Esophageal Cancer

Towards Active Surveillance

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Chapter 1

General introduction and outline of the thesis

General introduction

Yearly, esophageal cancer is diagnosed in approximately 572,000 patients worldwide and in approximately 2,300 patients in the Netherlands.[1-4] The prognosis of esophageal cancer remains poor, nearly reaching 25% after five years. Two histological subtypes which mainly occur are squamous cell carcinoma and adenocarcinoma. Worldwide, squamous cell carcinoma represents 84% of all cases and adenocarcinoma 15% of all cases (and the rest of histological subtypes consisting of small cell carcinoma and other subtypes). Geographically, squamous cell carcinoma is the most common subtype in all regions worldwide except for Northern America, Northern Europe and Oceania.[2 3] This can mainly be explained by the risk factors specifically associated with both subtypes. The incidence of squamous cell carcinoma has been demonstrated to be increased due to low vitamin A and C, zinc deficiencies, infections (*e.g.* human papillomavirus) and tobacco use. The most important factor for adenocarcinoma is obesity, resulting in gastric reflux and consequently a Barrett's esophagus. In a Barrett's esophagus, the regular cell architecture is disrupted, possibly progressing in esophageal adenocarcinoma.[4]

The treatment of choice depends on the stage of the tumor at the time of diagnosis. In patients who have early staged tumors, an endoscopic resection can suffice (*i.e.* endoscopic mucosal resection or endoscopic submucosal dissection), avoiding major surgery and loss of function of the organ.[5, 6] Most patients present with locally advanced disease. For these patients, standard treatment generally consists of neoadjuvant chemo(radio)therapy followed by esophagectomy.[7] Patients who have disseminated disease will be treated with palliative intent, consisting of, among others, palliative chemotherapy, palliative radiotherapy, palliative intraluminal stenting of the esophagus or best supportive care.[8]

(Neo)adjuvant treatment for locally advanced esophageal cancer consists of either preoperative chemoradiotherapy or perioperative chemotherapy. Several trials have been performed advocating the use of chemoradiotherapy prior to surgery for patients with locally advanced esophageal cancer.[9-18] The first trial that was performed and reported survival benefit for patients undergoing neoadjuvant chemoradiotherapy followed by surgery compared to surgery alone was published in 1996.[16] This study was criticized, however, for its limited sample size of only 55 patients in each group. Furthermore, this study reported poor survival for patients undergoing surgery alone (five-year

survival <5%). Another trial reporting survival benefit was the Chemoradiotherapy for Oesophageal cancer followed by Surgery Study (CROSS)-trial.[17, 19] In this trial, 366 patients were randomized and underwent either five cycles of chemoradiotherapy consisting of carboplatin, paclitaxel and concurrent 41.4 Gray radiotherapy in 23 fractions followed by surgery or surgery alone. Patients undergoing surgery alone had five-year survival of 33% versus 47% for patients undergoing neoadjuvant chemoradiotherapy followed by surgery. The regimen was proven to be mild concerning toxicity (*e.g.* grade 3-4 neutropenia was observed in only 2% of patients). Furthermore, the rate of resections with a microscopically tumor-free resection margin (≥1mm) increased from 69% to 92% and a pathologically complete response rate of 29% was reported (23% for patients with adenocarcinoma and 49% for patients with squamous cell carcinoma). After the publication of the CROSS-trial, chemoradiotherapy prior to surgery was implemented in large parts of the world as a standard treatment for locally advanced esophageal cancer.

Perioperative chemotherapy has been assessed in several randomized trials as well.[20-24] One landmark trial assessing the efficacy of perioperative chemotherapy followed by surgery was the Medical research council Adjuvant Gastric Infusional Chemotherapy (MAGIC)-trial.[21] Patients with adenocarcinoma of the stomach (and to a lesser extent of the esophagogastric junction or distal esophagus) were randomized between perioperative chemotherapy (three preoperative and three postoperative cycles of epirubicin, cisplatin and fluorouracil) followed by surgery or surgery alone. Patients undergoing chemotherapy followed by surgery had a statistically significantly improved overall survival compared to patients undergoing surgery alone (five-year survival of 36% versus 23%). The use of perioperative chemotherapy for esophageal adenocarcinoma has been implemented as part of standard treatment after the publication of the MAGIC-trial in some countries (*e.g.* the United Kingdom). A recently published trial compared chemotherapy according to the MAGIC regimen to the FLOT regimen (four preoperative and four postoperative cycles of fluorouracil, leucovorin, oxaliplatin and docetaxel).[20] After inclusion of 716 patients, the authors reported that the FLOT-regimen resulted in grade 3-4 neutropenia in 51% of patients (compared to 39% of patients undergoing ECF/ECX chemotherapy). The five-year overall survival was 36% for patients undergoing chemotherapy according to MAGIC and 45% for patients undergoing chemotherapy according to FLOT. In several countries, FLOT has replaced MAGIC ever since.

Whether patients with adenocarcinoma of the esophagus or esophagogastric junction should be treated in the neoadjuvant setting with chemoradiotherapy or chemotherapy is not yet clear. Although some indirect analyses suggested a modest benefit for chemoradiotherapy over chemotherapy, no direct and sufficiently-powered randomized trials have been completed.[25-27] The currently ongoing Neo-Aegis and ESOPEC trials are comparing MAGIC or FLOT chemotherapy versus CROSS chemoradiotherapy for patients with locally advanced esophageal adenocarcinoma.[28, 29] The results of these studies will definitively report whether there exists a superiority for either neoadjuvant treatment.

Following neoadjuvant therapy, patients undergo esophagectomy according to standard treatment. This is, however, associated with substantial morbidity, mortality and lasting symptoms.[30-32] Furthermore, a lasting deterioration is described in health-related quality of life.[33, 34] An esophagectomy can be performed in two different approaches: the transhiatal or the transthoracic procedure. The transhiatal procedure aims to decrease postoperative risks and lacks an extended lymphadenectomy. A thoracotomy is avoided and the anastomosis is in the neck. With the transthoracic approach, an extended lymphadenectomy can be performed, requiring an additional thoracotomy. The transthoracic approach can be further subdivided in the Ivor Lewis esophagectomy, with an intrathoracic anastomosis, and the McKeown esophagectomy, with a cervical anastomosis. The transthoracic approach showed a trend towards better survival compared to the transhiatal approach in patients undergoing primary esophagectomy.[35]
Over time, several minimally invasive techniques have evolved.[36] It is hypothesized that by reducing the invasiveness of the procedure, postoperative complications, quality-of-life and possibly even overall survival can be improved. Both totally minimally invasive esophagectomy (laparoscopy and thoracoscopy) and hybrid esophagectomy (laparoscopy and thoracotomy) are reported to have advantages over the open esophagectomy procedure (laparotomy and thoracotomy), *e.g.* a decrease in pneumonia and major pulmonary complications.[37, 38] Since a thoracoscopically challenging intrathoracic anastomosis is avoided with the hybrid technique, it was hypothesized that this could decrease the anastomotic leakage rate in hybrid versus totally minimally invasive technique. Whether there exists superiority for either hybrid or totally minimally invasive esophagectomy is not yet clear.

As previously reported, 29% of the patients who undergo neoadjuvant chemoradiotherapy have a pathologically complete response in the resection specimen.[17] These patients respond so well to neoadjuvant chemoradiotherapy that no vital tumor cells can be detected in the resection specimen of the esophagus. Therefore, the need for esophagectomy in every patient with esophageal cancer after neoadjuvant chemoradiotherapy has been topic of debate, especially when taking in mind the high morbidity and complication rate of esophagectomy. Possibly, an active surveillance strategy could be implemented for patients with a clinically complete response. In patients with a clinically complete response, no vital tumor cells are detected using a combination of diagnostics. In an active surveillance strategy, clinical response evaluations are performed regularly and esophagectomy is only performed in those patients with pathologically proven or highly suspected residual disease, without the presence of distant metastases. The advantages of avoiding unbeneficial esophagectomy seem clear. An active surveillance comes, however, with some disadvantages as well. First of all, if patients remain in active surveillance while having undetected residual disease, there is a potential risk for substantial delay in detecting locoregional recurrences which appear to be unresectable at time of detection. Due to the longer presence of undetected residual disease in the esophagus, it could also be that distant metastases develop out of this residual disease resulting in an increased distant dissemination rate for patients undergoing active surveillance.

A previous meta-analysis reported that preoperative diagnostics have insufficient individual sensitivity or specificity to accurately detect residual disease in patients with esophageal cancer after neoadjuvant chemoradiotherapy.[39] The preSANO-trial assessed a combination of diagnostics to detect residual esophageal cancer.[40, 41] It was reported that 90% of patients with a Tumor Regression Grade (TRG) 3-4 (>10% residual vital tumor cells) were adequately detected. This means, however, that 10% of the patients with substantial residual tumor were still missed. In the preSANO-trial, it is assumed that patients with a minor residual TRG2 tumor (≤10% tumor cells) can be safely and timely detected and resected after they progressed to TRG3-4 residual tumors. If TRG2 residual tumors are taken into account as well, 23% of patients were still missed. Furthermore, the results of the clinical response evaluations were correlated with the TRG of the primary tumor in the esophageal resection specimen, not taking into account patients with isolated nodal disease (ypT0N1-3). Since 10-23% of residual tumors are still missed with current clinical response evaluations, concerns on overall survival for patients undergoing active surveillance with a clinically complete response remain. Some

retrospective studies assessed overall survival in these patients and most studies reported a comparable overall survival between active surveillance and standard esophagectomy.[42-47] These studies, however, all have insufficient individual power to draw robust conclusions and the retrospective nature of these studies inevitably results in a selection bias. The accuracy of the combined diagnostic set used in the preSANO-trial together with retrospective studies on overall survival for patients undergoing active surveillance were considered sufficient to initiate the Surgery As Needed for Oesophageal cancer (SANO)-trial. This is a multicenter stepped-wedge cluster randomized non-inferiority trial comparing active surveillance versus standard surgery for patients with esophageal cancer and a clinically complete response after neoadjuvant chemoradiotherapy.[48] In this trial, patients undergo neoadjuvant chemoradiotherapy according to the CROSS-regimen. (Figure 1) Four to six weeks after completion of neoadjuvant chemoradiotherapy, patients undergo a first clinical response evaluation consisting of endoscopy with bite-on-bite biopsies. If no tumor is detected, patients will undergo a second response evaluation consisting of PET-CT followed by endoscopy with bite-on-bite biopsies and endoscopic ultrasound with fine-needle aspiration of suspected lymph nodes. Patients will be considered a clinically complete responder if no locoregional or distant residual tumor is detected during both response evaluations. Subsequently, patients will undergo either active surveillance or standard surgery, according to stepped-wedge cluster randomization (*i.e.* randomization on institute level instead of randomization at patient level). The primary endpoint of the SANO-trial is overall survival. The recruitment phase has been completed at December 2020 and the first analyses on overall survival will be initiated after a minimal follow-up of two years. The results of the SANO-trial will point out whether active surveillance can be adopted as part of standard treatment for patients with locally advanced esophageal cancer and a clinically complete response after neoadjuvant chemoradiotherapy.

Outline of the thesis

This thesis consists of three parts. Several studies aiming to improve clinical response evaluations after neoadjuvant chemoradiotherapy will be described in **part I**. Hybrid and totally minimally invasive esophagectomy will be compared in **part II**. The aims to improve future shared decision making and the most recent data on overall survival after active surveillance will be described in **part III** of this thesis.

Part I: Improving clinical response evaluations

Clinical response evaluations are performed after neoadjuvant chemoradiotherapy. An overview of the different neoadjuvant therapies is discussed in **chapter 2.** Since 23% of the residual tumors is still missed after neoadjuvant chemoradiotherapy in the preSANO-trial, the locations of these undetected residual tumors in the resection specimens are assessed in **chapter 3.** Subsequently, the value of endoscopic evaluation of the esophagus for detection of residual esophageal disease and the value of endoscopic ultrasound with fine-needle aspiration for detection of malignant lymph nodes is assessed in **chapters 4 and 5**, respectively. The value of PET-CT for detecting residual disease during active surveillance is assessed in **chapter 6**.

Part II: Comparing surgical approaches

Both totally minimally invasive and hybrid esophagectomy have been reported to have advantages over open esophagectomy in randomized trials. It is not clear, however, whether there exists superiority for either totally minimally invasive esophagectomy or hybrid esophagectomy. Postoperative complications and lasting symptoms after both techniques are compared in **chapters 7 and 8**, respectively.

Part III: Towards active surveillance

Active surveillance is a strategy which might partly replace standard surgery in a subgroup of patients with a major response to neoadjuvant chemoradiotherapy. An overview of the history and the route towards active surveillance is described in **chapter 9.** Predictors for poor quality of life after neoadjuvant chemoradiotherapy and esophagectomy are described in **chapter 10**. A systematic review of all existing decision aids in cancers with active surveillance as treatment option is presented in **chapter 11**. In **chapter 12,** preferences between active surveillance or standard esophagectomy of

patients who had undergone esophagectomy themselves is described. Overall survival of patients undergoing active surveillance or standard surgery is described in **chapter 13 and chapter 14**. An update of the currently ongoing SANO-protocol is described in **chapter 15**.

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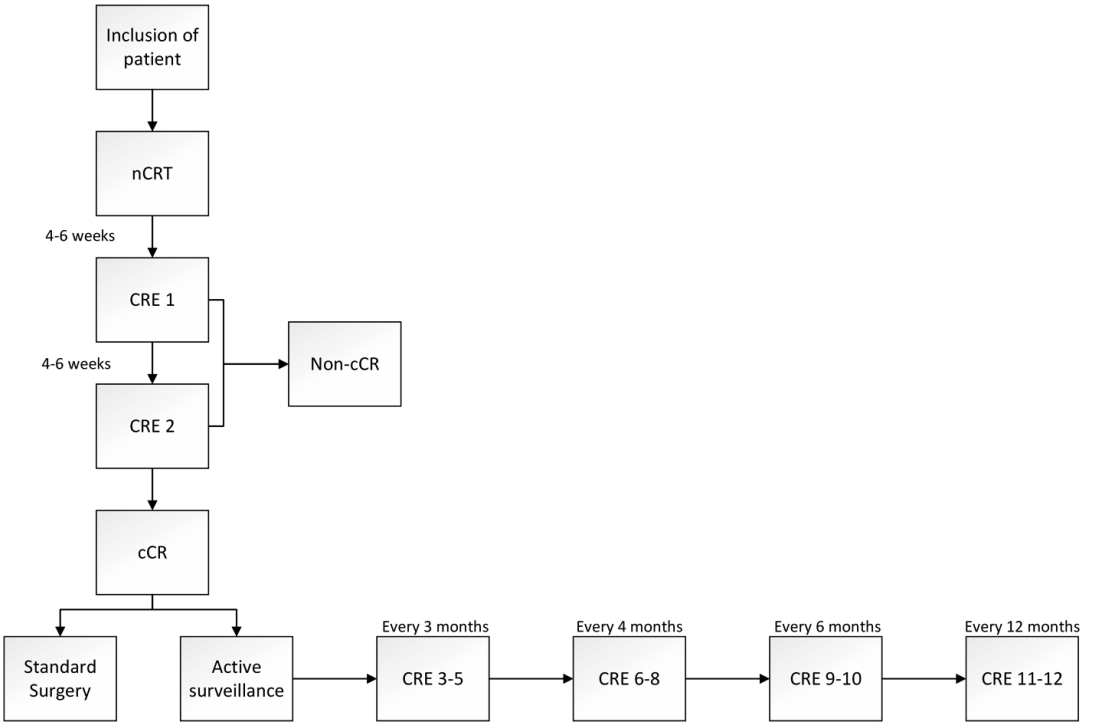

Figure 1. Schematic overview of the SANO-trial, comparing active surveillance versus standard surgery in patients with esophageal cancer and a clinically complete response after neoadjuvant chemoradiotherapy. Patients in whom no residual tumor is detected after neoadjuvant chemoradiotherapy are considered a clinically complete responder, patients who do not have a clinically complete response (non-cCR) undergo esophagectomy if no distant metastases are detected. If patients have residual disease at CRE 3-12, postponed esophagectomy will be performed if no distant metastases are detected and no subsequent CREs will be performed. nCRT: neoadjuvant chemoradiotherapy, CRE: clinical response evaluation, cCR: clinically complete responder.

Part I

Improving clinical response evaluations

2

Chapter 2

The optimal neoadjuvant treatment of locally advanced esophageal cancer

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Abstract

Esophagectomy is the cornerstone of intentionally curative treatment in patients with locally advanced esophageal cancer. Neoadjuvant treatments have been introduced to minimize the risk of development of locoregional- and/or distant recurrences. Chemotherapy is used based on the results of the MAGIC- and the OEO2-trials and chemoradiotherapy became part of standard treatment after the publication of the CROSS-trial. Although several studies have compared the efficacy of neoadjuvant chemotherapy and chemoradiotherapy, no robust evidence on the optimal neoadjuvant treatment has been obtained as yet. Several studies indirectly comparing both modalities suggest a benefit for chemoradiotherapy in the number of pathologically complete responders, radical resection rate and possibly even in overall survival. Large randomized controlled trials like the NEO-AEGIS-, ESOPEC- and NeXT-trials are currently addressing this topic. A relatively new aspect of esophageal cancer treatment is the administration of monoclonal antibodies. Several monoclonal antibodies have been tested in, mostly, advanced esophageal cancer treatment. Cetuximab has also been tested as addition to neoadjuvant- and definitive treatment in patients with locally advanced esophageal cancer, showing mixed results. This review aims at providing an overview of the currently available neoadjuvant treatments in esophageal cancer.

Introduction

Esophagectomy is still the cornerstone of intentionally curative treatment in patients with locally-advanced esophageal cancer. Outcomes of esophageal cancer surgery have been reported since 1950. Between 1950 and 2000, 5-year overall survival (OS) of patients after surgery alone has improved from approximately 12% to 39% [1-4]. Probably, this might be explained by better patient selection, improvement in perioperative care and introduction of more radical resections (*e.g.* transthoracic resection with extended *en bloc* lymphadenectomy). However, the proportion of patients with microscopically positive resection margins; including circumferential resection margin (R1) was seen in 25 – 30% of the patients [3, 5]. Furthermore, after primary esophagectomy, nearly half of the patients developed distant metastases and nearly 40% of patients developed locoregional recurrences [6, 7]. In order to decrease locoregional- and distant recurrences and irradical resections, several neoadjuvant therapies have been tested.

Neoadjuvant therapies in esophageal cancer mostly consist of chemotherapy-, chemoradiotherapy and more recently monoclonal antibodies (mAbs). Both chemotherapy and chemoradiotherapy

followed by esophagectomy improve OS compared to esophagectomy alone [6, 8, 9]. In large parts of the western world neoadjuvant chemoradiotherapy followed by esophagectomy has been adopted as standard intentionally curative treatment for esophageal cancer. However, some countries advocate the use of chemotherapy as standard therapy prior to surgery. Currently, controversy exist on which therapy is superior. Radiotherapy mostly relies on locoregional disease control while chemotherapy has the potential to also eliminate micrometastases and thus, possibly prevent outgrowth of metastases in other organs. This review aims at providing an overview of the currently available neoadjuvant therapies and as such, to determine the optimal neoadjuvant treatment for locally advanced esophageal cancer.

Chemotherapy

Chemotherapy acts both locally and systemically by downstaging of the primary tumor to increase the chance of a radical resection and elimination of (subclinical) micrometastases to decrease the risk of development of distant metastases. Chemotherapy is divided in several subclasses according to the mechanisms of action. For (gastro)esophageal cancer, mostly the platinum-based chemotherapeutics, taxanes and pyrimidine analogues are used. Platinum-based chemotherapeutics (*e.g.* cisplatin, oxaliplatin and carboplatin) induce DNA damage by production of inter- and intrastrand DNA crosslinks which inhibits the synthesis of DNA, RNA and proteins [10]. As a result, platinum-based chemotherapeutics tend to eliminate the proliferating (carcinogenic) cells. Taxanes (*e.g.* paclitaxel and docetaxel) are a class of chemotherapeutics synthetically constructed from derivatives of the needles of Yew plants [11]. Depolymerization of the cytoskeletal structures in a cell is essential for cell proliferation. Taxanes stabilize the cytoskeletal structures and thus, prevent depolymerization and cell division, resulting in cell-cycle arrest. Docetaxel is more potent than paclitaxel in enhancing the stability of cytoskeletal structures and is also able to induce apoptosis. The pyrimidine analogues (*e.g.* 5-fluorouracil) are competing structural analogs to naturally occurring metabolites that are involved in the synthesis of DNA and RNA [12]. They are most effective against cells that are in the DNA duplication phase of the cell-cycle. Consequently, these cytostatic agents tend to eliminate cells with a high growth fraction. The addition of chemotherapy to the treatment-regimen of patients with gastric-, junctional- and esophageal cancer is mainly based on two large randomized clinical trials; the MAGIC-trial and the OEO2-trial [8, 13, 14]

The MAGIC-trial was published in 2006. Some 503 patients were randomized between 1994 - 2002 with resectable adenocarcinoma of the stomach, gastroesophageal junction or lower esophagus between perioperative chemotherapy followed by surgery and surgery alone [13]. Both pre- and postoperatively, three cycles were administered consisting of epirubicin (60 mg/m^2) and cisplatin (60 mg/ m^2) on day 1 and a continuous infusion of fluorouracil (200 mg/m^2) for 21 days. Of the 237 patients that started with chemotherapy, 215 patients (90.7%) completed the preoperative cycles and 137 (57.8%) subsequently started the postoperative cycles. Eventually, 104 (43.9%) patients underwent all chemotherapy-cycles. Relatively high rates of grade 3-4 adverse events were seen, most frequently granulocytopenia (23.8% preoperatively and 27.8% postoperatively). No information was reported concerning pathologically complete response rate or radical resection rate. Median follow-up was 47 and 49 months for the chemotherapy plus surgery and surgery only group, respectively. After addition of perioperative chemotherapy, three and 5-year OS significantly improved from 31% to 44% and 23% to 36.3% respectively. However, since only a minority of patients had esophageal- (14.5%) or junctional (11%) cancer, the results of this study cannot indisputably be extrapolated to patients with esophageal cancer.

The largest trial including mostly esophageal cancer patients undergoing neoadjuvant chemotherapy followed by surgery versus surgery alone was the British OEO2-trial [8, 14]. This trial randomized 802 patients in the period 1992 and 1998 between two 4-day cycles of cisplatin (80 mg/m^2), 3 weeks apart, and continuous infusion of fluorouracil (1000 mg/m^2) for 4 days followed by surgery versus surgery alone. Nearly one-third of the patients had squamous cell carcinoma and two-thirds had adenocarcinoma. Of 372 patients that started pretreatment, 350 (94%) underwent both cycles. Only 65% of patients undergoing neoadjuvant chemotherapy and surgery had an R0 resection and no tumor could be detected in the resected esophagus in 4%, suggesting a pathologically complete response (pCR, *i.e.* no vital tumor cells in the resection specimen). The median follow-up was approximately 37.4 months. After the addition of neoadjuvant chemotherapy, 3- and 5-year OS significantly improved from 25% to 32% and from 13% to 23%, respectively. The benefit in OS after addition of chemotherapy was confirmed in the publication of the long-term results of this study. Surprisingly, there was no difference in rate of distant metastases between the two groups, suggesting a modest systemic effect of this chemotherapy regimen.

However, the results of the OEO2-trial were not confirmed by the RTOG-trial 8911 that was performed in the USA [15, 16]. Approximately in the same period of time the study randomized 440 patients with esophageal cancer between three cycles of cisplatin (100 mg/m^2) on day 1 and continuous infusion of fluorouracil (1000 mg/m^2) for 4 days followed by surgery versus surgery alone. Approximately half of the patients had squamous cell carcinoma and half of the patients had adenocarcinoma. Of all patients that underwent chemotherapy followed by surgery, 78% had R0-resection and 2.5% of patients that underwent at least one cycle of chemotherapy achieved pCR. In contrast to the OEO2-trial, OS did not improve after addition of chemotherapy prior to surgery. The median follow-up was 46.5 months. Patients undergoing preoperative chemotherapy followed by surgery or surgery alone had a 3-year OS of 23% versus 26%, respectively and a 5-year OS of 22% versus 19%, respectively. In the RTOG-trial 8911, 133 of the 233 patients (57%) that were assigned to the preoperative chemotherapy group underwent surgery compared to 361 of the 400 patients (90%) in the OEO2-trial. This could be due to the high toxicity that was seen in the RTOG-trial 8911; ≥grade 3 neutropenia in 29% of patients. No results were reported concerning graded adverse events in the OEO2-trial. However, the authors reported that in 8% of the patients that underwent neoadjuvant chemotherapy, the total dose of chemotherapy was reduced due to neutropenia. This suggests that the chemotherapy regimen in the RTOG-trial was more toxic than the chemotherapy regimen used in the OEO2-trial. This could be a possible explanation for the differences between the two studies.

Recently, the preliminary results of the FLOT4-trial, which were presented at the American Society of Clinical Oncology meeting in 2017, have drawn great attention [17]. This multicenter phase III study included 716 patients with adenocarcinoma of the stomach or gastroesophageal junction. One group of patients was treated with 3 preoperative and 3 postoperative cycles of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) on day 1 and either fluorouracil (200 mg/m^2) as continuous infusion or capecitabine (1250 mg/m^2) on days 1 to 21 orally (ECF/ECX) according to the MAGIC regimen [13]. The second group of patients were treated with 4 preoperative and 4 postoperative 2 week-cycles of fluorouracil (2600 mg/m^2), leucovorin (100 mg/m^2), oxaliplatin (85 mg/m^2) and docetaxel (50 mg/m^2) (FLOT), all as continuous infusion. The preliminary results indicate that 91% of the patients undergoing ECF/ECX completed the preoperative cycles and 37% completed the postoperative cycles, versus 90% and 50% of patients undergoing the FLOT regimen. Most importantly, median OS significantly improved from 35 months for ECF/ECX to 50 months for FLOT after a median follow-up

43 months (HR 0.77; 95% CI 0.63 – 0.94; p=0.012). Three-year OS rate was 48% for patients undergoing ECF/ECX versus 57% for patients undergoing FLOT. However, until all results concerning survival, toxicity profiles and methods are published, caution is needed to draw final conclusions.

The Japanese JCOG9204 trial showed that also adjuvant chemotherapy resulted in significantly improved disease free survival in in patients with esophageal squamous cell cancer [18]. This resulted in the initiation of the JCOG9907-trial that compared neoadjuvant chemotherapy versus adjuvant chemotherapy [18, 19]. The JCOG9907-trial randomized 330 patients with squamous cell cancer between either neoadjuvant or adjuvant chemotherapy treatment consisting of two cycles of cisplatin (80 mg/m^2) intravenously on day 1, and 5-fluorouracil (800 mg/m^2) by continuous infusion on days 1 to 5. Only patients with a node-positive status (pN1, according to the 6th edition of the TNM-staging) received adjuvant chemotherapy. In the neoadjuvant chemotherapy group, 95% of patients undergoing surgery had R0-resection versus 91% in the adjuvant chemotherapy group. Toxicity of the used regimen was mild with most common occurring grade 3 or 4 adverse events in 3% and 5% (leukopenia) of patients undergoing neoadjuvant and adjuvant chemotherapy, respectively. Complete responses were observed in 2.5% of patients that underwent surgery. The Data and Safety Monitoring Board recommended early publication of the results after OS showed to be superior in patients undergoing neoadjuvant chemotherapy (HR 0.64; 95% CI 0.45 – 0.91; p=0.01) at an interim analysis. The results of the final analysis reported a significantly improved 5-year OS in patients undergoing neoadjuvant chemotherapy from 43% to 55%.

A chemotherapy regimen that has long been solely used and is developed in Japan is S-1, an oral fluoropyrimidine alternative for infusional 5-fluorouracil. This regimen, consisting of tegafur, gimeracil and oteracil potassium, is widely being used in Asian countries for the treatment of advanced gastric cancer, mostly based on several phase II studies [20-22]. Furthermore, S-1 has been suggested to be effective in the treatment of advanced esophageal cancer patients in Japan [23, 24]. One of the substances of S-1, tegafur, is a prodrug which is converted to the active form 5-fluorouracil by the liver enzyme CYP2A6 [25]. However, patients in Japan more frequently harbor variants of CYP2A6 which results in a lower concentration of the active form 5-fluorouracil in the plasma of the patient because of lower clearance of tegafur [26]. When a phase I study was conducted in the United States, this resulted in dose-limiting toxicities [27]. The phase III FLAGS-trial that was conducted in the United States compared S-1 (50 mg/m^2) in two daily doses for 21 days and cisplatin (75 mg/m^2) on day 1 for 28 days

versus 5-fluorouracil (1000 mg/m^2) as continuous infusion for 120 hours with cisplatin (100 mg/m^2) on day 1 for 28 days [28]. Although no difference in OS was observed, administration of S-1/cisplatin resulted in a significantly improved safety profile compared to 5-fluorouracil/cisplatin. As such, S-1 was introduced as feasibly oral alternative for 5-fluorouracil for the treatment of advanced gastric- and gastroesophageal junctional cancer among Western countries. It is postulated that the difference in presence of variant CYP2A6 in patients in Japan and Western countries resulted in the differences in toxicity profiles and thus, the delay of application of S-1 in Western countries.

Chemoradiotherapy

Trimodality treatment, consisting of chemotherapy, radiotherapy and surgery was introduced mainly for the treatment of esophageal cancer after the RTOG – 8501 study reported an advantage of chemoradiotherapy over radiotherapy alone[29, 30]. In addition to the systemic effects, chemotherapy has shown its efficacy in potentiating the anti-tumor effects of radiotherapy. For platinum analogues such as cisplatin and carboplatin, the enhanced elimination of tumor cells, if continued by radiotherapy is believed to depend on a variety of mechanisms including radiation-induced increase in cellular platinum uptake, inhibition of DNA-repair and enhanced cell-cycle arrest [31-33].

The first adequately powered randomized controlled trial that reported on the outcomes of neoadjuvant chemoradiotherapy (nCRT) followed by surgery versus surgery alone was published in 1996 by Walsh *et al* [34]. Between 1990 and 1995, 113 patients with adenocarcinoma of the esophagus were randomized between nCRT consisting of two cycles of fluorouracil (15 mg/kg) on days 1 to 5 and cisplatin (75 mg/m^2) on day 7 concurrently with 40 Gy radiotherapy in 15 fractions followed by surgery versus surgery alone. The treatment-related morbidity was low (10% grade 3 and 3.3% grade 4 adverse events) in patients undergoing nCRT. Of 52 patients that underwent nCRT and surgery, 13 (25%) reached pCR. The median follow-up was 18 months. After addition of nCRT, three-year OS significantly improved from 6% to 32%. This was one of the first studies that provided robust evidence that nCRT followed by surgery provides a significant survival advantage over surgery alone in patients with adenocarcinoma.

The results of another significant trial that reported on the outcomes of nCRT treatment in esophageal cancer were published in 2012 [6, 9]. This Dutch CROSS-trial randomized 366 patients between nCRT that consisted of five weekly cycles of carboplatin (AUC 2 mg/ml/) on day 1 and

paclitaxel (50 mg/m²) on day 1 with concurrent 41.4 Gy in 23 fractions followed by surgery versus surgery alone. This nCRT-regimen was associated with modest presence of ≥grade 3 adverse events with leukopenia as most frequently occurring adverse event in 6% of the patients undergoing nCRT. One patient died after nCRT due to bleeding from an esophago-aortic fistula, in the absence of thrombocytopenia. A modest effect on the health-related quality of life was reported [35, 36]. After nCRT, 92% of patients had R0-resection, compared to 69% in the surgery alone group. Overall, nearly one-third of the patients achieved pCR (23% in patients with adenocarcinoma and 49% in patients with squamous cell carcinoma). Most importantly, 5-year OS improved from 33% to 47% after addition of nCRT. Since the publication of the results of the CROSS-trial, nCRT has been part of standard treatment for locally advanced esophageal cancer in large parts of the western world. However, although the effects of nCRT on squamous cell carcinoma were larger, only a fraction of the patients in the CROSS-trial had squamous cell carcinoma (41 in the nCRT group and 43 in the surgery group) which makes it hard to widely extrapolate the results of the study for this subgroup. However, very recently, Yang *et al.* published the NEOCRTEC5010-trial that randomized 451 patients between 2007 and 2014 with squamous cell carcinoma between nCRT consisting of two three-weekly cycles of vinorelbine (25 mg/m^2) on days 1 to 8 and 75 mg/m^2 cisplatin on day 1 or 25 mg/m2 on days 1 to 4, with concurrent 40 Gy radiotherapy in 20 fractions, followed by surgery versus surgery alone [37]. A pathologically complete response was achieved in 43.2% of patients undergoing nCRT. The median follow-up was 41 months for patients undergoing nCRT followed by surgery and 34.6 months for patients undergoing surgery alone. After addition of nCRT, 3-year OS significantly improved from 60% to 69% and 5-year OS significantly improved from 51% to 61%. The NEOCRTEC5010-trial provides strong evidence in favor of nCRT in adequately sized groups of patients with squamous cell cancer. This study reported R1-resections in only 7.9% of patients undergoing surgery alone versus 31% in the CROSS-trial. However, the CROSS-trial defined R1 resection as having positive proximal, distal and/or circumferential resection margins. The NEOCRTEC5010-trial did not include positive circumferential margins as R1 resection. This could be an explanation for the discrepancy in rate of R1 between the two trials. Furthermore, in this study, a considerable number of patients undergoing nCRT developed grade 3 and/or 4 hematologic adverse events (54.3%). Another study using a similar nCRT-regimen also reported high rates of grade 3–4 adverse hematological events, mostly grade 4 neutropenia (23%), in the treatment of metastatic esophageal squamous cell cancer [38]. In the NEOCRTEC5010-trial, two different cisplatin-regimens were used. Interestingly, administrating two cycles of cisplatin

25mg/m^2 on days 1 to 4 resulted in significantly higher grade 3–4 leukopenia and/or neutropenia than the alternative regimen of 75mg/m^2 on day 1. The authors state that 82.6% of patients completed the whole multimodality therapy. However, the supplementary material suggests that only 61.6% underwent the total dose of the 25mg/m^2 cisplatin-regimen. Even after exclusion of the more toxic cisplatin-regimen of 25mg/m^2, compliance to the chemotherapy-regimen seems relatively low, since only 56.5% of patients underwent the total dose of the vinorelbine-regimen. Hence, the reported 82.6% who completed multimodality therapy most probably includes patients in whom the total chemotherapy dose was reduced. This resulted in an overall compliance to the total dose chemotherapy of at most 56.5% (versus an overall compliance to the total dose chemotherapy of 91% in the CROSS-trial). Although no direct comparison has been made, these results suggest that the proposed regimen seems relatively toxic compared to the CROSS-regimen.

Another treatment strategy that has been investigated is induction chemotherapy followed by nCRT. A phase II trial randomized patients between induction chemotherapy followed by nCRT versus nCRT alone [39]. Induction chemotherapy consisted of 4-week cycles of oxaliplatin (100 mg/m^2) and fluorouracil (2200 mg/m^2) as continuous infusion for 48 hours, both on days 1 and 15. nCRT consisted of 5 weekly cycles of oxaliplatin (40 mg/m^2) intravenously once a week with fluorouracil (250 mg/m^2) as continuous infusion for days 1 to 5 concurrently with 50.4 Gy radiotherapy in 28 fractions. None of the grade 3 – 4 adverse events were reported in more than 5% of patients. The primary outcome of this study was the rate of pCR. Fourteen of 54 (26%) patients that underwent induction chemotherapy followed by nCRT and surgery had pCR versus 13% of patients that underwent nCRT followed by surgery (p=0.094). Moreover, no differences were seen in OS between patients undergoing nCRT followed by surgery with or without prior induction chemotherapy (p=0.69). However, a secondary analysis of this randomized trial reported that induction chemotherapy significantly prolonged OS in patients that had well to moderately differentiated tumors [40]. Furthermore, having well or moderately differentiated tumors while undergoing induction chemotherapy prior to nCRT and surgery was an independent prognostic factor in multivariate analysis. Possibly, a three-step strategy consisting of induction chemotherapy, nCRT and surgery could be beneficial in a subset of patients with locally advanced esophageal cancer. However, prospective evaluation is needed.

Chemotherapy versus chemoradiotherapy

Two neoadjuvant treatments, chemotherapy and chemoradiotherapy, for both squamous cell- and adenocarcinoma have been adopted after the publication of the OEO2, MAGIC- and CROSS-trials. Some direct comparisons have been made between these neoadjuvant treatments but these studies were of moderate to poor quality.

Earlier meta-analyses were published on this topic and suggested that both chemotherapy and chemoradiotherapy are of benefit for adenocarcinoma of the esophagus while in squamous cell carcinoma, the advantage for chemoradiotherapy is greater than that of chemotherapy [41, 42]. A larger effect on all-cause mortality was observed for nCRT versus surgery alone (HR 0.78; 95% CI 0.70 – 0.88; p=0.0001) than for chemotherapy versus surgery alone (HR 0.87; 95% CI 0.79 – 0.96; p=0.005). However, no significant benefit in all-cause mortality for either chemoradiotherapy or chemotherapy could be observed by indirect comparison between the two regimens (HR 0.88; 95% CI 0.76 – 1.01; p=0.07). A more recent meta-analysis that solely included clinical trials directly comparing neoadjuvant chemotherapy versus nCRT included six studies concerning 866 patients with esophageal or gastroesophageal adeno- or squamous cell cancer [43]. This study reported a benefit of nCRT over chemotherapy in 3- and 5-year OS (RR 0.78, 95% CI 0.62 – 0.98, p=0.03; RR 0.69, 95% CI 0.50 – 0.96, p=0.03, respectively), R0 resection rate (RR 0.87, 95% CI 0.81 – 0.92, p=<0.0001) and pathologically complete response rate (RR 0.16, 95% CI 0.09 – 0.28, p<0.00001). This meta-analysis included mostly studies with small sample size. Furthermore, the heterogeneity between studies was considered high and the earliest study that was included was published in 1992 and included patients between 1983 and 1988 and included solely patients staged T1-2NxM0.

A retrospective multicenter propensity-score matched study aimed to compare OS in patients with esophageal adenocarcinoma undergoing either nCRT or chemotherapy [44]. Between 2001 – 2012, 608 patients were included. After propensity-score matching, no differences in 3-year OS (57.9% versus 53.4%, p=0.391) nor in DFS (52.9% versus 48.9%, p=0.443) were reported in patients undergoing nCRT or chemotherapy, respectively. However, utilization of nCRT significantly increased incidence of ypT0 (26.7% versus 5%, p=0.001), ypN0 (63.3% versus 32.1%, p=<0.001) and significantly reduced R1/2 resection margins (7.7% versus 21.8%, p=<0.001).

Neither of the previously mentioned studies directly compared the chemotherapy regimens according to MAGIC, OEO2 or FLOT versus nCRT according to CROSS, although these are the most widely used

regimens. Currently, several randomized controlled trials are addressing this topic. In the Neo-AEGIS trial, patients with adenocarcinoma of the esophagus or gastroesophageal junction are randomized between pre- and postoperative chemotherapy according to the MAGIC-regimen or FLOT-regimen versus nCRT according to the CROSS-regimen [45]. This study aims at recruiting 594 patients and will be sufficiently powered to detect a 10% difference in favor of CROSS with a power of 80% and a significance of 5%. The primary endpoint of this study is OS. The ESOPEC-trial is a phase III two-arm trial that randomizes patients with adenocarcinoma of the esophagus or gastroesophageal junction between perioperative chemotherapy according to the FLOT-regimen followed by surgery versus nCRT according to the CROSS-regimen followed by surgery [46]. This trial aims at including 438 patients at 16 centers. The primary aim of the study is OS and is calculated to detect a superiority in OS of the FLOT-regimen over the CROSS-regimen with a power of 80% and a significance of 5%. The NeXT-trial is a trial with a three-arm design that aims to include 501 with squamous cell carcinoma of the thoracic esophagus, with OS as primary endpoint [47]. Patients are randomized between two 3-weekly courses of preoperative cisplatin (80 mg/m^2) on day 1 with 5 fluorouracil (800 mg/m2) on days 1-5 or three 3-weekly courses of cisplatin (70 mg/m^2) on day 1 with 5 fluorouracil (750 mg/m^2) on days 1-5 and docetaxel (70 mg/m^2) on day 1 or 41.4 Gy radiotherapy in 23 fractions with two 4-weekly courses of cisplatin (75 mg/m^2) on day 1 with 5 fluorouracil (1000 mg/m^2) on days 1-5. With an expected increase of 10% in 3-year survival for preoperative DCF or RT-CF compared to CF alone, this study has a power of 70% with a significance of 5%.

Monoclonal antibodies

In the medical treatment of esophageal cancer patients, also immune-based therapies have been explored consisting of, among others, administration of monoclonal antibodies (mAbs). mAbs are known for their recognition of a specific DNA-sequence of a single epitope (*i.e.* the part of an antigen that is recognized by the antibodies). This potentially results in highly selective inhibition of molecular pathways or in enhanced response of a patient's own immune system resulting in elimination of tumor cells [48]. In order to diminish immune responses against mAbs, Riechmann *et al.* succeeded in 'humanizing' the monoclonal antibodies in 1988, by modifying the DNA in human antibodies in such a way that antibody regions of interest of, for example mice, are incorporated in the human antibody [49]. This paved the way for widespread use of mAbs in human research and eventually lead to the first FDA-approval for usage of mAbs in the treatment of solid tumors in 1999. Single-agent administration

of trastuzumab in patients with metastatic breast cancer resulted in durable objective responses and the side-effects were mostly mild to moderate [50]. Trastuzumab is an antibody that binds and inhibits the Human Epidermal growth factor Receptor 2 (HER2/neu) which is expressed by the proto-oncogene *HER2/neu* and is responsible for proliferation and inhibition of apoptosis of the cell. Subsequently, the publication from Bonner *et al.*, reported an improvement of locoregional control and a reduction in mortality after addition of cetuximab to radiotherapy in patients with head and neck squamous cell carcinoma. This resulted in the FDA-approval of cetuximab, which binds and inhibits Epidermal Growth Factor Receptor (EGFR) and has similar functions as HER2/neu [51].
Currently two mAbs, ramucirumab and trastuzumab, are used in the clinical practice for the treatment of advanced upper-GI cancers. Ramucirumab inhibits angiogenesis by blockage of the Vascular Endothelial Growth Factor (VEGF)-receptor in regions where this receptor is overexpressed, mostly on tumor cells. Ramucirumab became part of clinical practice mainly after publication of the results of the REGARD-study that randomized 355 patients with gastric or gastroesophageal junctional adenocarcinoma who had disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy between ramucirumab monotherapy or a placebo [52]. The median OS significantly improved from 3.8 months to 5.2 months after the addition of ramucirumab (HR 0.776, 95% CI 0.603 – 0.998, p=0.047), while OS at 6 months improved from 31.6% to 41.8% and at 12 months from 11.8% to 17.6%.
Trastuzumab was incorporated in clinical practice mainly based on the study by Bang *et al* [53]. This study randomized 594 patients with gastric or gastroesophageal junctional cancer between trastuzumab plus chemotherapy versus chemotherapy alone. The median follow-up was 18.6 months for patients undergoing trastuzumab and chemotherapy versus 17.1 months for patients undergoing chemotherapy alone. Median OS significantly improved from 11.1 months to 13.8 months after the addition of cetuximab (HR 0.74, 95% CI 0.60 – 0.91, p=0.0046).

Several studies have been performed administrating monoclonal antibodies for treatment of esophageal cancer mainly using nivolumab, pembrolizumab or cetuximab [54-56]. Both nivolumab and pembrolizumab are immune checkpoint inhibitors that block Programmed cell Death protein (PD)-1 expressed on immune cells. Normally, PD-1 has an immunoregulatory role in the immune system's response to the cells of the human body with help of its ligands, by downregulation of the immune system and promoting self-tolerance [57]. These ligands consist of PD-Ligand 1 (PD-L1) and PD-L2 and

are often overexpressed on esophageal cancer cells (43.9%), resulting in an immune suppressive effect, preventing the immune system to attack tumor cells [58]. By blockage of PD-1 using nivolumab or pembrolizumab, an immune suppressive effect by its ligands can be avoided and thus, the immune system will be better able to eliminate tumor cells. Consequently, blockage of PD-1 could result in immune related adverse events (Figure 1) [59]. A phase II study by Kudo *et al.* administered nivolumab to 65 patients with esophageal squamous cell carcinoma that did not respond to, or were intolerant to fluoropyrimidine-based, platinum-based and taxane-based chemotherapy [55]. After a median follow-up of 10.8 months, 17% had an objective response and the highest grade 3 and 4 adverse events were lung infection (8%) and dyspnoe or hyponatraemia (2%), respectively. Following this phase II study, a phase III study is currently randomizing patients with unresectable advanced or recurrent esophageal cancer between nivolumab monotherapy or docetaxel (75 mg/m^2) every two weeks in combination with paclitaxel (100 mg/m^2) weekly for six weeks until documented disease progression; the primary outcome of this study is OS [60]. The estimated completion date of this study is September 2019. The KEYNOTE-590 study is currently investigating treatment of advanced or metastatic esophageal cancer by inhibition of PD-1 [56].This randomized, double-blind, placebo-controlled phase III trial aims to randomize 700 patients between cisplatin (80 mg/m^2) every three weeks, 5-fluorouracil (800 mg/m^2/day) via continuous infusion on days 1 to 5 in combination with either pembrolizumab or placebo. Primary outcomes of this study are progression-free survival and OS with subanalyses for PD-L1 positive patients. The estimated completion date of the study is planned in August 2021.

Only cetuximab has currently been tested in resectable esophageal cancer patients. The Swiss Group for Clinical Cancer Research (SAKK) has performed several studies using cetuximab in potentially curative esophageal cancer treatment. First, a phase Ib/II-SAKK 75/06 trial indicated that cetuximab could be safely added to induction chemotherapy followed by chemoradiotherapy showing high response rates and no increase in toxicity [(41)]. Subsequently, a phase III trial was initiated [54, 61]. Between 2010 and 2013, 300 patients were included. The study randomized between two cycles of docetaxel (75 mg/m^2) with cisplatin (75 mg/m^2) on days 1 and 22 followed by chemoradiation consisting of 5 weekly cycles with intravenous docetaxel (20 mg/m^2) and cisplatin (25 mg/m^2) administered weekly for 5 weeks with concurrent 45 Gy in 25 fractions followed by surgery either with or without neoadjuvant and adjuvant cetuximab treatment. Neoadjuvant cetuximab consisted of

250 mg/m^2 administered weekly during induction chemotherapy and during chemoradiotherapy, adjuvant treatment consisted of 500 mg/m^2 every two weeks for three months. This resulted in a pathologically complete response rate for patients undergoing cetuximab of 37% (versus 33% in the control group). After a median follow-up of 4.0 years, median OS was 5.1 years and 3.0 years for the cetuximab and control group, respectively (HR 0.73, 95% CI 0.52 – 1.10, p=0.055) with 5-year OS rates of 56% and 43%. For patients undergoing cetuximab, time to locoregional failure after R0-resection was significantly longer (HR 0.53, 95% CI 0.31 – 0.90, *p=0.017*). However, systemic effects of addition of cetuximab seemed modest since time to distant failure did not differ between the two arms (HR 1.01, 95% CI 0.64 – 1.59). Furthermore, one needs to realize that earlier studies of addition of cetuximab to definitive chemoradiotherapy failed to show a benefit in the nonoperative treatment of esophageal cancer [62-64]. Given the limited data concerning the use of mAbs in the treatment of intentionally curative and resectable esophageal cancer, its value as part of the (neo)adjuvant treatment remains unclear.

Conclusion

Both chemotherapy and chemoradiotherapy have been adopted in the neoadjuvant armamentarium of potentially curative esophageal cancer, mainly based on the MAGIC-, OEO2- and CROSS-trials. The 5-year OS-advantage in the MAGIC- and OEO2-trials was 13% and 6%, respectively, compared to 14% in the CROSS-trial. The results of the FLOT-trial may change the landscape in chemotherapy treatment of esophageal cancer. Several studies, mostly retrospective, compared chemotherapy and chemoradiotherapy treatment in esophageal cancer patients. The results of these studies suggest a benefit for chemoradiotherapy in the number of pCR, R0-resections and possibly even in OS. The proposed higher rates of pCR after nCRT suggest that nCRT is more appropriate for a potential organ-sparing therapy in esophageal cancer, which has extensively been topic of debate. Results of large randomized clinical trials have to be awaited before a definitive answer can be given on the survival benefits in one of the two treatments. Furthermore, only cetuximab has been tested in the neoadjuvant setting and suggested a trend towards a better OS, a statistically significant improvement in locoregional recurrence and higher rates of pathologically complete response in one study. This is accompanied, however, by several other studies that failed to show benefit of cetuximab addition to definitive non-operative treatments for esophageal cancer. The currently applied neoadjuvant treatment regimens only show modest systemic effects. This results in relatively

high rates of distant progression after neoadjuvant treatment and (unbeneficial) surgery. Future studies should mainly focus on enhanced systemic disease control.

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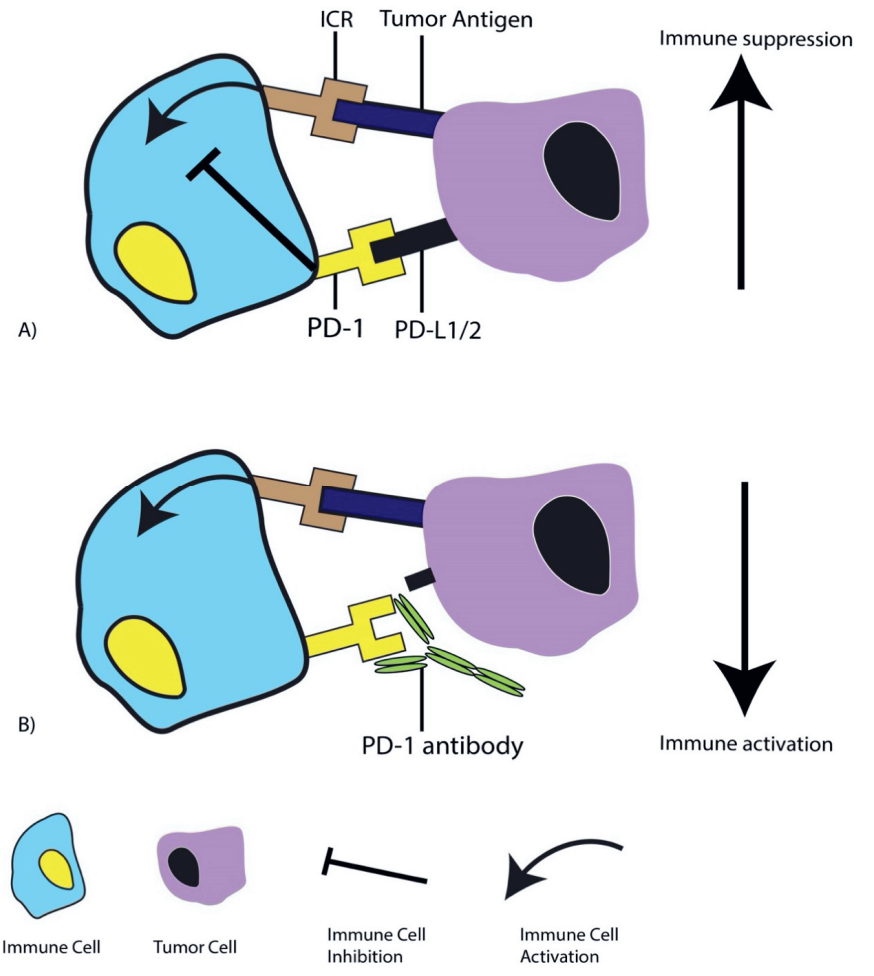

Figure 1. PD-1 Blockage by a monoclonal antibody. **A)** Normally, presentation of a tumor antigen will result in activation of the ICR and thus, elimination of the tumor cell. PD-L1/2 is often overexpressed on tumor cells and results in prevention of immune cell activation by binding to PD-1. **B)** After binding of PD-1 antibody to PD-1, immune cell inhibition will be prevented and thus, immune cell activation will occur. PD-1 blockage could thus result in several immune-related serious adverse events like dermatitis, pneumonitis, hepatitis and colitis. **ICR**: immune cell receptor; **PD-1**: Programmed Cell Death Protein-1; **PD-L1/2**: PD-ligand 1/2

3

Chapter 3

Residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer: locations undetected by endoscopic biopsies in the preSANO trial

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Abstract

Background

Active surveillance has been proposed for patients with oesophageal cancer in whom there is a complete clinical response after neoadjuvant chemoradiotherapy (nCRT). However, endoscopic biopsies have limited negative predictive value in detecting residual disease. This study determined the location of residual tumour following surgery to improve surveillance and endoscopic strategies.

Methods

The present study was based on patients who participated in the prospective preSANO trial with adenocarcinoma or squamous cell carcinoma of the oesophagus or oesophagogastric junction treated in four Dutch hospitals between 2013 and 2016. Resection specimens and endoscopic biopsies taken during clinical response evaluations after nCRT were reviewed by two expert gastrointestinal pathologists. The exact location of residual disease in the oesophageal wall was determined in resection specimens. Endoscopic biopsies were assessed for the presence of structures representing the submucosal layer of the oesophageal wall.

Results

In total, 119 eligible patients underwent clinical response evaluations after nCRT followed by standard surgery. Residual tumour was present in endoscopic biopsies from 70 patients, confirmed on histological analysis of the resected organ. Residual tumour was present in the resection specimen from 27 of the other 49 patients, despite endoscopic biopsies being negative. Of these 27 patients, residual tumour was located in the mucosa in 18, and in the submucosa beneath tumour-free mucosa in eight. One patient had tumour in muscle beneath tumour-free mucosa and submucosa.

Conclusion

Most residual disease after nCRT missed by endoscopic biopsies was located in the mucosa. Active surveillance could be improved by more sampling and considering submucosal biopsies.

Introduction

After neoadjuvant chemoradiotherapy (nCRT) for locally advanced oesophageal cancer, nearly one-third of patients have a pathologically complete response (pCR; no residual tumour cells in the resection specimen).[1] This underlines the need to reconsider standard oesophageal resection for all patients after nCRT. Oesophagectomy is associated with postoperative mortality and high morbidity rates. Therefore, it would be beneficial if patients who continue to have a clinically complete response (cCR) during active surveillance could be spared oesophagectomy.[2] During active surveillance, frequent clinical response evaluations (CREs) are performed to assess the presence of residual locoregional disease or distant metastases. The main concern in active surveillance is residual disease remaining undetected during follow-up. Small nests of residual disease could progress to an unresectable tumour or metastases. Accurate CREs are crucial to an active surveillance strategy.
The preSANO trial[3, 4] assessed the accuracy of detecting residual disease after nCRT. Endoscopy with biopsies had a sensitivity of 69 per cent for detecting residual tumour with a tumour regression grade (TRG) of 3–4 (more than 10 per cent residual tumour cells), according to the modified Mandard score described by Chirieac and colleagues.[5] The sensitivity increased to 90 per cent when the endoscopic biopsy protocol included bite-on-bite biopsies to obtain tissue from the deeper layers of the oesophageal wall. Theoretically, bite-on-bite biopsies have the potential to reach deeper layers of the oesophageal wall and therefore to detect submucosal tumours located underneath a tumour-free mucosa.[6] Submucosal tissue can be identified histologically by the presence of specific anatomical structures that are absent from mucosal biopsies, that is mucinous glands and thick-walled blood vessels.[7] Although the sensitivity for detection of residual disease increased after the introduction of bite-on-bite biopsies, it remains unclear whether this was achieved by deeper sampling of the oesophageal wall or by the fact that, for instance, more biopsies were taken. Furthermore, biopsies alone still have a limited negative predictive value for detection of residual disease after nCRT.[8]
There is a need to investigate how endoscopic surveillance and biopsy protocols can be optimized to minimize sampling errors in this patient population. The aims of this study were to assess the exact location of undetected residual disease after nCRT and to determine the depth of bite-on-bite biopsies.

Methods

The present study included patients who participated in the prospective preSANO trial.[4] All patients diagnosed with adenocarcinoma or squamous cell carcinoma of the oesophagus or oesophagogastric junction in four Dutch hospitals (2 academic hospitals and 2 high-volume teaching hospitals) between 2013 and 2016 were screened for eligibility. Patients were considered eligible for the study if they were scheduled to undergo nCRT followed by oesophagectomy. The nCRT regimen consisted of weekly administration of carboplatin (area under the curve 2 mg per ml per min) and paclitaxel (50 mg per m2 body surface area) for 5 weeks concurrently with 41·4 Gy radiotherapy in 23 fractions. Patients for whom surgical resection specimens were not available for review were excluded from analysis. All patients with detected residual disease from the initiating centre (Erasmus MC – University Medical Centre) were included consecutively and comprised the control group. This group was included to gain more insight in the location of residual tumours that could be detected during CREs. Patients with undetected residual disease from all centres were defined as the study group. The study protocol was approved by the medical ethics committee of Erasmus MC (Rotterdam, MEC-2013-211). All patients provided written informed consent for analysis and publication. The study was registered with the Netherlands Trial Register (NTR4834).

Baseline clinical staging and response evaluations

All patients underwent baseline clinical staging using endoscopic biopsies, endoscopic ultrasonography (EUS) with fine-needle aspiration (FNA) of suspected relevant lymph nodes, and PET–CT. During baseline endoscopy, the distance between the incisors and upper and lower border of the primary tumour was measured. The quadrants of the oesophagus that involved tumour were specified as well. After completion of nCRT, patients underwent one or two clinical response evaluations (CREs). The first (CRE-1) was planned 4–6 weeks after completion of nCRT, and included endoscopy with biopsies. During CREs, white-light endoscopy was used with either regular or bite-on-bite biopsies using standard-sized forceps. If no lesions were visible, at least four random biopsies were taken from the original location of the primary tumour described at baseline endoscopy. Additionally, biopsies were taken from all suspected lesions and from the borders of all ulcers. When residual vital tumour cells were detected, patients underwent PET–CT to exclude distant metastases, before oesophagectomy was performed. When no tumour cells were detected during CRE-1, a second examination (CRE-2) was planned 10–14 weeks after completion of nCRT. CRE-2 consisted of PET–CT

followed by endoscopic biopsies and EUS with FNA of all suspected lymph nodes. When distant metastases were detected, patients were referred for palliative care. Patients were considered to have achieved a cCR if no residual vital tumour cells were detected during CRE-1 and CRE-2 in endoscopic biopsies and in EUS-guided FNA cytology. In the preSANO trial, all patients underwent standard oesophagectomy. In the present study, undetected residual disease was defined as all residual tumour with TRG 2–4 (at least 1 per cent residual tumour) in the resection specimen that was not detected during CRE-1 and CRE-2.

Pathological analysis

Resection specimens and endoscopic biopsies were reviewed in all patients with residual tumour that was not detected by endoscopy during CRE (study group). The exact location of the residual tumour in the resection specimen was determined and compared with that from the control group of patients who had residual tumour detected endoscopically during CRE. Review of the resection specimens and biopsies was done independently by two experienced upper gastrointestinal pathologists. All resection specimens were processed and sampled using a standard protocol9. In brief, the surgical tumour bed was sampled extensively or totally. Tissue slides were stained using haematoxylin and eosin, and were subsequently evaluated to acquire information on resection margins, presence of vital tumour cells, tumour type and differentiation grade.

Tumour cells in the resection specimen were considered vital if their cytomorphological integrity was intact. A microscopically radical resection (R0) was defined by the absence of cancer cells at the proximal, distal and circumferential margin of the resection specimen. The resection specimen was scored for overall TRG using the modified Mandard score[5]: TRG 1, no residual tumour cells; TRG 2, 1–10 per cent residual tumour cells; TRG 3, 11–50 per cent residual tumour cells; and TRG 4, more than 50 per cent residual tumour cells. The TRG was also determined for each oesophageal layer: mucosa, submucosa, proper muscle layer and adventitia. The presence of vital tumour cells was assessed relative to the area showing regressional changes (Fig. 1). Further quantification of residual vital tumour cells was undertaken in all resection specimens that had undetected residual tumour cells in the mucosal layer, or in the submucosal layer underneath a tumour-free mucosa. To evaluate the potential for detecting specific submucosal histological structures in the submucosal layer of the oesophageal wall, the relative presence of these structures (mucinous glands and thick-walled

vessels) was assessed in the non-irradiated distal part of the oesophageal submucosa from three randomly chosen oesophageal resection specimens (Fig. 2).[7]

To gain insight into the depth of tissue sampled by endoscopic biopsies, and the potential to detect mucosal and submucosal tumours, all endoscopic biopsies taken during CRE-1 and CRE-2 were reviewed for both the presence of mucosal and submucosal tissue, and the presence of vital tumour cells in the submucosal tissue if applicable. The presence of submucosal tissue was defined as described above. If only mesenchymal or ulcerative tissue was detected, the nature of the tissue present in the biopsy was defined as uncertain; otherwise, the tissue was defined as mucosal.

Statistical analysis

Descriptive statistics were used to describe baseline characteristics. Continuous variables are reported as median (i.q.r.). Student's t test or Mann–Whitney U test was used for analysis of continuous variables, and $\chi 2$ or Fisher's exact test for comparison of categorical data (the latter when comparing 2 categorical variables, or when events were rare). $P < 0{\cdot}050$ (2-sided) was considered statistically significant. All statistical analyses were done using the tableone package of R version 3.5.1 (R Core Team, R Foundation for Statistical Computing, Boston, Massachusetts, USA).

Results

Between 2013 and 2016, 207 patients underwent nCRT, of whom 119 had one or two CREs followed by standard surgical resection. Tumour cells were detected in 70 of 119 patients during CREs, including 32 patients from the Erasmus MC – University Medical Centre who served as control group. No tumour cells were detected at CREs in 49 of 119 patients, of whom 22 had a pCR in the resection specimen. Vital tumour cells were identified in the resection specimen, which had not been detected in the endoscopic biopsies, in 27 of 49 patients (study group) (Fig. 3; Table S1, supporting information). All included patients underwent CRE-1 and CRE-2 within a range of 28–44 and 68–91 days respectively. The bite-on-bite technique was used less frequently in patients with residual tumour that remained undetected. These patients also had a lower pathological T status and more often had TRG 2 residual tumour than patients in whom residual tumour was detected during CREs (control group) (Table 1).

Analysis of control group with detected residual disease

Some 21 of 32 patients with detected residual disease had vital tumour cells in all layers of the oesophageal wall (Fig. 4a). The mucosa and submucosa were most frequently involved; both layers were involved in 30 of 32 patients. One patient had residual disease in the submucosal layer underneath a tumour-free mucosal layer. For these 32 patients, tissue from endoscopic biopsies taken during 41 CREs in total were available for review (32 CRE-1, 9 CRE-2) (Table 2). Only specific mucosal tissue was detected in the endoscopic biopsies from 16 of 41 CREs. Specific submucosal structures were detected in the endoscopic biopsies from one of the 41 CREs, using bite-on-bite biopsies. The origin of the tissue was uncertain in endoscopic biopsies from 24 of 41 CREs.

Analysis of study group with undetected residual disease

Nine of 27 patients with undetected residual disease had tumour cells involving all layers of the oesophageal wall. Residual disease was present in the mucosa in 18 patients, and in the submucosa underneath a tumour-free mucosa in eight patients. In one patient tumour cells were present underneath tumour-free mucosal and submucosal layers (Fig. 4b). In the 26 patients with residual tumour present in the mucosa and/or submucosa, residual vital tumour cells were further quantified (Fig. 4c). The 27 patients underwent 54 CREs (Table 2). Of these, pathological material from endoscopic biopsies was available from 47 CREs. Specific mucosal tissue was detected in the biopsies from 34 of 47 CREs. Specific submucosal structures were identified in biopsies of three of 47 CREs from two patients, and the origin of the tissue was uncertain in ten of 47 CREs. No tumour cells were present in the biopsies that contained submucosal structures.

Specific submucosal structures in oesophageal submucosa

In all three resection specimens, specific submucosal structures in the normal non-irradiated oesophagus comprised 1–2 per cent of the submucosal area. Furthermore, in the irradiated part of the oesophagus, (deep) ulceration, scarring and atrophy of the subepithelial layers of the oesophagus in several instances resulted in a more superficial location of these layers than expected. Fig. 5 shows an example of a resection specimen in which the subepithelial tissue (lamina propria) and the submucosal tissue are fibrotic and so the upper border of the proper muscle layer lies adjacent to the epithelial surface.

Discussion

In this study, cancer cells were still located in the oesophageal mucosa in two-thirds of patients with residual disease after nCRT that could not be detected by endoscopic biopsies during CREs. Furthermore, nearly one-third of patients had undetected residual disease in the submucosa underneath a tumour-free mucosa. Whether endoscopic biopsies or bite-on-bite biopsies had the potential to detect these submucosal tumours is unclear, as submucosal structures were identified in only two of the 27 patients with undetected residual disease. Only one patient had undetected residual disease in deeper layers of the oesophagus beneath a tumour-free mucosa and submucosa. All patients included in the present study participated in a multicentre prospective trial with the objective to identify patients who might benefit from an active surveillance strategy in the future. As a result, all patients underwent standardized CREs at two fixed time points after completion of nCRT. Undetected residual disease was found in the mucosa in two-thirds of patients, comparable to the findings of a previous retrospective study[10] that reported 68 per cent mucosal involvement. That study from Taiwan included solely patients with squamous cell carcinoma who had a cCR as determined by one CRE at 4–6 weeks after completion of nCRT. Unfortunately, the limited number of patients with squamous cell carcinoma in the present study makes it hard to compare squamous cell carcinoma and adenocarcinoma based on the available data. The undetected residual mucosal disease in the present study was most likely missed owing to sampling error. This could be explained by the presence of very limited and scattered residual disease in the mucosa and submucosa, which could be why endoscopic biopsies alone have shown limited negative predictive value for detection of residual disease after nCRT, both for oesophageal cancer and rectal cancer.[8, 11, 12] Sampling of larger mucosal areas, additional biomarkers or imaging is needed to decrease such sampling errors. Wide-area transepithelial sampling (WATS) involves use of a brush (WATS3D®; CDx diagnostics, Suffern, New York, USA) that is able to sample larger areas of the oesophageal mucosal surface as deep as the muscularis mucosae. WATS has previously been used in an RCT[13] for the detection of high-grade dysplasia or adenocarcinoma in patients undergoing surveillance for Barrett's oesophagus. An absolute increase of 14 per cent in detection of high-grade dysplasia and oesophageal adenocarcinoma was reported in a high-risk referral Barrett's oesophagus population by using WATS compared with random endoscopic biopsies. No studies yet have reported on the use of WATS for CREs in patients with oesophageal cancer after nCRT.

Potentially valuable imaging or biomarker techniques include PET–CT with radiomics or circulating tumour DNA (ctDNA).[14-16] Although use of PET–CT 12 weeks after completion of nCRT in the preSANO trial resulted in high false-positive rates, its value is currently being tested in the therapeutic SANO trial beyond 12 weeks after completion of nCRT.[17] Radiomics analysis of PET–CT images (quantification of numerous imaging features) could help enhance prediction of pCR after nCRT.[18, 19] Use of ctDNA has shown potential in several malignancies, such as colorectal cancer, non-small cell lung cancer and also oesophageal squamous cell cancer.[20-23] Imaging and biomarkers could also be of value in patients who have residual disease beneath a normal mucosa and submucosa (4 per cent (1 of 27) here versus 9 per cent in the study of Chao et al.[10]) as routine endoscopic biopsies do not have the potential to reach these deeper layers.

In this study, 30 per cent of patients (8 of 27) had submucosal residual tumour below a tumour-free mucosal layer, which is comparable to the 22 per cent reported previously.[10] Earlier studies[6, 24] suggested that such tumours limited to the submucosa could be detected by bite-on-bite biopsies in 17–38 per cent of patients. However, most of these patients had gastric tumours and none underwent neoadjuvant therapy or had carcinoma. Therefore, these results cannot be extrapolated to the setting of oesophageal cancer after nCRT. Here, bite-on-bite biopsies were able to detect the cancer cells in only one of nine patients with submucosal residual disease underneath a tumour-free mucosa. It should be noted, however, that all residual submucosal tumours underneath a tumour-free mucosa had 10 per cent or less residual tumour (TRG 2). The preSANO trial reported that the sensitivity for detection of TRG 3–4 residual tumours increased from 69 to 90 per cent after the introduction of bite-on-bite biopsies. It was hypothesized that this was due to the detection of residual submucosal tumours underneath a tumour-free mucosa. It is possible that the percentage of detected residual tumours could increase more in a surveillance setting, with endoscopic biopsies performed beyond 12 weeks after nCRT.

This study has several limitations. First, submucosal mucinous glands and thick-walled vessels comprised only 1–2 per cent of the submucosal layer in the distal part of the non-irradiated, normal oesophagus. Therefore, it cannot be concluded that the submucosa had not been sampled when these structures were absent from biopsies, especially if radiation-induced atrophy and therefore the possible disappearance of these specific submucosal structures is also taken into consideration.

Conversely, structures located in the deeper layers of the oesophageal wall in the healthy oesophagus could be present more superficially after nCRT owing to ulceration and fibrosis (Fig. 5). As such, specific structures do not unconditionally correlate with the depth of biopsy. Second, the group of patients with undetected residual tumour was relatively small and not all resection specimens or pathological material from endoscopic biopsies were available for review. Finally, only patients with detected residual tumour from the initiating centre (Erasmus MC – University Medical Centre) were included, which could have resulted in selection bias. As the primary aim of this study was to determine the location of undetected residual tumour, additional inclusion of patients with detected residual disease would most likely not have affected the main outcomes of this study.

Acknowledgements

The authors declare no conflict of interest.

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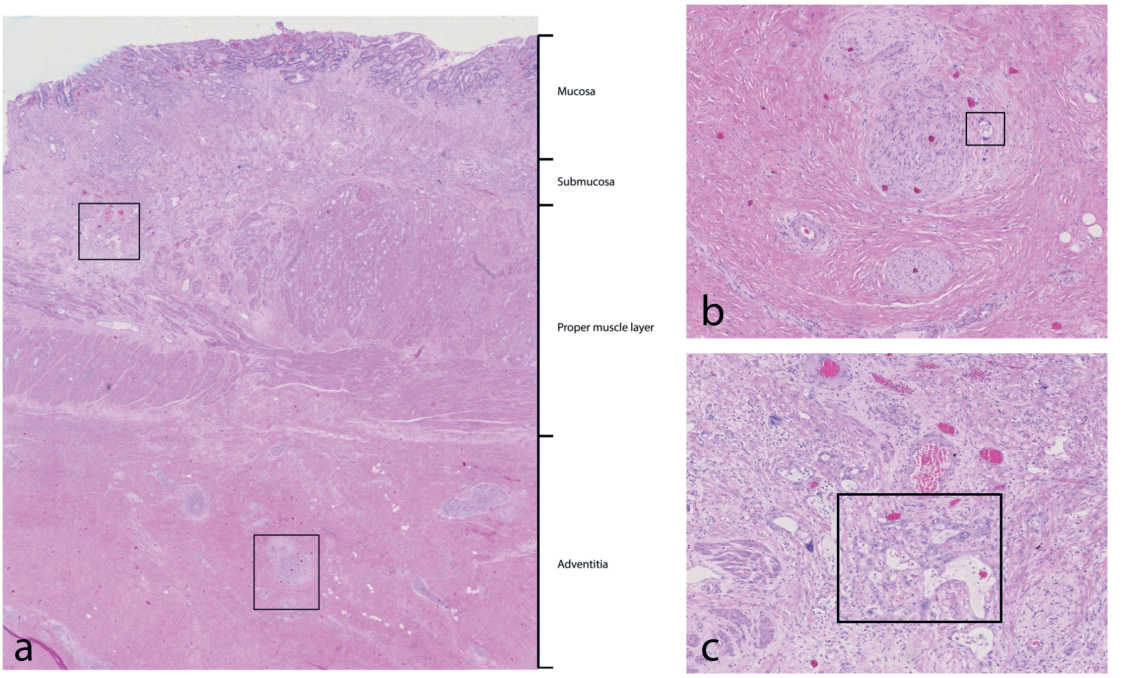

Figure 1. Histology of oesophageal resection specimen**. a)** Section from an oesophageal resection specimen showing sublayers. Detailed examples of boxed areas in the submucosa and adventitia are shown in b and c respectively. **b**) The boxed area indicates glandular adenocarcinoma within an area of regressional changes in the submucosa. The submucosa was scored as tumour regression grade (TRG) 3 (more than 10 per cent vital tumour cells). **c)** The boxed area shows vital tumour cells within an area of regressional changes in the adventitia. The adventitia was scored TRG 2 (10 per cent or less vital tumour cells). (Haematoxylin and eosin staining; a × 10 magnification, b,c × 40 magnification.)

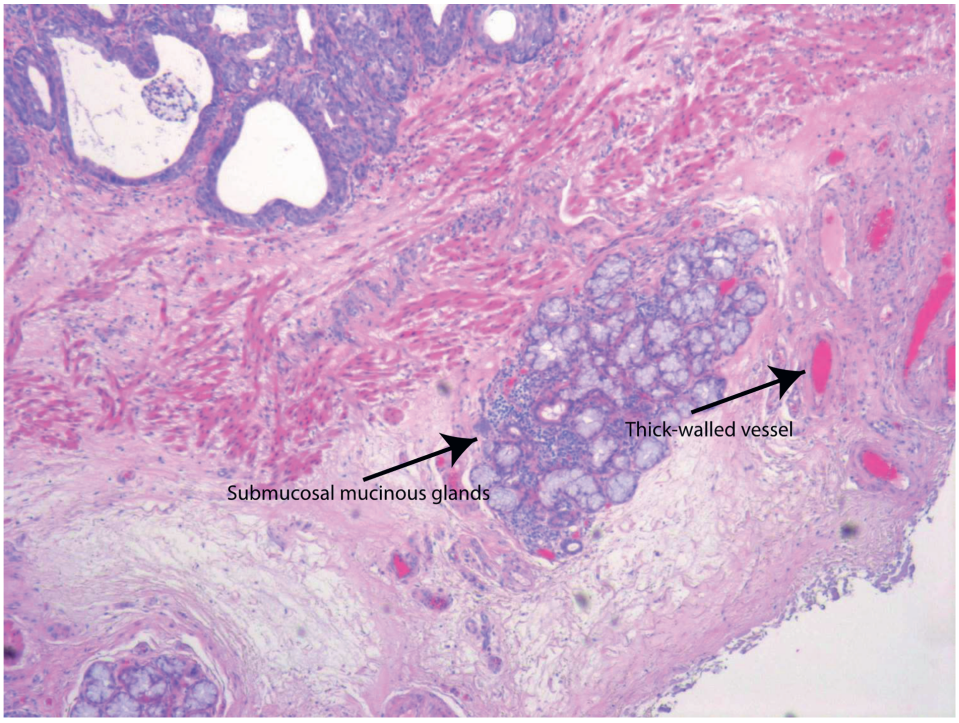

Figure 2. Submucosal mucinous glands and thick-walled vessels. Histological example of a non-irradiated (normal) area in an oesophageal resection specimen. The arrows indicate submucosal structures used to identify submucosal tissue in the endoscopic biopsies (haematoxylin and eosin staining, × 40 magnification).

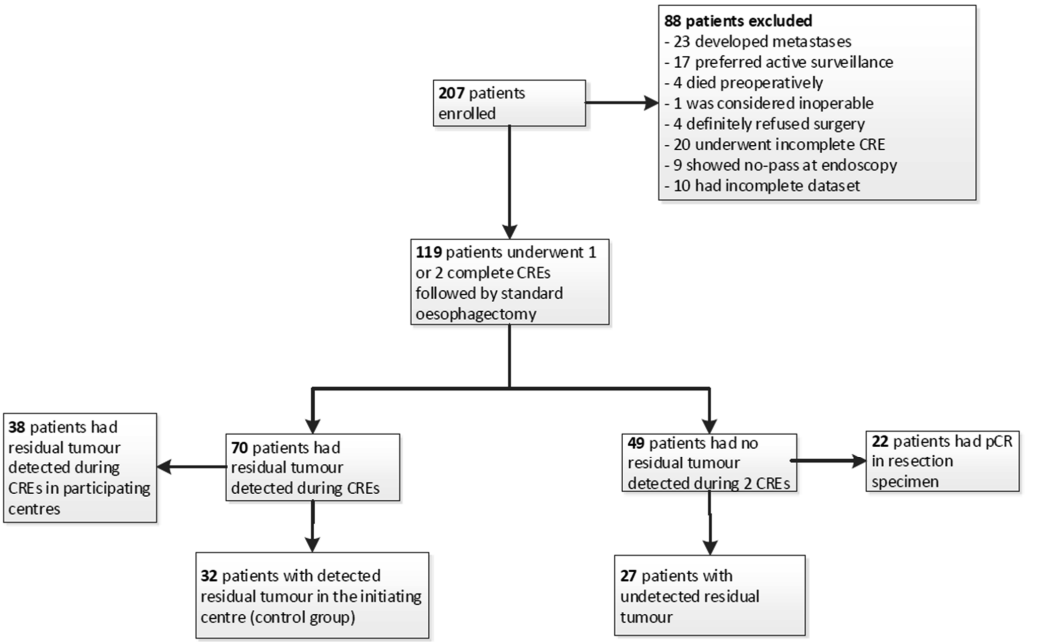

Figure 3. Study flow chart. CRE, clinical response evaluation; pCR, pathologically complete response.

Figure 4. Location of residual tumours and percentage that remained undetected. Location of residual tumours in **a)** 32 resection specimens (control group) that were detected accurately by endoscopic biopsy after neoadjuvant chemoradiotherapy and **b)** 27 resection specimens (study group) that remained undetected by endoscopic biopsy after neoadjuvant chemoradiotherapy, according to biopsy type used during clinical response evaluation (CRE). The number in each cell represents the tumour regression grade (TRG): TRG 1, no residual tumour; TRG 2–4, residual tumour. **c)** Percentage of residual tumour cells present in the mucosa or submucosa that remained undetected during CRE in the study group. The results of further quantification are shown in the most superficial layer containing residual tumour cells in the mucosa or submucosa. The number in each cell in the lower part represents the percentage of vital residual tumour cells presen

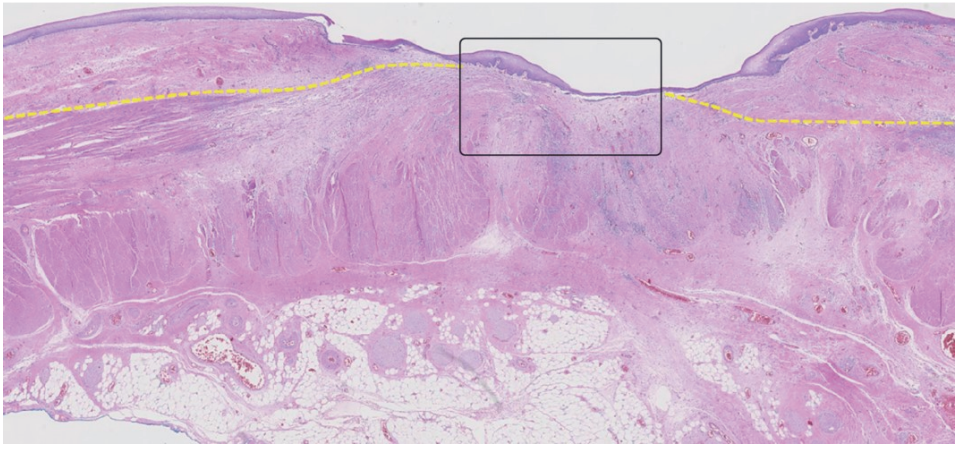

Figure 5. Proper muscle layer adjacent to epithelium. Histological example of a resection specimen showing that the proper muscle layer, which is normally located beneath the submucosal layer, is now located adjacent to the epithelium (box), most probably owing to fibrosis after neoadjuvant chemoradiotherapy. Structures normally present in the deeper layers of the oesophageal wall have the potential to be present more superficially after neoadjuvant chemoradiotherapy. The yellow line represents the upper border of the proper muscle layer (haematoxylin and eosin staining, × 10 magnification).

Table 1. Clinicopathological characteristics of patients included in analysis

	Detected residual tumour (*n* = 32)	Undetected residual tumour (*n* = 27)	*P*†
Age (years)*	66 (59–70)	66 (62–70)	0.937
Sex ratio (M : F)	28 : 4	22 : 5	0.782
Histology			0.447
Adenocarcinoma	25	24	
Squamous cell carcinoma	6	3	
Adenosquamous cell carcinoma	1	0	
Preoperative T status			0.112
cT2	2	6	
cT3	25	20	
cT4	5	1	
Preoperative N status			0.554
cN0	12	7	
cN1	11	9	
cN2	8	10	
cN3	1	0	
cNx	0	1	
Type of biopsy			0.016
Regular	6	14	
Bite on bite	26	13	
R0 resection status	32	27	1.000
ypT category			0.016
ypT1	3	11	
ypT2	8	4	
ypT3	21	12	
ypN category			0.079
ypN0	17	21	
ypN1	10	4	
ypN2	5	1	
ypN3	0	1	
TRG			0.016
TRG 2	8	16	
TRG 3	15	9	
TGR 4	9	2	

*Values are median (i.q.r.). TRG, tumour regression grade. †c^2 or Fisher's exact test, except ‡Mann–Whitney *U* test.

Table 2. Specific submucosal structures in endoscopic biopsies

	Detected residual tumour (32 patients)			Undetected residual tumour (27 patients)		
	All CREs (*n* = 41)	**CRE-1 (*n* =**	**CRE-2 (*n* = 9)**	**All CREs (*n* = 47)**	**CRE-1 (*n* = 23)**	**CRE-2 (*n* = 24)**
Submucosal structures present						
Yes	1	1	0	3	1	2
No	16	12	4	34	17	17
Uncertain	24	19	5	10	5	5
Type of biopsy overall						
Regular	10	6	4	26	13	13
Bite on bite	31	26	5	21	10	11
Type of biopsy containing						
Regular	0			1		
Bite on bite	1			2		
Tumour cells present in truly submucosal biopsies	0			0		

CRE: clinical response evaluation.

Supplementary Table S1. ypTNM status and TRG-status of five patients with undetected residual disease of which resection specimens were not available for revision.

Patient	ypTNM	TRG
1	ypT1aN0	TRG2
2	ypT2N0	TRG2
3	ypT2N0	TRG2
4	ypT3N0	TRG2
5	ypT3N1	TRG4

TRG: Tumour Regression Grade

4

Chapter 4

Predictive value of endoscopic esophageal findings for residual esophageal cancer after neoadjuvant chemoradiotherapy

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Abstract

Background and study aims

Endoscopic evaluation of the esophageal mucosa may play a role in an active surveillance strategy after neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer. This study investigated the yield of endoscopic findings for detection of residual disease.

Patients and methods

Patients from the multicenter preSANO cohort were included, who underwent nCRT followed by surgery for esophageal or junctional cancer. Upper endoscopy was performed six and twelve weeks after nCRT. In case of residual disease at six weeks, patients underwent immediate surgery. Endoscopic records were reviewed for presence of stenosis, suspicion of residual tumor, scar tissue, or ulceration. Presence and type of endoscopic findings were compared to outcome of the resection specimen.

Results

118 of 156 (76%) patients had residual disease in the resection specimen. Endoscopic suspicion of residual tumor was significantly associated with presence of residual disease. At six weeks, 40/112 patients with residual disease and 4/33 patients with a complete response had endoscopic suspicion of residual tumor (36% *vs* 12%, P=0.01), while this was reported in 16/73 patients compared to 0/28 patients at twelve weeks (22% vs 0%, P<0.01). Positive predictive value of endoscopic suspicion of residual tumor was 91% at six weeks and 100% at twelve weeks. Endoscopic finding of a non-passable stenosis, passable stenosis, scar tissue, and ulceration were not associated with residual disease.

Conclusions

Endoscopic suspicion of residual tumor was the only endoscopic finding associated with residual disease. Based on its positive predictive value, it may attribute to the diagnostic strategy used in active surveillance.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery has been widely accepted as a new standard of treatment with curative intent for esophageal cancer patients [1, 2]. Besides the positive impact of nCRT on overall survival, a substantial part of patients has a histopathologically confirmed complete response [1-3]. Therefore, an active surveillance strategy has been suggested in patients with a clinically complete response after nCRT, with surgery only offered in case of proven residual disease [4-7]. This strategy could prevent complete responders from unnecessarily undergoing major surgery and thereby improve health-related quality of life, provided that residual disease can be detected timely and accurately during clinical response evaluations [7, 8].

In active surveillance strategies for rectal cancer, endoscopic evaluation of the rectal mucosa plays an important role during clinical response evaluations [9, 10]. Endoscopic findings such as a stenosis, suspicion of residual tumor, and ulceration should be absent to be classified as a clinically complete responder after nCRT. Little is known on the predictive value of endoscopic findings during active surveillance for esophageal cancer. Previous studies in esophageal squamous cell carcinoma patients have suggested that the degree of endoscopic response is related to the observed response in the resection specimen and that certain endoscopic findings (*e.g.* stenosis, ulceration) should be considered as a sign of residual disease [11, 12]. In this light, endoscopic evaluation of the esophagus may be of added value in an active surveillance strategy. Hence, this study aimed to investigate the yield of endoscopic findings for detection of residual esophageal cancer after nCRT.

Patients and methods

A retrospective chart review of patients included in the diagnostic, multicenter, single-arm preSANO trial was performed [4]. All patients included in the preSANO trial were scheduled to undergo nCRT according to the CROSS regimen followed by surgical resection for esophageal cancer or junctional cancer [1]. Clinical response evaluations including upper endoscopy with biopsies were performed six and twelve weeks after nCRT. In case of any evidence of residual disease at six weeks, as evidenced by biopsies with histopathologically vital tumor cells or an endoscopically non-passable stenosis, patients underwent immediate surgery. All remaining patients underwent surgery at twelve weeks, unless intercurrent distal metastases were identified. Only patients that proceeded to surgery were included in this study.

Upper endoscopy

According to the preSANO study protocol, the level of the upper esophageal sphincter, upper tumor border, lower tumor border, squamocolumnar junction, esophagogastric junction, and diaphragmatic impression were identified during baseline upper endoscopy. During clinical response evaluations after nCRT, at least four random endoscopic biopsies were obtained of the original primary tumor site. Additional biopsies were taken from the borders of all ulcers and any suspicious lesions. All endoscopies were performed by experienced upper-GI endoscopists using high definition endoscopes (Olympus GIF-H180/GIF-H180J/GIF-HQ190, Fujifilm EG-590WR/EG-600WR, and Pentax i10 Series HD+). Endoscopists had at least ten years of experience in high-volume centers (≥20 esophagectomies per year).

For the purpose of this retrospective study, endoscopy reports were independently reviewed by two blinded investigators (RvdB, BvdW) based on a predefined case record form with input from upper GI-endoscopists and previous studies [9, 11, 12]. The following endoscopic findings were recorded: non-passable stenosis, passable stenosis, suspicion of residual tumor, scar tissue, and ulceration (Figure 1). A finding that was documented in the endoscopic record was scored "present", whereas a finding that was not documented was scored "not present". Multiple features were allowed to be present in a single patient. Any discrepancies between investigators were resolved by consensus discussion. If the investigators were unable to reach consensus, the senior author gave a binding verdict.

To define features that drive endoscopic suspicion of residual tumor, photographic recordings of the last clinical response evaluation in patients with endoscopic suspicion of residual tumor were revised by two investigators (SN, MS) using a list of predefined features. An overview of used definitions is provided in Supplementary table 1.

Histopathological examination

After performance of surgical resection, response to nCRT was classified according to the modified Tumor Regression Grade (TRG) by Chirieac *et al.*, by comparing the amount of vital tumor cells and nCRT induced fibrosis at the primary tumor site [13]. In this classification, complete responders are given score TRG1 (*i.e.* no evidence of residual disease), whereas patients with residual disease are given score TRG2, TRG3, or TRG4 in case of 1-10%, 11-50%, or more than 50% of residual vital tumor cells, respectively. All resection specimens were centrally revised by two experienced upper-GI pathologists.

Analysis of data

The primary aim of this study was to investigate which endoscopic findings were related to the presence of TRG2-3-4 residual disease in the resection specimen after nCRT for esophageal cancer. Reported endoscopic findings at six and twelve weeks after nCRT were compared to the histopathological outcome in the resection specimen using a chi-squared test. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with corresponding 95% confidence intervals (CI) were reported. In case of an endoscopically non-passable stenosis, patients were excluded from further analysis as this did not allow complete examination of the esophagus. Furthermore, test characteristics of this feature were not reported for endoscopy performed at twelve weeks, as the preSANO study protocol required all patients with a non-passable stenosis at 6 weeks to undergo immediate surgery.

Secondary aim of this study was to assess the additional yield of endoscopic findings for detection of locoregional residual disease. Outcomes of statistically significantly associated findings were compared to the outcomes of the currently recommended diagnostic strategy. Diagnostic strategy includes endoscopic biopsies at six and twelve weeks and EUS with fine-needle aspiration of suspicious lymph nodes at twelve weeks after nCRT [4]. Analyses were performed with SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp.) and R (R Foundation for Statistical Computing, Vienna, Austria). The epiR package of R was used to calculate 95% CI. Tests were considered statistically significant in case of a $P<0.05$ (two-tailed test).

Results

Baseline characteristics of the 156 patients included are shown in Table 1. In summary, median age was 66 years, 83% were male and 79% had adenocarcinoma. All patients completed the clinical response evaluation at six weeks. A total of 102 (65%) patients underwent clinical response evaluation at twelve weeks. One report of an upper endoscopy performed at twelve weeks after nCRT was not available, leaving 101 patients for analysis of the 12-weeks outcome. Histopathological examination of the resection specimen revealed residual disease in 118 (76%) patients and a complete response in 38 (24%) patients.

Upper endoscopy six weeks after nCRT

A non-passable stenosis was present in 11 (7%) of 156 patients; six of these patients had residual disease in the resection specimen, five patients had a complete response (residual disease *vs* complete response, 5% [6/118] *vs* 13% [5/38], P=0.09). In the remaining 145 patients, ulceration (n=82, 57%) was the most prevalent endoscopic finding. Sixty-two patients with ulceration had residual disease in the resection specimen, while twenty patients had a complete response (55% [62/112] *vs* 61% [20/33], P=0.59). Comparable outcomes were observed for the endoscopic finding of a passable stenosis and scar tissue, as summarized in Table 2.

Endoscopic suspicion of residual tumor was reported in 44 (30%) of 145 patients. Forty of these 44 patients were confirmed to have residual disease in the resection specimen, while four patients had a complete response. The proportion of patients with endoscopic suspicion of residual tumor was statistically significantly higher in patients with residual disease (36% [40/112] *vs* 12% [4/33], P = 0.01). Sensitivity, specificity, PPV and NPV for endoscopic suspicion of residual tumor at six weeks after nCRT were 36% (40/112, 95% CI 27-45), 88% (29/33, 95% CI 72-97), 91% (40/44, 95% CI 78-97), and 29% (29/101, 95% CI 20-39), respectively. Test characteristics of other endoscopic findings are reported in Table 3.

Upper endoscopy twelve weeks after nCRT

The tumor was passable in all patients. Ulceration (n=41, 41%) and scar tissue (n=22, 22%) were the most frequently reported endoscopic findings, but were not associated with residual disease in the resection specimen (Table 4). Endoscopic suspicion of residual tumor was reported in 16 (16%) of 101 patients, of whom all patients were confirmed to have residual disease in the resection specimen (22% [16/73] vs 0% [0/28], P<0.01). Corresponding sensitivity, specificity, PPV, and NPV were 22% (16/73, 95% CI 13-33), 100% (28/28, 95% CI 88-100), 100% (16/16, 95% CI 79-100), and 33% (28/85, 95% 23-44), respectively (Table 3).

Yield of endoscopic suspicion of residual tumor

Biopsies were obtained from 43 of 44 patients with endoscopic suspicion of residual tumor at six weeks after nCRT. Seventeen (40%) patients had positive biopsies and 26 (60%) patients had negative biopsies. Of these 26 patients, 22 (85%) had residual disease in the resection specimen and four (15%) had a complete response.

Likewise, at twelve weeks after nCRT, eight (50%) patients with endoscopic suspicion of residual tumor had positive biopsies and eight (50%) patients had negative biopsies. Two patients with negative biopsies had suspicious lymph nodes at EUS. FNA outcome of the suspicious lymph nodes was uncertain in both patients. All patients with negative biopsies and/or uncertain FNA outcome had residual disease in the resection specimen.

Features of endoscopic suspicion of residual tumor

To identify endoscopic features that may guide endoscopic suspicion of residual tumor, photographic recordings of the last clinical response evaluation of 51 patients with endoscopic suspicion of residual tumor were collected. After exclusion of sixteen clinical response evaluations due to insufficient image quality and four clinical response evaluations because of a complete response in the resection specimen, photographic recordings of 31 patients were included in the sub-analysis. Revision of the recordings showed residual mass (87%), villous pattern (71%), and focal retraction (65%) as the endoscopic features that were most frequently present in case of endoscopic suspicion of residual tumor (Table 5). A representative image of these features is provided in Figure 2. Less frequent features were deep ulceration, easy bleeding, esophageal tapering, and loss of architecture.

Discussion

This is the first study that aims to investigate the diagnostic value of endoscopic esophageal findings for detection of residual esophageal cancer after nCRT in a Western population. Our study demonstrates that endoscopic suspicion of residual tumor was the only endoscopic finding associated with residual disease in the resection specimen. Based on its high PPV (91% at six weeks, 100% at twelve weeks), the endoscopic suspicion of residual tumor may be of added value when applied in a combined diagnostic strategy during active surveillance. Ultimately, it has the potential to improve the detection rate of residual disease, as reflected by the fact that endoscopic biopsies and FNA did not reveal the residual tumor in a substantial number of patients.

Currently available evidence on the association between endoscopic findings and response to nCRT in esophageal cancer patients are scarce, and restricted to retrospective chart reviews of patients with squamous cell carcinoma. Previous studies have shown that the overall endoscopic response after

neoadjuvant therapy is of prognostic value [11, 14]. Furthermore, Chao *et al.* showed that negative biopsies were less reliable in case of certain endoscopic findings [12]. Specifically, NPVs of biopsies obtained in patients with a stenosis, endoscopic suspicion of residual tumor, or ulceration were 23%, 20%, and 31%, respectively. Hence, the authors concluded that endoscopic biopsies should not play a role in these patients as residual disease cannot reliably be ruled out, and presence of any of these findings should therefore be considered as a sign of residual esophageal cancer.

The present study confirms that certain endoscopic findings (*i.e.* endoscopic suspicion of residual tumor) may contribute to a diagnostic strategy for detection of residual esophageal cancer. In addition, and similar to findings by Chao *et al.*, a substantial rate of falsely negative biopsies was observed in patients with endoscopic suspicion of residual tumor after nCRT [12]. Outcome should, however, be interpreted with caution because of the small number of patients with this finding in this study. Nevertheless, it provides an interesting insight into the reason of falsely negative biopsies. It is believed that falsely negative biopsies result from either incorrect identification of the primary tumor site or insufficient sampling due to tumor distribution [15-17]. As it can be argued that the location of the residual tumor has been correctly identified in the majority of patients with endoscopic suspicion of residual tumor, insufficient sampling seems the most likely explanation, for example caused by a tumor-free mucosa or scattered (residual) tumor distribution after nCRT [15-17]. More aggressive sampling strategies – deeper penetration or a larger sampling area – have the potential to improve this outcome. Furthermore, standard performance of deeper sections and additional stainings may be considered during the histopathological examination of endoscopic biopsies obtained in patients with endoscopic suspicion of residual tumor.

Another remarkable finding in the present study is the relatively high rate of complete responders in patients with an endoscopically non-passable tumor at six weeks after nCRT. Of eleven patients with this finding, five had a complete response in the resection specimen. It can be hypothesized that the extensive tissue reaction in complete responders leads to local edema, impeding passage of the endoscope. Falsely classifying these patients as positive for residual disease may be reduced by extending the time interval until the first clinical response evaluation, as it has been shown to be safe to delay surgical resection up to at least twelve weeks after nCRT without performing clinical response

evaluations [18, 19]. Increasing the time interval may reduce local edema resulting from quiescence of nCRT induced inflammation.

In the present study, an effort has been made to objectify features that lead to an endoscopic suspicion of residual tumor. Based on the current study, a residual mass, villous pattern and/or focal retraction may be indicators for endoscopic suspicion of residual tumor. To improve generalizability and clinical usability prospective evaluation is needed. This may also take into account additional factors such as changes over time (*e.g.* healing of an nCRT induced ulcer) and the use of optical image enhancing technologies. Furthermore, prospective evaluation allows further specification of different features (e.g. deep/superficial ulceration) and stratification for tumor type. Ultimately, an endoscopic scoring system may be developed to identify residual esophageal cancer.

Limitations of this study include its retrospective nature. Although the preSANO study procedures were highly standardized (*e.g.* nCRT regimen, time until response evaluations) and generalizability is increased by its multicenter design, preSANO study protocol did not include standardized definitions for documentation of endoscopy outcomes. Some heterogeneity among performing endoscopists can therefore not be ruled out. Furthermore, endoscopic assessment for evidence of residual tumor was not incorporated in the standard procedures of the preSANO study. As a result, current cohort may mainly consist of patients with an obvious presence of residual tumor, possibly leading to a lower discriminative ability when assessed prospectively. Lastly, images of some patients with endoscopic suspicion of residual tumor were excluded due to low image quality. Suggested features should therefore be considered among other endoscopic features in future prospective studies.
In conclusion, based on its positive predictive value, endoscopic suspicion of residual tumor has the potential to be of additional value in the diagnostic strategy for active surveillance in esophageal cancer. Before implementation of this parameter, further standardization and prospective evaluation of its discriminative ability and inter-observer agreement are needed.

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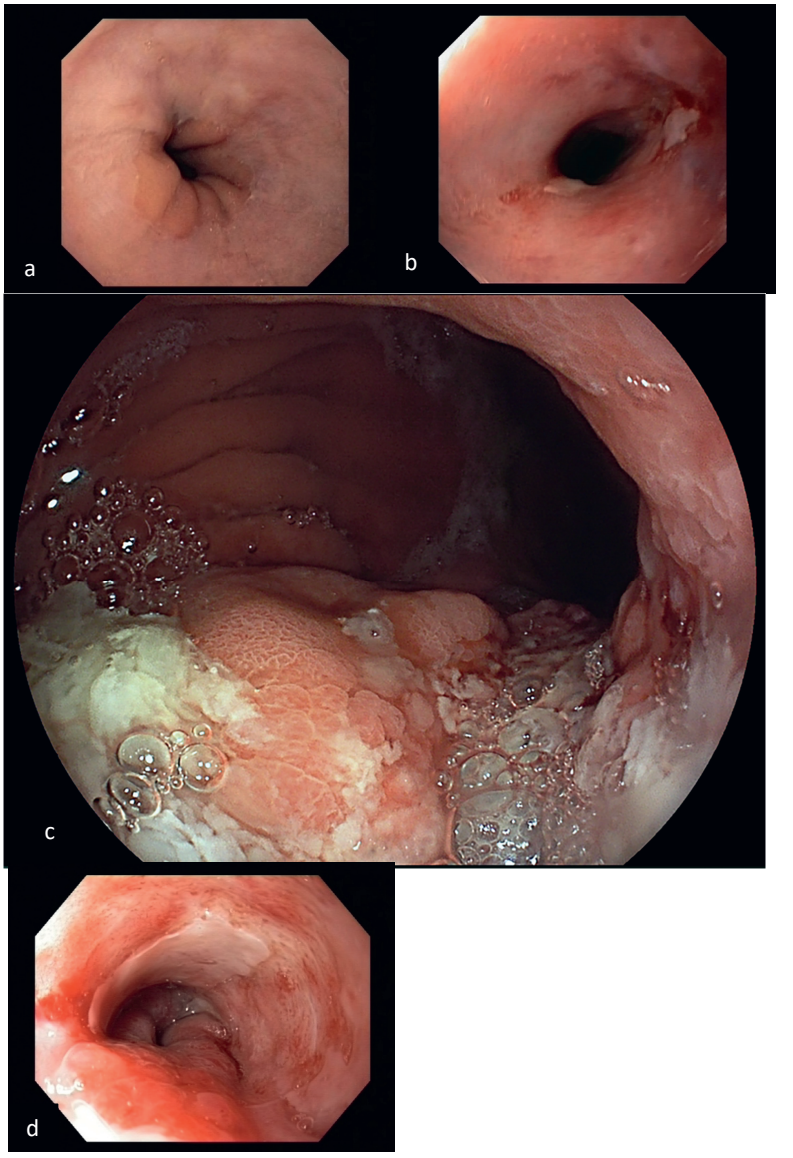

Figure 1. A representative image of **a)** stenosis, **b)** scar tissue, **c)** suspicion of residual tumor, and **d)** ulceration.

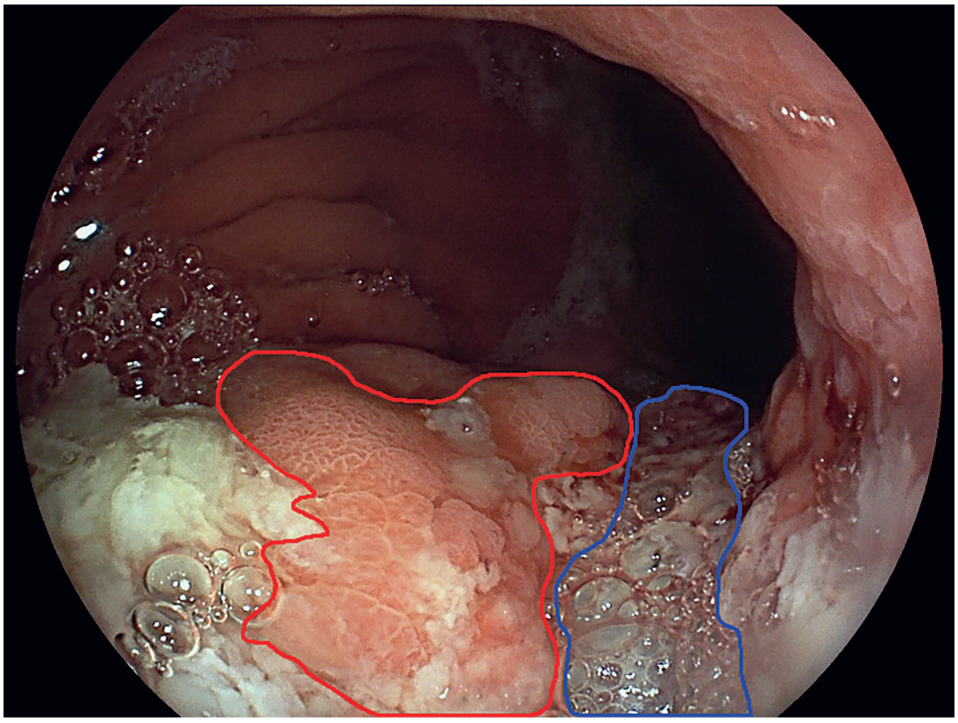

Figure 2. A patient with a residual mass with villous elements (delineated by red line) and retraction of the surrounding tissue (delineated by blue line) at the gastroesophageal junction six weeks after neoadjuvant chemoradiotherapy.

Table 1. Baseline characteristics of 156 patients undergoing neoadjuvant chemoradiotherapy followed by surgical resection for esophageal or junctional cancer.

	n = 156
Median age, years (IQR)	66 (10)
Male sex, n (%)	130 (83)
Tumor type, n (%)	
Adenocarcinoma	123 (79)
Squamous cell carcinoma	32 (21)
Adenosquamous carcinoma	1 (1)
Clinical tumor stage, n (%)	
T1	1 (1)
T2	27 (17)
T3	120 (77)
T4	8 (5)
Clinical nodal stage, n (%)	
N0	51 (33)
N1	63 (40)
N2	38 (24)
N3	3 (2)
Nx	1 (1)
Response in the resection specimen, n (%)	
Residual disease	118 (76)
Complete response	38 (24)

IQR, interquartile range.

Table 2. Presence of endoscopic findings at six weeks after neoadjuvant chemoradiotherapy in 145 patients with an endoscopically passable tumor.

	Total (n=145)	**Residual disease (n=112)**	**Complete response (n=33)**	**p-value***
Passable stenosis, n (%)	28 (19)	20 (18)	8 (24)	0.41
Scar tissue, n (%)	16 (11)	11 (10)	5 (15)	0.39
Suspicion of residual tumor, n (%)	44 (30)	40 (36)	4 (12)	0.01
Ulceration, n (%)	82 (57)	62 (55)	20 (61)	0.59

*calculated with chi-squared test comparing residual disease vs complete response.

Table 3. Diagnostic accuracy of different endoscopic findings at 6 and 12 weeks after nCRT.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Non-passable stenosis				
6 weeks	5 (2-11)	87(72-96)	55 (23-83)	23 (16-30)
12 weeks*	-	-	-	-
Passable stenosis				
6 weeks	18 (11-26)	76 (58-89)	71 (51-87)	21 (14-30)
12 weeks	18 (10-29)	86 (67-96)	76 (50-93)	29 (19-39)
Scar tissue				
6 weeks	10 (5-17)	85 (68-95)	69 (41-89)	22 (15-30)
12 weeks	19 (11-30)	71 (51-87)	64 (41-83)	25 (16-36)
Suspicion of residual tumor				
6 weeks	36 (27-45)	88 (72-97)	91 (78-97)	29 (20-39)
12 weeks	22 (13-33)	100 (88-100)	100 (79-100)	33 (23-44)
Ulceration				
6 weeks	55 (46-65)	39 (23-58)	76 (65-84)	21 (11-33)
12 weeks	40 (28-52)	57 (37-76)	71 (54-84)	27 (16-40)

*Test characteristics were not calculated since all patients with a non-passable stenosis at 6 weeks underwent immediate surgery. CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value

Table 4. Presence of endoscopic findings at twelve weeks after neoadjuvant chemoradiotherapy in 101 patients with an endoscopically passable tumor.

	Total (n=101)	Residual disease (n=73)	Complete response (n=28)	p-value*
Passable stenosis, n (%)	17 (17)	13 (18)	4 (14)	0.67
Scar tissue, n (%)	22 (22)	14 (19)	8 (29)	0.31
Suspicion of residual tumor, n (%)	16 (16)	16 (22)	0	<0.01
Ulceration, n (%)	41 (41)	29 (40)	12 (43)	0.77

*calculated with chi-squared test comparing residual disease vs complete response.

Table 5. Endoscopic features objectified during revision of 31 examinations of patients with endoscopic suspicion of residual tumor and residual disease in the resection specimen.

	Present	Absent	Uncertain
Deep ulceration, n (%)	7 (23)	24 (77)	-
Easy bleeding, n (%)	11 (36)	18 (58)	2 (7)
Esophageal tapering, n (%)	14 (45)	16 (52)	1 (3)
Focal retraction, n (%)	20 (65)	10 (32)	1 (3)
Loss of architecture, n (%)	7 (23)	22 (71)	2 (7)
Residual mass, n (%)	27 (87)	4 (13)	-
Villous pattern, n (%)	22 (71)	9 (29)	-

Supplementary table 1. List of definitions used for revision of photographic recordings [1-3].

Finding	Definition
Deep ulceration	A subacute or chronic focal excavated defect of the esophageal wall with/without fibrin, usually more than a few millimeters
Easy bleeding	Vulnerability of the mucosa with signs of (spontaneous) bleeding
Esophageal stenosis	Tapering of the esophagus not related to peristalsis or esophageal spasm
Focal retraction	A focal depression of the esophageal wall, which remains after insufflation.
Loss of architecture	An altered mucosal pattern characterized by a loss of surface structure (*e.g.* pit pattern, vascular pattern)
Residual mass	A protruding lesion or focal wall thickening
Villous pattern	A mucosal pattern characterized by a villiform pattern

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Chapter 5

Endoscopic ultrasound and fine-needle aspiration for the detection of residual nodal disease after neoadjuvant chemoradiotherapy for esophageal cancer

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Abstract

Background

Endoscopic ultrasound (EUS) and fine-needle aspiration (FNA) are potential tools for the detection of residual disease after neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer. This study investigated yield of EUS and FNA for detection of malignant lymph nodes (LNs) after nCRT.

Methods

This was a post hoc analysis of the preSANO trial. EUS was performed 10–12 weeks after nCRT. 18F-fluorodeoxyglucose positron emission tomography–computed tomography (18F-FDG PET-CT) was used to guide targeting of suspicious LNs. Consecutive FNA sampling was performed for suspicious LNs identified on EUS and/or PET-CT. EUS nodal staging was compared with histopathological examination of the resection specimen. The primary outcome was the proportion of correctly identified patients with malignant LNs by radial EUS.

Results

101 consecutive patients were included: 79 patients had no malignant LNs, of whom 62 were classified correctly by EUS (specificity 78%); 22 patients had malignant LNs, of whom 11 were identified (sensitivity 50%). Six of these patients had ≥1 suspicious LN not fulfilling EUS criteria (round, hypoechogenic, >5 mm). Malignant LNs in falsely negative patients were predominantly located at distal LN stations. Specificity and sensitivity of conclusive FNA outcomes were 100% (7/7) and 75% (3/4), respectively. FNA outcome was uncertain in eight patients, half of whom appeared to have malignant LNs.

Conclusions

EUS only detected 50% of patients with malignant LNs 10–12 weeks after nCRT. To optimize sensitivity and minimize the risk of missing residual disease, FNA of LNs should be performed even in cases of low endosonographic suspicion.

Introduction

Given the substantial rate of pathologically complete responders after neoadjuvant chemoradiotherapy (nCRT) in esophageal cancer patients, the necessity of standard esophagectomy has been a topic of debate [1-4]. An active surveillance strategy has been suggested in patients with a clinically complete response [3-5]. During active surveillance, patients undergo regular clinical response evaluations, and surgery is only offered in cases of proven or highly suspected residual disease in the absence of distant dissemination. This strategy is currently under investigation by the Dutch SANO group and the French ESOSTRATE group [6,7].

Prior to the SANO trial, the preSANO trial was initiated to investigate the optimal diagnostic strategy for detection of residual disease after nCRT [3,4,8,9]. Outcomes of different diagnostic tests were correlated to regressive changes observed in the resection specimen. Based on study outcomes of the preSANO trial, a combination of 18F-fluorodeoxyglucose positron emission tomography – computed tomography (^{18}F-FDG PET-CT), bite-on-bite biopsies, and radial endoscopic ultrasound (EUS) followed by EUS-guided fine-needle aspiration (FNA) of suspicious lymph nodes (LNs) was recommended [3]. The addition of EUS-FNA led to an increase in the detection rate by providing histopathological confirmation of residual nodal disease in patient with false-negative bite-on-bite biopsies [3].

Current clinical guideline recommendations advise the use of radial EUS over other imaging modalities in initial nodal staging of esophageal cancer [10]. As sensitivity based on endosonographic features alone is suboptimal, radial EUS is preferably combined with consecutive FNA sampling. However, controversy exists on its application after nCRT, as sensitivity is known to decrease and EUS criteria to distinguish malignant from benign LNs may be less reliable [11-16]. As EUS-FNA was shown to be of substantial value in the preSANO trial, the aim of the current post hoc analysis was to investigate the diagnostic value and potential yield of radial EUS and EUS-FNA for detection of malignant LNs after completion of nCRT for esophageal cancer.

Methods

A post hoc analysis of the prospective, multicenter, single-arm diagnostic preSANO trial was performed. Full details of the study procedures in the preSANO trial have been published previously [3,4]. Consecutive patients with histologically proven esophageal or junctional cancer who were scheduled to undergo nCRT according to the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) regimen – consisting of five weekly cycles of carboplatin and paclitaxel with

concurrent radiotherapy (41.4 Gy) – followed by surgical resection were eligible for the preSANO trial [1]. Additional criteria for eligibility in the current study were completion of clinical response evaluation with nodal staging at 10 – 12 weeks after nCRT and performance of surgical resection. Before onset of the inclusion period, approval of the study protocol was granted by the medical ethics committee of the Erasmus University Medical Center (Rotterdam, MEC-2013 – 211) and the study was registered at the Netherlands National Trial Register (NTR4834). All patients provided written informed consent.

Radial EUS

Radial EUS was performed 10 – 12 weeks after completion of nCRT. Prior to the scheduled radial EUS, an 18F-FDG PET-CT scan was performed and evaluated by a local nuclear radiologist. Reports were available to the endosonographer to guide targeting of suspicious LNs and lesions during radial EUS (Figure 1A-B). PET-avid LNs were defined as LNs with an increased uptake compared with surrounding tissues and/or previous baseline PET-CT findings. The following LN stations were assessed by radial EUS for presence of suspicious LNs: celiac trunk (i. e. stations 18, 19, and 20), lesser curvature (i. e. stations 16 and 17), paraesophageal (i. e. stations 8 M and 8 L), subcarinal (i. e. station 7), aortopulmonary window (i. e. station 5), and mediastinal/paratracheal stations (i. e. stations 2 R, 2 L, 4 R, and 4 L).

Identified LNs were assessed for their size, shape, echogenicity, and demarcated border. LNs that did not fulfill all of the EUS criteria for suspicious LNs (round, hypoechogenic, > 5 mm) were recorded separately [17,18]. Final endosonographic N stage (yuN) was reported according to the seventh edition of the Union for International Cancer Control (UICC) TNM classification [19]. All procedures were performed with electronic radial echoendoscopes (Pentax EG-3670URK, Olympus GF-UE160-AL5).

Fine needle aspiration

FNA was performed for all suspicious LNs (based on endosonographic and/or PET-CT findings) (Figure 1C), even when located directly behind the primary tumor site. A risk of potential contamination was accepted, as the exact source of vital tumor cells (i. e. primary tumor site or LN) would not impact the clinical decision making during active surveillance [3]. FNA procedures were performed with linear

echoendoscopes (Pentax EG-3870UTK, Olympus GF-UCT180) according to the current European clinical standards [20].

Histopathological examination

Resection specimens were assessed for evidence of malignant LNs and regressive changes at the primary tumor site. Location and number of malignant LNs were recorded. Final histopathological N stage (ypN; gold standard) was reported according to the seventh edition of the UICC TNM classification [19]. Regressive changes observed at the primary tumor site were classified according to the modified tumor regression grade (TRG) by Chirieac [21]. TRG1 represents no evidence of vital tumor cells, and TRG2, TRG3, and TRG4 represent 1%–10%, 11%–50%, and >50% residual vital tumor cells, respectively. Two experienced independent pathologists performed central revision of all resection specimens and of FNA samples with uncertain outcome.

Statistical analysis

The primary outcome of this study was the proportion of patients with at least one malignant LN that was correctly identified by radial EUS at 10–12 weeks after completion of nCRT (i.e. sensitivity). Specificity was defined as the proportion of correctly identified patients with no malignant LNs. Agreement of endosonographic findings and findings in the resection specimen was assessed by use of Cohen's kappa coefficient (κ statistic). Secondary outcomes included the proportion of suspicious LNs not fulfilling EUS criteria, location of missed malignant LNs, and the diagnostic value of consecutive FNA sampling. Sensitivity analysis was performed by excluding patients with fewer than 15 LNs in the resection specimen, which is a commonly applied quality threshold [22]. Furthermore, to investigate whether EUS-FNA could potentially be used for detection of residual disease, independence of regressive changes at the primary tumor site (TRG) and ypN stage was tested using a Fisher's Exact test.

Statistical analyses were performed with IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, New York, USA). Tests were considered statistically significant when $P < 0.05$ (two sided).

Results

A total of 219 participants were recruited in the preSANO trial between July 2013 and December 2016. A total of 12 patients were excluded: 8 withdrew consent and 4 did not undergo nCRT (Figure 2). In all, 72 patients did not undergo clinical response evaluation at 10–12 weeks, predominantly due to evidence of residual tumor at 4–6 weeks after nCRT (i.e. positive biopsies or an endoscopic no pass). After exclusion of 2 patients in whom yuN stage was not adequately reported and 32 patients who did not undergo surgery, a total of 101 patients were included in the present study. In these patients, median age was 65 years, 85% were male, and 79% had an esophageal or junctional adenocarcinoma (Table 1).

Identification of malignant lymph nodes by EUS during response evaluation

The results of radial EUS performed at 10–12 weeks after nCRT are shown in Table 2. Suspicious LNs were found in 28 (28%) of 101 patients. In 11 (39%) of these patients, at least one of the identified LNs did not meet all of the EUS criteria for suspicious LNs, most frequently because they were too small (i.e. < 5 mm). The three most common locations for suspicious LNs were the paraesophageal stations in 16 patients (16%) followed by the paratracheal stations in 6 patients (6%), and the celiac trunk stations in 5 patients (5%). Results for nodal staging by EUS were no suspicious LNs (yuN0) in 73 patients (72%), 1–2 suspicious LNs (yuN1) in 21 patients (21%), and 3–6 suspicious LNs (yuN2) in 7 patients (7%).

FNA was performed in 19 (68%) of 28 patients with suspicious LNs based on EUS findings, 16 of whom underwent complete sampling of all suspicious LNs. The most commonly used needle was a 22 gauge FNA needle (58%), median number of passes was 3 (range 1–6), primary tumor site was transversed in eight patients (42%), and on-site pathology was available in four patients (21%). Evidence of residual disease was found in aspirates of three patients (16%); in one of these patients the primary tumor site was transversed. No evidence of residual disease was found in eight patients (42%) and outcome was uncertain in eight patients (42%). The number of passes did not differ between patients with conclusive (i.e. positive/negative) and uncertain outcomes (data not shown). Central revision of uncertain FNA outcomes did not change the outcome.

Histopathological examination of the resection specimen

The median number of harvested LNs was 23 (Supplementary table 1). Malignant LNs were present in 22 (22%) of the 101 patients; most commonly located at the lesser curvature stations (n = 11, 11%) and at the paraesophageal stations (n = 10, 10%). Results for final histopathological nodal staging were no malignant LNs (ypN0) in 79 patients (78%), 1–2 malignant LNs (ypN1) in 14 patients (14%), 3–6 malignant LNs (ypN2) in 5 patients (5%), and more than 6 malignant LNs (ypN3) in 3 patients (3%).

Outcome of response evaluation compared to findings in the resection specimen

Positive and negative findings by radial EUS and histopathological examination of the resection specimen are shown in Table 3. Overall, 11 of the 22 patients with malignant LNs were classified correctly by radial EUS (sensitivity 50%, 95% confidence interval [CI] 28–72), compared with 62 out of 79 patients with no malignant LNs (specificity 78%, 95%CI 68–87). Positive predictive value (PPV) and negative predictive value (NPV) were 39% (11/28, 95%CI 22–59) and 85% (62/73, 95%CI 75–92), respectively. Of the 11 correctly identified patients with malignant LNs, 6 (55%) had at least one suspicious LN that did not meet the EUS criteria and was classified as positive at the discretion of the endoscopist.

The nodal stage of the 11 patients who were not detected by radial EUS was ypN1 in 9 patients and ypN3 in 2 patients (Table 4). All but one malignant LN were located at the distal LN stations (i.e. distal to the carina); at the lesser curvature stations in six patients, at the paraesophageal stations in five patients, at the celiac trunk stations in two patients, and at the subcarinal stations in one patient (some patients had malignant LNs at multiple LN stations).

Agreement of positive and negative findings by radial EUS and histopathological examination of the resection specimen was fair (κ statistic 0.26, P < 0.01). When taking into account nodal staging, agreement was not statistically significant (κ statistic 0.14, P = 0.07). Exclusion of 16 patients with fewer than 15 LNs in the resection specimen showed comparable outcomes (sensitivity 56%, specificity 75%, PPV 37%, NPV 86%, κ statistic 0.26, P = 0.02).

Sensitivity and specificity of conclusive FNA findings were 75 % (3/4, 95 %CI 19 – 99) and 100 % (7/7, 95 %CI 59 – 100), respectively. PPV was 100 % (3/3, 95 %CI 29 – 100) and NPV was 88 % (7/8, 95 %CI 47 – 100). Half of patients (4/8) with uncertain outcome of FNA had malignant LNs. Test accuracy for uncertain outcomes classified either positive or negative are provided in Supplementary table 2.

Residual disease and N stage

Residual disease at the primary tumor site was observed in 73 patients (72 %), 21 of whom (29 %) had malignant LNs in the resected specimen compared with 1 patient (1/28, 4 %) with no evidence of residual disease at the primary tumor site (Supplementary table 3). Fisher's exact test showed a statistically significant association between TRG and ypN stage ($P < 0.01$).

Discussion

This is the first study to prospectively investigate the diagnostic yield of radial EUS and EUS-guided FNA for the detection of malignant LNs 10 – 12 weeks after nCRT in patients with esophageal cancer. Our results showed malignant LNs to be present in 22 % of esophageal cancer patients after nCRT. The most common locations of malignant LNs were the lesser curvature and the paraesophageal stations. Radial EUS detected 50 % of residual nodal disease correctly. Malignant LNs that were not identified by radial EUS were mostly located at the distal LN stations.

The observed sensitivity of radial EUS for the detection of malignant LNs after nCRT is comparable to outcomes reported in previous meta-analyses [14-16]. Owing to its relatively low accuracy after nCRT, EUS has been reported as not being useful in re-staging of esophageal cancer [23,24]. Controversy exists on the applicability of the EUS criteria to define suspicious LNs [11-13]. In our opinion, it is conceivable that the application of nCRT changes the endosonographic appearance of malignant LNs. For instance, nCRT-induced inflammation and fibrosis might lead to a more heterogeneous aspect of malignant LNs, possibly resulting in understaging [13]. Adapted criteria have therefore been suggested to improve diagnostic accuracy of radial EUS after nCRT. The present results support this hypothesis, as more than half of correctly identified patients with malignant LNs had at least one suspicious LN not fulfilling EUS criteria. By performing a study with extensive LN sampling – irrespective of EUS findings – these criteria can be optimized.

Awareness of the location of malignant LNs might improve the accuracy of detecting residual disease as well. Our results showed that malignant LNs were located predominantly at distal LN stations. Interestingly, all but one malignant LN that were missed by EUS were found at the same locations. Similar results have been reported by Griffin et al. in their retrospective review comprising 24 patients with malignant LNs, in which none of the malignant LNs located at the celiac trunk (n = 7) were identified by EUS [24]. From a previous study on initial staging by EUS, it is known that accuracy decreases for distally located LNs [25]. Although the present findings suggest a similar outcome, caution is warranted when interpreting these data, as predominant location of missed LNs may also be explained by observed LN distribution. Despite this, we observed a substantial difference between the number of malignant LNs identified during clinical response evaluations at, for instance, the lesser curvature and the histopathological examination of the resection specimen.

Another suggestion for improving the outcome of EUS after nCRT is the application of FNA [13]. To date, promising results have been reported based on retrospective chart reviews [26,27]. The sampling of LNs located directly behind the primary tumor site has been reported as a major restriction because of the risk of contamination [26-28]. To our knowledge, the present report is the first study to allow sampling of suspicious LNs located directly behind the primary tumor. In a situation of active surveillance, the exact source of vital tumor cells does not impact decision making, which allows potential contamination [3]. However, this strategy may have led to an overestimation of the sensitivity of FNA for malignant LN detection. Furthermore, interpretation of study outcome is encumbered by the relatively low number of suspicious LNs that were sampled by FNA. We are unable to explain this inconsistency with the study protocol and are not sure whether any kind of selection bias may have occurred. Another point of concern remains the proportion of patients with inconclusive FNA outcomes; half of these patients had residual malignant LNs. It can be hypothesized that inconclusive findings as well as false-negative findings are more likely in cases of a low distribution of vital tumor cells [13,28]. Application of on-site cytopathological evaluation or performance of at least three needle passes may help to reduce the incidence of these outcomes [20]. From a clinical point of view, inconclusive findings should not be taken into consideration and FNA should rather be repeated.

Taken together, based on the outcomes of the present study, the application of EUS-FNA as a single diagnostic tool for detection of residual disease should be discouraged. Nevertheless, outcomes of the preSANO trial showed EUS-FNA to be of substantial added value when combined with other diagnostic tools [3]. Furthermore, in a situation of active surveillance, its application is paramount in patients who have residual disease restricted to the LNs only, which is reported to occur in 3%–11% of patients [29-31]. Given the persistent challenge of accurately defining a malignant LN after nCRT, performance of FNA sampling should not depend on the endosonographic aspect of identified LNs. Routine use of EUS-FNA in this setting with sampling of all visible LNs has the potential to improve performance and clinical usability. Furthermore, imaging techniques such as contrast-enhanced harmonic EUS and elastography may also improve the diagnostic yield of EUS-FNA.

The strengths of this study include its prospective design and therefore standardized nCRT regimen and response evaluation. Furthermore, to our knowledge this is the first study to allow classification of suspicious LNs even if they did not fulfill the EUS criteria for malignant LNs. Limitations of this study include the uncertainty with regard to the impact of PET-CT findings on the accuracy of EUS. As endosonographers were not blinded to PET-CT outcomes, some LNs may have otherwise remained undetected. Furthermore, patient selection of this sub study might have led to a selection bias. The study cohort consisted of patients with a negative response evaluation at 4–6 weeks (the preSANO study protocol mandated immediate surgery in cases of any evidence of residual disease) who proceeded to surgery. Nevertheless, the present study cohort still had 72% patients with residual disease at the primary tumor site. Finally, as mentioned above, FNA was performed in a relatively low number of suspicious LNs, which limits interpretation of this secondary outcome. Uncertainty remains if outcomes were missed at random or if any kind of selection bias may have occurred.

In conclusion, radial EUS detected only half of the patients with malignant LNs at 10–12 weeks after nCRT for esophageal cancer. Despite the limited sensitivity of radial EUS, concurrent sampling by FNA has shown to improve the detection rate of patients with residual disease [3]. As long as EUS criteria to accurately define malignant LNs after nCRT are lacking, FNA of LNs should be performed even in cases of low endosonographic suspicion in order to improve sensitivity and minimize the risk of missing substantial residual disease after nCRT.

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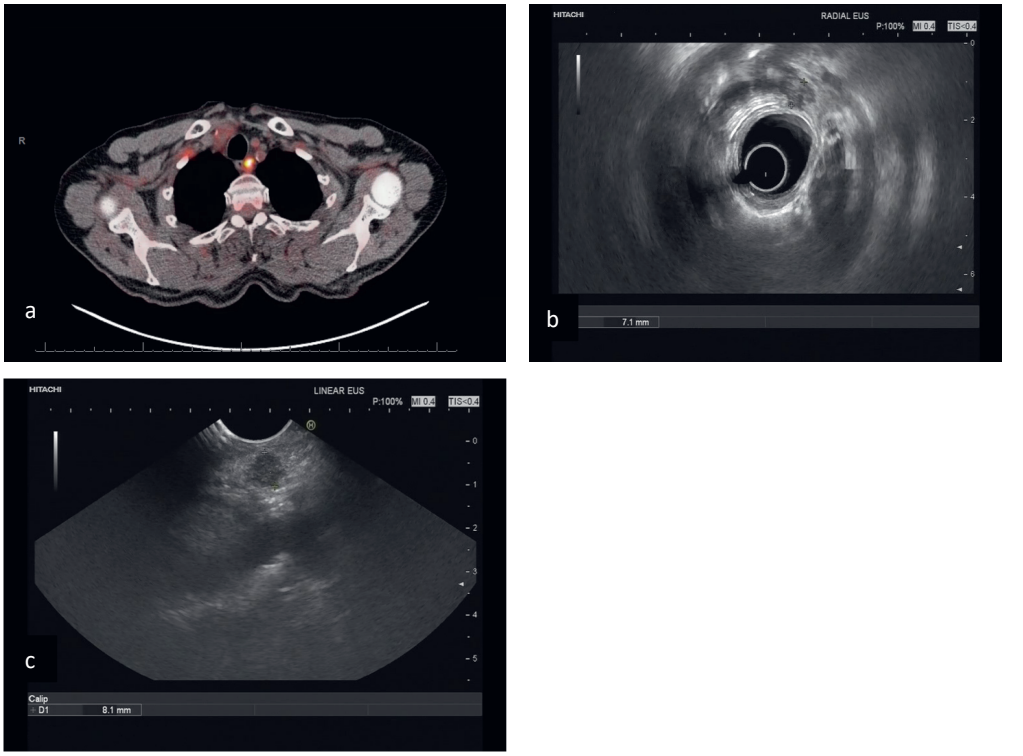

Figure 1. Evaluation of a paratracheal lymph node 12 weeks after neoadjuvant chemoradiotherapy. **a)** PET-CT acquired to guide targeting of suspicious lymph nodes. **b)** Radial EUS image of the suspicious lymph node. **c)** View of linear endoscopic ultrasound before FNA-sampling.

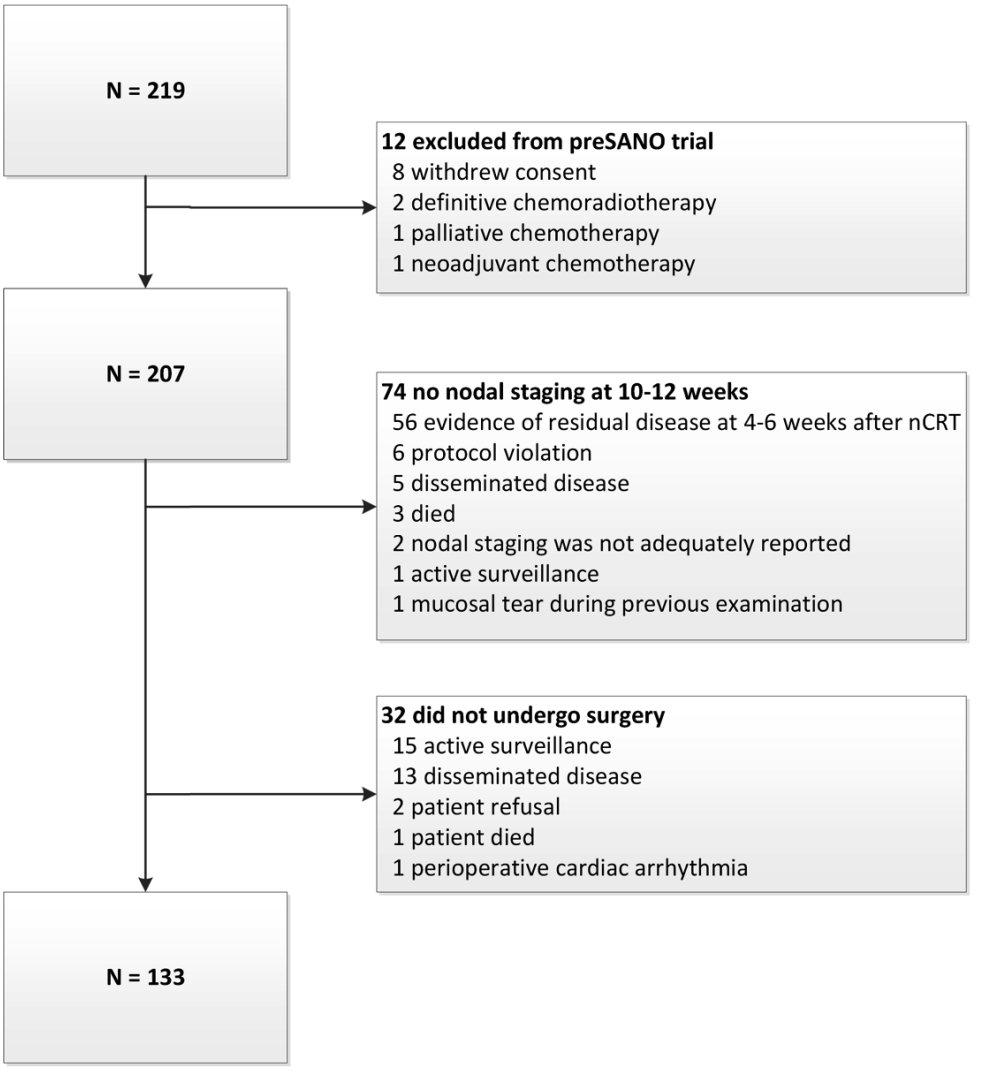

Figure 2. Flowchart of study population.

Table 1. Baseline characteristics of 101 patients before neoadjuvant chemoradiotherapy.

Characteristics	N = 101
Median age, years (IQR)	65 (11)
Male sex, n (%)	86 (85)
Tumor type, n (%)	
Adenocarcinoma	80 (79)
Squamous-cell carcinoma	21 (21)
Clinical T-stage, n (%)[1]	
cT1	1 (1)
cT2	23 (23)
cT3	75 (74)
cT4	2 (2)
Clinical N-stage, n (%)[1]	
cN0	35 (35)
cN1	43 (43)
cN2	21 (21)
cN3	2 (2)

IQR, interquartile range.[1]according to the 7th edition of the UICC TNM classification [19].

Table 2. Endoscopic ultrasound evaluation of lymph nodes at 10-12 weeks after neoadjuvant chemoradiotherapy.

	N = 101
Endoscopic passage, n (%)	101 (100)
Presence of suspicious lymph nodes, n (%)	28 (28)
Presence of suspicious lymph nodes per station, n (%)	
Aortopulmonary window	3 (3)
Celiac trunk	5 (5)
Lesser curvature	1 (1)
Paraesophageal	16 (16)
Paratracheal	6 (6)
Subcarinal	1 (1)
EUS-based N-stage, n (%)[1]	
yuN0	73 (72)
yuN1	21 (21)
yuN2	7 (7)
yuN3	0

[1]according to the 7th edition of the UICC TNM classification [19].

Table 3. Positive and negative findings by endoscopic ultrasound (yuN-) and histopathological examination of the resection specimen (ypN).

	ypN-	**ypN+**	**Total**
yuN-	62	11	73
yuN+	17	11	28
Total	79	22	101

Diagnostic characteristics of radial EUS in detecting malignant lymph nodes (ypN+) after nCRT were: sensitivity 50% (95% CI 28-72), specificity 78% (95% CI 68-87), positive predictive value 39% (95% CI 22-59), negative predictive value 85% (95% CI 75-92), and overall accuracy 72% (95% CI 62-81).

Table 4. Nodal staging by endoscopic ultrasound (yuN) compared to histopathological examination of the resection specimen (ypN)*.

	ypN0	**ypN1**	**ypN2**	**ypN3**	**Total**
yuN0	62	9	0	2	73
yuN1	16	2	3	0	21
yuN2	1	3	2	1	7
yuN3	0	0	0	0	0
Total	79	14	5	3	101

Presence or absence of malignant lymph nodes (ypN) was correctly diagnosed by EUS in 66 (65%) patients, in 20 (20%) patients the number of malignant lymph nodes was overstaged by EUS, and in 15 (15%) patients the number of malignant lymph nodes was understaged.

Supplementary table 1. Type of surgical resection and histopathological examination of the resection specimen.

	N=101
Type of surgical resection, n (%)	
Transthoracic esophagectomy	79 (78)
Transhiatal esophagectomy	21 (21)
Total gastrectomy with distal esophagectomy	1 (1)
Median number of lymph nodes harvested, n (IQR)	23 (13)
Patients with malignant lymph nodes in the resection specimen, n (%)	22 (22)
Patients with presence of malignant lymph nodes per station, n (%)	
Aortopulmonary window	1 (1)
Celiac trunk	4 (4)
Lesser curvature	11 (11)
Paraesophageal	10 (10)
Paratracheal	0
Subcarinal	3 (3)
Unknown	1 (1)
N-stage based on histopathological examination, n (%)[1]	
ypN0	79 (78)
ypN1	14 (14)
ypN2	5 (5)
ypN3	3 (3)

IQR, interquartile range.

[1]according to the 7th edition of the UICC TNM classification [19].

Supplementary 2. Outcomes of fine-needle aspiration compared to histopathological examination of the resection specimen.

	Uncertain excluded	Uncertain positive	Uncertain negative
Sensitivity (95% CI)	75 (19-99)	88 (47-100)	38 (9-76)
Specificity (95% CI)	100 (59-100)	64 (31-89)	100 (72-100)
PPV (95% CI)	100 (29-100)	64 (31-89)	100 (29-100)
NPV (95% CI)	88 (47-100)	88 (47-100)	69 (41-89)

CI, confidence interval

Supplementary table 3. Histopathological regressive changes at the primary tumor site (TRG) compared to nodal staging (ypN).

	ypN-	ypN+	Total
TRG 1	27	1	28
TRG 2-4	52	21	73
Total	79	22	101

TRG, tumor regression grade.

Chapter 5

Letter of correspondence

Endosonography-guided fine-needle aspiration for re-evaluation of lymph node status after neoadjuvant therapy in patients with esophageal cancer: is there any role for it?

E. Vazquez-Sequeiros

Preoperative staging of esophageal carcinoma usually relies on the sequential assessment of the tumor TNM stage by computed tomography (CT) scan and/or positron emission tomography (PET)-CT, followed by endoscopic ultrasound (EUS).[1] Identification of patients with locally advanced cancer (T3 and, more importantly, N1 disease) is crucial to indicate preoperative neoadjuvant therapy and increase the chances of cure.[1] EUS appears to be superior to other techniques for locoregional (TN) staging of these patients.[1] However, although highly accurate (80%–85%), lymph node (LN) status assessment relies on subjective EUS criteria such as echogenicity, and roundness or sharpness of the LN border, which has somehow limited the credibility and reproducibility of EUS nodal stage assessment.[1] EUS-guided fine-needle aspiration (EUS-FNA) of LNs for cytologic confirmation of nodal status has been shown to be the best technique in patients with esophageal cancer.[1]

Although oncology societies support the routine use of EUS-FNA in this setting in clinical practice, economic issues and, more importantly, the prolonged examination time required to perform EUS-FNA, have limited its incorporation into routine clinical practice. Some attempts have been made to improve the positive predictive value of EUS LN criteria by adding LN location, number of nodes identified or presence of an advanced tumor stage to the standard criteria.[2] Application of these modified EUS criteria for LN assessment could theoretically avoid EUS-FNA of LNs in 42% of cases, as patients with ≤1 positive modified criteria or ≥6 positive modified criteria would have 100% negative and positive predictive values, respectively.[2]

"These results suggest that EUS lymph node (LN) criteria should not be applied for re-staging of LNs in patients with esophageal cancer and, more importantly, if a treatment decision after neoadjuvant therapy is to be taken based on LN status, EUS-FNA should be performed definitively, even in cases of nonmalignant-appearing LNs."

It is important to state upfront that standard and modified EUS criteria for LN assessment have been designed and validated only for patients who have not undergone neoadjuvant therapy.[1, 2] Moreover, we do not really know how LN aspect may be modified after chemoradiotherapy, and how inflammation or edema may alter LN morphology, borders or echogenicity. It may be possible that we cannot rely on those criteria if LNs have to be re-evaluated after neoadjuvant therapy in order to decide on the next treatment, if applicable: 1) surgery vs. surveillance without surgery; 2) continue or discontinue chemoradiotherapy; 3) initiate salvage or novel therapies such as immune therapy.

In this issue of Endoscopy, results from the prospective study by van der Bogt et al. [3] suggest that EUS criteria for LN malignancy are not accurate enough to differentiate benign from malignant LNs in patients with esophageal cancer after neoadjuvant chemoradiotherapy. The study, conducted in 101 patients, showed that EUS was only able to detect 50 % of patients with malignant LNs 10 – 12 weeks after neoadjuvant chemoradiotherapy, with a specificity of 78 %.[3] However, when EUS-FNA of LNs was performed, sensitivity and specificity improved up to 75 % and 100 %, respectively. These results suggest that EUS LN criteria should not be applied for re-staging of LNs in patients with esophageal cancer and, more importantly, if a treatment decision after neoadjuvant therapy is to be taken based on LN status, EUS-FNA should be performed definitively, even in cases of nonmalignant-appearing LNs.

Although one may argue that, at the present time, re-evaluation of tumor extension after neoadjuvant therapy is probably not very useful in this setting (treatment is rarely modified after that), and available techniques such as CT, PET-CT or EUS are not really accurate to differentiate between inflammation and tumor, it seems reasonable to not give too much attention to this area.[4] However, there is no doubt that treatment of esophageal cancer requires further improvement to increase the likelihood of cure, which is currently quite low. Different measures have already been taken in this direction, such as the new edition (8th) of the TNM classification, which takes into consideration different subclassifications that may have important implications in therapeutic strategy and were not considered in previous editions: 1) clinical staging (cTNM): tumor extension prior to therapy; 2) pathologic staging (pTNM): determined after surgical resection; and 3) neoadjuvant pathologic staging (ypTNM): tumor stage after neoadjuvant therapy followed by surgery.[5] The new TNM classification of esophageal cancer includes differential aspects such as tumor histology type, location, and grade. Refinements to the TNM assessment made in the 8th edition make the classification more accurate and adaptable to current practice, and may influence therapeutic strategy.[5] A more precise and selective assessment of tumor extension in different clinical scenarios may help to identify, for example, elderly patients who could avoid surgery after adequate response to neoadjuvant therapy. There is an increasing number of patients with esophageal cancer who, either because of advanced age or high surgical risk, are not willing to undergo surgery after neoadjuvant therapy. It has been shown that up to 29 % of these patients have no residual disease on

ypTNM (complete response) and it seems reasonable that survival may not be increased by undergoing surgery after completing adjuvant therapy.[6] To prove this concept, ongoing studies aim to determine whether active surveillance leads to noninferior survival, improved quality of life, and reduction in costs, compared with standard esophagectomy.[7] Definitive answers on this field are expected in the next few years. We believe that in these cases, a more accurate re-staging technique, such as EUS-FNA of LNs, will be of increasing interest in the future. Whether or not a positive or negative PET-CT result after neoadjuvant chemoradiotherapy may help in the selection of LNs that need to be sampled or even in the avoidance of EUS-FNA remains unclear, but studies in that direction are definitely needed.

Promising therapies, such as those specifically directed against human epidermal growth factor receptor-2 (e. g. trastuzumab or pertuzumab) or immune checkpoint inhibitors against programmed cell death receptor-1 (e. g. pembrolizumab and nivolumab) or programmed death ligand-1 (e. g. durvalumab) are currently being evaluated, with excellent results.[8] This more aggressive approach may revolutionize our diagnostic and therapeutic approach in esophageal cancer. The role of EUS and, more importantly, EUS-FNA is likely to increase in the future and we need to be prepared for that. The study by van der Bogt et al. is a step in that direction.[8]

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Chapter 5

Letter of correspondence

Lymph node staging in esophageal/junctional tumors after chemoradiotherapy: should we change strategy?

Gianenrico Rizzatti, Mihai Rimbaș, Alberto Larghi

We read the paper by van der Bogt et al. [1] that prospectively evaluated the role of radial endoscopic ultrasound (EUS) for lymph node (LN) restaging in esophageal/junctional tumors after chemoradiotherapy. Among the 101 patients, suspicious LNs were detected by radial EUS in 28 (22 %), of whom 19 (68 %) underwent EUS-guided fine-needle aspiration (FNA). Surgical pathology demonstrated LN involvement in 22 % of patients, with only 50 % of these being discovered by radial EUS. EUS-FNA revealed malignancy in only three patients (16 %), was negative in eight, and inconclusive in eight further patients.

This represents the first prospective study that assessed the performance of radial EUS in this clinical setting. From the present experience and a recent meta-analysis [2], it is clear that EUS criteria defining malignant LNs cannot be applied after chemoradiotherapy. Other techniques, such as positron emission tomography–computed tomography (PET-CT), also failed to detect residual tumor in small LNs, raising the question of how to make this important step more efficient.[2]

One lesson can be learnt from Vasquez-Sequeros and colleagues [3], who not only showed the superiority of EUS-FNA over radial EUS for LN staging of esophageal cancer, but also developed a staging algorithm including rapid on-site cytopathological evaluation (ROSE). In contrast to what was performed in the present study, where no algorithm or EUS-FNA procedure standardization existed, with consequent overall poor results, Vasquez-Sequeros et al. started their staging procedure with EUS-FNA and ROSE from the celiac and non-peritumoral perigastric LN stations, and the procedure was terminated after a positive result.[3]

The observation that almost all malignant LNs after chemoradiotherapy were located distal to the carina should mean restaging of such tumors by EUS-FNA and ROSE starting at these LN stations would increase the procedure performance [4], and decrease the number of LNs sampled and overall procedural time in these usually debilitated patients. Protocols implementing this restaging strategy should provide us with answers in order to avoid unnecessary surgery.

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Chapter 5

Letter of correspondence

Reply to Rizzatti, G. et al

Ruben D. van der Bogt, Berend J. van der Wilk, J. Jan B. van Lanschot, Manon C.W. Spaander

We would like to thank Dr. Rizzatti and colleagues for their interest in our paper entitled “Endoscopic ultrasound and fine-needle aspiration for the detection of residual nodal disease after neoadjuvant chemoradiotherapy for esophageal cancer”.[1]

In their letter to the editor, Dr. Rizzatti and colleagues stress the need for standardization of restaging strategies to improve the detection rate of residual nodal disease after neoadjuvant chemoradiotherapy for esophageal cancer. The authors suggest a systematic approach in which sampling of an adjacent lymph node (LN) station is only performed in the absence of a positive smear from the previously sampled LN station – comparable to an algorithm that was previously published on initial staging of esophageal cancer.[2]

We agree that a change of diagnostic strategy is needed in this clinical setting. After neoadjuvant chemoradiotherapy, residual nodal disease cannot reliably be ruled out based on endoscopic ultrasound (EUS) features alone, necessitating concomitant fine-needle aspiration (FNA) sampling, preferably in the presence of rapid on-site cytopathological evaluation (ROSE). However, we believe that, even in the presence of ROSE, adequate sampling of LNs will remain challenging owing to neoadjuvant chemoradiotherapy-induced fibrosis and the focal distribution of vital tumor cells.[3] Indeed, development of a restaging algorithm may be an important step forward. Ideally, such a restaging algorithm should take into account LN distribution based on both patient and disease characteristics, and enable targeting of the LNs that are most likely to be affected. The results of the ongoing TIGER study – a study on the LN distribution in resectable esophageal cancer after neoadjuvant therapy – may serve to develop such tool.[4]

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6

Chapter 6

Surveillance of clinically complete responders using serial ^{18}F-FDG PET/CT scans in patients with esophageal cancer after neoadjuvant chemoradiotherapy

Maria J. Valkema, Berend J. van der Wilk, Ben M. Eyck, Bas P.L. Wijnhoven, Manon C.W. Spaander, Michail Doukas, Sjoerd M. Lagarde, Wendy M.J. Schreurs, Mark J. Roef, J. Jan B. van Lanschot, Roelf Valkema

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Abstract

Introduction

Active surveillance for patients with esophageal cancer with a clinically complete response (cCR) after neoadjuvant chemoradiotherapy (nCRT) is being studied. Active surveillance requires accurate clinical response evaluations (CREs). ^{18}F-FDG PET/CT might be able to detect local tumor recurrence after nCRT as soon as the esophagus recovers from radiation-induced esophagitis. The aims of this study were to assess the value of serial ^{18}F-FDG PET/CT to detect local recurrence in patients beyond 3 months after nCRT and to determine when radiation-induced esophagitis has resolved.

Methods

This retrospective multicenter study selected patients with a cCR after nCRT, who initially declined surgery and subsequently underwent active surveillance. CREs included ^{18}F-FDG PET/CT, endoscopic biopsies and endoscopic ultrasound with fine-needle aspiration at regular intervals. Maximum standardized uptake values normalized for lean body mass (SUL_{max}) were measured at the primary tumor site. The percentage change in SUL_{max} ($\Delta\%SUL_{max}$) between the last follow-up scan and the scan 3 months post-nCRT was calculated. Tumor recurrence was defined as biopsy-proven vital tumor at the initial tumor site.

Results

Of forty-one eligible patients, 24 patients had recurrent disease at a median of 6.5 months post-nCRT and 17 patients remained cancer-free during a median follow-up of 24 months post-nCRT. Five of 24 patients with tumor recurrence had sudden intense SUL_{max}-increases of >180%. In 19 of 24 patients with tumor recurrence, SUL_{max} gradually increased (median $\Delta\%SUL_{max}$ +18%), whereas SUL_{max} decreased (median $\Delta\%SUL_{max}$ -12%) in patients with ongoing cCR ($P < 0.001$, independent-samples *t* test). In patients with ongoing cCR, SUL_{max} was lowest at 11 months post-nCRT.

Conclusion

Serial ^{18}F-FDG PET/CT might be a useful tool to detect tumor recurrence during active surveillance. In patients with ongoing cCR, lowest-SUL_{max} is reached at 11 months post-nCRT, suggesting that radiation-induced esophagitis has mostly resolved by that time. These findings warrant further evaluation in a larger cohort.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is emerging as a standard treatment for locally advanced esophageal cancer. This approach is largely based on results of the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study, that showed improved survival with multimodality treatment compared to surgery alone [1, 2]. In this trial, the surgical resection specimen of 29% of patients treated with nCRT showed no evidence of residual tumor [1]. These patients may not have benefitted from surgery, since surgery is tied to an increased risk of mortality, postoperative morbidity and decreased quality of life [1, 3, 4]. For this reason, the feasibility and efficacy of active surveillance for patients with a clinically complete response (cCR) to nCRT are being investigated [4]. Active surveillance implies that surgery is offered only when locoregional tumor is detected in absence of distant metastases. Clinical response evaluations (CREs) are needed to select patients who can safely undergo active surveillance and to monitor disease recurrence. The optimal set of diagnostics has been investigated previously and comprises endoscopy with bite-on-bite biopsies, endoscopic ultrasound with fine-needle aspiration of suspected lymph nodes and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) [5].

Detection of local residual tumor by qualitative and quantitative assessment of a single ^{18}F-FDG PET/CT at 3 months after nCRT alone is inaccurate, because of persistent ^{18}F-FDG uptake probably due to post-radiation esophagitis [6]. Thus, after nCRT, ^{18}F-FDG PET/CT is primarily being performed to detect regional lymph node metastases and hematogenous metastases [5]. In the context of an active surveillance strategy, however, the efficacy of ^{18}F-FDG PET/CT for the detection of local tumor recurrence is unclear.

We hypothesize that the inflammatory response in the esophagus will diminish beyond 3 months after nCRT as the esophagus continues to recover from radiotherapy [6]. Accordingly, increasing ^{18}F-FDG uptake over time could well be a sensitive parameter to detect local residual tumor regrowth during active surveillance. The standardized uptake value corrected for lean body mass (SUL_{max}), a quantification of ^{18}F-FDG uptake, could possibly serve as an imaging biomarker to monitor disease recurrence from the lowest value observed, which is defined as the so-called “nadir” [7].

The primary aim of this retrospective study was to assess the value of serial ^{18}F-FDG PET/CT scans to identify local tumor recurrence in patients undergoing active surveillance beyond 3 months after nCRT. The secondary aim was to determine a lowest value of SUL_{max} (nadir-SUL_{max}) during follow-up of patients with ongoing cCR, to determine the time point at which radiation-induced esophagitis has mostly resolved.

Materials and methods

Study design

The present study is a retrospective observational cohort study using data obtained from the prospective diagnostic pre- *S*urgery *A*s *N*eeded in *O*esophageal cancer (preSANO) trial (www.trialregister.nl: NTR4834), a local prospectively maintained database and the surgery arm of the ongoing therapeutic SANO trial (NTR6803) [4, 5, 8]. The multicenter preSANO trial assessed the accuracy of a set of diagnostic modalities to detect substantial residual tumor (>10% residual tumor). The multicenter SANO trial has been initiated to assess the effectiveness and cost-effectiveness of active surveillance compared to immediate surgery. All patients included in the present study underwent nCRT with the intention to undergo immediate surgery after nCRT. The data in the present study have been obtained from three Dutch hospitals: the Erasmus University Medical Center, the Zuyderland Medical Center and the Catharina Hospital Eindhoven. The trials have been approved by the medical–ethical committee of the Erasmus University Medical Center (MEC-2013-211 and MEC-2017-392). All patients provided informed consent.

Patients

Patients had been diagnosed with potentially curable esophageal cancer and received neoadjuvant treatment consisting of five weekly cycles of carboplatin (AUC 2 mg/mL/min) and paclitaxel (50 mg/m^2) on day 1 in combination with a total radiotherapy dose of 41.4 Gy delivered in 23 daily fractions of 1.8 Gy, 5 days per week. At 1.5 month after nCRT, the first clinical response evaluation (CRE-1) was performed with endoscopy and biopsies of the primary tumor site. If no histological evidence of vital tumor was detected, a second CRE (CRE-2) took place at 3 months after nCRT. To exclude disseminated disease prior to the scheduled surgery, at CRE-2 also an ^{18}F-FDG PET/CT scan was performed. Moreover, patients underwent endoscopy with biopsies and endoscopic ultrasound with fine-needle aspiration of suspected lymph nodes.

Patients were eligible for this study if they had a cCR without signs of distant metastases at CRE-2, but had declined surgery for various reasons or had become unfit for surgery due to a deteriorating physical condition. cCR at CRE-2 was defined as absence of residual tumor on biopsies and negative fine-needle aspiration of suspected lymph nodes. Instead of surgery, patients were offered an active surveillance protocol with frequent CREs similar to the active surveillance arm of the SANO trial [4]. After CRE-2, the following CREs (*i.e.* CRE-3, CRE-4, and so on) were scheduled every 3 months in the first year, every 4 months in the second year, every 6 months in the third year, and yearly thereafter, up to a five-year follow-up period in total (Fig. 1). If during active surveillance regrowth of tumor was histologically proven or highly suspected (*e.g.* because of non-traversable tumor at endoscopy), patients were referred to either immediate surgery or palliative care (Fig. 1). Patients with ^{18}F-FDG non-avid tumors before start of nCRT were excluded from analysis.

Definition of tumor recurrence

Local tumor recurrence was defined as histologically proven vital tumor located at the initial tumor site. This definition ignores the locoregional lymph node status, since this study relates changes in ^{18}F-FDG uptake in the esophagus – at the primary tumor site – to corresponding histopathology. Histopathological assessment was performed on tissue from biopsies or on the resection specimen. Assessment of the primary tumor in the resection specimen was by means of the modified tumor regression grade (TRG) system according to Chirieac et al.: TRG1 (0% residual carcinoma), TRG2 (1-10% residual carcinoma), TRG3 (11-50% residual carcinoma) and TRG4 (>50% residual carcinoma) [9]. Ongoing cCR was defined as no histological evidence of recurrence of tumor at the initial tumor site at the time of analysis.

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

^{18}F-FDG PET/CT scans were acquired in three different centers that applied the scanning protocol similar to the SANO trial [4]. In brief, scanning was performed according to European Association Research Limited (EARL) qualifications for qualitative standardized uptake value (SUV) measurements [10]. Start of ^{18}F-FDG PET/CT acquisition was 60 ± 5 minutes after injection of 2.3 MBq/kg ^{18}F-FDG. All follow-up scans were performed on the same scanners under the same conditions.

^{18}F-FDG PET/CT analysis

On every follow-up ^{18}F-FDG PET/CT scan, regions of interest were manually drawn over the primary tumor site determined from the baseline ^{18}F-FDG PET/CT scan (OsiriX MD v.7.5, Pixmeo SARL, Bernex, Switzerland). The placement of regions of interest was independently reviewed by an experienced nuclear medicine physician (R.V.). If this investigator disagreed with the placement of the region of interest of the first investigator, a consensus was established between the two investigators. Regions of interest were also placed at the normal esophagus, blood pool and liver to obtain internal reference measurements. At the regions of interest, standardized uptake values corrected for lean body mass (SUL) were measured. Lean body mass was calculated according to the James equation [10].

The percentage change in maximum SUL during active surveillance ($\Delta\%SUL_{max}$) was calculated with the SUL_{max} values of the scan at 3 months after nCRT and the last follow-up scan in active surveillance. In patients who developed local tumor recurrence, the last follow-up scan corresponded to the moment that local recurrence was histologically proven. In patients with ongoing cCR, the last follow-up scan corresponded to the most recent scan performed during active surveillance at the moment of analysis. If active surveillance had been stopped in patients with ongoing cCR at the primary tumor site because of distant or lymph node metastases, the last follow-up scan corresponded to the moment of the last histopathological evaluation of the initial tumor with biopsies.
In patients with ongoing cCR, the nadir-SUL_{max} was determined [7]. Nadir-SUL_{max} was defined as the lowest SUL_{max} measurement obtained during follow-up. This nadir-SUL_{max} served to determine the moment when ^{18}F-FDG uptake caused by radiation-induced esophagitis is supposed to have normalized.

Statistical analysis

Continuous data are presented with a median value and interquartile range (IQR). Values of ΔSUL_{max} were analyzed between groups using the parametric independent-samples *t* test for normally distributed data or the non-parametric Mann-Whitney U test for non-normally distributed data. Extreme outliers of $\Delta\%SUL_{max}$ were identified by data visualization with boxplots and are described separately. The extreme outliers were removed from the statistical tests for comparison of means and medians, because we expect that these outliers distort the assessment of clinically relevant subtle differences in ΔSUL_{max} between patients with and without local tumor recurrence. To indicate

precision of results, 95% confidence intervals (95% CI) were used. A two-sided *P*-value of < 0.05 was considered statistically significant. Since this is an explorative study, sample size calculation was not performed. Statistical analysis was performed using R-3.6.1 for MacOS (R: A language for statistical computing version; Vienna, Austria).

Results

Study group

Between March 2013 and July 2019, 43 patients with FDG-avid tumors who had cCR at CRE-2, declined planned surgery and underwent active surveillance off-protocol were identified from the prospective database of 278 patients (15%) who underwent nCRT with the intention to undergo immediate surgery thereafter. Baseline characteristics are shown in Table 1. The ^{18}F-FDG PET/CT scan at CRE-2 was performed at a median of 11.6 weeks (IQR 10.4 – 12.3) after completion of nCRT.

The flowchart of the study is shown in Fig. 2. Two of the 43 patients had clinically manifest distant metastases at 3 months after nCRT and did not undergo further analysis of the primary tumor with endoscopy and biopsies. Since the histological status of the primary tumor was therefore unknown, these patients were excluded from further analysis. Thus, data of 41 patients were eligible for analysis of serial ^{18}F-FDG PET/CT scans during active surveillance.

At a median follow-up of 6.5 months after completion of nCRT (IQR 5.9 – 11), the primary tumor had recurred in 24 of 41 (59%) patients. In most cases of local tumor recurrence, this was at CRE-3 (15/24, 63%). Esophagectomy was performed in 21 of 24 patients; 20 of them had biopsy-proven local tumor recurrence and one patient had non-traversable tumor at endoscopy with TRG4 in the resection specimen. Three of 24 patients did not undergo esophagectomy for the following reasons respectively: unfit for surgery; definitely declined surgery; unresectable tumor (Fig. 2).

During a median follow-up of 24 months after nCRT (IQR 12 – 25), no biopsy-proven recurrence of the primary tumor was found in 17 of 41 (41%) patients (*i.e.* ongoing cCR). Ten of these 17 patients were in active surveillance at time of analysis. Active surveillance had been ended for 7 of 17 patients with cCR at time of analysis: one patient underwent esophagectomy because of a solitary lymph node recurrence without biopsy-proven tumor at the primary tumor site (ypT0N3, TRG1); two patients definitely declined surgery after CRE-3; one patient was conditionally inoperable at CRE-3; one patient died due to cardiovascular disease; and two patients had distant metastases after CRE-3 and CRE-4 respectively (Fig. 2).

For all patients with either local tumor recurrence or ongoing cCR, the individual courses of SUL_{max} at the primary tumor site and the SUL values at the reference regions are shown in Supplemental Tables 1 and 2.

SUL_{max} in patients with local tumor recurrence

Two different patterns of ^{18}F-FDG uptake were observed indicative of local recurrence. Five of 24 patients had sudden intense increases in SUL_{max}, all >180% (*i.e.* extreme outliers). In these patients, median $\Delta\%SUL_{max}$ was +283% (IQR 262 – 316) and absolute ΔSUL_{max} was +6.1 (IQR 5.6 – 8.3). These increases took place at the following time-moments after nCRT: between 3 and 6 months (n=2); between 6 and 9 months (n=1); between 12 and 16 months (n=1); and between 24 and 30 months, after a first increase between 20 and 24 months (n=1, Fig.3).

In the remaining 19 of 24 patients with local tumor recurrence, a gradual increase of median $\Delta\%SUL_{max}$ of +18% (IQR 14 – 43) was seen. By contrast, median $\Delta\%SUL_{max}$ was -12% (IQR -36 – 1.4) in the 17 patients with ongoing cCR. The mean difference of $\Delta\%SUL_{max}$ between these groups was statistically significant ($P < 0.001$, 95% CI 21 – 58%, independent-samples *t* test) (Fig. 4). In patients with local tumor recurrence, the median absolute ΔSUL_{max} was +0.69 (IQR 0.35 – 1.0); in patients with ongoing cCR this was -0.28 (IQR -1.1 – 0.30; $P < 0.001$, 95% CI 0.65 – 1.69, Mann-Whitney U test) (Fig. 4).

Patients' tumor characteristics, separated for the different ^{18}F-FDG uptake patterns, are shown in Supplemental Table 3.

SUL_{max} in patients with ongoing cCR

In patients with ongoing cCR, the nadir-SUL_{max} was found at a median time of 11 months (IQR 5.9 – 18) after nCRT. The median value of nadir-SUL_{max} was 1.80 (IQR 1.4 – 2.1). At CRE-2, median SUL_{max} was 2.6 (IQR 2.1 – 3.2), at CRE-3 this was 2.1 (IQR 1.8 – 2.4), at CRE-4 2.2 (IQR 1.7 – 2.4) and at CRE-5 2.2 (IQR 1.8 – 2.5) (Fig. 5).

In Fig. 6, ^{18}F-FDG PET/CT scans are shown of a patient with ongoing cCR of the distal esophagus, illustrating a pattern of SUL_{max} increase at a location different from the location of the primary tumor. Approximately a year after nCRT, linear ^{18}F-FDG uptake develops cranially to the initial tumor site, of unknown cause. At the primary tumor site in the distal esophagus, SUL_{max} remains comparable to the

background ^{18}F-FDG-activity level. No histologically proven recurrence of tumor was found during all CREs.

Discussion

This study identified two patterns of SUL_{max} increases ($\Delta\%SUL_{max}$) in patients with local tumor regrowth beyond 3 months after nCRT. Some patients showed a pattern of sudden increase in FDG-metabolism ($\Delta\%SUL_{max}$ >180%), which was indicative of residual disease in all. Most patients with local tumor regrowth, however, had an insidious gradual increase in $\Delta\%SUL_{max}$. In contrast, patients with ongoing cCR had stable or decreasing $\Delta\%SUL_{max}$. These findings suggest that ^{18}F-FDG PET/CT can be used during active surveillance after nCRT, not only to detect distant metastases or to guide endoscopic ultrasound with fine-needle aspiration of suspected lymph nodes, but also to monitor local tumor recurrence. These findings apply to patients with cCR who, like in the present cohort, choose to refrain from surgery after nCRT. This would also become relevant for patients who will undergo active surveillance if that strategy becomes a standard alternative treatment to immediate surgery in patients with cCR [4, 8, 11-13]. This policy is currently being investigated in the ongoing therapeutic Dutch SANO trial and the French ESOSTRATE trial [4, 14].

To our knowledge, this is the first study that describes repeated ^{18}F-FDG PET/CT in an active surveillance setting for esophageal cancer patients with cCR. For rectal carcinoma, serial ^{18}F-FDG PET/CT was used in a watch-and-wait protocol in patients with cCR after nCRT [15]. In that study, complete responses on ^{18}F-FDG PET/CT corresponded with negative clinical and endoscopic examinations. Moreover, for squamous cell head-and-neck cancer, surveillance with ^{18}F-FDG PET/CT was shown cost-effective to guide the decision to perform surgery after nCRT [16].

Response assessment with a single ^{18}F-FDG PET/CT scan at 3 months after completion of nCRT is not accurate, partly because of persisting post-radiation inflammation [6]. In the present study, ^{18}F-FDG uptake decreased after 3 months post-nCRT and further normalized at 6 months post-nCRT and onwards, supported by a median nadir-SUL_{max} of 1.80 (IQR 1.4 – 2.1) at 11 months (IQR 5.9 – 18) post-nCRT. These findings indicate an ongoing recovery of esophagitis beyond 3 months after nCRT, presumably reaching stability within a year.

Increased ^{18}F-FDG uptake after completion of nCRT, as shown in Fig. 6, should be interpreted carefully with respect to its distribution and location. A linear pattern of ^{18}F-FDG uptake located outside the initial tumor site suggests benign inflammatory conditions such as Candida esophagitis or gastro-

esophageal reflux disease, whereas focal ^{18}F-FDG uptake at the initial tumor site suggests recurrent tumor [17].

A major strength of the present study is that ^{18}F-FDG PET/CT data were prospectively and systematically obtained. This allowed comparison of serial SUL_{max} measurements with histological biopsies at all CREs. Nevertheless, several limitations need to be addressed. First, the cohort size was too small to define a cut-off value for ΔSUL_{max} that reliably discriminates between a clinically manifest recurrence and ongoing cCR. Hypothetically, a cut-off value for ΔSUL_{max} could be formulated similarly to the definition of biochemical failure in prostate cancer based on prostate-specific antigen. This is defined as a certain increase higher than the nadir prostate-specific antigen value [7]. Such a cut-off value incorporates the information of the course of SUL_{max} over time, rather than of one moment in time. Second, the nadir-SUL_{max} for defining the moment at which radiation-induced esophagitis has extinguished, may change when a larger number of patients is analyzed than in the present study. Third, regions of interest were manually placed on the initial tumor site. An automatic registration of regions of interest at multiple scans might possibly improve robustness of serial SUL_{max} measurements. Fourth, this cohort of patients might be a highly-selected group, imposing selection bias to the results. This may be reflected by for example the median age of 70 years in this cohort, as opposed to a median of 66 years of patients in the preSANO trial, although the other baseline characteristics are relatively similar [5]. Fifth, in order to optimize sensitivity in SUL_{max}-changes with serial ^{18}F-FDG PET/CT, adherence to scanning protocols should become even more strict. Fluctuations of SUL_{max} in patients with ongoing cCR (Supplemental Table 2) may partially be attributed to variations in scanning parameters apart from physiologic causes. By performing scanning exactly under the same circumstances every time, the signal-to-noise ratio might be further improved.

Results of the present study have potential implications for clinical decision-making. As shown in Fig. 3, an increase in SUL_{max} at the initial tumor site after a relatively stable signal at more than two years in active surveillance might be more suspect of residual tumor than of physiological fluctuations or other benign causes such as reflux-esophagitis. If such a deviation takes place without confirmation by biopsy-proven recurrence, shortening the interval to the next CRE should be considered. Alternatively, one could even decide to proceed to surgery without further delay.

Before such clinical implications can be accepted, these results require validation in a larger group of patients randomly allocated to active surveillance, e.g. in the experimental active surveillance arm of the ongoing SANO trial [4]. Furthermore, new techniques for response assessment should be explored

as well. Integrated PET/MRI seems promising, since it could provide additional anatomical and functional value over PET/CT [18, 19]. Visualization of the esophagus with PET/MRI however is still challenging because of the cardiorespiratory motion in the mediastinum [20]. Additionally, complex imaging features could be explored by radiomics. Radiomic features are able to describe, for instance, shape characteristics or heterogeneity of the tumor [21]. Theoretically, change in radiomic features may reveal early tissue changes within an active surveillance setting.

Conclusion

Results of this explorative study show that serial ^{18}F-FDG PET/CT might be a useful tool to distinguish recurrence of tumor from physiological SUL_{max} fluctuations in complete responders during active surveillance. A steep increase in FDG-activity over a short period of time should be a warning sign for recurrent local tumor. Furthermore, a gradual increase in FDG-activity over the course of time should also alert to recurrence of tumor. Radiotherapy-induced esophagitis will usually have dissolved at eleven months after completion of chemoradiotherapy.

Disclosure

The preSANO trial was funded by the Dutch Cancer Foundation (project number EMCR-2014-7430). The SANO trial is currently funded by ZonMW (project number 843004104) and the Dutch Cancer Foundation (project number 10825). No other potential conflicts of interest relevant to this article exist.

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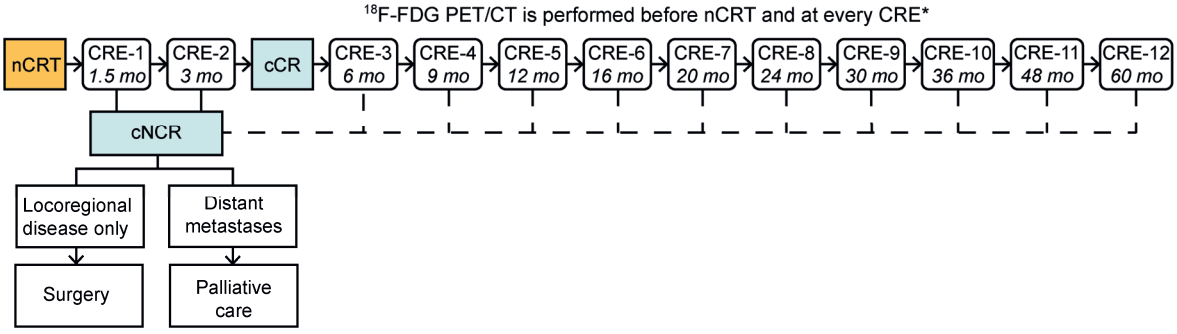


Figure 1. Timeline of CREs during active surveillance according to the SANO trial protocol.

*At CRE-1 ^{18}F-FDG PET/CT is performed in case of cNCR to exclude distant metastases. nCRT = neoadjuvant chemoradiotherapy; CRE = clinical response evaluation; mo = months after nCRT; cCR = clinically complete response; cNCR = clinically non-complete response

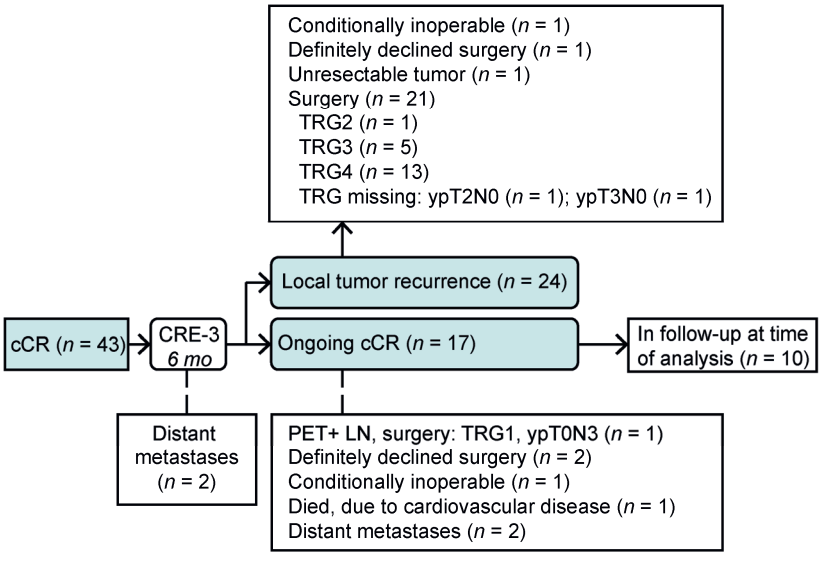


Figure 2. Flowchart of study patients with cCR at 3 months after nCRT. cCR = clinically complete response; CRE = clinical response evaluation; mo = months after neoadjuvant chemoradiotherapy; TRG = tumor regression grade; PET+ LN = positive lymph nodes detected with ^{18}F-FDG PET/CT

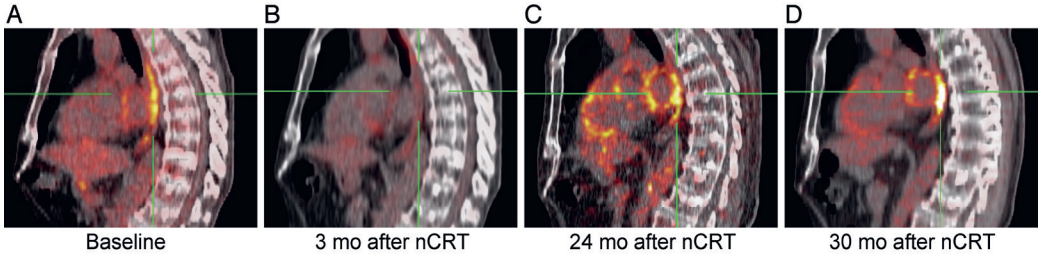


Figure 3. Sagittal view of a patient who developed local tumor recurrence during active surveillance. (A) Baseline scan. (B) Normalized ^{18}F-FDG uptake in the esophagus at 3 months after nCRT. (C) From 20 to 24 months after nCRT, SUL_{max} increases with 20% without histological evidence for recurrence of tumor. (D) From 24 to 30 months after nCRT, SUL_{max} increases with 51% and local tumor recurrence is diagnosed with biopsies. Esophagectomy at 30 months after nCRT was performed (TRG3, ypT1bN0).mo = months; nCRT = neoadjuvant chemoradiotherapy

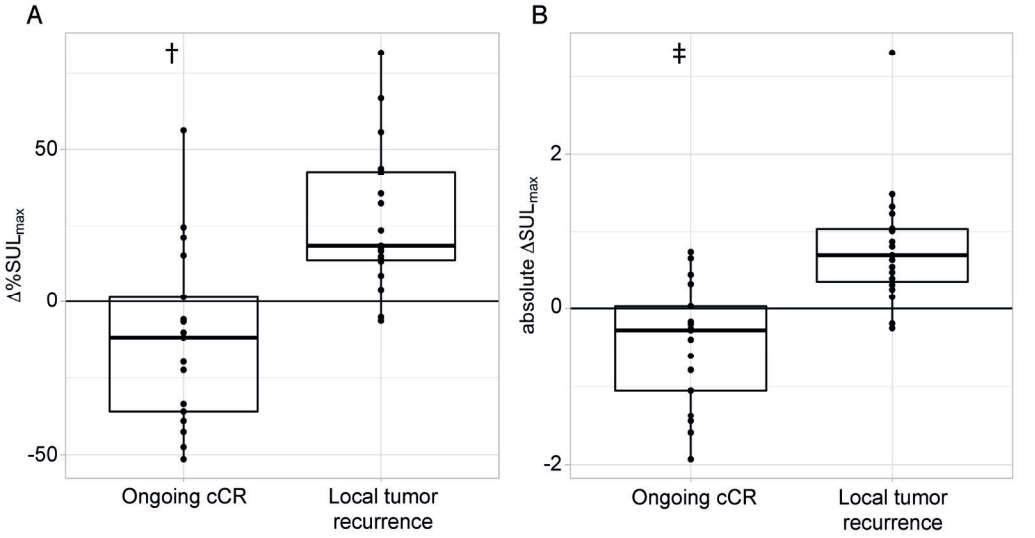


Figure 4. Boxplots of (A) $\Delta\%SUL_{max}$ and (B) absolute ΔSUL_{max} of the primary tumor site in patients with ongoing cCR versus patients who developed local tumor recurrence. Five outliers with extreme high $\Delta\%SUL_{max}$-values of >180% are not shown and are described separately in the Results (see Statistical Analysis). † $P < 0.001$ (independent-samples *t* test), ‡ $P < 0.001$ (Mann Whitney U-test), cCR = clinically complete response

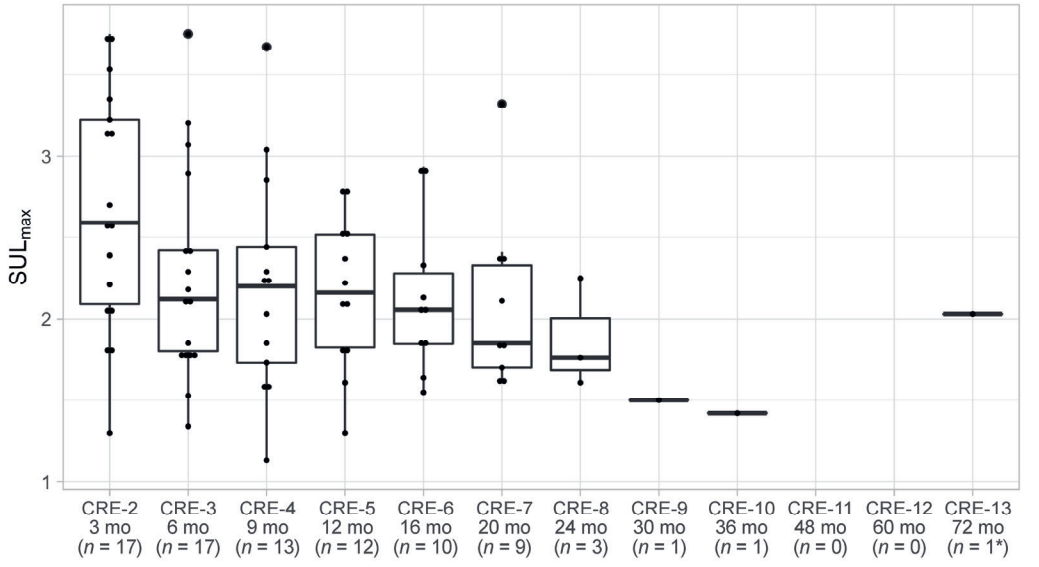


Figure 5. Boxplots representing median and interquartile range of SUL_{max} in patients with ongoing cCR.

* This patient had no scans performed between CRE-6 and CRE-13. CRE = clinical response evaluation; mo = months after nCRT

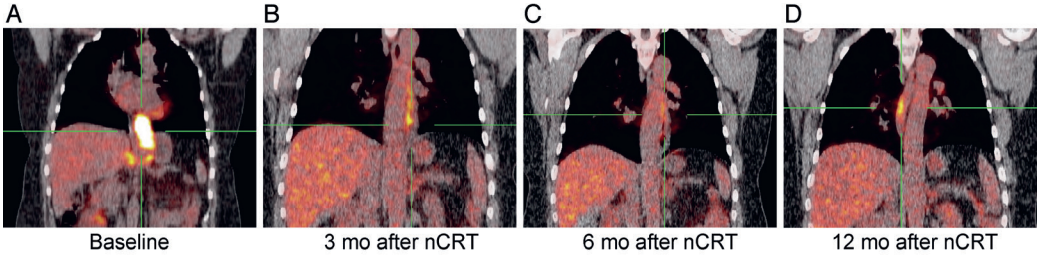


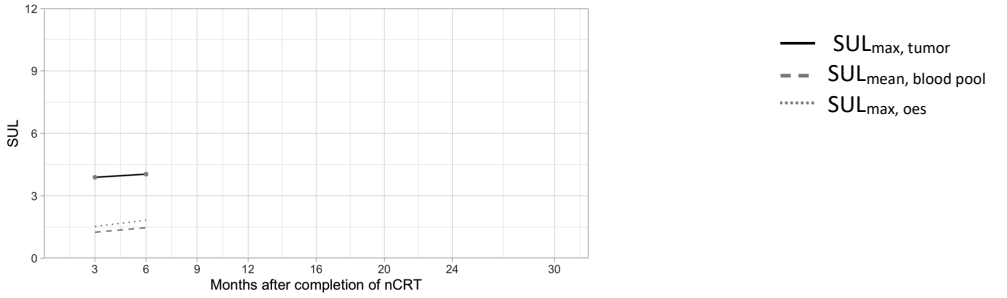
Figure 6. Coronal view of a patient with ongoing cCR. (A) Baseline scan. (B, C) Normalization of ^{18}F-FDG uptake in the esophagus until 6 months after nCRT. (D) Development of linear ^{18}F-FDG uptake at 12 months after nCRT cranially to the initial tumor site, of unknown cause. No histologically proven recurrence of tumor was found during all CREs. mo = months; nCRT = neoadjuvant chemoradiotherapy,

Table 1. Baseline patient and tumor characteristics

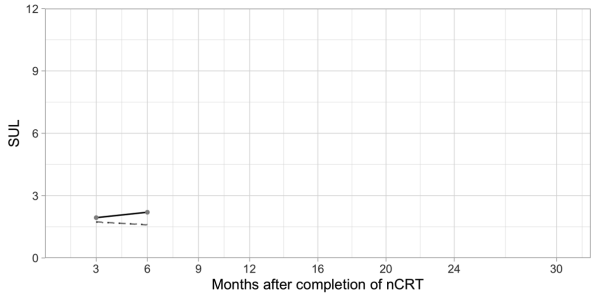
Variable	**Data *n* (%) (total of 43 patients)**
Male	33 (77)
Age in years (median, interquartile range)	70 (62 – 74)
Histology	
Squamous cell carcinoma	11 (26)
Adenocarcinoma	31 (72)
Adenosquamous carcinoma	1 (2)
cT*	
cT1	0 (0)
cT2	11 (26)
cT3	28 (65)
cT4	1 (2)
cTx	1 (2)
Missing	2 (5)
cN*	
cN0	17 (41)
cN1	11 (26)
cN2	12 (28)
cNx	1 (2)
Missing	2 (5)
Differentiation grade	
Good-moderate	16 (37)
Poor	10 (23)
Missing	17 (40)

Supplemental Table 1. Patients with histologically proven recurrence of primary tumor at latest response evaluation in active surveillance

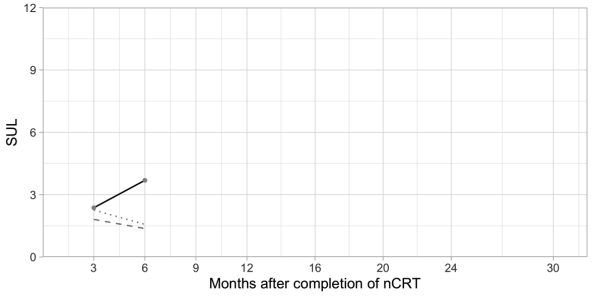
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
1	2	3.89	4.94	75	59	5.2	63	1.25	1.86	1.53
	3	4.04	5.19	77	60	missing	61	1.47	1.93	1.83



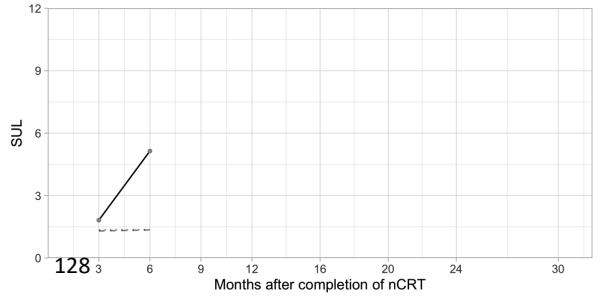
2	2	1.94	2.49	81	63	9.3	57	1.74	2.13	1.72
	3	2.20	2.83	82	64	9.1	64	1.59	2.13	1.61



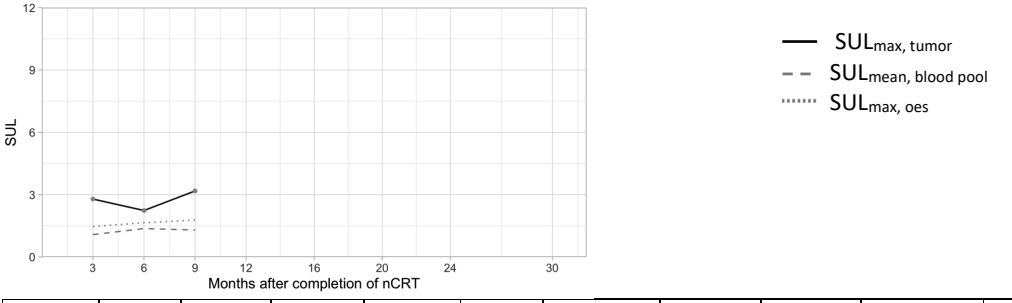
3	2	2.37	2.96	74	59	8.0	59	1.81	2.21	2.26
	3	3.69	4.52	70	57	7.1	54	1.37	1.67	1.57



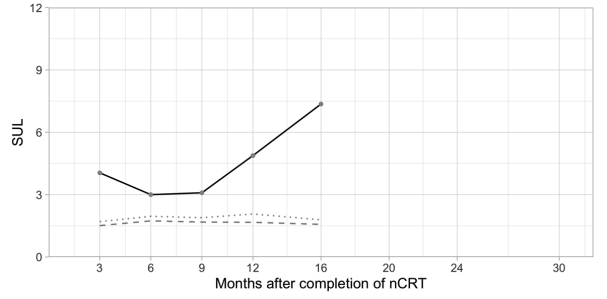
4	2	1.82	2.75	68	45	6.5	67	1.3	2.04	1.35
	3	5.14	7.77	68	45	6.2	50	1.35	1.99	1.36



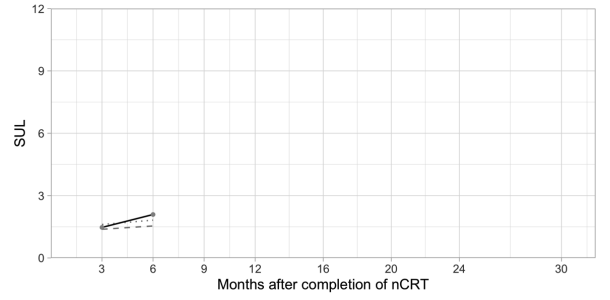
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
5	2	2.79	3.54	70	55	6.4	72	1.08	1.70	1.47
	3	2.24	2.84	70	55	6.1	58	1.37	1.68	1.65
	4	3.18	4.07	72	56	5.9	61	1.30	1.78	1.78



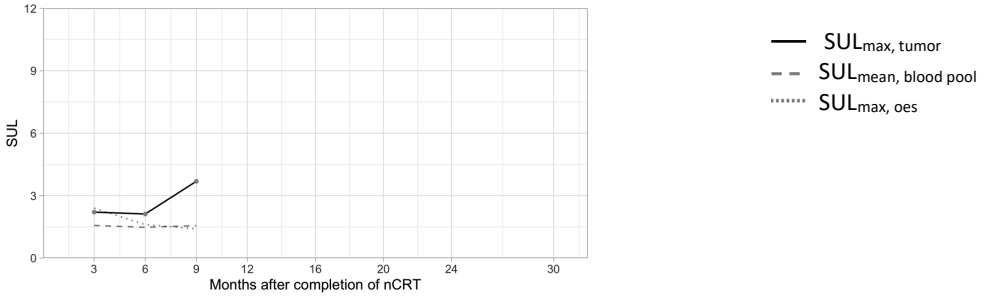
6	2	4.05	5.30	85	65	7.4	59	1.51	1.88	1.70
	3	3.00	3.93	85	65	7.2	55	1.74	2.06	1.96
	4	3.09	4.04	85	65	6.7	55	1.68	2.18	1.89
	5	4.88	6.41	86	65	6.4	58	1.67	2.05	2.07
	6	7.36	9.39	80	63	5.2	62	1.57	2.03	1.79



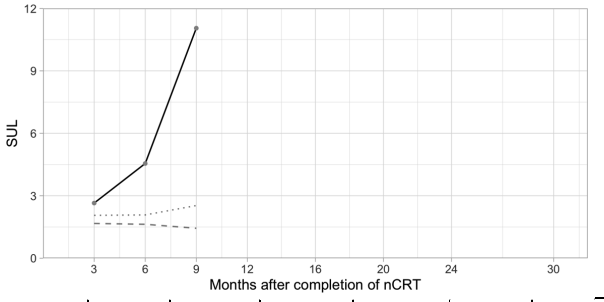
7	2	1.47	1.82	80	64	7.7	59	1.38	1.61	1.61
	3	2.09	2.63	82	65	9.7	56	1.54	1.84	1.82



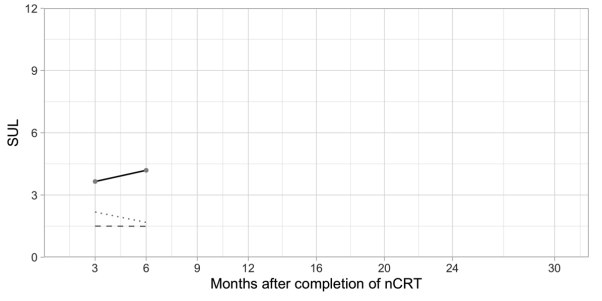
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
8	2	2.21	3.04	93	68	7.6	44	1.57	2.02	2.40
	3	2.12	2.87	90	67	7.2	59	1.48	1.89	1.61
	4	3.69	5.10	94	68	8.0	51	1.56	2.10	1.41



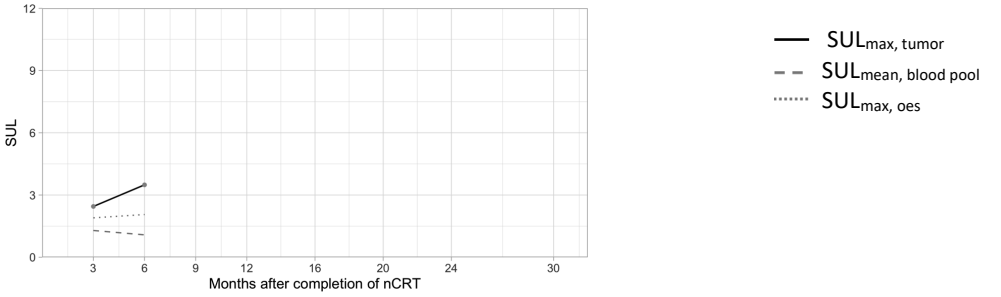
9	2	2.65	3.01	58	51	5.9	50	1.67	2.02	2.06
	3	4.55	5.27	63	54	5.4	50	1.63	2.14	2.08
	4	11.05	12.90	65	56	4.8	59	1.44	1.79	2.53



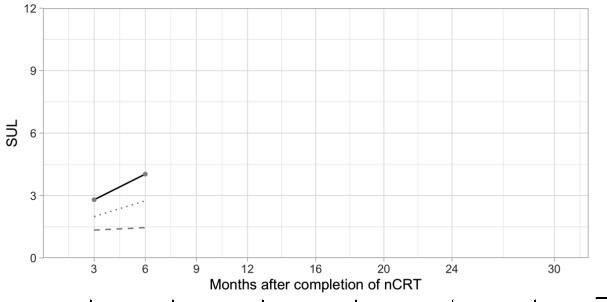
10	2	3.65	5.28	107	74	5.5	60	1.50	2.46	2.18
	3	4.19	6.06	107	74	6.0	58	1.49	2.43	1.68



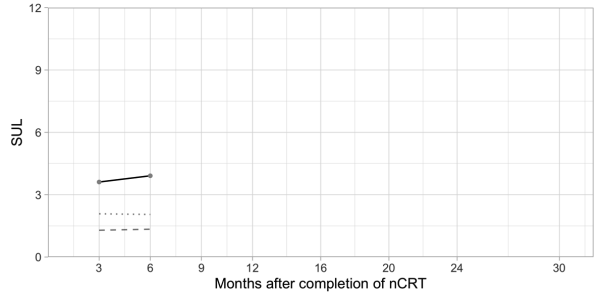
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
11	2	2.45	3.73	76	50	5.4	55	1.29	1.53	1.90
	3	3.49	5.31	76	50	5.7	66	1.08	1.60	2.06



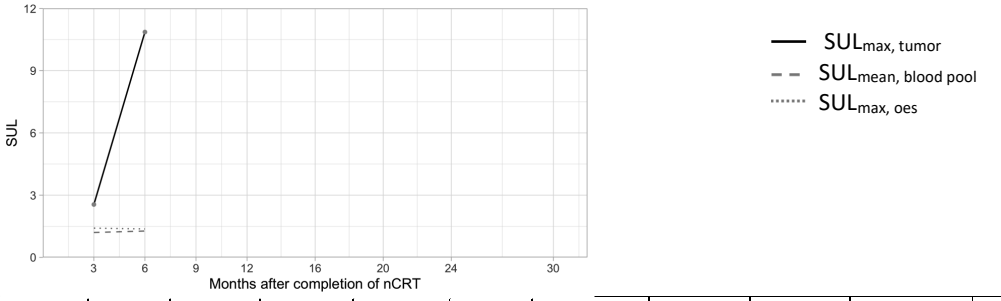
12	2	2.8	3.31	56	47	6.9	61	1.34	1.68	1.99
	3	4.03	4.81	58	49	7.7	60	1.46	1.87	2.75



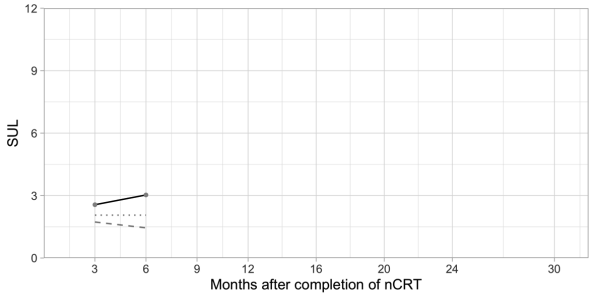
13	2	3.61	4.85	88	66	5.0	40	1.29	1.78	2.08
	3	3.91	5.26	88	66	5.2	60	1.34	1.88	2.05



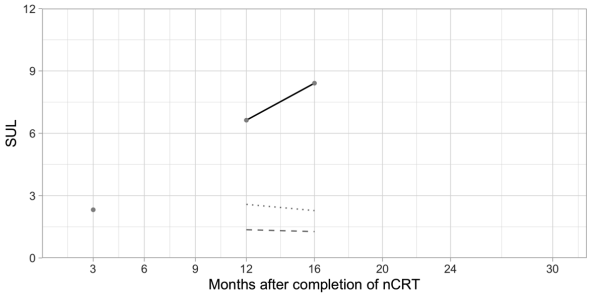
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
14	2	2.55	3.96	108	69	6.1	61	1.2	1.65	1.41
	3	10.86	17.00	109	70	6.0	55	1.27	1.93	1.37



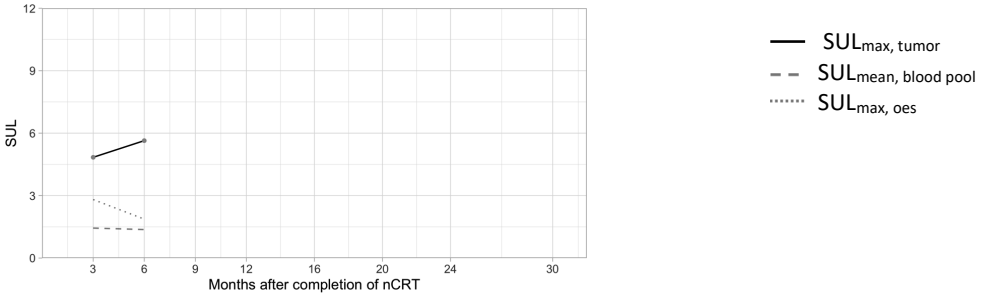
15	2	2.56	3.33	81	62	5.7	55	1.73	2.08	2.06
	3	3.03	3.88	78	61	5.1	54	1.45	1.78	2.06



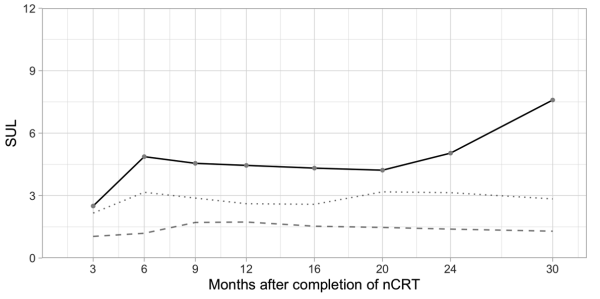
16	2	2.32	2.83	73	60	5.8	62	1.34	1.82	1.65
	No scans performed at CRE-3 or CRE-4									
	5	6.63	8.46	75	59	missing	50	1.36	1.92	2.58
	6	8.41	10.69	74	58	5.8	54	1.27	1.87	2.28



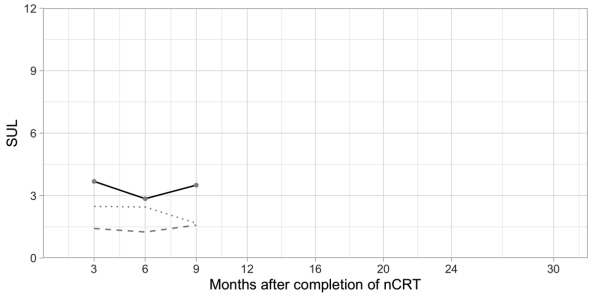
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
17	2	4.84	6.88	112	79	8.4	53	1.44	2.13	2.81
	3	5.64	8.33	112	76	8.0	52	1.37	2.00	1.87



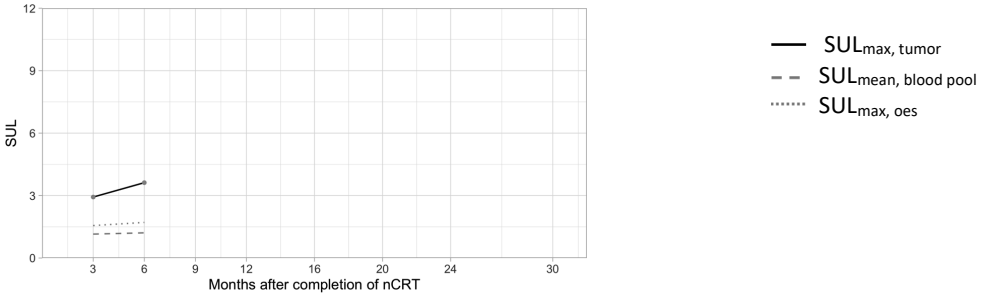
18	2	1.98	2.48	76	61	4.3	69	1.05	1.34	1.74
	3	4.87	6.09	76	61	5.7	67	1.19	1.74	3.16
	4	4.55	5.80	80	63	5.1	51	1.71	1.96	2.88
	5	4.45	5.57	76	61	5.3	51	1.73	2.04	2.61
	6	4.32	5.40	76	61	5.0	53	1.53	1.85	2.58
	7	4.22	5.33	78	62	6.2	55	1.47	1.86	3.18
	8	5.04	6.37	78	62	5.3	59	1.39	1.85	3.14
	9	7.59	9.49	76	61	missing	57	1.29	1.71	2.84



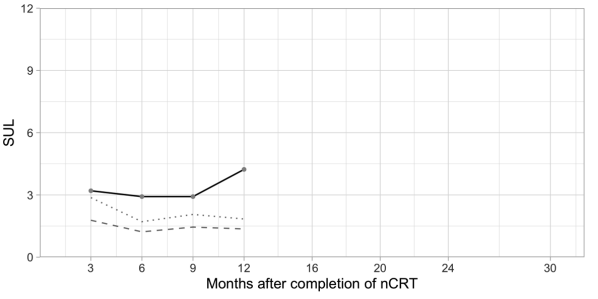
19	2	3.68	5.52	67	45	5.6	50	1.42	1.90	2.48
	3	2.85	4.23	66	44	6.3	59	1.25	1.82	2.45
	4	3.50	5.11	65	45	4.9	60	1.58	1.98	1.67



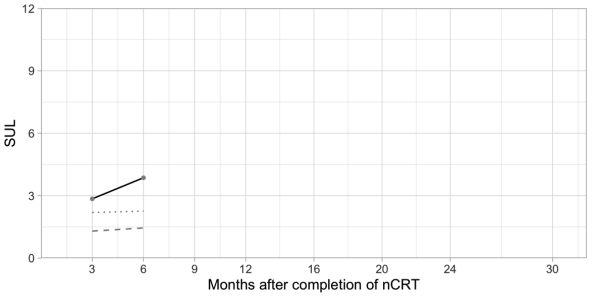
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
20	2	2.93	3.66	79	63	4.9	65	1.15	1.53	1.56
	3	3.62	4.60	83	65	5.1	65	1.21	1.57	1.71



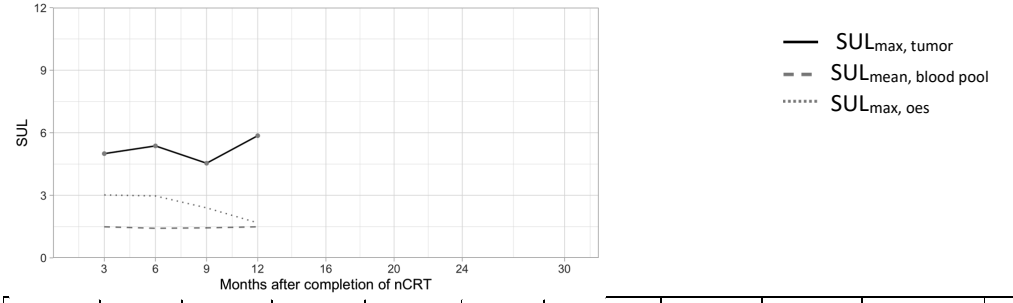
21	2	3.20	3.98	62	50	5.4	52	1.78	2.11	2.87
	3	2.92	3.73	65	51	5.2	63	1.22	1.56	1.71
	4	2.92	3.62	62	50	4.7	55	1.45	2.85	2.06
	5	4.23	5.39	63	49	5.2	56	1.36	1.68	1.84



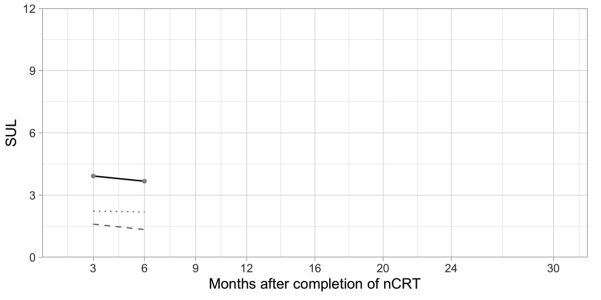
22	2	2.85	3.62	67	53	5.1	60	1.30	1.78	2.19
	3	3.86	4.86	67	53	4.9	56	1.45	1.90	2.26



Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
23	2	5.00	7.44	122	82	6.7	50	1.49	2.01	3.02
	3	5.37	7.98	122	82	7.0	50	1.42	2.17	2.97
	4	4.54	7.32	128	80	8.0	58	1.44	2.00	2.40
	5	5.86	9.55	130	80	8.8	63	1.49	2.00	1.68



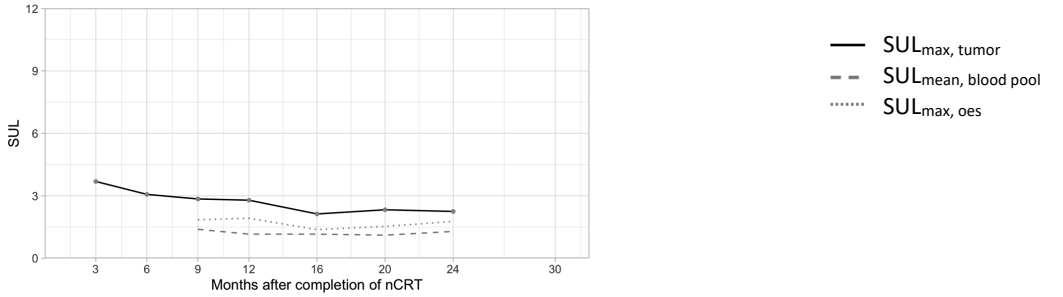
24	2	3.92	4.60	64	55	5.3	50	1.60	1.83	2.23
	3	3.67	4.39	64	53	4.9	50	1.34	1.78	2.19



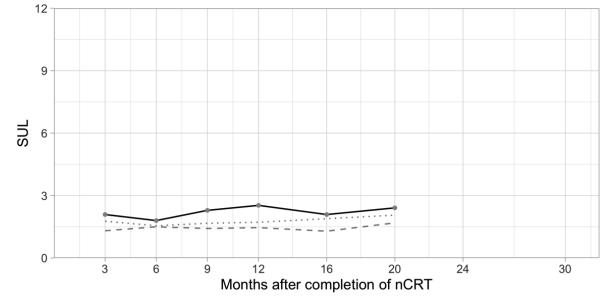
LBM = lean body mass; SUL_{max} = maximum standardized uptake value corrected for lean body mass; $SUL_{max, oes}$ = SUL_{max} in the physiological esophagus; nCRT = neoadjuvant chemoradiotherapy.

Supplemental Table 2. Patients with ongoing clinically complete response of primary tumor during active surveillance

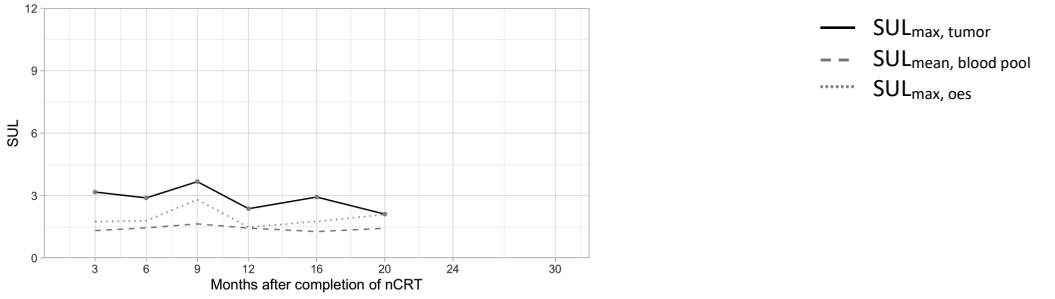
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
25	2	3.69	5.45	90	61	6.4	51	1.15	1.53	1.89
	3	3.07	4.60	92	61	6.0	67	missing	missing	missing
	4	2.85	4.11	97	67	5.8	62	1.39	1.62	1.85
	5	2.79	4.46	101	63	6.6	59	1.16	1.59	1.92
	6	2.13	3.40	101	63	5.8	62	1.16	1.60	1.38
	7	2.33	3.84	105	64	5.7	63	1.11	1.43	1.53
	8	2.25	3.71	105	64	6.4	68	1.29	1.41	1.77



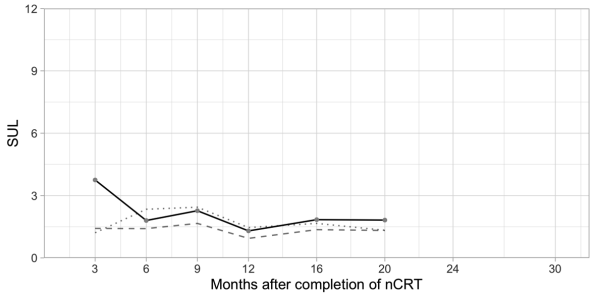
26	2	2.09	3.05	98	67	4.9	59	1.31	1.80	1.77
	3	1.8	2.61	97	67	5.1	59	1.5	1.77	1.55
	4	2.29	3.32	97	67	5.1	56	1.42	1.95	1.67
	5	2.53	3.67	97	67	5.1	61	1.46	1.74	1.72
	6	2.09	3.03	97	67	4.6	59	1.29	1.72	1.89
	7	2.41	3.44	95	66	5.2	58	1.69	1.97	2.06



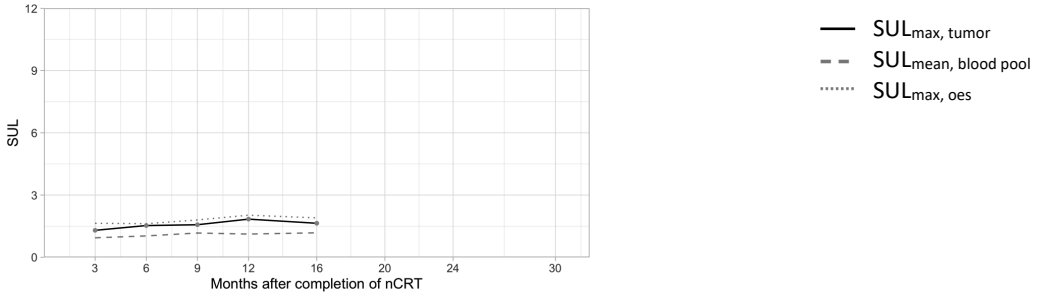
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
27	2	3.17	4.07	77	60	5.2	57	1.32	1.68	1.75
	3	2.89	3.71	77	60	5.9	64	1.45	1.75	1.79
	4	3.67	4.71	77	60	4.7	56	1.64	1.96	2.81
	5	2.37	3.13	82	62	6.1	61	1.44	1.71	1.48
	6	2.93	3.73	75	59	5.8	68	1.27	1.60	1.76
	7	2.11	2.69	75	59	5.3	59	1.43	1.74	2.09



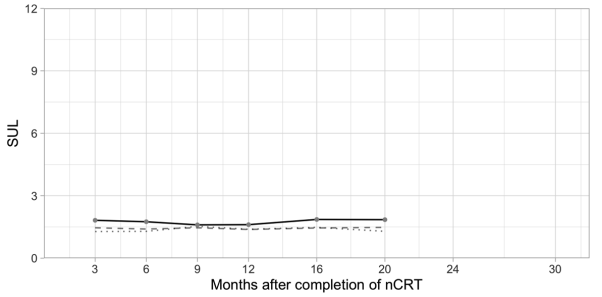
28	2	3.75	4.65	73	59	7.0	66	1.42	1.95	1.21
	3	1.80	2.26	76	61	4.3	73	1.41	2.08	2.34
	4	2.27	2.90	79	62	5.0	59	1.66	2.37	2.44
	5	1.30	1.65	78	62	5.5	63	0.94	1.51	1.46
	6	1.84	2.34	78	62	4.7	64	1.36	1.79	1.66
	7	1.82	2.72	98	66	6.6	63	1.32	1.51	1.33



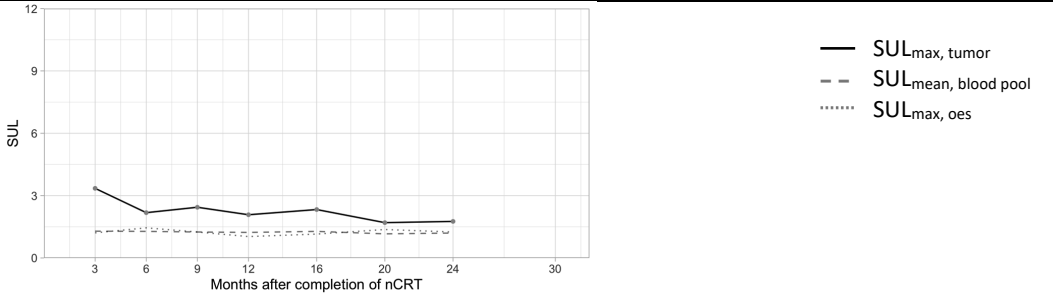
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
29	2	1.30	1.63	47	38	5.8	63	0.94	1.38	1.64
	3	1.53	1.91	47	38	5.6	56	1.03	1.42	1.62
	4	1.57	1.93	45	37	5.4	66	1.17	1.39	1.80
	5	1.84	2.27	45	37	5.4	65	1.12	1.47	2.03
	6	1.64	2.01	45	37	4.8	61	1.18	1.47	1.90
no scans performed between CRE-6 and CRE-13										
	13	2.03	2.46	42	35	5.7	65	1.11	1.44	2.31



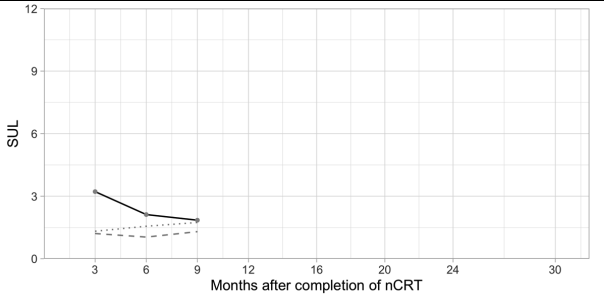
30	2	1.82	2.80	78	51	7.9	60	1.46	1.95	1.28
	3	1.75	2.70	78	51	7.7	58	1.40	2.47	1.29
	4	1.60	2.46	78	51	8.9	58	1.46	1.93	1.53
	5	1.61	2.45	77	51	8.3	58	1.38	1.90	1.39
	6	1.86	2.74	73	49	7.8	61	1.45	2.07	1.48
	7	1.85	2.66	70	49	8.7	56	1.48	2.05	1.29



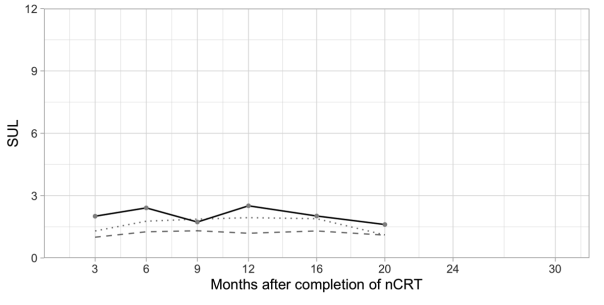
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
31	2	3.35	4.17	42	34	4.5	62	1.29	1.58	1.21
	3	2.18	2.71	42	34	5.1	59	1.28	1.65	1.45
	4	2.44	2.96	39	32	4.7	58	1.25	1.60	1.25
	5	2.08	2.48	37	31	5.2	60	1.23	1.61	1.03
	6	2.33	2.79	37	31	4.9	59	1.28	1.60	1.15
	7	1.70	2.02	37	31	5.7	63	1.16	1.55	1.37
	8	1.76	2.11	38	32	4.8	63	1.2	1.71	1.25



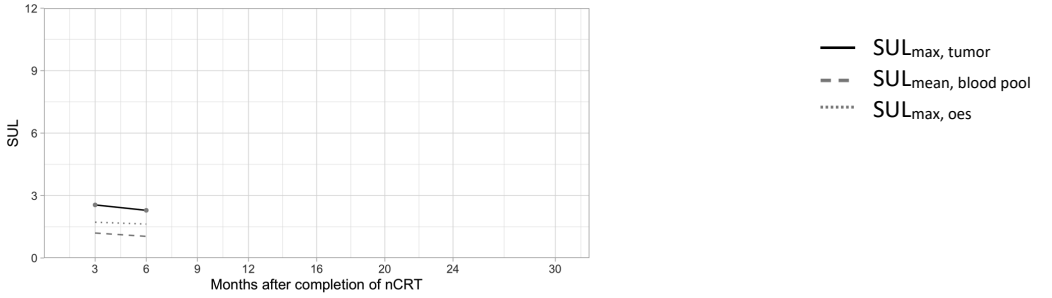
32	2	3.22	4.92	83	54	5.6	60	1.21	1.92	1.32
	3	2.12	3.29	85	55	5.6	56	1.04	1.85	1.56
	4	1.85	2.87	85	55	5.4	58	1.3	1.61	1.74



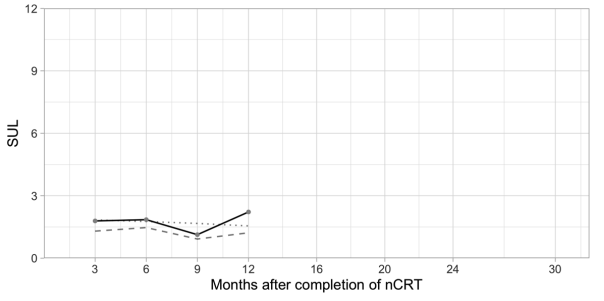
33	2	2.01	2.50	55	44	5.9	60	1.00	1.20	1.30
	3	2.41	3.01	56	45	6.1	62	1.26	1.47	1.77
	4	1.73	2.19	58	46	5.1	55	1.31	1.61	1.87
	5	2.51	3.18	58	46	5.5	60	1.19	1.44	1.94
	6	2.02	2.56	58	46	5.2	58	1.30	1.51	1.89
	7	1.61	1.99	54	44	4.8	58	1.10	1.31	1.11



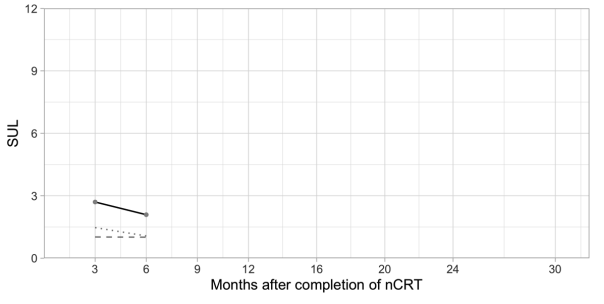
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
34	2	2.55	3.27	72	56	4.8	55	1.20	1.47	1.72
	3	2.29	2.97	74	57	5.5	64	1.04	1.41	1.63



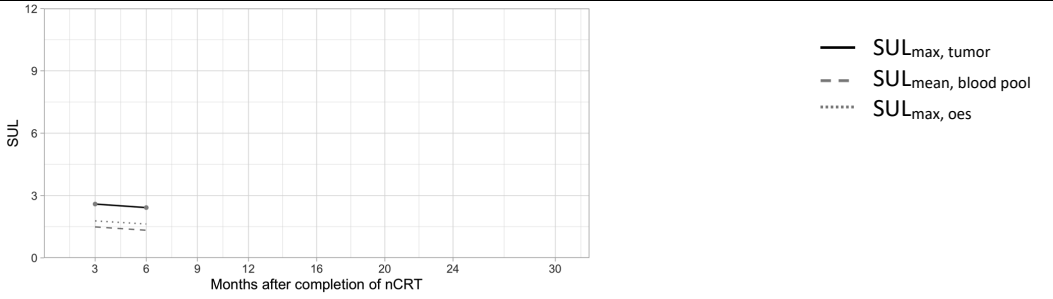
35	2	1.79	2.25	73	58	5.5	60	1.30	1.6	1.84
	3	1.85	2.33	73	58	6.7	56	1.47	1.72	1.76
	4	1.13	1.42	73	58	7.3	68	0.92	1.23	1.67
	5	2.22	2.81	74	59	7.3	65	1.22	1.51	1.55



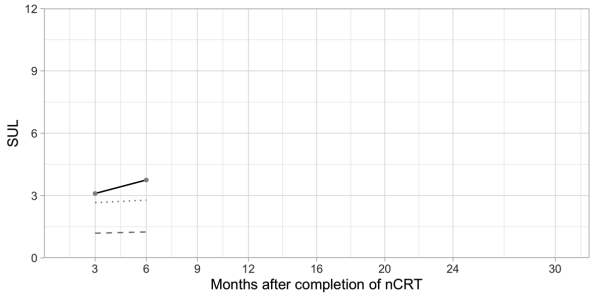
36	2	2.70	4.28	85	54	6.3	60	1.02	1.50	1.47
	3	2.09	3.41	88	54	5.9	60	1.01	1.53	1.07



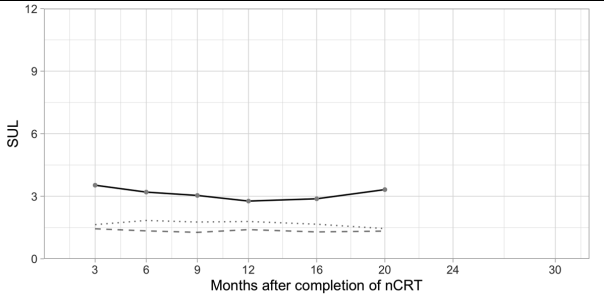
Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
37	2	2.59	3.33	77	60	8.0	61	1.49	1.71	1.78
	3	2.42	3.06	77	61	8.5	65	1.33	1.61	1.63



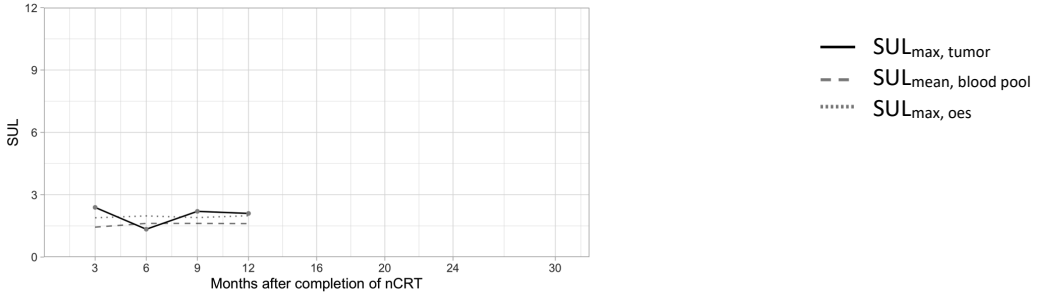
38	2	3.10	5.06	82	50	5.6	64	1.19	1.46	2.66
	3	3.75	5.84	76	49	5.2	76	1.25	1.53	2.78



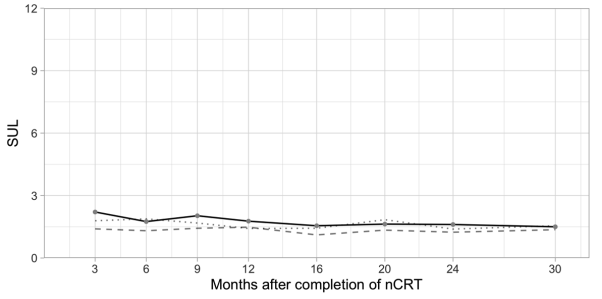
39	2	3.53	4.37	73	59	5.3	55	1.44	2.60	1.64
	3	3.20	4.00	75	60	5.2	58	1.34	1.76	1.84
	4	3.04	3.86	74	58	5.5	64	1.27	1.80	1.76
	5	2.77	3.54	75	59	5.3	58	1.40	1.88	1.79
	6	2.88	3.70	75	58	5.9	56	1.29	1.68	1.66
	7	3.32	4.31	77	59	5.6	59	1.33	1.78	1.45



Patient	CRE	SUL_{max} tumor	SUV_{max} tumor	Weight (kg)	LBM (kg)	Glucose (mmol/L)	Interval (min)	SUL_{mean} Blood pool	SUL_{mean}~ Liver	SUL_{max} Oesophagus
40	2	2.39	3.43	102	71	6.2	59	1.44	2.31	1.89
	3	1.34	1.87	98	70	6.3	64	1.62	2.15	1.98
	4	2.20	3.11	100	71	5.5	60	1.62	2.03	1.90
	5	2.10	3.07	106	73	6.7	57	1.61	2.05	1.99



41	2	2.21	2.83	89	70	5.2	60	1.40	1.85	1.79
	3	1.75	2.29	94	72	5.7	61	1.31	1.70	1.88
	4	2.03	2.76	95	70	5.2	64	1.43	1.92	1.68
	5	1.77	2.43	97	71	5.7	55	1.48	1.76	1.42
	6	1.55	2.14	98	71	5.4	59	1.11	1.62	1.43
	7	1.63	2.25	98	71	5.2	60	1.34	1.73	1.84
	8	1.61	2.22	98	71	5.6	65	1.24	1.64	1.39
	9	1.50	2.07	98	71	5.0	58	1.36	2.29	1.55
	10	1.42	1.94	96	70	5.6	58	1.36	1.65	1.52



LBM: lean body mass; SUL_{max} = maximum standardized uptake value corrected for lean body mass; $SUL_{max, oes}$ = SUL_{max} in the physiological esophagus; nCRT = neoadjuvant chemoradiotherapy

Supplemental Table 3. Tumor characteristics of patients who developed local tumor recurrence, shown separately for different patterns of SUL_{max} increases, and of patients with ongoing clinically complete response.

	Local tumor recurrence (*n* = 24)			**Ongoing cCR (*n* = 17)**
	Gradual SUL_{max} increase (*n* = 19)	Steep (>180%) SUL_{max} increase (*n* = 5)	Total (*n* = 24)	
Histology				
Squamous cell carcinoma	2	2	4	6
Adenocarcinoma	17	3	20	10
Adenoscquamous carcinoma	0	0	0	1
cT*				
cT1	0	0	0	0
cT2	7	1	8	3
cT3	12	4	16	11
cT4	0	0	0	1
cTx	0	0	0	1
Missing	0	0	0	1
cN*				
cN0	8	2	10	7
cN1	5	0	5	6
cN2	6	3	9	2
cNx	0	0	0	1
Missing	0	0	0	1
Differentiation grade				
Good-moderate	7	3	10	6
Poor	6	0	6	4
Missing	6	2	8	7

*Clinical tumor staging was according to the 7th edition of the International Union against Cancer's TNM classification.

cCR = clinically complete response

Supplemental Table 3. Tumor characteristics of patients who developed local tumor recurrence, shown separately for different patterns of SUL_{max} increases, and of patients with ongoing clinically complete response. Data represent number of patients.

	Local tumor recurrence (*n* = 24)			**Ongoing cCR (*n* = 17)**
	Gradual SUL_{max} increase (*n* = 19)	Steep (>180%) SUL_{max} increase (*n* = 5)	Total (*n* = 24)	
Histology				
Squamous cell carcinoma	2	2	4	6
Adenocarcinoma	17	3	20	10
Adenoscquamous carcinoma	0	0	0	1
cT*				
cT1	0	0	0	0
cT2	7	1	8	3
cT3	12	4	16	11
cT4	0	0	0	1
cTx	0	0	0	1
Missing	0	0	0	1
cN*				
cN0	8	2	10	7
cN1	5	0	5	6
cN2	6	3	9	2
cNx	0	0	0	1
Missing	0	0	0	1
Differentiation grade				
Good-moderate	7	3	10	6
Poor	6	0	6	4
Missing	6	2	8	7

*Clinical tumor staging was according to the 7th edition of the International Union against Cancer's TNM classification.

cCR = clinically complete response

Part II

Comparing surgical approaches

7

Chapter 7

Outcomes after totally minimally invasive versus hybrid and open Ivor Lewis oesophagectomy: results from the International Esodata Study Group.

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International Esodata Study Group Collaborators

**, ^Both authors contributed equally*

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Abstract

Background

No large studies compared totally minimally invasive oesophagectomy (TMIE) versus laparoscopically assisted (hybrid) oesophagectomy. Randomised trials compared TMIE to open oesophagectomy. Daily clinical practice does not always resemble results reported in randomised trials. The aim of the present study was to compare complications following TMIE, hybrid and open Ivor Lewis oesophagectomy in patients with oesophageal cancer.

Method

The present study was performed using data from the International Esodata Study Group. Primary outcome was pneumonia, secondary outcomes included incidence and severity of anastomotic leakage, (major) complications, length of stay, escalation of care and 90-day mortality. Data were analysed using multivariate multilevel models.

Results

In 61 hospitals from 21 countries, 8640 patients were registered between February 2015 and December 2019. Patients undergoing TMIE had lower incidence of pneumonia compared to hybrid (10.9% versus 16.3%, Odds Ratio (OR):0.56, 95%CI: 0.40–0.80) and open oesophagectomy (10.9% versus 17.4%, OR:0.60, 95%CI: 0.42–0.84) and had shorter length of stay (median 10 days (IQR 8–16)) compared to hybrid (14 (11–19), p=0.041) and open esophagecomy (11 (9–16), p=0.027). Patients undergoing TMIE had higher rate of anastomotic leakage compared to hybrid (15.1% versus 10.7%, OR:1.47, 95%CI: 1.01–2.13) and open oesophagectomy (7.3%, OR:1.73, 95%CI: 1.26–2.38).

Conclusions

Compared to hybrid and open Ivor Lewis oesophagectomy, TMIE resulted in a lower pneumonia rate, a shorter hospital length of stay, but higher anastomotic leakage rates. Therefore, no clear advantage was seen for either TMIE, hybrid or open Ivor Lewis oesophagectomy when performed in daily clinical practice.

Introduction

Neoadjuvant therapy plus oesophagectomy is the cornerstone of potentially curative treatment for patients with oesophageal cancer.[1-4] An oesophagectomy, however, is associated with substantial morbidity, mortality and lasting symptoms with reduced health-related quality of life.[5-7] Furthermore, it is known that postoperative complications might have detrimental prognostic consequences.[8-11] To reduce the risk of postoperative complications, a variety of minimally invasive surgical techniques have evolved over time.[12] Totally minimally invasive oesophagectomy (TMIE) resulted in short-term benefits (*e.g.* less in-hospital pulmonary infections, less pain and less intraoperative blood loss) compared to open oesophagectomy in two randomised controlled trials using the McKeown technique.[13,14] In a population based setting, TMIE was associated with an increase in reoperation rate, major complications and pulmonary complications.[15,16] Recent reports show that an intrathoracic anastomosis performed using minimally invasive techniques has a long proficiency gain curve and high leak rates during the learning curve phases.[17] This may explain why daily clinical practice does not resemble the complication rate as reported in the randomised setting.

A hybrid minimally invasive approach, in which an open thoracic phase (thoracotomy) is combined with a minimally invasive abdominal phase (laparoscopy), was compared to open oesophagectomy in the MIRO-trial.[18] Using hybrid oesophagectomy resulted in a decrease in major complications, specifically major pulmonary complications. Thus, both McKeown TMIE and Ivor Lewis hybrid oesophagectomy seem to have advantages compared to open oesophagectomy particularly related to incidence of pneumonia and/or pulmonary complications.[13,14,18] Using the hybrid Ivor Lewis approach, the intrathoracic anastomosis is performed via thoracotomy, and as such it can be hypothesised that there may be a lower anastomotic leakage rate compared to totally minimally invasive Ivor Lewis oesophagectomy. However, the thoracotomy could result in more pulmonary complications (*e.g.* pneumonia) compared to the thoracoscopy.

The International Esodata Study Group (IESG) consists of high-volume oesophagectomy centres and previously reached consensus on definitions of complications after oesophagectomy.[19,20] All participating centres now register complications after oesophagectomy according to the definitions and standards of the IESG. The primary aim of the present study was to compare the incidence of postoperative pneumonia between TMIE, hybrid and open Ivor Lewis oesophagectomy using data from the IESG. Additionally, we wished to assess and compare the rate and severity of anastomotic

leakage, the rate of (major) complications, length of hospital stay, rate of escalation of care, readmission rate within 30 days and 90-day mortality.

Methods

ECCG Database

This international cohort study was performed using data from the Esophagectomy Complications Consensus Group (ECCG) database. This database was developed by all contributing centres who are part of the International Esodata Study Group (IESG). Outcomes were reported according to the STROBE reporting guidelines for reporting observational research.[21] The IESG currently consists of 61 high-volume centres from 21 countries. All centres had previously signed an agreement to meet all requirements of the institutional ethics committee to supply anonymised patient information to the database. The publications and audit subcommittee of the International Society for Diseases of the Esophagus research and database committee approved the present study and supplied all of the original data required for this study.

Complications after oesophagectomy were reported standardised and uniformly through web-based data retrieval forms. Complications were registered according to the uniform definitions of ECCG.[19] All complications within 30 days postoperatively or during postoperative hospital stay were reported.

Patients

Patients registered between February 2015 and December 2019 were included in this study. Only patients who underwent potentially curative oesophagectomy using the Ivor Lewis approach (abdominal, open / laparoscopic approach and right-sided thoracotomy/thoracoscopy with intrathoracic anastomosis) were included. Patients who underwent palliative or transhiatal oesophagectomy, patients who underwent definitive chemo(radio)therapy, hybrid oesophagectomy consisting of laparotomy and thoracoscopy, patients who had an oesophageal conduit other than stomach and patients who had a neck anastomosis were excluded from further analysis. Three separate groups were defined: patients who underwent a totally minimally invasive oesophagectomy, laparoscopy and thoracoscopy (TMIE); laparoscopically assisted oesophagectomy, laparoscopy and thoracotomy (hybrid); and open oesophagectomy, laparotomy and thoracotomy.

Outcomes

The primary outcome of the present study was pneumonia, defined as "new lung infiltrates plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation", according to the definition of the American Thoracic Society, the infectious Diseases Society of America and as used uniformly by IESG in previous ECCG publications. [19,22,23]

Secondary outcomes were the rate and severity of anastomotic leakage, rate of complications and rate of major complications, length of hospital stay, rate of escalation of care (*i.e.* transfer of patient to higher level of care, such as a transfer from the ward to ICU), readmission rate within 30 days, after hospital discharge and 90-day mortality. Finally, an overview has been provided of all postoperative complications that are uniformly registered in the ECCG database.

Anastomotic leakage was defined as "a full thickness gastrointestinal defect involving the esophagus, anastomosis, staple line or conduit irrespective of presentation or method of identification", according to the ECCG definitions.[19] The severity of anastomotic leakage was categorised according to three types.[19] Type I anastomotic leakage was defined as local defect without requirement of changing treatment, or treated medically or with dietary modification. Type II anastomotic leakage was defined as a local defect requiring non-surgical intervention (*e.g.* percutaneous drainage, stent placement or packing of incision). Type III anastomotic leakage was a local defect requiring surgical therapy. Major complications were defined as any postoperative complication graded ≥3b according to Clavien-Dindo classification, requiring an intervention under general anesthesia.[24]

Statistical analysis

Continuous variables were presented as medians with interquartile range and categorical data were presented as frequencies with percentages. To assess the influence of surgical approach on postoperative complications, logistic multilevel model analysis was used for categorical outcomes and linear multilevel model analysis was used for linear outcomes. A hospital-specific random intercept and a hospital-specific random slope for surgical approach were used in the models to adjust for inter-hospital variability for all outcomes. Furthermore, we adjusted for fixed effects, which were gender, age, WHO performance score, clinical T-stage, clinical N-stage, tumour location, preoperative treatment and tumour histology. Associations were presented as adjusted odds ratios (aOR) with

corresponding 95% confidence intervals (CI) for categorical outcomes and as standardised coefficients with corresponding 95% CI for linear outcomes.

The variance in a model measures the average spread of each value from the mean. We report the variance of the multilevel models, which encompasses how much of the variance in outcomes can be explained due to the variability of the inter-hospital differences. According to the latent variable method, the variance is divided by the variance plus a constant quantity ($\pi^2/3 = 3.29$). Therefore, a variance of, for example, 0.32 means that: 0.32 / (0.32+3.29) = 8.9% of the variation in the outcome is attributable to differences between hospitals.[25] The larger this variance value is, the more the variance can be explained by inter-hospital differences. In the multilevel models, the outcomes are adjusted for these inter-hospital differences. Incomplete cases are efficiently handled by multilevel model analysis.[26]

All statistical analyses were performed with R version 3.6.2 (R Core team, R foundation for statistical computing, 2013, Boston, MA) using the 'lme4' package. Tests were considered statistically significant when $p < 0.05$ (two-sided).

Results

Between February 2015 and December 2019, the IESG registered 8640 patients, who underwent an oesophagectomy, in 39 hospitals from 20 countries. From this group, 4733 patients fulfilled the study requirements with 1472 patients who underwent TMIE, 1364 hybrid oesophagectomy and 1897 open Ivor Lewis oesophagectomy. (Figure 1) Baseline characteristics of the included patients are shown in Table 1.

Inter-hospital variability

Participating centres performed a median (interquartile range (IQR)) of 181 procedures (120 – 325) during the study period. TMIE was performed in 31 hospitals, hybrid oesophagectomy in 31 hospitals and open oesophagectomy in 36 hospitals. The number of TMIE procedures performed during the study period ranged from 3 to 367 with a median number of procedures (interquartile range (IQR)) of 46 (30 – 129) per hospital. Twenty-five hospitals had performed ≥20 TMIE procedures during the study period. For hybrid oesophagectomy the number of procedures ranged from 1 to 599 with a median number of procedures (interquartile range (IQR)) of 16 (3 – 49) per hospital. and 15 hospitals had performed ≥20 procedures during the study period. Supplementary figure 1 summarises the

variance for all outcomes, explaining how much of the variability in the results after either surgical approach is explained due to the inter-hospital variability.
The incidences of postoperative complications for each of the groups are summarised in Table 2, and the relevant comparisons are shown in Table 3. Supplementary Table 4 summarises the univariate analyses of all comparisons.

TMIE compared to hybrid Ivor Lewis oesophagectomy
The pneumonia rate was lower for patients undergoing TMIE (10.9% vs 16.3%, aOR: 0.56, 95%CI: 0.40 – 0.80, p=0.001) and this group had a shorter length of hospital stay (median: 10 days (IQR 8 – 16) versus 14 days (IQR 11 – 19), adjusted p=0.041) compared to patients undergoing hybrid oesophagectomy. The anastomotic leakage rate was higher for patients undergoing TMIE than for patients undergoing hybrid oesophagectomy (15.1% vs 10.7%, aOR: 1.47, 95%CI: 1.01 – 2.13, p=0.045). The severity of anastomotic leakage (0.57, 95%CI: 0.27 – 1.18), the rate of any complications (0.89, 95%CI: 0.68 – 1.17), the rate of major complications (1.17, 95%CI: 0.83 – 1.65), the rate of escalation of care (0.89, 95%CI: 0.63 – 1.26), the readmission rate within 30 days (0.97, 95%CI: 0.48 – 1.98) and the 90-day mortality (1.01, 95%CI: 0.51 – 2.01) were comparable between both groups.

TMIE compared to open Ivor Lewis oesophagectomy
The pneumonia rate was lower for patients undergoing TMIE (10.9% vs 17.4%, aOR: 0.60, 95%CI: 0.42 – 0.84, p=0.003) and the length of stay as well (median (IQR) stay 10 (8 – 16) vs 11 (9 – 16), adjusted p= 0.027) compared to open oesophagectomy. The anastomotic leakage rate was higher for patients undergoing TMIE (15.1% vs 7.3%, aOR: 1.73, 95%CI: 1.26 – 2.38, p<0.001). The severity of anastomotic leakage (aOR: 0.95, 95%CI: 0.46 – 1.96), the rate of any complications (aOR: 0.82, 95%CI: 0.59 – 1.14), the rate of major complications (aOR: 1.25, 95%CI: 0.95 – 1.65), the rate of escalation of care (aOR: 0.62, 95%CI: 0.36 – 1.07), the readmission rate within 30 days (aOR: 1.16, 95%CI: 0.73 – 1.86) and the 90-day mortality (aOR: 0.83, 95%CI: 0.47 – 1.44) were comparable between both groups.

Hybrid Ivor Lewis oesophagcetomy versus open Ivor Lewis oesophagectomy
The rate of pneumonia (aOR: 0.99, 95%CI: 0.74 – 1.32) and the rate of anastomotic leakage (aOR: 0.79, 95%CI: 0.52 – 1.20) was comparable for hybrid or open Ivor Lewis oesophagectomy. The same

was true for the severity of anastomotic leakage (aOR: 0.61, 95%CI: 0.29 – 1.27), the rate of any complications (aOR: 1.03, 95%CI: 0.74 – 1.43) and the rate of major complications (aOR: 0.91, 95%CI: 0.59 – 1.41). And also for the rate of escalation of care (aOR: 1.39, 95%CI: 0.81 – 2.36), the readmission rate within 30 days (aOR: 0.73, 95%CI: 0.39 – 1.37), the length of stay (standardised coefficients: -0.3, adjusted p=0.779) and the 90-day mortality (aOR: 1.65, 95%CI: 0.80 – 3.40).

Pathological outcomes

An overview of the incidence of pathological outcomes is summarised in Table 4. Patients undergoing TMIE had a microscopically radical resection rate of 94% compared to 93% for patients undergoing hybrid oesophagectomy (aOR: 0.71 95%CI 0.43 – 1.18, p = 0.189) and compared to 89% for patients undergoing open oesophagectomy (aOR: 1.05, 95%CI: 0.64 – 1.72, p = 0.584). For hybrid versus open this was: aOR: 0.72, 95%CI: 0.45 – 1.17, p = 0.183).

The number of resected lymph nodes for patients undergoing TMIE (median: 30, IQR: 21 – 40) was comparable to that of patients undergoing hybrid oesophagectomy (median: 29, IQR: 22 – 37, standardised coefficients: -1.3, adjusted p = 0.209) and comparable to that of open oesophagectomy (median: 26, IQR: 19 – 34, standardised coefficients: 1.07, adjusted p = 0.262). This was also the case when hybrid was compared to open oesophagectomy (standardised coefficients: -1.18, p = 0.091). The number of positive resected lymph nodes were comparable between the three surgical techniques as well (for all surgical techniques: median: 0, IQR: 0 – 2). Supplementary Tables 1-3 summarise all postoperative complications registered in the ECCG database.

Discussion

This study investigated the incidence of postoperative complications after TMIE, hybrid or open Ivor Lewis oesophagectomy using data from the IESG. Patients undergoing TMIE had a lower pneumonia rate and a shorter length of stay compared to patients undergoing hybrid or open approaches. The rate of anastomotic leakage, however, was significantly higher in patients undergoing TMIE. No differences were reported between patients undergoing hybrid or open Ivor Lewis approaches.

A recently published meta-analysis of non-randomised studies compared TMIE with hybrid oesophagectomy.[27] Four studies were pooled that reported on the incidence of pneumonia, including 297 patients in total. The authors did not report a higher incidence of pneumonia for hybrid

oesophagectomy compared to TMIE. In these studies, however, there was heterogeneity in the definitions of pneumonia between the studies. The present study, using uniform definitions from the ECCG for pneumonia and comparing over 2800 patients undergoing TMIE or hybrid Ivor Lewis oesophagectomy, clearly report a statistically significant difference in pneumonia rate favoring TMIE over hybrid and open Ivor Lewis oesophagectomy. This increase most probably reflects the more invasive thoracic procedure performed in laparoscopically-assisted hybrid and open oesophagectomy, both requiring thoracotomy. The results confirmed the results of the randomised TIME-trial and ROBOT trial, comparing TMIE or RAMIE to open oesophagectomy (*i.e.* a decrease in rate of pneumonia and pulmonary complications).[13,14] We found, however, no difference in pneumonia rate between open or hybrid oesophagectomy, in spite of the same approaches being compared as per the MIRO-trial which randomised and compared patients undergoing either a hybrid (laparoscopy and open thoracotomy) or open oesophagectomy. This trial reported a significant decrease in major pulmonary complications for hybrid oesophagectomy, defined as pulmonary complications according to Clavien-Dindo ≥2.[18] The pneumonia rates, however, were not separately analyzed. In the database of the present study, the severity of postoperative complications according to Clavien-Dindo were not specified for each complication making it difficult to make direct comparisons with that study.

In the present study, a higher anastomotic leakage rate was reported for patients undergoing TMIE compared to patients undergoing hybrid oesophagectomy. The previously mentioned meta-analysis which compared TMIE to hybrid oesophagectomy reported a significant increase in anastomotic leakage rate for patients undergoing TMIE compared to patients undergoing hybrid Ivor Lewis oesophagectomy.[27] Most probably, this is due to the technically challenging minimally invasive intrathoracic anastomosis. Hypothetically, the increase in anastomotic leakage rate for patients undergoing TMIE in the present study reflects a proficiency gain curve of centres during implementation of this new technique, since collection of data took place while TMIE was being implemented. If so, it is expected that anastomotic leakage rates will drop after more patients have been treated.[17] However, after adjustment for inter-hospital variability, the increased anastomotic leakage rate remained for patients undergoing TMIE. Furthemore, the hospitals who performed most TMIE procedures, did not have lowest anastomotic leakage rates per se, which is partly reflected by the estimated rate of variability which can be explained by inter-hospital differences. Lastly, it is

remarkable that, despite a decrease in pneumonia, the anastomotic leakage rate for TMIE is higher even though these complications often coincide.

A previous meta-analysis reported a decrease in overall survival after development of anastomotic leakage or after pneumonia in patients undergoing any type of oesophagectomy.[8] Furthermore, a study that only included patients undergoing TMIE, anastomotic leakage resulted in decreased long-term survival compared to patients who did not develop anastomotic leakage.[10] In the present study, the 90-day postoperative mortality was, however, comparable between the groups. The only way to definitively assess the importance of differences in postoperative complications is to prospectively and directly compare both surgical techniques, powered on outcomes such as overall survival and long-term postoperative health-related quality of life.

To our knowledge, this is the largest study comparing postoperative outcomes from different approaches in patients, who had an Ivor Lewis oesophagectomy for oesophageal cancer. The IESG previously reached an international consensus on standardised reporting of the most important postoperative complications.[19,20] This resulted in a robust and standardised comparison between surgical approaches used throughout the world.

The present study has some limitations. Health care personel were not blinded for the procedure performed in this study. The length of stay could be influenced by surgical approach as known to the health care provider in the surgical ward. The anastomotic technique used (*e.g.* end-to-side, side-to-side and circular stapled or linear-stapled) in oesophagectomy has been associated with the risk of anastomotic leakage.[28] These anastomotic techniques were not registered in the database and therefore, the analyses could not be adjusted for these techniques. Finally, although the definition for the presence of pneumonia was highly standardised, there still was no clear definition specifically developed for postoperative pneumonia. Aditionally, a standardised severity score should be reported for pneumonia to gain insight in the possible impact of postoperative pneumonia. To the best of our knowledge, the only randomised trial including both laparoscopically assisted hybrid and TMIE (both McKweown and Ivor Lewis) is the ROMIO-trial.[29] This ongoing trial, however, randomises only a small amount of patients in the TMIE group by means of a substudy with the aim to evaluate the safety of TMIE. Overall survival and postoperative complications will therefore probably not be tested with sufficient power to find an improved outcome for either surgical technique.

In conclusion, this study shows that patients undergoing Ivor Lewis oesophagectomy had lower pneumonia rates and a shorter length of hospital stay if the procedure was performed using a totally minimally invasive approach. The rate of anastomotic leakage on the contrary, was higher for patients undergoing totally minimally invasive Ivor Lewis oesophagectomy. There were no differences in complication rates or 90-day survival comparing the laparoscopically assisted hybrid and open Ivor Lewis oesophagectomy. Therefore, no clear advantage was seen for either TMIE, hybrid or open Ivor Lewis oesophagectomy when performed in daily clinical practice.

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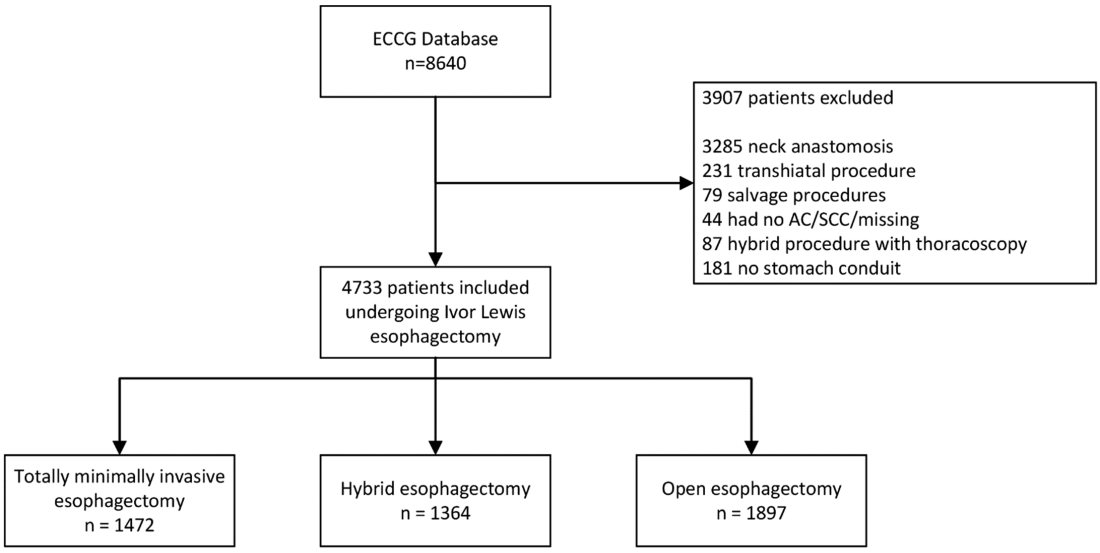


Figure 1. Flow diagram of included patients who underwent Ivor Lewis oesophagectomy.

Table 1. Basic characteristics of patients undergoing TMIE, hybrid or open Ivor Lewis oesophagectomy

	TMIE n = 1472	**Hybrid^ n = 1364**	**Open n = 1897**
Age, median (IQR)	65 (58 - 71)	64 (57 - 71)	65 (58 – 71)
Female gender	269 (18)	241 (18)	332 (18)
Comorbidities present	920 (63)	1183 (87)	1468 (77)
WHO (%)			
PS 0	841 (57)	617 (45)	1029 (54)
PS 1	580 (39)	571 (42)	798 (42)
PS 2	48 (3.3)	130 (9.5)	60 (3)
PS 3	3 (<1)	45 (3.3)	10 (<1)
PS 4	0	1 (<1)	0
ASA (%)			
ASA I	145 (9.9)	118 (8.7)	158 (8)
ASA II	667 (45)	758 (56)	875 (46)
ASA III	632 (43)	487 (36)	860 (45)
ASA IV	28 (1.9)	1 (<1)	3 (<1)
ASA V	0	0	1 (<1)
Tumour location (%)			
Proximal 1/2 of esophagus	41 (2.8)	81 (5.9)	68 (4)
Distal 1/2 of esophagus	852 (58)	757 (56)	863 (46)
GEJ	558 (38)	505 (37)	920 (49)
Missing	21 (1.4)	21 (1.5)	46 (2)
Histology (%)			
Adenocarcinoma	895 (61)	732 (54)	1072 (57)
Squamous cell carcinoma	146 (9.9)	134 (9.8)	191 (10)
Adenosquamous cell carcinoma	6 (<1)	3 (<1)	9 (<1)
Missing	425 (29)	495 (36)	625 (33)
cT stage (%)*			
cT0	4 (<1)	5 (<1)	3 (<1)
cTis	7 (<1)	4 (<1)	15 (<1)
cT1	139 (9.4)	91 (6.7)	131 (7)
cT2	258 (18)	166 (12)	278 (15)
cT3	944 (64)	1043 (77)	1302 (69)
cT4	77 (5.2)	26 (1.9)	90 (5)
cTx	22 (1.5)	8 (<1)	32 (2)
Missing	21 (1.4)	21 (1.5)	46 (2)
cN stage (%)*			
cN0	544 (37)	236 (17)	728 (38)
cN1	554 (38)	403 (30)	690 (36)
cN2	226 (15)	100 (7.3)	284 (15)
cN3	32 (2.2)	11 (<1)	61 (3)
cNx	95 (6.5)	593 (44)	88 (5)
Missing	21 (1.4)	21 (1.5)	46 (2)
Preoperative treatment (%)			
None	265 (18)	234 (17)	354 (19)
Chemoradiotherapy	973 (66)	683 (50)	765 (40)
Chemotherapy	212 (14)	424 (31)	731 (39)
Radiotherapy	1 (<1)	2 (<1)	1 (<1)
Missing	21 (1.4)	21 (1.5)	46 (2.4)

ASA: American Society of Anesthesiology, cN-stage: clinical nodal stage, cT-stage: clinical tumour stage, GEJ: gastro-oesophageal junction, IQR: interquartile range, TMIE: totally minimally invasive oesophagectomy, WHO: World Health Organization

^ Laparoscopically assisted oesophagectomy (laparoscopy and thoracotomy)

Table 2. Incidence of postoperative complications and length of stay in patients undergoing TMIE, hybrid or open Ivor Lewis oesophagectomy.

	TMIE	**Hybrid**	**Open**
Pneumonia	160 (10.9)	222 (16.3)	331 (17.4)
Anastomotic leakage			
Rate	223 (15.1)	146 (10.7)	139 (7.3)
Severity			
I	39 (2.6)	19 (1.4)	51 (2.7)
II	113 (7.7)	79 (5.8)	51 (2.7)
III	70 (4.8)	48 (3.5)	37 (1.9)
Complications			
Any	881 (59.9)	855 (62.7)	1100 (58.0)
Major (CD≥3b)	283 (19.2)	219 (16.1)	298 (15.7)
Escalation of care	183 (12.4)	198 (14.5)	516 (27.2)
Readmission<30 days	191 (13.0)	81 (5.9)	184 (9.7)
Length of stay, median (IQR)	10 (8 - 16)	14 (11 - 19)	11 (9 - 16)
90-day mortality	65 (4.4)	46 (3.4)	75 (4.0)
CD: Clavien-Dindo, IQR: interquartile range, TMIE: totally minimally invasive oesophagectomy			

Table 3. Multilevel models comparing postoperative complications after TMIE, hybrid or open Ivor Lewis oesophagectomy.

	TMIE vs hybrid^		**TMIE versus open^**	**p**	**Open vs hybrid^**	**p**
	aOR (95% CI)	**p**	**aOR (95% CI)**		**aOR (95% CI)**	
Pneumonia	0.56 (0.40 – 0.80)	0.001	0.60 (0.42 – 0.84)	0.003	0.99 (0.74 – 1.32)	0.948
Anastomotic leakage						
Rate	1.47 (1.01 – 2.13)	0.045	1.73 (1.26 – 2.38)	<0.001	0.79 (0.52 – 1.20)	0.267
Severity*	0.57 (0.27 – 1.18)	0.131	0.95 (0.46 – 1.96)	0.886	0.61 (0.29 – 1.27)	0.188
Complications						
Any	0.89 (0.68 – 1.17)	0.404	0.82 (0.59 – 1.14)	0.239	1.03 (0.74 – 1.43)	0.874
Major (CD≥3b)	1.17 (0.83 – 1.65)	0.365	1.25 (0.95 – 1.65)	0.116	0.91 (0.59 – 1.41)	0.684
Escalation of care	0.89 (0.63 – 1.26)	0.505	0.62 (0.36 – 1.07)	0.09	1.39 (0.81 – 2.36)	0.229
Readmission<30 days	0.97 (0.48 – 1.97)	0.940	1.16 (0.73 – 1.86)	0.534	0.73 (0.39 – 1.37)	0.329
Length of stay; standardised coefficients (95%CI)	-2.6 (-5.0 - -0.24)	0.041	-2.2 (-3.8 - -0.5)	0.027	-0.3 (-2.8 – 2.0)	0.779
90-day mortality	1.01 (0.51 – 2.01)	0.978	0.83 (0.47 – 1.44)	0.497	1.65 (0.80 – 3.40)	0.179

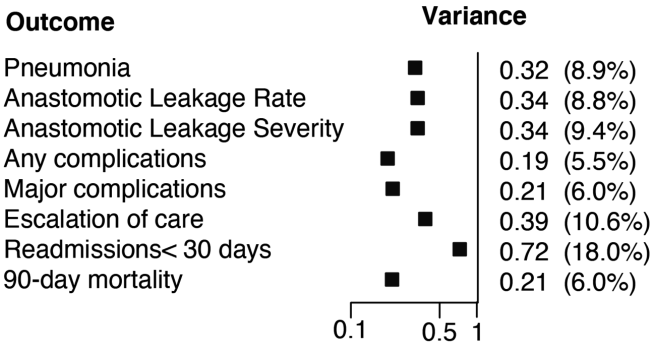
* type I/II versus type III anastomotic leakage, ^reference group

Adjusted for random hospital effects, tumour histology, preoperative treatment, age, gender, WHO-score, cT-stage, cN-stage and tumour location

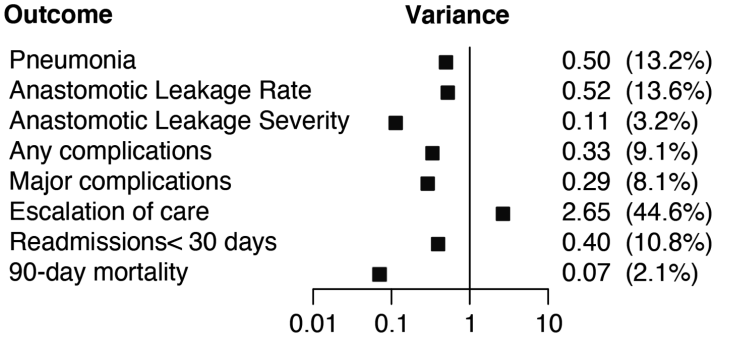
95%CI: 95% Confidence Interval, aOR: adjusted odds ratio, CD: Clavien-Dindo, IQR: Interquartile range, TMIE: totally minimally invasive oesophagectomy

Table 4. Pathological outcomes for patients undergoing TMIE, hybrid or open Ivor Lewis oesophagectomy.

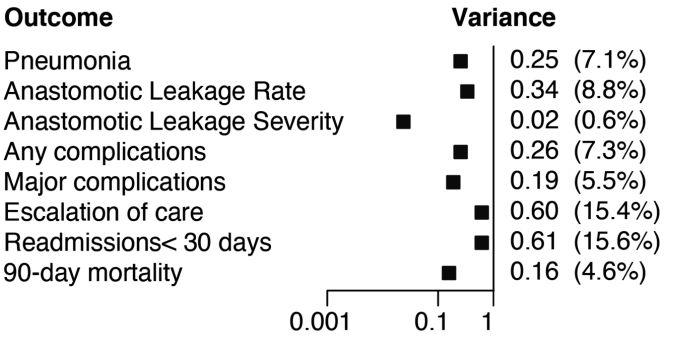
	TMIE	**Hybrid**	**Open**
	n=1472	**n=1364**	**n=1897**
Pathologic T-stage			
pT0	280 (19.0)	239 (17.5)	253 (13.3)
pTis	11 (0.7)	2 (0.1)	9 (0.5)
pT1	324 (22.0)	282 (20.7)	345 (18.2)
pT2	227 (15.4)	197 (14.4)	269 (14.2)
pT3	569 (38.7)	577 (42.3)	875 (46.1)
pT4	33 (2.2)	36 (2.6)	91 (4.8)
pTx	7 (0.5)	2 (0.1)	9 (0.5)
missing	21 (1.4)	21 (1.5)	46 (2.4)
Pathologic N-stage			
pN0	855 (58.1)	743 (54.5)	953 (50.2)
pN1	310 (21.1)	305 (22.4)	449 (23.7)
pN2	187 (12.7)	165 (12.1)	253 (13.3)
pN3	98 (6.7)	128 (9.4)	195 (10.3)
pNx	1 (0.1)	2 (0.1)	1 (0.1)
missing	21 (1.4)	21 (1.5)	46 (2.4)
Pathologic M-stage			
pM0	1363 (92.6)	1254 (91.9)	1592 (83.9)
pM1	13 (0.9)	25 (1.8)	46 (2.4)
pMx	75 (5.1)	64 (4.7)	213 (11.2)
missing	21 (1.4)	21 (1.5)	46 (2.4)
Radicality			
R0	1381 (93.8)	1271 (93.2)	1693 (89.2)
R1	70 (4.8)	70 (5.1)	152 (8.0)
R2	0	2 (0.1)	6 (0.3)
missing	21 (1.4)	21 (1.5)	46 (2.4)
Resected lymph nodes			
Median (IQR)	30 (21 – 40)	29 (22 – 37)	26 (19 – 34)
Lymph nodes containing tumour cells			
Median (IQR)	0 (0 – 2)	0 (0 – 2)	0 (0 – 2)
IQR: interquartile range, R0: microscopically tumour-free resection margin, TMIE: totally minimally invasive oesophagectomy			



Supplementary figure 1A. Variance when comparing TMIE versus hybrid Ivor Lewis oesophagectomy. The variance reports inter-hospital random effects per outcome. Percentages shown are estimates how much of the variance can be explained due to variability of the inter-hospital differences, according to the latent variable method.



Supplementary figure 1B. Variance when comparing TMIE versus open Ivor Lewis oesophagectomy. The variance reports inter-hospital random effects per outcome. Percentages shown are estimates how much of the variance can be explained due to variability of the inter-hospital differences, according to the latent variable method.



Supplementary figure 1C. Variance when comparing open versus hybrid Ivor Lewis oesophagectomy. The variance reports inter-hospital random effects per outcome. Percentages shown are estimates how much of the variance can be explained due to variability of the inter-hospital differences, according to the latent variable method.

Supplementary Table 1. All gastrointestinal and pulmonary complications according to ECCG for patients undergoing TMIE, hybrid or open Ivor Lewis oesophagectomy.

	TMIE n = 1472	**Hybrid n = 1364**	**Open n = 1897**
Gastrointestinal			
Overall	340 (23.1)	404 (29.6)	282 (14.9)
Esophagoenteric leakage	223 (15.1)	146 (10.7)	139 (7.3)
Conduit necrosis/failure requiring surgery	16 (1.1)	14 (1.0)	13 (0.7)
Ileus defined as small bowel dysfunction preventing or delaying enteral feeding	14 (1.0)	2 (0.1)	22 (1.2)
Small bowel obstruction	5 (0.3)	3 (0.2)	12 (0.6)
Feeding J-tube complication	26 (1.8)	5 (0.4)	21 (1.1)
Pyloromyotomy/Pyloroplasty complication	5 (0.3)	1 (0.1)	1 (0.1)
Clostridium difficile infection	7 (0.5)	7 (0.5)	10 (0.5)
Pancreatitis	9 (0.6)	10 (0.7)	14 (0.7)
GI bleeding requiring intervention or transfusion	1 (0.1)	4 (0.3)	2 (0.1)
Liver dysfunction	0	10 (0.7)	7 (0.4)
Delayed conduit emptying requiring intervention or delaying discharge or requiring maintenance of NG drainage >7 days post-op	68 (4.6)	236 (17.3)	64 (3.4)
Pulmonary			
Overall	337 (22.9)	272 (27.3)	529 (27.9)
Pneumonia	160 (10.9)	222 (16.3)	331 (17.4)
Pleural effusion requiring additional drainage procedure	130 (8.8)	141 (10.3)	153 (8.1)
Pneumothorax requiring intervention	41 (2.8)	25 (1.8)	37 (2.0)
Atelectasis mucous plugging requiring bronchoscopy	14 (1.0)	11 (0.8)	30 (1.6)
Respiratory failure requiring reintubation	69 (4.7)	83 (6.1)	117 (6.2)
Acute respiratory distress syndrome	25 (1.7)	34 (2.5)	41 (2.2)
Acute aspiration	14 (1.0)	18 (1.3)	9 (0.5)
Tracheobronchial injury	10 (0.7)	7 (0.5)	6 (0.3)
Chest drain requirement for air leakage for >10 d post-op	5 (0.3)	9 (0.7)	5 (0.3)
GI: gastrointestinal, NG: nasogastric, post-op: postoperatively, TMIE: totally minimally invasive oesophagectomy			

Supplementary Table 2. All cardiac, thromboembolic, urologic and neurological/psychiatric complications according to ECCG for patients undergoing TMIE, hybrid or open Ivor Lewis oesophagectomy.

	TMIE n = 1472	**Hybrid n = 1364**	**Open n = 1897**
Cardiac			
Overall	244 (16.6)	154 (11.3)	320 (16.9)
Cardiac arrest requiring CPR	5 (0.3)	8 (0.6)	19 (1.0)
Myocardial infarction	6 (0.4)	4 (0.3)	9 (0.5)
Atrial dysrhythmia requiring intervention	229 (15.6)	130 (9.5)	286 (15.1)
Ventricular dysrhythmia requiring intervention	5 (0.3)	13 (1.0)	12 (0.6)
Congestive heart failure requiring intervention	3 (0.2)	5 (0.4)	9 (0.5)
Pericarditis requiring intervention	4 (0.3)	0	1 (0.1)
Thromboembolic			
Overall	44 (3.0)	26 (1.9)	56 (3.0)
DVT	12 (0.8)	7 (0.5)	21 (1.1)
PE	28 (1.9)	16 (1.2)	29 (1.5)
Stroke	1 (0.1)	2 (0.1)	4 (0.2)
Peripheral thrombophlebitis	6 (0.4)	3 (0.2)	4 (0.2)
Urologic			
Overall	56 (3.8)	78 (5.7)	115 (6.1)
Acute renal insufficiency (defined as doubling of baseline creatinine)	12 (0.8)	23 (1.7)	30 (1.6)
Acute renal failure requiring dialysis	5 (0.3)	8 (0.6)	13 (0.7)
Urinary tract infection	18 (1.2)	26 (1.9)	42 (2.2)
Urinary retention requiring reinsertion of urinary catheter, delaying discharge, or discharge with urinary catheter	21 (1.4)	27 (2.0)	33 (1.7)
Neurologic/Psychiatric			
Overall	69 (4.7)	107 (7.8)	110 (5.8)
Recurrent nerve injury	28 (1.9)	27 (2.0)	17 (0.9)
Other neurologic injury	3 (0.2)	12 (0.9)	13 (0.7)
Acute delirium	38 (2.6)	67 (4.9)	76 (4.0)
Delirium tremens	0	5 (0.4)	5 (0.3)

CPR: cardiopulmonary resuscitation, DVT: deep venous thrombosis, PE: pulmonary embolus, TMIE: totally minimally invasive oesophagectomy

Supplementary Table 3. All infections or dehiscence/hernia complications according to ECCG or other complications for patients TMIE, hybrid or open Ivor Lewis oesophagectomy.

	TMIE n = 1472	**Hybrid n = 1364**	**Open n = 1897**
Infection			
Overall	146 (9.9)	137 (10.0)	263 (13.9)
Wound infection requiring opening wound or antibiotics	26 (1.8)	25 (1.8)	71 (3.7)
Central IV line infection requiring removal or antibiotics	11 (0.7)	42 (3.1)	20 (1.1)
Intrathoracic/Intra-abdominal abscess	31 (2.1)	19 (1.4)	30 (1.6)
Generalised sepsis	25 (1.7)	27 (2.0)	42 (2.2)
Other infections requiring antibiotics	62 (4.2)	36 (2.6)	122 (6.4)
Wound/Diaphragm			
Overall	12 (0.8)	23 (1.7)	37 (2.0)
Thoracic wound dehiscence	2 (0.1)	11 (0.8)	22 (1.2)
Acute abdominal wall dehiscence/hernia	0	9 (0.7)	8 (0.4)
Acute diaphragmatic hernia	10 (0.7)	3 (0.2)	7 (0.4)
Other complications			
Overall	118 (8.0)	75 (5.5)	138 (7.3)
Chyle leakage	93 (6.3)	46 (3.4)	103 (5.4)
Reoperation for thoracic bleeding	0	4 (0.3)	2 (0.1)
Reoperation for abdominal bleeding	3 (0.2)	2 (0.1)	5 (0.3)
Reoperation for reasons other than bleeding, anastomotic leakage or conduit necrosis	22 (1.5)	20 (1.5)	26 (1.4)
Multiple organ dysfunction syndrome	3 (0.2)	8 (0.6)	10 (0.5)
Non-ECCG complications as well	171 (11.6)	103 (7.6)	156 (8.2)
ECCG: Oesophagectomy Complications Consensus Group, IV: intravenous			

Supplementary Table 4. Univariate analysis comparing postoperative complications after TMIE, hybrid or open Ivor Lewis oesophagectomy.

	TMIE versus hybrid^		**TMIE vs open^**		**Open vs hybrid^**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Pneumonia	0.63 (0.50 – 0.78)	<0.001	0.58 (0.47 – 0.71)	<0.001	1.09 (0.90 – 1.31)	0.379
Anastomotic leakage						
Rate	1.49 (1.19 – 1.86)	<0.001	2.26 (1.81 – 2.83)	<0.001	0.66 (0.52 – 0.84)	<0.001
Severity*	0.93 (0.60 – 1.46)	0.765	1.26 (0.79 – 2.03)	0.334	0.74 (0.44 – 1.23)	0.249
Complications						
Any	0.89 (0.76 – 1.03)	0.122	1.08 (0.94 – 1.24)	0.276	0.82 (0.71 – 0.95)	0.007
Major (CD≥3b)	1.24 (1.02 – 1.51)	0.027	1.27 (1.07 – 1.53)	0.007	0.97 (0.81 – 1.18)	0.789
Escalation of care	0.84 (0.67 – 1.04)	0.104	0.38 (0.32 – 0.46)	<0.001	2.20 (1.84 – 2.64)	<0.001
Readmission<30 days	1.25 (0.86 – 1.81)	0.241	1.06 (0.75 – 1.52)	0.745	1.18 (0.83 – 1.66)	0.352
Length of stay; standardised coefficients (95%CI)	-3.4 (-4.5 - -2.3)	<0.001	-0.7 (-1.7 - -0.29)	0.161	-2.7 (-3.7 - -1.6)	<0.001
90-day mortality	1.32 (0.90 – 1.96)	0.153	1.13 (0.80 – 1.58)	0.489	1.17 (0.81 – 1.72)	0.399

* type I/II versus type III anastomotic leakage, ^reference group

95% CI: 95% Confidence Interval, CD: Clavien-Dindo, IQR: Interquartile range, OR: odds ratio, TMIE: totally minimally invasive oesophagectomy

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Chapter 8

Lasting symptoms and long-term health-related quality of life after totally minimally invasive, hybrid and open Ivor Lewis esophagectomy

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Abstract

Aim

Compared to open esophagectomy (OE), both totally minimally invasive (TMIE), laparoscopy-assisted hybrid minimally invasive (HMIE) reduce postoperative morbidity and improve short-term health-related quality of life (HRQoL). We aimed to compare lasting symptoms and long-term HRQoL in an international population-based setting between patients who underwent Ivor Lewis TMIE, HMIE or OE.

Methods

Patients who were relapse-free at least one year after TMIE, HMIE or OE for esophageal or junctional carcinoma between January 2010 and June 2016 were included. Patients completed the LASER questionnaire to assess lasting symptoms after esophagectomy and the EORTC QLQ-C30 and QLQ-OG25 questionnaires to assess HRQoL. Primary endpoint was chest pain and secondary endpoints were pain from chest scars or abdominal scars, abdominal pain, fatigue and physical functioning. Differences in lasting symptoms and HRQoL were assessed with multivariable logistic and ANCOVA regression, respectively.

Results

A total of 362 patients were included (TMIE n=91, HMIE n=85, OE n=186). Median follow-up was 3.9 years (IQR 2.8-5.4). Chest pain was reported less after TMIE compared with HMIE (adjusted OR 0.21, 95% CI 0.05-0.84), but was comparable between TMIE and OE (adjusted OR 0.41, 95% CI 0.12-1.41) and between HMIE and OE (adjusted OR 1.85, 95% CI 0.71-4.81). All secondary endpoints were comparable between TMIE, HMIE and OE. The impact of symptoms on taking medication, return to work, and performance status were comparable between groups.

Conclusion

Surgical technique seems to have little effect on lasting symptoms and long-term HRQoL after a median of four years after Ivor Lewis esophagectomy.

Introduction

Esophagectomy is the cornerstone of treatment for patients with esophageal cancer. One of the most common surgical approaches and the preferred approach for tumors located in the middle or distal esophagus is an Ivor Lewis esophagectomy (*i.e.* transthoracic esophagectomy with intrathoracic anastomosis). Open esophagectomy (OE), however, is associated with relatively high postoperative morbidity and mortality, lasting symptoms in two thirds of patients and decreased long-term health-related quality of life (HRQoL).[1-3] In order to minimize postoperative morbidity and improve HRQoL, especially of transthoracic esophagectomy, minimally invasive approaches have been introduced. Randomized trials have suggested that compared to OE, totally minimally invasive esophagectomy (TMIE) leads to less pulmonary complications and shorter hospital stay and hybrid minimally invasive esophagectomy (HMIE) leads to less pulmonary and less total major complications.[4, 5] Also, both surgical techniques may lead to better short-term HRQoL than OE.[6, 7] With Ivor Lewis TMIE, however, a thoracoscopic intrathoracic anastomosis is required, which is known to be technically challenging and can lead to severe anastomotic leakage.[8] While no randomized studies have compared TMIE and HMIE, a meta-analysis has suggested that TMIE may be associated with less wound infections and pneumonia whereas HMIE may lead to less anastomotic leakage.[9]

However, the effect of these different minimally invasive techniques on lasting symptoms and long-term HRQoL remains unclear. In the present study, we aimed to assess whether Ivor Lewis TMIE is associated with reduced long-term pain and better long-term physical functioning than HMIE and OE. Moreover, we aimed to assess the impact of surgical complications on lasting symptoms and HRQoL as well as the impact of lasting symptoms on work and functional ability.

Methods

Study design and patients

The present study is a side-study of the multicenter cross-sectional LASER study, of which details have been published previously.[2] Briefly, patients with carcinoma of the esophagus or gastroesophageal junction (Siewert type I and II) who underwent esophagectomy with curative intent between January 1, 2010 and June 30, 2016 were included from 15 European centers. Patients were eligible if they were relapse-free at least 12 months after completion of curative esophagectomy, adjuvant treatment, or salvage esophagectomy for failed endoscopic or definitive oncological treatment, and if they had no ongoing surgical complications besides an anastomotic stricture or diaphragmatic hernia.

Assessment of relapse-free status varied, but most centers performed a CT scan after 1 year of follow-up. Patients who still required non-oral nutrition were excluded. For the present study, we only included patients who underwent an Ivor Lewis esophagectomy. Hence, patients with a cervical anastomosis were excluded. The institutional review board at each participating center had approved the study protocol.

Exposure

The exposure within this study was surgical technique: TMIE, HMIE or OE. Ivor Lewis esophagectomy consists of an abdominal phase (mobilization of the stomach) and a right-sided thoracic phase (resection of the esophagus and intrathoracic anastomosis). During TMIE, both phases are performed minimally invasively, requiring a thoracoscopic intrathoracic anastomosis. For the present study, the procedure was considered a HMIE if the abdominal phase was performed minimally invasively and the thoracic phase was open. During OE, both phases are performed in an open fashion.

Data collection

Data from the LASER study were used.[2] In this study, eligible patients were identified from institutional databases and were invited at the outpatient clinic, by telephone or by letter to participate in the study. At least a year after surgery, patients were asked to once complete three questionnaires: the LASER questionnaire, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-OG25.[2, 10, 11] Questionnaires could be completed either web-based or paper-based.

Measurements

Lasting symptoms over the past 6 months of long-term survivors after esophagectomy were assessed by the self-completed LASER questionnaire. This questionnaire has been developed by a cooperation of European upper GI-surgeons and patient panels in the United Kingdom, Sweden, Italy and France. The LASER questionnaire contains 28 symptoms, of which the frequency is scored on a 5-point scale (never, rarely, weekly, daily or multiple times per day) and impact on quality of life (QoL) on a 3-point scale (none, some, substantial). These scores are combined into a composite score from 0 to 5: 0, no symptom present; 1, present but no impact on QoL; 2, rarely or weekly and some impact on QoL; 3,

daily or multiple times per day and some impact on QoL; 4, rarely or weekly and substantial impact on QoL; 5, daily or multiple times per day and substantial impact on QoL.

Cancer-related HRQoL was assessed by the validated EORTC QLQ-C30 questionnaire, which consists of five functional scales, three symptom scales and one global HRQoL scale.[10] Esophageal cancer-specific HRQoL was assessed by the validated EORTC QLQ-OG25 questionnaire, which consists of six multi-item symptom scales and ten single items.[11] Scores are measured on a 4-point Likert scale: 1, not at all; 2, a little; 3, quite a bit; 4, very much. Only global HRQoL is measured on a 7-point scale ranging from 'poor' to 'excellent'.

Predefined primary endpoint was chest pain (LASER). Predefined secondary endpoints were: pain from chest scars (LASER), abdominal pain (LASER), pain from abdominal scars (LASER), fatigue (QLQ-C30) and physical functioning (QLQ-C30). Prior to the analysis, these endpoints were defined by consensus discussion with experienced esophageal surgeons, based on clinical relevance and hypothesized association with the surgical techniques.

Statistical analysis

Patients were stratified into three groups according to surgical technique: TMIE, HMIE or OE. Follow-up time was calculated from date of surgery until date of completion of the questionnaire.

The composite LASER symptom scores were dichotomized into low (0, 1, 2) and high (3, 4, 5). Differences between the three surgical techniques were calculated by using multivariable logistic regression and were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI). In case a primary or secondary endpoint was reported with only low or only high scores and thus no aOR could be estimated, association was tested using Fisher's exact test.

Scores from QLQ-C30 and QLQ-OG25 were linearly transformed to a 0–100 score according to the EORTC manual.[12] Differences between groups were calculated by using multivariable ANCOVA regression and were expressed as adjusted mean scores differences (aMD) with 95% CIs. For interpretation of QLQ-C30 scores, medium or large mean score differences according to the evidence-based guidelines were considered clinically relevant.[13] For the QLQ-OG25, for which no evidence-based cut-offs are available, a difference of 10 points or more was considered medium or large and thus clinically relevant.[14]

All multivariable regression models were adjusted for confounding factors, including age (continuous), sex (male or female), pathological stage (0-I, II, or III-IV; according to the Union for International

Cancer Control TNM staging manual, 7th edition) and neoadjuvant therapy (yes or no). To investigate the impact of surgical complications on LASER scores and HRQoL, the same multivariable regression models were fitted but also adjusted for occurrence of surgical complications (yes or no). Statistical analyses were performed by an experienced biostatistician with expertise in HRQoL analyses (A.J.).

Results

Patients

In total, 91 patients were included in the TMIE group, 85 patients in the HMIE group, and 186 in the OE group. A flowchart of patients included in the study stratified by group is shown in Figure 1. Median follow-up time was 3.1 years (IQR 2.7-4.0) in the TMIE group, 3.2 years (IQR 2.5-5.3) in the HMIE group, and 4.8 years (IQR 3.4-6.0) in the OE group. Demographic and clinical characteristics are summarized in Table 1. Age, BMI, sex and the proportion of patients undergoing neoadjuvant therapy were comparable between groups. The proportion of patients with pathological stage III-IV was higher in the TMIE group than in the other two groups. Postoperative complications occurred most frequently in the OE group but the proportion of patients having complications of Clavien-Dindo score ≥ 3 was comparable between the groups.

Primary endpoint

Patients who underwent TMIE had a lower composite chest pain score than patients who underwent HMIE (aOR 0.21, 95% CI 0.05-0.84) (Table 2). No statistically significant difference in chest pain was observed between patients who underwent TMIE and OE (aOR 0.41, 95% CI 0.12-1.41) nor between patients who underwent HMIE and OE (aOR 1.85, 95% CI 0.71-4.81) (Table 2). After adjustment for surgical complications, the association between chest pain and TMIE versus HMIE remained statistically significant (aOR 0.19, 95% CI 0.05-0.80) (Supplementary Table 1).

Secondary endpoints

Pain from chest scars was comparable between TMIE and HMIE (aOR 0.47, 95% CI 0.09-2.52), TMIE and OE (aOR 0.45, 95% CI 0.11-1.88) and HMIE and OE (aOR 0.95, 95% CI 0.28-3.29) (Table 2). Abdominal pain was also comparable between TMIE and HMIE (aOR 0.73, 95% CI 0.28-1.94), TMIE and OE (aOR 0.75, 95% CI 0.33-1.69) and HMIE and OE (aOR 1.06, 95% CI 0.48-2.31) (Table 2). Pain

from abdominal scars was comparable between HMIE and OE (aOR 1.38, 95% CI 0.11-17.87) (Table 2). Since none of the patients in the TMIE group reported pain from abdominal scars with a high score, the odds ratios could not be estimated for TMIE vs. HMIE and TMIE vs. OE. Association tests showed no difference between TMIE vs. HMIE (p=0.48) and TMIE and OE (p=1.00). Unadjusted LASER questionnaire responses of the primary and secondary endpoints are reported in Supplementary Table 2.

Fatigue levels were neither statistically nor clinically significantly different between HMIE and TMIE (aMD -5, 95% CI -12 to +3), HMIE and OE (aMD +1, 95% CI -5 to +8), and TMIE and OE (aMD -3, 95% CI -10 to +3) (Table 3). Also, physical functioning levels were neither statistically nor clinically significantly different between HMIE and TMIE (aMD +2, 95% CI -4 to +7), HMIE and OE (aMD -1, 95% CI -6 to +3), and TMIE and OE (aMD 1, 95% CI -4 to +5) (Table 3).

Other symptom and HRQoL scores

Other LASER symptom scores and HRQoL scores are reported in Table 2 and 3. Scores adjusted for surgical complications are reported in Supplementary Table 1 and 3.

Impact of symptoms

In the TMIE group, 17 of 91 patients (19%) reported to have sought medical treatment for their symptoms, while in the HMIE group 26 of 85 patients (31%) and in the OE group 67 of 186 (36%) did (Table 5). After TMIE, HMIE and OE, the proportions of patients taking pain killers (15% vs. 13% vs. 19% resp., p=0.56) and taking proton pump inhibitors were comparable (79% vs. 87% vs. 82% resp., p=0.45).

Of those who worked before their diagnosis with esophageal cancer, the proportion of patients who had returned to work was comparable between the three groups (p=0.85). Only 32% in the TMIE group, 21% in the HMIE group and 28% in the OE group reported to have returned to work with the same activities as before. The functional ability of patients was also comparable between the three groups (p=0.48), with 36% in the TMIE group, 41% in the HMIE group and 44% in the OE group being fully active without restrictions.

Discussion

Although a difference in chest pain was found between TMIE and HMIE, no such difference was found between TMIE and OE. Pain from chest scars, abdominal pain and pain from abdominal scars were all comparable between patients who underwent TMIE, HMIE or OE, suggesting little effect of surgical technique on long-term chest pain. None of the HRQoL scores, including fatigue and physical functioning, were reported with a clinically relevant difference between TMIE, HMIE and OE. The impact of symptoms on medical treatment, on the ability to return to work and functional ability was also comparable between the groups.

TMIE and HMIE have been compared to OE in the respective randomized TIME trial and MIRO trial, both showing less postoperative complications after minimally invasive surgery with comparable oncological outcomes.[4] In the TIME trial, patients had less pain and better global HRQoL at six weeks after TMIE, which persisted up to one year.[5] Physical functioning was also better at 6 weeks and 1 year, but with limited clinical relevance. In the MIRO trial, both HMIE and OE negatively affected short-term HRQoL, including physical functioning, fatigue and pain.[15] Three years after surgery, however, all HRQoL domains of both techniques had restored to comparable preoperative levels.[16] In the present study, pain (QLQ-C30 and QLQ-OG25), physical functioning, fatigue and global HRQoL were all comparable after TMIE, HMIE and OE, which is in line with the results of the MIRO trial. The differences between the TIME trial and the present study can best be explained by the fact that the questionnaires in our study were taken after a median follow-up of 3.9 years after surgery. Hence, differences in HRQoL scores that were observed in the TIME trial after one year may have been eased off in the present study.

A meta-analysis of nine studies showed that patients who underwent minimally invasive transthoracic esophagectomy had better short-term physical functioning, fatigue, pain and global HRQoL than patients who underwent open transthoracic esophagectomy.[6] These differences were no longer present at 6 months and 1 year after surgery, which is in line with our findings. Within this meta-analysis, no difference was made between HMIE or TMIE nor between Ivor Lewis, McKeown or Oringer esophagectomy. In a recent Swedish national population-based study, HRQoL was compared at one and two years after surgery between TMIE, HMIE and OE.[7] Although no differences in any of the cancer-related or tumor-specific HRQoL domains were observed, no difference was made between Ivor Lewis esophacetomy and other surgical approaches. In the present study, some HRQoL scores were statistically significantly different. None of these differences, however, were clinically

relevant as prespecified in our methods. The present study hence shows that in a cohort of only patients who underwent Ivor Lewis esophagectomy, long-term HRQoL is comparable between TMIE, HMIE and OE.

Besides HRQoL, we focused on lasting symptoms. The only significant difference in the predefined endpoints was a lower LASER score for chest pain after TMIE than after HMIE. After adjusting for surgical complications, the strength of the associations between surgical technique and chest pain did not decrease, showing that complications did not explain this symptoms. From a clinical perspective, the difference in chest pain could be explained by a smaller incision and less retraction of the ribs during thoracoscopy, both reducing direct and indirect surgical trauma to the intercostal nerve or to the muscle and fascia compared to thoracotomy.[17] Even though it would be expected, no such difference in chest pain was reported between TMIE and OE. This may be explained by a difference in managing patients' expectations prior to open surgery compared to minimally invasive surgery, leading to other expectations about the severity of chest pain. As a consequence, the impact of the patients' perception on chest pain may have decreased after OE, resulting in comparably reported chest pain between TMIE and OE. While the median follow-up times in the TMIE group and HMIE group were shorter than in the OE group, we do not expect chest pain to have changed substantially from 3.1 to 4.8 years. This is supported by previous literature, showing only a slight decrease in post-thoracotomy pain in this period.[18] Moreover, we did not find a difference in pain reported in the QLQ-C30 questionnaire, which makes the difference in chest pain between HMIE and TMIE being caused by a type I error another plausible explanation. Some other differences in lasting symptoms were reported, but similar to chest pain, these differences were reported between only two groups. Therefore, management of expectations and type I errors seem more likely to explain these differences than the abdominal or thoracic phase being minimally invasive or open. In summary, although a difference in chest pain was observed between TMIE and HMIE, the clinical relevance of this difference and the other few differences between groups seem to be limited. Evidently, the impact of these lasting symptoms on medical treatment, the ability to return to work and functional ability was also comparable between TMIE, HMIE and OE.

The present study had several strengths. As a side-study of the LASER study, we used an international multicenter cohort with a high participation rate (81%), guaranteeing cross-cultural validity of our findings. We only included patients who underwent Ivor Lewis esophagectomy to ensure a clear comparison of minimally invasive techniques for this approach. Also, studies assessing many HRQoL

outcomes are prone to type I errors due to multiple testing. Since each surgical technique was compared with two other techniques in the present study, more reliable information on the impact of a minimally invasive abdominal or thoracic phase could be obtained. This reduced the risk of falsely assuming that a type I error is true.

Several limitations should also be mentioned. By using composite scores on a scale from 0 to 5, the LASER questionnaire was designed to capture smaller differences in symptom frequency and impact on QoL. For the present study, however, this scale has been dichotomized, which may have led to the loss of more delicate information. If linear transformation would have been performed, smaller differences would potentially have been captured. Since linear transformation of the LASER questionnaire has not yet been validated, we chose to dichotomize the scores to generate more robust outcomes. Comparable to the LASER study, other limitations were the cross-sectional design which does not allow for assessment of effects over time and the fact that patients were asked to report symptoms that occurred in the past six months, potentially leading to recall bias.

Conclusions

The present study suggests that surgical technique has little effect on lasting symptoms and long-term HRQoL in patients who underwent Ivor Lewis esophagectomy and are alive and relapse-free after a median of four years after surgery. Although some differences were observed in lasting symptoms or HRQoL scores, the clinical relevance of these differences seems limited. These findings can be used to specifically inform patients about expected outcome after surgery. Whether HMIE should be preferred over TMIE or vice versa, may be determined from prospective direct comparisons such as the ongoing randomized ROMIO trial.[19]

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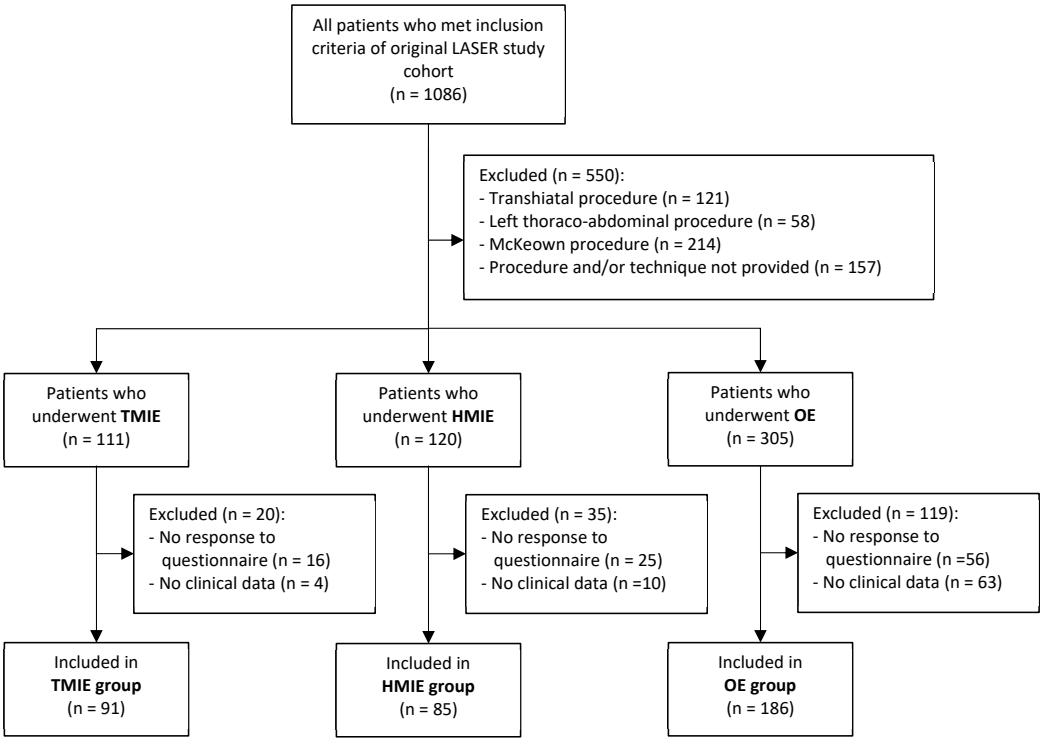

Figure 1. Flow chart of included from the LASER study into the present side-study.

Table 1. Demographic and clinical characteristics of patients who underwent totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), or open Ivor Lewis esophagectomy (OE).

Characteristic	Total	TMIE	HMIE	OE
Total number	362	91	85	186
Age, median (IQR)	65 (52-78)	65 (51-79)	65 (51-79)	64 (52-76)
BMI				
at surgery, median (IQR)	26.4 (20.8-31.9)	24.4 (19.5-29.4)	26.6 (20.8-32.3)	26.6 (21.6-31.6)
at questionnaire, median (IQR)	23.9 (19.5-28.3)	23.3 (18.6-28.1)	23.6 (17.7-29.6)	24.2 (20.4-28.0)
Sex, n (%)				
Female	60 (17)	17 (19)	13 (15)	30 (16)
Male	302 (83)	74 (81)	72 (85)	156 (84)
Neoadjuvant therapy, n (%)				
Yes	290 (80)	73 (80)	66 (78)	151 (81)
No	72 (20)	18 (20)	19 (22)	35 (19)
Adjuvant therapy, n (%)				
Yes	75 (21)	4 (4)	19 (22)	52 (28)
No	248 (69)	54 (59)	63 (74)	131 (70)
Missing	39 (11)	33 (36)	3 (4)	3 (2)
Pathological TNM stage, n (%)*				
Stage 0	65 (18)	19 (21)	19 (22)	27 (15)
Stage I	109 (30)	22 (24)	32 (38)	55 (30)
Stage II	98 (27)	9 (10)	24 (28)	65 (35)
Stage III-IV	90 (25)	41 (45)	10 (12)	39 (21)
Complications, n (%)				
No complications	176 (49)	55 (60)	42 (49)	79 (42)
Clavien-Dindo 1-2	102 (28)	17 (19)	20 (24)	65 (35)
Clavien-Dindo ≥ 3	78 (22)	18 (20)	20 (24)	40 (22)
Missing	6 (2)	1 (1)	3 (4)	2 (1)
Type of anastomosis, n (%)				
End to end	87 (24)	0 (0)	27 (32)	60 (32)
End to side	246 (68)	64 (70)	56 (66)	126 (68)
Side to side	29 (8)	27 (30)	2 (2)	0 (0)
Anastomosis construction, n (%)				
Hand-sewn	113 (31)	1 (1)	22 (26)	90 (48)
Linear stapler	47 (13)	28 (31)	10 (12)	9 (5)
Circular stapler	202 (56)	62 (68)	53 (62)	87 (47)

IQR: interquartile range, BMI: body mass index, TNM: tumor-node-metastasis

* according to the Union for International Cancer Control TNM staging manual, 7th edition.

Table 2. Adjusted odds ratios for LASER symptom scores of patients who were alive and relapse-free after a median of four years after totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), and open Ivor Lewis esophagectomy (OE).

	TMIE vs. HMIE aOR (95% CI)*	**TMIE vs. OE aOR (95% CI)***	**HMIE vs. OE aOR (95% CI)***
Chest pain†	**0.21 (0.05-0.84)** §	0.41 (0.12-1.41)	1.85 (0.71-4.81)
Abdominal pain‡	0.73 (0.28-1.94)	0.75 (0.33-1.69)	1.06 (0.48-2.31)
Pain from chest scars‡	0.47 (0.09-2.52)	0.45 (0.11-1.88)	0.95 (0.28-3.29)
Pain from abdominal scars‡	<0.001 (<0.001->999.999)	<0.001 (<0.001->999.999)	1.38 (0.11-17.87)
Difficulty getting food down	0.68 (0.25-1.84)	1.02 (0.42-2.47)	1.51 (0.67-3.41)
Difficulty getting liquids down	0.57 (0.12-2.67)	0.68 (0.17-2.72)	1.28 (0.41-4.01)
Regurgitation of food	**0.35 (0.13-0.94)** §	0.68 (0.28-1.68)	1.91 (0.90-4.06)
Nausea	0.87 (0.30-2.54)	1.11 (0.45-2.77)	1.22 (0.49-3.05)
Vomiting	0.69 (0.21-2.32)	3.37 (0.97-11.72)	**4.69 (1.41-15.63)** §
Early feeling of fullness after eating	1.47 (0.71-3.02)	0.99 (0.55-1.77)	0.68 (0.37-1.26)
Heart palpitation after eating	2.20 (0.48-10.14)	1.25 (0.43-3.70)	0.56 (0.15-2.13)
Sweating after eating	0.51 (0.08-3.17)	0.34 (0.08-1.44)	0.63 (0.16-2.44)
Dizziness after eating	0.21 (0.02-2.16)	0.18 (0.02-1.46)	0.79 (0.23-2.66)
Bloating or cramping after eating	1.28 (0.45-3.64)	1.00 (0.42-2.35)	1.03 (0.44-2.41)
Loose bowel motions/diarrhea after eating	0.52 (0.16-1.66)	**0.33 (0.13-0.86)** §	0.63 (0.27-1.45)
Heartburn/acid or bile regurgitation	0.71 (0.31-1.62)	0.80 (0.39-1.62)	1.12 (0.57-2.18)
Waking up because of choking sensation	0.78 (0.18-3.31)	0.77 (0.22-2.69)	1.09 (0.36-3.32)
Persistent cough	1.01 (0.42-2.45)	1.28 (0.59-2.77)	1.22 (0.58-2.57)
Stools that float and are difficult to flush	<0.001 (<0.001->999.999)	<0.001 (<0.001->999.999)	1.15 (0.36-3.64)
Diarrhea unrelated to eating	0.28 (0.06-1.34)	0.76 (0.17-3.36)	2.60 (0.77-8.80)
Lack of appetite	0.29 (0.07-1.17)	0.33 (0.09-1.21)	1.08 (0.46-2.54)
Tiredness	0.66 (0.33-1.34)	0.89 (0.49-1.62)	1.31 (0.74-2.33)
Low mood	0.27 (0.06-1.11)	0.28 (0.08-1.01)	0.97 (0.40-2.35)
Reduced energy/activity tolerance	0.88 (0.44-1.77)	0.83 (0.46-1.50)	0.92 (0.51-1.64)
Voice problems	0.80 (0.29-2.17)	1.51 (0.59-3.87)	1.84 (0.75-4.49)
Polyneuropathy	0.39 (0.13-1.13)	0.60 (0.23-1.54)	1.54 (0.70-3.38)
Dental problems	<0.001 (<0.001->999.999)	<0.001 (<0.001->999.999)	2.28 (0.76-6.85)
Hiccups	1.29 (0.39-4.27)	2.79 (0.85-9.15)	2.13 (0.66-6.92)

aOR: adjusted odds ratio, CI: confidence interval.

* Adjusted for age, sex, pathological TNM stage and neoadjuvant therapy. † Predefined primary endpoint.

‡ Predefined secondary endpoints. § Statistically significantly different odds ratios.

Table 3. Adjusted mean health related quality of life (HRQoL) scores and mean difference from the EORTC QLQ-C30 and QLQ-OG25 questionnaires of patients who were alive and relapse-free after a median of four years after totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), and open Ivor Lewis esophagectomy (OE).

	TMIE MS (95% CI)	**HMIE** MS (95% CI)	**OE** MS (95% CI)	**TMIE vs. HMIE** MD (95% CI)*	**TMIE vs. OE** MD (95% CI)*	**HMIE vs. OE** MD (95% CI)*
QLQ-C30						
Global HRQoL	73 (68-78)	70 (65-75)	67 (63-71)	4 (-2-10)	**6 (1-12)** §	3 (-3-8)
Functional status						
Physical Functioning‡	81 (77-86)	79 (75-84)	81 (77-84)	2 (-4-7)	1 (-4-5)	-1 (-6-3)
Role Functioning	87 (81-93)	80 (74-86)	83 (78-88)	7 (-1-14)	4 (-3-10)	-3 (-9-3)
Emotional Functioning	85 (80-91)	79 (73-84)	79 (74-83)	7 (0-14)	**7 (1-13)** §	0 (-6-6)
Cognitive Functioning	88 (83-93)	83 (78-88)	82 (78-86)	5 (-2-11)	5 (0-11)	1 (-4-6)
Social Functioning	82 (76-88)	80 (74-86)	79 (74-84)	2 (-5-10)	3 (-3-10)	1 (-5-7)
Symptom scales						
Fatigue‡	30 (24-36)	35 (29-41)	34 (29-38)	-5 (-12-3)	-3 (-10-3)	1 (-5-8)
Nausea / Vomiting	16 (11-20)	19 (14-23)	14 (11-18)	-3 (-8-3)	1 (-3-6)	4 (-1-9)
Pain	17 (11-22)	19 (13-25)	20 (15-24)	-2 (-9-4)	-3 (-9-3)	-1 (-6-5)
Dyspnea	21 (14-27)	24 (17-31)	25 (19-30)	-3 (-11-5)	-4 (-11-3)	-1 (-8-6)
Insomnia	25 (18-32)	30 (23-37)	27 (21-32)	-5 (-14-3)	-2 (-9-6)	3 (-4-11)
Appetite loss	19 (13-25)	22 (15-29)	21 (15-26)	-3 (-11-5)	-2 (-9-5)	1 (-5-8)
Constipation	15 (10-21)	19 (14-24)	15 (11-19)	-3 (-10-3)	1 (-5-6)	4 (-1-9)
Diarrhea	16 (11-22)	22 (16-28)	21 (17-26)	-5 (-13-2)	-5 (-11-1)	0 (-6-7)
Body image	87 (81-93)	83 (77-89)	84 (79-89)	5 (-3-12)	3 (-3-10)	-1 (-8-5)
QLQ-OG25						
Symptom scales						
Dysphagia	10 (7-14)	15 (11-19)	8 (5-11)	-4 (-9-0)	3 (-1-7)	**7 (3-11)** §
Problems with eating	26 (21-31)	30 (24-35)	25 (21-30)	-4 (-11-3)	1 (-5-7)	5 (-1-10)
Reflux	30 (23-36)	35 (29-42)	33 (28-39)	-6 (-14-3)	-4 (-11-4)	2 (-5-9)
Odynophagia	12 (8-17)	20 (15-24)	16 (13-20)	**-7 (-13--2)** §	-4 (-9-1)	3 (-2-8)
Pain and discomfort	20 (15-25)	24 (18-29)	26 (22-30)	-4 (-10-3)	-6 (-12-0)	-2 (-8-3)
Anxiety	27 (20-33)	36 (29-43)	31 (25-36)	**-9 (-18--1)** §	-4 (-11-3)	5 (-2-13)
Eating with others	11 (5-16)	12 (6-17)	8 (4-12)	-1 (-8-5)	3 (-3-8)	4 (-2-10)
Dry mouth	21 (14-28)	24 (17-31)	23 (18-29)	-3 (-12-6)	-2 (-10-5)	1 (-7-8)
Trouble with taste	15 (9-21)	18 (11-24)	13 (8-18)	-3 (-11-5)	2 (-5-9)	5 (-2-11)
Trouble swallowing saliva	8 (4-11)	3 (0-7)	5 (2-8)	4 (0-9)	3 (-1-7)	-1 (-5-2)
Choked when swallowing	14 (10-19)	12 (8-17)	11 (8-15)	2 (-4-8)	3 (-2-8)	1 (-4-6)
Trouble with coughing	34 (27-41)	27 (20-35)	29 (23-34)	7 (-2-16)	5 (-2-13)	-1 (-9-6)
Trouble talking scale	10 (5-15)	9 (4-14)	9 (5-12)	1 (-5-7)	1 (-4-6)	0 (-5-6)
Weight loss scale	17 (10-24)	21 (14-28)	18 (13-24)	-4 (-13-5)	-1 (-8-7)	3 (-4-10)
Hair loss scale	28 (24-31)	25 (22-29)	27 (24-29)	2 (-2-7)	1 (-3-5)	-1 (-5-2)

MS: mean score, MD: mean score difference, CI: confidence interval.

* Adjusted for age, sex, pathological TNM stage and neoadjuvant therapy. Because the values are rounded, the MDs may not exactly match the difference between the mean scores. ‡ Predefined secondary endpoints. § Statistically significant difference, but not clinically relevant difference in mean scores.

Table 4. Personal impact of symptoms of patients who were alive and relapse-free after a median of four years after totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), and open Ivor Lewis esophagectomy (OE).

	Total	**TMIE**	**HMIE**	**OE**	**p**
Total number	362	91	85	186	
Sought treatment for symptoms, n (%)					
Yes	110 (30)	17 (19)	26 (31)	67 (36)	0.07
No	108 (30)	30 (33)	25 (29)	53 (28)	
Missing	144 (40)	44 (48)	34 (40)	66 (35)	
Taking PPI for symptoms, n (%)					
Yes	299 (83)	72 (79)	74 (87)	153 (82)	0.45
No	61 (17)	18 (20)	11 (13)	32 (17)	
Missing	2 (1)	1 (1)	0 (0)	1 (1)	
Taking pain killers for symptoms, n (%)					
Yes	60 (17)	14 (15)	11 (13)	35 (19)	0.56
No	287 (79)	70 (77)	69 (81)	148 (80)	
Missing	15 (4)	7 (8)	5 (6)	3 (2)	
Returned to work (if worked before), n (%)					
Yes - same work activities as before	58 (28)	14 (32)	10 (21)	34 (28)	0.85
Yes - but with some limitations/reduction in activities	50 (24)	8 (18)	13 (27)	29 (24)	
No, I have not returned to work because of my symptoms	24 (11)	4 (9)	7 (15)	13 (11)	
Now retired	75 (36)	16 (36)	16 (33)	43 (35)	
Missing	3 (1)	2 (5)	2 (4)	3 (2)	
Functional ability in past 6 months, n (%)					
0 - Fully active able to carry on all pre-disease performance without restriction	150 (41)	33 (36)	35 (41)	82 (44)	0.48
1 - Restricted in physically strenuous activity but ambulatory and able to carry out light work	176 (49)	47 (52)	39 (46)	90 (48)	
2 - Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours	26 (7)	8 (9)	6 (7)	12 (6)	
3 - Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	5 (1)	1 (1)	3 (4)	1 (1)	
4 - Cannot carry out any self-care. Totally confined to bed or chair.	0 (0)	0 (0)	0 (0)	0 (0)	
Missing	5 (1)	2 (2)	2 (2)	1 (1)	

Table S1. Adjusted odds ratios for LASER symptom scores of patients who were alive and relapse-free after a median of four years after totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), and open Ivor Lewis esophagectomy (OE). These models were also adjusted for the occurrence of any surgical complications to investigate the impact of surgical complications on LASER symptoms.

	TMIE vs. HMIE aOR (95% CI)*	**TMIE vs. OE aOR (95% CI)***	**HMIE vs. OE aOR (95% CI)***
Chest pain†	**0.19 (0.05-0.80)** §	0.36 (0.10-1.27)	1.87 (0.70-4.96)
Abdominal pain‡	0.73 (0.28-1.94)	0.76 (0.34-1.73)	1.06 (0.49-2.32)
Pain from chest scars ‡	0.47 (0.09-2.55)	0.45 (0.11-1.88)	0.93 (0.27-3.23)
Pain from abdominal scars ‡	<0.001 (<0.001->999.999)	<0.001 (<0.001->999.999)	1.42 (0.11-18.58)
Difficulty getting food down	0.69 (0.25-1.87)	1.06 (0.43-2.58)	1.54 (0.68-3.47)
Difficulty getting liquids down	0.58 (0.12-2.70)	0.69 (0.17-2.76)	1.28 (0.41-4.02)
Regurgitation of food	**0.35 (0.13-0.94)** §	0.67 (0.27-1.67)	1.90 (0.89-4.05)
Nausea	0.95 (0.32-2.83)	1.34 (0.52-3.45)	1.31 (0.51-3.34)
Vomiting	0.70 (0.21-2.35)	3.44 (0.99-11.98)	**4.71 (1.41-15.71)** §
Early feeling of fullness after eating	1.47 (0.72-3.03)	1.01 (0.56-1.83)	0.69 (0.37-1.28)
Heart palpitation after eating	2.22 (0.48-10.27)	1.28 (0.43-3.80)	0.56 (0.15-2.16)
Sweating after eating	0.50 (0.08-3.09)	0.33 (0.08-1.39)	0.63 (0.16-2.44)
Dizziness after eating	0.22 (0.02-2.16)	0.18 (0.02-1.48)	0.79 (0.23-2.70)
Bloating or cramping after eating	1.28 (0.45-3.64)	1.02 (0.43-2.41)	1.04 (0.44-2.45)
Loose bowel motions/diarrhea after eating	0.52 (0.16-1.67)	**0.34 (0.13-0.89)** §	0.63 (0.27-1.47)
Heartburn/acid/bile regurgitation	0.71 (0.31-1.62)	0.80 (0.39-1.62)	1.11 (0.57-2.17)
Waking up because of choking sensation	0.78 (0.18-3.31)	0.79 (0.23-2.77)	1.10 (0.36-3.36)
Persistent cough	1.01 (0.42-2.44)	1.23 (0.57-2.68)	1.19 (0.56-2.52)
Stools that float and are difficult to flush	<0.001 (<0.001->999.999)	<0.001 (<0.001->999.999)	1.12 (0.35-3.56)
Diarrhea unrelated to eating	0.28 (0.06-1.34)	0.76 (0.17-3.35)	2.60 (0.77-8.78)
Lack of appetite	0.30 (0.07-1.20)	0.35 (0.10-1.28)	1.11 (0.47-2.61)
Tiredness	0.67 (0.33-1.35)	0.92 (0.50-1.68)	1.34 (0.75-2.37)
Low mood	0.27 (0.06-1.11)	**0.27 (0.08-0.99)** §	0.97 (0.40-2.34)
Reduced energy/activity tolerance	0.88 (0.44-1.78)	0.83 (0.46-1.51)	0.92 (0.51-1.65)
Voice problems	0.79 (0.29-2.17)	1.46 (0.57-3.75)	1.80 (0.73-4.40)
Polyneuropathy	0.38 (0.13-1.12)	0.59 (0.23-1.53)	1.53 (0.70-3.37)
Dental problems	<0.001 (<0.001->999.999)	<0.001 (<0.001->999.999)	2.31 (0.77-6.94)
Hiccups	1.28 (0.39-4.28)	2.68 (0.81-8.84)	2.06 (0.63-6.71)

aOR: adjusted odds ratio, CI: confidence interval. * Adjusted for age, sex, pathological TNM stage, neoadjuvant therapy and surgical complications. † Predefined primary endpoint. ‡ Predefined secondary endpoints. § Statistically significantly different odds ratios.

Table S2. LASER symptom scores of the primary and secondary endpoints reported by patients who were alive and relapse-free after a median of four years after totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), and open Ivor Lewis esophagectomy (OE). The scores are not adjusted for confounding factors.

Symptom	Symptom level	TMIE	HMIE	OE
Total number		91	85	186
Chest pain	0	69 (76)	49 (58)	127 (68)
	1	10 (11)	17 (20)	30 (16)
	2	8 (9)	11 (13)	16 (9)
	3	3 (3)	6 (7)	7 (4)
	4	0 (0)	1 (1)	0 (0)
	5	1 (1)	1 (1)	6 (3)
Pain from chest scars	0	76 (84)	62 (73)	139 (75)
	1	11 (12)	12 (14)	30 (16)
	2	1 (1)	8 (9)	7 (4)
	3	2 (2)	1 (1)	7 (4)
	4	0 (0)	0 (0)	0 (0)
	5	1 (1)	2 (2)	3 (2)
Abdominal pain	0	44 (48)	48 (56)	82 (44)
	1	17 (19)	15 (18)	41 (22)
	2	19 (21)	12 (14)	37 (20)
	3	5 (5)	4 (5)	17 (9)
	4	1 (1)	3 (4)	3 (2)
	5	5 (5)	3 (4)	6 (3)
Pain from abdominal scars	0	82 (90)	76 (89)	156 (84)
	1	8 (9)	5 (6)	16 (9)
	2	1 (1)	1 (1)	10 (5)
	3	0 (0)	2 (2)	3 (2)
	4	0 (0)	0 (0)	0 (0)
	5	0 (0)	1 (1)	1 (1)
Symtom levels: 0, no symptom present; 1, present but no impact on QoL; 2, rarely or weekly and some impact on QoL; 3, daily or multiple times per day and some impact on QoL; 4, rarely or weekly and substantial impact on QoL; 5, daily or multiple times per day and substantial impact on QoL				

Table S3. Adjusted mean health-related quality of life (HRQoL) scores and mean difference from the EORTC QLQ-C30 and QLQ-OG25 questionnaires of patients who were alive and relapse-free after a median of four years after totally minimally invasive (TMIE), hybrid minimally invasive (HMIE), and open Ivor Lewis esophagectomy (OE). These models were also adjusted for the occurrence of any surgical complications to investigate the impact of surgical complications on HRQoL.

	TMIE	**HMIE**	**OE**	**TMIE vs. HMIE**	**TMIE vs. OE**	**HMIE vs. OE**
	MS (95% CI)	MS (95% CI)	MS (95% CI)	MD (95% CI)*	MD (95% CI)*	MD (95% CI)*
QLQ-C30						
Global HRQoL	73 (68-78)	70 (64-75)	67 (63-71)	4 (-2-10)	6 (0-11)	2 (-3-7)
Functional status						
Physical Functioning‡	81 (77-85)	79 (75-84)	81 (77-84)	1 (-4-7)	0 (-4-5)	-1 (-6-3)
Role Functioning	86 (81-92)	80 (74-86)	83 (79-88)	6 (-1-14)	3 (-3-9)	-3 (-10-3)
Emotional Functioning	85 (80-91)	79 (73-84)	79 (74-83)	7 (0-14)	6 (0-12)	0 (-6-6)
Cognitive Functioning	88 (83-93)	83 (78-88)	82 (78-86)	5 (-2-11)	5 (0-11)	1 (-4-6)
Social Functioning	82 (76-88)	80 (74-86)	79 (74-84)	2 (-5-10)	3 (-4-9)	1 (-6-7)
Symptom scales						
Fatigue‡	31 (25-37)	35 (29-41)	33 (29-38)	-5 (-13-2)	-3 (-9-4)	2 (-4-8)
Nausea / Vomiting	16 (12-21)	19 (14-23)	14 (10-18)	-3 (-8-3)	2 (-3-7)	5 (0-9)
Pain	17 (12-22)	19 (14-25)	19 (15-24)	-2 (-9-5)	-2 (-8-3)	0 (-6-5)
Dyspnea	21 (15-28)	24 (17-31)	24 (19-29)	-3 (-11-6)	-3 (-10-4)	0 (-7-7)
Insomnia	25 (18-32)	30 (23-37)	27 (21-32)	-4 (-13-5)	-1 (-9-6)	4 (-4-11)
Appetite loss	20 (13-26)	22 (16-29)	20 (15-25)	-2 (-10-6)	-1 (-7-6)	2 (-5-9)
Constipation	15 (10-21)	19 (14-24)	15 (11-19)	-4 (-10-3)	1 (-5-6)	4 (-1-10)
Diarrhea	17 (11-23)	22 (16-28)	21 (17-26)	-6 (-13-2)	-4 (-11-2)	1 (-6-7)
Body image	87 (81-93)	83 (77-89)	84 (80-89)	4 (-3-12)	3 (-4-9)	-2 (-8-5)
QLQ-OG25						
Symptom scales						
Dysphagia	11 (7-14)	15 (11-19)	8 (5-11)	-4 (-9-0)	3 (-1-7)	**7 (3-11)** §
Problems with eating	27 (21-32)	30 (25-35)	25 (21-29)	-3 (-10-3)	2 (-4-7)	5 (-1-11)
Reflux	30 (23-36)	35 (28-42)	33 (28-39)	-4 (-13-4)	-4 (-11-3)	2 (-5-9)
Odynophagia	13 (8-17)	20 (15-24)	16 (13-20)	**-6 (-12--1)** §	-4 (-8-1)	3 (-1-8)
Pain and discomfort	21 (15-26)	24 (18-29)	25 (21-30)	-3 (-9-4)	-5 (-11-1)	-2 (-7-4)
Anxiety	27 (20-34)	36 (29-43)	31 (25-36)	**-10 (-18--1)** §	-4 (-11-3)	6 (-2-13)
Eating with others	11 (5-16)	12 (6-17)	8 (4-12)	-2 (-8-5)	3 (-3-8)	4 (-2-10)
Dry mouth	21 (14-28)	24 (17-31)	23 (17-29)	-2 (-11-7)	-2 (-10-6)	1 (-7-9)
Trouble with taste	14 (8-21)	17 (11-24)	13 (8-18)	-3 (-11-5)	2 (-5-8)	5 (-2-11)
Trouble swallowing saliva	8 (4-11)	3 (0-7)	5 (2-8)	5 (0-9)	3 (-1-7)	-1 (-5-2)
Choked when swallowing	14 (10-19)	12 (8-17)	11 (8-15)	3 (-3-9)	3 (-2-8)	1 (-4-6)
Trouble with coughing	34 (27-41)	27 (20-35)	28 (23-34)	8 (-2-17)	6 (-2-14)	-1 (-9-7)
Trouble talking scale	10 (5-15)	9 (4-14)	9 (5-13)	1 (-5-8)	1 (-4-6)	0 (-5-6)
Weight loss scale	18 (11-25)	21 (14-28)	18 (12-23)	-5 (-14-4)	0 (-8-7)	3 (-4-11)
Hair loss scale	28 (24-31)	25 (22-29)	27 (24-29)	2 (-2-7)	1 (-3-5)	-1 (-5-2)

MD: mean score difference, CI: confidence interval.

* Adjusted for age, sex, pathological TNM stage, neoadjuvant therapy and surgical complications. Because the values are rounded, the MDs may not exactly match the difference between the mean scores.

‡ Predefined secondary endpoints.

§ Statistically significant difference, but not clinically relevant difference in mean scores.

Appendix 1 – LASER questionnaire

Question	Answer
Q1. What is your current age?	
Q2. What is your sex? (Male/Female)	
Q3. In the last 6 months have you had any symptoms that you associated with your oesophagectomy? (Yes / No)	

	Q4. Do you have any of the following symptoms and how often? Please mark						Q5. What is the impact of these symptoms to your quality of life?		
Symptom	**Never**	**Rarely**	**Weekly**	**Daily**	**Multiple times per day**		**None**	**Some**	**Substantial**
a) Chest pain									
b) Abdominal pain									
c) Pain from scars on your chest									
d) Pain from scars on your abdomen									
e) Difficulty getting food down									
f) Difficultly getting liquids down									
g) Regurgitation of food									
h) Nausea									
i) Vomiting									
j) Early feeling of fullness after eating									
k) Heart palpitation after eating									
l) Sweating after eating									
Symptom	**Never**	**Rarely**	**Weekly**	**Daily**	**Multiple times per day**		**None**	**Some**	**Substantial**
m) Dizziness after eating									

n) Bloating after cramping after eating									
o) Loose bowel motions / diarrhea after eating									
p) Heartburn/acid/bile (sour/bitter tasting) regurgitation									
q) Waking up during the night because of choking sensation									
r) Persistent cough									
s) Stools that float and are difficult to flush									
t) Diarrhea (>3 times per day) unrelated to eating									
u) Lack of appetite									
v) Tiredness									
w) Low mood									
Symptom	**Never**	**Rarely**	**Weekly**	**Daily**	**Multiple times per day**		**None**	**Some**	**Substantial**
x) Reduced energy/activity tolerance									
y) Voice problems									
z) Abnormal sensation in fingers and toes									
aa) Dental problems									
bb) Hiccups									
Other (please specify):									
Other (please specify):									

Q6. Have you sought medical treatment for any of these symptoms?
(Yes or No)

Q7. Have you had any of the following medical tests in the last 6 months for the symptoms listed above in Q4?

Test	Yes or No	Number of times		
		1	2 – 4	>5
Endoscopy (camera test)				
CT Scan, X-ray or other radiology				
Blood test				
Stool test				
Other test (specify):				
Other test (specify):				

Q8. Do you take any of the following medications for heartburn and/or reflux symptoms?

Medication	Yes or No	Frequency			
		Daily	Weekly	Monthly	As required
Proton pump inhibitor (e.g. Omeprazole, lansoprazole)					
Ranitidine					
Gaviscon					
Sucralfate					
Other medications (specify):					

Q9. Do you take any painkillers or additional medications because of these symptoms?

Medication	Yes or No	Frequency

		Daily	Weekly	Monthly	As required
Painkillers					
Creon					
Other medications:					

Question	**Answer**
Q10. Are you continuing to lose weight? (Yes or No)	
Q11. Do you struggle to keep your weight on? (Yes or No)	
Q12a. What is your average weight as an adult before your illness (Kg)? Q12b. What is your current weight (Kg)?	
Q13. What is your current height (cm)?	
Q14. Are your diet and eating habits different from before you were diagnosed with cancer? (Yes or No)	
Q15. Has this affected your social life? (Yes or No)	
Q16. How many times a day do you have meals or snacks? (3 or 4–5 or 6–7 or 8–9)	
Q17. Do you take any supplemental nutrition? 0 – Not at all 1 – Oral 2 – Feeding jejunostomy 3 – By a different route	
Q18. Did you work before you were diagnosed with cancer? (Yes or No)	
Q19. Have you returned to work? 0 – Now retired 1 – No, I have not returned to work because of my symptoms 2 – Yes, but with some limitations/ reductions in activities 3 – Yes with the same activities as before	
Q20. Are your hobbies and social activities the same as before you were diagnosed with cancer? (Yes or No)	
Q21. Are you happy that you have survived your cancer? (Yes or No or I do not wish to answer)	

Please feel free to add free to expand your answer for Q21 here:	
Q22. Overall, are you satisfied with your cancer treatment? (Yes or No)	

Q23. How would you grade your functional status over the past 6 months? (please tick)

- o Fully active able to carry on all pre-disease performance without restriction.
- o Restricted in physically strenuous activity but able to carry out work of a light or sedentary nature e.g. light housework, office work.
- o Capable of all self-care but unable to carry out any work activities. Up to and about more than 50% of waking hours.
- o Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- o Cannot carry out any self-care. Totally confined to bed or chair.

9

Chapter 9

Towards an organ-sparing approach for locally advanced esophageal cancer

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Abstract

Background

Active surveillance after neoadjuvant therapies has emerged among several malignancies. During active surveillance, frequent assessments are performed to detect residual disease and surgery is only reserved for those patients in whom residual disease is proven or highly suspected without distant metastases. After neoadjuvant chemoradiotherapy (nCRT), nearly one-third of esophageal cancer patients achieve a pathologically complete response (pCR). Both patients that achieve a pCR and patients that harbor subclinical disseminated disease after nCRT could benefit from an active surveillance strategy.

Summary

Esophagectomy is still the cornerstone of treatment in patients with esophageal cancer. Non-surgical treatment via definitive chemoradiotherapy (dCRT) is currently reserved only for patients not eligible for esophagectomy. Since salvage esophagectomy after dCRT (50-60Gy) results in increased complications, morbidity and mortality compared to surgery after nCRT (41.4Gy), the latter seems preferable in the setting of active surveillance. Clinical response evaluations (CREs) can detect substantial (*i.e.* TRG3-4) tumors after nCRT with a sensitivity of 90%, minimizing the risk of development of non-resectable recurrences. Current scarce and retrospective literature suggests that active surveillance following nCRT might not jeopardize overall survival and postponed surgery could be performed safely.

Key message

Before an active surveillance approach could be considered as standard treatment, results of phase III randomized trials should be awaited.

Introduction

Organ-sparing treatment has been emerging for several malignancies and avoids loss-of-function of the organ due to surgical resection. Over two decades ago, this treatment strategy was introduced for head and neck cancers, more specifically for laryngeal cancer[1, 2]. Salvage surgery after initial organ-preservation was reported with acceptable rates of postoperative complications[3]. After promising results in laryngeal cancer, similar strategies were reported for prostate- and rectal cancer[4-9]. During the surveillance period, mostly after neoadjuvant therapy consisting of chemo- and radiotherapy, frequent checks are performed to detect residual- or progression of disease. Surgical resection is then reserved only for those patients in whom residual disease is proven or highly suspected in the absence of distant metastases. In laryngeal-, prostate- and rectal cancer, active surveillance has been reported a safe strategy without compromising overall survival (OS).

In esophageal cancer, 29% of patients show a pathologically complete response (pCR) after neoadjuvant chemoradiotherapy (nCRT) according to the CROSS-regimen[10]. Literature concerning organ-sparing treatment in esophageal cancer patients with a clinically complete response (cCR) after neoadjuvant therapy is scarce. Some studies show an OS comparable to standard esophagectomy[11-13]. The retrospective nature and small number of included patients in these studies urge the need for further research on this topic. Several challenges currently restrict widespread use of organ-sparing strategies in esophageal cancer. This review aims at providing an overview of the current treatment options and possible opportunities towards an organ-sparing treatment in esophageal cancer.

Surgery and (neo)adjuvant therapy

Esophagectomy is still considered a crucial step in the curative treatment of locally advanced esophageal cancer. One of the first review articles reporting on the outcome of esophageal cancer surgery between 1953-1978 reported a mean 5-year survival rate of 12% and a hospital mortality rate of 29%[14, 15]. This 5-year survival rate increased to 20% between 1980-1988 with a hospital mortality of 13%[16]. Both transthoracic- and transhiatal esophagectomy showed similar OS of 20% as reported in a meta-analysis[17]. However, a Dutch trial (HIVEX-study) randomized 220 patients with adenocarcinoma of the mid-to-distal esophagus or the gastric cardia involving the distal esophagus and showed a 5-year OS of 27% for the transhiatal approach and 39% for the transthoracic approach with extended *en bloc* lymphadenectomy[18]. Although better patient selection and improvement of perioperative care

resulted in higher survival rates over the last decades, the percentage of patients with tumor-free resection margins remained an issue. For both approaches, the HIVEX-trial reported 30% microscopically non-radical resections.

In order to reduce the number of non-radical resections, neoadjuvant therapies consisting of chemo- and/or radiotherapy-regimens have been thoroughly studied. The first completed, sufficiently powered, randomized controlled trial comparing trimodality treatment to surgery alone was published in 1996[19]. This study included 113 patients with esophageal adenocarcinoma and reported a 3-year survival improvement from 6% to 32% after nCRT was added to surgery. Another trial comparing trimodality-therapy to surgery alone was the CROSS-trial[10, 20]. This Dutch multicenter randomized controlled trial included 366 patients with esophageal or junctional cancer. After nCRT, 92% of the patients underwent a radical resection of the esophagus versus 69% in the surgery alone group. A pCR was achieved in 29% of the patients (23% in adenocarcinoma and 49% in squamous cell carcinoma). Importantly, 5-year OS improved from 33% to 47% after adding nCRT to surgery. No increased postoperative complications were found in the patients undergoing nCRT. Since the publication of the CROSS-trial, nCRT followed by surgery has been adopted as a standard treatment for locally-advanced esophageal cancer in large parts of the western world.

Also, (neo)adjuvant chemotherapy has been shown effective in the treatment of esophageal cancer. The OEO2-trial was the largest trial that investigated the efficacy of neoadjuvant chemotherapy for esophageal cancer[21]. Between 1992-1998, 802 patients with locally-advanced squamous cell or adenocarcinoma of the esophagus from 42 European centers were randomized between preoperative chemotherapy (cisplatin and fluorouracil) followed by surgery versus surgery alone. In the preoperative chemotherapy group, both disease-free survival (DFS) (hazard ratio (HR): 0.75; P=.0014) and 2-year OS (HR: 0.79; P=0.004) were higher. Long-term results confirmed the improvement in DFS and OS[22]. The MAGIC- and the ACCORD-07-trials confirmed the efficacy of perioperative chemotherapy in patients with esophageal- and gastric cancer[23, 24]. Surprisingly, the RTOG-8911 trial, randomizing 440 patients with locally-advanced squamous cell or adenocarcinoma of the esophagus in the period 1990-1995 between preoperative chemotherapy followed by surgery and surgery alone, failed to show an improvement in 5-year and 9-year OS after addition of preoperative chemotherapy, using cisplatin and fluorouracil[25, 26].

Both chemotherapy and chemoradiotherapy show a statistically significant improvement in OS compared to surgery alone. The improvement in OS that was observed in the CROSS-trial by adding nCRT to surgery (13%) was comparable to the improvement in the MAGIC- and the ACCORD-07-trials (13% and 15%, respectively). Chemoradiotherapy probably shows less morbidity and only moderately decreases quality of life[27-30]. To date, no randomized clinical trials powered on OS comparing chemotherapy to nCRT according to the CROSS-regimen have been published. Currently, two studies are addressing this question; the Neo-AEGIS trial and the ESOPEC trial[31, 32].

Twenty-nine percent of patients undergoing nCRT according to the CROSS-regimen showed pCR compared to 3% and 0% in the MAGIC- and ACCORD-07-trials, respectively. Distant progression was seen after neoadjuvant therapy and surgery in 39% of the patients in the CROSS-trial after a median follow-up of 84.1 months and in 30% after a median follow-up of 68.4 months in the ACCORD-07 trial. This suggests that micrometastases are already present in many patients at time of diagnosis. Both the high pCR rate after CROSS and frequent development of distant metastases after (neo)adjuvant therapy followed by surgery imposes the dilemma whether all patients would eventually benefit from esophagectomy, or whether surgery should be reserved only for those patients in whom residual disease after nCRT has been proven or is highly suspected, in the absence of distant metastases. In this way, esophagectomy could be postponed or even avoided, not only in patients who happen to attain biologically complete response after nCRT, but also in patients developing distant metastases during active surveillance, since distant metastases will heavily determine survival in these patients.

Definitive chemoradiotherapy

For patients unveiling unfit for surgery due to frailty or serious comorbidities or with an unfavorable location (e.g. the cervical esophagus) or stage of the tumor (cT4b), definitive chemoradiotherapy is the preferred curative standard treatment[33]. Definitive non-surgical therapy mostly consists of concurrent chemoradiotherapy, since the RTOG 85-01 study reported superiority of chemoradiotherapy over radiotherapy alone[34-36].

Several trials have been performed to compare surgical and non-surgical therapies in operable patients. Between 1994-2002, Stahl et al. randomized 172 patients with locally-advanced squamous cell carcinoma between nCRT followed by esophagectomy and dCRT[37]. Three-year OS was similar in both groups. Although the local progression-free survival was better in the group undergoing

esophagectomy (64.3% versus 40.7%; HR 2.1, *P=0.003*), treatment related mortality was higher (12.8% versus 3.5%;*P=0.03*). Bedenne et al. randomized 259 patients between 1993-2000 with locally-advanced esophageal cancer between nCRT followed by esophagectomy and dCRT[38]. Although the local recurrence rate after two years was higher in the patients undergoing dCRT (HR 1.63, *P=0.03*), mortality in the first 3 months postoperatively was higher in the esophagectomy group (HR 1.63, *P=0.002*). These results should be interpreted with caution since 2-year OS after neoadjuvant chemoradiotherapy and surgery was only 33.6% in contrast to, for example, 67% in the CROSS-trial. Furthermore, the Bedenne trial excluded 43% of the patients not responding to nCRT. Subsequent analysis showed similar survival between responders and non-responders undergoing esophagectomy, which seems hard to explain[39].

Although patients undergo dCRT mostly because they are not eligible for esophagectomy, a subgroup of patients become eligible after dCRT and undergo esophagectomy for residual or recurrent disease (so called salvage surgery). Several studies reported higher mortality and morbidity rates for surgery after dCRT compared to surgery after nCRT or compared to surgery alone[40-42]. Since 5-year OS was reported 25% in these patients undergoing salvage esophagectomy, the higher rates of complications, morbidity and mortality were considered acceptable. However, the indication for salvage esophagectomy should be considered with caution and only for a selected group of patients. Furthermore, the term salvage esophagectomy is sometimes used for postponed esophagectomy after nCRT and thus, the definition seems unclear. However, salvage surgery after dCRT (50–60 Gy) and postponed surgery after nCRT (41.4 Gy) should be considered two different entities. Because postponed surgery after nCRT in the context of active surveillance is expected to be necessary in a considerable number of patients and dCRT substantially increases adverse postoperative outcomes, nCRT according to the CROSS-regimen (41.4 Gy) seems preferable in the setting of active surveillance[43, 44].

Clinical response evaluation

Before an active surveillance strategy can be implemented, one should address several challenges. Most importantly, OS should not be jeopardized. In order to prevent development of non-resectable recurrences, residual disease should be detected at an early stage. Such clinical response evaluations (CREs), mostly comprising endoscopy with biopsies, endoscopic ultrasonography (EUS), positron

emission tomography with ^{18}F-fluorodeoxyglucose (PET), computed tomography (CT) and/or magnetic resonance imaging (MRI), should determine whether or not a patient is considered a clinically complete responder. Accurate CREs should have the ability to detect residual cancer while it is still resectable with a high chance of a complete tumor removal (radical resection). To justify an active surveillance strategy and to safely postpone surgery, the value and accuracy of CREs after nCRT should be thoroughly studied.

Since there are no standard protocols for CREs, studies concerning these evaluations come with large heterogeneity. For endoscopic biopsies, sensitivity of 30-40% and specificity of 100% were reported in three prospective studies[45-47]. Three prospective studies reported sensitivity and specificity for EUS ranging from 95-100% and 0-47%, respectively[46, 48, 49]. Although PET-CT after nCRT is mainly used for detection of distant interval metastases, the value in CREs has also been assessed. Two prospective studies reported a sensitivity of 51-60% and a specificity of 60-67%[45, 50]. One prospective study including 64 patients assessed a combination of any of these diagnostic modalities (endoscopic biopsies, PET and CT) and reported a sensitivity of 76% and specificity 82%[45]. The most recent and largest trial assessing a combination of diagnostic modalities is the preSANO-trial[51]. This prospective multicenter trial evaluated the accuracy of CREs and aimed to determine the optimal set of diagnostic modalities to accurately unveil residual esophageal cancer after nCRT. Some 207 patients with squamous cell- or adenocarcinoma of the esophagus or esophagogastric junction were included between 2013 and 2016. The aim of this study was to assess the correlation between the CRE-results and the tumor regression grades (TRGs) in the resection specimen. The primary endpoint of the study was the proportion of tumor regression grade (TRG) 3-4 tumors (>10% residual tumor cells) as detected during CREs. It is assumed that TRG2 tumors (1-10% residual tumor cells) can initially be missed based on the assumption that these tumors will develop into detectable TRG3-4 residual disease during active surveillance and can be resected timely and safely. Consequently, falsely negative results were reflected by the number of patients showing TRG3-4 residual disease not detected with endoscopic biopsies, EUS with fine-needle aspiration (FNA) of suspected lymph nodes and/or PET-CT.

Six weeks after completion of nCRT according to the CROSS-regimen patients underwent a first CRE (CRE-1) with only endoscopic biopsies. If CRE-1 turned out to be negative, a second CRE (CRE-2) was

performed 12 weeks after completion of nCRT, consisting of PET-CT followed by endoscopic biopsies and EUS with FNA of all suspected lymph nodes. Afterwards, all patients underwent surgery. If no vital tumor cells were proven during both response evaluations, patients were considered cCR and these results were compared to the surgical specimen of the patients. Thirty-one percent of patients with TRG3-4 tumors were considered cCR using endoscopic biopsies and EUS with FNA of all suspected lymph nodes. This drastically improved to 10% after introduction of bite-on-bite biopsies. It is thought that with bite-on-bite biopsies deeper layers of the esophageal wall can be reached and thus, are theoretically capable of unveiling buried tumors[52]. Furthermore, 10% of patients showed interval metastases, as detected with PET-CT during CRE-1 and CRE-2. These results were considered sufficient to proceed with the SANO-trial (Surgery As Needed for Oesophageal cancer); a phase-3 multicenter randomized controlled trial comparing active surveillance with immediate surgery[53].

Active surveillance in esophageal cancer

Although literature on the outcomes of nCRT plus active surveillance compared to nCRT followed by immediate surgery in patients with esophageal cancer is scarce, some studies have been published. In 2012, Taketa et al. retrospectively reviewed 622 patients after chemoradiotherapy and surgery. A cCR, was defined as no vital tumor cells in biopsies and having a physiologic range of uptake by PET-CT[11]. Sixty-one patients with a cCR refused surgery after nCRT and preoperative staging with endoscopic biopsies and PET-CT. These patients showed a 5-year overall- and recurrence-free survival of 58.1% and 35.3%, respectively. One year later, outcomes between patients declining immediate surgery and patients that underwent standard trimodality-therapy were compared using propensity-score matching and no difference in 3-year OS was reported (62% versus 56% respectively;*P=0.28*)[12]. Thirty-one percent of patients that declined immediate surgery eventually underwent a postponed resection because of residual disease without distant metastases and all resections were radical. Castoro et al. retrospectively included 77 patients with cCR after neoadjuvant therapy of whom 38 had declined surgery and 39 had undergone immediate surgery[13]. After propensity-score matching, no differences were reported in 5-year OS and DFS.

Currently, the Dutch SANO- and the French ESOSTRATE-trials are comparing active surveillance with immediate surgery in patients with squamous cell- or adenocarcinoma of the esophagus showing cCR after nCRT according to the CROSS-regimen[53]. In the SANO-trial, cCR is defined as endoscopy with

multiple bite-on-bite biopsies, EUS with FNA of all suspected lymph nodes and PET-CT, all showing no signs of residual disease or distant metastases twelve weeks after completion of nCRT. After having reached cCR, patients are randomized to either active surveillance or immediate resection according to a stepped-wedge design, i.e. based on randomization on institutional level and not on individual level since randomization between conservative- and surgical treatment on individual level often fail due to disappointing inclusion rates[54, 55].

Future perspectives

Safe and careful implementation of an organ-sparing approach in esophageal cancer depends on several cornerstones. First of all, CREs need to be further improved in order to avoid the risk of developing irresectable residual disease during active surveillance. For this purpose, it should be analyzed why endoscopic bite-on-bite biopsies still show false-negative results. Probably, there are two main reasons; either the location of the residual tumor was superficial but biopsies were not accurately targeted or the residual tumor was too deep for endoscopic biopsies to reach the tumor as already suggested in earlier studies[56, 57]. Sampling of large areas of the esophagus during CREs could overcome the issue of sampling errors. For instance, the Endosponge® (Medtronic, Minneapolis, USA) and the wide-area transepithelial sampling (WATS) procedure[58, 59]. The latter technique uses a minimally invasive brush biopsy technique which samples layers as deep as the muscularis muosae. New biopsy instruments reaching deeper parts of the esophageal wall, like fine-needle biopsies (FNB), could overcome the issue of residual tumor buried under a tumor-free (sub)mucosal layer[57, 60, 61]. FNB is considered safe and is widely used in the gastrointestinal tract. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has shown potential benefit in detection of residual disease after nCRT[62]. Although PET-CT does not seem accurate enough to determine whether or not a patient should undergo surgery early after nCRT due to high false-positive rates (mostly because of radiation esophagitis), the value of semi-quantitative assessment of residual disease with PET-CT could be of value during surveillance and is currently part of the surveillance strategy in the SANO-trial[51]. Furthermore, new biomarkers could possibly unveil residual tumors in the peripheral blood[63]. An example of such biomarkers is circulating tumor DNA (ctDNA) that is shedded from necrotizing tumor cells freely into the peripheral blood. With help of next-generation sequencing and whole exome sequencing, very small amounts of DNA containing esophageal cancer-specific mutations can be

detected and thus, can possibly detect residual tumors in early phases and as such act as "liquid biopsies"[64, 65]. Even though CREs are considered accurate enough in unveiling residual disease, delayed detection of recurrences could theoretically result in increased distant dissemination rate due to prolonged *in situ* time of the primary tumor. Although previous studies showed no differences in distant dissemination rate between patients undergoing nCRT with and without surgery, this must be monitored with caution during active surveillance[12, 13]. Secondly, implementation of an active surveillance strategy should come with some side notes. Although an active surveillance strategy would have clear clinical advantages, concerns exist about whether the active surveillance strategy is warranted for all patients with cCR. Such a strategy comes with more frequent hospital visits and additional invasive diagnostic tests that could result in a psychological burden. Furthermore, patients could experience anxiety due to the fact that, potentially, the tumor has not been treated optimally and postponed surgery could still be necessary. These factors could outweigh the advantage of preventing surgery[66]. Earlier studies reported a discrepancy in decision-making between the patients and their doctors which underlines the necessity of shared-decision making[67]. A recent study suggested that, in the preoperative stage, esophageal cancer patients were willing to trade-off an average of 15% 5-year survival to decrease the need for esophagectomy from 100% to 35%[68]. Future studies should confirm these results in the postoperative setting. Furthermore, patient factors should be identified that are clearly correlated with a preference for either immediate surgery or active surveillance to better inform and advice patients in decision-making[69].

Conclusion

After nCRT up to one-third of patient shows pCR in the resection specimen. This evokes a discussion if active surveillance might be appropriate in patients with cCR. Currently, the main challenge is to improve the clinical identification of tumor residue.

The scarce retrospective literature suggests that an organ-sparing approach with active surveillance after nCRT might not jeopardize OS and postponed surgery could be performed safely. Before an active surveillance approach can be considered part of standard treatment in patients with esophageal cancer, the results of randomized trials such as the ESOSTRATE- and the SANO-trial, should be awaited.

Conflicts of interest

The authors declare no conflicts of interest

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11

Chapter 11

Interventions that facilitate shared decision making in cancers with active surveillance as treatment option: a systematic review of the literature

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Abstract

Background

Medical decisions concerning active surveillance are complex, especially when evidence on superiority of one of treatments is lacking. Decision aids have been developed to facilitate shared decision making on whether to pursue an active surveillance strategy. However, it is unclear how these decision aids are designed and which outcomes are considered relevant. The aim of this study is to systematically review all decision aids in the field of oncological active surveillance strategies and outcomes used by authors to assess their efficacy.

Methods

A search was performed in Embase, Medline, Web of Science, Cochrane, PsycINFO Ovid and Google Scholar until June 2019. Eligible studies concerned interventions aiming to facilitate shared decision making for patients confronted with several treatment alternatives, with active surveillance being one of the treatment alternatives.

Results

Twenty-three eligible articles were included. Twenty-one articles included patients with prostate cancer, one with thyroid cancer and one with ovarian cancer. Interventions mostly consisted of an interactive web-based decision aid format. After categorization of outcomes, seven main groups were identified: knowledge, involvement in decision making, decisional conflict, treatment preference, decision regret, anxiety and health-related outcomes.

Conclusion

Although active surveillance has been implemented for several malignancies, interventions that facilitate shared decision making between active surveillance and other equally effective treatment alternatives are scarce. Future research should focus on developing interventions for malignancies like rectal cancer and oesophageal cancer as well. The efficacy of interventions is mostly assessed using short-term outcomes.

Introduction

Treatment modalities for cancer include a combination of radiotherapy, chemotherapy and surgery. In addition, active surveillance has been introduced as an alternative treatment option in prostate-, colorectal-, thyroid- and head and neck cancer [1-7]. In other malignancies such as oesophageal cancer, active surveillance is under investigation as a viable treatment option [8, 9]. Active surveillance involves frequently performed response evaluations after neoadjuvant therapy using diagnostics (*e.g.* imaging scans and endoscopic biopsies) to detect remnants of residual disease. Additional treatment is only indicated in those patients with residual disease or progression of disease. Active surveillance strategies have potential advantages, such as the possibility to avoid or delay the need for invasive treatments associated with morbidity and even mortality. However, pitfalls in an active surveillance strategy include the development of an unresectable recurrence, possibly resulting in deterioration of overall survival. Furthermore, distant dissemination rates could theoretically increase due to longer presence of residual tumour in the primary organ, possibly resulting in shedding of tumour cells and development of metastases [10]. In addition, several studies reported that active surveillance induces a certain degree of uncertainty and anxiety for patients, because they might feel like they are living with 'untreated' cancer [11-13]. Finally, the repeated diagnostic measures may also cause a physical burden (*e.g.* endoscopy) and periodical peaks of anxiety, with possible negative effects on quality of life [14].

Medical decisions concerning active surveillance are often complex, especially because there are multiple treatment options without a clear indication for the best oncological outcome at a group level, let alone at an individual level. The choice of treatment therefore depends on the preferences and values of individual patients as well as their treating physicians. It is preferable that physicians and patients participate in shared decision making to ensure that the decision made is consistent with the patient's preferences [15]. Shared decision making involves informing the patient that a decision is to be made, explaining the potential advantages and disadvantages of each relevant option, discussion of patient's preferences and finally making the decision together [16]. In order to help patients and physicians making informed decisions together, various interventions have been developed. However, it is unclear how to measure whether these interventions indeed facilitate shared decision making [17, 18].

In this systematic review, we aim to summarize the design of an intervention and the outcomes that are considered relevant to measure the effectiveness of an intervention used to facilitate shared decision making in cancer patients for whom active surveillance is a treatment alternative.

Methods

Protocol and registration

The protocol for this study was specified in advance and registered on Prospero (CRD42020139240). The study was performed according to the PRISMA guidelines for systematic reviews [19].

Eligibility criteria

Studies were considered eligible if (1) patients were included with malignant disease, (2) on the patients a choice was imposed between several treatment options, with active surveillance being one of the alternatives, (3) an intervention was used to facilitate shared decision making and (4) the outcomes used to measure the effectiveness of the intervention were reported. Interventions were defined as all methods or approaches designed to facilitate involvement in the decision making process for medical treatment. No restrictions were placed on outcome measures. There was no restriction on publication date. Letters to the editor, editorials, conference abstracts, systematic reviews, narrative reviews and studies written in other languages than English were excluded from further analysis. Also, studies including only patients with palliative options were excluded from further analysis.

Information sources and search

The search strategy was developed in collaboration with an experienced research librarian with an expertise in systematic review searching. The search was applied to Embase, and adapted to Medline Ovid, Web of Science, Cochrane Central, PsychINFO Ovid and Google Scholar until June 13, 2019. In addition to these electronic databases searches, included papers were checked for relevant references. Search terms included: 'watchful waiting' or 'active surveillance' combined with 'shared decision' or 'decision making' or 'patient preference' or 'decision aid/tool' and 'cancer (treatment)'. The full search strategy is reported in *Supplementary Table 1*.

Endnote X9 (Thomas Reuters, New York, NY) was used for the reference management of the literature search results. After deduplication, two authors (GC and BvdW) independently screened titles and abstracts of the articles from the search results and selected studies based on the predefined inclusion and exclusion criteria. Inconsistencies were resolved by discussion between the two authors. If no consensus was reached, a third author (LK) resolved any disagreement. The full-text articles were then screened and motivations for exclusion were recorded. Finally, references of eligible studies were screened for relevance and references of previously published reviews on this topic were screened for cross-referencing.

Data extraction

A data extraction form was developed in order to identify key information and recurring themes within studies. The data extraction form was pilot-tested and refined accordingly. One author (GC) extracted data from included studies, and a second author (BvdW) checked the extracted data. Again, disagreements were resolved by discussion, if no agreement was reached, a third author made a final decision (LK). Information was extracted from the included studies on: (1) characteristics of included participants and studies, including number of patients and type of malignancy as well as the design of the study; (2) type of intervention used; (3) outcomes as measured by authors; (4) instruments used for the assessment of the effectiveness of intervention; (5) reported results for every outcome. In the present study, the Critical Appraisal Skills Programme (CASP) was used for the assessment of quality of included qualitative studies [20]. For included randomised controlled trials, the risk of bias was assessed using the Cochrane Collaboration's tool for RCTs and the ROBINS-I tool was used for assessing risk of bias in non-randomised studies [21, 22].

Results

Study selection

A total of 23 articles, describing 22 unique interventions, were included in this systematic review. 4 856 articles were identified from six databases and 16 articles were identified through cross-referencing. 2 912 articles were eligible for title and abstract screening after adjusting for duplicates. Of these, 2 884 were excluded through title and abstract screening, not meeting the inclusion criteria. After 28 full-text analyses, five additional studies were excluded, ultimately leaving 23 relevant articles. A detailed flowchart for exclusion at each stage and reasons for exclusion after

full-text analyses is reported in Figure 1. Two articles were based on the same trial, but since they measured different outcomes both studies were included [23, 24]. The results of the risk of bias assessments of all studies are summarized in supplementary Figure 1a-c. Results and outcomes of the included articles are summarized in Table 1a and Table 1b.

Study and patient characteristics

Of 23 articles included in this study, twelve were randomised controlled trials, which all except one included over 100 patients. Non-randomised trials were mainly cohort studies of which four studies included over 100 patients. Twenty-one articles included patients with prostate cancer, one article included only patients with thyroid cancer and one only included patients with ovarian cancer.

Type of intervention

In the majority of studies, an interactive web-based Decision Aid (DA) format was used [23-31]. These DAs included written information, videos, and/or exercises offering patients the opportunity to consider what they deemed important regarding the treatment choice of their disease. Six studies used an informational booklet, containing information on the disease, different treatment options and the possible side effects of each treatment option [28, 32-36]. In four studies, a video presentation was the main tool of the DA [34, 37-39]. In one study, participants received an audiotape DA [28]. Two studies assessed the effect of providing an audiotape of the consultation of the patients with their physician [27, 40]. In five studies, the DA primarily involved an additional consultation with an expert [27, 31, 41-43]. Three studies explicitly mentioned the added value of clarification exercises to the DA [26, 30, 35]. Please note that some studies did not use only one type of intervention, but a combination of, for example, an information booklet and a web-based DA.

Effectiveness of decision aid

An overview of the different outcomes measured by the authors is offered in Table 1a and Table 1b. A large heterogeneity exists in these outcomes. In order to acquire more insight into the outcome measures, seven groups were constructed by categorizing the outcomes according to most occurring related outcome measures. These groups are: knowledge, involvement in decision making, decisional conflict, treatment preference/choice, decision regret/satisfaction with decision,

anxiety/coping/mood and health-related outcomes. Knowledge was measured in 7 studies, involvement in decision making in 10 studies, decisional conflict in 9 studies, treatment preference/choice in 13 studies, decision regret/satisfaction with decision in 6 studies, anxiety/coping/mood in 5 studies and health-related outcomes in 1 study.

Four questionnaires were used frequently by different authors: the Preparation for Decision Making Scale, the Decisional Conflict Scale, the Decision Regret Scale and the Satisfaction with Decision Scale. Knowledge and evaluation of DA were often measured with questionnaires developed by the authors. The results of each individual study assessing the effectiveness of the intervention used are summarised in *Table 2*. Only one study measured outcomes specific to active surveillance, this outcome was 'knowledge of the rationale for active surveillance' [39].

Out of the 23 studies, eleven added the patients' evaluation of their DA as an outcome measure [23, 25, 27, 28, 32, 33, 36, 38, 40, 44, 45]. In these studies, patients were asked for their feedback concerning acceptability, feasibility, clarity, usefulness, satisfaction with timing and format of the information, satisfaction with DA in general or communicative effectiveness.

Discussion

This systematic review presents an overview of interventions aimed at facilitating shared decision making in cancer patients who are confronted with a treatment choice in which active surveillance is a treatment alternative, and the outcomes considered relevant in this respect. Surprisingly, even though active surveillance is an established treatment alternative also for patients with rectal cancer, head and neck cancer and is under investigation for oesophageal cancer, current interventions are mostly limited to patients with prostate cancer. The present study is the first systematic review that provides an overview of outcomes used to test the effectiveness of in interventions aimed at facilitating shared decision making in cancer when active surveillance is a treatment alternative. This resulted in an insight in the spectrum of interventions used, for what purpose and which outcomes have been measured.

Of the 23 included studies, 21 have developed decision aids for patients with prostate cancer. This is remarkable given that active surveillance has also been performed in patients with rectal cancer and head and neck cancer for over 15 years. Furthermore, in several malignancies, an active surveillance strategy has been topic of debate (*e.g.* oesophageal cancer). A recent systematic review assessed all

studies that used decision aids for patients with colorectal cancer [46]. The authors of this study screened 3 773 articles and eventually included three articles [47-49]. Of these three articles, two articles used the decision aid to support the decision between chemotherapy or no chemotherapy treatment. One article used the aid to choose between two surgical techniques. No decision aids were developed to support the decision including active surveillance, as is the focus of this systematic review.

The present study reported on 22 unique interventions. It seems that there is no consensus on which type of intervention is most effective. Booklets, videos and web-based DAs are the most commonly used interventions, and more recent studies sometimes included a consultation with a professional to talk about the preferences of the patient. Most interventions rely on the patients' own motivation to use the decision aid and to improve their understanding of the (dis)advantages of each treatment. As such, patients are expected to return to their physician with a better understanding of their disease after having used the specific DA. Most interventions also encourage the patient to consider their values and preferences. However, it remains unclear to what extent these values and preferences are taken into account in the consultation and final decision making with the physician.

Finally, there is a large heterogeneity in the outcomes used by authors to assess the effectiveness of the tested interventions. After categorisation of the outcomes, treatment choice or preference was most reported to test efficacy of interventions. The reason for this remains unclear, because DAs should not aim to increase the choice for a specific treatment, but rather to facilitate shared decision making by helping patients and their health care professionals make a treatment choice best fitted to their unique circumstances [50]. Whether or not the interventions succeeded in this respect, is most probably not measured by assessing the treatment choice of the patient. We propose that self-reported involvement in decision-making could be a representative short-term outcome and decisional conflict could be a representative long-term outcome for the effectiveness of DAs. Indeed, self-reported involvement in decision making was used as outcome in a large number of the articles. Decisional conflict, however, was used as outcome only in a minority of studies. This could be due to the fact that a longer follow-up is needed for this outcome. Even though all studies included in this review had active surveillance as a treatment option, only one study used an outcome measure specific to active surveillance, *i.e.* knowledge of the rationale for active surveillance [39]. There are usually no outcome measures specific to the other treatment options either; however, active surveillance seems different from the other treatment options. For active surveillance to be

successful, it is very important that patients who choose active surveillance understand what it entails for both acceptance and adherence to the active surveillance strategy, as reported in a previous study [51].

The present study is associated with limitations. Firstly, because of the limited variety in malignancies discussed: mostly DAs for prostate cancer were analysed. Consequently, we assessed the outcomes for a selected group of patients and as such, these results might not be one to one extrapolated to the general population. However, we included only malignancies that also involved active surveillance as treatment alternative, enhancing the generalizability among the malignancies with active surveillance as treatment option. Secondly, due to the large heterogeneity in outcomes used by the authors to assess the effectiveness of the intervention, a categorisation of these outcomes was necessary for overview. Inevitably, in this way interpretation of the results could not be avoided. Lastly, since both patients and physicians are involved in shared decision making it would be interesting to gain more insights in the evaluation of the developed interventions from a physician-perspective. The current search strategy was not designed to answer this question.

Conclusion

In conclusion, interventions facilitating the choice between several treatment options with active surveillance as one of the alternatives have been developed mostly for prostate cancer, thus far. The outcomes used to assess the effectiveness of the interventions are highly heterogenic and it remains unclear how interventions are exactly supposed to facilitate shared decision making. Future research should focus on developing interventions for malignancies other than prostate cancer, like rectal cancer, head and neck cancer and oesophageal cancer. Furthermore, interventions that facilitate shared decision making might benefit from more long-term follow-up research, measuring outcomes like decision regret. With active surveillance, patients have to return to the hospital regularly for a few years, and it would be interesting to see how the intervention affects patients after a year or more, especially regarding patient-reported outcomes like anxiety and decision regret.

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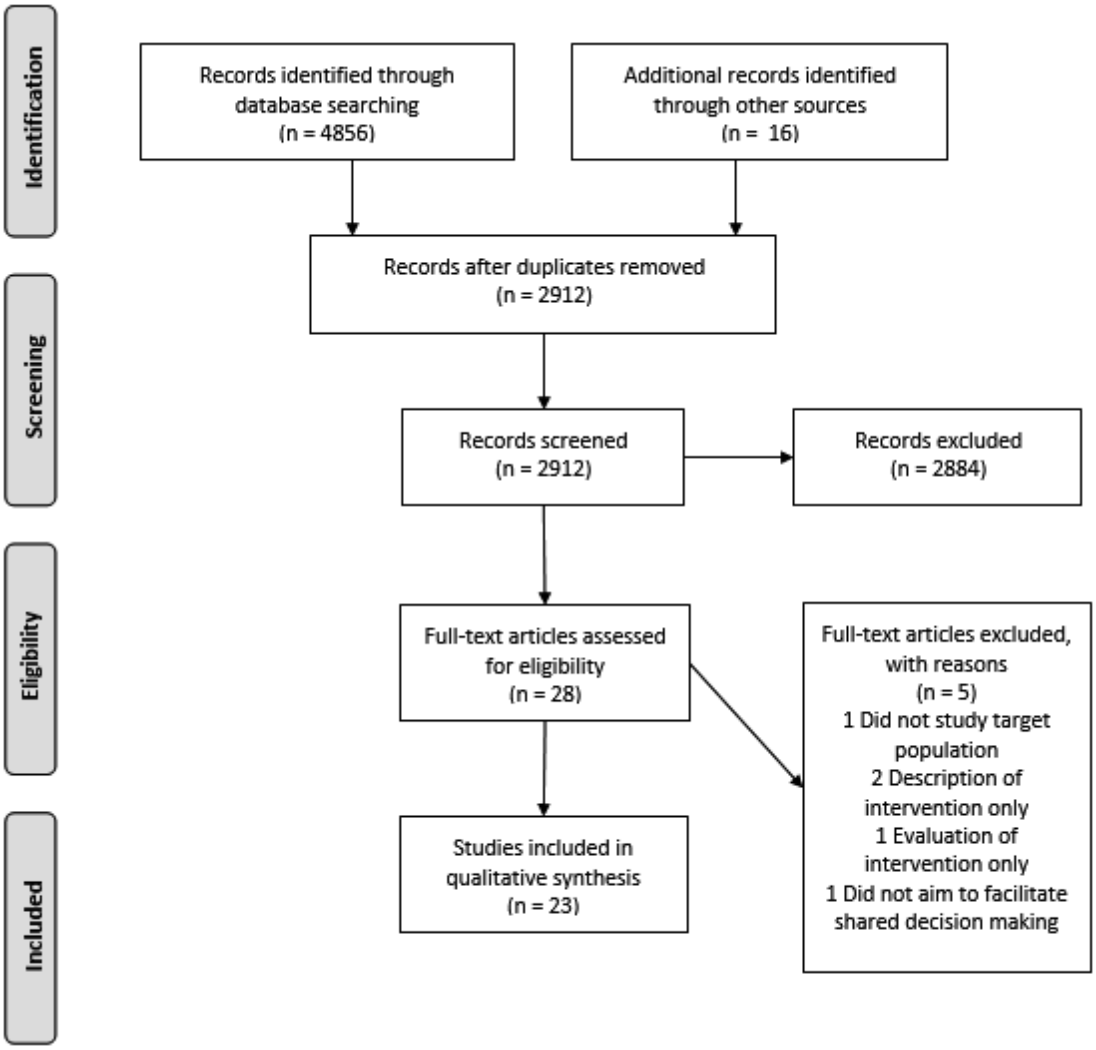


Figure 1. Flow Diagram of Literature Search and Study Selection

Table 1a. Overview of characteristics from 12 randomised controlled trials that were included

First author	Type of cancer	Participants (N)	Intervention	Control	Outcome measures
Auvinen, 2004 [43]	Prostate	210	Enhanced participation: emphasis on patient role in decision making, structured information on treatment options and discussion with physician	Usual care + discussion with physician	Choice of treatment
Feldman-Stewart, 2006 [36]	Prostate	180	Newly developed information booklet	Standard information booklet	Evaluation of DAs, satisfaction with preparation, anxiety, adjustment, decisional conflict
Hack, 2007 [40]	Prostate	425	Audio-tape of consult	Usual care	Role in decision making, communication satisfaction with oncologist, audiotape use and satisfaction, perceived degree of information provision, mood state, cancer related quality of life
Diefenbach, 2012 [25]	Prostate	72	Internet/CD-ROM-based interactive virtual health centre (with or without tailoring)	Usual care	Evaluation of educational material, decisional variables, treatment preferences
Feldman-Stewart, 2012 [26]	Prostate	156	Decision aid on computer with well-structured information and values clarification exercises	Decision aid with only well-structured information	Decisional conflict, preparation for decision making, decision regret
Bosco, 2012 [24]	Prostate	448	Computerized decision support system	Standard education + links to websites	Concordance of treatment choice with self-reported influential side-effects
Berry, 2013 [23]	Prostate	494	Computerized decision support system	Standard education + links to websites	Decisional conflict, time-to-treatment, treatment choice, program acceptability/usefulness

Hacking, 2013 [27]	Prostate	113	Decision navigation: preparing of personal consultation plan	Usual care	Decisional self-efficacy, decisional conflict, decision regret, mental adjustment to cancer, anxiety and depression, navigation service feedback, final treatment choice
Chabrera, 2015 [35]	Prostate	147	Booklet with information, preparation material for consultation and values clarification exercises	Usual care	Knowledge about prostate cancer, decisional conflict, satisfaction with decision, coping
Song, 2017 [34]	Prostate	156	Video, booklet, tear-out sheet for personal concerns, phone calls to formulate questions	Usual care + handout on staying healthy during treatment	Provision of information, asking questions
Cuypers, 2018 [44]	Prostate	336	Online DA counselling	Standard counselling	Decisional conflict, patients' perceived role during decision making, perceived preparedness to make the treatment decision, Pca knowledge, satisfaction with timing and format of the information received, additional questions to evaluate DA
Jayadevappa, 2019 [52]	Prostate	743	Web-based tool for preference assessment	Usual care	Satisfaction with care, satisfaction with decision, decision regret, treatment choice

RCT: randomised controlled trial, DA: decision aid, Pca: Prostate Cancer

Table 1b. Overview of characteristics from 11 non-randomised controlled trials that were included

Study	Cancer	Participants	Intervention	Outcome measures
Onel, 1998 [37]	Prostate	111	Video presentation	Knowledge of prostate cancer, subjective participation in treatment decision, final treatment decision, satisfaction with choice, would choose again
Kim, 2001 [45]	Prostate	30	Interactive CD-ROM decision aid	Prostate cancer knowledge, satisfaction with DA, treatment preference, likelihood of following treatment preference, relationship between Pca knowledge and health literacy
McGregor, 2003 [38]	Prostate	22	Video presentation	Insight and knowledge after consultation, communicative effectiveness of video DA, effect of diagnosis on memory and perception, mastery over situation
Feldman-Stewart, 2004 [42]	Prostate	60	Decision aid (one-on-one) interview	Attributes important to the decision, cognitive challenges as determined by patients, changes in important attributes over decision process, changes in treatment ratings, cognitive processes associated with stability of preferred treatment options, cognitive processes associated with regret
Holmes-Rovner, 2005 [28]	Prostate	60	Booklet DA, internet DA and audiotape DA	Different media outcomes, clarity and usefulness of DA, knowledge of pathology results, knowledge of treatment options, discussion of treatment options with physician, active role in treatment decision
Isebaert, 2008 [32]	Prostate	50	Decision aid booklet (based on Holmes-Rovner)	Patients' general evaluation of the decision aid, final treatment choice, impact of decision aid on treatment choice and consultation according to patients, impact of decision aid on treatment choice and consultation according to doctor
Anderson, 2011 [33]	Ovarian	20	Decision aid booklet	Information and involvement preferences, decision aid feedback, understanding of information contained in DA, difficulties and satisfaction with the decision-making process, anxiety levels
Formica, 2017 [39]	Prostate	452	Video presentation	Knowledge of the rationale for active surveillance
Lamers, 2017 [30]	Prostate	181	Web-based DA with information + values clarification exercises	Concordance of treatment preference before and after DA use, concordance of treatment preference after DA and final choice, concordance initial treatment preference patient and urologist, concordance urologist preference with final decision
Myers, 2018 [31]	Prostate	30	Nurse mediated online software application	Knowledge about Pca and treatment, patient perceptions regarding Pca and treatment, decisional conflict, treatment preference, treatment status
Brito, 2018 [41]	Thyroid	278	Conversation aid	Final treatment choice

DA: decision aid, Pca: prostate cancer

Table 2. Categorised outcomes used by authors to assess the effectiveness of the intervention used as well as a summary result described by the authors

Study	Knowledge	Involvement in decision-making	Decisional conflict	Treatment preference/choice	Decision regret/satisfaction with decision	Anxiety/coping/mood	Health-related outcomes
Auvinen, 2004[43]	n.a.	n.a.	n.a.	58% of men in the intervention group chose the standard treatment, vs. 86% in the control group (p<.001)	n.a.	n.a.	n.a.
Feldman-Stewart, 2006[36]	n.a.	Patients in the intervention group felt better prepared for decision-making compared to the control group (p=.047)[a]	Patients in the intervention group appear to experience less decisional conflict[b]	n.a.	n.a.	Anxiety appears lower in the intervention group, and adjustment seems higher, but for both no significant effect was found	n.a.
Hack, 2007 [40]	n.a.	n.a.	n.a.	n.a.	n.a.	No significant difference in mood state was found between the two groups	Audiotape benefit was not significantly related to patient satisfaction with cancer-related quality of life at 12 weeks post-consultation.

Diefenbach, 2012[25]	n.a.	Patients in the intervention group felt more confident about decision-making	Patients in the intervention group scores lower on decisional conflict[b]	No significant impact of intervention on treatment preferences was found	n.a.	n.a.	n.a.
Feldman-Stewart, 2012[26]	n.a.	Patients in the intervention group felt better prepared for decision-making at follow-up[a]	Decisional conflict decreased in both groups[b]	n.a.	At >1 year follow-up the mean regret of the intervention group was lower (p=.047)[c]	n.a.	n.a.
Bosco, 2012[24]	n.a	n.a.	n.a.	45% of men in the intervention group chose treatment in concordance with self-reported influential side effects, vs. 50% in the control group	n.a.	n.a.	n.a.
Berry, 2013[23]	n.a.	n.a.	n.a.	Men in the intervention group chose brachytherapy more often (p=0.01)	n.a.	n.a.	n.a.
Hacking, 2013[27]	n.a.	Decisional self-efficacy increased in both groups, but was higher	Scores on decisional conflict were lower in the	Control group: Surgery (22), external beam radiotherapy (17), hormone therapy	Lower in intervention group at 6-month follow-up (p=.036)	No significant difference between groups was found for mental adjustment to	n.a.

		in the intervention group (p=0.011)	intervention group (p=.047)[b]	(2), brachytherapy (2), active monitoring (14) Intervention group: Surgery (17), external beam radiotherapy (11), hormone therapy (5), brachytherapy (5), active monitoring (9)		cancer, anxiety or depression	
Chabrera, 2015[35]	Men in the intervention group scored significantly higher on knowledge after DA use compared to the control group (p<.001)	n.a.	Patients in the intervention group had lower decisional conflict scores (p<.001)	n.a.	Higher satisfaction with decision scores in intervention group (p<.001)[4]	Patients in the intervention group made more extensive use of coping mechanisms (p<.001)	n.a.
Song, 2017[34]	n.a.	Higher percentages of patients and family members in the intervention group provided information and asked questions	n.a.	n.a.	n.a.	n.a.	n.a.

		during the consult					
Cuypers, 2018[44]	n.a.	Patients in the intervention group felt less prepared to make the treatment decision[a]	No significant difference between groups[b]	n.a.	n.a.	n.a.	n.a.
Jayadevappa, 2019[52]	n.a.	n.a.	n.a.	66% of men in the intervention group chose active surveillance, vs. 54% in the control group (p<.001)	Regret declined in both groups, after 24 months intervention group showed less regret (p<.05); satisfaction improved in both groups, improvement was greater in the intervention group (p<.05)[d]	n.a.	n.a.
Onel, 1998[37]	Increase in self-reported knowledge	75% to 84% of patients felt they participated 'a lot' in the treatment decision	n.a.	Surgery (32), radiotherapy (33), hormonal therapy (8), watchful waiting (22)	93% of patients were satisfied with their treatment decision, 100% of patients who chose hormonal treatment were satisfied, whereas 84% of patients who chose surgery	n.a.	n.a.

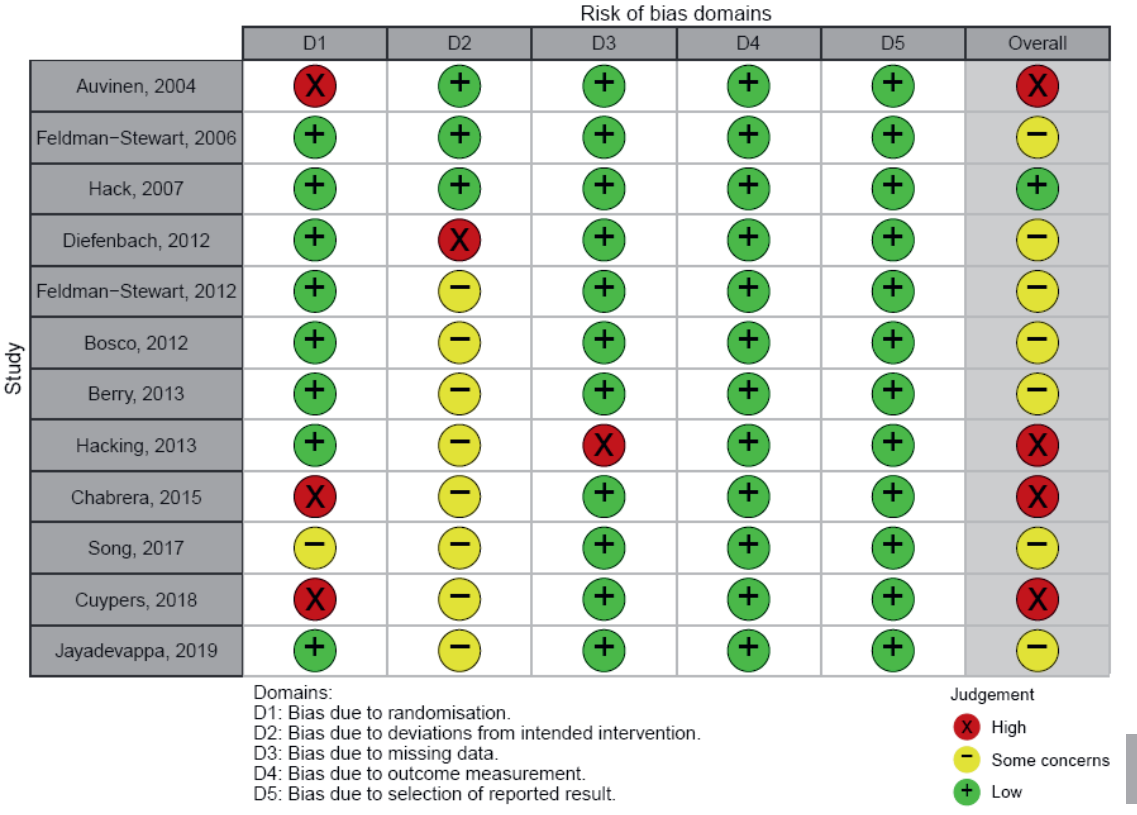
					were satisfied with their choice		
Kim, 2001[45]	Mean score of 74%, correlation between knowledge scores and health literacy	n.a.	n.a.	Treatment preferences: hormonal therapy (20%), radiation (13.3%), radical prostatectomy (10%) and combined hormonal and radiation therapy (13.5%). 66.7% received treatments different from those preferences	n.a.	n.a.	n.a.
McGregor, 2003[38]	Patients reported increased understanding of their disease and its management	Patients felt empowered to take an active role in the decision-making process	n.a.	n.a.	n.a.	n.a.	n.a.
Feldman-Stewart, 2004[42]	n.a.	n.a.	92% strongly agreed they were clear about the importance of benefits, 88% strongly agreed they were clear about the	76% of men chose the treatment preference they had at the end of the intervention	Lack of regret after the decision was positively associated with increasing differentiation between treatment options over time	n.a.	n.a.

			importance of risks and side-effects and 47% strongly agreed it was hard for them to decide whether the benefits or the risks were important to them				
Holmes-Rovner, 2005[28]	Intervention group shows some increase in knowledge, especially on watchful waiting and on side effects	Increase in discussion of surgery with physician (p=.02); 72% of men reported that they were more likely to take an active role in their treatment decision	n.a.	n.a.	n.a.	n.a.	n.a.
Isebaert, 2008[32]	n.a.	Intervention resulted in more active involvement in decision-making, according to both patient and doctor	n.a.	Radical prostatectomy (19), external beam radiation (14), brachytherapy (10) watchful waiting (6), 1	n.a.	n.a.	n.a.

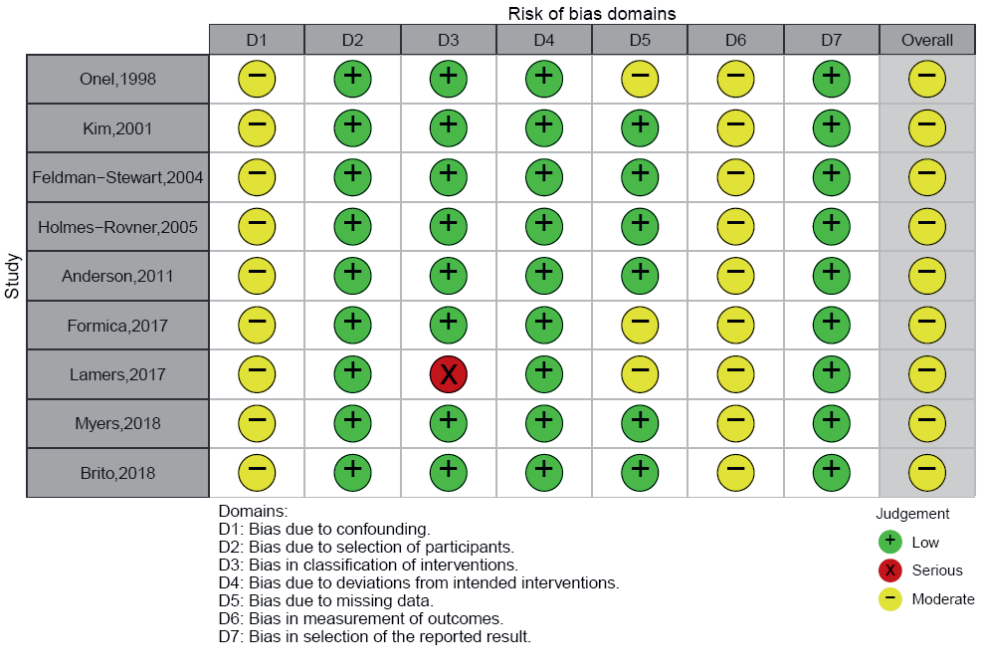
				remained inconclusive			
Anderson, 2011[33]	n.a.	n.a.	The average decisional conflict score was lower than in comparable samples[b]	n.a.	n.a.	Anxiety scores were high, but similar to one comparable study	n.a.
Formica, 2017[39]	Patients who watched DA had more knowledge of the rationale for active surveillance	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Lamers, 2017[30]	n.a.	n.a.	n.a.	Final treatment choice was in excellent agreement with treatment preference after DA and in good agreement with urologist preference	n.a.	n.a.	n.a.
Myers, 2018[31]	Increase in knowledge after DA (p<.001)	n.a.	Decisional conflict scores decreased (p<.001)[b]	Active surveillance (83%), active treatment (17%)	n.a.	n.a.	n.a.
Brito, 2018[41]	n.a.	n.a.	n.a.	Patients in intervention group were more	n.a.	n.a.	n.a.

				likely to choose active surveillance (89% vs. 77% in control group)			

a: Preparation for Decision Making Scale, b: Decisional Conflict Scale, c: Decision Regret Scale, d: Satisfaction with Decision Scale, DA: decision aid, n.a.: not applicable



Supplementary Figure 1a. Risk of bias for randomised controlled trials using the Cochrane ROB2-tool



Supplementary Figure 1b. Risk of bias for non-randomised studies using the Cochrane ROBINS-I-tool

	Section A						Section B		
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Isebaert, 2009	Yes	Yes	No	Yes	Yes	No	No	No	Yes
McGregor, 2003	Yes	Yes	Yes	No	No	No	No	No	No

Q: Question
Section A: Are the results of the study valid?
Section B: What are the results?

Supplementary Figure 1c. Risk of bias for qualitative studies using the CASP checklist

Supplementary Table 1. Full search strategy and results until June 13, 2019

Embase.com	('watchful waiting'/de OR 'active surveillance'/de OR (((watch* OR see) NEAR/3 wait*) OR (wait NEAR/3 see) OR (active NEAR/3 surveillan*) OR ('not' NEXT/2 'to treat')):ab,ti) AND ('decision making'/exp OR 'decision support system'/exp OR 'decision tree'/exp OR 'patient preference'/de OR (((decision* OR choice* OR choose OR chose OR wish) NEAR/6 (making OR support* OR system* OR tree* OR shared OR aid OR tool* OR model* OR analy* OR patient* OR informed* OR regret* OR clinical* OR treatment* OR factor* OR affect* OR prefer*)) OR (patients* NEAR/3 (treatment* OR therap*) NEAR/3 (selection* OR prefer*))):ab,ti) AND ('neoplasm'/exp OR 'cancer patient'/de OR 'cancer surgery'/de OR (neoplasm* OR tumo* OR cancer* OR malign* OR carcinom*):ab,ti) AND [English]/lim NOT ([animals]/lim NOT [humans]/lim)
Medline Ovid	(Watchful Waiting/ OR (((watch* OR see) ADJ3 wait*) OR (wait ADJ3 see) OR (active ADJ3 surveillan*) OR "not to treat").ab,ti.) AND (exp Decision Making/ OR Decision Support Techniques/ OR Decision Trees/ OR Patient Preference/ OR (((decision* OR choice* OR choose OR chose OR wish) ADJ6 (making OR support* OR system* OR tree* OR shared OR aid OR tool* OR model* OR analy* OR patient* OR informed* OR regret* OR clinical* OR treatment* OR factor* OR affect* OR prefer*)) OR (patients* ADJ3 (treatment* OR therap*) ADJ3 (selection* OR prefer*))).ab,ti.) AND (exp Neoplasms/ OR (neoplasm* OR tumo* OR cancer* OR malign* OR carcinom*).ab,ti.) AND english.la. NOT (exp animals/ NOT humans/)
Web of science	TS=(((((watch* OR see) NEAR/2 wait*) OR (wait NEAR/2 see) OR (active NEAR/2 surveillan*) OR ("not" NEAR/2 "to treat"))) AND ((((decision* OR choice* OR choose OR chose OR wish) NEAR/5 (making OR support* OR system* OR tree* OR shared OR aid OR tool* OR model* OR analy* OR patient* OR informed* OR regret* OR clinical* OR treatment* OR factor* OR affect* OR prefer*)) OR (patients* NEAR/2 (treatment* OR therap*) NEAR/2 (selection* OR prefer*)))) AND ((neoplasm* OR tumo* OR cancer* OR malign* OR carcinom*))) AND LA=(english)
Cochrane CENTRAL	((((watch* OR see) NEAR/3 wait*) OR (wait NEAR/3 see) OR (active NEAR/3 surveillan*) OR ('not' NEXT/2 'to treat')):ab,ti) AND ((((decision* OR choice* OR choose OR chose OR wish) NEAR/6 (making OR support* OR system* OR tree* OR shared OR aid OR tool* OR model* OR analy* OR patient* OR informed* OR regret* OR clinical* OR treatment* OR factor* OR affect* OR prefer*)) OR (patients* NEAR/3 (treatment* OR therap*) NEAR/3 (selection* OR prefer*))):ab,ti) AND ((neoplasm* OR tumo* OR cancer* OR malign* OR carcinom*):ab,ti)
PsychINFO Ovid	((((watch* OR see) ADJ3 wait*) OR (wait ADJ3 see) OR (active ADJ3 surveillan*) OR "not to treat").ab,ti.) AND (exp Decision Making/ OR Decision Support Systems/ OR (((decision* OR choice* OR choose OR chose OR wish) ADJ6 (making OR support* OR system* OR tree* OR shared OR aid OR tool* OR model* OR analy* OR patient* OR informed* OR regret* OR clinical* OR treatment* OR factor* OR affect* OR prefer*)) OR (patients* ADJ3 (treatment* OR therap*) ADJ3 (selection* OR prefer*))).ab,ti.) AND (exp Neoplasms/ OR (neoplasm* OR tumo* OR cancer* OR malign* OR carcinom*).ab,ti.) AND english.la. NOT (exp animals/ NOT humans/)
Google scholar	"watchful waiting"|"wait*see"|"active surveillance"|"not to treat" "decision making|support|system|tree|aid|tool|model"|"patient|shared decision" neoplasm|tumor|cancer|malignancy|carcinoma

12

Chapter 12

Preferences for active surveillance or standard oesophagectomy: a discrete choice experiment.

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A short report of this study has been published

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Abstract

Background

Active surveillance after neoadjuvant chemoradiotherapy (nCRT) for resectable oesophageal cancer is presently under study. The aim of this study was to assess patients' preferences for active surveillance or standard oesophagectomy one year or more after nCRT and standard oesophagectomy.

Methods

Patients undergoing nCRT plus oesophagectomy >1 year earlier stated their preferences regarding active surveillance or standard oesophagectomy in a discrete choice experiment. These preferences were subsequently quantified. Treatment alternatives were described by five attributes: five-year survival, short-term and long-term health-related quality of life (HRQOL), the annual number of diagnostic tests required and the risk that postponed oesophagectomy is still necessary. The importance of attributes and willingness to trade-off survival for another attribute were assessed using a panel latent class model.

Results

Hundred patients from three hospitals were included. Some 28 patients preferred active surveillance in all eighteen choice sets, regardless of attribute outcomes. These patients had worse short- and long-term HRQOL compared to 28 patients who preferred standard oesophagectomy in all eighteen choice sets. Fifty-four patients considered both treatments, five-year survival and long-term HRQOL were considered most important attributes to influence patients' preferences. Patients would trade-off 5.4% five-year survival to obtain much better long-term HRQOL.

Conclusion

Over a quarter of patients would choose not to undergo standard oesophagectomy again, at least one year after they underwent nCRT and standard oesophagectomy. These patients had worse short-term and long-term HRQOL compared to patients who chose standard oesophagectomy. When considering both treatments, five-year survival and long-term HRQOL were considered most important factors by the individual patients.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) is standard treatment for locally advanced oesophageal cancer[1-4] and the benefit of oesophagectomy after nCRT has been questioned because a high pathological complete response rate is anticipated.[5] Active surveillance with frequent clinical/endoscopic/imaging evaluation has been proposed as an alternative. Several retrospective studies suggest that overall survival of patients with a clinically complete response (*i.e.* no vital tumour cells detected using diagnostics) after chemoradiotherapy undergoing active surveillance is comparable to that of patients undergoing standard oesophagectomy.[6-13] The phase-III, multicentre stepped-wedge cluster randomised SANO trial and ESOSTRATE trial are currently testing whether oncological outcome of active surveillance is non-inferior to that of standard oesophagectomy for these patients.[14,15]

Active surveillance should preserve quality of life by avoiding surgical morbidity and the consequences of anatomicophysiological disruption.[16-18] However, regular diagnostic tests used for response evaluations are a physical and psychological burden.[19] A previous discrete choice experiment in patients after nCRT (but before surgery) showed that overall survival, the likelihood to undergo postponed surgery, and quality of life were factors influencing treatment preferences.[20] Furthermore, patients scheduled for oesophagectomy because of oesophageal cancer were willing to trade off 16% five-year survival to decrease the risk that oesophagectomy is necessary.[20] In that study, patients were asked for their preferences shortly before undergoing oesophagectomy. However, these attitudes may change after surgery so those insights may help to better inform patients on the impact of the operation. The present study assessed patient preferences for active surveillance or standard surgery after oesophagectomy.

Methods

Patients

A multicentre prospective cohort study was performed. Patients were invited to participate in the present study if they presented at the outpatient clinic during follow-up of oesophageal or oesophagogastric junctional cancer in three Dutch high-volume centres. Patients were eligible if they had undergone neoadjuvant chemoradiotherapy according to CROSS-regimen followed by standard oesophagectomy at least one year earlier. Patients were consecutively included. Patients who were not able to fully understand or read the Dutch language, patients aged <18 years or patients who

underwent induction, adjuvant or palliative therapy were excluded. The medical ethics committee of the Erasmus MC – University Medical Centre approved the study protocol (MEC-2018-1259). All patients provided written informed consent. Some patients in this discrete choice experiment had already participated in a comparable discrete choice experiment prior to their standard oesophagectomy.[20]

Discrete choice experiment

In a discrete choice experiment, patients' treatment preferences can be assessed and quantified by asking patients to state their preference over hypothetical treatment alternatives. It is assumed that patients' preferences are determined by several attributes (*i.e.* outcome characteristics, for example five-year survival) and that these preferences are influenced by different hypothetical levels (*i.e.* outcomes of those attributes, for example: five-year survival of 45%, 60% or 75%). In this discrete choice experiment, patients were asked to pick one out of three options describing two treatments (two options describing active surveillance and one option describing standard oesophagectomy) that suited best to their preferences. An example of the three different treatment options including their specific levels, a so called choice set, is shown in Figure 1. Patients were exposed to a series of 18 choice sets. By varying the levels of the attributes in each choice set, the significance of the attributes could be quantified. Additionally, it was assessed to what extent patients are willing to trade off improved outcome of one attribute for a decrease in another.

Attributes and levels

Prior to the start of this study, three upper gastrointestinal surgeons, one oncological nurse and one patient who underwent neoadjuvant chemoradiotherapy followed by standard oesophagectomy and was representing the Dutch patient association for oesophagogastric cancer patients (SPKS), were asked to determine the most relevant attributes in the choice between active surveillance or standard oesophagectomy for oesophageal cancer. Based on this discussion, based on assumed clinical relevance and based on previously published literature, five attributes were considered most relevant.[17,20,21] These attributes were: five-year survival, short-term health-related quality of life (HRQOL, three months after treatment), long-term HRQOL (> one year after treatment), the risk that (postponed) oesophagectomy is still necessary later in time and the annual frequency of clinical examinations with PET-CT and endoscopy after treatment. The risk that oesophagectomy is still

necessary represents the percentage of patients in active surveillance who will develop a locoregional recurrence without distant metastases and therefore need to undergo (postponed) oesophagectomy. The risk for developing distant metastases or developing irresectable recurences during active surveillance is incorporated in the five-year survival.

For the active surveillance treatment alternatives there were three different levels associated with each attribute. The attribute 'five-year survival' consisted of the levels 45%, 60% or 75%. These survival rates were based on the assumption that patients who have no detectable residual disease after neoadjuvant chemoradiotherapy, have a tumour regression grade (TRG) 1-3 residual tumour (0-50% residual tumour) in the majority of cases with associated survival rates.[3] The attribute 'short-term HRQOL' consisted of the levels 'a little bit better', 'much better' and 'a whole lot better than your situation three months postoperatively'. The attribute 'long-term HRQOL' consisted of the levels 'your current situation', 'a little bit better', and 'much better than your current situation'. We deliberately used the general term HRQOL instead of more specific domains such as physical functioning or eating problems. In this way, less frequently occurring problems were not excluded in this discrete choice experiment. The attribute 'risk that postponed oesophagectomy is still necessary' consisted of the levels 15%, 35% and 55%, based on literature.[7,8,12] The attribute 'annual number of diagnostic tests' consisted of the levels 2, 3 or 4 examinations yearly, based on the surveillance protocol of the SANO-trial.[14]

The standard oesophagectomy option was considered the 'opt-out' option and thus, every attribute is associated with one level, which does not vary during the questionnaire. Five-year survival is considered 75%, given that active surveillance is at most non-inferior to standard oesophagectomy. Both short- and long-term HRQOL are considered to be comparable to patients' own situations and 'the risk that surgery is necessary' is 100%, since all patients did actually undergo neoadjuvant chemoradiotherapy followed by standard oesophagectomy. In Dutch practice, diagnostics in follow-up are performed only on indication. We estimated that diagnostics are performed less in patients who underwent standard oesophagectomy than in patients who underwent active surveillance. Therefore, we estimated that patients who underwent nCRT followed by oesophagectomy undergo diagnostics once a year.

Taking into account the three treatment options and five attributes with the associated levels, it is not feasible to expose patients to all choice sets theoretically possible. Hence, a selection of subsets was

constructed using JMP statistical software version 10.0 (Buckinghamshire, England) to provide to the patient, while maintaining the possibility to take into account all parameters. This resulted in a questionnaire with a selection of 18 choice sets.

Questionnaires

Prior to providing the questionnaires, patients were informed on the standard treatment for oesophageal cancer, the rationale of an active surveillance strategy and the potential advantages and disadvantages of active surveillance and standard oesophagectomy. Patients received this information face-to-face or by telephone from the coordinating researcher and were subsequently asked to complete the questionnaire themselves, either at the outpatient clinic or at home. This general information was described in the introduction section of the questionnaire as well.

The questionnaire consisted of two main parts; sociodemographic factors and HRQOL were measured using the EQ-5D-5L questionnaire in the first part.[22] This questionnaire was used to measure HRQOL on the day of participation in the discrete choice experiment and was modified to measure HRQOL three months postoperatively. For this modified questionnaire, patients were asked to recall their situation three months postoperatively. This time point was chosen to represent the short-term HRQOL shortly after oesophagectomy and was used as a proxy to quantify the recalled impact of oesophagectomy for the specific patient. The EQ-5D-5L consists of five domains (*i.e.* problems with: mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with five response options (*i.e.* no problems, slight problems, moderate problems, severe problems, and extreme problems).[23] Based on these five domain scores, a summary score between 0 (a state as bad as 'being dead') and 1 (full health) was calculated using the Dutch value set.[24] The EQ-5D-5L also includes a visual analogue scale (VAS) that assesses the patient's health on a scale from 0 (worst imaginable health) to 100 (best imaginable health).

Patients were asked to imagine to be in the situation with the following three situations: 1) they have to undergo treatment for oesophageal cancer again, keeping in mind their previous experiences with neoadjuvant chemoradiotherapy and oesophagectomy, 2) no residual tumour is detected after neoadjuvant chemoradiotherapy, and 3) the treating surgeon asks them to consider either active surveillance or standard oesophagectomy as safe treatment options. Subsequently, during the second part of the experiment, patients were asked to consider the 18 choice sets. Above each choice set the main question was stated: "*Imagine that no residual oesophageal cancer would have been detected*

after neoadjuvant chemoradiotherapy. Your surgeon tells you that you can choose between active surveillance or standard surgery. Which alternative would you choose?". Two treatment options consisted of neoadjuvant chemoradiotherapy followed by active surveillance with varying levels for the attributes. The third treatment option consisted of neoadjuvant chemoradiotherapy followed by standard oesophagectomy, *i.e.* the treatment that all patients had actually undergone.
A pilot questionnaire was tested in the first ten patients, and refined afterwards where deemed necessary. Patients were asked to rank the difficulty to understand the questionnaires from 'very easy' to 'very hard' on a 5-points scale.

Statistical analysis

Descriptive statistics were applied to assess characteristics of participants and HRQOL outcomes. Continuous variables were reported as median and interquartile range. Categorical data were reported as incidence and percentages. HRQOL outcomes were compared between three groups of participants: those who always opted for active surveillance; those who always opted for standard surgery; and those who alternated between active surveillance and surgery. Differences in scores were studied with the Kruskal Wallis H test. For the subgroup of patients who participated both in a discrete choice experiment shortly prior to their oesophagectomy and in the present discrete choice experiment, basic characteristics were separately analyzed.
The participants' preferences and choice observations were analyzed using a panel latent class model.[25] A panel latent class model determines different preference patterns (classes) while considering the panel structure of the data. The number of classes was determined by comparing the model fit using the Bayesian Information Criterion (BIC) of each model. Different specifications for the utility function (*i.e.*, categorical or numerical attribute levels) were tested. The utility functions in the model with the best fit were chosen. Different specifications for the utility function were tested. Details of the best model fit are described in Appendix 1. The statistical significance ($p<0.05$, two-sided) of the class coefficient (β) in the model indicates whether participants considered a specific attribute to be important for their preference. The direction of the coefficient reflects whether the attribute has a positive or negative effect on the utility (*i.e.* chance belonging to one of the classes of the model). Associations between the probability of belonging to a specific class and patient and clinical characteristics were analyzed.

The importance score of each attribute relative to the other attributes was calculated as the difference in the utility of the highest and lowest level of that attribute, divided by the sum of differences of all attributes. This analysis was stratified for each class. An importance score of 1 represents the most important attribute and a score of 5 the least important attribute.
Lastly, the willingness to trade off five-year survival (in percentage) was calculated for the different statistically significant attributes using the following equation:

Willingness to trade off five-year survival = $\frac{-\beta a}{\beta 1}$

This coefficient represents how much five-year survival a patient is willing to trade off for one unit of change (or to change from one level to another) in an attribute, and is calculated by the ratio of the coefficient for attribute α to the coefficient of attribute 'five-year survival' (β1). This analysis was stratified for each latent class. Treatment preferences prior to oesophagectomy were compared to treatment preferences at least one year after oesophagectomy in the subgroup of patients who filled out both questionnaires before (previous study) and after oesophagectomy (present study).
Estimation of sample sizes in discrete choice experiments is complicated, since it depends on the true values that patients will give to the choice sets.[26] Previous studies have indicated that sample sizes of 40-100 patients are sufficient for statistical analyses.[27-29] The aim of the present study was to include 100 patients.

Results

Patients

Between August 2018 and October 2020, 107 patients were included and 100 of 107 patients (93%) returned the completed questionnaire at a median of 16.4 months (interquartile range (IQR): 12.4 – 24.5). Median age was 69 (IQR: 64 – 73) years. Most patients were men (74%) and had an intermediate educational level (44%). The majority of patients had an adenocarcinoma, a cT3 tumour, and at least one clinically suspected regional lymph node. Most patients rated the difficulty of the questionnaire as intermediate (*i.e.* 'not hard, not easy'). In general, patients reported a worse HRQOL three months postoperatively compared to their actual situation at least one year postoperatively. An overview of the baseline patient and tumour characteristics is shown in Table 1. The HRQOL and associated Visual Analogue Scale (EQ-VAS) scores of the total study population are summarised in Table 2.

Willingness of patients to consider treatment options

Some patients chose active surveillance or standard oesophagectomy in all 18 choice sets, regardless of the attribute levels. Firstly, the willingness of patients to consider either treatment option was examined. Of 100 patients who completed the discrete choice experiment, 28 patients (28%) picked the active surveillance option in all 18 choice sets. On the other hand, 28 patients (28%) picked the standard oesophagectomy option in all 18 choice sets. In Table 3a and Table 3b the short-term and the long-term HRQOL of these individual groups is summarised, respectively. Patients who picked active surveillance in all 18 choice sets had significantly more short-term pain- and discomfort problems and had significantly worse long-term EQ-VAS score, compared to patients who opted for standard oesophagectomy.

A subset of 31 patients who participated in the present discrete choice experiment, had also participated in an earlier discrete choice experiment prior to their oesophagectomy.[20] Basic characteristics of this subset of patients are reported in Appendix 2. Prior to oesophagectomy, 11 of 31 (35%) patients picked the active surveillance treatment option and one patient (3%) picked the standard oesophagectomy treatment option in all 18 choice sets. One year after oesophagectomy, 11 of 31 (35%) patients picked the active surveillance treatment option and eight patients (26%) picked the standard oesophagectomy treatment option in all 18 choice sets. In all groups, some patients switched treatment preference. The results of the preferences of patients who participated in a discrete choice experiment both prior to and one year after oesophagectomy are summarised in Table 4.

Discrete choice experiment

The pilot questionnaire was tested in the first ten participants. Three patients rated the difficulty of the questionnaire as ‘very easy’ to ‘easy’ and five patients rated its difficulty as ‘not easy, not hard’. These reports together with the feedback of patients implied that the questionnaire was comprehensible in its initial form. Therefore, no adjustments were considered necessary to the questionnaire and pilot results were also used for the final analyses.

Using the latent class model, which also takes into account patients considering both treatment options, three preference classes were identified; patients with a preference for active surveillance, patients with a preference for standard oesophagectomy and patients who had no clear preference

for either treatment. The average probability belonging to one class was 0.32 for active surveillance, 0.36 for standard oesophagectomy, and 0.32 for no clear preference. None of the investigated clinicopathological or sociodemographic factors were associated with the probability of belonging to one of these three identified classes. The three attributes that significantly influenced patients' treatment preferences were five-year survival, long-term HRQOL and the risk that postponed oesophagectomy would still be necessary later in time. The positive coefficients for five-year survival indicate that patients (in all three classes) prefer a treatment strategy that generates a positive effect on five-year survival. A positive effect on long-term HRQOL significantly influenced patients' preferences (β = 0.71, 95%CI: 0.36 – 1.06) belonging to the active surveillance class. A lower risk of postponed oesophagectomy being necessary significantly influenced patients' treatment preferences (β = -0.02, 95%CI: -0.04 – -0.01) belonging to the 'no clear preference' class. The results of the discrete choice experiment and the effect of attributes on patients' treatment preferences are summarised in Table 5.

The importance scores were comparable for patients who had a clear preference for active surveillance or a clear preference for standard oesophagectomy. The most important attribute was considered the five-year survival, followed by the long-term HRQOL and the short-term HRQOL. The number of annual diagnostic tests sessions and the risk that (postponed) oesophagectomy was still necessary later in time were considered less important (4^{th} and 5^{th}, respectively). This was comparable for the class of patients with no clear preference, with one exception: short-term HRQOL was ranked second most important followed by the long-term HRQOL.

Willingness to trade of survival

Patients who had a preference for active surveillance were willing to trade-off 5.4% (95% CI: 3.0 – 7.8) five-year survival to obtain a long-term HRQOL which was much better than their current HRQOL. In the other classes, patients were not willing to trade-off five-year survival.

Discussion

The advantages and disadvantages of active surveillance after neoadjuvant chemoradiotherapy for oesophageal cancer emphasize the need for shared decision making. This is underlined by the present results, showing identical probabilities for patients to have a strong preference for either active surveillance or standard surgery. Some 28% of patients who underwent standard oesophagectomy at least one year earlier would choose to undergo active surveillance, if they would have to undergo

treatment for oesophageal cancer again. Patients' treatment preferences were significantly influenced by five-year survival, long-term HRQOL and the risk that postponed oesophagectomy would still be necessary. Patients with a preference for active surveillance were willing to trade-off 5.4% of five-year survival for a long-term HRQOL which would be much better than their current situation.

More than a quarter of patients who underwent standard oesophagectomy at least one year earlier, would not choose this treatment again, but would choose active surveillance instead. When taking into account the subgroup of 31 patients who participated in an earlier discrete choice experiment príor to their standard oesophagectomy, this proportion seems to remain stable before and after oesophagectomy. Patients tend to prefer the treatment that they have already undergone, even if patients had been randomised to this treatment.[30,31] Patients who were randomised to either day-care or clinical observation after laparoscopic cholecystectomy all preferred their own treatment, even though they did not opt for this regimen themselves. If this holds true in general, than the percentage of patients who would not choose their actual treatment again in the present study is high. Another study, however, suggested that patients tend to prefer an organ-sparing treatment over oesophagectomy.[32] Probably explained by the high complication rate, the substantial decrease in health-related quality of life and the lasting symptoms which are associated with oesophagectomy.[16-18,33] In the present study, no patients were included who actually underwent active surveillance. Hence, no information is available on the percentage of patients who would not choose to undergo active surveillance again in hindsight.

The attribute levels were not taken into account by 56% of patients who would choose active surveillance over standard oesophagectomy (28%) or vice versa (also 28%). It could be that patients did not understand the concept of the discrete choice experiment and therefore did not take into account these attributes. Only a small minority of the patients, however, rated the experiment as 'hard' or 'very hard'. Another explanation can be extrapolated from Tables 3a and 3b, in which the group of patients who strongly preferred active surveillance over standard oesophagectomy had significantly more short-term pain and discomfort problems and had significantly lower long-term HRQOL compared to patients who opted for standard oesophagectomy. Apparently, (long-term) HRQOL is an important factor to influence patients' treatment preferences. This has been confirmed by the results of the present discrete choice experiment, in which five-year survival, long-term HRQOL

and the risk that postponed oesophagectomy is necessary later in time significantly influenced patients' treatment preferences. Overall, patients focused on long-term outcomes rather than short-term outcomes. These results are in line with the results of previous studies[20,21] and emphasize the importance of long-term outcomes. At the time of writing, the inclusion of the SANO-trial has been completed. The primary endpoint of this study is overall survival and one of the secondary endpoints is long-term HRQOL (up to five years after completion of neoadjuvant chemoradiotherapy). The results of the present study emphasize that HRQOL is an important secondary (long-term) endpoint of the currently ongoing SANO-trial. The future results of the SANO-trial can be used to inform patients accurately on long-term outcomes and to support in shared decision making. These results should be awaited before active surveillance can be recommended as a standard treatment for locally advanced resectable oesophageal cancer.

Patients who preferred active surveillance in the present discrete choice experiment, were willing to trade off 5.4% five-year overall survival in order to obtain HRQOL which was much better than their current HRQOL. This seems modest compared to a previous discrete choice experiment in which patients were willing to trade off 16% five-year overall survival when asked shortly príor to standard oesophagectomy.[20] Furthermore, if patients were asked to pick either active surveillance or standard oesophagectomy shortly prior to standard oesophagectomy, 1 of 31 patients would choose to undergo standard oesophagectomy irrespective of the attribute levels. If the same question was asked to the same group of patients at least one year after oesophagectomy, 8 of 31 patients would now choose to undergo standard oesophagectomy irrespective of the attribute levels. Possibly, the subjective impact of oesophageal surgery on their HRQOL was not as negative as they expected shortly prior to esophagecomy. It could also reflect the fact that the present study comprised patients who were disease-free and alive at least one year after oesophagectomy and therefore, oesophagectomy seems oncologically successful so far for these patients. Even in this selected group of patients, a subgroup was willing to trade off five-year survival. Other discrete choice experiments of patients with, for instance, prostate cancer did also report that sometimes, patients were willing to trade off overall survival for improvement in other domains (*e.g.* limitations in physical energy and gastrointestinal symptoms).[34-36] For treating physicians, it is important to realize that the treatment preferences of patients and doctors often do not match.[21,37,38] Therefore, all treatment options should

be openly discussed with patients in order to attain a shared decision, even if this means discussing a treatment option that does not offer the highest chance for cure.

A strength of the present study is the timing of the discrete choice experiment. Considering the poor prognosis for patients with oesophageal cancer, it is expected that patients are in an emotional and anxious state during the process of treatment. It can be assumed that patients who are disease-free at least one year after oesophagectomy can more reliably consider which treatment they would choose if they would have to undergo this treatment again. The fact that patients could take into account their own experiences increases the generalizability of their considerations. This does, however, also introduce a selection bias, since all included patients were alive and disease-free for at least one year after surgery.

The present study has some limitations. First of all, the process of choosing between surgical or non-surgical treatment is obviously more complex than the five attributes used in this study. Individual preferences could evoke choices which cannot be covered by the five attributes. Additionally, recall-bias might have been introduced due to the fact that patients were asked to recall their own experiences three months after standard oesophagectomy. In Table 5, the group of patients who preferred standard oesophagectomy were often not willing to consider other attributes, resulting in wide confidence intervals due to loss of information on the importance of the different attributes for this group. Lastly, since active surveillance is not yet part of standard treatment, no patients were included who actually underwent active surveillance. A discrete choice experiment including patients who actually underwent active surveillance should be the focus of a future study. The results of that future discrete choice experiment could be compared to the results of the present study.

In conclusion, over a quarter of patients who had undergone neoadjuvant chemoradiotherapy followed by standard oesophagectomy, would choose not to undergo this treatment again, but would have picked active surveillance instead. These patients had significantly worse short-term and long-term HRQOL domains compared to patients who opted for standard oesophagectomy. These patients would trade off five-year survival to obtain HRQOL which is much better than their own. This is, however, less than when patients were asked shortly prior to standard oesophagectomy. When considering both treatments, five-year survival and long-term HRQOL were most important for

patients. A similar discrete choice experiment should now be performed in patients actually undergoing active surveillance in order to further clarify the preferences in patients with active surveillance versus standard oesophagectomy.

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There are differences between treatment 1, 2 and 3. Which alternative would you choose?
Imagine that no residual oesophageal cancer can be detected after neoadjuvant chemoradiotherapy. Your surgeon asks you to choose between an active surveillance or standard surgery treatment.

Figure 1. Example of a choice set

	1. Active surveillance A	2. Active surveillance B	3. Standard surgery
Chance of being alive in five years	 **45%** (45 of 100 patients)	 **60%** (60 of 100 patients)	 **75%** (75 of 100 patients)
Short-term quality of life (three months after treatment) due to pain, fatigue, tube feeding or hospitalisation.	Much better than your situation three months postoperatively	A little bit better than your situation three months postoperatively	Comparable to your situation three months postoperatively
Long-term quality of life (≥one year after treatment) due to condition, eating problems, sleeping slightly elevated and defecation problems.	Your current situation	A little bit better than your current situation	Your current situation
Risk that (postponed) surgery is necessary	 **55%** (55 of 100 patients)	 **35%** (35 of 100 patients)	 **100%** (100 of 100 patients)
Physical burden of … (number) examinations annually with endoscopy and PET-CT scanning after initial treatment.	2	4	1
Which alternative would you choose?	☐	☐	☐

Table 1. Basic patient and tumour characteristics

	Patients (n=100)
Median age in years (IQR)	69.2 (63.7 – 73.0)
Sex ratio (Male : Female)	74 : 26
Educational level*	
Low	29
Intermediate	44
High	26
Missing	1
Household situation	
With partner/family member	85
Single	14
Missing	1
Tumour type	
Squamous cell carcinoma	23
Adenocarcinoma	73
Other	4
Clinical T stage**	
cT1	1
cT2	14
cT3	80
cT4	3
Unknown	2
Clinical N stage**	
cN0	41
cN1	40
cN2	18
cN3	1
ASA fitness grade^	
I	17
II	62
III	19
Missing	2

*Level of education was categorized into low (primary school or lower vocational training), middle (secondary school or intermediate vocational training) and high (higher vocational training or university education).
** according to the seventh edition of the UICC TNM classification
^ lower score represents a better fitness score, 1: Normal healthy patient, 2: Patient with mild systemic disease, 3: Patient with severe systemic disease

IQR: interquartile range, ASA: American Society of Anesthesiologists

Table 2. Short-term and long-term health-related quality of life of the study population, measured with the EQ-5D-5L

	Short-term HRQOL**	Long-term HRQOL ^
EQ-5D-5L domains (%)*		
Problems with mobility	51	32
Problems with self-care	33	7
Problems with usual activities	72	44
Pain/discomfort	71	49
Anxiety/depression	37	23
Summary score (median – IQR)	0.81 (0.57-0.89)	0.89 (0.79-0.89)
VAS score (median – IQR)	65 (50-75)	80 (70-90)
* Measured with EQ-5D-5L questionnaire and presented as percentage of patients who reported problems in the specific domain (defined as reporting 'serious problems' or worse) ** Patients were asked to recall their HRQOL three months postoperatively ^ Patients' HRQOL on the day of participation in the experiment HRQOL: Health-Related Quality Of Life, IQR: interquartile range, VAS: Visual Analogue Scale (self-reported well-being scale ranging 0-100, a higher score represents a better score).		

Table 3a. Short-term HRQOL, measured with EQ-5D-5L, in patients who opted for active surveillance versus patients who opted for standard oesophagectomy or who considered both treatments

	Active surveillance (n=28)	Standard oesophagectomy (n=28)	Both (n=44)	P-value
EQ-5D-5L domains* (%)				
Problems with mobility	54	46	49	0.713
Problems with self-care	39	31	30	0.449
Problems with usual activities	86	69	66	0.173
Problems with pain/discomfort	71	56	81	0.047
Problems with anxiety/depression	29	26	50	0.076
Summary score (median – IQR)	0.81 (0.38 – 0.85)	0.83 (0.69 – 0.91)	0.81 (0.57 – 0.89)	0.223
VAS score (median – IQR)	55 (41 – 75)	70 (50 – 80)	63 (50 – 79)	0.202
* Measured with EQ-5D-5L questionnaire and presented as percentage of patients who reported problems in the specific domain (defined as reporting 'serious problems' or worse) HRQOL: Health-Related Quality of Life, EQ VAS: Euroqol Visual Analogue Scale (self-reported well-being scale ranging from 0-100, a higher score represents a better score)				

Table 3b. Long-term HRQOL, measured with EQ-5D-5L, in patients who opted for active surveillance versus patients who opted for standard oesophagectomy or who considered both treatments.

	Active surveillance (n=28)	Standard oesophagectomy (n=28)	Both (n=44)	P-value
EQ-5D-5L domains* (%)				
Problems with mobility	32	26	36	0.831
Problems with self-care	14	3.7	4.5	0.214
Problems with usual activities	52	31	47	0.225
Problems with pain/discomfort	54	42	49	0.524
Problems with anxiety/depression	18	19	30	0.527
Summary score (median – IQR)	0.89 (0.74-1.00)	0.89 (0.82-1.00)	0.87 (0.77-1.00)	0.423
VAS score (median – IQR)	78 (65-90)	90 (80-95)	80 (70-89)	**0.045**

***** Measured with EQ-5D-5L questionnaire and presented as percentage of patients who reported problems in the specific domain (defined as reporting 'serious problems' or worse)

HRQOL: Health-Related Quality of Life, EQ VAS: Euroqol Visual Analogue Scale (self-reported well-being scale ranging from 0-100, a higher score represents a better score)

Table 4. Willingness of 31 patients to consider treatment options prior to oesophagectomy compared to ≥one year after oesophagectomy

	≥one year after oesophagectomy*		
Prior to oesophagectomy*	Active surveillance (n=11)	Standard oesophagectomy (n=8)	Both treatments (n=12)
Active surveillance (n=11)	6	2	3
Standard oesophagectomy (n=1)	0	0	1
Both treatments (n=19)	5	6	8

Table 5. Patients' preferences for active surveillance or standard oesophagectomy after neoadjuvant chemoradiotherapy and oesophagectomy.

Treatment preference	Latent Class 1 Active surveillance	#	Latent Class 2 Standard oesophagectomy	#	Latent Class 3 No clear preference	#
Class probability	0.320		0.358		0.322	
Attribute levels						
Alternative specific constant (standard oesophagectomy treatment), β (95% CI)	**-2.484* (-3.39;-1.58)**		15.487 (NA)		**1.776* (0.43; 3.13)**	
Five-year overall survival		1		1		1
45% (reference)						
60%	**1.152*** (0.90; 1.41)		-27.369 (-97.63; 42.89)		**1.445*** (0.77; 2.12)	
75%	**1.976*** (1.60; 2.35)		**36.101* (NA)**		**4.568*** (3.83; 5.31)	
Short-term HRQOL		3		3		2
A little bit better (reference)^						
Much better^	-0.039 (-0.28; 0.21)		3.214 (-195.07; 201.50)		0.332 (-0.11; 0.78)	
A whole lot better^	0.180 (-0.20; 0.56)		-6.178 (-164.82; 152.47)		-0.087 (-0.66; 0.49)	
Long-term HRQOL		2		2		3
Their current HRQOL (reference)						
A little bit better than their current HRQOL	0.085 (-0.16; 0.33)		-1.276 (-199.57; 197.01)		-0.091 (-0.57; 0.38)	
Much better than their current HRQOL	**0.710*** (0.36; 1.06)		14.853 (-104.13; 133.94)		0.202 (-0.31; 0.71)	
Risk that postponed surgery is necessary	-0.006 (-0.01; 0.00)	5	-0.383 (-8.31; 7.55)	5	**-0.022*** (-0.04; -0.01)	5
Annual number of diagnostic tests (per number)	-0.058 (-0.23; 0.11)	4	-6.390 (-46.06; 33.28)	4	-0.261 (-0.56; -0.04)	4

*statistically significant at p<0.05,
^than their recalled situation three months after oesophagectomy
importance score

β: class coefficient, 95%CI: 95% confidence interval, NA: not applicable, HRQOL: Health-Related Quality of Life,

Appendix 1

The model with the best model fit was:

$$V(active\ surveillance)_{nj|c} = \beta_{0|c} + \beta_{1|c}\ \text{risk surgery necessary}_{nj|c} + \beta_{2|c}\ \text{annual no. of diagnostic tests}_{nj|c} + \beta_{3|c}\ \text{five year survival\_60}_{nj|c} + \beta_{4|c}\text{five year survival\_75}_{nj|c} + \beta_{5|c}\ \text{short} - \text{term HRQL\_much better}_{nj|c} + \beta_{6|c}\ \text{short} - \text{term HRQL}_{a}\text{whole lot better}_{nj|c} + \beta_{7|c}\ \text{long} - \text{term HRQL\_a bit better}_{nj|c} + \beta_{8|c}\ \text{long} - \text{term HRQL\_much better}_{nj|c}$$

where

$V_{nj|c}$ is the observed utility that respondent *n* belongs to class *c* for alternative *j*;

$\beta_{0|c}$ is the alternative specific constant;

$\beta_{1\text{-}2|c}$ are class-specific coefficients linearly associated with each attribute of the DCE;

$\beta_{3\text{-}8|c}$ are class-specific coefficients categorically associated with each attribute of the DCE.

Appendix 2. Basic patient and tumour characteristics of subgroup of 31 patients who participated in two discrete choice experiments

	Subgroup of patients (n=31)
Median age in years (IQR)	69.8 (67.6 – 73.6)
Sex ratio (Male : Female)	61 : 36
Educational level*	
Low	9
Intermediate	17
High	4
Missing	1
Household situation	
With partner/family member	26
Single	4
Missing	1
Tumour type	
Squamous cell carcinoma	8
Adenocarcinoma	23
Other	0
Clinical T stage**	
cT1	0
cT2	6
cT3	24
cT4	1
Unknown	0
Clinical N stage**	
cN0	12
cN1	14
cN2	4
cN3	1
ASA fitness grade^	
I	4
II	21
III	6
Missing	0

*Level of education was categorized into low (primary school or lower vocational training), middle (secondary school or intermediate vocational training) and high (higher vocational training or university education).
** according to the seventh edition of the UICC TNM classification
^ lower score represents a better fitness score, 1: A normal healthy patient, 2: A patient with mild systemic disease, 3: A patient with severe systemic disease
IQR: interquartile range, ASA: American Society of Anesthesiologists

13

Chapter 13

Active surveillance versus immediate surgery in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal cancer: a multicenter propensity matched study

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Abstract

Objective

This study compared outcomes of patients with esophageal cancer and clinically complete response (cCR) after neoadjuvant chemoradiotherapy (nCRT) undergoing active surveillance or immediate surgery.

Background

Since nearly one-third of patients with esophageal cancer show pathologically complete response after nCRT according to CROSS-regimen, the oncological benefit of immediate surgery in cCR is topic of debate.

Methods

Patients with cCR based on endoscopic biopsies and EUS-FNA initially declining or accepting immediate surgery after nCRT were identified between 2011-2018. Primary endpoint was overall survival (OS). The secondary endpoints were progression free survival (PFS), rate and timing of distant dissemination and postoperative outcomes.

Results

Some 98 patients with cCR were identified: 31 in the active surveillance- and 67 in the immediate surgery group with median follow-up of survivors of 27.7 and 34.8 months, respectively. Propensity score matching resulted in two comparable groups (n=29 in both groups). Patients undergoing active surveillance or immediate surgery had a 3-year OS of 77% and 55% (HR 0.41;95% CI 0.14–1.20,p=0.104), respectively. The 3-year PFS was 60% and 54% (HR 1.08;95% CI 0.44–2.67,p=0.871), respectively. Patients undergoing active surveillance or immediate surgery had a comparable distant dissemination rate (both groups 28%), radical resection rate (both groups 100%) and severity of postoperative complications (Clavien-Dindo grade≥3: 43% versus 45%, respectively).

Conclusion

In this retrospective study, OS and PFS in patients with cCR undergoing active surveillance or immediate surgery were not significantly different. Active surveillance with postponed surgery for recurrent disease was not associated with a higher distant dissemination rate or more severe adverse postoperative outcomes.

Introduction

Treatment of locally advanced esophageal cancer generally involves neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy. A frequently used nCRT regimen consists of five weekly cycles of carboplatin and paclitaxel with concurrent 41.4 Gy, based on the regimen used in the CROSS trial[1, 2]. The CROSS trial revealed that nearly one-third of patients has a pathologically complete response (pCR, *i.e.* no vital tumor cells detected in the resection specimen) and the benefit of standard esophagectomy after nCRT is currently a topic of debate. Especially since an esophagectomy is a major operation, associated with substantial postoperative complications (>50%), mortality (1-6%) and a profound negative effect on patients' short- and long-term health-related quality of life[3-8]. Active surveillance can be applied in patients with a clinically complete response (cCR, *i.e.* no signs of residual disease as determined by clinical diagnostic tests after completion of nCRT) and consists of frequent clinical response evaluations (CREs) with surgery performed only until after recurrence is proven or highly suspected. However, there are several potential risks during active surveillance. Missing vital tumor cells during CREs could result in the development of irresectable locoregional disease later in time. Furthermore, due to longer presence of residual tumor, distant dissemination rate could increase. Previous studies already prospectively compared survival of patients undergoing definitive chemoradiotherapy followed by selective salvage surgery versus patients undergoing immediate surgery and assessed survival of patients with cCR with postponed surgery for recurrent disease[9-12]. However, only a limited number of retrospective cohort studies have compared outcomes of patients with cCR declining surgery versus patients undergoing immediate surgery, none of these studies used the relatively mild CROSS-regimen[13-17]. Also, not all studies performed frequent and standardized response evaluations to detect locoregional recurrence. Despite this, most of these studies showed overall survival (OS) rates comparable to patients receiving immediate surgery after nCRT[13-15, 17].

The primary aim of the present study was to compare OS and progression free survival (PFS) between patients with cCR after nCRT undergoing active surveillance or immediate surgery. In these groups, also the rate and timing of distant dissemination and the rate of postoperative complications were assessed. The hypothesis was that OS, PFS and rate and timing of distant dissemination are comparable between patients undergoing active surveillance or immediate surgery. Possibly, postponement of surgery could result in more severe postoperative complications.

Methods

Patients

Patients were selected from the databases of the prospective multicenter (pre)SANO-trials ((pre)Surgery As Needed for Oesophageal cancer-trial) and from local prospectively maintained databases. Details of the trials have recently been published[18-20]. All patients with cCR after nCRT were identified. When no cyto/histological evidence (*i.e.* no vital tumor cells) of locoregional residual disease (at endoscopic biopsies or EUS-FNA) and distant metastases (on PET-CT) was detected during two clinical response evaluations (CREs) six and twelve weeks after completion of nCRT, patients were classified as cCR. The active surveillance group was defined as all patients with cCR that preferred active surveillance and declined immediate surgery, despite recommendation of immediate surgery by the treating surgeon. All patients in the active surveillance group were considered surgical candidates at the time of evaluation and were willing to undergo postponed surgery after potential detection of residual disease during subsequent CREs (without the presence of distant metastases). Patients with cCR who underwent immediate surgery after the second CRE were defined as the immediate surgery group. Patients in whom residual disease was detected during the first two clinical response evaluations were considered clinically non-complete responders and were excluded. Postponed surgery was defined as esophagectomy that was performed beyond the second CRE after initial cCR was reached. The retrospective study protocol was approved by the medical ethics committee of the Erasmus MC (Rotterdam, MEC-2018-1279). All patients provided informed consent.

Neoadjuvant chemoradiotherapy

All patients underwent nCRT consisting of five weekly cycles of carboplatin (AUC 2 mg/ml) and paclitaxel (50 mg/m^2) with concurrent radiotherapy (41.4 Gy in 23 fractions).

Clinical staging, clinical response evaluations and follow-up

Patients underwent clinical staging including endoscopy with biopsies, endoscopic ultrasonography with fine-needle aspiration (EUS-FNA) in case of suspected lymph nodes and ^{18}FDG-PET-CT to exclude distant metastases. All patients were reviewed and discussed at a multidisciplinary team meeting. After neoadjuvant treatment, re-staging including endoscopic (bite-on-bite) biopsies and PET-CT was performed with EUS in most patients. EUS-guided FNA was done in case of suspected lymph node(s) at EUS or in case of FDG-avid lesion(s) on PET-CT. CRE-1 and CRE-2 were performed six and twelve

weeks after completion of nCRT, respectively. The technique of bite-on-bite biopsies implies that two biopsies are taken at the exact same location in the area where the primary tumor was (previously) located, resulting in a superficial and a deeper biopsy. Patients that refused surgery after CRE-2 were offered active surveillance. Patients in the active surveillance group were planned to undergo CREs every 3 months during the first year, every 4 months during the second year, twice a year during the third year and annually during the 4th and 5th year. These CREs consisted of PET-CT followed by endoscopic (bite-on-bite) biopsies and EUS-FNA of all suspected lymph nodes in most patients (supplementary Table 1). If diagnostic modalities showed no distant and/or locoregional residual disease, patients were considered to have persisting cCR. In case of locoregional cyto/histological evidence or high suspicion of residual tumor (*e.g.* based on increasing FDG-avidity of the primary esophageal lesion on PET-CT in the absence of tumor cells in endoscopic biopsies), patients underwent surgery with curative intent or were referred for palliative care in case of metastatic/irresectable disease.

Surgery

Patients who developed locoregional regrowth during active surveillance or who had immediate surgery underwent trianshiatal or transthoracic esophagectomy, depending on patient's condition and decision made during the multidisciplinary team-meeting. It was aimed to remove at least 15 lymph nodes. A microscopically radical resection (R0) was defined as no tumor cells at the proximal, distal and circumferential resection margin.

Outcomes

The primary endpoint was OS, defined as the time between date of diagnosis and date of all-cause death or last follow-up. Patients were followed until February 2, 2019 and censored afterwards. Secondary endpoints were proportion of R0-resection, 30- and 90-day postoperative mortality, frequency and severity of postoperative complications, rate and timing of distant dissemination and PFS.

Severity of postoperative complications was defined according to the Clavien-Dindo classification and complications were grouped according to severity in ≤2 or ≥3[21]. Type of complications were classified according to the definitions of the Esophagectomy Complications Consensus Group (ECCG)[22, 23]. Rate and timing of distant dissemination was defined as the time between date of diagnosis and date of

detection of distant metastases. PFS was defined as the time between date of diagnosis and date of detection of progression or last follow-up (with censoring afterwards). Progression was defined as the development of distant metastases or development of irresectable locoregional recurrence.

Statistical analysis

Baseline characteristics and postoperative outcomes of patients are presented as proportions (percentage) or medians with interquartile range (IQR). The Student's t-test was used to compare continuous variables and the Chi-square test was used to compare categorical variables. Fisher's exact test was used when comparing two categorical variables or when events were rare.

In order to reduce the effects of potential confounding factors, propensity-score matching according to the nearest-neighbor method was performed [24]. The following confounding variables were included in the propensity-score matching: age, histology, clinical T-status (cT-status), clinical N-status (cN-status), comorbidities according to the Charlson Comorbidity index and type of biopsies performed during the first two CREs (either regular biopsies or bite-on-bite biopsies).

Median follow-up was calculated using the reverse Kaplan-Meier method, only determining follow-up of survivors. Survival data were presented using Kaplan-Meier curves for the active surveillance group and the immediate surgery group and survival was compared using the log-rank test and Hazard Ratios (HR) with 95% confidence intervals (95% CI). R version 3.5.0 (R Core team, R foundation for statistical computing, 2013, Boston, MA, USA) was used for all statistical analyses.

Results

Patient characteristics

*S*ome 98 patients were identified with cCR during CREs six and twelve weeks after completion of nCRT. Ninety-three patients were identified from the prospectively maintained (pre)SANO databases from four Dutch hospitals (two academic hospitals and two high-volume teaching hospitals) and five patients were consecutively identified from a local prospectively maintained database. This resulted in 31 patients in the active surveillance group and 67 patients in the immediate surgery group (Figure 1). Median (IQR) overall follow-up of unmatched surviving patients was 30.8 (22.0 – 49.1) months and the minimum follow-up was 12 months. Median (IQR) follow-up of unmatched surviving patients in the active surveillance- and the immediate surgery group was 27.7 (19.9 – 46.6) and 34.8 (24.5 – 51.0) months, respectively. In Table 1 the patient- and tumor characteristics of unmatched and matched

groups are reported. Before matching, patients undergoing active surveillance were significantly older (median 73.0 versus 68.0 years) and had more comorbidities (Charlson Comorbidity Index ≥3 (CCI): 21 of 31 versus 26 of 67). Using propensity-score matching, two groups of 29 patients each were created. After matching, there were no statistically significant differences in patient characteristics between the two groups.

Surgery outcomes

In the active surveillance group, 14 of 29 patients underwent postponed esophagectomy at a median (IQR) of 10.0 (8.6 – 14.5) months following completion of nCRT. Eleven of 14 patients that underwent postponed surgery had histologically proven recurrent disease, two patients had high suspicion on recurrent disease based solely on PET-CT and one patient had high suspicion on recurrent disease based on both endoscopy and PET-CT. In the immediate surgery group, median (IQR) time between completion of nCRT and surgery was 3.4 (3.2 – 3.7) months. The majority of patients underwent transthoracic esophagectomy. In both groups, all patients had tumor-free resection margins (R0), both before and after matching. In the active surveillance group, there was no 30- or 90-day postoperative mortality after postponed surgery for recurrent disease. In the immediate surgery group, 30- and 90-day mortality was 3% and 7%, respectively. In the active surveillance group and the immediate surgery group, 0% and 24% had pCR, respectively. No ypT4 tumors were detected in the active surveillance group and the immediate surgery group. The three patients who underwent postponed surgery based on high suspicion of locoregional regrowth (without histological evidence of recurrence) had a ypT3N1 (clinical suspicion based on PET-CT and endoscopy), ypT2N1 (clinical suspicion based on PET-CT only) and ypT0N3 (clinical suspicion based on PET-CT only) residual tumor, respectively. Pathological T- and N-status of the unmatched group of patients that underwent immediate surgery are summarized in supplementary Table 2. Six of 14 patients who underwent postponed surgery for recurrent disease after active surveillance developed postoperative complications grade ≥3 according to the Clavien-Dindo classification versus 13 of 29 patients in the immediate surgery group (p = 1.000). Furthermore, no differences were observed between the number and type of complications. Postoperative outcome parameters and a detailed specification of postoperative complications are summarized in Tables 2 and 3, respectively.

Survival

Median (IQR) overall follow-up of surviving patients after matching was 30.8 (19.9 – 47.2) months. Median (IQR) follow-up of surviving patients undergoing active surveillance and immediate surgery was 27.6 (19.9.0 – 47.2) and 45.3 (18.4 – 51.0) months, respectively. OS was not significantly different between both groups (Figure 2a). One- and three-year OS in the active surveillance group was 100% and 77%, respectively. In the immediate surgery group, one- and three-year OS was 83% and 55%, respectively (HR 0.41; 95% CI 0.14 – 1.20, p = 0.104). The median OS was not reached for patients undergoing active surveillance and was 45.6 months for patients in the immediate surgery group. There were no significant differences in PFS between both groups (Figure 2b). One- and three-year PFS in the active surveillance group was 100% and 60%, respectively . Patients undergoing immediate surgery had one- and three-year PFS rates of 85% and 54%, respectively (HR 1.08;95% CI 0.44–2.67,p=0.871). Median PFS was 39.5 months for patients in the active surveillance group and was not reached in the immediate surgery group. Furthermore, when comparing survival according to histology (adenocarcinoma versus squamous cell carcinoma), no significant differences were observed between both groups (data not shown). If patients were deemed definitively unfit or definitively declined surgery, even in case of proven recurrent disease, active surveillance was ceased since this would have had no clinical consequences anymore. These patients were censored in the survival analysis. However, if these censored patients were included in the survival analysis, OS was still comparable between both groups (supplementary Figure 2). The results of OS and PFS in unmatched groups are summarized in supplementary Figures 1a and 1b. The clinical course of the unmatched group of 31 patients undergoing active surveillance is summarized in Figure 3.

Distant dissemination

Some 8 patients from the active surveillance group and 8 from the immediate surgery group developed distant metastases. Median (IQR) time between date of diagnosis and detection of distant metastases for patients undergoing active surveillance or immediate surgery was 17.8 (12.5 – 26.7) months and 12.1 (10.7 – 19.6) months, respectively (p = 0.413). Of all 8 patients undergoing active surveillance that developed distant metastases, 3 were detected during active surveillance and five were detected after postponed surgery for recurrent disease (Figure 4).

Discussion

The oncological benefit of standard esophagectomy in patients with cCR after nCRT is yet unclear. The present study reports no significant differences in OS and PFS in patients with cCR undergoing active surveillance or immediate surgery. All patients who underwent (postponed or immediate) surgery had a resection with tumor-free resection margins. Also, no significant differences were observed in rate, severity and type of postoperative complications, suggesting that surgery could be safely postponed until recurrent disease was histologically proven or highly suspected after nCRT. Finally, rate and timing of distant dissemination were comparable in both groups.

To our knowledge, this is the first study that assessed and compared survival and postoperative outcomes of patients undergoing active surveillance versus immediate surgery with data that were mainly collected from an extension of a prospective trial. This resulted in highly standardized CREs after completion of nCRT, usage of the neoadjuvant CROSS-regimen in all patients and a detailed and standardized description of the postoperative course in terms of complications and recurrent locoregional disease or distant dissemination, providing insights in the safety of an active surveillance strategy and postponed surgery in case of recurrent disease. This study used a relatively low radiation dose of 41.4 Gy in all patients, compared to 45 – 60 Gy used in most previous studies. Furthermore, neoadjuvant schemes in previous studies were highly variable, probably due to their retrospective nature. Finally, in contrast to most previous studies, nearly all patients that developed histologically proven or highly suspected locoregional recurrence during active surveillance, underwent subsequent esophagectomy.

Three-year OS for the matched patients who underwent active surveillance or immediate surgery was 77% and 55%, respectively. Other studies reported three-year OS rates ranging from 48% to 62% for patients undergoing active surveillance and 48% to 69% for patients undergoing immediate surgery[13-17, 25]. A possible explanation for the better survival of patients undergoing active surveillance in the present study is that only patients who were willing to undergo surgery in case of regrowth during surveillance were included. Furthermore, if patients definitely refused surgery or were considered unfit for surgery, active surveillance was stopped. These patients were (appropriately) censored in the survival analysis. Sixteen of 29 patients in our study developed locoregional recurrences during active surveillance. This is in line with other studies, that reported locoregional regrowths in 21% to 47%[13-17, 25].

Fourteen of these 16 patients (88%) underwent postponed surgery for histologically proven or highly suspected locoregional regrowth (versus 15% - 75% in other studies)[13-16]. Only Taketa *et al* reported that all patients under active surveillance in whom locoregional regrowth was detected, underwent resection[17, 25]. Interestingly, the only study that reported a significantly compromised OS after surveillance compared to immediate surgery, performed postponed surgery in only 2 of 14 patients after development of locoregional recurrence during active surveillance[16].

Of the patients with cCR that underwent immediate surgery in the matched group, 24% had pCR (ypT0N0) after nCRT. This is low compared to earlier studies that reported pCR rates in 29% of patients with esophageal cancer undergoing nCRT followed by esophagectomy[1, 2]. Due to propensity-score matching, several patients that reached pCR were excluded from further analysis, which results in an underestimation of the rate of pCR in the (matched) immediate surgery group. As outlined in supplementary Table 2, pCR rate of the unmatched group of patients undergoing immediate surgery was 33%, which seems more in line with prior publications[1, 2, 26].

Experience with postponing surgery after chemoradiotherapy for esophageal cancer treatment derives from reports on salvage surgery after definitive chemoradiotherapy (dCRT). dCRT aims to achieve a higher complete response rate than nCRT by the use of high radiation dosages (>50 Gy). In many countries, dCRT is reserved for patients with locally unresectable tumors, or who are unfit for surgery. Subsequent salvage esophagectomy after dCRT is only performed in a selected group of patients who are still operable during follow-up (*e.g.* due to improvement of nutritional status) and then develop a resectable locoregional recurrence. Earlier reports on salvage esophagectomy reported higher morbidity and mortality rates, as compared to immediate standard esophagectomy after nCRT[27-29]. Interestingly, the current study shows comparable severity and frequency of postoperative complications of patients who had immediate surgery versus postponed surgery for recurrent disease. These findings indicate that postponing surgery is probably safe after the relatively mild CROSS regimen used in this study. As such, salvage surgery after higher doses of radiotherapy and postponed surgery for recurrent disease after nCRT using 41.4 Gy should be considered different strategies. In the currently used active surveillance strategy, a substantial group of patients still undergoes surgery. Thus, a mild nCRT regimen followed by postponed surgery in case of recurrent disease is probably preferable over a dCRT regimen followed by salvage surgery, which is accompanied by increased subsequent postoperative complications[27-29].

Approximately half of the patients from the active surveillance group underwent postponed surgery for locoregional recurrence. This indicates that residual vital tumor was already present during the early phase of active surveillance but could not be detected during earlier CREs. Theoretically, this might result in shedding of tumor cells and development of new distant metastases during active surveillance[30]. However, both the rate and the timing of distant dissemination were not significantly different between both groups. Previous studies suggest that after nCRT and surgery the majority of metastases will become clinically detectable within 24 months postoperatively[2]. But, even 40 months postoperatively some patients develop distant metastases[31]. This is in line with the data from the present study. Possibly, some subclinical metastases were already present at the time of diagnosis and thus, our active surveillance strategy avoided a futile esophagectomy in maximum three of the eight patients who developed distant metastases during surveillance. Several hypotheses exist on the effects of surgery on the development of metastatic disease. Manipulation of the primary tumor has been suggested to result in shedding of tumor cells in the peripheral circulation[32]. Furthermore, a number of preclinical studies have shown that surgery results in enhanced concentrations of pro-inflammatory cytokines with stimulation of adhesion of circulating tumor cells to vascular endothelium[33, 34]. These findings suggest that development of metastases might be enhanced by the surgical procedure and might possibly occur less frequently in patients undergoing active surveillance. So far, the data in the present small study can neither confirm nor reject this hypothesis.

There are some limitations in this study. This is a retrospective non-randomized study which introduces a selection bias. Although propensity-score matching can help to overcome imbalances between the study groups, unknown confounding factors cannot be balanced for and a selection bias might therefore still be present. Furthermore, in an ideal situation, an active surveillance strategy comes with highly standardized and frequent clinical response evaluations constantly using bite-on-bite biopsies in order to timely detect residual disease and thus, to prevent irresectable regrowths. Heterogeneity across surveillance strategies could not be avoided in this study. However, even with suboptimal surveillance strategies, all 14 patients who developed a locoregional regrowth could be operated without compromising the safety of the operation and radical resectability of the tumor. Finally, due to the small sample size and the relatively short follow-up, the current study lacks power to detect subtle but potentially relevant differences between both treatment strategies. The large SANO- and ESOSTRATE-trials are prospectively comparing active surveillance with immediate surgery in patients with cCR after nCRT in a randomized manner[20, 35]. Results of these randomized trials will

further determine whether or not an active surveillance strategy is inferior to immediate surgery in patients with cCR.

In conclusion, active surveillance appears to be safe when compared to immediate surgery in patients with cCR as determined by endoscopic (bite-on-bite) biopsies and endoscopic ultrasonography with FNA of suspected lymph nodes undergoing nCRT with 41.4 Gy radiotherapy. Both strategies resulted in comparable survival. A substantial group of patients in active surveillance eventually undergoes postponed surgery for locoregional recurrent disease. In this small group of patients undergoing postponed surgery, postoperative complications and radical resections were comparable to those patients undergoing immediate surgery. This postponement results in the avoidance of unbeneficial esophagectomy in patients that show continued cCR, and in patients who develop interval metastases during active surveillance. However, active surveillance should not be considered part of standard treatment for patients with locally advanced esophageal cancer with a clinically complete response until the results of currently performed randomized trials support this strategy.

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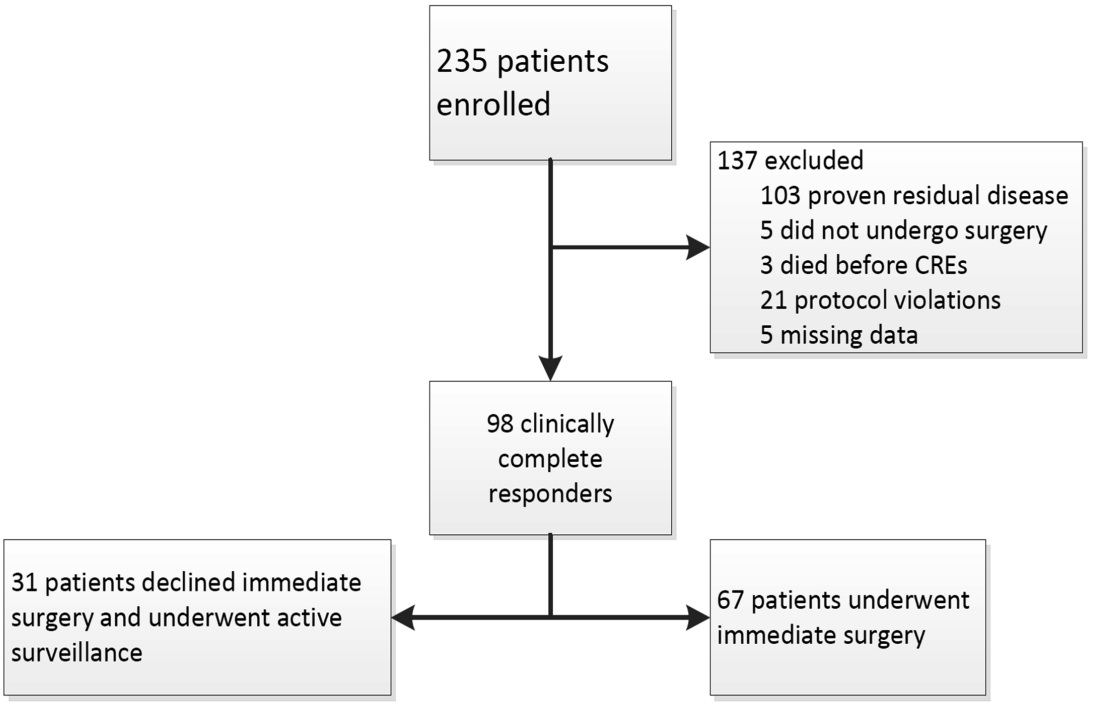


Figure 1. Patient flowchart

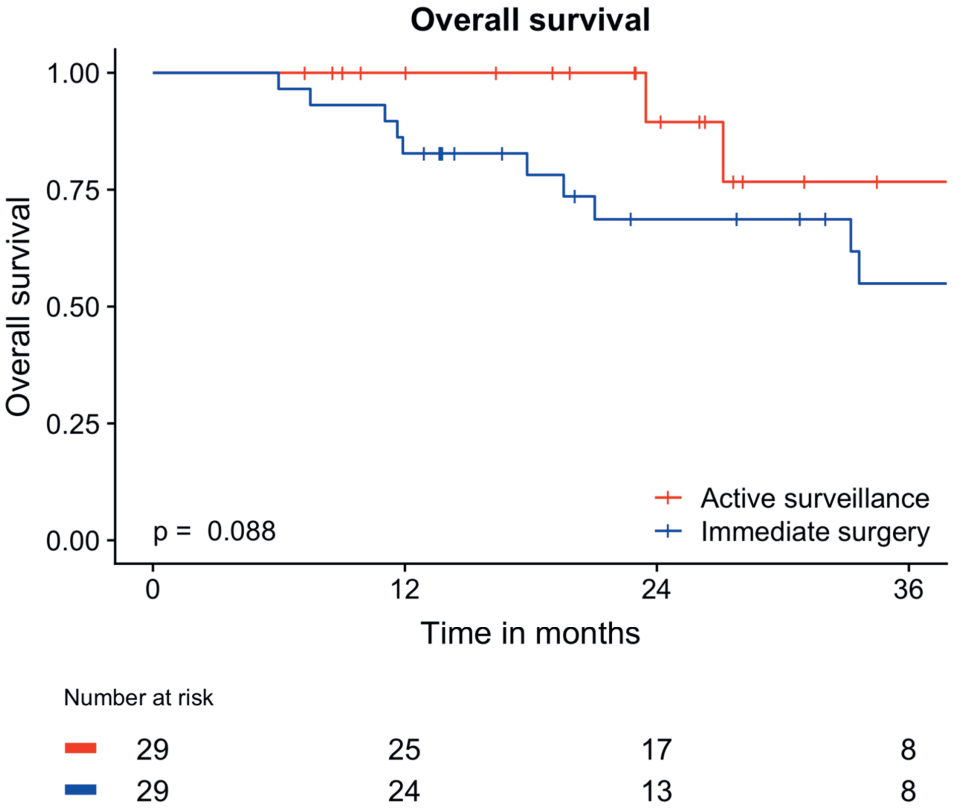


Figure 2A. Overall survival curves of patients undergoing active surveillance with postponed surgery in case of recurrent disease (n=29, red line) or immediate surgery (n=29, blue line) after propensity-score matching, from time between date of diagnosis and date of all-cause death.

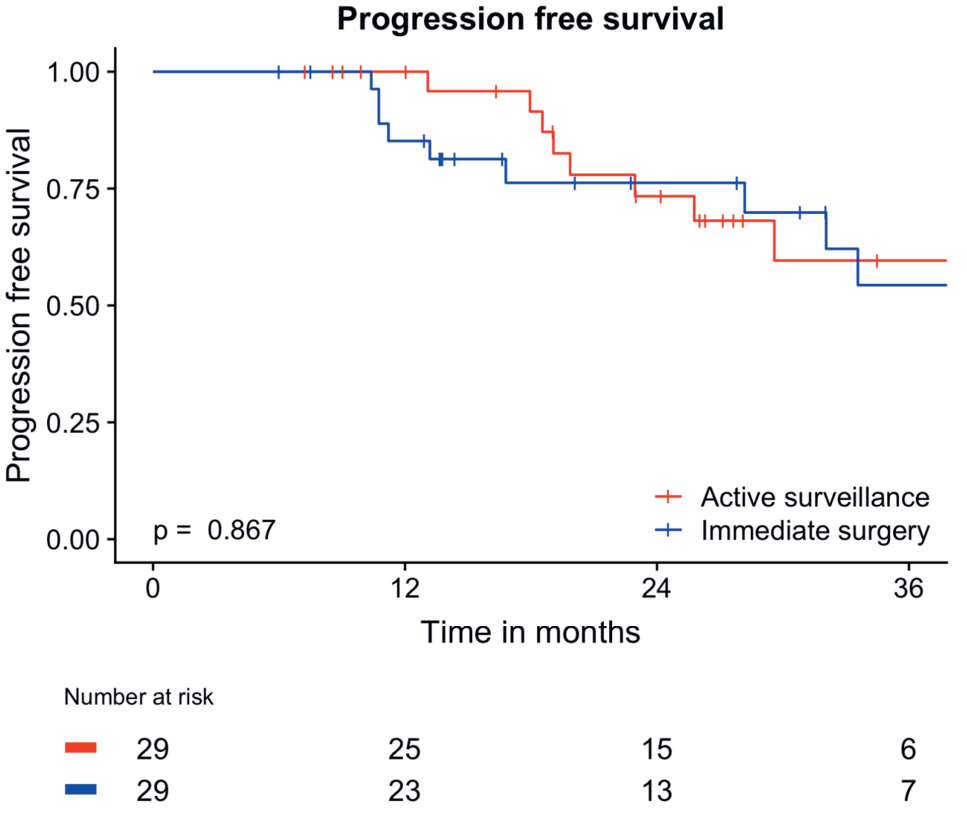


Figure 2B. Progression free survival curves of patients undergoing active surveillance with postponed surgery in case of recurrent disease (n=29, red line) or immediate surgery (n=29, blue line) after propensity-score matching, from time between date of diagnosis and date of detection of progression.

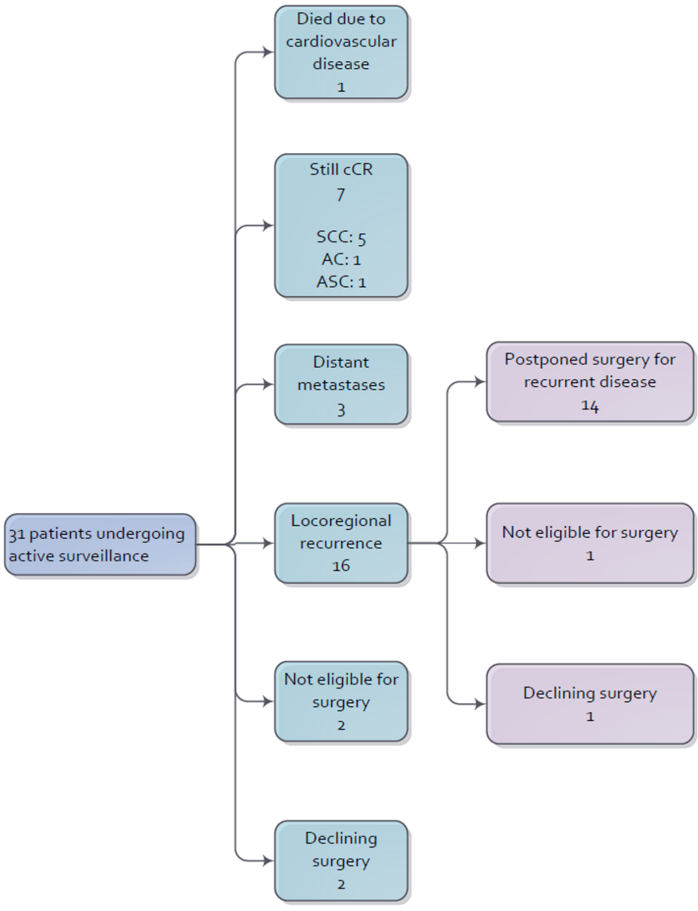


Figure 3. Overview of 31 patients (unmatched group) that underwent active surveillance. During active surveillance, one patient died due to cardiovascular disease without signs of locoregional- or distant disease, seven patients still have cCR, three patients developed distant metastases, 16 patients developed locoregional recurrence and active surveillance was ceased in four patients because this would have had no clinical consequences anymore (two patients were unfit for surgery and two patients refused surgery). Median (IQR) follow-up of the seven patients with cCR was 23.0 months (IQR = 20.0 – 28.1) and the range was 20.0 – 66.2 months. Of these patients, five had squamous cell carcinoma, one had adenocarcinoma and one had adenosquamous cell carcinoma.
cCR: clinically complete response,
SCC: squamous cell carcinoma, AC: adenocarcinoma, ASC: adenosquamous cell carcinoma.

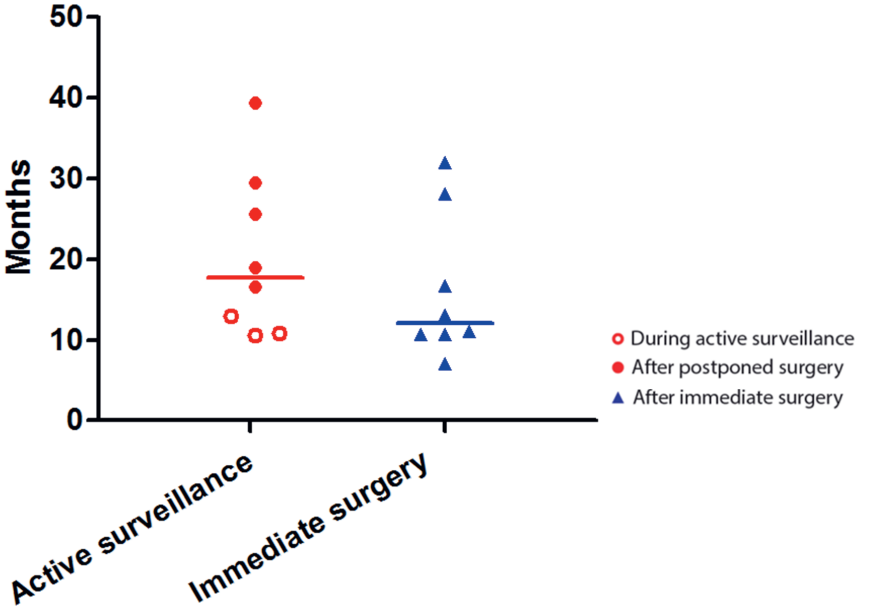


Figure 4. Rate and timing of development of distant metastases in patients undergoing active surveillance followed by postponed surgery for recurrent disease (red) or immediate surgery (blue). The red open circles represent patients that developed metastases during active surveillance, without surgery. The red dots represent patients that developed metastases after postponed surgery for recurrent disease. The red and blue horizontal lines represent the median time between date of diagnosis and date of detection of distant metastases for patients undergoing active surveillance or immediate surgery, respectively. Both the rate ($p = 1.000$) and the median time to development of metastases ($p = 0.413$) were not significantly different between the two groups.

Table 1. Patient and tumor characteristics before and after propensity-score matching

	Unmatched			Matched		
	Active surveillance (n=31)	Immediate surgery (n=67)	p	Active surveillance (n=29)	Immediate surgery (n=29)	p
Age in years			*0.021*			*0.433*
Median (IQR)	73.0 (69.5 – 77.0)	68.0 (63.0 – 73.0)		72.0 (69.0 – 77.0)	70.0 (67.0 – 73.0)	
Charlson comorbidity index (%)			*0.009*			*1.000*
CCI = 2	10 (32)	41 (61)		10 (34)	11 (38)	
CCI ≥ 3	21 (68)	26 (39)		19 (66)	18 (62)	
Histology (%)			*1.000*			*1.000*
Adeno	22 (71)	49 (73)		22 (75)	21 (72)	
Squamous Cell	8 (26)	18 (27)		7 (25)	8 (28)	
Adenosquamous*	1 (3)	0		0	0	
Clinical tumor status (%)**			*0.153*			*1.000*
cT1-2	12 (39)	16 (24)		11 (38)	10 (34)	
cT3-4	19 (61)	51 (76)		18 (62)	19 (66)	
Clinical nodal status (%)**			*0.826*			*0.599*
cN-	14 (45)	27 (40)		12 (41)	15 (52)	
cN+	17 (55)	39 (58)		17 (59)	14 (48)	
cNx*	0	1 (2)		0	0	
Post-nCRT biopsy type (%)			*0.237*			*0.846*
Regular	12 (39)	23 (34)		12 (41)	10 (34)	
Mixed (regular and bite-on-bite)	6 (19)	6 (9)		5 (18)	5 (17)	
Bite-on-bite	13 (42)	38 (57)		12 (41)	14 (48)	

*Excluded from analysis as perfect separator, ** Classified according to the 7th edition of the Union for International Cancer Control's TNM classification (UICC)[36] IQR: interquartile range, CCI: Charlson Comorbidity Index, cT: clinical tumor status, cN: clinical nodal status, nCRT: neoadjuvant chemoradiotherapy

Table 2. Postoperative outcomes

	Active surveillance (n=14)	Immediate surgery (n=29)	p
Time to operation in months*			0.001
Median (IQR)	10.0 (8.6 – 14.5)	3.4 (3.2 – 3.7)	
Radicality (%)			1.000
R0	14 (100)	29 (100)	
R1	0	0	
R2	0	0	
Median days in hospital (IQR)~	15 (10 - 22)	14 (10 - 17)	0.205
30-day mortality (%)	0	1 (3)	1.000
90-day mortality (%)	0	2 (7)	1.000
Stage (ypTNM)^ (%)			0.160
0	1 (7)	0 (0)	
IA	0 (0)	6 (21)	
IB	2 (14)	5 (17)	
IIA	5 (36)	3 (10)	
IIB	2 (14)	2 (7)	
IIIA	1 (7)	2 (7)	
IIIB	2 (14)	1 (3)	
IIIC	0 (0)	1 (3)	
IV	0 (0)	0 (0)	
ypT0N0	0 (0)	7 (24)	
ypT0N0-3	1 (7)	2 (7)	
Severity of complications $ (%)			1.000
CD≤2	8 (57)	16 (55)	
CD≥3	6 (43)	13 (45)	

* Time from completion of nCRT to date of operation
~ Including stay in Intensive Care unit
$ According to the Clavien-Dindo classification
^ Classified according to the 7th edition of the Union for International Cancer Control's TNM classification (UICC)
IQR: interquartile range, R0: resection margin free of tumor cells, CD: Clavien-Dindo

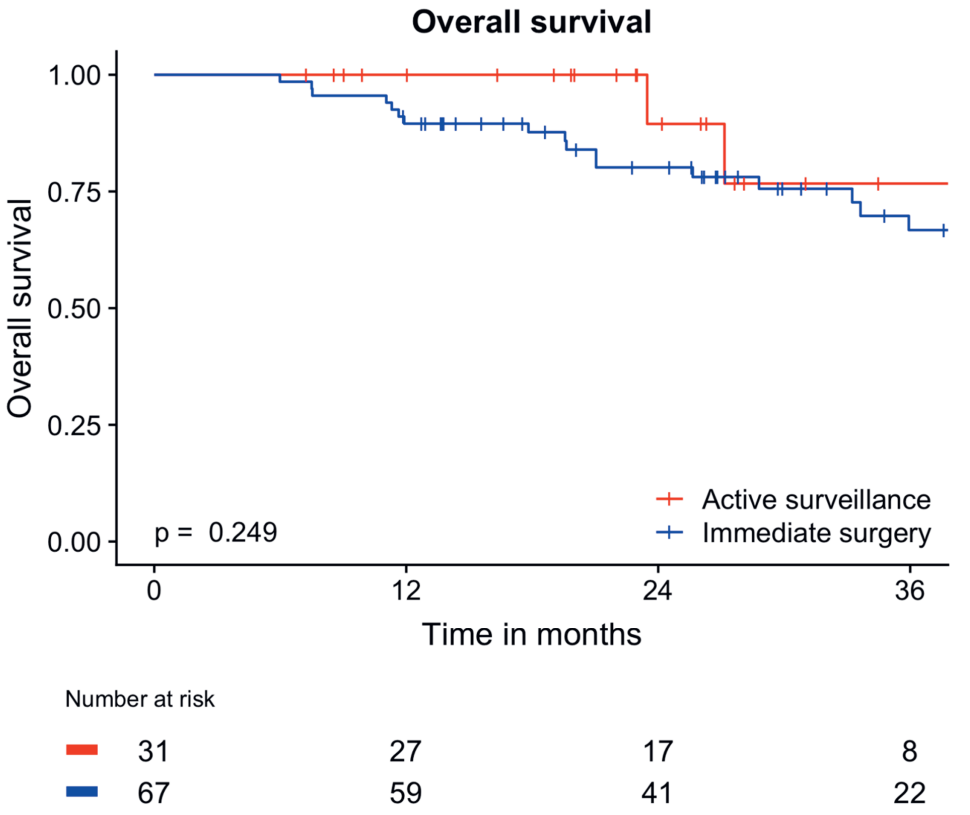
Table 3. Specification of postoperative complications

Complication*	Active surveillance (n=14)	Immediate surgery (n=29)	p~
None (%)	3 (21)	10 (34)	0.491
Pulmonary (%)			0.093
Pneumonia	6 (40)	5 (17)	
Pleural effusion requiring additional drainage	3 (21)	2 (7)	
Pneumothorax requiring treatment	0	2 (7)	
Atrial dysrhythmia (%)	4 (29)	5 (17)	0.442
Gastrointestinal (%)			1.000
Anastomotic leak			
Type II	3 (21)	4 (14)	
Conduit Necrosis			
Type I	0	1 (3)	
Type II	0	2 (7)	
Type III	1 (7)	0	
Urinary tract infection (%)	0	2 (7)	1.000
Urinary retention requiring bladder catheter (%)	0	1 (3)	1.000
Pulmonary embolus (%)	0	1 (3)	1.000
Neurologic/psychiatric (%)			0.373
Vocal cord injury/palsy			
Type IA/B	1 (7)	1 (3)	
Acute delirium	2 (14)	1 (3)	
Infection (%)			1.000
Wound infection**	1 (7)	3 (10)	
Generalized sepsis	1 (7)	1 (3)	
Acute abdominal wall dehiscence (%)	0	1 (3)	1.000
Other (%)			0.693
Infected hematoma requiring surgical intervention	0	1 (3)	
Chyle leakage	1 (7)	3 (10)	
Empyema requiring surgical intervention	1 (7)	0	
Pulmonary herniation requiring surgical intervention	0	1 (3)	
Splenic infarction	0	1 (3)	
Duodenal ischemia	1 (7)	0	
Anastomotic stenosis requiring dilatation	0	2 (7)	

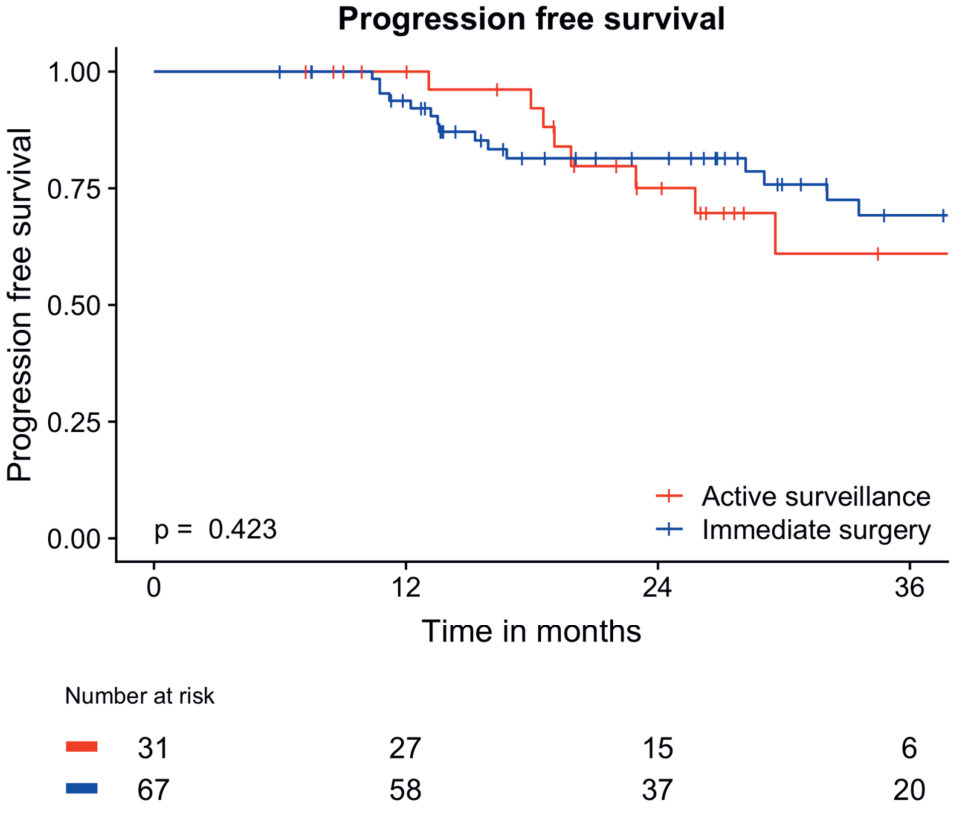
* According to the Esophagectomy Consensus Complication Group [22]

** Requiring opening of wound or antibiotics

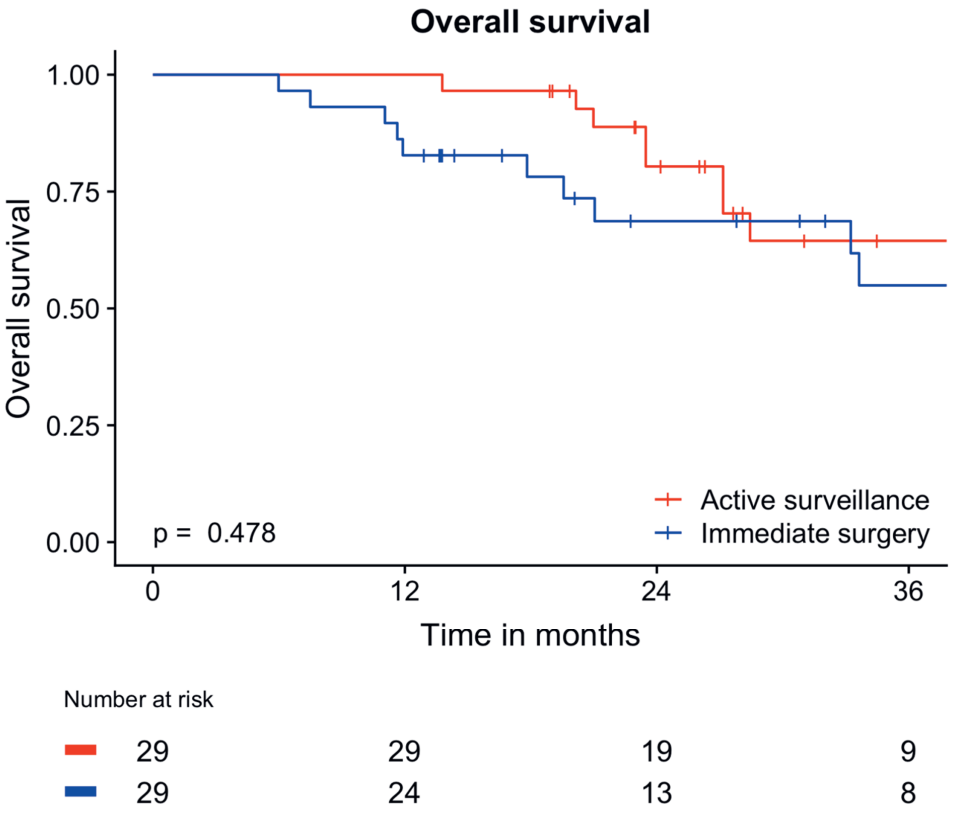
~ Represents the difference in rate of groups of complications



Supplementary figure 1A. Overall survival curves of patients undergoing active surveillance with postponed surgery for recurrent disease (n=31, red line) or immediate surgery (n=67, blue line) before propensity-score matching, from time between date of diagnosis and date of all-cause death.



Supplementary figure 1B. Progression free survival curves of patients undergoing active surveillance with postponed surgery for recurrent disease (n=31, red line) or immediate surgery (n=67, blue line) before propensity-score matching, from time between date of diagnosis and date of detection of progression.



Supplementary figure 2. Overall survival curves of patients undergoing active surveillance with postponed surgery for recurrent disease (n=29, red line) or immediate surgery (n=29, blue line) after propensity-score matching, from time between date of diagnosis and date of all-cause death. These curves represent the overall survival including complete follow-up of patients after active surveillance was ceased (n=6).

Supplementary table 1. Specification of active surveillance strategy

CRE number	Months after nCRT	Patients	Endoscopy	EUS ± FNA	PET-CT
1	1.5	31	31	21	10
2	3	31	31	21	28
3	6	31	30	20	24
4	9	18	18	11	16
5	12	11	11	4	11
6	16	6	6	4	6
7	20	4	4	1	4
8	24	3	3	1	2
9	30	2	2	1	1
10	36	2	2	1	1
11	48	1	1	0	0
12	60	1	1	0	0

CRE: Clinical Response Evaluation, nCRT: neoadjuvant chemoradiotherapy, EUS: endoscopic ultrasonography, FNA: Fine-Needle Aspiration, PET-CT: ^{18}FDG-PET-CT

Supplementary table 2. Pathological outcomes of all patients undergoing immediate surgery

Stage*	Immediate surgery (67)
0	1 (1)
IA	15 (22)
IB	9 (13)
IIA	10 (15)
IIB	3 (4)
IIIA	2 (3)
IIIB	1 (1)
IIIC	1 (1)
IV	0 (0)
ypT0N0	22 (33)
ypT0N1-3	2 (3)
ypTxN0	1 (1)

***** Classified according to the 7th edition of the Union for International Cancer Control's TNM classification (UICC)

Chapter 13

Letter of correspondence

Comment on: “Active surveillance versus immediate surgery in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal cancer.

Daniela Molena, Brian E. Louie, Steven R. Demeester

To the Editor:

We read with interest the recently published study "Active Surveillance Versus Immediate Surgery in Clinically Complete Responders After Neoadjuvant Chemoradiotherapy for Esophageal Cancer."[1] This study suggested that esophagectomy might be safely avoided or postponed until recurrence is found in patients with evidence of complete clinical response (cCR) to neoadjuvant therapy. The premise for this conclusion is that patients designated as having cCR were likely to have pathologic complete response (pCR) were they to undergo esophagectomy and lymph node dissection. The authors used the pre-SANO method of restaging after neoadjuvant therapy that included PET-CT scan, bite-on-bite endoscopic biopsies and endoscopic ultrasound with FNA of suspicious nodes.[2] These clinical response assessments (CREs) were done at 6 and 12 weeks after completion of neoadjuvant therapy. Only patients who were free of disease following both CREs were considered to have cCR and formed the basis of this study. From this group of patients with cCR some had "immediate surgery" while others refused surgery and underwent "active surveillance."

First, it is surprising to note that in the patients who had "immediate surgery" the actual pCR rate was only 24%. This is lower than the pCR rate seen in the CROSS trial and other studies.[3-6] Thus, rather than being a highly selected group of patients with a high likelihood of having pCR, patients in the cCR group in fact had a low likelihood of having pCR after esophagectomy. This suggests that the pre-SANO restaging methodology may be unreliable for selecting patients likely to have true pCR. It also suggests that the majority of patients (76%) in the "active surveillance" group had residual disease and would be expected to show recurrence in time. These findings raise concern about the ongoing SANO study, particularly in patients with esophageal adenocarcinoma where overall pCR rates are much lower than in patients with squamous cell cancer. Can the authors discuss the implications of their low pCR rate in patients designated as having cCR based on the pre-SANO CRE studies? Further, can the authors justify the time and expense of the pre-SANO protocol given these poor results?

Second, can the authors explain why the median follow-up was so much shorter in the active surveillance group compared to the immediate surgery group (27.7 vs 34.8 months for the unmatched patients and 27.6 vs 45.3 months in the matched patients respectively)? Why were patients not matched for length of follow-up and why was the follow-up so different if the patients were drawn largely from the databases of the prospective pre-SANO trial? The shorter follow-up in

the active surveillance group may artificially improve overall survival in the active surveillance group since recurrences may not have led to cancer death yet. This concern is perhaps best expressed in Supplementary Figure 1B which shows progression-free survival (PFS) before matching in both groups. In this figure, PFS was better in the immediate surgery group, despite having far more patients at risk at 36 months in the immediate surgery group (20) compared to the surveillance group (6 patients only). The low numbers preclude statistical significance, but can the authors discuss the significance of this graph in comparison to Figure 2B? Figure 2B shows PFS for the matched patients, and since the active surveillance group had older patients with more co-morbid conditions (CCI≥3), the effect of matching was to exclude some of the healthier and younger patients that had immediate surgery in the matched analysis. This data suggests that PFS is better in all comers with immediate surgery, but is similar between immediate surgery and active surveillance in older, sicker patients. Can the authors comment on this?

Third, can the authors please provide complete cancer recurrence details on the 31 patients in the active surveillance group, particularly the 17 patients that did not have postponed esophagectomy? Figure 3 shows that 5 patients either died, were not eligible or declined surgery. How many of these 5 patients were known to have recurrent disease? The authors state that surveillance patients that developed recurrence and refused surgery were censored in the survival analysis, potentially biasing the results. The authors do show overall survival including these patients in supplementary Figure 2, but there is no information on PFS with these patients included. Further, we think it is important that the authors point out that among the 7 patients in Figure 3 with continued cCR in the active surveillance group, 5 had squamous cell histology. Only one patient with pure adenocarcinoma remained in the active surveillance group with cCR, suggesting that a strategy of active surveillance is perhaps a poor option for patients with adenocarcinoma fit for surgical resection. Can the authors discuss this in more detail?

Lastly, we believe the term “immediate” in the title may be misrepresentative, since it implies that the surgery took place after completion of neoadjuvant therapy. Instead, “immediate” meant after completion of CREs at 6 and 12 weeks. This meant that surgery did not occur for at least 3 months after neoadjuvant therapy finished, a far longer interval than is typical in US clinical practice. Further, the authors state that surgery was considered “postponed” if it occurred after 4 CREs. This means “postponed” surgery occurred at a minimum of 9 months after completion of neoadjuvant therapy, an interval commonly considered to represent salvage esophagectomy in the US. The choice of 9

months seems arbitrary. Why did the authors choose 9 months for postponed esophagectomy instead of including anyone that had esophagectomy for disease recurrence after the initial 2 CREs? We look forward to a response to these questions by the authors. Further, we encourage clinicians in the US to be cautious about adopting the practice of surveillance after neoadjuvant therapy until these issues are better vetted.

Sincerely,

Daniela Molena, MD

Brian Louie, MD

Steven DeMeester, MD

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Chapter 13

Letter of correspondence

Response to the comment on: “Active surveillance versus immediate surgery in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal cancer.”

Berend J. van der Wilk, J. Jan B. van Lanschot

We would like to thank the authors for their interest in our paper entitled: “Active Surveillance Versus Immediate Surgery in Clinically Complete Responders After Neoadjuvant Chemoradiotherapy for Esophageal Cancer.” [1]

The authors comment on the pathologically complete response (pCR) rate of 24% for the matched group of patients undergoing immediate surgery. As reported in the discussion section of the paper, a considerable number of patients having pCR were excluded due to propensity-score matching. In the unmatched immediate surgery group, a pCR rate of 33% was reported. For this paper, data from patients undergoing surgery from the preSANO-trial were used.[2] In the preSANO-database, several patients with a clinically complete response refused surgery. In these patients, the response to neoadjuvant chemoradiotherapy in the resection specimen could not be determined. As such, 33% most probably was an underestimation of the true pCR rate in this group. Furthermore, two types of endoscopic biopsies were used to detect locoregional recurrence in the preSANO-trial: regular endoscopic biopsies and bite-on-bite biopsies. In this paper, both patients undergoing regular endoscopic biopsies and patients undergoing bite-on-bite biopsies were included. However, the sensitivity of the CREs increased considerably after introduction of the bite-on-bite technique in the preSANO-trial. Consequently, both the pCR rate and the accuracy of the CREs in this paper cannot be extrapolated to the CREs and surveillance scheme as performed in the preSANO-trial after introduction of the bite-on-bite biopsy technique or in the currently ongoing SANO-trial (also using this technique).[3] We believe that a sensitivity of 90% for detection of TRG3-4 tumors (as reported in the preSANO-trial) is sufficient to assess the value of an active surveillance strategy in a randomized setting.

Furthermore, the chance for reaching pCR is indeed higher for patients with squamous cell carcinoma. For this reason, the preSINO trial has recently started in Asia assessing the accuracy of CREs solely in patients with squamous cell cancer.[4] If CREs prove to be accurate enough in Asia, the SINO-trial will be initiated to assess an active surveillance strategy specifically for patients with squamous cell cancer only. However, nearly a quarter of patients with adenocarcinoma have pCR. We do not agree with the authors that we should exclude these patients from participation in the SANO-trial assessing the value of an active surveillance strategy, thus precluding these patients from the chance on organ preservation.

From the CROSS-trial, we know that the majority of the patients develop distant metastases within two years after surgery.[5, 6] Hence, it is expected that the majority of distant metastases have developed after a median follow-up of 27 months. Furthermore, only 5 of 29 patients had a follow-up of less than two years and the minimum follow-up of these five patients was 19 months. Hence, progression-free survival curves seem to have matured reasonably. Possibly, overall-survival curves for patients undergoing active surveillance will follow the curves of progression-free survival after longer follow-up. However, it is not expected that overall-survival of patients undergoing active surveillance becomes worse than that of patients undergoing immediate surgery. It would indeed be interesting to perform an additional long term overall-survival analysis of patients undergoing active surveillance. Although the absolute numbers of patients at risk at 36 months suggest a large difference (6 patients undergoing active surveillance versus 20 patients undergoing immediate surgery), the relative difference seems modest (19% versus 30% respectively). This difference in numbers at risk at 36 months decrease when we take into account the overall-survival (supplementary Figure 1A: 26% versus 33%). The comparisons between matched patients (Figure 1A and Figure 1B), show no differences on the numbers at risk at 36 months.

None of the five patients that died due to other causes, were not eligible for surgery or definitively declined surgery were known to have locoregional recurrence at the time of stopping active surveillance. The reason for censoring is that active surveillance was ceased, considerably decreasing chances for successful postponed surgery if locoregional recurrence would have been detected. As stated by the authors, the supplementary data do provide overall-survival analysis including patients that refused surgery or were not eligible for surgery but in whom locoregional recurrence was already detected at the time of ceasing active surveillance. Additional analyses show that progression-free survival is not significantly different between the two groups after inclusion of these censored patients as well. Even after inclusion of all censored patients (despite prematurely having ceased active surveillance), overall-survival between the two groups stays comparable (log-rank: p = 0.946, HR: 1.027 95% CI = 0.48 – 2.20).

Because we were aware of the fact that used definitions can be confusing, we have clearly defined all terms in the methods section of our paper. In short, patients were considered a clinically complete responder when no tumor cells were detected six and twelve weeks after completion of nCRT (*i.e.* CRE-1 and CRE-2). Immediate surgery was defined as surgery performed immediately after clinically complete response was reached (*i.e.* after CRE-2). Postponed surgery was defined as surgery after

detection of locoregional recurrence in active surveillance from 6 months after completion of nCRT (*i.e.* CRE-3, in contrary to the 9 months the authors state in their letter).

We do agree with the authors that active surveillance is not yet recommended as part of standard treatment for esophageal cancer, as stated in the conclusion of our paper. Data from sufficiently powered and randomized trials (*e.g.* the SANO-trial, the ESOSTRATE-trial and the future SINO-trial) are needed to definitively clarify the value of an active surveillance strategy. Our group is currently performing the SANO-trial and the inclusion is expected to be completed by the end of 2020.

Sincerely,

Berend J. van der Wilk, MD

J. Jan B. van Lanschot, MD, PhD

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14

Chapter 14

Chemoradiotherapy followed by active surveillance versus standard esophagectomy for esophageal cancer: a systematic review and individual patient data meta-analysis

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Abstract

Objective

To compare overall survival of patients with a clinically complete response (cCR) undergoing active surveillance versus standard esophagectomy.

Summary background data

One-third of patients with esophageal cancer have a pathologically complete response in the resection specimen after neoadjuvant chemoradiotherapy. Active surveillance may be of benefit in patients with cCR, determined with diagnostics during response evaluations after chemoradiotherapy.

Methods

A systematic review and meta-analysis was performed comparing overall survival between patients with cCR after chemoradiotherapy undergoing active surveillance versus standard esophagectomy. Authors were contacted to supply individual patient data. Overall and progression free survival were compared using random effects meta-analysis of randomized or propensity score matched data. Locoregional recurrence rate was assessed. The study-protocol was registered (PROSPERO:CRD42020167070).

Results

Seven studies were identified comprising 788 patients, of which after randomization or propensity score matching yielded 196 active surveillance and 257 standard esophagectomy patients. All authors provided individual patient data. The risk of all-cause mortality for active surveillance was 1.08 (95%Confidence Interval (CI):0.62–1.87,p=0.75) after intention-to-treat analysis and 0.93 (95%CI:0.56–1.54,p=0.75) after per-protocol analysis. The risk of progression or all-cause mortality for active surveillance was 1.14 (95%CI:0.83–1.58,p=0.36). Five-year locoregional recurrence rate during active surveillance was 40% (95%CI:26%-59%). 95% of active surveillance patients undergoing postponed esophagectomy for locoregional recurrence had radical resection.

Conclusions

Overall survival was comparable in patients with cCR after chemoradiotherapy undergoing active surveillance or standard esophagectomy. Diagnostic follow up is mandatory in active surveillance and postponed esophagectomy should be offered to operable patients in case of locoregional recurrence.

Introduction

Overall survival of patients with locally advanced esophageal cancer has improved after the introduction of neoadjuvant therapies.[1-5] A pathologically complete response rate of 25-30% of patients after neoadjuvant chemoradiotherapy (nCRT) has been reported.[2, 3, 6] This relatively high pathologically complete response rate imposes an ethical dilemma to reconsider the benefit of standard esophagectomy after nCRT. Since esophagectomy is associated with substantial postoperative mortality (1-5%) and morbidity (50%), the advantages of avoiding unbeneficial surgery seem clear.[7-11] Therefore, an active surveillance strategy has been proposed for patients with a clinically complete response (cCR).[12-14] If no residual tumor is detected after nCRT during clinical response evaluations, patients are considered to have a cCR. Subsequent esophagectomy might be reserved only for patients with proven or highly suspected residual disease.[14] Active surveillance instead of standard esophagectomy after nCRT, however, has the potential for harm. Previously it was determined that using a combination of endoscopic bite-on-bite biopsies, endoscopic-ultrasound and fine-needle aspiration of suspected lymph nodes during clinical response evaluations, 10% of substantial residual tumors was still missed (>10% residual tumor).[15] These patients were erroneously considered to have a pathologically complete response. Undetected remnant locoregional cancer cells after nCRT may progress to locoregionally unresectable recurrence or distant metastases.[16] This could result in a worse overall survival. Moreover, active surveillance could cause feelings of anxiety in patients due to the risk of locoregional recurrence that may require postponed esophagectomy.[17-19] Two randomized controlled trials are currently ongoing. The long-term results of these trials are not expected before 2026. Several smaller and mostly retrospective studies comparing active surveillance with standard esophagectomy have been published.[12, 13, 20-22] These individual studies all have, however, insufficient power to provide convincing evidence in favor of either strategy. A systematic review and meta-analysis were performed with the primary aim to compare overall survival of patients with cCR after nCRT undergoing active surveillance or standard esophagectomy.

Methods

Systematic search

A systematic review and meta-analysis were performed in accordance with the PRISMA-IPD statement and the Cochrane Handbook for Systematic Reviews of Interventions.[23, 24] The protocol for this study was registered in PROSPERO prior to data extraction (CRD42020167070). A systematic

search was performed in collaboration with a librarian specialized in systematic searches. Embase, Medline, Web of Science, Scopus and Cochrane Central Register of Trials databases were searched for relevant studies until February 12, 2020. Keywords used were 'esophageal cancer', 'surgery' and 'active surveillance' and relevant variations thereof, not restricted to English language. The full search strategy is reported in Appendix I. After removal of duplicates, two researchers (B.J.W. and B.M.E.) independently screened titles and abstracts of all retrieved publications. Inclusion criteria for a full-text analysis were: 1) studies included patients with esophageal cancer and cCR after chemoradiotherapy (prior to surgery, no restrictions were defined for the chemoradiotherapy scheme); 2) studies included both patients who underwent active surveillance and patients who underwent standard esophagectomy and 3) overall survival was compared between patients undergoing active surveillance or standard esophagectomy. Systematic reviews or case-reports were excluded. To increase the range of the search, systematic reviews were assessed by cross-referencing. Differences between selections of both researchers were resolved by consensus discussion. If consensus was not reached, the senior author (J.J.B.L.) was consulted for a final verdict. The corresponding authors were contacted to provide individual patient data on overall survival period, locoregional and distant progression rates, incidence of postponed surgery for locoregional recurrence during active surveillance and postoperative outcomes. The authors were allowed, but not obliged to update the databases. Two researchers (B.J.W. and B.M.E) independently assessed the risk of bias for all included studies using the Cochrane RoB2 tool for randomized trials and the Cochrane ROBINS-I tool for cohort studies.[25, 26]

Outcomes

The primary outcome of the study was overall survival, defined as the interval between date of treatment initiation (or date of diagnosis if date of treatment initiation was not available) and date of all-cause mortality or last follow-up. Secondary outcomes were progression free survival, defined as the interval between date of treatment initiation (or date of diagnosis if date of treatment initiation was not available) and date of progression, all-cause mortality or last-follow-up. Progression was defined as development of distant metastases and/or locoregional recurrence after esophagectomy. Additional secondary outcomes were rate of locoregional recurrence during active surveillance and rate of resections with microscopically tumor-free margin (R0).

Data extraction

A report form was developed, pilot-tested and refined afterwards in order to systematically extract data from the individual patient databases. Two researchers (B.J.W. and B.M.E) independently extracted basic study characteristics, basic patient characteristics and predefined outcomes. Data were extracted from individual patient databases if possible. If individual patient data were not available for a specific item, data were extracted from the published article, if possible. If time to distant metastasis was not available, but it was known that an event had occurred, time to distant metastasis was set to the date of last follow-up. Disagreements were resolved by consensus discussion. If consensus could not be reached or if inconsistencies were found in the individual patient databases, the author responsible for the database was consulted.

Statistical analysis

The individual patient data meta-analysis was performed according to the *two-stage approach*.[27] Analyses on overall survival and progression free survival were performed using data from patients included after randomization or after propensity score matching. This population was defined as the intention-to-treat (ITT) population. If no propensity score matching had been performed in the original studies, this was done on provided individual patient data using age, tumor stage, tumor grade and ECOG status of the patient, if available, according to the nearest neighbour method with 0.2 caliper.

An additional overall survival analysis was performed for the per-protocol (PP) population. In this population, patients were included after randomization or after propensity score matching. Subsequently, patients with locoregionally unresectable disease or distant metastases prior to initiation of active surveillance or standard esophagectomy were excluded. In the active surveillance arm, patients were excluded who did not undergo postponed esophagectomy in case of an isolated locoregional recurrence. In the standard esophagectomy arm, patients were excluded if no esophageal resection was performed (*e.g.* due to peroperatively detected non-resectability). Locoregional recurrence rates during active surveillance were pooled with random effects meta-analysis of cumulative incidence and radical resection rates were pooled with random effects meta-analysis of the proportion. Statistical heterogeneity was assessed using both I^2 and Cochrane's Q statistic. Additionally, Kaplan-Meier curves were constructed of overall survival and progression free survival. Conditional risk of locoregional recurrence curves were constructed for patients undergoing

active surveillance. This conditional risk was defined as the probability of developing locoregional recurrence during follow-up, given that a patient had not already developed locoregional recurrence for a given period of time. Median follow-up was determined using the reversed Kaplan-Meier method.

Additional overall survival analyses were performed of unmatched data. Subgroup analyses were performed for patients with adenocarcinoma or squamous cell carcinoma. Publication bias was assessed with contour enhanced funnel plot of the primary outcome and tested with the Egger's test.[28] All statistical analyses were performed using R version 3.6.2 (R Core team, R foundation for statistical computing, 2013, Boston, MA, USA).

Results

Included studies

The systematic search resulted in 1069 articles after removal of duplicates. After screening of titles and abstracts, full-texts of 45 articles were assessed. Seven articles fulfilled all inclusion criteria.[20-22, 29-32] The PRISMA IPD-flow diagram is shown in Figure 1 for detailed information on study selection and number of patients included for each analysis. Of seven studies, five studies used propensity score matching or adjusted for propensity scores in outcome[21, 22, 29, 30, 32], one study was a phase-3 randomized controlled trial[31] and one retrospective cohort study neither used propensity score matching nor randomization.[20] Low risk of bias was observed for selection of participants, missing data, and selection of reported results, for all studies. Three studies had moderate risk of bias, three studies had high risk of bias and one study had critical risk of bias for deviation from intended interventions, assuming postponed esophagectomy was initially planned in case of isolated locoregional recurrence (Appendix II). No statistically significant asymmetry was observed in the funnel plot, indicating no presence of publication bias (Appendix III). All studies included patients with cCR, which was determined by endoscopic biopsies in all but one study, in which only a PET-CT scan was used.[30] All corresponding authors agreed to provide individual patient data on overall survival, progression of the disease, locoregional recurrence rates and radicality of resections. In total, data were obtained comprising 788 patients with esophageal cancer and cCR after chemoradiotherapy either undergoing active surveillance (255 patients) or standard esophagectomy (533 patients). Some 500 patients had adenocarcinoma and 283 patients had squamous cell carcinoma, while five patients had other histology. Patients in the active surveillance arm were either initially unfit for surgery,

refused surgery themselves or were randomized after chemoradiotherapy. One patient with unresectable progression of disease and one patient with distant metastasis were included prior to initiation of active surveillance in one retrospective study. All patients underwent chemoradiotherapy with a median of (interquartile range (IQR)) 45 Gray (45–50.4) radiotherapy, this was comparable in both groups. Details of basic study characteristics are summarized in Table 1 and details on treatment characteristics are reported in Table 2.

Overall survival

Data on overall survival of two patients were missing, resulting in inclusion of 451 patients in the ITT population for overall survival (195 active surveillance and 256 standard esophagectomy). The statistical heterogeneity for overall survival analysis was 25% - 55%, which was considered low to moderate. The median follow-up and median overall survival of individual studies is reported in Appendix IV. The risk of all-cause mortality for patients undergoing active surveillance was 1.08 (95%CI: 0.62–1.87, p=0.75) compared to standard esophagectomy (Figure 2A and 2B). The PP population consisted of 417 patients, after exclusion of 34 patients (29 active surveillance patients and five standard esophagectomy patients). In the active surveillance group, 28 patients did not undergo postponed esophagectomy after detection of isolated locoregional recurrence and one patient was included with distant metastases. In the standard esophagectomy group, five patients were excluded because no esophageal resection was performed. Risk of all-cause mortality for patients undergoing active surveillance was 0.93 (95%CI: 0.56–1.54, p=0.75) compared to standard esophagectomy (Figure 2C and 2D). Subgroup analyses were performed of patients with either squamous cell carcinoma or adenocarcinoma and after inclusion of all patients (including unmatched patients). No statistically significant difference in overall survival between patients undergoing active surveillance or standard esophagectomy was found in supplementary analyses (Appendix V and VI).

Progression free survival

Data on progression were missing for four patients, resulting in inclusion of 449 patients in the ITT population for progression free survival (192 active surveillance and 257 standard esophagectomy). The statistical heterogeneity for this analysis between studies was 0%, which was considered low. The risk of progression or all-cause mortality for active surveillance was 1.14 (95%CI: 0.83–1.58, p=0.36) compared to standard esophagectomy (Figure 3A and 3B).

Locoregional recurrences

Data on timing of locoregional recurrences of 21 patients was missing, resulting in 767 patients (236 patients in the active surveillance arm and 531 in the standard esophagectomy arm).
Of the 236 patients in the active surveillance group, 93 (39%) patients developed locoregional recurrence after a median (IQR) follow-up of 50.0 (28.8–68.2) months, of whom seven patients had synchronous distant metastases. Random-effects meta-analysis of the cumulative incidence of locoregional recurrence in patients undergoing active surveillance was 23% at one year (95%CI: 13-38%), 34% at two years (95%CI: 21-50%) and 40% at five years (95%CI: 26–59%, Figure 4A and 4B). Of 86 patients with isolated locoregional recurrence (without distant metastases), 49 patients underwent postponed surgery (57%). Nineteen patients who had isolated locoregional recurrence refused postponed surgery themselves, six patients were deemed unfit and the reasons were not recorded for 12 patients. Patients in active surveillance undergoing postponed esophagectomy had R0 resection rate of 95% (95%CI: 86-100%). No macroscopically non-radical resections were reported.
Of the 531 patients in the standard esophagectomy arm the R0 resection rate was 99% (95%CI: 97-100%). No macroscopically non-radical resections were reported. Thirty-five of 533 patients (7%) developed locoregional recurrence after initial surgery, one salvage esophagectomy was performed. The remaining patients were considered to have unresectable recurrences.

Discussion

The role of active surveillance for patients with locally advanced esophageal cancer who have cCR after neoadjuvant chemoradiotherapy is controversial. In the present meta-analysis no statistically significant differences were observed in overall survival or in progression free survival. 40% of patients developed a locoregional recurrence (with or without synchronous distant metastases) during active surveillance, most of whom (34%) within two years. Postponed esophagectomy for isolated locoregional recurrence during active surveillance was microscopically radical in 95% of patients.
Postponed esophagectomy was not performed in nearly half of the patients who developed isolated locoregional recurrence during active surveillance. Mostly, due to patients' refusal or condition. Patients refusing surgery or unfit for surgery were obviously not included in the standard esophagectomy group, resulting in substantial selection bias between the two study groups in the different datasets. This selection bias is also reflected in the risk of bias assessments, due to deviation of intended interventions (Appendix II) which had major impact on the overall risk of bias

assessments. Although propensity score matching was used to correct for most confounders, not all confounders could be matched for and thus a selection bias still plays a role. Hence, the per-protocol analysis of this meta-analysis most probably reflects the situation where patients are systematically offered active surveillance, but with inclusion of only those fit for surgery and willing to undergo postponed esophagectomy, which was not the case in the retrospective studies. Even with this selection bias present, which was in favor of standard esophagectomy, overall survival was not statistically significantly different between the two groups. Furthermore, when postponed esophagectomy was performed in patients with isolated locoregional recurrence, a radical resection was achieved in 95% of patients. Therefore, it is important to emphasize to patients, prior to initiation of active surveillance, both the frequency of locoregional recurrences (up to 40% after five years) and the relevance of postponed esophagectomy in case of isolated locoregional recurrence. To prevent the occurrence of unresectable isolated recurrences, frequent diagnostic follow-up is mandatory in an active surveillance strategy.

A previous meta-analysis suggested that endoscopy with biopsies, endoscopic ultrasonography or PET-CT as single modalities are moderately accurate for detecting locoregional residual disease after nCRT.[33] Even if these modalities are combined, 23% of all residual tumors after nCRT are still missed.[15] Theoretically, prolonged presence of residual tumor within the esophageal wall and/or within the regional lymph nodes, that remains undetected during active surveillance, could result in more distant dissemination compared to the situation in those patients who undergo standard esophagectomy after nCRT. Progression free survival was comparable between both groups in the present study. The rate and timing of distant dissemination specifically were not sufficiently reported for a reliable comparison between the groups. For definitive answers on distant dissemination rates between both groups, diagnostics to detect metastases should be performed on more standardized time points and compared between both groups.

Patients with squamous cell carcinoma have a greater chance of a pathologically complete response. Nearly a quarter of patients with adenocarcinoma, however, have a pathologically complete response as well. There are no indications that clinical response evaluations are less accurate for detecting adenocarcinoma compared to squamous cell carcinoma. Therefore, it is not expected that residual tumors are missed more often in patients with adenocarcinoma compared to patients with squamous cell carcinoma. Although patients with squamous cell carcinoma have higher *a priori* chance of a pathologically complete response, we believe that an active surveillance strategy could be beneficial

as well for patients with adenocarcinoma. The supplementary data of this study seem to support this hypothesis.

All identified and approached study groups agreed to collaborate and provided data from individual patients resulting in a large database and an accurate representation of all potentially available data on this topic. The use of individual patient data sets instead of a traditional meta-analysis allowed for assessment of overall and progression free survival in a standardized and consistent manner. Pooling of all available datasets profoundly increased the power of the conclusion, compared to the conclusion of each individual study.

The included studies in this meta-analysis have some limitations. Most studies were retrospective and included small samples resulting in a selection bias in these individual studies. By pooling the data, it was possible to increase the sample size and to increase the robustness of the conclusion. Selection bias, however, cannot be overcome in this meta-analysis. Furthermore, an active surveillance strategy ideally comes with standardized chemoradiotherapy protocols as well as standardized surveillance regimens and uniform definitions for a clinically complete response. These factors were not standardized between studies which resulted in a relatively heterogeneous group of patients in the present meta-analysis. The heterogeneity and the selection bias in this study will most probably have a detrimental effect on the outcomes of patients undergoing active surveillance. Even with these limitations, no statistically significant difference in overall survival was reported.

The data from our meta-analysis have some limitations as well. It was not possible to collect sufficient data on postoperative complications after (postponed) esophagectomy. Therefore, we could not reliably compare postoperative complications between the active surveillance and the standard esophagectomy group, which would be an interesting topic of future research. There was a difference in follow-up time between the two matched groups in the present study. An additional sensitivity analysis suggested that this did not influence the results of the conclusion on overall survival in the matched group. To definitively overcome this problem, however, additional follow-up survival data of all included patients until one specific timepoint (*e.g.* at five years of follow-up) should be collected for all patients. Lastly, due to the limited number of patients (7%) with locoregional recurrence in the standard esophagectomy arm and the variation between studies, it was not possible to compare the outcomes of this specific subgroup to another.

When introducing a new treatment which has potential benefits over standard treatment (*i.e.* less invasive treatment), non-inferiority should be tested in a homogeneous group of patients with a non-

inferiority margin defined *a priori*. A randomized trial with such characteristics is still needed to definitively prove non-inferiority of active surveillance compared to standard esophagectomy.
The main question remains whether active surveillance for locally advanced esophageal cancer is ready for clinical practice. It has been reported that the demand from patients is high and that some patients are willing to trade off survival to a certain extent in order to decrease the risk of an esophagectomy being necessary.[34] Two randomized trials are currently comparing active surveillance with standard esophagectomy and will definitively answer whether or not active surveillance is non-inferior.[12, 13] The long-term results of these trials will most probably not be published before 2026. Meanwhile, clinicians will have to rely on non-randomized data. The results of this study could be used to discuss an active surveillance strategy with patients who have cCR after chemoradiotherapy.

Acknowledgements

We would like to acknowledge mr. Wichor M. Bramer from the medical library of Erasmus University Medical Center for his assistance in the systematic search of the literature.

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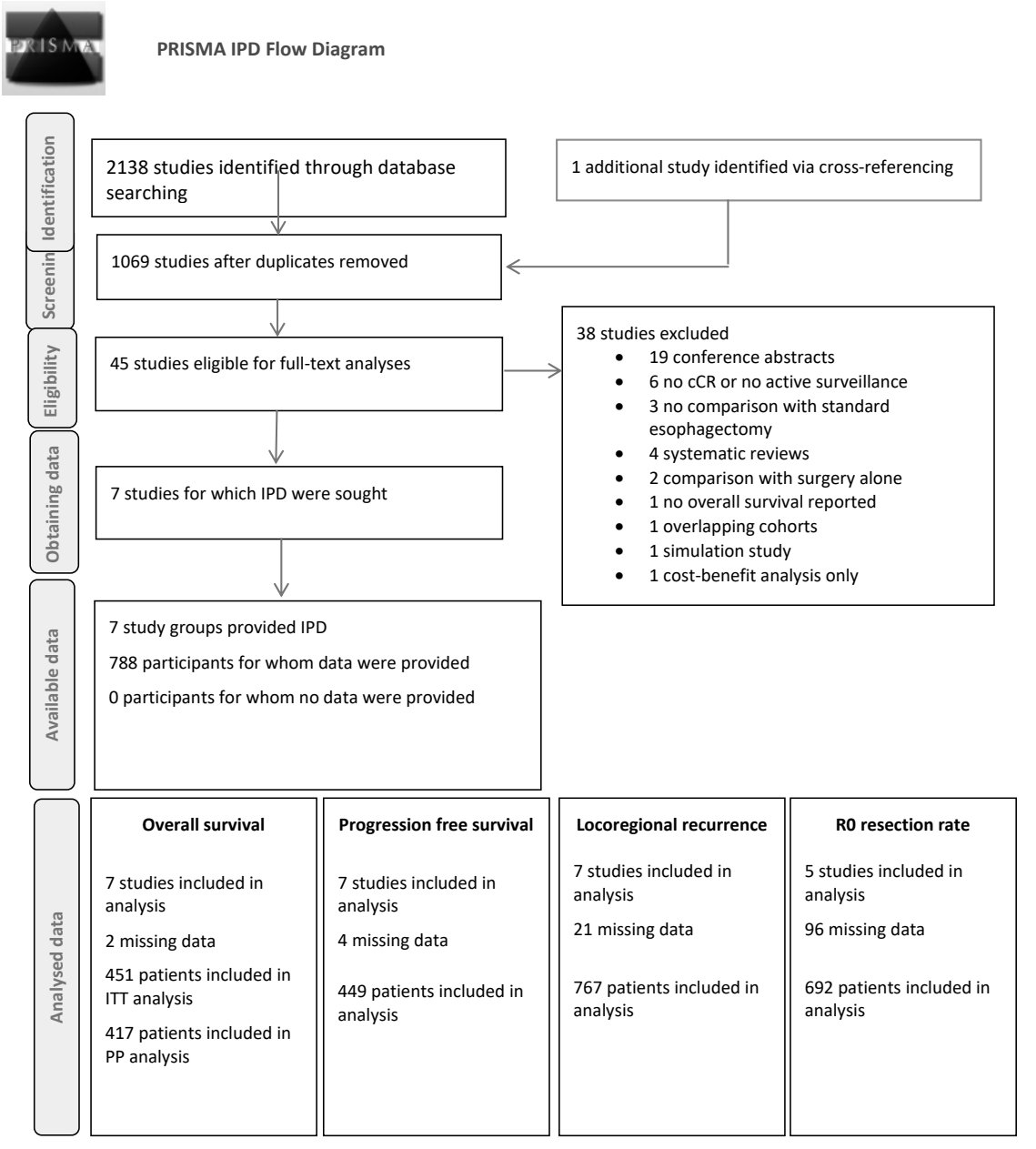
Figure 1. Detailed flow diagram reporting on selection process and obtaining individual patient data (IPD). cCR: clinically complete response, R0: microscopically radical.



The PRISMA IPD flow diagram

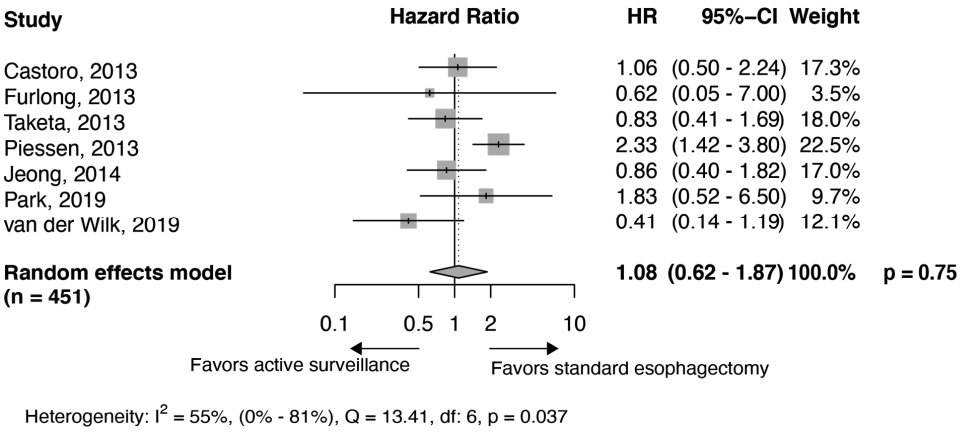


Figure 2A. Random effects meta-analysis of the ITT population for the risk of all-cause mortality for patients undergoing active surveillance compared to standard esophagectomy. The size of the squares represents the sample size of each individual study. The vertical line within the squares represents the hazard ratio of each individual study with corresponding 95% confidence intervals represented as the horizontal lines. Weights are determined according to sample size of the study and confidence intervals of hazard ratio. HR: Hazard Ratio, CI: Confidence Interval, ITT: Intention To Treat.

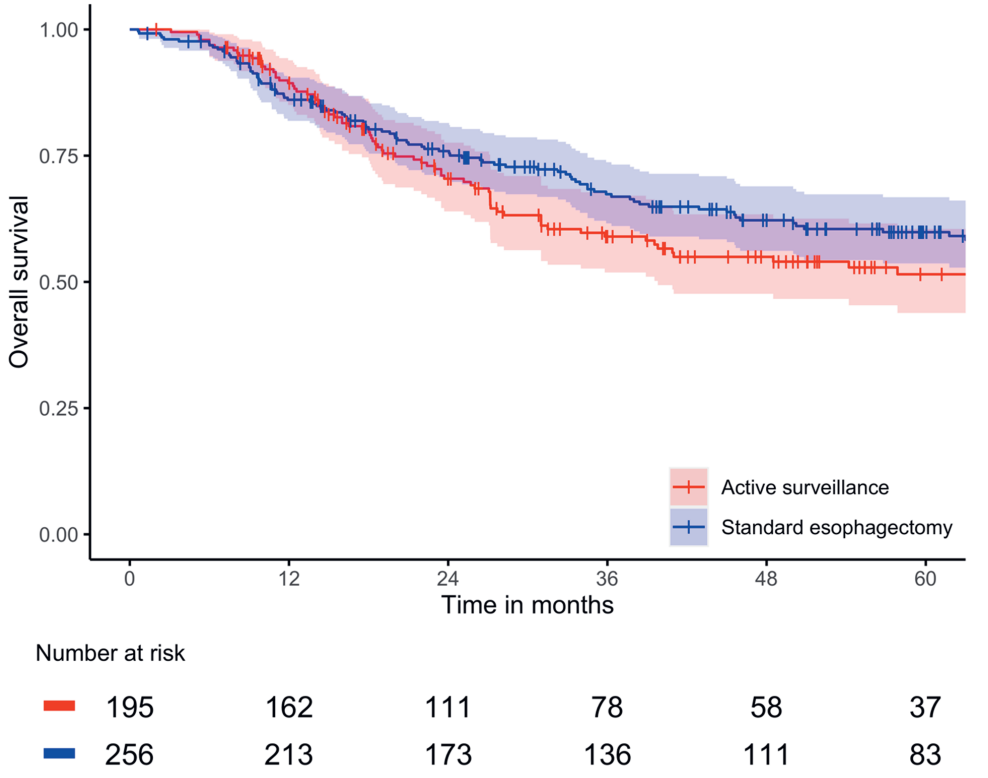
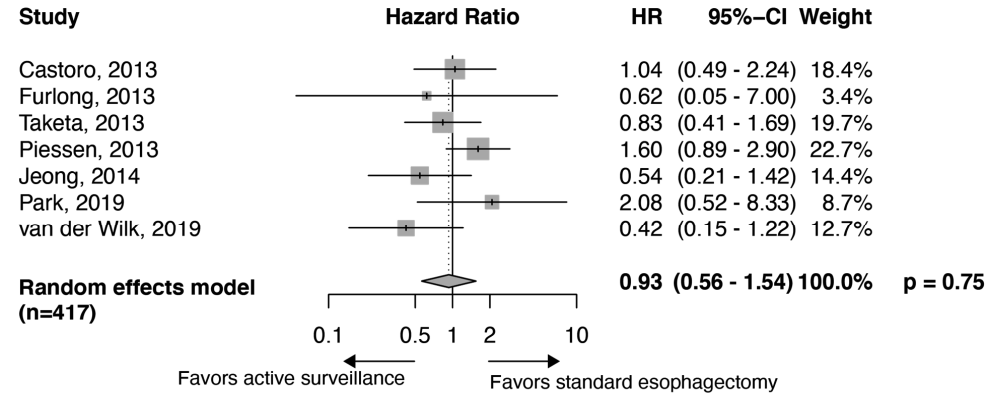


Figure 2B. Pooled Kaplan-Meier curves of the ITT population with corresponding 95% confidence interval curves of overall survival for patients undergoing active surveillance or standard esophagectomy. These Kaplan–Meier curves represent all patients after randomization or propensity score matching and do not account for any deviations from intended intervention. Additionally, the curves do not account for random effects or weights of individual studies. Therefore, no statistical analyses have been performed. ITT: Intention To Treat.



Heterogeneity: I^2 = 25%, (0% - 67%), Q = 8.04, df: 6, p = 0.24

Figure 2C. Per-protocol sensitivity analysis of the PP population for the risk of all-cause mortality for patients undergoing active surveillance compared to standard esophagectomy. The size of the squares represents the sample size of each individual study. The vertical line within the squares represents the hazard ratio of each individual study with corresponding 95% confidence intervals represented as the horizontal lines. Weights are determined according to sample size of the study and confidence intervals of hazard ratio. HR: Hazard Ratio, CI: Confidence Interval, ITT: Intention To Treat.

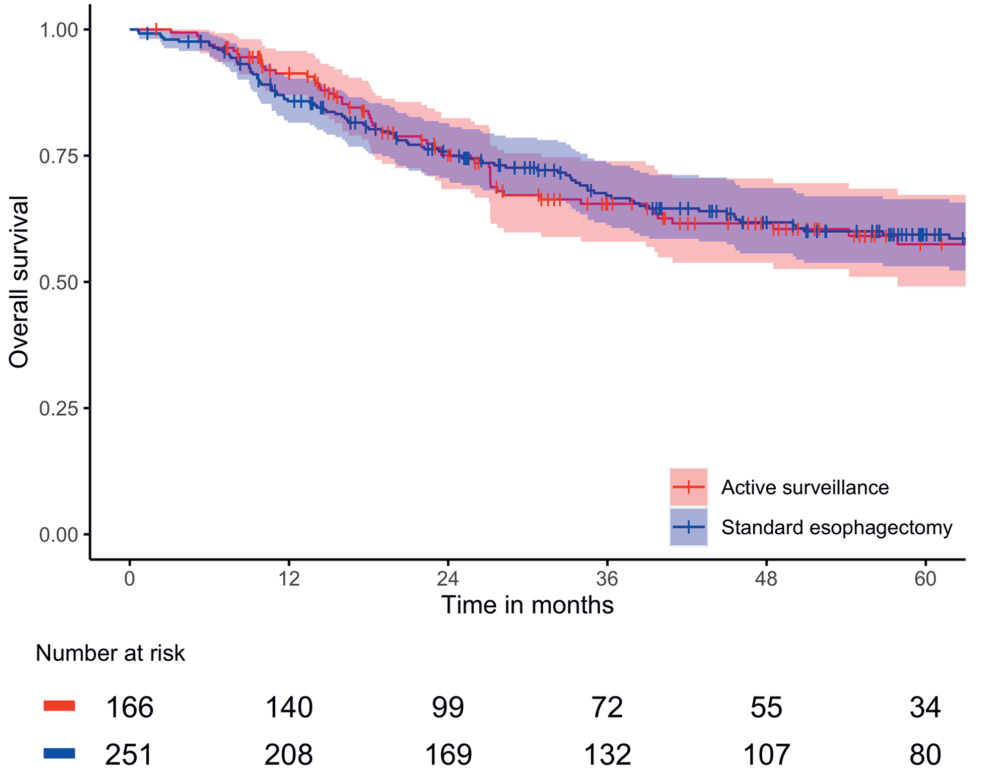
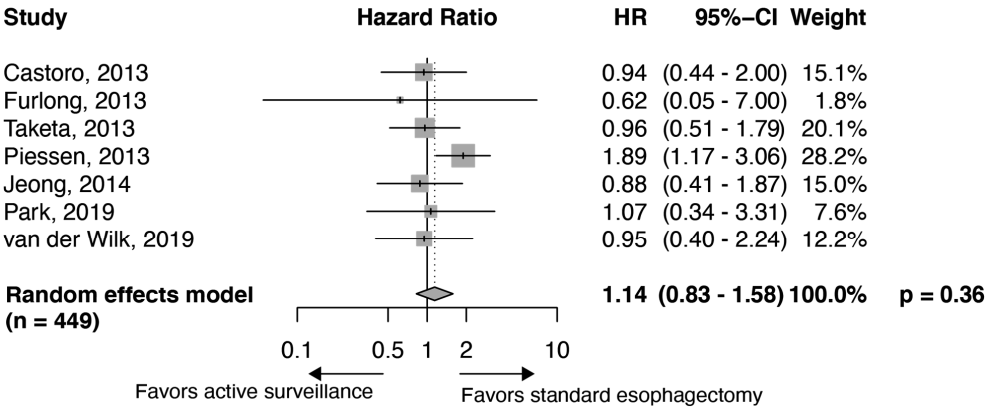


Figure 2D. Pooled Kaplan-Meier curves of the PP population with corresponding 95% confidence interval curves. These Kaplan – Meier curves represent the per-protocol sensitivity analysis of overall survival for patients undergoing active surveillance or standard esophagectomy. The curves do not account for random effects or weights of individual studies. Therefore, no statistical analyses have been performed. PP: Per Protocol.



Heterogeneity: I^2 = 0%, (0% - 69%), Q = 5.62, df: 6, p = 0.47

Figure 3A. Random effects meta-analysis of the ITT population for risk of progression or all-cause mortality for patients undergoing active surveillance compared to standard esophagectomy. The size of the squares represents the sample size of each individual study. The vertical line within the squares represents the hazard ratio of each individual study with corresponding 95% confidence intervals represented as the horizontal lines. Weights are determined according to sample size of the study and confidence intervals of hazard ratio. HR: Hazard Ratio, CI: Confidence Interval, ITT: Intention To Treat.

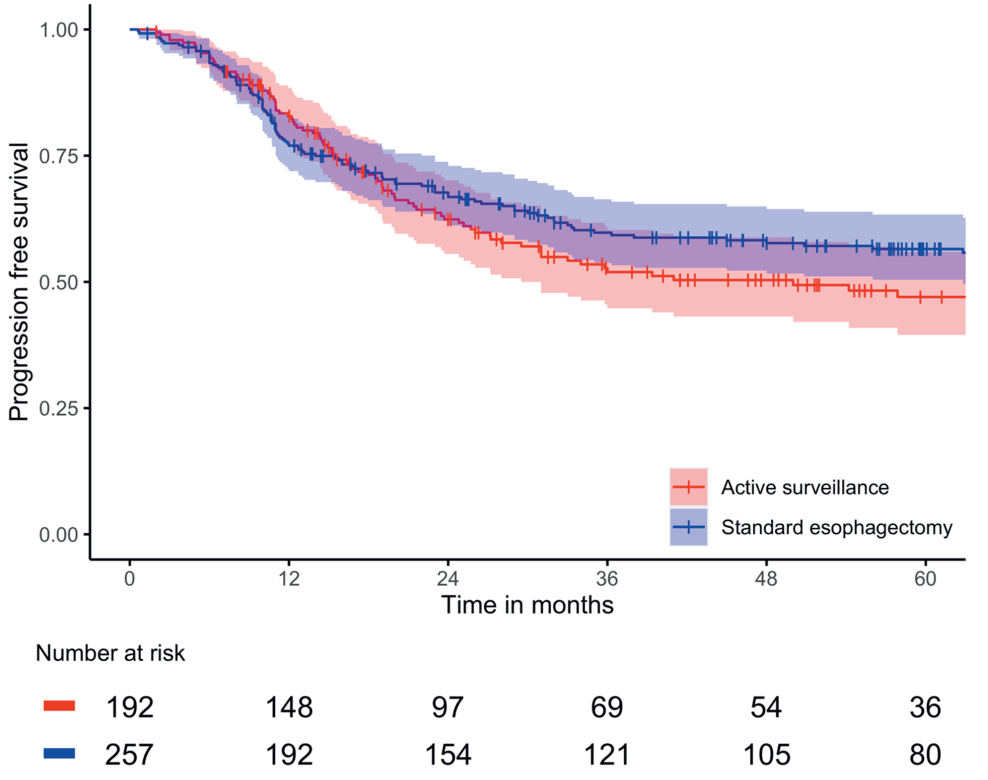


Figure 3B. Pooled Kaplan-Meier curves of the ITT population with corresponding 95% confidence interval curves of progression free survival for patients undergoing active surveillance or standard esophagectomy. These Kaplan–Meier curves represent all patients after randomization or propensity score matching and do not account for any deviations from intended intervention. Additionally, the curves do not account for random effects or weights of individual studies. Therefore, no statistical analyses have been performed. ITT: Intention To Treat.

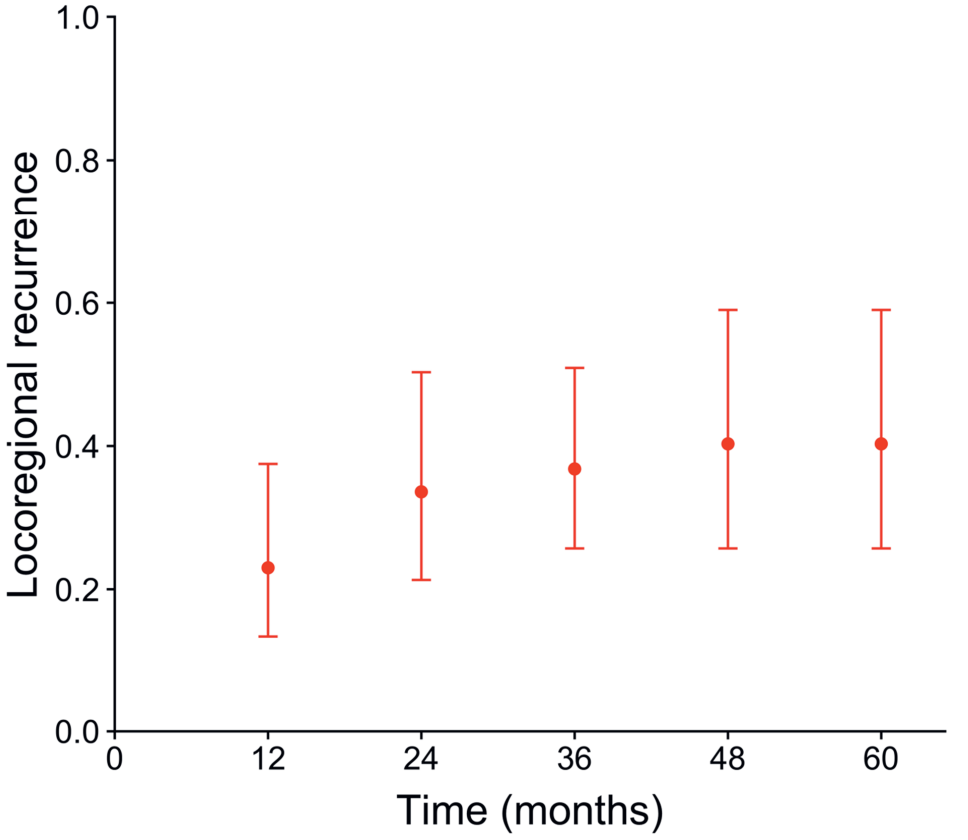


Figure 4A. Random effects meta-analysis of the cumulative incidence of locoregional recurrences, prior to esophagectomy (including synchronous distant metastases) in patients undergoing active surveillance (n=236), with 95% confidence interval.

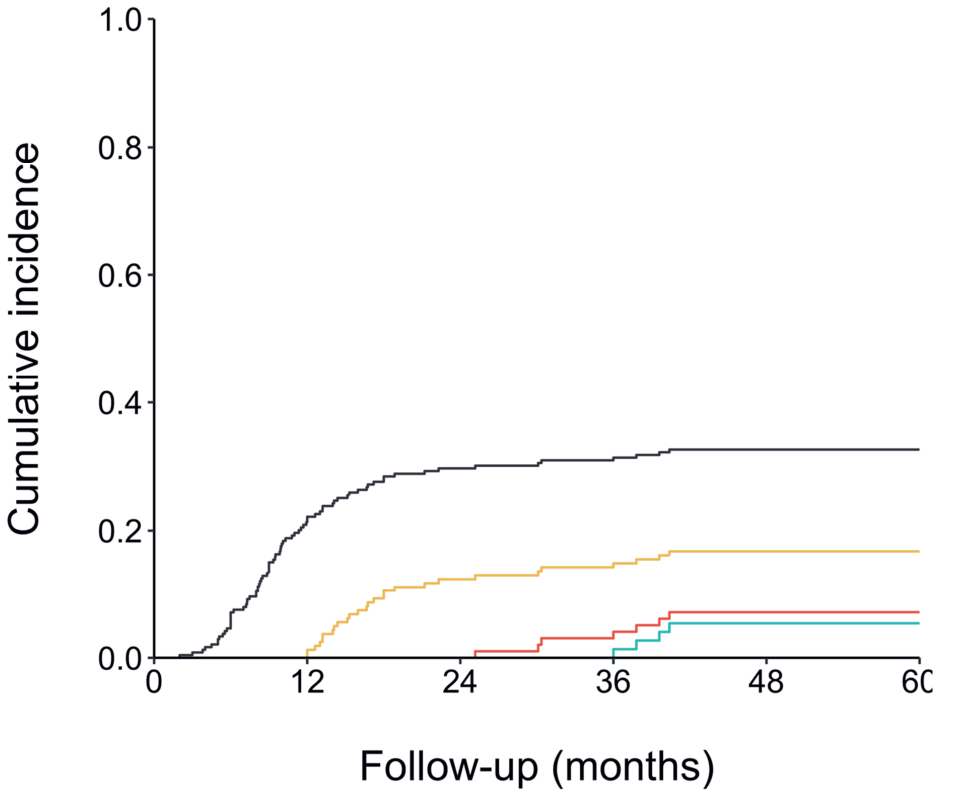
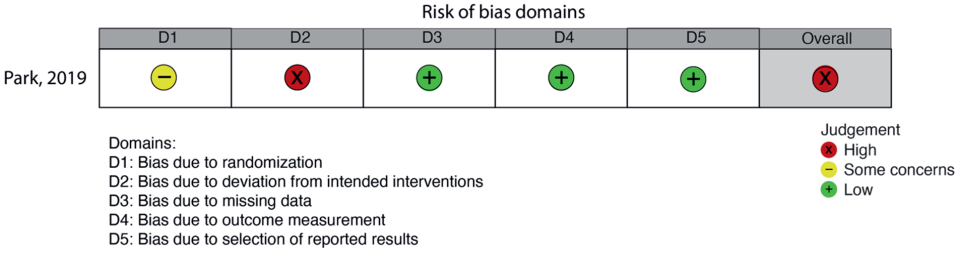


Figure 4B. Conditional risk of development of locoregional recurrence (including patients with synchronous metastases) in patients undergoing active surveillance (n=236) after a locoregional recurrence free interval of 0 months (black line), 12 months (yellow line), 24 months (red line) and 36 months (blue line). No locoregional recurrences developed after a locoregional recurrence free interval of 40 months.

Appendix I. Full search strategy

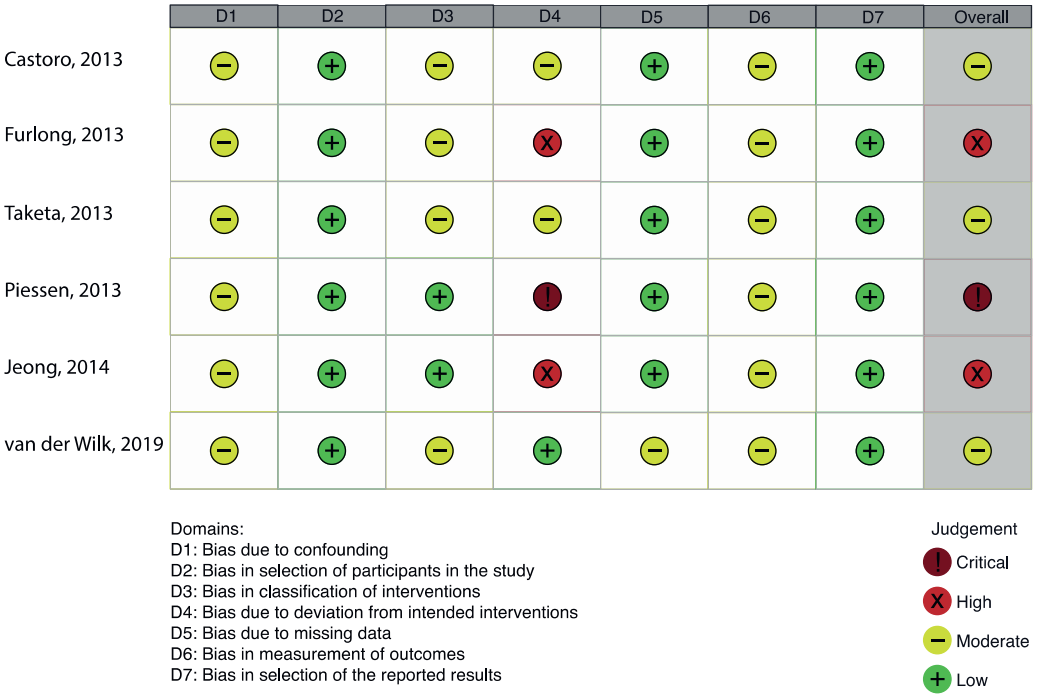
Database	Full search strategy
Embase	('esophageal cancer'/exp OR 'esophageal tumor'/de OR (((esophag* OR oesophag*) NEAR/6 (cancer* OR neoplas* OR carcino* OR adenocarcino* OR tumor* OR tumour* OR malign*))):ab,ti) AND ('watchful waiting'/de OR 'observation'/de OR 'observational method'/de OR 'observational study'/de OR (((watch* OR see) NEAR/3 wait*) OR surveil* OR observation* 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)
Medline	("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 Observation/ OR Observational Study/ OR (((watch* OR see) ADJ3 wait*) OR surveil* OR observation* 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.)
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 surveil* OR observation* 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)
Web of Science	AB=(((((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 surveil* OR observation* 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*))))
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 surveil* OR observation* 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*))))

Appendix II. Risk of bias assessments of included studies; randomized clinical trials.

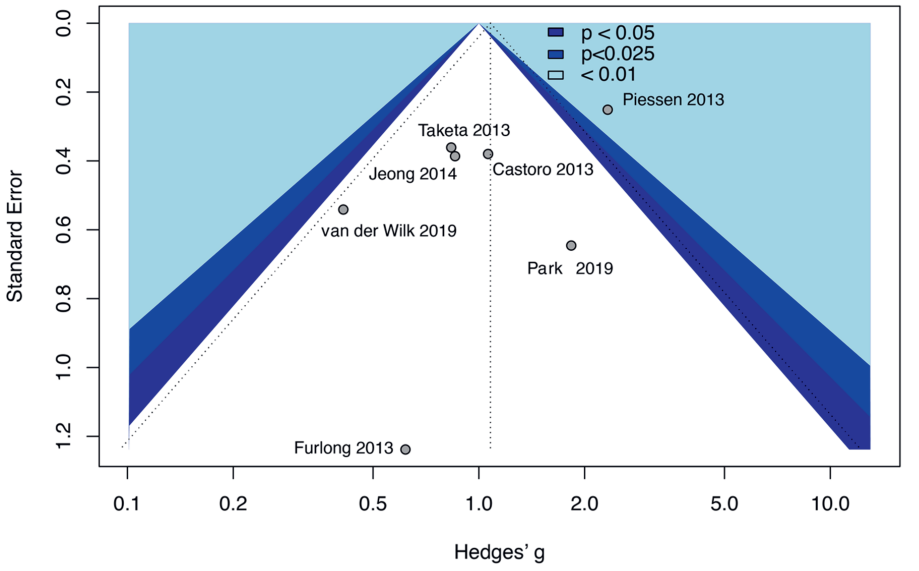


Risk of bias assessment of included randomized clinical trial using Cochrane ROB-2 tool[25]

Appendix II. Risk of bias assessments of included studies; observational cohort studies.



Risk of bias assessment of included cohort studies using Cochrane ROBINS-I tool[26]



Appendix III. Publication bias assessment of included studies. Publication bias assessment using contour enhanced funnel plot and tested with the Egger's test. The X-axis represents the Hedges' g to estimate the effects of individual studies. The Y-axis represents the standard error to estimate the accuracy of the individual studies. Publication bias is assumed to be present if the funnel plot is asymmetrical, this was tested using the Egger's test. No significant asymmetry was reported using the Egger's test ($p = 0.21$), indicating that publication bias was not present.

Appendix IV. Overview of median follow-up and median overall survival for individual studies

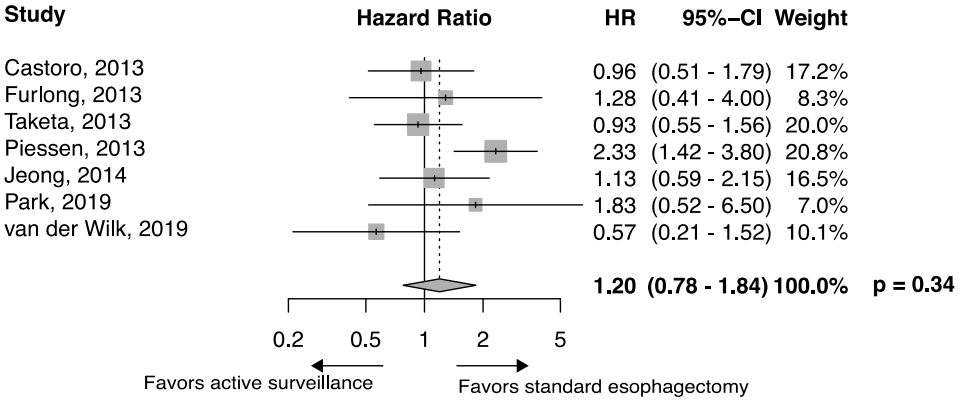
		Active surveillance			Standard esophagectomy		
Study		Patients	Follow-up**	OS***	Patients	Follow-up**	OS***
Castoro, 2013[29]	Unmatched	38	55 (32 - 96)	80 (19 - 94)	39	86 (66 - 113)	63 (17 - NR)
	Matched*	27	66 (32 – 96)	80 (26 – NR)	27	86 (72 – 113)	63 (19 – 105)
Furlong, 2013[20]	Unmatched	19	88 (64 - 88)	28 (16 - 84)	6	112 (111 - 112)	61 (12 - NR)
	Matched*	2	39 (39 – 39)	23 (6 – NR)	2	NR (NR – NR)	37 (35 – 38)
Taketa, 2013[21]	Unmatched	61	39 (29 - 62)	66 (28 - NR)	244	41 (19 - 54)	85 (32 - NR)
	Matched*	36	52 (38 - 86)	58 (26 - NR)	36	40 (25 - 60)	51 (16 - NR)
Piessen, 2013[32]	Matched*	59	52 (19 - 77)	40 (13 - 115)	118	69 (44 - 93)	NA (38 - NR)
Jeong, 2014[30]	Unmatched	31	57 (42 - 76)	36 (17 - NR)	39	71 (56 - 77)	72 (17 - NR)
	Matched*	26	57 (45 – 76)	36 (18 – NR)	26	62 (56 – 73)	35 (11 – NR)
Park, 2019[31]	Randomized	17	65 (48 - 68)	NR (23 - NR)	19	60 (49 - 71)	75 (75 - 75)
van der Wilk, 2019[22]	Unmatched	31	28 (20 - 47)	NR (40 - NR)	67	35 (25 - 51)	62 (33 - 62)
	Matched*	29	28 (20 - 47)	NR (40 - NR)	29	45 (18 - 51)	46 (20 - NR)
Overall	Matched		50 (45 – 56)			63 (59 – 68)	

*Matched according to propensity scores, **Median follow-up in months with (interquartile range),

***Median overall survival in months with (interquartile range)

OS: Overall Survival, NR: Not Reached

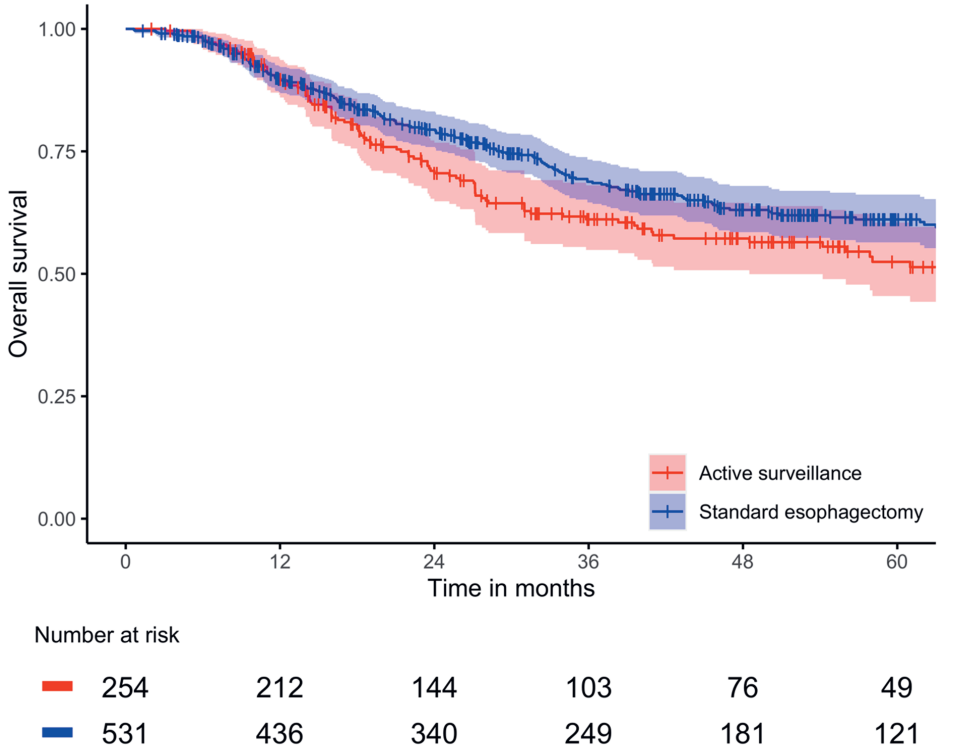
Appendix V. Random effects meta-analysis including unmatched patients



Heterogeneity: I^2 = 46%, (0% - 77%), Q = 11.01, df: 6, p = 0.09

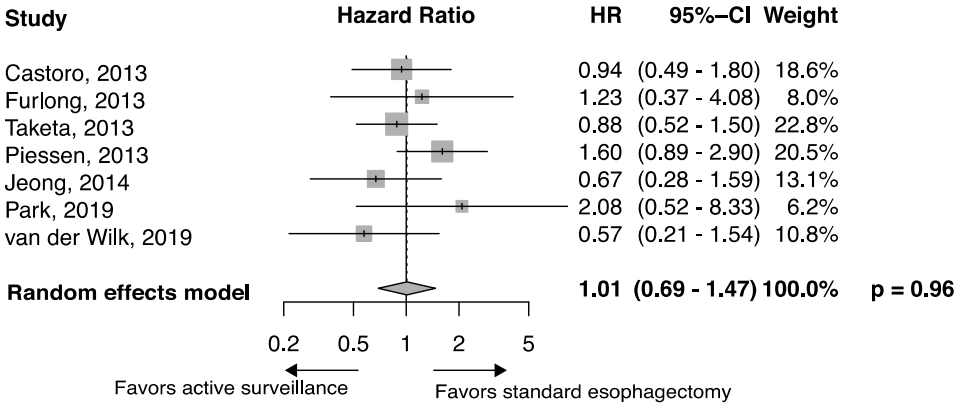
Unmatched random effects meta-analysis of risk of all-cause mortality for patients undergoing active surveillance compared to standard esophagectomy. The size of the squares represents the sample size of each individual study. The vertical line within the squares represents the hazard ratio of each individual study with corresponding 95% confidence intervals represented as the horizontal lines. Weights are determined according to sample size of the study and confidence intervals of hazard ratio. HR: Hazard Ratio, CI: Confidence Interval.

Appendix V. Kaplan Meier curves of unmatched patients



Pooled unmatched Kaplan-Meier curves with corresponding 95% confidence interval curves of overall survival for patients undergoing active surveillance or standard esophagectomy. These Kaplan–Meier do not account for any deviations from intended intervention. Additionally, the curves do not account for random effects or weights of individual studies. Therefore, no statistical analyses have been performed.

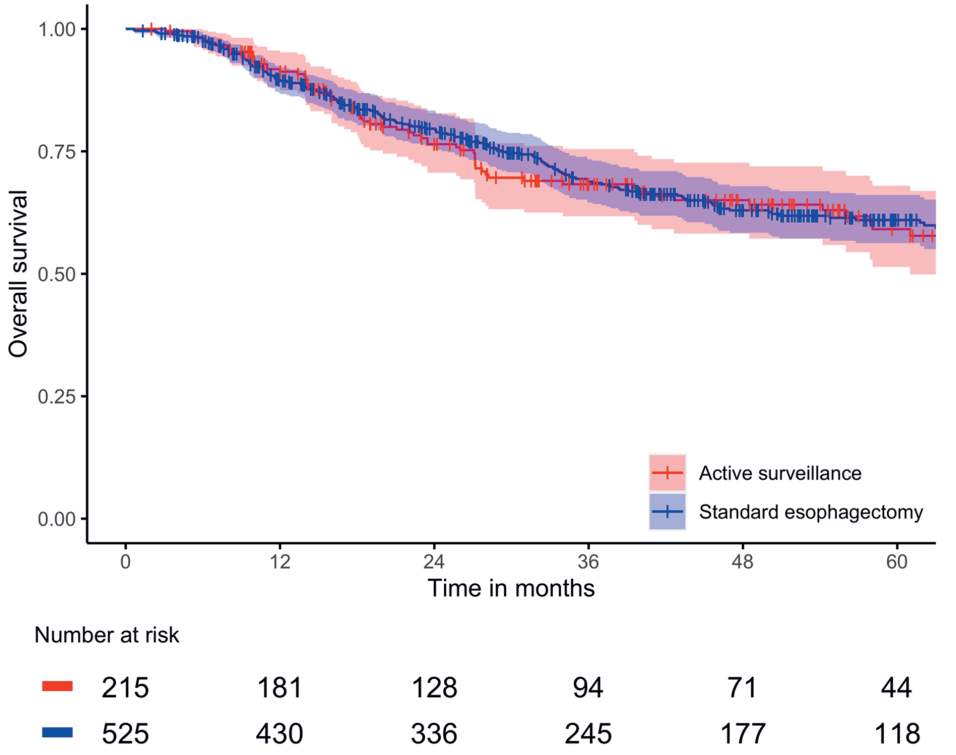
Appendix V. Per-protocol sensitivity meta-analysis including unmatched patients



Heterogeneity: I^2 = 0%, (0% - 70%), Q = 5.92, df: 6, p = 0.43

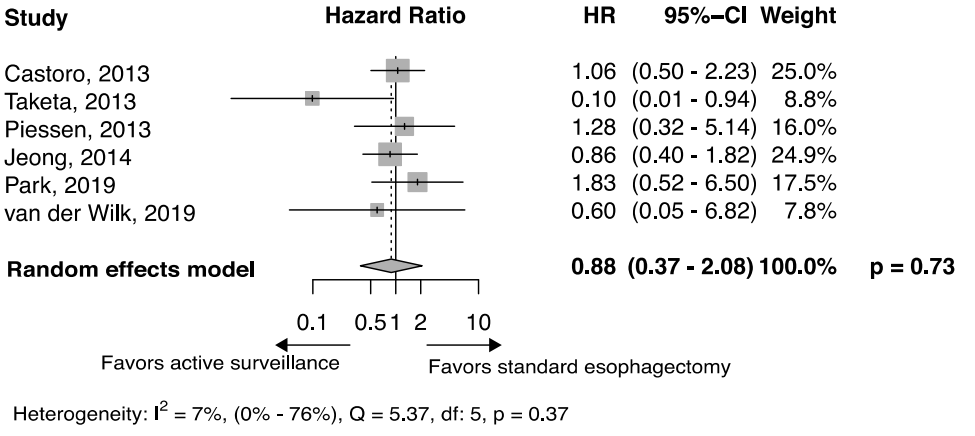
Unmatched per-protocol sensitivity analysis of risk of all-cause mortality for patients undergoing active surveillance compared to standard esophagectomy. The size of the squares represents the sample size of each individual study. The vertical line within the squares represent the hazard ratio of each individual study with corresponding 95% confidence intervals represented as the horizontal lines. Weights are determined according to sample size of the study and confidence intervals of hazard ratio. HR: Hazard Ratio, CI: Confidence Interval.

Appendix V. Kaplan Meier curves of per-protocol sensitivity analysis of unmatched patients



Pooled Kaplan-Meier curves with corresponding 95% confidence interval curves of overall survival for patients undergoing active surveillance or standard esophagectomy. These Kaplan–Meier curves represent the per-protocol sensitivity analysis of all patients from all studies. The curves do not account for random effects or weights of individual studies. Therefore, no statistical analyses have been performed.

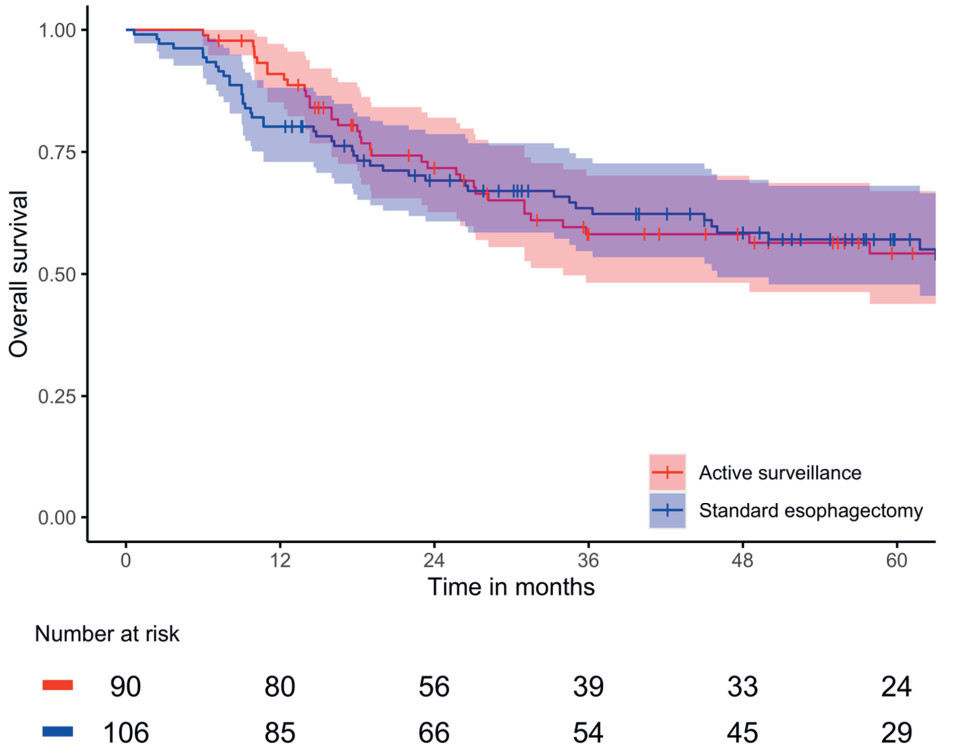
Appendix V. Meta-analysis including patients with squamous cell carcinoma



Heterogeneity: I^2 = 7%, (0% - 76%), Q = 5.37, df: 5, p = 0.37

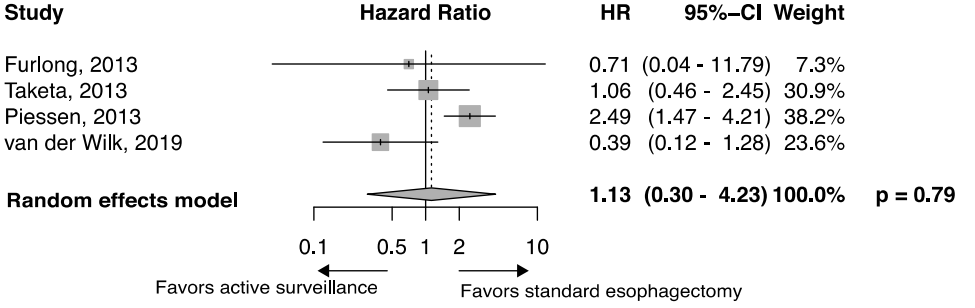
Random effects meta-analysis of risk of all-cause mortality for patients with squamous cell carcinoma undergoing active surveillance compared to standard esophagectomy after randomization or propensity score matching. The size of the squares represents the sample size of each individual study. The vertical line within the squares represents the hazard ratio of each individual study with corresponding 95% confidence intervals represented as the horizontal lines. Weights are determined according to sample size of the study and confidence intervals of hazard ratio. HR: Hazard Ratio, CI: Confidence Interval.

Appendix V. Kaplan Meier curves of patients with squamous cell carcinoma



Pooled Kaplan-Meier curves with corresponding 95% confidence interval curves of overall survival for patients undergoing active surveillance or standard esophagectomy. These Kaplan–Meier curves represent the patients with squamous cell carcinoma after randomization or propensity score matching. The curves do not account for random effects or weights of individual studies. Therefore, no statistical analyses have been performed.

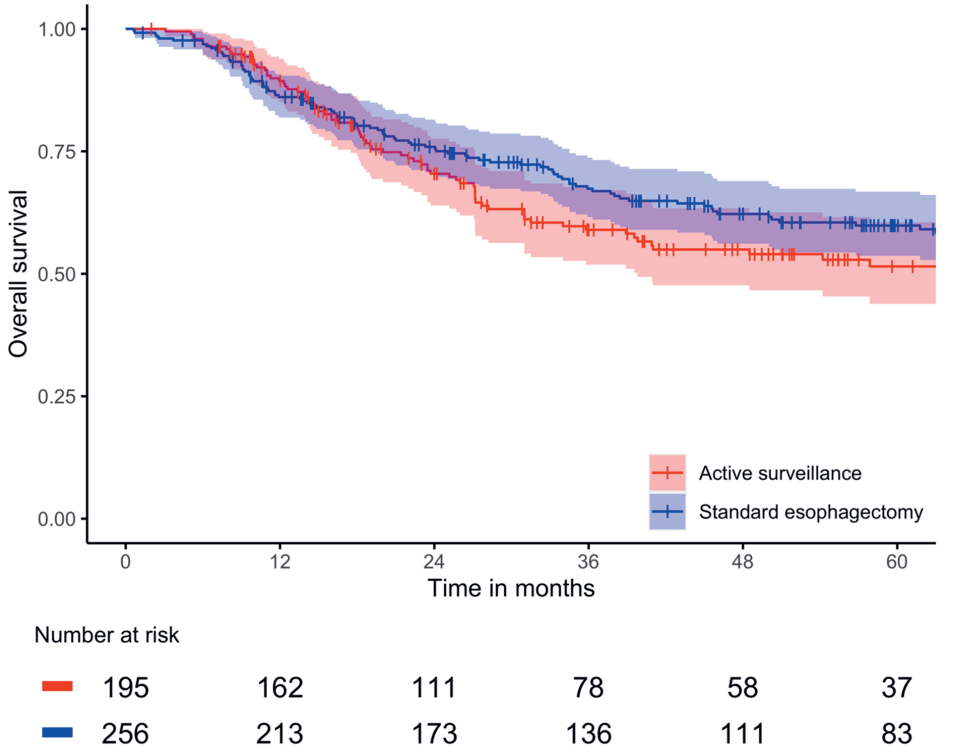
Appendix V. Meta-analysis including patients with adenocarcinoma



Heterogeneity: I^2 = 68%, (7% - 89%), Q = 9.34, df: 3, p = 0.03

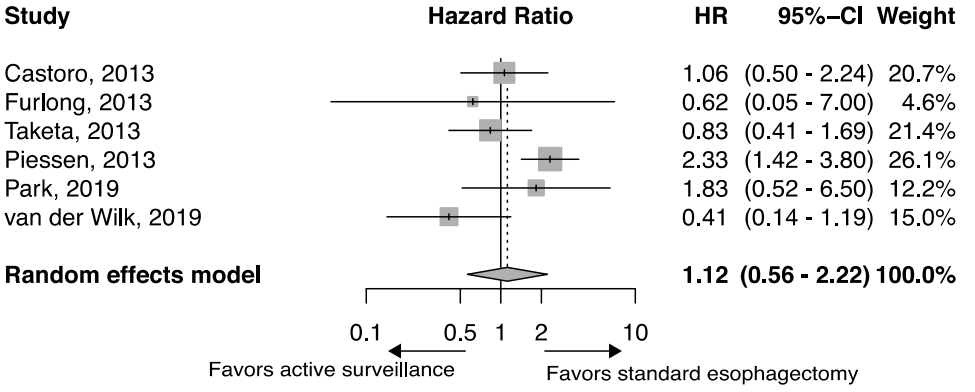
Random effects meta-analysis of risk of all-cause mortality for patients with adenocarcinoma undergoing active surveillance or standard esophagectomy after randomization or propensity score matching. The size of the squares represents the sample size of each individual study. The vertical line within the squares represents the hazard ratio of each individual study with corresponding 95% confidence intervals represented as the horizontal lines. Weights are determined according to sample size of the study and confidence intervals of hazard ratio. HR: Hazard Ratio, CI: Confidence Interval.

Appendix V. Kaplan Meier curves of patients with adenocarcinoma



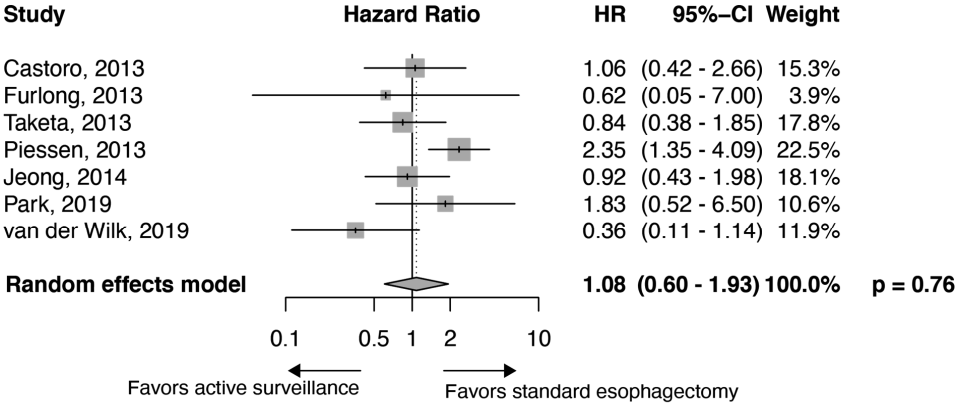
Pooled Kaplan-Meier curves with corresponding 95% confidence interval curves of overall survival for patients undergoing active surveillance or standard esophagectomy. These Kaplan–Meier curves represent the patients with adenocarcinoma after randomization or propensity score matching. The curves do not account for random effects or weights of individual studies. Therefore, no statistical analyses have been performed.

Appendix V. Sensitivity analysis after exclusion of the study by Jeong et al.



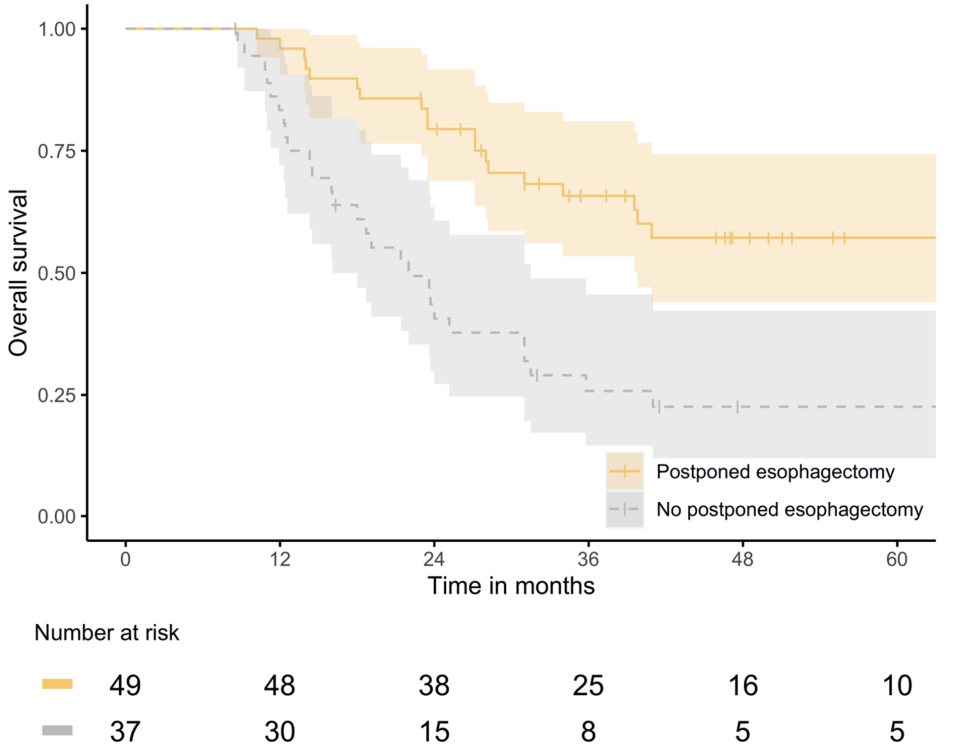
Heterogeneity: I^2 = 59%, (0% - 84%), Q = 12.31, df: 5, p = 0.031

Appendix V. Sensitivity analysis for overall survival truncated at 36 months of follow-up



Heterogeneity: I^2 = 49%, (0% - 79%), Q = 11.83, df: 6, p = 0.07

Appendix VI. Kaplan Meier curves of patients who had isolated locoregional recurrence and underwent postponed esophagectomy versus patients who had isolated locoregional recurrence and did not undergo postponed esophagectomy



Pooled Kaplan-Meier curves with corresponding 95% confidence interval curves of overall survival for patients undergoing active surveillance. These Kaplan–Meier curves represent patients with locoregional recurrence (without synchronous distant metastases) during active surveillance either undergoing postponed surgery or not undergoing postponed surgery. The curves do not account for random effects or weights of individual studies. Therefore, no statistical analyses have been performed.

15

Chapter 15

Updated protocol of the SANO-trial: a stepped-wedge cluster randomised trial comparing surgery with active surveillance after neoadjuvant chemoradiotherapy for oesophageal cancer.

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**Both authors contributed equally to this work*

Trials. 2021 May 17 17;22(1):345

Abstract

Background

The Surgery As Needed for Oesophageal cancer (SANO) trial compares active surveillance with standard oesophagectomy for patients with a clinically complete response (cCR) to neoadjuvant chemoradiotherapy. The last patient with a clinically complete response is expected to be included in May 2021. The purpose of this update is to present all amendments to the SANO trial protocol as approved by the Institutional Research Board (IRB) before accrual is completed.

Design

The SANO trial protocol has been published (https://doi.org/10.1186/s12885-018-4034-1). In this ongoing, phase-III, non-inferiority, stepped-wedge, cluster randomised controlled trial, patients with cCR (*i.e.* after neoadjuvant chemoradiotherapy no evidence of residual disease in two consecutive clinical response evaluations [CREs])) undergo either active surveillance or standard oesophagectomy. In the active surveillance arm, CREs are repeated every 3 months in the first year, every 4 months in the second year, every 6 months in the third year, and yearly in the fourth and fifth year. In this arm, oesophagectomy is offered only to patients in whom locoregional regrowth is highly suspected or proven, without distant metastases. The primary endpoint is overall survival.

Update

Amendments to the study design involve the first cluster in the stepped-wedge design being partially randomised as well and continued accrual of patients at baseline until the predetermined number of patients with cCR is reached. Eligibility criteria have been amended, stating that patients who underwent endoscopic treatment prior to neoadjuvant chemoradiotherapy cannot be included and that patients who have highly suspected residual tumour without histological proof can be included. Amendments to the study procedures include that patients proceed to the second CRE if at the first CRE the outcome of the pathological assessment is uncertain and that patients with a non-passable stenosis at endoscopy are not considered cCR. The sample size was recalculated following new insights on response rates (34% instead of 50%) and survival (expected 2-year overall survival of 75% calculated from moment of reaching cCR instead of 3-year overall survival of 67% calculated from diagnosis). This reduced the number of required patients with cCR from 264 to 224, but increased the required inclusions from 480 to approximately 740 patients at baseline.

Conclusion

Substantial amendments were made prior to closure of enrolment of the SANO trial. These amendments do not affect the outcomes of the trial compared to the original protocol. The first results are expected late 2023. If active surveillance plus surgery as needed after neoadjuvant chemoradiotherapy for oesophageal cancer leads to non-inferior overall survival compared to standard oesophagectomy, active surveillance can be implemented as a standard of care.

Update

Introduction

The Surgery As Needed for Oesophageal cancer (SANO) trial is an ongoing phase-III trial that compares active surveillance with standard oesophagectomy for patients with a clinically complete response (cCR; i.e. no evidence of residual disease on diagnostics) to neoadjuvant chemoradiotherapy for oesophageal or oesophagogastric junctional cancer.[1] The trial is designed as a non-inferiority, multi-centre, stepped-wedge, cluster randomised controlled trial. Primary aim is to assess the effectiveness of active surveillance compared to standard oesophagectomy.

Patients are recruited from 12 high-volume centres in the Netherlands. After completion of neoadjuvant chemoradiotherapy (CROSS regimen),[2] two clinical response evaluations (CREs) are performed; the first (CRE-1) at 4-6 weeks and the second (CRE-2) at 10-14 weeks after completion of neoadjuvant chemoradiotherapy. CRE-1 consists of endoscopy with bite-on-bite biopsies and CRE-2 consists of 18F-FDG PET/CT, followed by endoscopy with bite-on-bite biopsies and endoscopic ultrasonography (EUS) with fine-needle aspiration of suspected lymph nodes. If a patient has cCR at CRE-2, the patient will be assigned to either standard oesophagectomy or active surveillance, depending on which study arm the participating hospital was recruiting for (according to the stepped-wedge, cluster randomised design).[1] If locoregional residual or distant disease is detected during one of these CREs, the patient is excluded from further follow-up within the study.

Patients in the active surveillance arm undergo diagnostic evaluations similar to CRE-2 every 3 months in the first year, every 4 months in the second year, every 6 months in the third year, and yearly in the fourth and fifth year. During active surveillance, oesophagectomy will be offered only to patients in whom locoregional regrowth is highly suspected or proven in the absence of distant metastasis.

Ethical approval for the study has been obtained from the institutional review board (IRB) of the Erasmus MC (MEC2017–392). The trial has been registered in the Netherlands Trial Register (NTR 6803) and is being conducted in accordance with the Declaration of Helsinki (10th version, Fortaleza, 2013) and the Dutch Medical Research Involving Human Subjects Act (WMO).

The original SANO trial protocol has been published in BMC Cancer in 2018 (https://doi.org/10.1186/s12885-018-4034-1).[1] Patient accrual has been started in November 2017 and the last patient with a clinically complete response is expected to be included in May 2021.

Following the publication of the protocol and start of the trial, amendments have been made to the protocol to reflect new insights about the accuracy of the CREs and survival of the study population

and to further clarify the protocol regarding study procedures. The amendments to the protocol have been approved by the IRB of the Erasmus MC. The purpose of this update is to present all amendments to the SANO trial protocol before accrual will be completed.

Study design

Two amendments have been made to the study design.

According to the stepped-wedge cluster randomised trial design, clusters of centres are randomised from the control arm to the experimental study arm. The initial trial protocol stated that the centres in the first cluster would not be randomly determined, but would consist of Erasmus Medical Centre (coordinating centre and sponsor of the trial) and Zuyderland Medical Centre. Both centres have extensive experience in performing CREs and included a large number of patients in the preSANO-trial, ensuring maximal safety for introduction of the novel active surveillance strategy.[3] Meanwhile, there was another centre that gained extensive experience within the preSANO-trial. To provide a random effect to this first cluster but ensure optimal patient safety, we randomly assigned either Zuyderland Medical Centre or Catharina Hospital to the first cluster together with the Erasmus MC. Since the cCR rate and the rate of cross-over is variable (see statistical analysis), it is not possible to determine an exact number of patients that need to be included at baseline to end up with exactly the correct number of patients with cCR. Therefore, to ensure that we do not end up with a sample size that is too small and thus an underpowered trial, we will continue including patients at baseline until we reach the predetermined number of patients with cCR. As a result, some patients will be included at baseline but will not have reached the moment of cCR yet, while the baseline enrolment of the trial will be stopped. These additional patients will be included in the analysis of the trial to increase the statistical power.

Study population

Three amendments have been made to the eligibility criteria.

First, a new exclusion criterion has been added to the protocol to exclude patients who have had diagnostic or therapeutic endoscopic treatment (*e.g.* endoscopic mucosal resection or endoscopic submucosal dissection) before the start of neoadjuvant chemoradiotherapy. According to the eligibility criteria of the initial protocol, these patients could have been included in the trial at this moment. However, since the oesophageal tumour, and especially the luminal side of the tumour, has

been largely removed by the endoscopic resection, accurate detection of locoregional residual disease by means of endoscopic bite-on-bite biopsies and follow-up with PET/CT might be hampered. These patients are probably at increased risk of having undetected residual disease during the CREs and are thus possibly at increased risk of developing a non-resectable regrowth.
Second, a small number of patients could not decide to participate in the SANO trial before chemoradiotherapy was started. Since the first CRE is not planned until 4-6 weeks after completion of chemoradiotherapy, the trial protocol was amended to allow patients to be included during or shortly after completion of chemoradiotherapy. This might result in some missing baseline health-related quality of life questionnaires.
Third, the initial trial protocol dictated that patients with histologically proven squamous cell carcinoma or adenocarcinoma are eligible. An amendment was made that whenever pathology is inconclusive but a multidisciplinary tumour board concludes that there are sufficient (clinical) arguments for the diagnosis of oesophageal carcinoma (e.g. because of a radiologically, endoscopically and/or endosonographically highly suspected lesion) and subsequent treatment is neoadjuvant chemoradiotherapy followed by surgery, patients are eligible for the study as well. This situation occurs, however, very rarely. An example of such a situation is: a patient who is known with a history of Barrett's oesophagus presents with increasing dysphagia and weight loss. Endoscopy shows a tumorous lesion within the Barrett segment in the distal oesophagus, of which biopsies are taken. Endoscopic ultrasonography shows a cT3 tumour without positive lymph nodes. The PET/CT scan shows an intense FDG-avid lesion in the distal oesophagus without positive lymph nodes and no distant metastases. The diagnostic CT scan also shows a distal oesophageal tumour without nodal and distant metastases. Eventually, pathology of the biopsies shows high-grade dysplasia, with suspicion of but unconfirmed invasive carcinoma. Despite the absence of confirmation of invasive carcinoma, the patient is enrolled in the SANO trial and neoadjuvant chemoradiotherapy is started.

Study algorithm

Four amendments have been made to the study algorithm.
First, the targeting of endoscopic biopsies can be hindered and the pathological assessment of residual tumour cells in the biopsy specimen at CRE-1 can be unreliable due to radiation effects and inflammation. To avoid a high rate of false-positives at CRE-1 and since it is known that surgery can be safely postponed up to 10-14 weeks after completion of chemoradiotherapy, patients proceed to

CRE-2 if the outcome of the pathological assessment is uncertain at CRE-1.[4, 5] Of note, if patients have uncertain outcome of the pathological assessment of the biopsy specimen at CRE-2, patients will not be allowed to continue in the trial and will undergo surgery, as information on the safety of further postponement of surgery is lacking.

Second, the initial trial protocol described that at CRE-2, patients with (cyto)histological evidence of locoregional residual disease or highly suspected locoregional residual disease on PET/CT without distant metastases will undergo surgery, whereas patients without (cyto)histological evidence of residual disease are considered cCR. We clarified the protocol and stated that patients who have suspected lymph nodes on EUS which are unreachable with fine-needle aspiration are not considered cCR. If in the short term no representative cytology can be obtained from suspected lymph nodes during CRE-2, the patient will also not be considered cCR.

Third, the accuracy of endoscopic bite-on-bite biopsies is compromised if a smaller biopsy instrument is being used, for instance a paediatric endoscope. For this reason, we amended the protocol to state that patients who have a stenosis which cannot be passed with a normal Q-endoscope during endoscopy at CRE-1 or CRE-2 will not be considered cCR, regardless of traversability with the paediatric endoscope. Comparably, in patients who have a stenosis that cannot be passed with the ultrasound endoscope during CRE-II an ultrasonographic assessment of lymph nodes cannot be performed beyond the stenosis, compromising complete assessment of the regional lymph nodes. Therefore, patients with a non-passable stenosis during EUS will not be considered cCR.

Fourth, the initial trial protocol dictated that CRE and surveillance biopsies with uncertain outcome or with high-grade dysplasia would have to be revised at the Department of Pathology of the Erasmus MC. However, often this is not logistically feasible, as for safety reasons patients have to undergo surgery as soon as possible after a positive biopsy. Therefore, the amendment states that biopsies can be revised by a second independent expert GI pathologist in the participating centre following the same strategy, using a standard protocol. In case of discordant results, the specimens will be reviewed by a third independent expert GI pathologist and a consensus diagnosis should be reached if at least two pathologists agree. In case the revision concludes high-grade dysplasia, the CRE will be considered positive. In case the results remain uncertain, a multidisciplinary tumour board at the Erasmus MC will reach consensus on further treatment, taking into account the condition of the patient and other diagnostic modalities such as 18-FDG PET-CT.

Follow-up

One amendment has been made to the follow-up of patients.

To compare distant dissemination between both treatment arms, the initial trial protocol described that patients included in the standard surgery arm have to undergo PET-CT scans at 12 and 24 months after neoadjuvant chemoradiotherapy. However, the rationale for the timing of these scans was a 12 and 24 months follow-up period after surgery in the standard surgery arm, which translates to a longer follow-up period when calculated from completion of neoadjuvant chemoradiotherapy. To reach sufficient follow-up time for the development of metastases and thus make a fairer comparison between the two study arms, the timing at which the follow-up PET/CT scans are planned in the standard surgery arm have been changed from 12 and 24 months to 16 and 30 months after neoadjuvant chemoradiotherapy. These points in time match the sixth and ninth clinical response evaluations (CRE-6 and CRE-9) in the active surveillance arm at which PET/CT scans are also made. In this way, a distant dissemination rate can be calculated at these exact points in time.

Study parameters/endpoints

No amendments have been made to the study parameters/endpoints.

Safety and stopping rules

No amendments have been made to the safety and stopping rules.

Statistical analysis

One amendment has been made to the statistical analysis.

Initially, it was calculated that 264 patients with cCR would be required to demonstrate that active surveillance is non-inferior to standard surgery. For this sample size calculation, an expected 3-year overall survival of 67%, non-inferiority margin of 15%, intra-centre correlation coefficient of 0.02, power of 80% and significance level of 0.05 were used. These survival data were based on the CROSS trial and defined from the moment of randomisation (i.e. pre-treatment).[2, 6] Based on preliminary data of the preSANO trial, the initial sample size calculation accounted for a 50% cCR rate and a 12% drop-out rate (*e.g.* patients with cCR within the surgery arm who request active surveillance-arm, or vice versa; so called cross-over patients). Moreover, to reduce the number of newly included patients

needed and to optimally use the data from the preSANO trial, 60 patients with cCR from the preSANO trial were expected to be included in the SANO trial.
Based on the final data of the preSANO trial and monitoring data of the first part of the SANO trial, it appeared that the cCR rate was 34% and the crossover percentage was 20%. Moreover, it appeared that only 29 instead of 60 patients with cCR from the preSANO trial met all criteria of the SANO trial and could be included. Also, new data on survival of patients with cCR after neoadjuvant chemoradiotherapy have become available.[7] Based on these data, the sample size has been recalculated. The sample size was recalculated with expected 2-year overall survival of 75%, defined from the moment at which patients reach cCR (which is approximately 5 months after diagnosis). Accordingly, the sample size was recalculated with the predetermined power of 80%, significance level of 0.05, non-inferiority margin of 15% and intra-centre correlation coefficient of 0.02. As a result, 224 patients (*i.e.* 112 patients in each arm) with cCR will have to be enrolled in the trial. With a crossover rate of 20%, the total number of required inclusions will be 280 (= 224 / 0.8) patients with cCR. Taking into account that 29 patients with cCR that can be included from the preSANO trial and a cCR rate of 34%, this will translate into approximately 740 patients required at baseline.
Simulating trial outcomes on 2-year overall survival calculated from moment of cCR (approximately 5 months after diagnosis) is justified compared to 3-year overall survival calculated from diagnosis, as the power and significance levels are maintained and our primary endpoint will remain overall survival. Two year is a commonly used minimum follow-up time for comparable oncological trials, which is expected to capture the most relevant data for the short-term analysis. Moreover, the short-term results of the trial and thus the potential implementation of active surveillance as alternative treatment strategy can be performed a year earlier, avoiding unnecessary delay of providing organ sparing treatment for patients with locally advanced oesophageal cancer. Importantly, long-term analyses will be performed after the last included patient finished the active surveillance protocol (minimum follow-up of 5 year), as was previously defined.

Ethical and regulatory considerations

No amendments have been made to the ethical and regulatory considerations.

In conclusion, substantial amendments were made prior to closure of enrolment of the SANO trial. These amendments do not affect the outcomes of the trial compared to the original protocol. The last

patient with a clinically complete response is expected to be included in May 2021. Guaranteeing a minimum follow-up of 2 years, the first results are expected late 2023.

References

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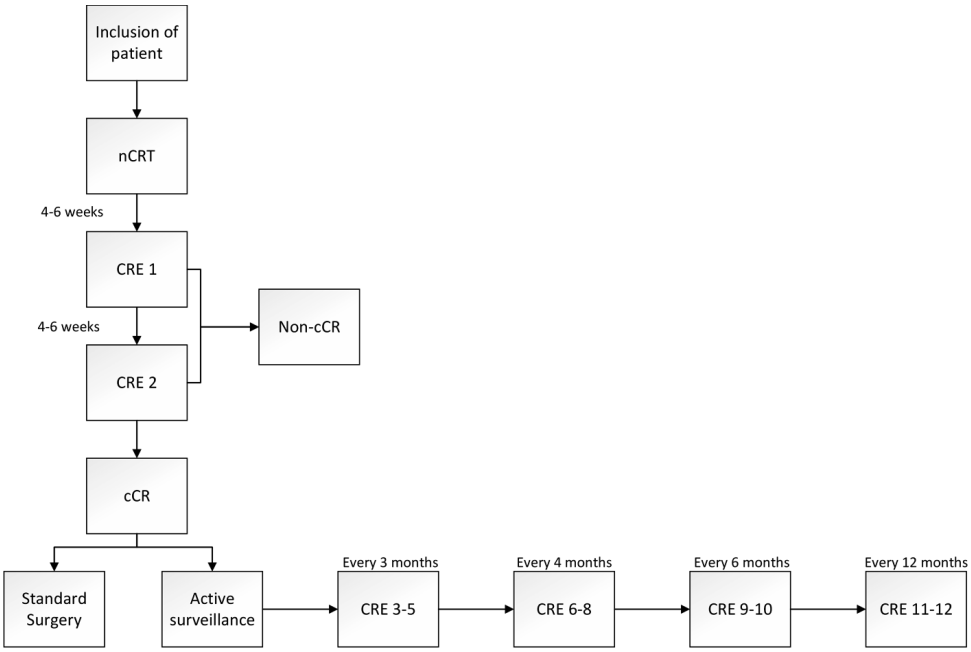

Figure 1. Schematic overview of the SANO-trial, comparing active surveillance versus standard surgery in patients with esophageal cancer and a clinically complete response after neoadjuvant chemoradiotherapy. Patients in whom no residual tumor is detected after neoadjuvant chemoradiotherapy are considered a clinically complete responder, patients who do not have a clinically complete response (non-cCR) undergo esophagectomy if no distant metastases are detected. If patients have residual disease at CRE 3-12, postponed esophagectomy will be performed if no distant metastases are detected and no subsequent CREs will be performed. nCRT: neoadjuvant chemoradiotherapy, CRE: clinical response evaluation, cCR: clinically complete responder.

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Chapter 16

Summary in English

Samenvatting in Nederlands

Summary in English

Esophageal cancer remains a disease with a poor prognosis. Improvement of overall survival was reached mostly after the introduction of additional therapies prior to surgery or perioperatively. Since nearly one-third of patients with esophageal cancer have a pathologically complete response (*i.e.* no vital tumor cells in the resection specimen), the benefit of standard esophagectomy for every patient after chemoradiotherapy has been topic of debate. The SANO-trial compares an active surveillance strategy with standard esophagectomy for patients with a clinically complete response after neoadjuvant chemoradiotherapy. A clinically complete response is identified in those patients in whom no tumor cells can be detected with clinical response evaluations, consisting of PET-CT, endoscopic bite-on-bite biopsies and endoscopic ultrasound. As of December 2020, the inclusion phase of the SANO-trial has been completed. The short-term analysis of overall survival will be performed after a minimum follow-up of two years. This thesis consists of three parts; studies aimed at improving clinical response evaluations are described in **Part I**, studies comparing open with hybrid and totally minimally invasive esophagectomy are described in **Part II** and studies aimed at improving shared decision making for active surveillance and studies describing current knowledge on overall survival after active surveillance are described in **Part III**.

Part I: Improving clinical response evaluations

Standard treatment of locally advanced esophageal cancer consists of (neo)adjuvant treatment followed by esophagectomy. Two treatments which are widely used are neoadjuvant chemoradiotherapy and perioperative chemotherapy and no clear benefit for either treatment exists. An overview is provided in **Chapter 2.** A modest benefit was described by several retrospective studies concerning pathologically complete response rate for neoadjuvant chemoradiotherapy compared to other treatments (*e.g.* perioperative chemotherapy). An active surveillance strategy was proposed for those patients. It is reported, however, that 23% of patients with a clinically complete response still have residual tumor after two clinical response evaluations. These patients were falsely classified as pathologically complete responder. The exact location of these undetected tumors in the resection specimen of patients was described in **Chapter 3**. It was reported that the majority (nearly two-thirds) of missed residual tumors were located in the mucosa of the esophageal wall, and nearly one-third of the tumors was located in the submucosa, underneath a tumor-free mucosa. Only a small minority (4%) of patients had tumor in the deeper layers of the esophageal wall, underneath a tumor-

free mucosa ánd submucosa. Possibly, these mucosal tumors could be identified by the gastroenterologist using endoscopy. The predictive value of several esophageal findings for the presence of esophageal cancer was assessed in **Chapter 4**. It was reported that endoscopic suspicion as reported by the gastroenterologist had a high positive predictive value for the presence of esophageal cancer. Other findings (*e.g.* relative esophageal stenosis, scar tissue and ulceration), were not associated with the presence of esophageal cancer. Besides residual tumor at the site of the primary tumor within the esophageal wall, locoregional lymph nodes should be assessed as well to determine whether a patient has a clinically complete response. In **Chapter 5** the value of endoscopic ultrasound and fine-needle aspiration of lymph nodes for the detection of residual nodal disease after neoadjuvant chemoradiotherapy is described. In this chapter it is reported that malignant lymph nodes were classified accordingly using endoscopic ultrasound in 50% of cases. Most lymph nodes that were not detected resided at the distal lymph node stations (*e.g.* lesser curvature). Fine-needle aspiration after neoadjuvant chemoradiotherapy showed uncertain outcomes in over 40% of procedures. The classical criteria for suspected lymph nodes (determined prior to chemoradiotherapy: diameter >5 millimeter, hypo-echogenic and) did not seem to hold after neoadjuvant chemoradiotherapy. Although PET-CT reported high rate of false-positives due to radiation-induced esophagitis at twelve weeks after completion of neoadjuvant chemoradiotherapy, the use of serial PET-CT's beyond twelve weeks was hypothesized to lead to improved accuracy for detecting local residual tumor. In **Chapter 6** the efficacy of PET-CT during active surveillance was described. It was reported that serial PET-CT could be a useful tool to detect locoregional disease and that the increased FDG-uptake due to radiation-induced esophagitis had mostly resolved 11 months after completion of neoadjuvant chemoradiotherapy.

Part II: Comparing surgical approaches

During clinical response evaluations, residual disease is still detected in the majority of patients. Hence, esophagectomy will remain the cornerstone treatment for locally advanced esophageal cancer. An esophagectomy is associated with mortality, morbidity and lasting symptoms. To decrease these negative effects of surgery, several minimally invasive techniques have been developed. Short-term advantages were described for both totally minimally invasive and laparoscopically assisted (hybrid) esophagectomy compared to open esophagectomy in the TIME trial and the MIRO-trial, respectively. The incidence of postoperative complications, health-related quality of life and lasting

symptoms one year after surgery were described in **Chapter 7 and 8**. The rate of pneumonia was lower and the rate of anastomotic leakage was higher for patients undergoing totally minimally invasive Ivor Lewis esophagectomy, compared to hybrid Ivor Lewis esophagectomy. Patients who underwent hybrid esophagectomy had more often and more severe chest pain compared to patients undergoing totally minimally invasive esophagectomy.

Part III: Towards active surveillance

Active surveillance might partly replace standard esophagectomy for patients with a clinically complete response after neoadjuvant chemoradiotherapy. In **Chapter 9** the evolution towards active surveillance, the challenges and the current literature on active surveillance for locally advanced esophageal cancer have been described. Several clinical and pathological factors (*i.e.* baseline global HRQOL, World Health Organisation (WHO) performance score, tumor histology, tumor stage and tumor location) prior to any treatment were assessed for their predictive value of a poor postoperative health-related quality of life in **Chapter 10**. Patients with high baseline global HRQOL and patients with stage 1-2 tumor suffered from a more severe deterioration in postoperative HRQOL than patients with low baseline global HRQOL or patients with stage 3 tumor, respectively.

If active surveillance is indeed proven non-inferior based on the results of the SANO-trial, treating physicians will offer active surveillance as one of the treatment alternatives in the standard treatment. The pros and cons of both active surveillance or standard esophagectomy emphasize the need for shared decision making. An overview of interventions that facilitate shared decision making for patients who have to make a decision, in which active surveillance is one of the treatment options, is described in **Chapter 11**. It was reported that these interventions were scarce and that the efficacy of these interventions were mostly assessed using short-term outcomes. Patients' preferences for either active surveillance or esophagectomy one year after they had undergone esophagectomy themselves, is described in **chapter 12**. It was reported that over a quarter of patients who had undergone neoadjuvant chemoradiotherapy followed by standard esophagectomy, would choose not to undergo this treatment again, but would have picked active surveillance instead. These patients would trade off five-year survival to obtain HRQOL which is much better than their own. Five-year survival and long-term HRQOL were most important factor for patients to determine which treatment they preferred. Currently, some patients already refuse surgery and choose to undergo active surveillance themselves. In **Chapter 13**, the overall survival of patients who refused surgery

themselves and underwent active surveillance was compared to patients who underwent standard esophagectomy, after having reached a clinically complete response to neoadjuvant chemoradiotherapy. After propensity score matching, 58 patients (two groups of 29 patients) were compared and showed comparable overall survival, suggesting active surveillance would be safe in patients with a clinically complete response. This study comprised, however, only a small group of patients. In **Chapter 14** we systematically searched all available literature on active surveillance for patients with esophageal cancer and a clinically complete response after chemoradiotherapy worldwide. After selection of seven studies, authors were contacted to supply individual patient data. Pooled analysis reported that overall survival of patients with a clinically complete response after chemoradiotherapy was comparable between active surveillance and standard esophagectomy. One of the conclusions was that active surveillance will not be part of standard treatment until results of randomized trials have been published. One of these trials is the stepped-wedge, cluster randomized SANO-trial, of which the inclusion period has been completed. During the SANO-trial, several amendments of the protocol have been submitted. An update of the definitive protocol of the SANO-trial before the start of any analyses has been described in **Chapter 15**. The first analyses of the SANO-trial will be performed after a minimal follow-up of two years. The results of this study will definitively answer whether or not active surveillance can be part of standard treatment for patients with locally advanced esophageal cancer and a clinically complete response after neoadjuvant chemoradiotherapy.

Samenvatting in Nederlands

Slokdarmkanker betreft een ziekte met een slechte prognose. De introductie van (neo)adjuvante therapieën resulteerde in een verbetering van de algehele overleving bij deze patiënten. Bijna een derde van de patiënten heeft een pathologisch complete respons na preoperatieve (neoadjuvante) chemoradiatie. Hierbij wordt geen vitale resttumor meer teruggevonden in het resectiepreparaat. Deze patiënten reageren zó goed op de chemoradiatie, dat een slokdarmresectie bij hen wellicht niet meer nodig is. De waarde van een standaard slokdarmresectie bij álle patiënten na chemoradiatie is daarom onderwerp van discussie bij patiënten met een klinisch complete respons. Een klinisch complete respons na neoadjuvante chemoradiatie wordt vastgesteld met behulp van responsevaluaties bestaande uit PET-CT, endoscopie met *bite-on-bite* biopten en endo-echografie met dunne-naald aspiratie van verdachte lymfeklieren. Eerder onderzoek toonde aan dat 77% van de resttumoren konden worden gedetecteerd met responsevaluaties. Een actieve surveillance beleid zou voordelig kunnen zijn voor patiënten die goed reageren op neoadjuvante chemoradiatie. Bij actieve surveillance worden regelmatig klinische responsevaluaties uitgevoerd en wordt een slokdarmresectie alleen verricht indien resttumor histologisch is aangetoond. In de SANO-trial (*Surgery As Needed for Oesophageal cancer*) wordt een beleid van actieve surveillance vergeleken met standaard slokdarmresectie bij patiënten met lokaal gevorderd slokdarmkanker en een klinisch complete respons na neoadjuvante chemoradiatie. De inclusiefase van deze SANO-trial is voltooid in december 2020. De analyse van de middellange-termijn resultaten zal plaatsvinden na een minimale follow-up van de patiënten van twee jaar. Dit proefschrift beschrijft de onderzoeksresultaten van studies die voornamelijk zijn gericht op het verbeteren van het toekomstig actieve surveillance beleid. Het proefschrift bestaat uit drie delen. In **Deel I** worden studies beschreven met als doel om de nauwkeurigheid van klinische responsevaluaties te verbeteren. Toch zal de meerderheid van de patiënten na chemoradiatie nog een slokdarmresectie moeten ondergaan. In **Deel II** worden verschillende chirurgische technieken voor een slokdarmresectie met elkaar vergeleken. Tot slot wordt in **Deel III** beschreven hoe het beslisproces van patiënten ondersteund zou kunnen worden en wat de huidige stand van zaken is omtrent de algehele overleving na actieve surveillance.

Deel I: verbeteren van de nauwkeurigheid van klinische responsevaluaties

De standaardbehandeling van lokaal gevorderde slokdarmkanker bestaat hoofdzakelijk uit (neo)adjuvante therapie gevolgd door een slokdarmresectie. De (neo)adjuvante therapieën die

wereldwijd worden uitgevoerd zijn neoadjuvante chemoradiatie en perioperatieve chemotherapie. Een overzicht van de verschillende vormen van (neo)adjuvante therapieën voor lokaal gevorderde slokdarmkanker wordt beschreven in **Hoofdstuk 2**. Een bescheiden voordeel wordt beschreven voor neoadjuvante chemoradiatie ten opzichte van perioperatieve chemotherapie wat betreft het percentage patiënten met een pathologisch complete respons. Een actief surveillance beleid zou mogelijk kunnen zijn voor deze subgroep van patiënten die goed reageert op neoadjuvante chemoradiatie. Echter, eerder onderzoek wees uit dat 23% van de patiënten met een klinisch complete respons, toch nog resttumor in de slokdarm heeft na twee klinische responsevaluaties. De locatie van deze gemiste resttumoren is onderzocht in **Hoofdstuk 3**. Hierin werd beschreven dat de meerderheid (bijna twee derde) van de gemiste resttumoren gelokaliseerd was in de mucosa van de slokdarm. Bijna een derde van de gemiste resttumoren bleek gelokaliseerd in de submucosa, onder een tumorvrije mucosa. Slechts een fractie (4%) van de gemiste resttumoren was gelokaliseerd in de diepere lagen van de slokdarm, onder een tumorvrije mucosa én submucosa. Mucosale tumoren zouden mogelijk gedetecteerd kunnen worden door de MDL-arts middels endoscopie. Verschillende endoscopische kenmerken van de slokdarm na neoadjuvante chemoradiatie werden onderzocht op potentieel voorspellende waarde voor de aanwezigheid van resttumor. Indien de MDL-arts verdachte laesies zag tijdens endoscopie, dan bleek dit vaak resttumor te betreffen. De aanwezigheid van andere specifieke aspecten van de slokdarm (zoals relatieve vernauwing, littekenweefsel of ulceratie) bleek niet voorspellend voor de aanwezigheid van resttumor. Naast de aanwezigheid van resttumor in de slokdarm, kan er ook resttumor aanwezig zijn in de regionale lymfeklieren. In **Hoofdstuk 5** wordt beschreven wat de waarde is van endo-echografie in combinatie met dunnenaald aspiratie van verdachte lymfeklieren na neoadjuvante chemoradiatie. In dit hoofdstuk werd beschreven dat 50% van de maligne lymfeklieren kon worden geïdentificeerd middels endo-echografie. De meeste klieren die niet konden worden geïdentificeerd waren distaal gelokaliseerd (d.w.z. nabij de kleine curvatuur van de maag). Dunnenaald aspiratie resulteerde in een niet te beoordelen uitslag bij 40% van de procedures. In het algemeen worden lymfeklieren als maligne beschouwd indien zij, vooraf aan chemoradiatie, voldoen aan 3 criteria; >5 mm groot, hypo-echogeen, bolrond. Deze criteria blijken niet goed op te gaan voor lymfeklieren na neoadjuvante chemoradiatie. In eerder onderzoek bleek de beoordeling van de PET-CT op 12 weken na einde neoadjuvante chemoradiatie voor de aanwezigheid van resttumor in de slokdarm te resulteren in een hoog aantal fout-positieve uitslagen. Dit wordt waarschijnlijk verklaard door een ontstekingsreactie in de slokdarm naar aanleiding van

chemoradiatie, resulterend in verhoogde FDG-opname in de slokdarm op de PET-CT. In **Hoofdstuk 6** wordt de waarde van seriële PET-CT onderzocht voor detectie van resttumor in de slokdarm, langer dan 12 weken na einde neoadjuvante chemoradiatie. In dit hoofdstuk wordt beschreven dat PET-CT mogelijk van waarde kan zijn gedurende actieve surveillance, om resttumor in de slokdarm aan te tonen. De ontstekingsreactie in de slokdarm bleek bij de meerderheid van de patiënten na 18 maanden na chemoradiatie grotendeels verdwenen te zijn.

Deel II: vergelijken van verschillende chirurgische technieken

Een slokdarmresectie zal een belangrijk onderdeel blijven van de standaardbehandeling van slokdarmkanker. Immers, bij de meerderheid van de patiënten wordt nog resttumor in de slokdarm aangetoond; voor hen zal een slokdarmresectie een belangrijke optie blijven om genezing te bereiken. Een slokdarmresectie is een ingrijpende en invasieve operatie die gepaard gaat met een snede in de buik (laparotomie) en een snede in de thorax (thoracotomie). De operatie gaat gepaard met mortaliteit, hoge kans op postoperatieve complicaties, aanhoudende symptomen en een daling in kwaliteit van leven. Om deze nadelige bijeffecten van de operatie te minimaliseren zijn minimaal invasieve chirurgische technieken ontwikkeld. Er zijn korte-termijn voordelen aangetoond voor patiënten die een totaal minimaal invasieve slokdarmresectie ondergaan (middels kijkoperatie in de buik en thorax) en voor patiënten die een operatie ondergaan waarbij één van de twee sneden wordt vervangen door een kijkoperatie (een zgn. hybride slokdarmresectie). De totaal minimaal invasieve en de hybride slokdarmresectie zijn echter niet direct met elkaar vergeleken. De incidentie van de meest voorkomende postoperatieve complicaties na beide chirurgische technieken werd beschreven in **Hoofdstuk 7** en de kwaliteit van leven en aanhoudende symptomen één jaar na een dergelijke operatie werden beschreven in **Hoofdstuk 8**. Longontsteking kwam minder vaak voor en een naadlekkage kwam vaker voor bij patiënten die een totaal minimaal invasieve operatie ondergingen ten opzichte van de hybride slokdarmresectie. Patiënten die een totaal minimaal invasieve operatie ondergingen hadden minder vaak en minder ernstig last van pijn ter plaatse van het litteken op de thorax.

Deel III: op weg naar actieve surveillance

Actieve surveillance zou onderdeel kunnen worden van de standaardbehandeling bij patiënten met een klinisch complete respons na neoadjuvante chemoradiatie. In **Hoofdstuk 9** worden de uitdagingen bij een eventuele invoering beschreven en wordt de beschikbare literatuur over actieve surveillance samengevat. In hoofdstuk 10 werd nagegaan welke factoren (zoals baseline globale kwaliteit van leven, WHO-score, tumorhistologie, tumorstadium en tumorlocatie) van invloed zijn op de verandering van de kwaliteit van leven. Er werd vastgesteld dat patiënten met een hoge baseline globale kwaliteit van leven en patiënten met een relatief kleine tumor (stadium 1-2) een diepere daling in kwaliteit van leven doormaakten na een slokdarmresectie in vergelijking met patiënten met een lage baseline globale kwaliteit van leven of patiënten met een grotere (stadium 3) tumor. Een standaard slokdarmresectie en een beleid van actieve surveillance hebben beide voor- en nadelen. Om patiënten te kunnen helpen bij het maken van een keuze tussen verschillende beschikbare behandelingen, worden uiteenlopende interventies ontwikkeld (in de vorm van een zgn. keuzehulp). In **Hoofdstuk 11** wordt beschreven voor welke ziektebeelden er interventies beschikbaar zijn die het keuzeproces zouden kunnen ondersteunen, in de situatie dat actieve surveillance één van de behandelalternatieven is. Deze interventies blijken schaars te zijn. Verder werd beschreven dat de effectiviteit van deze interventies voornamelijk is getest met behulp van korte-termijn uitkomsten. De vookeuren voor behandeling met actieve surveillance of een slokdarmresectie bij patiënten met slokdarmkanker die reeds minstens een jaar eerder een slokdarmresectie hebben ondergaan worden beschreven in **hoofdstuk 12.** Hieruit wordt duidelijk dat meer dan een kwart van de patiënten bij wie minstens een jaar geleden een slokdarmresectie is verricht, deze behandeling niet opnieuw zouden willen ondergaan, maar zouden kiezen voor actieve surveillance in het geval dat ze opnieuw de behandeling zouden moeten ondergaan. Verder waren sommige patiëntengroepen bereid om overlevingskans in te leveren voor een veel betere kwaliteit van leven op lange termijn. De belangrijkste factoren voor patiënten om te kiezen voor een behandeling zijn overlevingskans, lange-termijn kwaliteit van leven en de kans dat een slokdarmresectie nodig is. Sommige patiënten geven uit zichzelf een duidelijke voorkeur voor een behandeling aan. Na het bereiken van een klinisch complete respons, zijn er nu al patiënten die de operatie zelf weigeren en per se actieve surveillance willen ondergaan. De overleving van deze patiënten en de opgetreden postoperatieve complicaties na een uitgestelde slokdarmresectie (d.w.z. langer dan 12 weken na einde chemoradiatie) zijn zorgvuldig bijgehouden en vergeleken met patiënten die na het bereiken van een klinisch complete respons

zonder uitstel een slokdarmresectie hebben ondergaan. De uitkomsten van deze vergelijking zijn beschreven in **Hoofdstuk 13** en suggereren dat de algehele overleving van deze patiëntengroepen vergelijkbaar is (29 patiënten in elke groep, 58 patiënten in totaal). Echter, de beschikbare patiëntengroepen waren klein. Om deze patiëntengroepen te vergroten en zo de generaliseerbaarheid van de conclusie te verhogen, werd een systematische zoekopdracht uitgevoerd om alle literatuur die een soortgelijke vergelijking maakte te identificeren. De auteurs van alle studies werden benaderd voor een samenwerking en de data van alle studies werden verzameld en geanalyseerd. De overleving van deze samengevoegde groepen werd beschreven en vergeleken in **Hoofdstuk 14**. Na analyse van 788 patiënten werd geconcludeerd dat de algehele overleving vergelijkbaar was tussen patiënten die actieve surveillance ondergingen of standaard een slokdarmresectie ondergingen, in geval van een klinisch complete respons na chemoradiatie. Echter, er werd ook geconcludeerd dat actieve surveillance pas onderdeel zou kunnen worden van de standaardbehandeling op basis van resultaten van gerandomiseerde studies. Eén van deze studies is de SANO-trial, waarbij de randomisatie is uitgevoerd volgens een bijzonder principe (zgn. *stepped-wedge* cluster randomisatie). De inclusieperiode van dit onderzoek is reeds afgerond. Gedurende de inclusieperiode zijn meerdere amendementen doorgevoerd in het onderzoeksprotocol. Een update van het definitieve protocol van de SANO-trial is beschreven in **Hoofdstuk 15.** De eerste analyses van de SANO-trial zullen worden verricht na een minimale follow-up van twee jaar. De resultaten zullen definitief antwoord geven op de vraag of actieve surveillance onderdeel kan worden van de standaardbehandeling van patiënten met lokaal gevorderde slokdarmkanker en een klinisch complete respons na neoadjuvante chemoradiatie.

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Chapter 17

General discussion and future perspectives

General discussion and future perspectives

Esophageal cancer remains a highly lethal malignancy. The 5-year overall survival of patients with potentially curative esophageal cancer has improved over the last decades from approximately 10% to 47% nowadays.[1, 2] This was mostly due to the introduction of neoadjuvant therapies, such as neoadjuvant chemoradiotherapy. After neoadjuvant chemoradiotherapy and esophagectomy, 29% of patients have a pathologically complete response (*i.e.* no vital tumor cells in the resection specimen).[2] These patients could benefit from an active surveillance strategy. If no tumor is detected with 18F-FDG PET-CT (PET-CT), endoscopic biopsies and endoscopic ultrasound with fine needle aspiration of suspected lymph nodes during two response evaluations, patients are considered a clinically complete responder and considered eligible to undergo active surveillance. With these two response evaluations, however, 23% of residual tumors is still missed.[3] These patients should still undergo esophagectomy safely and timely, with as little morbidity as possible.
Future research should focus on improving overall survival, improving the accuracy of clinical response evaluations, minimizing the morbidity of esophagectomy and, if proven non-inferior, safe and controlled implementation of active surveillance in daily clinical practice.

Improving overall survival

Current standard treatment for locally advanced esophageal cancer consists of neoadjuvant treatment followed by esophagectomy.[2, 4] An improvement in overall survival was clearly seen after the introduction of (neo)adjuvant therapies. Two widely used therapies are preoperative chemoradiotherapy following the publication of the CROSS-trial (paclitaxel, carboplatin and 41.4 Gy radiotherapy) and perioperative chemotherapy following the publication of the FLOT-trial (Fluorouracil, Leucovorin, Oxaliplatin and doceTaxel).[2, 5, 6]

After introduction of neoadjuvant chemoradiotherapy, overall survival increased from 34% to 47%.[2] Distant metastases still developed, however, in nearly 40% of patients after neoadjuvant chemoradiotherapy and esophagectomy. Subsequent analyses reported that only 1% of patients have an isolated recurrence within the radiotherapy field.[5, 7] This suggests that neoadjuvant chemoradiotherapy according to CROSS-regimen is efficacious in locoregional control of the primary tumor and the locoregional lymph nodes. It does, however, question its systemic efficacy. Perioperative chemotherapy according to the FLOT-regimen is widely adopted as well in some

countries. One of the substances in the FLOT regimen is docetaxel.[6, 8] Both in first-line and in second-line, docetaxel has proven efficacious against distant metastases in patients with gastroesophageal cancer.[9, 10] Although chemoradiotherapy according to CROSS seems highly effective in locoregional control, reflected by the high pathologically complete response rates, chemotherapy according to the FLOT regimen could have a more substantial systemic effect against distant metastases.

A phase III trial has already been performed in patients with head and neck squamous cell cancer, reporting an improvement in overall survival for patients undergoing docetaxel-containing chemotherapy followed by chemoradiotherapy when compared to chemoradiotherapy alone.[11] The addition of perioperative chemotherapy (FLOT) prior to chemoradiotherapy (CROSS) in patients with esophageal cancer could possibly result in early inhibition of distant dissemination while maintaining locoregional control. Thus, possibly improving overall survival.

Targeted therapies such as monoclonal antibodies are another example of promising systemic therapies. Monoclonal antibodies are known for their potential to bind to cell surface receptors and activate downstream signaling pathways, inhibiting oncogenic actions.[12] For example, dual blockade of the human epidermal growth factor receptor 2 (HER2) with trastuzumab plus pertuzumab in combination with chemoradiotherapy according to CROSS resulted in favorable overall survival when compared to a historical cohort, after propensity score matching for patients with HER-positive adenocarcinoma of the esophagus.[13] Additionally, the Checkmate-577 trial randomized patients with esophageal or gastroesophageal junctional cancer with residual tumor after neoadjuvant chemoradiotherapy and surgery between adjuvant nivolumab or a placebo.[14] In a pre-specified interim-analysis, the addition of adjuvant nivolumab resulted in a median disease-free survival of 22 months compared to 11 months for patients who received the placebo. Although the definitive results still need to be published, adjuvant nivolumab could potentially be beneficial in the adjuvant setting after neoadjuvant chemoradiotherapy and esophagectomy.

Improving the accuracy of clinical response evaluations

After neoadjuvant chemoradiotherapy, nearly one-third of the patients have a pathologically complete response.[2] Possibly, an active surveillance strategy could be feasible for patients who have a clinically complete response, as determined with PET-CT, endoscopic biopsies and endoscopic

ultrasound with fine-needle aspiration of suspected lymph nodes. The preSANO-trial previously reported that 90% of patients with a substantial residual tumor (>10% residual tumor cells) are detected and 67% of all residual tumors are detected.[3, 15] This means, however, that 23% of patients with any residual tumor are still missed during the first two clinical response evaluations. In this thesis, we reported that the undetected residual tumors in the preSANO-trial, mostly resided in the mucosal layer of the esophageal wall and that nearly a quarter of missed residual tumor is in the submucosa, underneath a tumor-free mucosa.

Therefore, the major step in improving clinical response evaluations should be achieved by more adequate sampling of the mucosal layer of the esophageal wall. The wide-area transepithelial sampling method (WATS$^{3D®}$, CDx Diagnostics, Suffern, New York, USA) uses a brush to extensively sample the esophageal wall as deep as the muscularis mucosae. Thus, hopefully decreasing the risk for sampling error. Earlier studies have been performed with WATS in patients with Barrett's esophagus, resulting in an increased detection of high-grade dysplasia when compared to conventional endoscopic biopsy sampling.[16] So far, no studies have been performed using WATS in patients with esophageal cancer after neoadjuvant chemoradiotherapy. The feasibility and safety of WATS in these patients should be assessed, followed by a randomized controlled trial adding WATS to the currently used diagnostic set in clinical response evaluations to determine the accuracy of the procedure. However, analysis of WATS specimens is done with initial aid of computer assisted 3-dimensional analysis using neural networks, screening suspicious areas of mucosal tissue. This is done in highly specialized pathological labs in the United States, limiting the use in daily clinical practice worldwide. If WATS is indeed proven effective, computer-assisted analysis should be made more readily available.

Besides mucosal tumors, a minority of patients still has submucosal or deeper tumors underneath a tumor-free mucosa. These residual tumors will most probably not be detected using endoscopic biopsies or WATS. For these patients, imaging could be a promising option to improve the accuracy of clinical response evaluations. In the preSANO-trial, it was reported that PET-CT had a good sensitivity. However, the specificity for detecting locoregional disease was poor, resulting in a high rate of false positive response evaluations when relying on PET-CT alone.

Current studies on MRI report comparable sensitivity and specificity after completion of neoadjuvant chemoradiotherapy.[17] The multicenter prospective PRIDE study is ongoing and assesses whether MRI has additional value for usage in clinical response evaluations up to twelve weeks after completion of neoadjuvant chemoradiotherapy.[18]
The high false-positivity rate of the PET-CT is probably due to radiation-induced FDG-positivity located at the site of the primary tumor, making it hard to distinguish between vital tumor or inflammatory tissue reaction. In this thesis, we report that PET-CT could be a useful tool to detect locoregional disease when used serially during active surveillance, as radiation-induced esophagitis seems to be resolved approximately one year after completion of neoadjuvant chemoradiotherapy.

A new technique which has drawn attention for usage during clinical response evaluations is the combination of PET and MRI.[19, 20] MRI has superior soft tissue contrast compared to CT. Furthermore, the additional functional information of diffusion weighted (DW) MRI could provide extra discriminative value between radiation-induced esophagitis and residual malignant disease in the esophagus. Therefore, a combination of FDG-PET and MRI could possibly discriminate better between radiation-induced esophagitis and true residual disease in the esophagus.
Lastly, new scintigraphic tracers are developed. One example is 68Ga-FAPI (Fibroblast Activation Protein Inhibitor). It is known that 68Ga-FAPI highly selectively binds and inhibits fibroblast activation protein, mostly residing on tumor cells. Recent studies reported that esophageal cancer has a high uptake of 68Ga-FAPI.[21] Since this tracer is specific for tumor tissue, it could possibly overcome the limitations of FDG when using PET-imaging. Future imaging research should focus on the value of PET-CT or MRI when performed serially in active surveillance. Moreover, a combination of PET and MRI should be tested and possibly the substitution of 18-FDG for 68Ga-FAPI.

Minimizing the morbidity of esophagectomy
Even if active surveillance would be proven non-inferior to standard esophagectomy after neoadjuvant chemoradiotherapy, surgical resection would still be necessary for the majority of patients with locally advanced esophageal cancer. An esophagectomy is associated with substantial morbidity and even mortality, and is accompanied with lasting symptoms and a reduction in health-related quality of life (HRQOL).[22-24] To decrease the negative effects of surgery, several minimally invasive techniques have been developed. In this thesis we report that patients who undergo

laparoscopically assisted hybrid Ivor Lewis esophagectomy have more often and more severe chest pain than patients who undergo totally minimally invasive Ivor Lewis esophagectomy (TMIE). No differences were reported, however, concerning postoperative complications or health-related quality of life. Definitive answers on whether TMIE or hybrid Ivor Lewis esophagectomy is preferred for patients with esophageal cancer, should be studied in prospective direct comparisons powered on long-term outcomes such as long-term health-related quality of life and overall survival.

Safe and controlled implementation of active surveillance in daily clinical practice

We have reported that several retrospective, smaller studies had previously been published comparing overall survival after active surveillance with standard surgery in patients with a clinically complete response after chemoradiotherapy.[25-31] These studies have, however, insufficient power to provide robust evidence on the efficacy of an active surveillance strategy. The currently ongoing Surgery As Needed for Oesophageal cancer (SANO)-trial compares active surveillance with standard esophagectomy in patients with a clinically complete response after neoadjuvant chemoradiotherapy.[32] As of December 2020, the inclusion phase has been completed. With a minimal follow-up of two years, the first results on overall survival are expected approximately in January 2023 while the long-term results will not be published before 2026.

It is known that uncontrolled implementation of complicated interventions could result in inferior results, compared to those results reached within a controlled trial-setting.[33] Hence, active surveillance should not be implemented in an unstructured and uncontrolled setting. A web-based registry of all patients who are undergoing active surveillance could assist in implementing active surveillance in daily clinical practice in the future. This could be accompanied by setting up a multidisciplinary active surveillance board, continuously monitoring outcomes of these patients.

We reported in this thesis, that a substantial number of patients still needs postponed esophagectomy for resectable locoregional residual or recurrent disease. Furthermore, it is expected that a substantial number of patients develops clinically manifest distant metastases as well during active surveillance. To accurately manage the expectations of patients on the risk of developing locoregional recurrences, requiring postponed esophagectomy, it would be helpful to assess the conditional recurrence free survival. The conditional recurrence free survival quantifies the

probability of developing a locoregional recurrence, given that a patient had not already developed a locoregional recurrence for a given period of time. Besides the informative value for patients, the conditional recurrence free survival could be used to assess and optimize the interval between clinical response evaluations used in active surveillance. The substantial number of locoregional recurrences hampers the efficacy of an active surveillance strategy. The previously mentioned Checkmate-577 trial reports a doubling in disease free survival in patients who still have residual tumor after neoadjuvant chemoradiotherapy and esophagectomy using nivolumab.[14] Possibly, the development of locoregional recurrences could be decreased using nivolumab as maintenance therapy during active surveillance after neoadjuvant chemoradiotherapy.

An active surveillance strategy comes with some pitfalls and drawbacks as well. If residual tumors remain undetected during active surveillance, the opportunity to perform radical (postponed) esophagectomy could be missed, due to advanced progression of the tumor. Furthermore, the longer time of undetected residual tumor in the esophagus could result in an increased rate of distant dissemination. If active surveillance is indeed proven non-inferior in the SANO-trial, physicians will offer patients the choice between either active surveillance or standard esophagectomy. This complex balance of pros and cons of either treatment requires shared decision making. We reported that interventions for supporting shared decision making on active surveillance are scarce. Furthermore, patients report that the choice between active surveillance or standard esophagectomy depends highly on the long-term health-related quality of life.[34] Future studies should focus on developing instruments to support shared decision making and on identifying clinicopathological and biological factors that are predictive for a poor quality of life in patients who have a clinically complete response. In this way, patients could be informed and more appropriately for active surveillance.

Substantial improvements in the treatment of locally advanced esophageal cancer have been made in the last decades. The inclusion period of the SANO-trial has been completed in December 10, 2020. The analyses for the short-term results will be performed after a minimum follow-up of two years. Hopefully, the results of the SANO-trial and the therapeutic and diagnostic opportunities discussed in this section, will improve health-related quality of life and overall survival of patients with locally advanced esophageal cancer in the near future.

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Appendices

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List of publications

2022 M. Hermus, **B.J. van der Wilk**, R. Chang, G. Collee, *et al.* Patient preferences for active surveillance versus standard surgery after neoadjuvant chemoradiotherapy in esophageal cancer treatment: the NOSANO-study
(submitted)

2022 R.D. van der Bogt, **B.J. van der Wilk**, L. Oudijk, E. J. Schoon, *et al.* Bite-on-bite biopsies for detection of residual esophageal cancer after neoadjuvant chemoradiotherapy.
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2022 B.M. Eyck, M.P.H.M. Jansen, B.J. Noordman, P.N. Atmodimedjo, **B.J. van der Wilk**, *et al.* Detection of circulating tumour DNA after neoadjuvant chemoradiotherapy in patients with locally advanced oesophageal cancer
(submitted)

2021 B.M Eyck, F. Klevebro, **B.J. van der Wilk**, A. Johar *et al.* Lasting symptoms and long-term health-related quality of life after totally minimally invasive, hybrid and open Ivor Lewis esophagectomy.
Eur J Surg Oncol, 2021 Nov 3:S0748-7983(21) epub ahead of print

2021 **B.J. van der Wilk**, I. Spronk, B.J. Noordman, B.M. Eyck *et al.* Patients' preferences for active surveillance or standard esophagectomy: a discrete choice experiment.
Br J Surg, 2022 Feb 1; 109(2): 169-171

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Br J Surg, 2022 Feb 24;109(3):283-290

2021 M. Gruijs, R. Braster, M.B. Overdijk, T. Hellingman, S. Verploegen, R. Korthouwer, **B.J. van der Wilk**, P.W.H.I. Parren, H.J. van der Vliet, M. Bögels, M. van Egmond. Epidermal growth factor receptor as target for perioperative elimination of circulating colorectal cancer cells.
J Oncol, 2022 Jan 7;2022:3577928

2021 J. Spoor, B.M Eyck, P.N. Atmodimedjo, M.P.H.M. Jansen, J.C.A. Helmijr, J.W.M. Martens, **B.J. van der Wilk**, J.J.B. van Lanschot, W.N.M. Dinjens. Liquid biopsy in esophageal cancer: false-positive circulating tumor DNA detection due to clonal hematopoiesis.
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Ann Surg, 2022 Mar 1;275(3):467-476

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J Nucl Med 2021 Apr;62(4):486-492

2020 **B.J. van der Wilk,** G.E. Collee, J.J.B van Lanschot, J.J. Busschbach, *et al.* Interventions that facilitate shared decision making in cancers with active surveillance as treatment option: A systematic review of literature.
Curr Oncol Rep. 2020 Jul 28;22(10):101

2020 **B.J. van der Wilk**, B.M. Eyck, M. Doukas, M.C.W. Spaander, *et al.* Location of residual disease undetected by endoscopic biopsies after neoadjuvant chemoradiotherapy for oesophageal cancer.
Br J Surg. Dec;107(13):1791-1800.

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2020 X. Zhang, B.M. Eyck, Y. Yang, J. Liu, Y.K. Chao, M.M. Hou, T.M. Hung, Q. Pang, Z.T. Yu, H. Jiang, S. Law, I. Wong, K.O. Lam, **B.J. van der Wilk**, A. van der Gaast, M.C.W. Spaander, R. Valkema, S.M. Lagarde, B.P.L. Wijnhoven, J.J.B. van Lanschot, Z. Li. Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for esophageal squamous cell carcinoma (preSINO trial): a prospective multicenter diagnostic cohort study.
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Endoscopy. 2020 Mar;52(3):186-192.
(a) E. Vazquez-Sequeiros. Endosonography-guided fine-needle aspiration for re-evaluation of lymph node status after neoadjuvant therapy in patients with esophageal cancer: is there any role for it? Endoscopy. 2020 Mar;52(3):164-165.
(b) G. Rizatta, M. Rimbas, A. Larghi. Lymph node staging in esophageal/junctional tumors after chemoradiotherapy: should we change strategy? Endoscopy. 2020 Apr;52(4):316.

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2019 **B.J. van der Wilk**, B.J. Noordman, L.K.A. Neijenhuis, D. Nieboer, *et al.* Active surveillance versus immediate surgery in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal cancer: a multicenter propensity matched study.
Ann Surg, 2021 Dec 1;274(6): 1009-1016
(a) D. Molena, B.E. Louie, S.R. DeMeester. Comment on: “Active surveillance versus immediate surgery in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal cancer. Ann Surg. 2020. Mar 6.

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Ann Surg. 2021 Dec 1; 274(6):e697-e698

2019 **B.J. van der Wilk**, B.M. Eyck, S.M. Lagarde, A. van der Gaast, *et al.* The optimal neoadjuvant treatment of locally advanced esophageal cancer.
J Thorac Dis. Apr;11(Suppl 5):S621-S631.

2018 B.M. Eyck, **B.J. van der Wilk**, M.C.W. Spaander, R. Valkema, *et al.* Orgaansparend behandelen bij het slokdarmcarcinoom.
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2018 B.M. Eyck, **B.J. van der Wilk**, S.M. Lagarde, B.P.L. Wijnhoven, *et al.* Neoadjuvant chemoradiotherapy for resectable oesophageal cancer.
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2018 **B.J. van der Wilk**, B.M. Eyck, M.C.W. Spaander, R. Valkema, *et al.* Towards an organ-sparing approach in locally advanced esophageal cancer.
Dig Surg. 2019;36(6):462-469.

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Supervisors:	Prof. dr. J.J.B. van Lanschot and prof. dr. B.P.L Wijnhoven

PhD training	**Year**	**Workload (ECTS)**
Oral presentations		
ISDE, Vienna	2018	1.0
ESSO, Budapest	2018	1.0
Heelkunde Science Day, Rotterdam	2018	1.0
DDD, Veldhoven	2018	1.0
Heelkunde Science Day, Rotterdam	2019	1.0
NVVH, Voorjaarsdagen	2019	1.0
DDD, Veldhoven	2019	1.0
ISDE 2020, Toronto	2020	1.0
Heelkunde Science Day, Rotterdam	2020	1.0
Poster presentations		
ESDE, Athens	2019	0.5
SSO, Boston	2020	0.5
UEG Week, Amsterdam	2020	0.5
Attendance at conferences (0.3 per day)		
ESDE Utrecht	2017	0.9
DUCG, Utrecht	2017	0.3
DUCG, Utrecht	2018	0.9
ISDE, Vienna	2018	0.9
ESSO, Budapest	2018	0.9
SEOHS, Rotterdam	2018	0.3
Heelkunde Science day, Rotterdam	2018	0.3
NVVH najaarsdag, Veldhoven	2018	0.3
NVVH voorjaarsdagen, Veldhoven	2018	0.6
DDD, Veldhoven	2018	0.9
DUCG, Utrecht	2019	0.3
ESDE, Athens	2019	0.9
Heelkunde Science Day, Rotterdam	2019	0.3
NVVH Voorjaarsdagen	2019	0.6
Heelkunde Science Day, Rotterdam	2020	0.3
ESDE, Athens	2020	0.9
DUCG, Utrecht	2020	0.3
NVVH Voorjaarsdagen	2020	0.6

General courses		
BROK recertification	2018	0.3
The course on R	2018	1.8
Research integrity	2018	0.3
Erasmus MC – CC02A Biostatistical methods I: basic principles	2018	2.0
The survival analysis course	2018	0.6
Teaching activities		
Basic Life Support examinations first year medical students	2018	0.5
Supervision master thesis (4x)	2018 – 2020	8.0
Other		
Peer reviewer for scientific journals - British Journal of Surgery - Radiation Oncology - World Journal of Surgical Oncology - BMC Cancer - Journal of Thoracic Disease - Oncotargets and Therapy - Scientific Reports	2018 – 2020	4.0
Total		**38.5**

About the author

Berend Jan van der Wilk was born in Alkmaar, the Netherlands on the 4th of June 1991. After graduating from secondary school in 2009 (Atheneum, Berger Scholengemeenschap, Bergen, Noord-Holland), he started the study Biomedical Sciences at the University of Amsterdam in 2010. After graduating in 2013, he applied for the selective medical master from the Free University in Amsterdam (Zij-Instroom Geneeskunde Master Amsterdam; ZIGMA) and commenced his Master's programme in 2013. The interest for surgery started to enhance during a prolonged research internship at the Department of Surgery in combination with the Department of Molecular Cell Biology and Immunology under supervision of prof. dr. Marjolein van Egmond, where he studied the role of preoperative Cetuximab treatment in patients with colorectal cancer. After going abroad for two internships; pediatrics and gynecology at Sint Maarten Medical Center, Saint Martin and an internship general practitioner at Paramaribo, Suriname, he decided to apply for a senior internship at the Department of Surgery at Spaarne Gasthuis in Hoofddorp under supervision of dr. S.J. Oosterling. The opportunity to be involved in a multicenter clinical trial in the surgically oncological field resulted in a new step to Rotterdam afterwards. He worked full-time on this PhD trajectory, as described in this thesis and under supervision of prof. dr. J.J.B. van Lanschot and prof. dr. B.P.L. Wijnhoven, from November 2017 until December 2020. Afterwards, he started to work as surgical resident not in training (ANIOS) at the Sint Franciscus Gasthuis en Vlietland Ziekenhuis (SFG, Rotterdam). From January 2022 onwards, he will commence his surgical training.

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