. PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. N Engl J Med. 2016;374(15):1444-54.
3. Renehan AG, Malcomson L, Emsley R et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol. 2016;17(2):174-83.
4. Rödel C, Wiess C, Sauer R. Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol. 2006;24(35):5536-44.
5. Noordman BJ, Shapiro J, Spaander MC et al. Accuracy of detecting residual disease after CROSS neoadjuvant chemoradiotherapy for esophageal cancer (preSANO Trial): rationale and protocol. JMIR Res Protoc. 2015;4(2):e79.
6. Noordman BJ, Spaander MC, Wijnhoven BP et al. Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO trial). In press, Lancet Oncol. 2017.
7. Chambers AF, Groom AC, MacDonald IC. Metastasis: Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer. 2002;2(8):563-72.
8. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
9. Shiozaki H, Sudo K, Xiao L et al. Distribution and timing of distant metastasis after local therapy in a large cohort of patients with esophageal and esophagogastric junction cancer. Oncology. 2014;86(5-6):336-9.
10. Castoro C, Scarpa M, Cagol M et al. Complete clinical response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic oesophagus: is surgery always necessary? J Gastrointest Surg. 2013;17(8):1375-81.
11. Taketa T, Correa AM, Suzuki A et al. Outcome of trimodality-eligible esophagogastric cancer patients who declined surgery after preoperative chemoradiation. Oncology. 2012;83(5):300-4.
12. Markar S, Gronnier C, Duhamel A et al. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: is it a viable therapeutic option? J Clin Oncol. 2015;33(33):3866-73.
13. Noordman BJ, Wijnhoven BPL, Lagarde SM et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial. BMC Cancer. 2018;18(1):142.

Chapter 21

Summary

Chapter 21A
Summary in English

Esophageal cancer is an aggressive disease with a poor prognosis. At the time of diagnosis, most patients are incurable due to distant metastases. For patients without distant metastases, surgery to remove part of the esophagus and surrounding lymph nodes has been the cornerstone of curative therapy for decades. Surgical techniques are described in **chapter 2**. However, these operations imply major surgery, associated with substantial morbidity and even mortality and have severe impact on quality of life. Moreover, even after intentionally curative surgery, around one third of all patients die due to relapse of the disease. In order to improve outcomes, preoperative chemo- and/or radiotherapy (so called *multimodality treatment*) have been tested in clinical studies (**chapter 3**). The randomized CROSS-trial compared preoperative concurrent chemo- and radiotherapy followed by surgery with surgery alone. Results showed a 5-year survival benefit of 14% in favor of the combined chemoradiotherapy plus surgery group.[1] Based on these results, preoperative chemoradiotherapy followed by surgery is now standard of care in many countries, including the Netherlands. In this thesis, we describe the treatment implications of this therapeutic approach as standard of care. Results of the presented research are discussed in two parts; PART I focusses on implications of preoperative chemoradiotherapy on surgical treatment and PART II focusses on a novel *active surveillance* treatment strategy in which surgery might be omitted in a substantial number of patients who had preoperative chemoradiotherapy.

PART I. Implications of neoadjuvant chemoradiotherapy on surgical treatment

Multimodality treatment of esophageal cancer is the standard of care in Western centers. Two preoperative approaches have been adopted. The first is preoperative chemoradiotherapy, generally based on the CROSS regimen.[1, 2] An alternative option mainly for patients with the adenocarcinoma subtype is perioperative or preoperative chemotherapy.[3, 4] In **chapter 4** it is shown that the survival differences between preoperative chemoradiotherapy and preoperative chemotherapy are modest, if present at all. Moreover, it is shown that preoperative chemoradiotherapy confers significant pathological benefits in terms of tumor and lymph node down-staging. Previously, it has been shown that extended lymphadenectomy (*i.e.* resection of lymph nodes) improves prognostication of survival and probably also has a beneficial therapeutic effect in patients who are treated with surgery alone.[5, 6] However, the down-staging effect of preoperative chemoradiotherapy has been suggested to reduce the prognostic and therapeutic effect of extended lymphadenectomy. We focused on the prognostic and therapeutic effect of lymphadenectomy in chapters 4-6. In **chapter 5**, we provide an overview of the current literature on this topic. In **chapter 6** we critically appraise a recent publication on this topic. Subsequently, the oncological

benefit of extended lymphadenectomy is analyzed in **chapter 7**. In a large series of patients from two Dutch high volume centers, a surgical technique with extended lymphadenectomy (*transthoracic esophagectomy*) is compared with a surgical technique with limited lymphadenectomy (*transhiatal esophagectomy*). The surgical technique with extended lymphadenectomy had differential effects on survival, with a favorable prognostic and (probably) therapeutic effect in the surgery alone group. However, this effect was absent in patients who had received preoperative chemoradiotherapy. Hence, the use of preoperative chemoradiotherapy may reduce the need for extended lymphadenectomy in an attempt to improve long-term survival. Therefore, we conclude that after preoperative chemoradiotherapy the choice for surgical approach should depend on the relative risk of complications and patient's quality of life rather than on long-term survival.

In **chapter 8-10**, we focus on the impact of preoperative chemoradiotherapy on patients' quality of life. In **chapter 8** it is shown that, although quality of life declined during chemoradiotherapy, no effect of chemoradiotherapy was apparent on postoperative recovery in terms of health-related quality of life, compared with surgery alone. In **chapter 9**, we further explore the course of health-related quality of life immediately after preoperative chemoradiotherapy in order to optimize the timing of surgery. Results show that health-related quality of life returns to pre-treatment levels eight weeks after completion of chemoradiotherapy, and that some aspects of health-related quality of life even improve after chemoradiotherapy, compared to pre-treatment levels. These results support delay of surgery, especially in vulnerable patients. In **chapter 10**, long-term effects of preoperative chemoradiotherapy on quality of life are investigated. Compared to surgery alone, no adverse impact of preoperative chemoradiotherapy was apparent on long-term quality of life. In addition to the earlier described improvement in long-term survival and the absent (negative) impact on postoperative recovery described in chapter 7, these results support the view that preoperative chemoradiotherapy according to CROSS is well tolerated and can be considered as a standard of care. Nevertheless, after long-term follow-up physical functioning and fatigue remain reduced, both with and without preoperative chemoradiotherapy. These results indicate a lasting (negative) impact of surgery on quality of life, regardless of the use of preoperative chemoradiotherapy.

After preoperative chemoradiotherapy, both the pretreatment and posttreatment number of suspected tumor positive lymph nodes are associated with survival.[7] In current practice, pretreatment lymph node status is determined by endoscopic ultrasound and PET-CT examination, whereas posttreatment lymph node status is determined by analysis of the number of tumor positive lymph nodes in the resection specimen. Previously, a novel staging system to assess the pretreatment number of suspected lymph nodes based on regressive changes resulting from chemoradiotherapy (*i.e.* scarring) in the resection specimen has been tested. This staging system was of superior prognostic performance compared to regular clinical lymph node staging using endoscopic ultrasound and PET-

CT.(8) In **chapter 11**, we externally validate and confirm these findings in an independent series of patients from a high volume institute (Cologne, Germany).

PART II. Active surveillance after neoadjuvant chemoradiotherapy

After preoperative chemoradiotherapy, one third of all patients does not have viable tumor cells in the resection specimen.[2] Based on this finding, the question is raised whether surgery is of benefit to these patients. Therefore, we propose to investigate the feasibility of an organ-sparing approach after completion of chemoradiotherapy. In this approach, patients will undergo active surveillance instead of standard surgery after completion of chemoradiotherapy. An active surveillance strategy implies frequent clinical examination to ensure timely detection of residual or recurrent locoregional disease. Surgery would be offered only to those patients in whom residual disease in the esophagus or surrounding lymph nodes is highly suspected or proven, without distant metastases. Before active surveillance can be tested safely, we need to accurately distinguish patients who need immediate surgery (with viable residual tumor) from patients who might benefit from active surveillance (without viable residual tumor). Therefore, the disease should be re-staged during so called *clinical response evaluations*. In **chapter 12**, an overview of the literature on the accuracy of the most common diagnostic tests for re-staging is provided. Results suggest insufficient reliability of endoscopy, endoscopic ultrasound and PET-CT for detecting residual disease after neoadjuvant chemoradiotherapy. However, most studies have been criticized because of their retrospective design and the use of only one diagnostic modality. Moreover, diagnostic tests in most studies were not performed with the aim to detect residual disease for the selection of patients who might benefit from active surveillance. This may have reduced diagnostic accuracy. In **chapter 13** we describe the study protocol of the diagnostic preSANO-trial, which prospectively investigated the accuracy of clinical response evaluations and the optimal diagnostic set for detecting residual disease after preoperative chemoradiotherapy using a combination of endoscopy, endoscopic ultrasound with puncture of suspected lymph nodes, and PET-CT. This trial included 219 patients from six centers in the Netherlands who were planned to undergo preoperative chemoradiotherapy according to CROSS followed by surgery. The main results of this trial are presented in **chapter 14**, showing that response evaluation after preoperative chemoradiotherapy for esophageal cancer is adequate using endoscopy with bite-on-bite biopsies and endoscopic ultrasound with puncture of suspected lymph nodes. This diagnostic set is able detect 90% of all patients with substantial residual tumor in the esophagus after preoperative chemoradiotherapy. Moreover, PET-CT detected new so called intercurrent distant metastases in 9% of all patients, sparing them from a non-beneficial esophagectomy. In-depth analyses of the results of endoscopic ultrasound and PET-CT are reported in

chapter 15 and **chapter 16**, respectively. Although endoscopic ultrasound measurements can accurately detect substantial residual tumors (low false-negative rate), these measurements frequently classify patients without residual disease as disease positive (high false-positive rate, **chapter 15**). Comparable results were found for in-depth PET-CT analyses (**chapter 16**). Therefore, we concluded that the value of endoscopic ultrasound and PET-CT in detection of residual disease in the esophagus after preoperative chemoradiotherapy is limited.

An organ-sparing approach theoretically has major advantages for patients, by avoiding the risk of postoperative complications and decreased quality of life. In **chapter 17** it is shown that patients are willing to trade-off a substantial 5-year survival chance (on average 16%) in order to achieve a reduction in the risk that surgery is still necessary from 100% (as in current practice) to 35%, as is expected during the to be tested active surveillance strategy. Furthermore, it is shown that two classes of patients can be identified. The first class consisted of patients with a strong preference for active surveillance and the second class comprised patients with a strong preference for standard esophagectomy. These findings may help patients and clinicians in the future to choose between active surveillance and standard esophagectomy and may have positive effects on quality of shared decision making. In an overview of the (scarcely available) literature provided in **chapter 18**, comparable long-term survival is described in patients without detectable disease after preoperative chemoradiotherapy who undergo either active surveillance or immediate surgery. Furthermore, it is suggested that after delayed resection surgical radicality can be achieved in nearly all patients with recurrent disease in the esophagus or surrounding lymph nodes that has been missed initially during clinical response evaluation. Also, distant dissemination rate (the percentage of patients who developed distant metastases) seems comparable after active surveillance and standard esophagectomy.[9] These results from small explorative studies support an active surveillance approach. Combined with the results from chapter 15, a large clinical trial comparing active surveillance with standard surgery is justified. The protocol of such trial is described in **chapter 19**. In this so called SANO-trial (Surgery As Needed for Oesophageal cancer), which is currently running in 12 Dutch centers, the (cost)effectiveness is examined of active surveillance after preoperative chemoradiotherapy using the diagnostic modalities described in chapter 15, as compared to standard surgery. If active surveillance and surgery as needed after preoperative chemoradiotherapy lead to non-inferior survival compared to standard esophagectomy, this organ-sparing approach can be implemented as a new standard of care. This would have important future implications for therapy. In **chapter 20** we describe outcomes in three typical patients without signs of residual disease after completion of preoperative chemoradiotherapy who underwent active surveillance, because they refused surgery or were considered medically unfit for surgery.

References

1. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
2. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
3. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062-7.
4. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
5. Peyre CG, Hagen JA, DeMeester SR et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549-56.
6. Talsma AK, Shapiro J, Looman CW et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. Ann Surg. 2014;260(5):786-93.
7. Shapiro J, van Klaveren D, Lagarde SM et al. Prediction of survival in patients with oesophageal or junctional cancer receiving neoadjuvant chemoradiotherapy and surgery. Br J Surg. 2016;103(8):1039-47.
8. Shapiro J, Biermann K, van Klaveren D et al. Prognostic value of pretreatment pathological tumor extent in patients treated with neoadjuvant chemoradiotherapy plus surgery for esophageal or junctional cancer. Ann Surg. 2017;265(2):356-62.
9. Taketa T, Xiao L, Sudo K et al. Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology. 2013;85(2):95-9.

Chapter 21B
Samenvatting in Nederlands

Slokdarmkanker is een agressieve ziekte en kent een slechte prognose. Op het moment van diagnose is de ziekte in veel gevallen al uitgezaaid naar andere organen, waardoor veel patiënten niet meer in aanmerking komen voor curatieve behandeling. Voor patienten zonder afstandsmetastasen is chirurgische verwijdering van de slokdarm en omliggende lymfeklieren een belangrijk onderdeel van de behandeling. Chirurgische technieken worden beschreven in **hoofdstuk 2**. Slokdarmoperaties kennen echter een aanzienlijke perioperatieve sterfte, potentieel ernstige postoperatieve complicaties en hebben een negatieve invloed op de kwaliteit van leven. Bovendien zal na operatie ongeveer een derde van alle patiënten alsnog overlijden door terugkeer van de ziekte. Om deze uitkomsten te verbeteren, is het nut van preoperatieve chemo- en/of radiotherapie (zogenaamde *multimodaliteit behandeling*) in vele onderzoeken getest (**hoofdstuk 3**). Recent heeft het Nederlandse 'ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study'(CROSS)-onderzoek aangetoond dat preoperatieve chemoradiotherapie, gevolgd door een slokdarmresectie, leidt tot een verbetering van de 5-jaarsoverleving, in vergelijking met alleen een operatie.[1] Deze behandeling is daarom nu eerste keus in veel landen. Dit proefschrift beschrijft de behandelconsequenties van deze nieuwe therapie. De resultaten van dit onderzoek zijn beschreven in twee delen; DEEL I richt zich op de implicaties van preoperatieve chemoradiotherapie voor chirurgische behandeling en DEEL II richt zich op een nieuw beleid van 'actieve surveillance', waarbij na preoperatieve chemoradiotherapie een slokdarmoperatiemogelijk achterwege kan worden gelaten bij een deel van de patiënten.

DEEL I. Implicaties van preoperatieve chemoradiotherapie voor operatieve behandeling

Multimodaliteit behandeling van slokdarmkanker is behandeling van eerste keus geworden in Westerse centra. Er zijn twee algemeen geaccepteerde preoperatieve behandelstrategieën. Allereerst preoperatieve chemoradiotherapie, meestal op basis van het CROSS-schema.[1, 2] Het alternatief, met name voor patiënten met het adenocarcinoom subtype, is perioperatieve of peroperatieve chemotherapie.[3, 4] In **hoofdstuk 4** wordt aangetoond dat eventuele verschillen in effect op overleving tussen beide behandelingen beperkt zijn. Wel heeft preoperatieve chemoradiotherapie in pathologisch opzicht voordelen in de zin van reductie van tumorgrootte en het aantal aangedane lymfklieren (zogenaamde *downstaging*). Eerder onderzoek heeft aangetoond dat uitgebreide lymfklierverwijdering leidt tot verbetering van het inschatten van de overleving, en waarschijnlijk ook een therapeutisch effect heeft bij patiënten die zijn behandeld met alleen chirurgie, d.w.z. zonder preoperatieve chemoradiotherapie.[5, 6] Het effect van preoperatieve chemoradiotherapie op de tumor en lymfeklieren vermindert deze prognostische en therapeu-

tische waarde van een uitgebreide lymfklierverwijdering. **Hoofdstuk 5-7** richten zich op het prognostische en therapeutische effect van lymfklierverwijdering. In **hoofdstuk 5** wordt een samenvatting van de literatuur over dit onderwerp gegeven. **Hoofdstuk 6** is een kritische reactie op een recente publicatie over dit onderwerp. In **hoofdstuk 7** wordt ingegaan op het oncologische voordeel (ten aanzien van de overlevingskans) van uitgebreide lymfklierverwijdering. In dit hoofdstuk wordt een chirurgische techniek met uitgebreide lymfklierverwijdering (transthoracale slokdarmverwijdering) vergeleken met een chirurgische techniek met beperkte lymfklierverwijdering (transhiatale slokdarmverwijdering) in een grote serie patiënten uit twee Nederlandse hoog-volume centra. De operatie met uitgebreide lymfklierverwijdering had wel een gunstig effect op overleving (met een prognostisch én therapeutisch voordeel) in de groep patiënten die alleen operatie onderging. Dit effect was echter afwezig in patiënten die preoperatieve chemoradiotherapie ondergingen. Concluderend vermindert het gebruik van preoperatieve chemoradiotherapie mogelijk de noodzaak tot uitgebreide lymfklierverwijdering. Daarom zou de keuze van operatietechniek na preoperatieve chemoradiotherapie ons inziens met name moeten afhangen van het bijbehorende risico op complicaties en de kwaliteit van leven, en niet zo zeer van de langetermijn overleving.

Hoofdstuk 8-10 richten zich op het effect van preoperatieve chemoradiotherapie op kwaliteit van leven. **Hoofdstuk 8** laat zien dat, hoewel de kwaliteit van leven verslechtert tijdens chemoradiotherapie, er geen nadelig effect meetbaar is van preoperatieve chemoradiotherapie op de postoperatieve kwaliteit van leven, in vergelijking met alleen chirurgie. **Hoofdstuk 9** gaat dieper in op het beloop van kwaliteit van leven direct na preoperatieve chemoradiotherapie, met als doel de timing van operatie te optimaliseren. Resultaten tonen dat kwaliteit van leven terugkeert op het niveau van vóór behandeling binnen 8 weken na het einde van de chemoradiotherapie, en dat sommige aspecten van kwaliteit van leven zelfs verbeteren na chemoradiotherapie, ten opzichte van de situatie vóór de behandeling. **Hoofdstuk 10** beschrijft de langetermijn effecten van preoperatieve chemoradiotherapie op kwaliteit van leven. In vergelijking met alleen chirurgie, was er geen sprake van verminderde kwaliteit van leven na preoperatieve chemoradiotherapie op lange termijn. Naast de verbetering in langetermijn overleving en de afwezigheid van invloed op korte termijn kwaliteit van leven (hoofdstuk 7), ondersteunen deze resultaten het gebruik van preoperatieve chemoradiotherapie volgens het CROSS-schema als behandeling van eerste keus. Echter, na langetermijn follow-up blijven de aspecten van kwaliteit van leven “fysiek functioneren” en “vermoeidheid” slechter dan voorafgaand aan de behandeling. Deze resultaten suggereren een langdurige negatieve invloed van chirurgie op kwaliteit van leven, ongeacht het gebruik van preoperatieve chemoradiotherapie.

Na preoperatieve chemoradiotherapie zijn zowel het aantal tumor positieve lymfklieren vóór als het aantal tumor positieve lymfklieren ná behandeling geassocieerd met

overleving.[7] Lymfklier status voorafgaand aan behandeling wordt in de huidige klinische praktijk bepaald met behulp van endoscopisch echo-onderzoek en PET-CT. Lymfklierstatus ná behandeling wordt bepaald door middel van analyse van het aantal tumor positieve lymfklieren in het resectiepreparaat. Een nieuw stadiëringssysteem om het aantal tumor positieve lymfklieren voorafgaand aan de behandeling nauwkeuriger te kunnen bepalen is gebaseerd op regressieve veranderingen ten gevolge van voorafgaande chemoradiotherapie (met name verlittekening) in het resectiepreparaat.[8] Eerder onderzoek heeft aangetoond dat dit nieuwe pathologische stadiëringssysteem een betere prognostische waarde heeft dan een systeem dat gebaseerd is op endoscopisch echo-onderzoek en PET-CT. In **hoofdstuk 11** valideren we deze bevindingen in een onafhankelijke serie patiënten uit een hoog-volume centrum (Keulen, Duitsland).

DEEL II. Actieve surveillance na preoperatieve chemoradiotherapie

Na behandeling met preoperatieve chemoradiotherapie, heeft 29% van de patiënten een complete respons in het resectiepreparaat.[2] Dit betekent dat er geen vitale tumorrest aantoonbaar is tijdens histopathologisch onderzoek. Deze bevindingen hebben ertoe geleid dat de noodzaak om alle patiënten na chemoradiotherapie te opereren ter discussie staat. Wij onderzoeken de haalbaarheid van een orgaansparende behandeling na het einde van de chemoradiotherapie. In deze strategie van zogenaamde actieve surveillance, zullen patiënten frequente klinische controles ondergaan na het einde van de chemoradiotherapie, in plaats van een standaard slokdarmoperatie. Een operatie zou dan alleen maar worden verricht bij patiënten met een sterke verdenking op, of een bewezen aanwezigheid van tumorrest in de slokdarm of omliggende lymfklieren, zonder uitzaaiingen op afstand. Voordat actieve surveillance veilig kan worden onderzocht, dient er betrouwbaar onderscheid te kunnen worden gemaakt tussen patiënten die direct moeten worden geopereerd (met vitale tumor) en patiënten die mogelijk baat hebben bij actieve surveillance (zonder vitale tumor). Daartoe dient de ziekte opnieuw te worden gestadieerd na chemoradiotherapie tijdens zogenaamde klinische respons evaluaties.

Hoofdstuk 12 toont een overzicht van de literatuur over de accuratesse van de meest gebruikte diagnostische tests voor herstadiëring na preoperatieve chemoradiotherapie. De resultaten suggereren dat endoscopie, endoscopisch echo-onderzoek en PET-CT onvoldoende in staat zijn om tumorrest na preoperatieve chemoradiotherapie aan te kunnen tonen. Echter, de meeste beschreven onderzoeken waren retrospectief en onderzochten slechts één diagnostische test. Ook waren de tests in de meeste onderzoeken niet verricht met als doel tumorrest aan te tonen om patiënten te selecteren voor een beleid van actieve surveillance. Dit kan de beschreven diagnostische accuratesse negatief hebben beïnvloed. **Hoofdstuk 13** beschrijft het studieprotocol van het diagnostische

preSANO-onderzoek. Dit prospectieve onderzoek test de nauwkeurigheid van klinische respons evaluaties en het optimale diagnostische pakket voor het klinisch aantonen van vitale tumorrest na preoperatieve chemoradiotherapie met endoscopie, endoscopische echografie met punctie van verdachte lymfklieren, en PET-CT. In totaal werden 219 patiënten uit 6 verschillende Nederlandse ziekenhuizen onderzocht die werden behandeld met preoperatieve chemoradiotherapie volgens het CROSS-schema. De belangrijkste resultaten worden beschreven in **hoofdstuk 14**. Respons evaluatie met endoscopie met bite-on-bite biopten en endoscopische echografie met punctie van verdachte lymfklieren detecteerde 90% van alle patiënten met substantiële tumorrest in de slokdarm na preoperatieve chemoradiotherapie. PET-CT detecteerde bovendien nieuwe zogenaamde intercurrente uitzaaiingen op afstand bij 9% van alle patiënten, waardoor hen een onnodige slokdarmoperatie bespaard is gebleven. **Hoofstuk 15** en **hoofstuk 16** beschrijven gedetailleerde analyses van respectievelijk endoscopische echografie metingen en PET-CT metingen. Hoewel endoscopische echografie metingen goed staat zijn tumorrest te detecteren (laag fout-positief percentage), wordt een groot deel van de patiënten zonder tumorrest onterecht als positief voor tumorrest geclassificeerd (hoog fout-positief percentage) (**hoofdstuk 15**). Vergelijkbare resultaten werden gevonden bij nadere analyse van de PET-CT data (**hoofdstuk 16**). Op basis hiervan concluderen wij dat de waarde van endoscopische echografie metingen en PET-CT metingen bij het aantonen van vitale tumorrest in de slokdarm na preoperatieve chemoradiotherapie beperkt is.

Een orgaansparende behandeling heeft theoretisch belangrijke voordelen voor patienten, omdat het risico op complicaties en vermindering van kwaliteit van leven wordt voorkómen. **Hoofdstuk 17** laat zien dat patiënten bereid zijn om een substantiële 5-jaars overlevingskans (gemiddeld 16%) in te leveren om het risico dat een slokdarmoperatie nodig is te verkleinen van 100% (zoals in de huidige praktijk) naar 35%, zoals wordt verwacht tijdens een (toekomstig) beleid van actieve surveillance. Verder zijn er twee groepen patiënten te onderscheiden. De eerste groep bestaat uit patiënten met een sterke voorkeur voor actieve surveillance, terwijl de tweede groep bestaat uit patiënten met een sterke voorkeur voor standaard operatie. Deze bevindingen kunnen clinici en patiënten in de toekomst helpen bij het maken van de keuze tussen actieve surveillance en standaard operatie, en komen gezamenlijke besluitvoering ten goede. De samenvatting van de literatuur in **hoofdstuk 18** toont vergelijkbare langetermijn overleving bij patiënten zonder aantoonbare ziekte na preoperatieve chemoradiotherapie die ofwel actieve surveillance ondergaan, ofwel standaard operatie. Bovendien suggereert de literatuur dat een uitgestelde operatie pathologisch radicaal kan worden verricht bij bijna alle patiënten bij wie tijdens actieve surveillance tumorrest wordt ontdekt in de slokdarm of in de omliggende lymfklieren. Ook het percentage patiënten dat uitzaaiingen op afstand ontwikkelt, lijkt vergelijkbaar na actieve surveillance en standaard operatie.[9] Deze resultaten van kleine exploratieve onderzoeken ondersteunen een beleid van actie-

ve surveillance. In combinatie met de resultaten van hoofdstuk 15, is een groot klinisch onderzoek naar actieve surveillance gerechtvaardigd. Van een dergelijk onderzoek is het onderzoeksprotocol beschreven in **hoofdstuk 19**. Deze zogenaamde SANO-trial (Surgery As Needed for Oesophageal cancer) loopt thans in 12 Nederlandse ziekenhuizen en onderzoekt de (kosten)effectiviteit van actieve surveillance na preoperatieve chemoradiotherapie met behulp van de diagnostische tests zoals beschreven in hoofdstuk 15, vergeleken met standaard operatie. Als actieve surveillance na preoperatieve chemoradiotherapie leidt tot een non-inferieure overleving vergeleken met standaard operatie, zal deze orgaansparende behandeling worden geïmplementeerd als nieuwe behandeling van eerste keus. In **hoofdstuk 20** beschrijven wij drie typische patiënten zonder aantoonbare tumorrest na het einde van preoperatieve chemoradiotherapie, die actieve surveillance ondergingen (in plaats van standaard operatie), omdat zij een operatie weigerden dan wel een sterk verhoogd operatierisico hadden.

Referenties

1. Shapiro J, van Lanschot JJ, Hulshof MC et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
2. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
3. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062-7.
4. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
5. Peyre CG, Hagen JA, DeMeester SR et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549-56.
6. Talsma AK, Shapiro J, Looman CW et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. Ann Surg. 2014;260(5):786-93.
7. Shapiro J, van Klaveren D, Lagarde SM et al. Prediction of survival in patients with oesophageal or junctional cancer receiving neoadjuvant chemoradiotherapy and surgery. Br J Surg. 2016;103(8):1039-47.
8. Shapiro J, Biermann K, van Klaveren D et al. Prognostic value of pretreatment pathological tumor extent in patients treated with neoadjuvant chemoradiotherapy plus surgery for esophageal or junctional cancer. Ann Surg. 2017;265(2):356-62.
9. Taketa T, Xiao L, Sudo K et al. Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology. 2013;85(2):95-9.

Chapter 22

Future perspectives

Esophageal cancer is currently the sixth most common cause of cancer death globally.[1] In Western countries, and the incidence of esophageal adenocarcinoma is growing rapidly. This aggressive disease has substantial impact on health-related quality of life, even in the curative setting. Over the last decades, survival after intentionally curative treatment for esophageal cancer has improved dramatically, as reflected by 5-year overall survival rates of 10% in the 1960's, 20% in the 1980's and 47% in the recent CROSS-trial. Nevertheless, about 50% of all patients still die from recurrent disease, mainly due to distant dissemination. Currently, no successful therapy for patients with disease recurrence after nCRT plus surgery is available. Future research should focus on less cancer, better quality of life and more cure.

Less cancer

Earlier diagnosis of (pre)malignant lesions would improve prognosis. However, screening and surveillance using the only currently available modality (endoscopy with biopsies) might not be feasible or cost-effective and can be accompanied by morbidity. Improved selection of high risk patients and the use of new minimally invasive screening modalities might allow for a future screening program. Currently, promising tools such as breath analysis and cytosponge are explored, but more research is necessary before these modalities can be applied in routine clinical practice.[2, 3]

Better quality of life

As is shown in part I of this thesis, esophagectomy has profound impact on patients' quality of life, irrespective of the use of neoadjuvant treatment. Minimally invasive and hybrid surgical techniques improve postoperative recovery, but it is questionable if this will reduce the long-term and lasting impact of surgery. Therefore, organ-sparing treatment strategies should be further explored. Definitive chemoradiotherapy without esophagectomy has been evaluated as such for patients with squamous cell carcinoma, reducing the long-term consequences of surgery. However, locoregional recurrence rates and long-term survival results have been suggested inferior, as compared to (nCRT followed by) surgery.[4] Based on the high pathologically complete response rate in the CROSS-trial, we propose testing of an active surveillance strategy after completion of nCRT, which is currently investigated in the French ESOSTRATE and Dutch SANO trials.[5, 6] In this new treatment strategy, patients are subjected to frequent clinical investigations after the completion of nCRT and (postponed) surgical resection is offered only to patients with a proven locoregional regrowth in the absence of distant metasta-

ses. It is estimated that an active surveillance strategy might reduce the need for esophagectomy in 30-40% of all patients, thereby reducing the lasting negative effects of surgery on HRQOL. This number might even increase when more effective neoadjuvant treatment will be developed (see below). However, oncological safety of active surveillance remains to be proven. Results of the SANO-trial are expected in 2023.

It is expected that the diagnostic accuracy of CREs will improve. Increased accuracy of CREs may reduce the number of patients who need postponed esophagectomy and the number of patients with irresectable regrowths detected during active surveillance. Promising results have been suggested by dynamic contrast-enhanced MRI and diffusion-weighted MRI, but these results need confirmation in larger diagnostic trials.[7, 8] Furthermore, molecular analysis of circulating cell-free tumor DNA (ctDNA) derived from blood samples might be useful. These so called *'liquid biopsies'* can be easily obtained from the patient with minimal burden and minimal potential harm. Liquid biopsies may be used to evaluate the presence of residual disease after nCRT and to monitor disease recurrence (locoregional and/or distant) during active surveillance with use of multiple assessments over time.[9, 10] Moreover, ctDNA analysis might be used to identify in an early phase which patients will develop distant disease recurrence during follow-up. These patients might be saved from a non-curative resection.

If the SANO-trial will show non-inferior survival after active surveillance compared to standard esophagectomy, future patients will be confronted with the choice between active surveillance or standard surgery. Despite the clinical advantages of active surveillance, there are concerns on whether this organ sparing approach can be applied to all patients with a clinically complete response. For some, the possible stress of frequent monitoring and invasive investigations might outweigh the possibility of unnecessary surgery.[11] Future research should focus on patients' motivation to opt (out) for active surveillance. An increased understanding of what truly matters to patients in making their treatment decisions will help physicians to attune to patients' needs. In this way shared decision making during clinical consultation can be facilitated. In addition, a decision aid for patients and physicians facing the complex decision between active surveillance or immediate surgery should be developed. This tool will further contribute to making well-balanced shared decisions.

More cure

Improvement of long-term survival might be achieved by improved efficacy of neoadjuvant treatment, application of adjuvant treatment or resection of metastatic disease.

After application of the CROSS-regimen followed by surgical resection, only 1% of all patients develop isolated recurrences within the radiotherapy field without distant dissem-

ination.[12] This indicates that intensification of the locally acting radiotherapy might improve outcome only in a small minority of all patients. Therefore, efficacy improvement of neoadjuvant treatment should focus on the systemic component in order to reduce the number of outfield recurrences. This might consist of adding chemotherapy cycles prior to nCRT. Although previous studies did not show any survival benefit of this strategy, a benefit for subgroups of patients with well or moderately differentiated tumors has been suggested.[13] Furthermore, new chemotherapy regimens such as the FLOT regimen have shown promising results in the perioperative setting (without radiotherapy).(14) Addition of this perioperative regimen to selected patients with high risk of distant dissemination might improve survival, but potentially at the cost of an increased toxicity.

The rapid development of targeted therapies has shown promising results in other types of cancer. Nevertheless, most trials investigating targeted therapies in esophageal cancer have not been successful. Only trials investigating HER2-inhibitors have shown a (modest) positive effect in patients with distant dissemination and should be further explored in patients with potentially curative disease.[15, 16] Potential future targets of therapeutic interest include impaired DNA repair mechanisms (e.g. CDK6) and dysregulation of cell cycle regulators.[17, 18]

In other cancers, immunotherapy using checkpoint inhibitors has shown substantial survival benefits. Especially cancers with high rates of somatic mutations, such as melanoma and lung cancer, have shown sensitivity for these new therapies. Interestingly, esophageal cancer is also characterized by a high number of somatic mutations, providing a rationale to study targeted immune therapy.[19] Explorative trials in metastatic esophageal cancer patients have shown promising results, with response rates to anti-PD-1 antibody pembroluzimab of 17%-40% and an acceptable adverse event rate.[20, 21]

Personalized immunotherapy, such as chimeric antigen-receptor T-cells or adoptive T-cell transfer of mutation specific T-cells, has been successful in other types of cancer.[22, 23] However, application of these therapies is in early development and requires considerable expertise.

Finally, in selected patients with oligometastatic esophageal cancer, multimodality treatment should be further explored as a potentially curative approach. Resection of a limited number of livermetastases from colorectal cancer is now considered standard treatment with 5-year survival rates of up to 60%.[24] Several small retrospective studies in patients with esophageal cancer have shown promising results, especially in patients with oligometastases treated with neoadjuvant or perioperative chemotherapy plus surgery.[25, 26] The feasibility of neoadjuvant chemo(radiotherapy) followed by hepatic resection and esophagectomy or gastrectomy is currently investigated in the LIME-trial, initiated by the Erasmus MC.

Based on the above mentioned therapeutic opportunities, the improvements made in the last decades can hopefully be continued in the near future.

References

1. Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D et al. The Global Burden of Cancer 2013. JAMA Oncol. 2015;1(4):505-27.
2. Benaglia T, Sharples LD, Fitzgerald RC, Lyratzopoulos G. Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for Barrett's esophagus. Gastroenterology. 2013;144(1):62-73 e6.
3. Kumar S, Huang J, Abbassi-Ghadi N et al. Mass Spectrometric Analysis of Exhaled Breath for the Identification of Volatile Organic Compound Biomarkers in Esophageal and Gastric Adenocarcinoma. Ann Surg. 2015;262(6):981-90.
4. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann oncol. 2016(27(suppl 5)):v50-v7.
5. Putora PM, Bedenne L, Budach W et al. Oesophageal cancer: exploring controversies overview of experts' opinions of Austria, Germany, France, Netherlands and Switzerland. Radiat Oncol. 2015;10:116.
6. Noordman BJ, Shapiro J, Spaander MC et al. Accuracy of detecting residual disease after CROSS neoadjuvant chemoradiotherapy for esophageal cancer (preSANO Trial): rationale and protocol. JMIR Res Protoc. 2015;4(2):e79.
7. Heethuis SE, van Rossum PS, Lips IM et al. Dynamic contrast-enhanced MRI for treatment response assessment in patients with oesophageal cancer receiving neoadjuvant chemoradiotherapy. Radiother Oncol. 2016;120(1):128-35.
8. van Rossum PS, van Lier AL, van Vulpen M et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. Radiother Oncol. 2015;115(2):163-70.
9. Carpinetti P, Donnard E, Bettoni F et al. The use of personalized biomarkers and liquid biopsies to monitor treatment response and disease recurrence in locally advanced rectal cancer after neoadjuvant chemoradiation. Oncotarget. 2015;6(35):38360-71.
10. Creemers A, Krausz S, Strijker M et al. Clinical value of ctDNA in upper-GI cancers: A systematic review and meta-analysis. Biochim Biophys Acta. 2017;1868(2):394-403.
11. Lamers RE, Cuypers M, de Vries M, van de Poll-Franse LV, Ruud Bosch JL, Kil PJ. How do patients choose between active surveillance, radical prostatectomy, and radiotherapy? The effect of a preference-sensitive decision aid on treatment decision making for localized prostate cancer. Urol Oncol. 2017;35(2):37 e9- e17.
12. Oppedijk V, van der Gaast A, van Lanschot JJ et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol. 2014;32(5):385-91.
13. Shimodaira Y, Slack RS, Harada K et al. Influence of induction chemotherapy in trimodality therapy-eligible oesophageal cancer patients: secondary analysis of a randomised trial. Br J Cancer. 2017.
14. Al-Batran SE, Hofheinz RD, Pauligk C et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17(12):1697-708.
15. Waddell T, Chau I, Cunningham D et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol. 2013;14(6):481-9.
16. Lordick F, Kang YK, Chung HC et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol. 2013;14(6):490-9.

17. Turner NC, Huang Bartlett C, Cristofanilli M. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015;373(17):1672-3.
18. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382-92.
19. Alexandrov LB, Nik-Zainal S, Wedge DC et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415-21.
20. Kudo T, Hamamoto Y, Kato K et al. Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. Lancet Oncol. 2017;18(5):631-9.
21. T D, SA P-P, Jalal SI et al. Updated Results for the Advanced Esophageal Carcinoma Cohort of the Phase 1b KEYNOTE-028 Study of Pembrolizumab (MK-3475). Gastrointestinal Cancers Symposium (ASCO-GI). 2016.
22. Maude SL, Frey N, Shaw PA et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-17.
23. Tran E, Turcotte S, Gros A et al. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. Science. 2014;344(6184):641-5.
24. Abdalla EK, Vauthey JN, Ellis LM et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Annals of surgery. 2004;239(6):818-25; discussion 25-7.
25. Huddy JR, Thomas RL, Worthington TR, Karanjia ND. Liver metastases from esophageal carcinoma: is there a role for surgical resection? Dis Esophagus. 2015;28(5):483-7.
26. Schmidt T, Alldinger I, Blank S et al. Surgery in oesophago-gastric cancer with metastatic disease: Treatment, prognosis and preoperative patient selection. Eur J Surg Oncol. 2015;41(10):1340-7.

Appendices

List of publications

W. De Jager, S.J. Vastert, G. Mijnheer, B.J. Noordman, W. Kuis, B.J. Prakken, N.M. Wulffraat. Recombinant IL-1RA restores the IL-18-NK cell axis in steroid naïve systemic Juvenile Idiopathic Arthritis. Submitted for publication.

S.J. Vastert, W. de Jager, B.J. Noordman, D. Holzinger, W. Kuis, B.J. Prakken, N.M. Wulffraat. Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. Arthritis Rheumatol. 2014;66(4):1034-43.

A.J.N. Bittermann, I. Wegner, B.J. Noordman, R. Vincent, G.J.M.G. van der Heijden. An introduction of genetics in otosclerosis: a systematic review. Otolaryngol Head Neck Surg. 2014;150(1):34-9.

B.J. Noordman, E.A. van Beeck Calkoen, B.I. Witte, S.T. Goverts, E.F. Hensen, P. Merkus. Prognostic factors for sudden drops in hearing level after minor head injury in patients with enlarged vestibular aqueducts: a systemic review. Otol Neurotol. 2015;36(1):4-11.

B.J. Noordman, C.C. Bommeljé, T. Smith, R.H. Heijmen, J.A.D. Jol. Linker nervus recurrens parese ten gevolge van een staande ruptuur van een aneurysma van de arcus aortae. Ned Tijdschr KNO-heelkunde. 2015;2:79-82.

L. van Dijk, B.J. Noordman, K.A. Hartholt, J.J.G. Scheepers. A young female with a jejunal intussusception. BMJ Case Rep. 2015 Nov 25.

B.J. Noordman, E.F.I. Comans, P. Lips, R.N.P.M. Rinkel. False-positive uptake of I-124 in a laryngeal cyst mimicking thyroid remnant after thyroidectomy and I-131 therapy for follicular thyroid carcinoma. Clin Nucl Med. 2014;39(10):898-9.

T. van Gorkom, B.J. Noordman, M. van der Elst, T. van Ginhoven. Acute traumatische epifysiolys van de heupkop bij kinderen. Ned Tijdschr Geneeskd. 2015;159:A8238.

B.J. Noordman, K.A. Hartholt, J.A. Halm. Simultaneous, bilateral fracture of the triquetral bone: a case report. BMJ Case Rep. 2015 Sep 21.

B.J. Noordman, B.P.L. Wijnhoven, J.J.B. van Lanschot. Nauwkeurigheid van het aantonen van tumorrest na neoadjuvante chemoradiotherapie bij het oesofaguscarcinoom; het preSANO-onderzoek. Ned Tijdschr Geneeskd. 2014;158:A8189.

B.J. Noordman, J. Shapiro, B.P.L. Wijnhoven, J.J.B. van Lanschot. Nauwkeurigheid van het aantonen van tumorrest na neoadjuvante chemoradiotherapie bij het oesophaguscarcinoom; de preSANO-trial. Ned Tijdschr Oncol. 2015;12:78-84.

B.J. Noordman, J. Shapiro, B.P.L. Wijnhoven, J.J.B. van Lanschot. Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO trial). JMIR Res Protoc. 2015;4(2):e79.

B.J. Noordman, J.J.B. van Lanschot. The role of lymphadenectomy in oesophageal cancer surgery. Nat Rev Clin Oncol. 2015;12(6):315-6.

B.J. Noordman, B.P.L. Wijnhoven, J.J.B. van Lanschot. The optimal surgical approach for esophageal cancer in the era of MIE and neoadjuvant therapy. Dis Esophagus. 2016;29(7):773-9.

B.J. Noordman, B.P.L. Wijnhoven. Dag van operatie en prognose van slokdarmkanker. Ned Tijdschr Geneeskd. 2016;160:D620.

B.J. Noordman, S.R. Markar, H. Mackenzie, J.M. Findlay, P.R. Boshier, M. Ni, E.W. Steyerberg, A. van der Gaast, M.C.C.M. Hulshof, N. Maynard, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, J.V. Reynolds, J.J.B. vann Lanschot, G.B. Hanna. Multimodality treatment for esophageal adenocarcinoma: multi-center propensity-score matched study. Ann Oncol. 2017;28(3):519-27.

B.J. Noordman, D. van Klaveren, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, S.S. Gisbertz, S.M. Lagarde, A. van der Gaast, M.C.C.M. Hulshof, K. Biermann, E.W. Steyerberg, J.J.B. van Lanschot. Impact of surgical approach on long-term survival in esophageal adenocarcinoma patients with or without neoadjuvant chemoradiotherapy. Ann Surg. 2018;267(5):892-897.

B.J. Noordman, M.G.E. Verdam, S.M. Lagarde, M.C.C.M. Hulshof, P. van Hagen, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, H.W.M. van Laarhoven, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R. Busch, F.J.W. ten Kate, G.J.M. Creemers, C.J.A. Punt, J.Th.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, E.W. Steyerberg, A. van der Gaast, M.A.G. Sprangers, J.J.B. van Lanschot. Effect of neoadjuvant chemoradiotherapy on health-related quality of life in esopageal or junctional cancer: results from the randomized CROSS trial. J Clin Oncol. 2018;36(3):268-75

B.J. Noordman, M.G.E. Verdam, S.M. Lagarde, M.C.C.M. Hulshof, J.Shapiro, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, G.A.P. Nieuwenhuijzen, J.J. Bonenkamp, M.A. Cuesta, J.Th.M. Plukker, E.J. Spillenaar Bilgen, E.W. Steyerberg, A. van der Gaast, M.A.G. Sprangers, J.J.B. van Lanschot. Impact of neoadjuvant chemoradiotherapy on long-term health related quality of life in esopageal or junctional cancer: results from the randomised cross trial. Ann Oncol. 2018;29(2):445-451.

B.J. Noordman, B.P.L. Wijnhoven, S.M. Lagarde, M.C.W. Spaander, R. Valkema, J.J.B. van Lanschot. Orgaansparende behandeling bij slokdarm carcinoom: haalbaar en verantwoord? Ned Tijdschr Geneeskd. 2017;161(0):D1818.

B.J. Noordman, B.P.L. Wijnhoven, S.M. Lagarde, K. Biermann, A. van der Gaast, M.C.W. Spaander, R. Valkema, J.J.B. van Lanschot. Active surveillance in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal or junctional cancer. Dis Esophagus. 2017;30(12):1-8.

B.J. Noordman, B.P.L. Wijnhoven, S.M. Lagarde, J.J. Boonstra, P.P.L.O. Coene, J.W. Dekker, M. Doukas, A. van der Gaast, J. Heisterkamp, E.A. Kouwenhoven, G.A.P. Nieuwenhuijzen, J.P.E.N. Pierie, C. Rosman, J.W. van Sandick, M.J.C. van der Sangen, M.N. Sosef, M.C.W. Spaander, R. Valkema, E.S. van der Zaag, E.W. Steyerberg, J.J.B. van Lanschot. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial. Accepted, BMC Cancer. 2018;18(1):142.

B.J. Noordman, E.W. de Bekker-Grob, P.P.L.O. Coene, E. van der Harst, S.M. Lagarde, J. Shapiro, B.P.L. Wijnhoven, J.J.B. van Lanschot. Patients' preferences for treatment after neoadjuvant chemoradiotherapy for oesophageal cancer: a discrete choice experiment. Br J Surg. 2018 Jun 27. [Epub ahead of print]

B.J. Noordman, S. Brinkmann, A.H. Hölscher, K. Biermann, D. van Klaveren, E. Bollschweiler, K. Pütz, J.J.B. van Lanschot, U. Drebber. External validation of pre-treatment pathological tumour extent in patients with neoadjuvant chemoradiotherapy plus surgery for oesophageal cancer. Submitted for publication.

B.J. Noordman, M.C.W. Spaander, R. Valkema, B.P.L. Wijnhoven, M.I. van Berge Henegouwen, J. Shapiro, K. Biermann, A. van der Gaast, R. van Hillegersberg, M.C.C.M. Hulshof, K.K. Krishnadath, S.M. Lagarde, G.A.P. Niewenhuijzen, L.E. Oostenbrug, P.D. Siersema, E.J. Schoon, M.N. Sosef, E.W. Steyerberg, J.J.B. van Lanschot. A prospective study on the accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO trial). Lancet Oncol. 2018 May 31. [Epub ahead of print]

B.J. Noordman, J. Shapiro, B.P.L. Wijnhoven, M.C.C.M. Hulshof, A. van der Gaast, J.J.B. van Lanschot. Chemoradiation in esophagogastric junction cancer. In: Adenocarcinoma of the esophagogastric junction: from Barrett's esophagus to cancer. S. Giacopuzzi (ed.). Verona, Italy, 2017, pp 149-161.

B.J. Noordman, S.M. Lagarde, B.P.L. Wijnhoven, J.J.B. van Lanschot. Surgical approaches to remove the esophagus: open. In: Shackelford's surgery of the alimentary tract, 8th edition. C.J. Yeo (ed.). Philedelphia, USA, 2017.

B.J. Noordman, M.G.E. Verdam, B. Onstenk, J. Heisterkamp, W.J.B.M. Jansen, I.S. Martijnse, S.M. Lagarde, B.P.L. Wijnhoven, C. Acosta, A. van der Gaast, M.A.G. Sprangers, J.J.B. van Lanschot. Quality of life during and after completion of neoadjuvant chemoradiotherapy for oesophageal and junctional cancer. Submitted for publication.

B. M. Eyck, B.D. Onstenk, B.J. Noordman, D. Nieboer, M.C.W. Spaander, R. Valkema, S.M. Lagarde, B.P.L. Wijnhoven, J. J.B. van Lanschot. The accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for esophageal cancer by endoscopy with biopsy, EUS and 18F-FDG PET: a systematic review and meta-analysis. Submitted for publication.

R.D. van der Bogt, B.J. Noordman, K.K. Krishnadath, C.A.M. Roumans, E.J. Schoon, L.E. Oostenbrug, P.D. Siersema, F.P. Vleggaar, J.J.B. van Lanschot, M.C.W. Spaander. Endosonographic measurements of tumour thickness and tumour area to detect residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer. Submitted for publication.

M.J. Valkema, B.J. Noordman, B.P.L. Wijnhoven, M.C.W. Spaander, S.M. Lagarde, R.J. Bennink, W.M.J. Schreurs, M.J. Roef, M.G.G. Hobbelink, M.J.R. Janssen, L.H. Graven, J.J.B. van Lanschot, R. Valkema. Accuracy of 18F-FDG PET/CT in predicting residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer. Submitted for publication.

B.J. Noordman, J.J.B. van Lanschot. Reply to "Radiation is not a solution for suboptimal surgery. A response to the conclusions drawn from the Impact of Surgical Approach on Long-term Survival in Esophageal Adenocarcinoma With or Without Neoadjuvant Chemoradiotherapy study." Submitted for publication.

PhD portfolio

Courses

2014	Research Integrity, Erasmus MC, Rotterdam	0,6
2014	BROK cursus	1,5
2015	Regression Analysis for clinicians, NIHES, Rotterdam	1,4
2015	Biostatistics for clinicians, NIHES, Rotterdam	0,7
2015	Center for Patient Oriented research course, Erasmus MC, Rotterdam	0,3

Oral presentations

2014	Dutch Upper-GI Cancer Group studieavond - Lange termijn resultaten CROSS trial en preSANO trial.	1
	Wetenschapsdag Heelkunde Erasmus MC - Lange termijn resultaten CROSS trial.	1
2015	European Society for Diseases of the Esophagus - The effect of lymphadenectomy on long-term survival in patients with esophageal carcinoma, treated with neoadjuvant therapy plus surgery.	1
	European Society for Diseases of the Esophagus - Multimodality treatment for hepatic metastases of esophageal or gastro-esophageal junctional carcinoma	1
2016	EUS-platform - Nauwkeurigheid van het aantonen van tumorrest na neoadjuvante chemoradiotherapie bij het oesofaguscarcinoom; het preSANO-onderzoek.	1
	International Society for Diseases of the Esophagus - Multimodality treatment for esophageal adenocarcinoma: multi-center propensity-score matched study.	1
	International Society for Diseases of the Esophagus – Long-term quality of life after neoadjuvant chemoradiation followed by surgery compared to surgery alone for esophageal cancer.	1
	International Society for Diseases of the Esophagus – Short-term quality of life after neoadjuvant chemoradiation followed by surgery compared to surgery alone for esophageal cancer.	1
	Nederlandse Vereniging voor GastroEnterologie najaarsvergadering - F-18-FDG PET/CT in the evaluation of tumour response after neoadjuvant chemoradiotherapy (nCRT) in locally advanced oesophageal cancer.	1
	Dutch Upper-GI Cancer Group studieavond – SANO-trial.	1
	Nederlandse Vereniging voor GastroEnterologie najaarsvergadering - Quality of life after neoadjuvant chemoradiation followed by surgery compared to surgery alone for esophageal cancer.	1
	European Society for Diseases of the Esophagus - Impact of surgical approach on long-term survival in esophageal adenocarcinoma patients with or without neoadjuvant chemoradiotherapy.	1
2017	Digestive Disease Days – Surgery As Needed for Oesophageal (SANO) cancer.	1
	European Society for Diseases of the Esophagus - Patients' preferences for treatment after neoadjuvant chemoradiotherapy for oesophageal cancer: a discrete choice experiment.	1
2018	Wetenschapsdag Heelkunde Erasmus MC - preSANO trial	1

Conferences and seminars

2014	Dutch Upper-GI Cancer Group	0,3
	ISDE Vancouver	1
	Wetenschapsdag Heelkunde	0,3
2015	NVGE voorjaarsdagen	1
	ESDE Stockholm	1
	Chirurgendagen	1
	DUCG Congres	0,3
	DUCG avond	0,3
	Daniël den Hoed dag	0,3
2016	NVGE najaarsdagen	1
	DUCG avond	0,3
	Chirurgendagen	1
	ISDE Singapore	1
	ESDE München	1
	Symposium Zorgevaluatie	0,3
2017	ESDE Utrecht (2 posters)	1
	DDD Veldhoven	1
	Chirurgendagen	0,3
	Symposium Zorgevaluatie	0,3
2018	Wetenschapsdag Heelkunde	0,3

Teaching

2014	EHBO examens	0,25
	Kennismaking beroepspraktijk	1
2015	EHBO examens	0,25
	Supervision master thesis	2
	Kennismaking beroepspraktijk	1
2016	EHBO examens	0,25
	Supervision master thesis (2x)	4
2017	EHBO examens	0,25
	Supervision master thesis	2

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About the author

Bo Jan Noordman werd geboren op 9 juni 1986 in Leiden als eerste van twee zonen en twee dochters. Op zijn 7e verhuisde hij naar Heiloo (Noord-Holland). In 2005 behaalde hij zijn Eindexamen aan het Murmelliusgymnasium in Alkmaar. Daarna begon hij de studie Biomedische Wetenschappen aan de Universiteit Utrecht. Hij behaalde zijn bachelordiploma Biomedisch Wetenschappen, waarna hij de Utrechtse SUMMA-opleiding volgde, een vierjarige selectieve master die opleidt tot basisarts en klinisch onderzoeker. Na het behalen van het artsendiploma richtte hij zich enkele maanden fulltime op zijn eigen medische uitzendbureau Auxilio, dat hij tijdens zijn studententijd had opgezet.

Om zich volledig te kunnen richten op een loopbaan als medisch specialist trok hij zich in 2013 terug uit het bedrijfsleven en begon hij als arts-assistent algemene chirurgie in het Renier de Graaf Gasthuis te Delft. Na een jaar lang met veel plezier klinische ervaring te hebben opgedaan, begon hij in 2014 als arts-onderzoeker bij de slokdarmoncologiegroep van het Erasmus MC (promotor: prof.dr. J.J.B. van Lanschot, copromotor: dr. B.P.L. Wijnhoven). Van januari 2018 tot en met juni 2018 werkte hij als arts-assistent chirurgie in het Ikazia Ziekenhuis, om vervolgens vanaf juli 2018 aan de opleiding tot chirurg te beginnen in het Franciscus Gasthuis & Vlietland, die zal worden vervolgd in het Erasmus MC.