Chemotherapy and Chemoradiotherapy Studies in Oesophageal Cancer

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CHEMOTHERAPY AND CHEMORADIOTHERAPY STUDIES IN OESOPHAGEAL CANCER

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Wat is het verschil tussen een geleerde die de kleinste en meest onvermoede levensverschijnselen onder de microscoop waarneemt, en de oude landbouwer, die nauwelijks kan lezen en schrijven, wanneer hij in het voorjaar nadenkend in zijn tuin zit en de bloesems bekijkt, die uit de twijgen van de boom ontspruiten? Beiden staan voor het raadsel van het leven, en de een kan het uitvoeriger beschrijven dan de ander, maar voor beiden is het even ondoorgrondelijk

(Albert Schweitzer)

Voor mijn ouders

Contents

Chapter 1

Introduction & outline to the thesis

EPIDEMIOLOGY

Worldwide almost 400.000 cases of oesophageal cancer are diagnosed. Because of the poor prognosis of these patients, the number of deaths almost equals the incidence (over 350.000 per year). Herewith cancer of the oesophagus ranks eighth on the list of most common cancers and sixth on the list of cancer mortality causes. The geographic variability in risk is very large, more than for almost any other type of cancer [1]. The highest risk areas of the world are in the Asian 'oesophageal cancer belt' (stretching from Northern Iran through the Central Asian republics to North-Central China). Squamous cell carcinomas account for the vast majority of oesophageal cancer in these regions. The special personal and dietary habits of the population are the most likely aetiological factors [2]. In the Western world the incidence of oesophageal adenocarcinoma predominates that of squamous cell carcinoma. In most areas, oesophageal cancer is more common in males than in females [1]. In the Netherlands the incidence of oesophageal cancer is about 13/100.00 for men, and 5/100.000 for women, with approximately 1450 newly diagnosed patients per year [3].
Studies constantly have shown the aetiological impact of tobacco smoking and alcohol abuse, particularly in combination. This strong effect of tobacco and alcohol on carcinogenesis is primarily associated with squamous cell carcinoma. Recent studies in the USA have established an elevated risk of oesophageal adenocarcinoma in smokers relative to non-smokers. There is, however, little evidence that alcohol consumption is associated with the risk of adenocarcinoma of the oesophagus [4]. Over the last decades there has been a substantial increase in the incidence of oesophageal adenocarcinomas of the lower third of the oesophagus in Western countries (compared with only a moderate increases for squamous cell carcinomas). The incidence increases at a rate that exceeds that of any other malignancy [5]. The increase in incidence seems to be related to the increased prevalence of Barrett's oesophagus, which is presumably due to gastro-oesophageal reflux becoming more common, perhaps as a consequence of increasing abdominal obesity [6-8].
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SYMPTOMATOLOGY & DIAGNOSIS

The most common presenting symptoms of oesophageal cancer are dysphagia, retrosternal pain, pain during food or liquid passage, weight loss, haematemesis/melaena, and/or anaemia. When oesophageal cancer is suspected, an upper gastrointestinal endoscopy with biopsy is the preferred diagnostic procedure. After the diagnosis has been established, the additional work-up consists of an endoscopic ultrasound in order to determine the depth of tumour invasion into the oesophageal wall (T-stadium) and to determine the presence of nodal involvement (N-stadium) [9, 10]. The presence of cervical lymph node is best evaluated by ultrasonography of the neck [11]. A computed tomography scan of the chest and upper abdomen is the best diagnostic tool to assess distant metastases [12]. A positron emission tomography (PET)-scan improves the selection of patients with oesophageal cancer for potentially curative surgery, especially in stages III–IV. However, the diagnostic benefit is limited after state-of the-art staging

[13]. After the diagnostic work-up almost half of the patients have metastatic or irresectable disease.

TREATMENT

Tumours of the oesophagus limited to the mucosa can be treated by local treatment, preferably endoscopic mucosal resection [14]. For tumours invading the oesophageal wall further than T1sm1, surgical resection is currently the mainstay of treatment if the tumour is resectable (T1-3N0-1M0) and the patient is fit enough to undergo major surgery. For patients with nodal involvement of the coeliac axis (M1a) there are several treatment options. When nodal involvement is limited, and a radical resection is expected, surgery is the preferred treatment with en bloc resections of the lymph nodes along the lesser curvature, the left gastric artery and the coeliac axis. However, when the lymph nodes are enlarged in such a way that irradical surgery is to be expected, patients at our institution are treated with induction chemotherapy followed by surgical resection in case of a major response to the chemotherapy [15]. Despite the curative intent of an oesophageal resection, the 5-year survival after a surgical resection is still poor (20-25%) [16]. This is in part due to the high rate of irradical resections (25-46%) [17-19].
In an attempt to improve the poor prognosis of patients with oesophageal cancer several treatment strategies have been used such as neoadjuvant chemotherapy and preoperative chemoradiotherapy. The rationale of these strategies is to achieve tumour shrinkage to increase the resectability rate and to enable a microscopic radical resection, and the treatment of micrometastases, thereby improving overall survival.
For tumours growing into adjacent structures (T4-tumours), radical surgery is not possible. For selected patients definitive chemoradiation might be a valuable treatment option. Patients with a local regional recurrence or distant metastases often need palliative therapy to treat symptoms, such as dysphagia. Placement of a self-expanding metal stent, external beam radiotherapy, intraluminal radiotherapy (brachytherapy) and chemotherapy are commonly used palliative modalities [20].

AIMS & OUTLINES OF THIS THESIS

The aim of this thesis was, first, to explore the use of preoperative chemoradiotherapy and palliative chemotherapy in the treatment of oesophageal cancer. Furthermore, the effects of a chemoradiotherapy regimen on histopathological and psychological and social level were studied.
Chapter 2 provides a review of the literature on systemic treatment for oesophageal cancer. An overview is given for preoperative and postoperative chemotherapy, preoperative chemoradiotherapy, definitive chemoradiotherapy, and palliative chemotherapy.
In **Chapter 3** the efficacy and safety of preoperative chemoradiotherapy consisting of carboplatin and paclitaxel and concurrent radiotherapy for patients with resectable oesophageal cancer is studied.

In **Chapter 4** the health related quality of life up to one year after surgery, in patients with oesophageal cancer treated with curative intent with neoadjuvant chemoradiotherapy consisting of the above mentioned regimen followed by oesophagectomy is evaluated.
Chapter 5 describes the histopathological effects of the above mentioned chemoradiotherapy regimen and correlates the effect of specific pathologic and clinical findings to overall survival.
Finally, in **Chapter 6** the analysis of a phase II study evaluating the safety and efficacy of the combination of oxaliplatin and capecitabine in patients with metastatic or local-regional unresectable carcinoma of the oesophagus, oesophagogastric junction, and cardia is given. In addition, the effect of this regimen of the patients' well-being is evaluated by performing a quality of life analysis on these patients during the treatment.
The studies described in this thesis are summarized in **Chapter 7**. Furthermore, potential directions for future studies are addressed.

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Chapter 2

Oesophageal Cancer and Chemotherapy
A Review

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ABSTRACT

Oesophageal cancer, in particular adenocarcinomas, has shown a rapid and largely unexplained increase in incidence in the Western world. Despite advances in diagnostic and surgical techniques and improved pre- and postoperative care, the prognosis of most of the patients is poor. The review will focus on the use of chemotherapy as part of multimodal treatment and for patients with metastatic disease. Randomized phase III trials have for the most part failed to demonstrate a survival advantage with the use of chemotherapy. It must be emphasized that many of these phase III trial were underpowered and do not meet today's standard. Recent phase II trials have suggested some progress when chemotherapy is incorporated into the management of patients with oesophageal cancer. However, confirmatory and adequately powered and designed phase III studies are urgently needed to improve patient outcomes and for better palliation of symptoms.

INTRODUCTION

Oesophageal cancer is a highly lethal disease, as reflected by an overall survival rate of 10 – 20%. With world-wide almost 400,000 new patients diagnosed annually, oesophageal cancer is the eight most common cancer, and sixth on the list of cancer mortality causes [1]. The incidence varies widely according to geographical region and racial background. In the Western World the incidence is rising [2, 3], especially due to a rapid increase in the incidence of adenocarcinoma of the distal oesophagus or the oesophageal-gastric junction. This rising incidence is not completely well understood, but obesity, gastric reflux and the occurrence of Barrett's epithelia may be contributory factors [3-5].

The majority of patients who present with complaints, such as dysphagia, has either locally advanced disease (cT2-3 N0-1M0) or already metastatic disease. A surgical resection is currently the preferred treatment for oesophageal cancer if a patients is fit enough to undergo surgery and the tumour is considered to be resectable without evidence of distant metastases. However, approximately 30% of operated patients, clinically considered to have resectable disease, have microscopically irradical resections performed on [6]. Furthermore, even after surgery with curative intent, the overall survival remains poor. In about two-third of the patients local recurrences and/or distant metastases are detected within 5 years of follow-up [7].

Chemotherapy together with radiotherapy and/or surgery is nowadays frequently integrated in the treatment of oesophageal cancer or is used for patients with metastatic disease. This review will focus on the use of chemotherapy alone or as part of combined modality treatment in patients with oesophageal cancer. The available evidence derived from the literature will be discussed to answer the question whether chemotherapy can be considered as an integral part of standard treatment or still should be considered to be experimental and that its impact on survival and quality of life is unproven or unknown.

PREOPERATIVE AND POSTOPERATIVE CHEMOTHERAPY

In general, surgery is considered the mainstay of treatment for patients with resectable oesophageal cancer. The goal of preoperative chemotherapy is a reduction of recurrence from occult lymphatic and/or distant metastases with improvement of survival and possible tumour shrinkage with an increased resectability rate. Many phase II trials have been published and the combination of cisplatin and 5-fluorouracil is one of the most frequently used regimes. Response rates of 15-60%, with a complete pathologic response rate of 4-7 %, after cisplatin-based combination chemotherapy are usually reported [8] and often in these studies it is concluded that compared to historical controls the outcome is improved after preoperative chemotherapy [9]. Patients who have an objective response to chemotherapy have usually a significant better survival compared to non-responding patients [10].

The number of randomised phase III studies comparing preoperative chemotherapy followed by surgery versus surgery alone is limited. Furthermore, the results of some of these studies are difficult to interpret for various reasons such as: only a small number of patients included, the used chemotherapy regime is nowadays not considered optimal or the results have not yet been fully published. An overview of a number of these trials is shown in Table 1.

Of the 2 largest conducted studies, no survival benefit was found in the Intergroup study [11], while in the Medical Research Council (MRC) study [12] a significant survival benefit was demonstrated with the use of preoperative chemotherapy. In the Intergroup trial 440 patients were randomised to preoperative treatment followed by surgery or surgery alone. Patients who had stable disease or an objective response after chemotherapy received also two post-operative courses of chemotherapy. The overall rate of clinical response (19%) to preoperative chemotherapy was surprisingly low. Survival after 2 years was also comparable in the both treatment arms. In the MRC study 802 patients were randomised to receive preoperative chemotherapy followed by surgery or surgery alone. The response rate after chemotherapy was not reported. The 2-year survival rate was significantly better for patients treated with preoperative chemotherapy and the 2-year survival rates were 43% and 34%, respectively.

The apparent difference in outcome is difficult to explain, particularly because in both studies comparable chemotherapy regimens were used. Possible explanations could be: patient selection, the type and adherence to the chemotherapy protocol of patients, chance and the type of surgical resection. In the Intergroup study an oesophagectomy through a thoracotomy was preferred while in the MRC study both a transhiatal resection and a transthoracic oesophagectomy were considered appropriate.

In a Cochrane review the results of a number published and not published studies [13] comparing chemotherapy followed by surgery versus surgery alone were analysed. The analysis was based on 11 randomised trials including a total of 2051 patients. At 3, 4 and 5 years an increase in survival was found for preoperative chemotherapy. The results were only significant at 5 years. Preoperative chemotherapy led to increased toxicity and mortality. Urschel and colleagues performed a meta-analysis of 11 controlled randomised trials including 1976 patients. Their conclusion was that neoadjuvant chemotherapy was associated with a lower rate of oesophageal resections but a higher rate of complete resections. Preoperative chemotherapy did not significantly increase

Table 1. Phase III studies of preoperative chemotherapy versus surgery alone

Author[ref]/Year	Histology	No. of patients		Regime	Survival	CT	Control	Significance
		CT	Control					
Roth[63]/1988	SCC	19	20	CP/Vind/BL	median	9 m	9 m	n.s.
Nygaard[64]/1992	SCC	56	50	CP/BL	3-year	3%	9%	n.s.
Schlag[65]/1992	SCC	22	24	CP/5FU	median	10 m	10 m	n.s.
Maipang[66]/1994	SCC	24	22	CP/Vind/BL	median	17 m	17 m	n.s.
Law[67]/1997	SCC	74	73	CP/5FU	median	16.8 m	13 m	n.s.
Kok[68]/1997	SCC	84	85	CP/VP	3-year	41%	17%	significant
Kelsen[11]/1998	SCC/AC	213	227	CP/5FU	median	14.9 m	16.1 m	n.s.
Ancona[69]/2001	SCC	48	48	CP/5FU	median	24 m	25 m	n.s
MRC[12]/2002	SCC/AC	400	402	CP/5FU	median	16.8 m	13.3 m	significant

ref = reference, SCC = squamous cell carcinoma, AC = adenocarcinoma, CT = chemotherapy, CP = cisplatin, BL = bleomycin, Vind = vindesine, 5FU = 5-fluorouracil, VP = etoposide, m = months, n.s = not significant

treatment related mortality. No survival benefit was demonstrated in their analysis [14]. Considering the above mentioned results of the available randomised phase III studies and the reviews, the possible survival benefit, if any, of neoadjuvant-chemotherapy for patients with oesophageal cancer is most likely small. Furthermore, it is uncertain whether such a potential survival benefit outweighs the morbidity caused by this treatment. A surgery only arm is therefore still considered to be appropriate in randomised phase III studies for patients with oesophageal cancer.

In only a few trials the effect of postoperative chemotherapy is investigated. Ando and colleagues were not able to demonstrate a survival benefit in a randomised trial for patients with squamous cell carcinomas. In this study 105 patients were treated with 2 courses cisplatin and vindesine and 100 patients received no adjuvant chemotherapy. The 5-years survival rates were 48.1% and 44.9%, respectively [15]. In a subsequent study 242 patients were randomised and 120 patients received two cycles of cisplatin and fluorouracil after surgery and 122 patients had surgery alone. Although the 5-year disease-free survival was significantly better with surgery followed by chemotherapy than with surgery alone (55% and 45% respectively), there was no difference in the 5-year overall survival rates [16]. Earlier Pouliquen and colleagues had reported a trial in which 124 patients after a complete or incomplete resection were randomly assigned to receive no chemotherapy or chemotherapy consisting of cisplatin and fluorouracil [17] for duration of 6 to 8 months. No difference in survival was found and the median survival was 13 months in the chemotherapy group and 14 months in the surgery alone group.

In conclusion, there is no evidence that postoperative chemotherapy improves survival in patients with oesophageal carcinoma. Another disadvantage of postoperative chemotherapy is that after major surgery such as an oesophageal resection many patients do not tolerate chemotherapy and this can have a detrimental effect on the anticipated dose intensity.

PREOPERATIVE CHEMORADIOTHERAPY

Preoperative chemoradiotherapy is nowadays widely used in the treatment of patients with potentially resectable oesophageal cancer. Theoretically, chemotherapy and radiotherapy can interact in several ways. Both treatment modalities may be active against different tumour cell populations; the chemotherapy may be effective against micrometastases while radiation is active locoregionally. Moreover, chemotherapy may synchronise cells in a vulnerable phase for radiotherapy, decrease repopulation after radiotherapy and enhance reoxygenation, which is advantageous for radiotherapy [18]. In numerous phase II studies this concept has been tested and cisplatin and 5-fluorouracil combined with radiotherapy is the most frequent used regime [19-22]. The limited sample size of most of these studies, the differences in patients selection criteria, the variations in chemoradiotherapy schemes, and the intermingling of both patients with resectable and unresectable tumours makes it difficult to compare these phase II studies with each other. The general conclusion that can be derived from these studies is that preoperative chemoradiotherapy is feasible and that those patients who achieve a complete pathologic response have a better overall survival than those who do not achieve a complete response. In some of these phase II studies historical controls are used to estimate the effect on survival and this carries the risk that the treatment effects may be overestimated [23].

Surprisingly few phase III studies have been reported in which preoperative chemoradiotherapy followed by surgery is compared with surgery alone. In Table 2 we have summarised a number of the published randomised trials. Only in the Walsh study a significant survival benefit was found [24]. The small sample size, short follow-up, early stoppage based on interim analysis, disproportionate number of patients withdrawn from the combined modality arm, and lack of stratification based on pretreatment stage are some of the concerns regarding the results of this trial.

Three meta-analyses have been published in which the effect of preoperative chemoradiotherapy on survival and treatment mortality was studied. Fiorica and colleagues included six randomised studies in their meta-analysis including 764 patients [25]. They

Table 2. Phase III trials of chemoradiotherapy plus surgery versus surgery alone

Author[ref]/Year	Histology	No.ofpatients		CT	RT(totaldose)	Mediansurvivalinmonths (3-year)		Significance
		CRT	Control			CRT	Control	
Nygaard[64]1992	SCC	53	50	CP/BL	35Gy	8.2(17%)	7.6(9%)	n.s.
Apinop[70]1994	SCC	35	34	CP/5FU	40Gy	9.7(26%)	7.4(20%)	n.s.
LePrise[71]1994	SCC	41	45	CP/5FU	20Gy	10(19.2%)	11(13.2%)	n.s.
Bosset[72]1997	SCC	143	139	CP	2x18.5Gy	18.6(39%)	18.6(37%)	n.s.
Walsh[24]1996	AC	58	55	CP/5FU	40Gy	16(32%)	11(6%)	P=0.01
Urba[73]2001	SCC/AC	50	50	CP/5FU/VBL	45Gy	16.9(30%)	17.6(16%)	n.s.

ref= reference, CRT = chemoradiotherapy, CT = chemotherapy, RT = radiotherapy, SCC = squamous cell carcinoma, AC = adenocarcinoma, CP = cisplatin, 5FU = 5-fluorouracil, BL = bleomycin, VBL = vinblastin, n.s. = not significant

found that chemoradiotherapy plus surgery compared with surgery alone significantly reduced the three-year mortality rate. However, postoperative mortality was significantly increased by preoperative chemoradiotherapy. The significant effect on survival was lost when the Walsh study was excluded from the analysis. Kaklamanos and colleagues performed a meta-analysis on five randomised studies. The 2-year survival was 6.4% better in the group of patients who received preoperative chemotherapy, but no statistical significance was reached [26]. Treatment mortality increased by 3.4% with chemoradiotherapy (95% CI, -.1% - 7.3%) compared to surgery alone. Urschel and colleagues analysed 9 randomised trials comparing neoadjuvant chemoradiotherapy and surgery to surgery alone for resectable oesophageal cancer [27]. Three of these nine studies were only published in abstract form. Survival of the two patient groups was similar at one and two years, but the 3-year survival was significantly higher in the group of patients treated with preoperative chemoradiotherapy. A flaw of these meta-analyses is that studies were included with study designs, treatment regimes and staging procedures, which are not longer considered optimal by today's standards.

An alternative trial design was used in a French study. Patients who had a response to preoperative chemoradiotherapy were randomised between continuing chemoradiotherapy or surgery [28]. A total of 259 patients were randomised and no significant difference in the 2-year survival was observed between these two groups. A more or less similar design was followed in a German multicenter study. In this study 177 patients with squamous cell carcinoma of the oesophagus were treated with 3 cycles chemotherapy consisting of 5-fluorouracil, leucovorin, etoposide and cisplatin followed by chemoradiotherapy (cisplatin, etoposide and 40 Gy radiotherapy) followed by surgery or definitive chemoradiotherapy [29]. There was no statistical difference in median survival and 3-year survival between both groups. Although longer follow-up is needed and the definitive publications have to be awaited, such approaches question the role of additional surgery in at least those patients who respond to chemoradiotherapy. Positron emission tomography allows early identification of non-responding patients to chemoradiotherapy and could probably be helpful in the decision whether the patient should continue chemoradiotherapy or should be operated on [30-32]. In a systematic review of 12 studies positron emission tomography as a diagnostic tool in preoperative staging had a moderate sensitivity and specificity for the detection of locoregional lymph node metastases, and a reasonable sensitivity and specificity for the detection of haematogenous metastases. Thus the role of positron emission tomography in the initial work-up of patients with oesophageal cancer is debatable [33].

In a number of phase I and II studies newer chemotherapeutic agent such as paclitaxel, docetaxel, irinotecan or biologicals have been combined with cisplatin or carboplatin and concurrent radiotherapy [34-37]. Although the results of these studies are encouraging the efficacy of these treatments has to be confirmed in randomised phase III studies.

Many questions remain concerning the optimal radiation dose and schedule and chemotherapy regime. In a number of patients organ preservation might be possible, thereby avoiding unnecessary additional surgery, although the appropriate selection criteria to identify such a subgroup of patients are still lacking.

DEFINITIVE CHEMORADIOTHERAPY

Patients with potentially resectable oesophageal cancer but not considered fit enough for major surgery are often treated with radiotherapy alone or definitive chemoradiotherapy. Unfortunately, the results of radiotherapy alone in the treatment of patients with oesophageal cancer are poor. Even with high-dose radiotherapy, failure at the primary tumour site is frequent up to 60 – 80% [38] and only a small number of patients treated with high-dose radiotherapy survive 5 years or longer. Chemotherapy is often added to radiotherapy with the aim of improving local control and survival. In more than a dozen randomised studies radiotherapy alone is compared with chemoradiotherapy. An overview of these studies is listed in Tables 3 and 4. No firm conclusions can be derived from the majority of these studies for the same reasons concerning study design as is the case with the studies in preoperative chemotherapy or chemoradiotherapy. Furthermore, in a number of studies patients were included with both resectable and not resectable tumours.

The Radiation Therapy Oncology Group (RTOG) 85-01 study is one the most frequently cited studies wherein radiotherapy combined with 2 courses of 5-fluorouracil and cisplatin followed by 2 additional courses was compared with radiotherapy alone [39]. The results of an interim analysis revealed statistically significant survival difference in favour of the chemoradiotherapy arm (median survival 12.5 months versus 8.9 months) which led to early closure of this study. In the RTOG 94-05 study patients were randomised to receive the same chemoradiotherapy regime as was used in the RTOG 85-01 study or the same chemotherapy regime combined with a higher dose of radiotherapy (64.8 Gy) [40]. After an interim analysis the trial was closed prematurely because of a high number of treatment related deaths in the high-dose radiotherapy arm. There was no significant difference in median or 2-year survival between the 2 arms. A randomised trial involving a total of 221 patients consisting of split-course radiotherapy with or without 2 courses cisplatin given 3 or 4 days before the start of radiotherapy and 4 courses afterwards was performed by the EORTC [41]. No significant difference in overall survival was found,

Table 3. Phase III trials of sequential chemoradiotherapy versus radiotherapy alone as definitive treatment in patients with oesophageal cancer

Author[ref]/Year	Histology	No. of patients		CT	RT(total dose)	One-year survival (%)		Significance
		CRT	Control			CRT	Control	
Roussel[74]1989	SCC	84	86	MTX	40.5 Gy +15.75 Gy boost	31	35	n.s.
Zhou[75]1991		32	32	CP/5FU	65-75 Gy	77	33	significant
Hishikawa[76]1991	SCC	24	25	Futrafur	50-70 Gy ± brachytherapy			n.s.
Hatlevoll[77]1992	SCC	46	51	CP/BL	2 x 18.5 Gy	18	29	n.s.
Lu[78]1995		30	30	A/CP/5FU	RT 60-70 GyCRT 50 Gy	63	37	significant

CRT=chemoradiotherapy, CT= chemotherapy, RT= radiotherapy, SCC=squamous cell carcinoma, MTX= methotrexate, CP=cisplatin, 5FU=5-fluorouracil, BL=bleomycin, A=doxorubicin, n.s.=not significant

Table 4. Phase III trials of concurrent chemoradiotherapy versus radiotherapy alone as definitive treatment in patients with oesophageal cancer

Author[ref]/Year	Histology	No. of patients		CT	RT	One-year survival (%)		Significance
		CRT	Control			CRT	Control	
Earle[79]1980	SCC	47	44	BL	50-60 Gy	22	32	n.s.
Zhang[80]1984	SCC/AC	48	51	BL	39-73 Gy (mean 63.5Gy)			n.s.
Andersen[81]1984	SCC	40	42	BL	55-60 Gy			
Araujo[82]1991	SCC	28	31	5FU/MMC/ BL	50 Gy / 25 fr	64	55	n.s.
Roussel[83]1994	SCC	110	111	CP	40 Gy	47	31	significant
Kaneta[84]1997	SCC	12	12	CP	70-72 Gy	40	24	n.s.
Slabber[85]1998	SCC	34	36	CP/5FU	40 Gy	28	20	n.s.
Cooper[86]1999	SCC/AC	61	62	CP/5FU	50 – 64 Gy	52	34	significant

CRT=chemoradiotherapy, CT= chemotherapy, RT=radiotherapy, SCC=squamous cell carcinoma, AC=adenocarcinoma, BL=bleomycin, 5FU=5-fluorouracil, MMC= mitomycin-C, CP=cisplatin

although the median time to local progression was in favour of the chemoradiotherapy arm.

A Cochrane Database Systematic Review has been published in which the effectiveness of chemoradiotherapy versus radiotherapy alone in the outcome of patients with localised oesophageal cancer was evaluated [42]. Thirteen randomised trials were included, with either concomitant (8) or sequential (5) chemoradiotherapy. Patients who were treated with concurrent chemoradiotherapy had a better survival compared to those treated with radiotherapy alone (reduction of one- and two-years mortality rate of 9% and 8% respectively). However chemoradiotherapy was associated with significantly more toxicity than radiotherapy alone. No studies can be found comparing definitive chemoradiotherapy with surgery alone.

There are several approaches to improve the results of chemoradiotherapy. By the use of newer chemotherapeutic agents such as the taxanes and irinotecan, weekly or continuous administration of chemotherapy together with concurrent radiotherapy, hyperfractionated radiotherapy schedules, better treatment results are possibly obtained [34-37]. Targeted therapy with a cyclooxygenase-2 (COX-2) inhibitors or epidermal growth factor receptor (EGFR) blocking antibodies are attractive agents for combining with radiotherapy alone or with chemoradiotherapy. Phase 1 studies with the combination of chemoradiotherapy therapy and celecoxib for patients with unresectable oesophageal carcinoma are underway [43, 44]. In a phase III trial patients with locoregionally advanced squamous cell carcinoma of the head and neck were randomised to receive radiation alone, or radiation plus weekly cetuximab [45]. A statistically significant prolongation in overall survival was found (median survival was 28 months for patients treated with radiotherapy only and 54 months with cetuximab and radiation), with only a minimal increase in overall toxicity. This is a promising approach that should also be

explored in other epithelial malignancies demonstrating overexpression of EGFR, such as oesophageal cancer.
In conclusion, patients with potentially resectable oesophageal cancer, but poor candidates for surgery can be treated with concurrent chemoradiotherapy. Concurrent chemoradiotherapy leads to a modest gain in overall survival compared to radiotherapy alone at the cost of increased treatment related toxicity. The radiosensitizing effect of biologicals needs to be further explored.

PALLIATIVE CHEMOTHERAPY

Improving or maintaining quality of live and symptom relief are important treatment goals in the management of patients with metastatic oesophageal cancer perhaps even more important than some prolongation of survival. Dysphagia is one of the most common symptoms and although chemotherapy can to some extent alleviate dysphagia [46, 47], most patients are palliated by selfexpanding metal stent placement or external beam radiation or brachytherapy [48].
The most frequently used chemotherapy regimen for patients with metastatic disease is a combination of 5-fluorouracil and cisplatin with response rates ranging from 15% to 45% [49]. In the last years agents, such as taxanes and irinotecan, have been tested as a single agent or in combination with cisplatin with encouraging response rates [50, 51].
The variation in results reported in several phase II studies, even when the same agent or combinations are used, is most probably due to both patient and disease characteristics of the treated patients. Polee and colleagues analysed prognostic factors in patients with advanced oesophageal cancer treated with cisplatin-based combination chemotherapy [52]. In a multivariate analysis performance status, serum lactate dehydrogenase and extent of disease were significant prognostic factors. The median survivals of patients with 0, 1, 2 and 3 risk factors were 12, 8, 6 and 4 months respectively. In a multivariate prognostic factor analysis performed in a group of 1080 patients with advanced and metastatic oesophagogastric cancer enrolled into three randomised trials, performance status, the presence of liver and/or peritoneal metastases, and serum alkaline phosphatase were identified as significant prognostic factors [53]. Patients with no risk factors had a better survival than patients with one or two risk factors (median survival 11.8 and 7.4 months respectively). Patients with three or four risk factors had the worst prognosis (median survival of 4 months). There were no survival differences among patients with oesophageal, oesophagogastric junction, or gastric cancers, 296, 248 and 512 patients, respectively.
We were able to identify seven randomised chemotherapy trials for patients with metastatic oesophageal cancer [54-61]. In the study of Nicolaou and colleagues [54] patients were randomised to tube insertion versus tube insertion with chemotherapy (cyclophosphamide and doxorubicin). Only 24 patients were included in this pilot study, so no meaningful conclusions can be drawn. Levard and colleagues randomised 156 patients to chemotherapy with 5-fluorouracil and cisplatin versus no treatment [55]. No difference in survival was found between both arms. However, only 14 patients had metastatic disease and the other patients were randomised after a complete resection of the tumour but with lymph node involvement, an incomplete resection of the tu-

mour or had irresectable disease. In a randomized phase II study reported by Bleiberg and colleagues patients with squamous cell carcinoma of the oesophagus were randomised to treatment with 5-fluorouracil and cisplatin or cisplatin alone [56]. A higher response rate and more severe side-effects were reported for the combination arm. No survival difference between both treatment arms was found but, noteworthy, the study was not powered to detect a meaningful difference in survival. In the study reported by Ezdinli 63 patients treated with either doxorubicin, methotrexate or 5-fluorouracil [57]. Median survival was 8.1, 13.7 and 23 weeks respectively. A substantial number of patients dropped out after randomisation.
In the three larger studies patients with oesophageal and gastric cancer were included. Webb and colleagues conducted a prospective randomised trial comparing combination chemotherapy with epirubicin, cisplatin and 5-fluorouracil (ECF) with a regimen consisting of 5-fluorouracil, doxorubicin and methotrexate (FAMTX) [58, 59]. Of the 256 eligible patients 51 had oesophageal cancer, 60 cancer of the oesophagogastric junction and 145 gastric cancer. The ECF regimen resulted in a survival advantage, 8.9 versus 5.7 months, with tolerable toxicity and better quality of life compared with the FAMTX regimen. In the study of Ross and colleagues ECF was compared with mitomycin, cisplatin and 5-fluorouracil in 580 patients with oesophagogastric cancer including 188 patients with oesophageal cancer and 125 with cancer of the oesophagogastric junction [60]. Equivalent efficacy was found, but quality of life was superior with ECF. Tebbut and colleagues compared protracted venous infusion of 5-fluorouracil with mitomycin with protracted venous infusion of 5-fluorouracil alone in 254 patients with cancer involving the oesophagus (56 patients), oesophagogastric junction (63 patients) or stomach (131) [61]. The median age of patients was high (72 years) and the overall response rate was low (19.1% versus 16.1%), but more than 64% of the patients had improvement in pain control, weight loss, dysphagia, or oesophageal reflux.
In summary in 2 trials a significant effect of chemotherapy on quality of life and/or overall survival was demonstrated [58, 60]. In both of these trials patients with oesophageal and gastric cancer, predominantly adenocarcinomas, were treated. Whether newer agents such as the taxanes, irinotecan, oxaliplatin, oral fluoropyrimidines and biologicals will have an additive positive effect on symptom relief, quality of life and survival needs further investigation.

CONCLUSIONS

Over the years much effort has been put in initiating and conducting studies with chemotherapy alone or combined with other modalities for patients with oesophageal cancer. Most of these studies are feasibility studies, phase II studies and underpowered phase III studies. Unfortunately, there are more reviews published of the management of oesophageal cancer than there are publications about phase III trials and only a limited number of patients are entered in trials. Munro estimated that of the 6.4 million people that developed oesophageal cancer during 1973 and 1995 only data of 4388 patients were included in systematic reviews [62].
What we have learnt until now is that it is feasible to administer chemotherapy preoperatively with or without radiotherapy or to combine chemotherapy with radiotherapy

as definitive treatment. For patients with metastatic disease patient characteristics such as performance status, extent of disease and elevated levels of serum alkaline phosphatase or lactate dehydrogenase are important prognostic factors when these patients are treated with chemotherapy [52, 53]. There are some indications that preoperative chemotherapy or preoperative chemoradiotherapy may have some impact on survival but the precise extent, if any, is still unknown and also whether it outweighs the increased treatment related toxicity [13, 25]. The evidence that chemotherapy may be beneficial for patients with metastatic disease can only be derived from 2 trials in which both patients with oesophageal and gastric cancer were treated [58, 60].

The results of chemoradiotherapy regimes with the use of newer chemotherapeutic agents and an increase in radiation dose and dose intensity look promising and the incorporation of biologicals in the management of patients with oesophageal cancer needs further investigation. The key issue is however that we need more well designed, adequately powered, randomised trials.

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Chapter 3

Neoadjuvant concurrent chemoradiation with weekly paclitaxel and carboplatin for patients with oesophageal cancer: a phase II study

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ABSTRACT

This study was performed to assess the efficacy and safety of preoperative chemoradiation consisting of carboplatin and paclitaxel and concurrent radiotherapy for patients with resectable (T2-3N0-1M0) oesophageal cancer. Treatment consisted of paclitaxel 50 mg/m^2 and carboplatin AUC=2 on day 1,8,15, 22 and 29 and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week), followed by oesophagectomy. All 54 entered patients completed the chemoradiation without delay or dose-reduction. Grade 3-4 toxicities were: neutropenia 15%, thrombocytopenia 2%, and oesophagitis 7.5%. After completion of the chemoradiotherapy 63% had a major endoscopical response. Fifty-two patients (96%) underwent a resection. The postoperative mortality rate was 7.7%. All patients had an R0-resection. The pathological complete response rate was 25%, and an additional 36.5% had less than 10% vital residual tumour cells. At a median follow-up of 23.2 months, the median survival time has not yet been reached. The probability of disease-free survival after 30 months was 60%.
In conclusion, weekly neoadjuvant paclitaxel and carboplatin with concurrent radiotherapy is a very tolerable regimen and can be given on an outpatient basis. It achieves considerable down staging and a subsequent 100% radical resection rate in this series. A phase III trial with this regimen is now ongoing.

INTRODUCTION

The prognosis of oesophageal cancer is poor in symptomatic patients, e.g. those with dysphagia. At the time of first diagnosis, almost half of such patients already have metastatic disease; the other half usually has locally advanced disease (T3N0 or T3N1). Furthermore, although surgical resection is still first choice of treatment for fit patients with resectable disease, most of these patients have a poor outcome. This is reflected by a 5-year survival rate of approximately 20 percent [1]. Despite the routine use of staging procedures such as Computed Tomography (CT), Magnetic Resolution Imaging (MRI) and Endoscopic Ultrasound (EUS), many oesophageal tumours are incompletely resected [2]. In a number of large randomized studies, the percentage of incomplete resections varied between 25 and 46 percent [3-5]. Hulscher et al. found an incomplete resection rate of 25% in extended transthoracic surgery versus 29% in limited transhiatal resection for adenocarcinoma of the oesophagus. In the study performed by the Medical Research Counsel, resection was microscopically complete (R0) in 60% when surgery was preceded by chemotherapy, and 54% in the surgery alone group. Kelsen et al. found incomplete resections in 14% of the patients when surgery was preceded by chemotherapy versus 30% for surgery alone.
Preoperative chemoradiotherapy may induce considerable tumour shrinkage and thereby increase the number of radical resections. In this setting, concurrent chemoradiotherapy with 5-fluorouracil (5-FU) and cisplatin is one of the most commonly used regimens. Unfortunately, the impact of preoperative chemoradiotherapy with 5-FU and cisplatin on survival is uncertain. An improved 3-year survival was shown in three meta-analyses of randomized controlled trials comparing neoadjuvant chemoradiotherapy and surgery to surgery alone [6-8], but if the study by Walsh et al [9] is excluded, this

benefit is lost. Furthermore, chemoradiotherapy with 5-FU and cisplatin can induce severe toxicity and most patients have to be hospitalized for this treatment. Thus, the best regimen of preoperative chemoradiation has not yet been established.
Recently, studies with radiotherapy combined with paclitaxel with or without cisplatin or carboplatin have shown promising results in other tumour types. Paclitaxel is a microtubule-stabilizing agent that blocks the cell cycle in the G2 and M phase, the most radiosensitive phase. The radioenhancing effects of paclitaxel have been demonstrated in vitro in a human leukaemic cell line and in cell lines of squamous cell carcinoma and astrocytoma [10-12]. Besides its radiosensitizing effect, it also enhances the result of radiotherapy by increasing apoptosis and tumour reoxygenation. A weekly schedule permits an increase in dose-intensity and can provide continuous radiosensitizing plasma drug levels.
The combination of paclitaxel and carboplatin with concurrent radiotherapy has been tested in patients with advanced non-small-cell lung cancer. In five phase II studies, the combination of paclitaxel and carboplatin was given weekly with concurrent radiotherapy, followed by two or four 21-day cycles of consolidation chemotherapy [13-17]. The overall response rate varied from 71 to 79%. The major toxicity was oesophagitis. In 10-46% of the patients a grade three or four oesophagitis was found. Treatment with paclitaxel and carboplatin and concurrent radiotherapy can be given on an outpatient basis, which is advantageous. Furthermore, this regimen is probably less toxic than cisplatin based therapy.
On the basis of these considerations, we initiated a phase II study to determine the response rate and toxicity of a preoperative chemoradiotherapy regimen consisting of carboplatin and paclitaxel with concurrent radiotherapy in patients with a potentially resectable carcinoma of the oesophagus.

METHODS

Eligibility criteria

Patients with histologically proven squamous cell carcinoma, adenocarcinoma, or undifferentiated carcinoma of the oesophagus with the upper border at least 3 cm below the upper oesophageal sphincter were included. Disease was limited to T1N1 or T2-3N0-1M0 tumours. Tumours extending below the gastro-oesophageal (GE) junction into the proximal stomach were also eligible, provided that the bulk of the tumour was located in the oesophagus. The longitudinal tumour length had to be ≤ 8 cm and the radial tumour length ≤ 5 cm. Patients were required to be aged 18 to 75 years and to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. Other criteria included adequate haematological, renal, hepatic and pulmonary functions as defined by: a granulocyte count of at least 1,500/mm^3 and a platelet count 100,000/mm^3; a serum creatinine level < 120 µmol/l and a bilirubin level ≤1.5x upper normal limit; and a forced expiratory volume in one second (FEV1) of at least 1.2 L. The Medical Ethics Committee of Erasmus University Medical Centre approved the study. Written informed consent was required. No previous chemotherapy and radiotherapy or a past or current history of malignancy other than entry diagnosis was allowed, except for non-melanomatous skin cancer, curatively treated carcinoma in situ of the cervix, or a "cured" malignancy

more than five years prior to enrolment. Patients were not eligible if they had lost more than 10% of their body weight or had an inadequate caloric- and/or fluid intake.

Staging

Pre-treatment evaluation included a detailed history taking, a physical examination and a routine complete blood work-up. All patients underwent a baseline upper gastrointestinal (GI) endoscopy and EUS, and a CT of the chest and the upper abdomen, plus ultrasonography of the neck and pulmonary function tests.

Treatment

Chemotherapy

Paclitaxel 50 mg/m^2 and Carboplatin targeted at an AUC of 2 were administered on days 1, 8, 15, 22 and 29. All patients received dexamethasone 10 mg, clemastine 2 mg and ranitidine 50 mg, administered intravenously 30 minutes prior to paclitaxel infusion. Paclitaxel was given as a 1-hour infusion diluted in 500 mL of sterile and isotonic sodium chloride solution (saline). After the completion of the paclitaxel infusion, 100 mL of saline was infused over 30 minutes followed by an infusion of 8 mg ondansetron or its equivalent diluted in 100 mL of saline given over 30 minutes. Hereafter, the total calculated dose of carboplatin diluted in 500 mL of 5% dextrose solution was administered over 1-hour. Dose modifications were made for toxicity, using the National Cancer Institute - Common Toxicity Criteria (NCI-CTC version 2).

Radiotherapy

All patients were irradiated by external beam radiation, using a 3-D conformal radiation technique. The Gross Tumour Volume (GTV) was defined by the primary tumour and any enlarged regional lymph nodes, and was drawn on each relevant CT slice. The Planning Target Volume (PTV) provided a 1.5 cm radial margin and a proximal and distal margin of 4 cm around the GTV. If the tumour extended into the stomach, a distal margin of 3 cm was chosen. Before the start of the irradiation, a planning CT scan was made from the cricoid to L1 vertebra with a slice thickness of ≤ 5 mm, with the patient in treatment position. Beams-eye-view (BEV) was used to ensure optimal target volume coverage and optimal normal tissue sparing. The prescription dose was specified at the ICRU 50/62 reference point, which was the isocenter for most patients. The daily prescription dose was 1.8 Gy at the ICRU reference point and the 95% isodose had to encompass the entire planning target volume (PTV). The maximum to the PTV was not allowed to exceed the prescription dose by >7% (ICRU 50/62) guidelines. Tissue density inhomogeneity correction was used. Portal images were obtained during the first fraction of all fields. A total dose of 41.4 Gy was given in 23 fractions of 1.8 Gy, with 5 fractions per week starting on the first day of the first cycle of chemotherapy.

Surgery

Surgery was planned within six weeks after the completion of the chemoradiation. For carcinomas located distally of the tracheal bifurcation, a transhiatal oesophageal resection was favoured. For carcinomas located proximally to the tracheal bifurcation, a transthoracic oesophageal resection was performed. In both techniques, a wide local

excision including the N1 lymph nodes was carried out, including a standard resection of the lymph nodes around left gastric artery. The continuity of the digestive tract was restored by means of a gastric tube reconstruction with an anastomosis in the neck.

Pathological Analysis

The resection specimen was evaluated using a standard protocol, providing information on margins, tumour type, extension of the tumour, and lymph nodes. The 6th edition of the International Union Against Cancer (UICC) was used for TNM-classification, tumour grade, and stage grouping [18]. When no tumour tissue could be seen, lesions such as an ulcer or an irregular area covered by mucosa were embedded in total together with surrounding areas in order to adequately judge the presence of residual tumour and therapy effects. The grading of the therapy response was performed as described by Junker et al. [19]. The degree of histomorphological regression, i.e. the effect of chemoradiation, was classified into four categories: grade I: more than 50% vital residual tumour cells; grade II: 10-50% vital residual tumour; grade III: less than 10% vital residual tumour cells; grade IV: complete tumour regression, no evidence of vital tumour cells.
A two-field lymph node dissection was carried out containing regional (mediastinal, oesophageal) and distant sites (coeliac region). The resection margins, especially the circumferential margin, were evaluated with a 1 mm cut-off point for vital tumour, implying that the tumour-free margin is >1mm. If vital tumour was present at ≤ 1mm from the surgical resection margin it was considered positive.

Restaging and follow-up

Upper GI endoscopy and CT of the chest and upper abdomen were repeated after the completion of the chemoradiation and ahead of the planned operation. Pulmonary function tests were repeated six and twelve months after therapy. Follow-up visit were performed every three months during the first 2 years and every 6 months thereafter to document late toxic effects, and, if applicable, disease relapse or progression, and death.

Statistical Analysis

As the statistical design was intended to allow us to detect a response percentage of at least 40%, it was calculated that 50 patients were needed. The pathological response to chemoradiation was defined as mentioned above. The response to chemoradiotherapy evaluated by endoscopy was classified as either no response, less than 50 per cent response, more than 50 per cent response, or complete response. These broad classifications were used in an attempt to reduce inter-observer variation [20]. Tumour response evaluated by radiology was assessed according to the Response Evaluation Criteria In Solid Tumours (RECIST) [21].
Survival time was calculated as the duration from the day of start of chemoradiotherapy to death or the last follow-up, and recurrence-free interval was calculated from the day of surgery to the day of diagnosis of recurrence. Overall and disease-free survivals were estimated using the Kaplan-Meier method. Median survival time was obtained from the time corresponding to 50% survival based on the Kaplan-Meier survival curve.

RESULTS

Patient Characteristics

Fifty-four eligible patients were enrolled between February 2001 and January 2004. Written informed consent was obtained from all patients. Characteristics of these 54 patients are summarized in Table 1. Ninety-one percent of patients were male and 76%

Table 1. Patient Characteristics

Characteristic	Number (%)
Total number of patients	54
Sex	
Male	49 (91)
Female	5 (9)
Age (years)	
Median	59
Range	40-75
Performance status (ECOG)	
0	35 (65)
1	18 (33)
Unknown	1(2)
Weight loss (%)*	
Median	2
Range	0-12
Histology	
Adenocarcinoma	41 (76)
Squamous cell carcinoma	12 (22)
Large cell carcinoma	1(2)
Barrett's oesophagus@	
Yes	19 (46)
No	17 (42)
Unknown	5 (12)
Stage (EUS)	
T2N0	5 (9)
T2N1	2 (4)
T3N0	18 (33)
T3N1	21 (39)
No pass	8 (15)
Primary site	
Thoracic oesophagus	5 (9)
Lower oesophagus	49 (91)

*calculated from the data of 52 patients

@calculated in 41 patients with adenocarcinoma. Yes=Barrett's oesophagus identified by upper endoscopy and confirmed by histopathologic examination. No=No Barrett's oesophagus identified by upper endoscopy or by histopathologic examination. Uncertain=Barrett's oesophagus identified by upper endoscopy or by histopathologic examination.

EUS=Endoscopic ultrasound

had an adenocarcinoma. Of these 41 adenocarcinomas, 23 were located at the gastro-oesophageal junction and 18 in the distal oesophagus. The patient with 12% weight loss was accepted for chemoradiotherapy, because the weight loss was partly due to de novo diagnosed diabetes mellitus.

Toxicity of and adherence to chemoradiotherapy

Fifty-three patients (98%) completed the preoperative treatment. One patient died at home after the second course of chemotherapy, probably due to a cardiac arrest. All other patients completed the neoadjuvant chemoradiotherapy as scheduled, without treatment delay or dose reduction. The 1.5 cm radial radiation margin was achieved in all patients, there were no compromises. The V20 was obtained in all patients and never exceeded 30% of the total lung volume. The acute toxicities due to the chemoradiation were usually mild. Haematological toxicity is listed in Table 2. Grade 3 or 4 toxicity consisted of leucopenia in 13 patients (23.5%), neutropenia in eight patients (15.1%), and thrombocytopenia in one patient (1.9%). Two patients required a blood transfusion for anaemia (3.8%). Infectious complications were rare, only one patient was treated for pneumonia due to aspiration, no neutropenia was found. Three other patients also developed fever, but no infectious focus was found (see below). Relevant non-haematological toxicity (Table 3) consisted mainly of oesophagitis and dysphagia. Four patients (7.5%) developed grade 3 oesophagitis. Dysphagia improved during chemoradiation in 17 of 35 patients (48.6%), three of whom had initial nutritional support because of grade 3 dysphagia, which could be discontinued. Dysphagia worsened in nine patients (17%), three of whom required nutritional support because of grade 3 dysphagia. In three patients needing nutritional support before starting chemoradiation the support could not be discontinued during the chemoradiation. Sensory neuropathy was seen in only 5 patients (9.4%), in 3 patients it resolved after completion of the chemoradiotherapy. Seven patients (13.2%) were hospitalized. Five of them were briefly hospitalized for placing a nasogastric tube for nutritional support, because of grade 3 oesophagitis or dysphagia. One also had a pulmonary embolism and fever with grade 3 neutropenia, one was also treated for pneumonia due to aspiration, and one patient also had fever with grade 3 neutropenia. One patient was hospitalized because of rectal bleeding. Colonoscopy revealed a non-malignant polyp, which was removed. One patient was hospitalized because of vomiting and fever with grade 2 neutropenia.

Table 2. Haematological toxicities

	Grade				
	0	1	2	3	4
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Anaemia	7 (13.2)	42 (79.2)	4 (7.5)	-	-
Leucopenia	4 (7.5)	11 (20.8)	25 (47.2)	12 (22.6)	1 (1.9)
Neutropenia	17 (32.1)	19 (35.8)	9 (17)	8 (15.1)	-
Thrombocytopenia	30 (56.6)	19 (35.8)	3 (5.7)	1 (1.9)	-

Data from 53 evaluable patients

Response to chemoradiotherapy

Evaluation with upper GI endoscopy and CT was done after a mean of ten days following the last radiotherapy session. Response evaluation with endoscopy showed a complete response in ten patients (18.9%), a major response in 23 patients (43.4%), a minor response in 11 patients (20.8%), and no response in one patient (1.9%). In five patients response evaluation by endoscopy was not possible (in one patient there was "no pass", in four patients the baseline endoscopy was performed in another hospital) and in three patients no endoscopy was performed after completing the chemoradiation. Response evaluated with CT showed no complete response or disease progression. In three patients (5.6%) a partial response was observed.

Surgical Results

One patient refused surgery after having completed the chemoradiotherapy. Endoscopy in this patient revealed a complete response. After 12 months of follow-up, a local recurrence of the oesophageal tumour was diagnosed, further workup also revealed supraclavicular lymph nodes. He refused further treatment. Thirteen months later he died from progressive disease. A transhiatal oesophagectomy was performed in 46 of the 52 patients, and a transthoracic resection in 6 patients. The median time between the completion of chemoradiotherapy and surgery was 42 days (range 20 to 74 days). The in hospital postoperative mortality rate was 7.7% (CI 0-15%). Two patients died from systemic complications due to anastomotic leakage, one patient from a cerebral vascular accident one day after surgery, and one from sepsis. Autopsy in the latter patient revealed a prostatitis as the probable focus of the sepsis. Postoperative complications were seen in 38 patients (73%). These complications were mainly pulmonary (42%) or cardiac (13%) (Table 4). Besides the two lethal anastomotic leaks, in 10 of the 48 (20.8%) patients surviving postoperatively an anastomotic leak was seen. In five of them (10.4%) the leakage was a radiological finding on routinely performed contrast swallow postoperatively. In all patients the clinical signs of the leak could be treated conservatively, but in two patients (4.2%) the leak resulted in long-term nutritional support. Twenty-two patients (45.8%) developed an anastomotic stricture requiring endoscopic dilatation (range 1-27, median 7). Eventually, all patients were able to eat solid food.

Pathological results

In 13 patients no residual tumour in the resected oesophagus or regional lymph nodes was found, corresponding to a pathological complete response (pCR) rate of 25%. The pathological stages of the other resection specimens were: pT1N0-1M0 in 12 patients

Table 3. Non-haematological toxicities

	Grade				
	0	1	2	3	4
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Nausea	15 (28.3)	35 (66)	3 (5.7)	-	-
Vomitus	36 (67.9)	15 (28.3)	2 (3.8)	-	-
Oesophagitis	11 (20.8)	23 (43.4)	15 (28.3)	4 (7.5)	-
Lethargy	23 (43.4)	23 (43.4)	7 (13.2)	-	-
Skin toxicity	34 (64.2)	18 (34)	1 (1.9)	-	-

Data from 53 evaluable patients

(23.1%), pT2N0-1M0 in 6 patients (11.5%), pT3N0-1M0 in 16 patients (30.8%), pT0-3N0-1M1A in 4 patients (7.7%), and pT1N1M1B in 1 patient (1.9%). In 19 patients (36.5%) a regression grade III, in 14 patients (26.9%) a regression grade II, and in 6 patients (11.5%) a histopathological regression grade I was seen. In 7 of the 18 patients (38.9%) with a pathological T3-stage only scattered tumour cells were found in the resection specimen. A radical resection with no evidence of tumour cells at the resection margins (R0-resection) was obtained in all patients. The lymph node dissection status showed a median of eight nodes (range 0-30), derived from both regional and distant sites. In 13 patients (25%) one or more positive lymph nodes were found (median 2, range 1-6). The N-stage improved from N1, as assessed by EUS, to N0 postoperatively in 19 patients (36.5%). In 4 patients (7.7%) the N0-stage, as assessed by EUS, was changed towards a N1-stage postoperatively.

Pulmonary toxicity

The post-treatment pulmonary function tests (measured 6 months and 1 year after surgery) deteriorated significantly compared to the pre-treatment tests. The total lung capacity (TLC) decreased from 103 percent of the predicted value to 92 percent ($p=0.002$). The vital capacity (VC) declined from 105 percent of the predicted value to 96 percent ($p<0.001$). The forced expiratory volume in 1 second (FEV1) decreased from 94 percent of the predicted value to 87 percent ($p<0.0001$). This decline in pulmonary function tests did not lead to major clinical symptoms.

Survival

All 54 patients were included in the survival analysis. At the time of evaluation (May 31, 2005) the median follow-up time for all patients was 23.5 months (range 0 to 52

Table 4. Postoperative complications

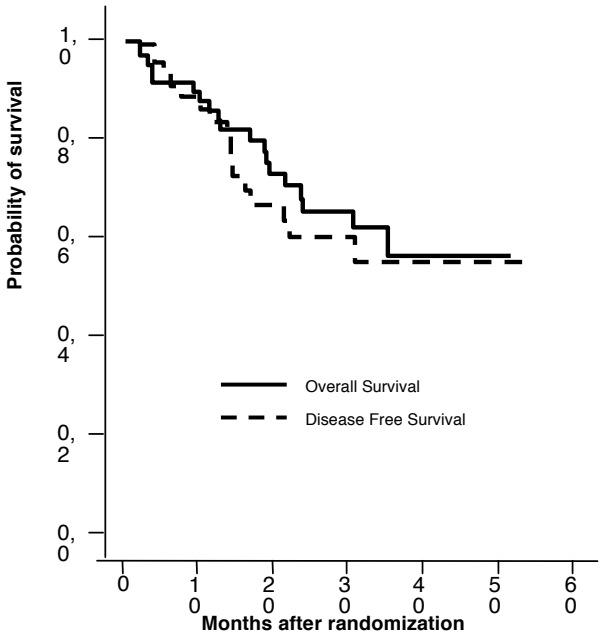
Complication	Number **of patients**
None	14
Pulmonary	22*
Upper airway infection	9
Pneumonia	7
Chylothorax	3
Pulmonary embolism	2
Pleural effusion	2
Atelectasis	1
Pleural empyema	1
Acute respiratory distress syndrome	1
Cardiac	12
Atrial fibrillation	10
Decompensation cordis	2
Asystole during intubation	1
Wound infection	5
Vocal cord paralysis	3
Other	9

Data from 52 evaluable patients

*In four patients two events

months). The median follow-up time for surviving patients was 31 months (range 11-52 months). Nineteen of the 54 patients (35.2%) died: 13 due to recurrent cancer, five during treatment (four postoperatively and one sudden death) and one due to a ruptured aortic aneurysm. The median survival time, however, has not yet been reached. The estimated 1-, 2-, and 3-year survival rates were 82%, 65%, and 56%, respectively. The Kaplan-Meier curve for overall survival is shown in Figure 1. The survival of patients with a pCR was not better than the survival of patients with no pCR. Recurrent disease after surgery was found in 15 patients surviving postoperatively (15/48, 31.2%). Three of them were still alive at the time of analysis. Recurrence was locoregional in seven patients. Distant metastases were found in 14 patients. The patient who refused surgery died from recurrent disease as well (see before). The Kaplan-Meier curve for disease free survival of the patients surviving postoperatively is shown in Figure 1. The patient who died without recurrence was censored at the time of death.

Figure 1. Kaplan-Meier survival curves



DISCUSSION

Preoperative chemoradiotherapy is nowadays widely used in the treatment of patients with potentially resectable oesophageal cancer. The concept that preoperative chemoradiotherapy may lead to a better tumour control and therefore to a better overall survival is appealing, as 29-43% incomplete resections are performed when patients are treated with surgery alone or with chemotherapy followed by surgery [3-5]. Many studies have reported that after chemoradiotherapy in 10-28% of the patients no tumour

cells are found in the resection specimen [9, 22-25]. However, surprisingly few phase III studies have been reported in which preoperative chemoradiotherapy followed by surgery was compared with surgery alone. Meta-analyses of these trials showed a small, if any, effect on survival [6-8]. In addition, the results of a recently reported study were disappointing, showing no survival benefit for those patients treated with preoperative chemoradiotherapy [26]. In most studies, the combination of 5-FU and cisplatin with radiotherapy has been applied. In our study we used paclitaxel and carboplatin with concurrent radiotherapy.

Our study showed that preoperative chemoradiotherapy with weekly paclitaxel and carboplatin was well tolerated. All patients completed the chemoradiotherapy as scheduled, without treatment delay or dose reduction. The major non-haematological toxicity was a grade 3 or 4 oesophagitis in 7.5% of the patients. Compared to other studies with chemoradiotherapy in oesophageal cancer, this incidence of grade 3 and 4 oesophagitis is low [25, 27].

The postoperative mortality of this study (7.7%; 95% CI 0-15%) was somewhat higher than the approximately 4% mortality rate found in other trials performed at our institution [4, 28, 29], however, the observed mortality rate still lies within the 95% confidence limits. Postoperative morbidity consisted mainly of pulmonary complications. This high pulmonary complication rate is partly due to the fact that we also scored minor pulmonary complications, such as upper airway infections. Whether preoperative chemoradiotherapy is responsible for a higher pulmonary complication rate cannot be excluded. In a retrospective study of Avendano et al preoperative chemoradiotherapy was associated with an increase risk of pulmonary complications (i.e., duration of mechanical ventilation) [30]. Whether the decline in pulmonary function tests (TLC, VC, and FEV1) that we observed in our study was due to the chemoradiotherapy is uncertain, as it has also been reported that the TLC and the VC were significantly reduced after an oesophagectomy without preoperative treatment [31].

During follow-up 22 patients required dilatations because of an anastomotic stricture. The dilatations resolved the dysphagia in all patients, eventually all patients had an adequate food intake. Neoadjuvant chemoradiotherapy has not been reported to be associated with a higher stricture formation rate [32].

In this study, the overall and disease free survivals compare favourably with those in other trials of preoperative chemoradiation for oesophageal cancer. With a median follow-up of 23.5 months, the median survival time has not yet been reached. However, such findings should be interpreted with caution, because phase II studies always carry the risk of selection bias. A complete (R0) resection was accomplished in all patients, using a 1 mm cut-off point for circumferential resection margin and this also compares favourably with other studies. The pathologically complete response rate of 25% in our study is consistent with that in other studies using preoperative chemoradiation. A major histomorphological regression was seen in another19 resected specimens. Thus, in a total of 32 patients (61.5%) a major or complete pathological response to preoperative chemoradiation was found. Several studies have shown that a pCR and an R0-resection are associated with a better prognosis [33, 34]. Surprisingly, we were not able to demonstrate a significant survival difference between patients who had a pCR and those who did not have a pCR. Since all operated patients had an R0 resection, a possible adverse effect of an incomplete resection on survival could not be assessed. The 100% complete

resection rate and high number of patients with a major or complete pathological response might explain the lack of survival benefit in patients who had a pCR.

In conclusion, this study shows that preoperative treatment with weekly paclitaxel and carboplatin with concurrent radiotherapy is well tolerated, with leucopenia and oesophagitis being the most common side effects. After chemoradiotherapy a high rate of radical resections could be achieved and the overall survival looks promising. A randomized phase III trial with this regimen followed by surgery versus surgery alone is now ongoing, which has, up to now, included more than 100 patients in the first year, to determine its role in the treatment of resectable oesophageal carcinoma.

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Chapter 4

Quality of life during neoadjuvant treatment and after surgery for resectable esophageal carcinoma

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ABSTRACT

Purpose. Because of the trade-off between the potentially negative quality of life (QoL) effects and the uncertain favorable survival effect of neoadjuvant chemoradiotherapy in patients with resectable esophageal cancer, we assessed the heath-related QoL (HRQoL) for up to one year postoperatively in these patients, treated with preoperative chemoradiotherapy with a non-platinum based outpatient regimen followed by esophagectomy.

Methods and Materials. Patients undergoing neoadjuvant paclitaxel and carboplatin concurrent with radiotherapy followed by surgery completed standardized HRQoL questionnaires before and after chemoradiotherapy and at regular moments up to one year postoperatively. We analyzed differences in generic Qol core questionnaire [QLQC30] and condition-specific (esophageal site-specific [OES-18]) HRQoL scores over time by using a linear mixed-effects model.

Results. Mean scores of most HRQoL scales deteriorated significantly during neoadjuvant chemoradiotherapy. The largest deterioration was observed for physical and role functioning scales. All but two symptom scores worsened significantly.
Postoperatively, most mean HRQoL scores improved until recovery to baseline level. Speed of improvement varied. The average taste score returned to baseline level three months postoperatively, while it took one year for the average role functioning score to restore. The emotional functioning score showed a different pattern; it was worst at baseline, and increased over time during chemoradiotherapy and postoperatively. The dysphagia and pain scores worsened considerably during chemoradiotherapy, restored to baseline three months postoperatively, and were even significantly better one year postoperatively.

Conclusions. Preoperative chemoradiotherapy with paclitaxel and carboplatin for resectable esophageal cancer had a considerable temporary negative effect on most aspects of HRQoL. Nonetheless, all HRQoL scores were restored or even improved one year postoperatively.

INTRODUCTION

Esophageal cancer is a devastating disease. Many patients, who present with dysphagia, already have irresectable and/or metastatic disease at the time of diagnosis. For those patients with assumingly resectable disease, who are fit enough to undergo a major surgical procedure, esophagectomy is the preferred treatment. However, esophageal surgery is associated with considerable peri-operative morbidity and mortality, especially in low-volume hospitals [1]. Apart from the severe physical impact, an esophageal resection and the underlying disease also have major psychological and social effects. Studies in patients who underwent an esophageal resection for esophageal cancer have shown a decrease in quality of life (QoL) following an esophagectomy. Health-related

QoL (HRQoL) scores are usually restored to baseline values within six to nine months after surgery [2-5].
The 5-year survival after an esophageal resection is approximately 20% [6]. Because of this poor outcome of surgery alone, many patients are nowadays treated with multimodality treatment including preoperative chemoradiotherapy (CRT). An advantage of neoadjuvant CRT may be an increase in the radical resection rate, thereby improving the overall survival. In most phase III studies a positive effect of neoadjuvant CRT on overall survival could not be demonstrated, albeit that in most studies only a small number of patients were included and that most studies had methodological flaws considered by today's standards. Meta-analyses of these studies, on the contrary, suggest a positive effect on overall survival [7].
Whether neoadjuvant CRT leads to a decreased HRQoL during treatment or leads to an impaired and/or delayed recovery of HRQoL after surgery is not well known. Only two papers have addressed this issue [8, 9]. HRQoL analyses are especially important now that neoadjuvant CRT is being increasingly used, because in this situation a negative impact on HRQoL outweighs an uncertain therapeutic benefit.
The aim of this prospective study was to evaluate the HRQoL up to one year after surgery in patients with esophageal cancer treated with curative intent by neoadjuvant CRT with a non-platinum based outpatient regimen followed by esophagectomy. This study adds to the previously published ones, because we used a different CRT regimen (carboplatin and paclitaxel concurrent with radiotherapy). Furthermore, post-CRT HRQoL was measured within one week after finishing CRT, at which time-point toxicity is usually highest.

METHODS AND MATERIALS

Between February 2001 and January 2004 patients with resectable esophageal cancer were asked to participate in a phase II study to determine the response rate and toxicity of a preoperative CRT regimen, consisting of weekly administrations of carboplatin and paclitaxel and concurrent radiotherapy. The details of this study were described elsewhere [10]. Patients who participated in this study were asked to fill in HRQoL questionnaires. Written informed consent was obtained from all patients. The Medical Ethics Committee of Erasmus University Medical Centre, The Netherlands, approved the study.

Treatment

After staging with endosonographic ultrasound, computed tomography of the chest and upper abdomen, and ultrasonography of the neck, patients with stage T1N1 or T2-3N0-1 were treated with paclitaxel 50 mg/m2 and carboplatin AUC 2 on days 1, 8, 15, 22 and 29 and concurrent radiotherapy, followed by esophagectomy. Radiotherapy consisted of a total dose of 41.4 Gy, given in 23 fractions of 1.8 Gy, 5 fractions per week starting on the first day of the first cycle of chemotherapy. All patients were irradiated by external beam radiation, using a 3-D conformal radiation technique. The gross tumor volume (GTV) was defined by the primary tumor and any enlarged regional lymph nodes. The planning target volume (PTV) provided a 1.5 cm radial margin and a proximal and distal margin of 4 cm around the GTV. If the tumor extended into the stomach, a distal margin of 3 cm was chosen.

Quality of life measures

HRQoL was assessed with the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (EORTC QLQ-C30, version 3.0), and with the esophageal site-specific module (OES18) [11-13]. The QLQ-C30 contains five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting), a global health/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The OES18 contains four symptom scales (dysphagia, eating, reflux, and pain) and six single items (trouble with saliva, choking, dry mouth, taste, cough, and speech). Dysphagia, eating, and pain from the OES18 questionnaire were considered disease related symptoms. The other symptom scales were regarded as treatment related. All scores range from 0 to 100. A high score for a functional scale represents a high level of functioning, a high score for the global health/quality of life scale represent a high global QoL, but a high score for a symptom scale or item represents a high level of symptoms.

Timing of assessments

Baseline HRQoL assessments were performed before starting CRT. Follow-up data were collected one week after finishing CRT, and 3, 6, 9, and 12 months postoperatively. The patients themselves filled in the questionnaires.

Statistics

HRQoL data are presented as mean values. For the handling of missing data the EORTC QLQ-C30 Scoring Manual [14] was used.

To analyze patterns of HRQoL data in time we used linear mixed-effects models [15] as implemented in S-plus. Time was taken as a categorical variable and patient's identification number as random intercept. Differences between pre-treatment baseline scores and follow-up measurements (after CRT, and 3, 6, 9 and 12 months after surgery) were tested. Significant time effects represent differences between follow-up and baseline. We defined the minimal important difference following common guidelines as 0.5 SD of the standard deviation at baseline [16].

To identify which scores or items had the greatest impact on the deterioration of the global QoL post-CRT, we performed univariate analyses of variance with global QoL as dependent variable and the scores and items as covariates.

We tested differences in HRQoL scores between responders and non-responders to neoadjuvant CRT by adding both response as such, and the interaction between response and time. The first analysis assumes the difference between responders and non-responders to remain the same during follow-up; the second gives information for every point in time, but naturally has less power to find significant differences. The distinction was only made after t=1. Response to CRT was defined as the presence of less than 10% vital residual tumor cells in the resected specimen (pathological response).

Calculations were performed with the Statistical Package for the Social Sciences (version 12.0; SPSS Inc., Chicago, IL, USA) and S-Plus (version 6.0 Professional Release 1, 1988-2001; Insightful Corporation, Seattle, WA, USA).

RESULTS

During the study period, 54 patients underwent CRT. After neoadjuvant treatment, two patients did not proceed to esophagectomy: one patient died during the second chemotherapy course (death unrelated to esophageal cancer or treatment) and one patient refused surgery. Baseline characteristics are shown in Table 1. The in-hospital mortality after esophagus resection was 4/52 (7.7%). Clinical outcome is shown in Table 2.

Questionnaire compliance and missing data

The compliance rate was 92.6% (50/54) at baseline for the QLQ-C30 and 90.7% (49/54) for the OES18. The questionnaires were all missed because of administrative errors (patients accidentally not handed the questionnaires or patients not completed or returned the questionnaires). Numbers of questionnaires available for analysis are shown in Table 3. The numbers decreased over time, due to random administrative problems (n= 20 missed questionnaires) and patients who died. One patient died during CRT, four patients died postoperatively due to complications of the surgery, one patient died due

Table 1. Patient Characteristics

Characteristic	Number (%)
Total number of patients	54
Sex	
Male	49 (91)
Female	5 (9)
Age (years)	
Median	59
Range	40-75
Performance status (ECOG)	
0	35 (65)
1	18 (33)
Unknown	1(2)
Histology	
Adenocarcinoma	41 (76)
Squamous cell carcinoma	12 (22)
Large cell carcinoma	1(2)
Stage (endoscopic ultrasound)	
T2N0	5 (9)
T2N1	2 (4)
T3N0	18 (33)
T3N1	21 (39)
No pass*	8 (15)
Primary site	
Thoracic oesophagus	5 (9)
Lower oesophagus	49 (91)

ECOG = Eastern Cooperative Oncology Group

*The probe for the endoscopic ultrasound was not able to pass the tumor

Table 2. Clinical outcomes after esophagectomy

Characteristic	No. (%)
Nasogastric tube for nutritional support	
Removed	3/6
Placed	3/47
Weight loss during chemoradiation (kg)	
Mean	1.4
Range	-5 to +4
pTNM†	
pCR	13 (25)
pT1N0-1M0	12 (23.1)
pT2N0-1M0	6 (11.5)
pT3N0-1M0	16 (30.8)
pT3N0M1A	4 (7.7)
pT1N1M1B	1 (1.9)
Postoperative in-hospital mortality†	4 (7.7)
Postoperative morbidity†	37 (73)
Hospital stay (days)†	
Median	13
Range	8-61
Overall survival (months)‡	
Median	35
Range	0.5-52

pTNM = pathological TNM-Stage; pCR = pathological complete response.

*calculated from the data of 53 patients

†calculated from the data of 52 patients

†† survival since start chemoradiation

to recurrent disease between three and six months postoperatively and another between six and nine months postoperatively, and between nine months and one year of follow-up two patients died due to recurrent disease and one due to an unrelated cause. Overall, 84% (272/324) of the QLQ-C30 and 82% (267/324) of the OES18 questionnaires were completed. Analyses were performed using the available data.

Health-related Quality of Life during neoadjuvant treatment

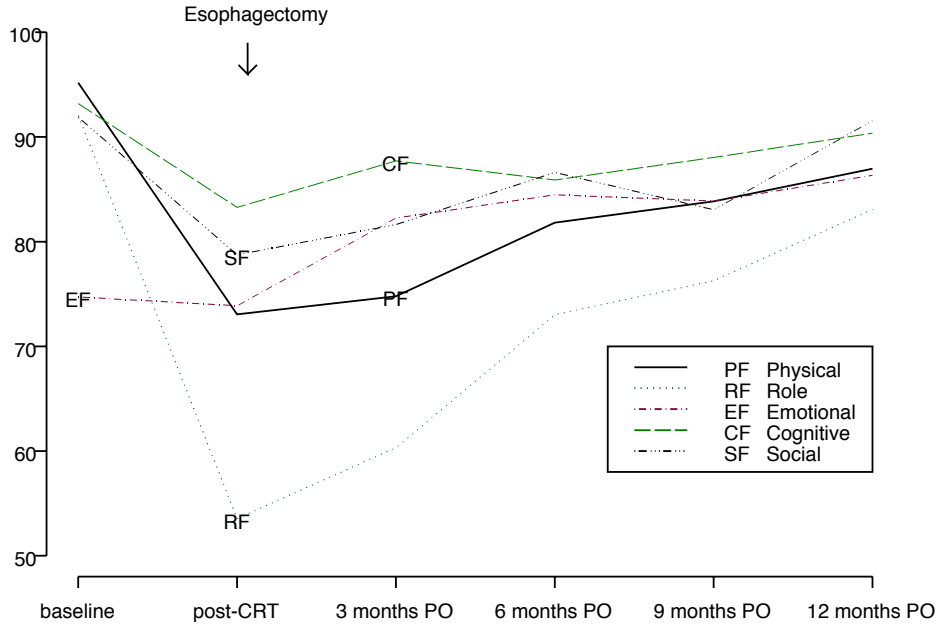
Patients reported a decrease in several aspects of HRQoL during preoperative CRT (Table 4). Differences between mean scores after CRT and baseline were significant and ≥ 0.5 SD (i.e.

Table 3. Questionnaires available for HRQoL analysis

	QLQ-C30 (%)	OES-18 (%)
Baseline	50/54 (92.6)	49/54 (90.7)
After CRT	49/53 (92.5)	48/53 (90.6)
3 months PO	46/49 (93.9)	46/49 (93.9)
6 months PO	43/48 (89.6)	41/48 (85.4)
9 months PO	44/47 (93.6)	44/47 (93.6)
1 year PO	40/45 (88.9)	39/45 (86.7)

CRT = chemoradiotherapy; PO = postoperative; OES-18 = esophageal site-specific questionnaire; QLQ-C30 = Quality of life core questionnaire.
Values expressed as real/expected (percent).

Figure 1. Mean functioning scores during treatment and follow-up. A high score is equivalent to a better quality of life. CRT = chemoradiotherapy; PO = postoperatively



clinically meaningful) for most functioning scores. In Figure1 the course of the functioning scores during treatment and follow-up is shown. Emotional functioning scores were low at baseline and remained low, on average, throughout CRT. Mean scores for most treatment related symptoms worsened significantly, the changes exceeding 0.5 SD. In Figure 2 the course of the fatigue score during treatment and follow-up is shown. Nausea/vomiting, pain, dyspnea, and appetite loss scores showed the same pattern as the data in Figure 2. Local tumor symptom scores (dysphagia, eating, and pain from the OES18 questionnaire) deteriorated during CRT, as well. In Figure 3 the course of the dysphagia score during treatment and follow-up is shown. Eating and pain scores from the OES 18 questionnaire showed the same pattern as the data in Figure 3. Scores from items assessing sleeping, financial problems, reflux, and choking did not change during CRT. Global QoL decreased significantly and on average 17 points during neoadjuvant treatment (Figure 4).
On univariate analysis, the difference in physical functioning, role functioning, cognitive functioning and fatigue between post-CRT and baseline had a significant effect on global QoL (p=0.035, p=0.019, p=0.03, and p=0.028, respectively).

Health-related Quality of Life after Esophagectomy

During the postoperative follow-up period, most aspects of HRQoL returned to baseline levels (Table 4). Differences between mean scores during follow-up and baseline decreased and finally, the average scores returned to baseline levels for role, cognitive, social functioning, and global QoL scores (Figures 1 and 4). The average global QoL score and the average cognitive functioning score returned stored to baseline within three months after surgery, the average social functioning score within six months post-

Figure 2. Mean fatigue scores during treatment and follow-up. A high score is equivalent to more symptoms. CRT = chemoradiotherapy; PO = postoperatively

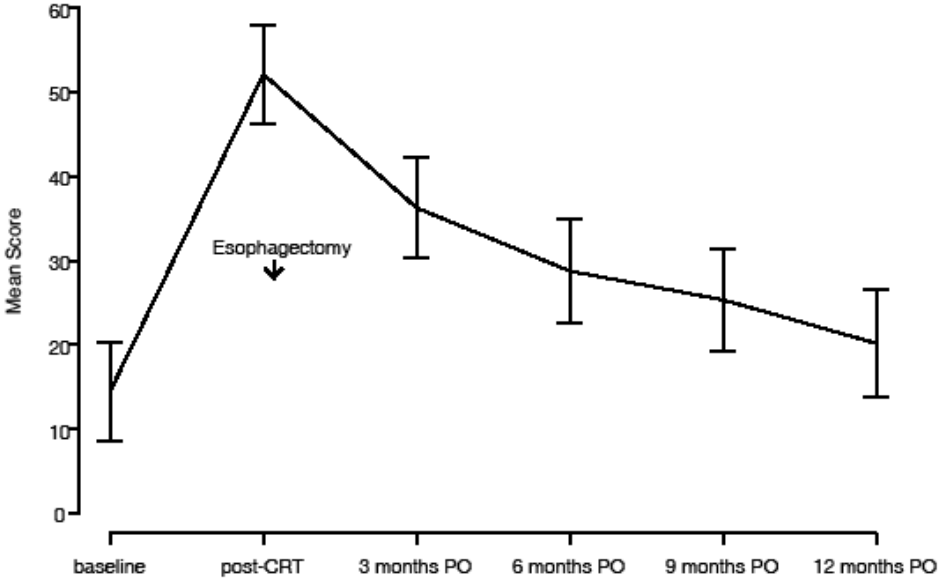


Figure 3. Mean dysphagia scores during treatment and follow-up. A high score is equivalent to more symptoms. CRT = chemoradiotherapy; PO = postoperatively

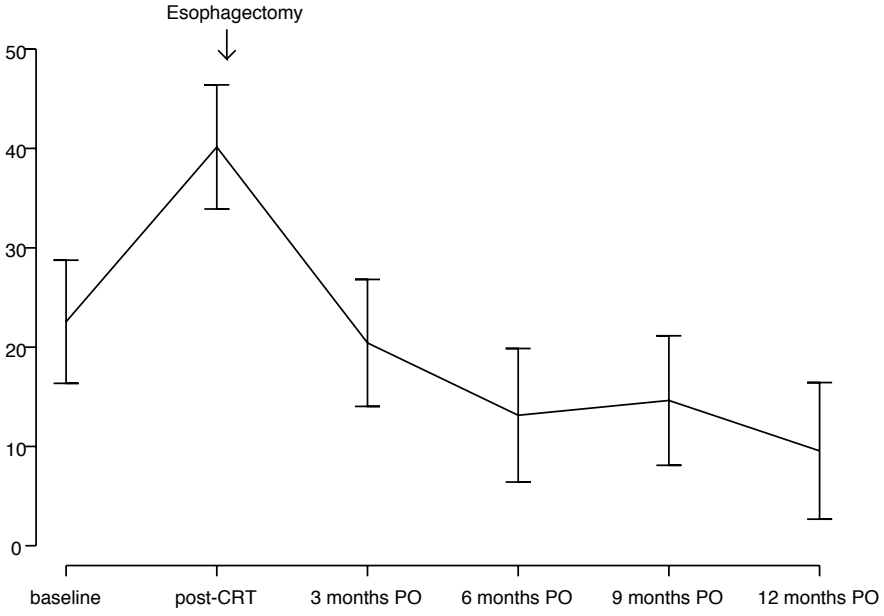
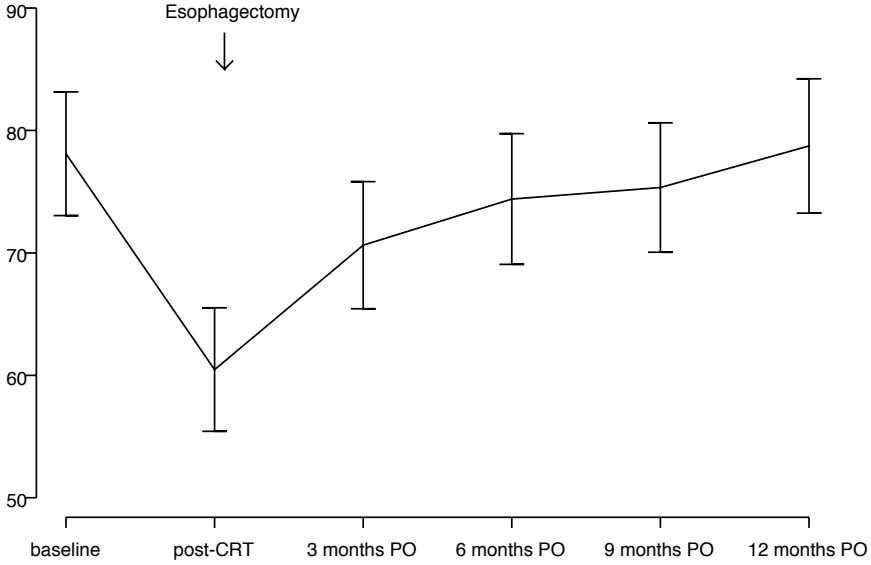


Figure 4. Mean global quality of life scores during treatment and follow-up. A high score is equivalent to a better quality of life. CRT = chemoradiotherapy; PO = postoperatively



operatively and the average role functioning score within one year after surgery. The average physical functioning score was still significantly and ≥ 0.5 SD decreased one year postoperatively compared to baseline.

The emotional functioning scores showed a different pattern over time. The mean score improved gradually and significantly during follow-up from three months after surgery.

Most treatment related symptoms and local tumor symptoms recovered to baseline levels by nine months postoperatively, except for dyspnea (Figure 2,3).

Over time, we observed no difference in global QoL between pathological responders (n=32) to CRT and pathological non-responders (n=20). However, global QoL was significantly higher in responders than in non-responders six months postoperatively (11 points, p=0.04). Over time, the pain score from the QLQ-C30 questionnaire was on average 8 points lower (i.e., less pain) in responders than in non-responders (p=0.04). This difference was larger three months postoperatively (17 points, p=0.01), and six months postoperatively (22 points, p=0.002).

DISCUSSION

We found significant and clinically relevant deterioration of most aspects of HRQoL during concurrent neoadjuvant CRT with paclitaxel and carboplatin for esophageal cancer. Analyses demonstrated a decline in average scores for four functioning HRQoL scores. All symptom scores worsened during CRT. One year postoperatively all scores from both questionnaires were restored to baseline scores. The emotional functioning score

Table 4. Mean Quality of Life scores ± SD during treatment and follow-up

	Baseline mean (SD)	PostCRT mean (SD)	3 months PO mean (SD)	6 months PO mean (SD)	9 months PO mean (SD)	1 year PO mean (SD)
QLQ-C30						
Number of questionnaires	50	49	46	43	44	40
Global health score	78 (15)	61* (22)	70* (15)	75 (18)	75 (22)	80 (13)
Functional scales						
Physical functioning	95 (8)	73* (18)	75* (20)	83* (19)	84* (20)	88* (13)
Role functioning	91 (17)	54* (30)	60* (25)	74* (28)	76* (32)	84 (20)
Emotional functioning	74 (19)	74 (23)	82 (20)	85* (18)	84 (24)	88* (15)
Cognitive functioning	93 (13)	84* (19)	88 (17)	87 (19)	88 (19)	92 (14)
Social functioning	92 (16)	79* (23)	82 (24)	87 (18)	83 (28)	92 (13)
Symptom scales/items						
Fatigue	14 (15)	52* (26)	36* (22)	28* (19)	25 (23)	19 (16)
Nausea/vomiting	7 (12)	26* (27)	21* (25)	13 (19)	12 (19)	9 (14)
Pain	11 (15)	34* (28)	17 (21)	11 (21)	15 (23)	11 (19)
Dyspnea	7 (15)	26* (23)	27* (26)	20* (24)	21* (25)	17 (24)
Insomnia	22 (27)	29 (26)	23 (31)	12 (23)	15 (23)	13 (21)
Appetite loss	6 (16)	45* (26)	25* (31)	15 (27)	13 (26)	10 (20)
Constipation	6 (16)	19* (25)	9 (18)	3 (10)	5 (12)	5 (14)
Diarrhea	3 (9)	16* (31)	22* (23)	19* (23)	11 (20)	12 (24)
Financial difficulties	2 (8)	5 (14)	8 (21)	3 (10)	8 (19)	8 (18)
OES18						
Number of questionnaires	49	48	46	41	44	39
Symptom scales/items						
Dysphagia	23 (23)	40* (30)	20 (21)	12* (16)	14 (22)	9* (13)
Eating	24 (22)	45 (26)	32 (23)	21 (19)	23 (24)	17 (14)
Reflux	8 (18)	14 (19)	13 (17)	13 (17)	18* (20)	18* (22)
Pain	16 (18)	32* (25)	11 (13)	8* (12)	7* (10)	8* (13)
Trouble swallowing saliva	7 (15)	18 (29)	8 (17)	10 (19)	11 (28)	9 (18)
Choking	2 (8)	4 (13)	11 (17)	8 (16)	5 (14)	8 (16)
Dry mouth	9 (19)	26* (29)	18 (28)	7 (14)	15 (25)	9 (15)
Taste	5 (18)	35* (36)	10 (22)	8 (19)	4 (13)	4 (11)
Cough	9 (15)	31* (29)	29* (29)	17 (29)	18 (25)	12 (18)
Speech	2 (8)	10 (22)	9 (19)	2 (7)	6 (9)	5 (16)

CRT = chemoradiotherapy; PO = postoperatively; QLQ-C30 = Quality of life core questionnaire; OES-18 = esophageal site-specific questionnaire.

Values expressed as mean ± SD.

* Change in score of ½ SD or greater and $p < 0.05$ compared with baseline

showed a different pattern; it was worst at baseline, and showed a gradual increase over time during CRT and after surgery.

Only two papers empirically addressed the impact of neoadjuvant CRT on HRQoL in patients with esophageal cancer undergoing an esophagectomy [8, 9]. Blazeby et al. [8] found that preoperative CRT for esophageal carcinoma had a temporary negative effect

on most aspects of HRQoL, but that neoadjuvant CRT did not delay the postoperative recovery of HRQoL. They even stated that patients who had undergone neoadjuvant CRT reported earlier recovery of some aspects of HRQoL than patients undergoing surgery alone (nausea, emesis, and dysphagia). Reynolds et al. [9] found that HRQoL was affected adversely by neoadjuvant CRT in the short term, despite a significant improvement in dysphagia score. HRQoL three months after surgery was significantly lower compared to baseline both in patients treated with surgery alone, as in patients treated with multimodality treatment. However, there was no difference between these both groups. Global QoL scores had returned to baseline values by one year after surgery in the multimodal group. Patients in the multimodal group even had a significantly higher global QoL score than those who had surgery alone at this time point.

The pattern of decline of the various aspects of HRQoL during neoadjuvant CRT in patients with esophageal cancer in our study was comparable to the patterns found in the studies from Blazeby [8] and Reynolds [9]. The largest differences between post-CRT and baseline scores found in their studies were also found in our study (physical and role functioning, and fatigue). However, in our study more aspects of HRQoL declined during CRT, and the deterioration after CRT was for most aspects more pronounced than in the studies from Blazeby [8] and Reynolds [9]. In addition, global QoL decreased significantly by 17 points during the neoadjuvant treatment, whereas global QoL scores did not significantly change in the studies by Blazeby [8] and Reynolds [9]. Besides, the mean dysphagia score worsened significantly by 17 points during the CRT, whereas the mean dysphagia score improved in the study from Reynolds, and worsened at the end of the treatment after an initial improvement in the study from Blazeby [8].

These differences are intriguing, because compared to other studies with neoadjuvant CRT in esophageal cancer the incidence of grade 3 and 4 toxicity (according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC)) in our study was low [10]. Apparently, in patients treated with neoadjuvant CRT, HRQoL is not only determined by the severity of toxicity according to the NCI-CTC. This is especially reflected by the discrepancy between the measured rate of esophagitis grade 3 of 7% (according tot the NCI-CTC), and the significant increased mean dysphagia score after CRT (according to the OES18 questionnaire). The more pronounced deterioration of symptom scores in our study may be caused by the different CRT regimens used. In the study from Blazeby [8] neoadjuvant CRT consisted of four cycles of cisplatin 60 mg/m2 and 12 weeks of continuous infusional 5-fluourouracil (5-FU) initially 300 mg/m2, reduced to 225 mg/m2 during radiotherapy. After week 6 radiotherapy, 45 Gy in 5 weeks was given. Results of the objective toxicity of this regimen have not been reported so far. In the study from Reynolds [9], chemotherapy consisted of two courses of 5-FU (15 mg/kg) and cisplatin (75 mg/m2), and was repeated at week 6. Radiotherapy, 40 Gy in 3 weeks, started on the first day of the first course of chemotherapy. The objective incidence of grade 3 and 4 toxicity of this regimen was slightly higher than in our study [17]. An explanation for the deterioration of global QoL during CRT may be that global QoL is at least partly determined by the severity of symptoms. This is supported by the results from the univariate analyses in our study, which showed that the difference in physical functioning, role functioning, cognitive functioning and fatigue between post-CRT and baseline had a significant effect on global QoL just after CRT. Another explanation for the more pronounced deterioration of symptom scores and the deterioration of global

QoL during CRT may be the timing of assessment of HRQoL after CRT. In our study, the questionnaires were filled in one week after finishing CRT. At this time point patients usually experience most toxicity. In the study from Blazeby [8], QoL was assessed at two time-points: 5 and 12 weeks after starting the preoperative treatment. In the study from Reynolds [9], the questionnaires were filled in 3-4 weeks after finishing CRT (personal communication with Professor J. V. Reynolds, 2007), at which time toxicity may already have recovered.

Despite the negative impact of the CRT and esophagectomy, some aspects of HRQoL improved during the postoperative follow-up period compared to baseline. The mean score for emotional functioning had significantly improved one year postoperatively. This improvement in emotional well-being post-therapy compared to baseline (i.e., post-diagnosis but preceding treatment) has been described before in cancer patients [18]. It may be hypothesized that the diagnosis of cancer is the main stressor (not the treatment) and that treatment reduces distress. The scores for dysphagia and pain from the OES18 questionnaire were also significantly better than at baseline. This improvement in symptoms can be ascribed to treatment success.

Most deteriorated aspects of treatment related symptoms had returned to baseline levels by nine months postoperatively. However, the dyspnea score was still significantly increased by 10 points compared to baseline one year postoperatively. Although we found a small objective decline in pulmonary function tests (total lung capacity (TLC), vital capacity (VC), and forced expiratory volume in one second (FEV1)), this may not be the only explanation. Another explanation may be a decline in physical condition, resulting in dyspnea. However, the physical functioning scale and the fatigue score were restored to baseline level one year postoperatively.

One other aspect was also negatively affected. From nine months postoperatively, the mean score for reflux was significantly increased compared to baseline. After esophagectomy the continuity of the upper digestive tract is restored by means of a gastric tube reconstruction. This reconstruction can lead to gastro-esophageal reflux in up to 20% of the patients [19]. It is unlikely that the preoperative CRT has had an effect on this; this deterioration in the reflux score was also described by Blazeby et al.[8], but surprisingly not by Reynolds et al [9].

No difference in global QoL between responders and non-responders could be found. However, over time the pain score was on average 8 points lower in responders compared to non-responders. Because we could not find a difference in overall survival between responders and non-responders [10], a good explanation for this difference cannot be given. The difference in pain score between responders and non-responders was most distinct six months postoperatively. This might have led to the significantly higher global QoL found in responders six months postoperatively.

A drawback / limitation of our study is the fact that the aspects of HRQoL of patients treated with neoadjuvant therapy and surgery are not compared with that of patients treated with surgery alone. Blazeby et al. [8] and Reynolds et al. [9] addressed this issue, but did so in a non-randomized assessment of patients treated with multimodality therapy or surgery alone, with the choice of treatment dependent on the doctor's or patient's preference. Prospective studies on the impact of an esophagectomy on HRQoL have shown that most aspect of HRQoL deteriorate in the early postoperative period, leading to reduced global QoL scores [20]. Nevertheless, these reduced scores gradually

recover within nine months after surgery. There is, however, a difficulty with interpreting the results from all these kind of studies. The reports on postoperative HRQoL only include data from patients who are still alive and sufficiently fit to fill in the questionnaires. This may lead to an overestimation of QoL, because Blazeby showed that in patients who died within 2 years of surgery QoL never recovered to baseline before death occurring from recurrent disease [3].

In conclusion, the current study shows that preoperative treatment with paclitaxel and carboplatin concurrent with radiotherapy for esophageal cancer has a profound, but temporary negative effect on most aspects of HRQoL. This effect is mostly restored one year after esophagectomy. Whether this neoadjuvant regimen leads to an impaired and/or delayed recovery of HRQoL after surgery needs to be examined in a randomized phase III trial with this CRT regimen followed by surgery versus surgery alone, which trial is now ongoing. However, in this study no indication for an impaired and/or delayed recovery was found. The time of assessment of HRQoL post-CRT (one week after finishing CRT) may have influenced the results, because at this time point the toxicity of CRT usually is at maximum. Given the discrepancy found between the seriousness of toxicity assessed by the NCI-CTC and by the symptom scales and items of the QLQ-C30 and OES18 questionnaires, one can conclude that HRQoL assessment gives additional information on toxicities of CRT regimens. HRQoL considerations are especially important for patients and their treating physicians because the survival benefit of preoperative CRT is still not well established. Therefore, the findings of the study presented here can be used to inform patients about what to expect from this multimodality treatment for resectable esophageal cancer and hence contribute to the process of shared decision-making on treatment choice.

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Chapter 5

Pathological analysis after neoadjuvant chemoradiotherapy for esophageal carcinoma: the Rotterdam experience

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ABSTRACT

Purpose. This study was performed in order to determine the residual tumor cells after preoperative chemoradiation and to correlate the effect of specific pathologic and clinical findings to overall survival.

Methods and Materials. Esophageal biopsies and surgical specimens of 67 patients treated with neoadjuvant paclitaxel and carboplatin concurrent with radiotherapy were reviewed for: histological type, tumor grade, resection margins, extension of the tumor through the esophageal wall, nodal involvement, and tumor regression grade. From all patients survival was calculated.

Results. After chemoradiotherapy tumors were more frequently graded as poorly differentiated than before treatment. Complete tumor regression was found in 24% of the patients. Although not statistically significant, this resulted in a prolonged survival for these patients. Squamous cell carcinoma responded significantly higher to chemoradiotherapy than adenocarcinoma. This was not associated with a survival benefit. Neoadjuvant chemoradiotherapy led to a significant down-staging. Patients with pre-treatment nodal involvement had a significantly worse survival compared to patients with no pre-treatment nodal involvement. This applied not for post-treatment nodal involvement.

Conclusions. Poorly differentiated esophageal tumors significantly more frequent reach complete tumor regression after neoadjuvant chemoradiotherapy. The presence of nodal involvement as assessed by endoscopic ultrasound is significantly associated with a worse survival.

INTRODUCTION

Neoadjuvant chemoradiotherapy for patients with resectable esophageal cancer is increasingly used in an attempt to improve these patients. After chemoradiotherapy several histological changes in the resected specimen can be identified. These changes include cytological alterations such as cytoplasmic vacuolation and/or eosinophilia, nuclear pleomorphism, and necrosis, as well as stromal changes such as fibrosis (with or without inflammatory infiltrate), including giant cell granuloma formulation around ghost cells and mucin pools or keratin pearls at the site of the previous tumor [1-4]. On the basis of these changes, the grade of tumor regression can be defined. Regression of the primary tumor can range from the absence of regressive changes to a total response with no vital residual tumor cells. Several morphologic criteria have been defined for various types of cancer to objectively evaluate pathological response to neoadjuvant chemoradiation [1, 2, 5].

The prognosis of resectable esophageal cancer is mainly determined by the achievement of a complete tumor resection (R0 resection), the depth of tumor infiltration, and the presence of lymph node metastasis [6-9]. Generally, the overall survival after neoadjuvant chemoradiotherapy is better in patients with a complete pathological response compared to patients with residual tumor cells [6, 8, 10-12]. Schneider et al. and Brücher

et al. found that patients with only a few residual tumor cells within the resection specimen (<10%) had a significant better survival compared with patients with >10% residual tumor cells.
In this article we review our experience with neoadjuvant carboplatin and paclitaxel concurrent with radiotherapy in patients with resectable esophageal cancer. We determined the residual tumor cells after preoperative treatment, and correlated the effect of specific pathologic and clinical findings to overall survival, in order to obtain prognostic information.

METHODS AND MATERIALS

Acquisition of clinical data

We examined the esophageal biopsies and surgical specimens of all patients who were treated with neoadjuvant chemoradiation followed by surgery for esophageal cancer at the Erasmus Medical Centre between February 2001 and August 2006. Patients with T1N1 or T2-3N0-1 esophageal cancer were treated at our institution with five weekly courses of paclitaxel and carboplatin with concurrent radiotherapy followed by surgery in a phase II or phase III trial as described elsewhere [13].
The clinical data collected included patient age, sex, and preoperative clinical stage (obtained from CT scan and EUS).

Pathological analysis

All haematoxylin and eosin (H&E) slides from preoperative tumor biopsies and from the resection specimens were evaluated by a specialized pathologist (H.v.D.). The preoperative tumor biopsies were viewed for histological tumor type, and grade. The resection specimen was evaluated using a standard protocol, providing information on margins, tumor type, tumor differentiation grade, extension of the tumor, and lymph nodes. If no macroscopically identifiable tumor was present, lesions such as an ulcer or an irregular area covered by mucosa were embedded in total together with surrounding areas in order to adequately judge the presence of residual tumor and therapy effects. The slides from the resection specimens were viewed for the presence of vital tumor cells near the oral, ab-oral and circumferential resection margins, tumor type, tumor differentiation grade, extension of the tumor in the esophageal wall, and number of involved lymph nodes. R0 was defined as histologically tumor-free resection margins with ≥ 1 mm distance between tumor and resection margins. The 6th edition of the International Union Against Cancer (UICC) was used for TNM-classification, tumor grade, and stage grouping [14].

Estimation of Treatment Effect

The grading of the therapy response was performed according to Junker et al. as described before [2, 13]. The degree of histomorphological regression in the esophageal wall, i.e. the effect of chemoradiation, was classified into four categories: tumor regression grade (TRG) I: more than 50% vital residual tumor cells; TRG II: 10-50% vital residual tumor; TRG III: less than 10% vital residual tumor cells; TRG IV: complete tumor regression, no evidence of vital tumor cells (Figure 1). Special attention was paid to therapy effects, such as mucin pools and squamous remnants in resection margins and lymph nodes (Figure 1).

Statistical analysis

Patient characteristics are described using tables for categorical data, medians and ranges for continuous variables. Association between clinical and pathological parameters was evaluated using the chi-square test.
Overall survival time was calculated from the time of start of the chemoradiotherapy to the date of death or last follow-up. November 15th 2007 was the censoring date for survival. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to evaluate the statistical significance of differences. The SPSS statistical package (version 12.0; SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

Patient characteristics

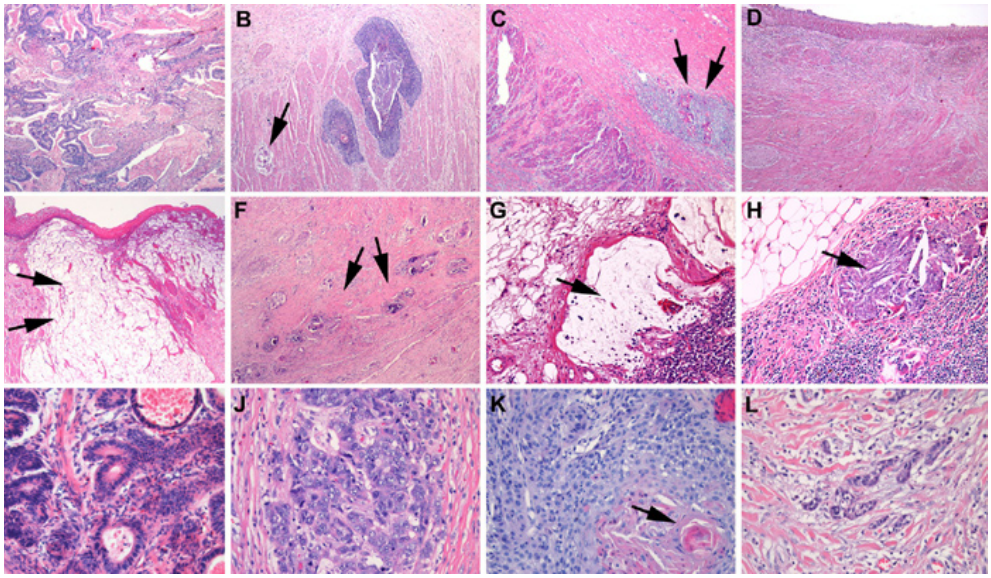
The 67 patients who were assessed in the current study had a median age of 59 years and the majority was male. Baseline patient characteristics are summarized in Table 1.

Table 1. Baseline Characteristics

Characteristic	Number (%)
Total number of patients	67
Sex	
Male	58 (87)
Female	9 (13)
Age (years)	
Median	59
Range	40-75
cT-stage (EUS)	
T2	9 (13)
T3	49 (73)
No pass	9 (13)
cN-stage (EUS)	
N0	29 (43)
N1	38 (57)
Primary site	
Thoracic oesophagus	13 (19)
Lower oesophagus	54 (81)
Histology	
Adenocarcinoma	46 (69)
Squamous cell carcinoma	29 (28)
Large cell carcinoma	2(3)
Grading	
Good	2 (3)
Moderate	50 (75)
Poor	13 (19)
Undifferentiated	2 (3)

cT-stage: pre-treatment tumour stage; EUS: endoscopic ultrasound; cN-stage: post-treatment nodal stage

Figure 1. H&E images illustrating the effects of chemoradiation on esophageal adeno- and squamous cell carcinomas. **A]** TRG I, adenocarcinoma with no or little therapy effect. **B]** TRG II, residual squamous cell carcinoma and therapy effects (squamous remnant, arrow). **C]** TRG III, few residual tumor cells (arrows) surrounded by fibrosis of the adventitia and the muscular layer. **D]** TRG IV, an ulcer is seen directly above the muscular layer showing fibrosis, but no vital tumor cells. **E, F]** TRG IV, showing mucin lakes and squamous remnants (arrows), respectively, but no vital tumor cells. **G, H]** lymph nodes displaying mucin and keratin squames, respectively, in the subcapsular sinus (arrow), no tumor cells. **I,J]** well differentiated adenocarcinoma in the preoperative biopsy **(I)**, and moderately (to poorly) differentiated adenocarcinoma in the resection specimen **(J)**, illustrating downgrading after chemoradiation. **K, L]** likewise, moderately differentiated (keratinizing, arrow) squamous cell carcinoma in the preoperative biopsy **(K)**, and poorly differentiated squamous cell carcinoma after chemoradiation **(L)**. A 4x objective was used in A-F, 10x in G-H, and 20x in I-L.



Pathological analysis and association with pre-treatment and postoperative pathological factors

The morphological changes in the tumor and in non-neoplastic tissue: such as mucin pools, squamous remnants, and stromal changes are shown in Figure 1. In Table 2 pathological characteristics of the resection specimens are summarized. A complete microscopic and macroscopic tumor resection was achieved in 66 of 67 patients (98.5%). In these 66 cases there were no mucin pools or areas containing keratin pearls or squamous remnants in the resection margins.

When there were still vital tumor cells left in the resection specimen, the tumor differentiation grade was poorer compared to the tumor differentiation grade in the esophageal biopsies before chemoradiotherapy: Seven patients had differentiation grade 3/4 before chemoradiotherapy versus 27 patients after chemoradiation ($p<0.001$). TRG IV was achieved in 16 patients (24%), in 10 resection specimens (15%), little or no regressive changes were seen (TRG I). The response to chemoradiotherapy (as defined by TRG III and IV) was significantly higher in patients with squamous cell carcinoma (SCC) than in patients with adenocarcinoma (AC) (68% versus 54%, $p=0.001$). Poorly differentiated tumors (grade 3/4, esophageal biopsies) achieved significantly more tumor regression grade IV than good or moderately differentiated tumors (53% vs. 15%, $p<0.01$).

Fifty-seven patients (85%) had tumor infiltration into the adventitia (T3) at baseline assessed by EUS, versus 25 patients (37%) after therapy as assessed by pathological analysis of the resection specimen, indicating significant downstaging by chemoradio-

Table 2. Histopathological Characteristics of oesophagectomy specimens

Characteristic	Number (%)
Completeness of resection	
R0	66 (99)
R1	1 (1)
Regressiongrade	
I	10 (15)
II	17 (25)
III	24 (36)
IV	16 (24)
ypT category	
T0	16 (24)
T	13 (19)
T2	13 (19)
T3	25 (37)
ypN category	
N0	45 (67)
N1	21 (31)
Unknown	1 (1)
Grading	
No tumour	16 (24)
Good	1 (1)
Moderate	23 (34)
Poor	27 (40)

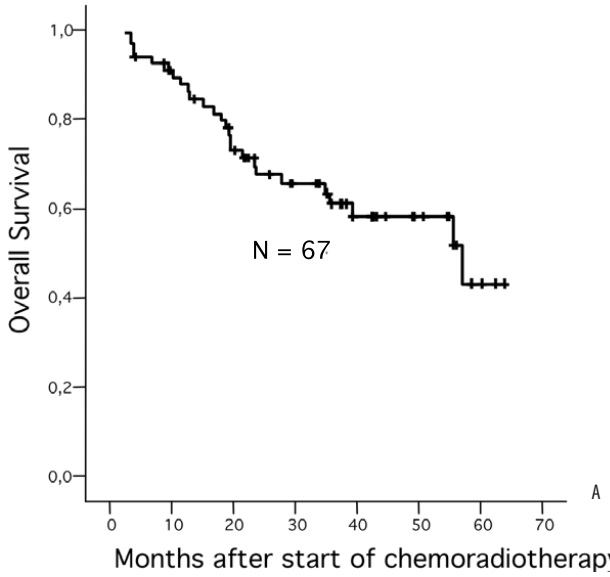
ypT: posttherapy pathological tumour stage; ypN-stage: posttherapy pathological nodal stage;

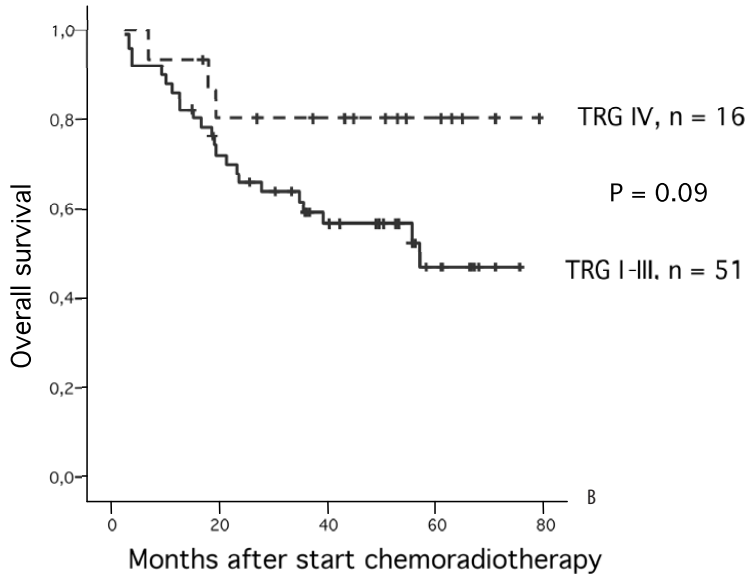
therapy (p<0.0001). Likewise, 38 patients (57%) had pre-treatment nodal involvement, as assessed by EUS, versus 21 patients (31%) post-therapy, as assessed by pathological examination of the resected specimen (p=0.006). In 11 of the 29 resected specimens with no pre-treatment nodal involvement (38%) regression effects were identified in the lymph nodes, suggesting downstaging from clinical stage N1 to pathological stage N0. The tumor regression grade of the primary tumor was significantly related to the risk of residual tumor cells in the esophageal wall: pT3 was found in 80% for TRG I, 65% for TRG II, and 25% for TRG III (p=0.01). This also applied for the resected lymph nodes: positive lymph nodes were found in 70% for TRG I, 50% for TRG II, 20% for TRG III, and 14% for TRG IV (p=0.008).

Pathological analysis and association with overall and disease free survival

After a median follow-up of 35 months (range 2-75), 20 patients relapsed (1 patient had a local/regional relapse, 9 patients developed distant metastases, and 10 patient developed both). The presence of pre-treatment nodal involvement was significantly associated with the development of distant metastases (14% vs. 42%, p=0.02). The median overall survival as calculated by the Kaplan Meier method has not yet been reached (Figure 2A). There was a trend towards a better overall survival in patients with a complete regression, i.e. TRG IV (p=0.09). The median overall survival for patients with TRG I-III was 57 months; the median survival for patients with TRG IV has not yet been reached (Figure 2B). Survival was significantly better in patients who had no nodal involvement

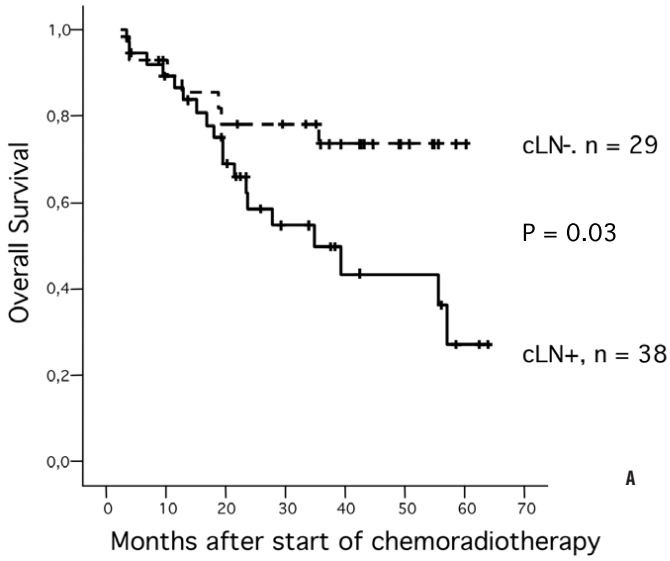
Figure 2. Overall Survival (A) and overall survival of patients with TRG IV compared to patients with residual disease (TRG I-III) (B)

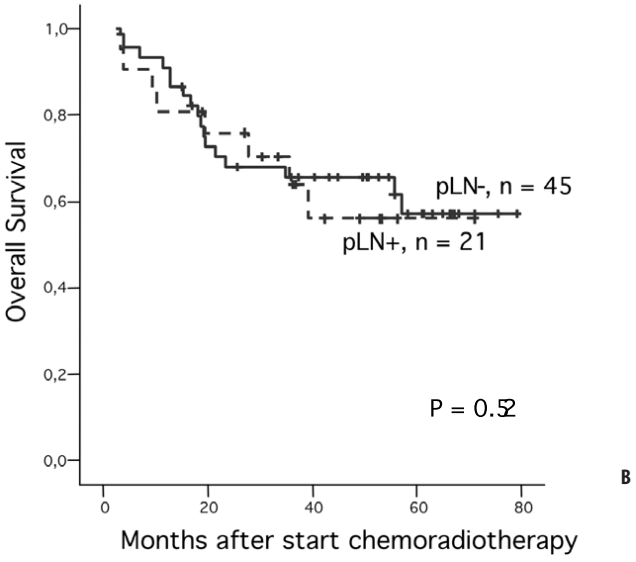




before the start of treatment (median survival has not yet been reached) compared to patients who had nodal involvement as assessed by EUS (median survival 39 months, p=0.03) (Figure 3). No difference in overall survival could be found between patients with pathological nodal involvement compared to patients with no pathological nodal

Figure 3. Overall survival of patients with (A) pre-treatment nodal involvement compared to patients with no nodal involvement, (B) post-treatment nodal involvement compared to patients with no nodal involvement





involvement, including 11 patients (16.7%) with therapy effects within the lymph nodes. There was no survival difference between patients with AC or SCC.

DISCUSSION

In this study we described the histopathological changes seen after neoadjuvant chemoradiotherapy with paclitaxel and carboplatin in 67 cases of esophageal carcinoma. When vital tumor cells were left in the esophageal wall after chemoradiotherapy, the tumor was graded more frequently as poorly differentiated than before treatment. There are 3 explanations for the worsened differentiation grade in the resected specimens. First, poorly differentiated tumor cells may be more resistant to the cytotoxic insult caused by neoadjuvant therapy. However, TRG IV was more frequently found in pretreatment poorly differentiated tumors, so this does not seem to be a likely explanation. Second, it might be caused by "sampling error" of the pretreatment esophageal biopsies, because the tumor differentiation grade of the resected specimen is determined by the worst differentiation found. Lastly, cytotoxic injury of chemoradiotherapy may induce dedifferentiation of tumor cells. Changes in differentiation of tumor cells after chemoradiotherapy have been described before [10, 15, 16]

We found complete tumor regression (TRG IV) in 24% of the patients, which corresponds with the rates found in other studies with neoadjuvant chemoradiotherapy in patients with esophageal cancer [17-20]. It has been well known that patients who achieve a pathological response after neoadjuvant chemoradiotherapy have a significantly prolonged survival compared to patients with residual vital tumor cells in the resection specimen [10, 12]. A survival difference between patients who had TRG IV and those who did not have TRG IV was observed, although it did not yet reach statistical significance. Because of the 98% complete resection rate in our study we could not assess the prognostic significance of a complete resection. It is however well known from other studies that a complete resection is associated with a better survival [9, 11].

In our study, the response to chemoradiotherapy was significantly higher in patients with SCC than in patients with AC. However, this did not translate in a better survival for these patients. This difference in response between SCC and AC has been described before [21]. Rohatgi et al. found that among the patients with a complete response in clinical stage II, there was a significantly greater proportion of SCC patients (77% versus 63%; $p < 0.001$) than AC patients. However, among the patients with a total response in clinical stage III, a significantly greater proportion were AC patients than SCC patients (38% versus 23%; $p < 0.001$) [22]. The difference in response to chemoradiotherapy between these two histological subtypes might be caused by the different etiological background, molecular profiles and patient genetics of these two subtypes.

The proportion of patients with tumor infiltration into the adventitia (T3) was significantly higher before treatment than after treatment. This applied for nodal involvement as well. This difference in pre-treatment and postoperative stage is most probably due to the chemoradiation, since we found an inverse correlation between the TRG and pathological tumor infiltration into the esophageal wall and the pathological nodal involvement.

In our study, patients with pre-treatment nodal involvement had a significantly worse survival compared to patients with no pre-treatment nodal involvement. This survival difference between patients with and without nodal involvement was not found after chemoradiotherapy. The presence of pre-treatment nodal involvement is predictive for the development of locoregional relapse and the development of distant metastases, so

it is possible although CRT had a beneficial effect on local control the outcome of these patients with pre-treatment nodal involvement is still poor because nodal metastases are indicative for occult distant metastases. This phenomenon was also found by Jiao et al. [23]. They found that the presence of pre-treatment lymph node metastases as determined by thoracoscopy was significantly correlated with a worse survival. Our finding that the overall survival did not differ between patients with or without nodal involvement assessed after neoadjuvant chemoradiotherapy followed by surgery is in contrast with the results found by others [4, 6, 24]. Rice et al. found that survival was significantly worse in patients with clinical and/or pathological nodal involvement [24]. Bollschweiler et al. even reported that the prognosis of patients with esophageal cancer treated with neoadjuvant chemoradiotherapy followed by esophagectomy was determined by the number of involved lymph nodes [6]. Patients with more than five involved regional lymph nodes had a significantly worse prognosis than patients with one to five affected lymph nodes, and those with no involved lymph nodes had the best prognosis.
In conclusion, in this study we found that poorly differentiated tumors significantly more frequent reached TRG IV in patients with resectable esophageal cancer after treatment with neoadjuvant chemoradiotherapy followed by surgery. Besides, we observed in this study that the presence of nodal metastasis as assessed by EUS was significantly associated with a worse survival, in contrary with the presence of nodal metastasis after CRT as assessed by pathological analysis.

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Chapter 6

First-line treatment with oxaliplatin and capecitabine in patients with advanced or metastatic esophageal cancer: a phase II study

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ABSTRACT

Background The purpose of the current phase II study was to assess the safety and efficacy of oxaliplatin and capecitabine in patients with metastatic or local-regional unresectable esophageal cancer.

Methods. Eligible patients received oxaliplatin 130 mg/m^2 intravenously on day 1 and capecitabine 1,000 mg/m^2 orally twice daily on days 1 to 14 in a 21-day treatment cycle.

Results. Fifty-one patients were enrolled. Grade 3/4 hematological toxicities were: grade 3 neutropenia (2%) and grade 3 anemia (2%). Grade 4 non-hematological toxicity (lethargy) occurred in one patient (2%). Grade 3 non-hematological toxicity was seen in 14 (27%) patients. In 22% of the patients toxicity was the reason for stopping the treatment. The overall response rate was 39%. The median overall survival was 8 months; the 1 year survival rate was 26%. In the quality of life (QoL) analysis the emotional well-being improved during treatment, the physical functioning scores declined. The fatigue score on the symptom scales increased. Overall, the global QoL score did not change during treatment.

Conclusions. The activity of oxaliplatin and capecitabine is comparable to other chemotherapy regimens in metastatic or local-regional unresectable esophageal cancer. The frequency of grade 3/4 toxicity was low and the quality of life was maintained during the treatment. Because this treatment is probably less toxic than cisplatin-based therapy, with preservation of quality of life during treatment, and because it can be given on an outpatient basis, this regimen is a viable treatment option in patients with advanced esophageal cancer.

INTRODUCTION

Patients with esophageal cancer generally have a poor prognosis, because the majority of them already have locally unresectable or metastatic disease at presentation. Furthermore, even after surgery with curative intent , local recurrences and/or distant metastases are detected in approximately two-third of the patients within five years of follow-up [1]. Many patients with esophageal cancer require palliative therapy to treat symptoms, such as dysphagia. Placement of a self-expanding metal stent, external beam radiotherapy, intraluminal radiotherapy (brachytherapy), and laser therapy are commonly used palliative modalities to treat dysphagia [2].
Palliative chemotherapy may result in local and distant tumor control and symptom control. The effect of chemotherapy on survival is unclear, mainly due to a lack of randomized trials. The most frequently used chemotherapy regimen for patients with metastatic disease is a combination of 5-fluorouracil and cisplatin, with response rates ranging from 15%-45% [3]. However, treatment with 5-fluorouracil and cisplatin can induce severe toxicity [4]. Besides, most patients have to be hospitalized for this treatment. In two trials a significant positive effect of chemotherapy on quality of life

and/or overall survival was demonstrated [5, 6]. However, in both trials patients with esophageal and gastric cancer (predominantly adenocarcinomas) were treated. There are no studies comparing the effect of chemotherapy and other palliative treatments on symptom control (e.g. dysphagia).

Capecitabine is a novel oral fluoropyrimidine carbamate, which is converted into 5-fluorouracil preferentially in tumors. Clinical studies with capecitabine have been predominantly performed in colorectal and breast cancer. In a study performed by Hoff et al. in patients with advanced colorectal cancer [7], treatment with capecitabine was at least as effective as treatment with 5-fluorouracil plus leucovorin, but leaded to less hospitalizations for adverse reactions.

Oxaliplatin is a third-generation platinum compound. It forms inter- and intrastrand cross-links with DNA. These cross-links inhibit DNA replication and transcription. It has demonstrated synergy with 5-fluorouracil in advanced colorectal cancer [8].

The combination of oxaliplatin and capecitabine has been tested in several phase II studies in patients with metastatic colorectal cancer [9, 10]. Grade 3/4 diarrhea was seen in 33-50% of the patients treated with capecitabine 1,250 mg/m^2 twice daily and oxaliplatin 130 mg/m^2 in the study performed by Borner et al [9]. Cassidy et al reported grade 3/4 diarrhea in 16% of the patients treated with oxaliplatin 130 mg/m^2 and capecitabine 1,000 mg/m^2 twice daily. The response rate was comparable, 49% and 55%, respectively. Therefore, a capecitabine dose of 1,000 mg/m^2 twice daily on days 1 to 14 in combination with oxaliplatin 130 mg/m^2 on day 1 in a 21-day treatment cycle is the recommended dose.

Based on these favorable results of oxaliplatin combined with capecitabine in other gastrointestinal malignancies, we conducted the present phase II study to evaluate the safety and efficacy of the combination of oxaliplatin and capecitabine in patients with metastatic or local-regional unresectable carcinoma of the esophagus, esophagogastric junction and cardia. In addition, to evaluate the effects of this schedule on the patients' well-being we performed a quality of life analysis in these patients during the treatment.

METHODS

Eligibility criteria

Eligible patients had histologically proven metastatic or local-regional unresectable carcinoma of the esophagus or gastric junction, and at least one unidimensionally measurable lesion ≥ 20 mm using conventional computed tomography (CT) or magnetic resonance imaging (MRI) scan or ≥ 10 mm using spiral CT scan had to be present. Patients were required to be aged at least 18 years, to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 and a life expectancy of ≥ 3 months. Other criteria included adequate hematological, renal, and hepatic functions as defined by: granulocyte count of at least 1,500/mm^3 and platelet count 100,000/mm^3; serum creatinine ≤ 1.25 x the upper normal limit (ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x the ULN (≤ 5 x the ULN in case of liver metastases) and bilirubin ≤ 1.25 x ULN. Previous neoadjuvant treatment for non-metastatic disease was allowed if completed at least six months prior to the initiation of study treatment. Prior

treatment with oxaliplatin or capecitabine was not allowed. No history of malignancy, apart from non-melanomatous skin cancer, curatively treated carcinoma in situ of the cervix or a "cured" malignancy more than five years prior to enrollment was allowed. Patients with evidence of central nervous system metastases, a lack of physical integrity of the upper gastrointestinal tract, a malabsorption syndrome, or an inability to take oral medication were excluded. Patients were not eligible if they had a preexisting motor or sensory neurotoxicity > grade 1 according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3). The Ethics Committee at Erasmus University Medical Center approved the study, and written informed consent was obtained.

Treatment

Treatment consisted of oxaliplatin 130 mg/m^2 intravenously on day one and capecitabine 1000 mg/m^2 orally twice daily on days 1-14 (28 doses), repeated every three weeks. Oxaliplatin diluted in 250 mL glucose 5% was administered as a continuous infusion over two hours. Capecitabine had to be ingested with water every 12 hours, approximately 30 minutes after a meal, starting at the evening of day one. Dose modifications were made for toxicity, using the NCI-CTC (version 3). The absolute neutrophil count and the platelet count had to be recovered to the required pretreatment values before start of the next treatment cycle. Non-hematological toxicity had to be ≤ grade 1 before start of every treatment cycle. If these conditions were not met, dosing was delayed for a maximum of two weeks. If hematological or non-hematological toxicity was not recovered to grade 1 or less after two weeks, patients were taken off-study.
Persistent (≥ 14 days) paresthesia or temporary (7-14 days) painful paresthesia or functional impairment prompted a 25% dose reduction of oxaliplatin. In case of persistent (≥ 14 days) painful paresthesia or functional impairment, oxaliplatin had to be omitted until recovery and had to be restarted at 50% of the dose. Patients went off-study if these toxicities recurred despite the dose reductions.
Capecitabine was reduced with 25% in case of grade 2 hand-foot-syndrome. In case of grade 2-4 diarrhea, capecitabine intake had to be interrupted immediately. Standard treatment for diarrhea was prescribed (i.e. loperamide). The omitted doses were not permitted to be administered after resuming treatment, and the total length of capecitabine treatment period was not allowed to exceed 14 days. If patients experienced severe capecitabine-related toxicity (> grade 2) despite two dose reductions, necessitating discontinuation of treatment with capecitabine, patients were taken off-study.
Patients who showed no disease progression and/or prohibitive toxicity continued treatment for six courses, with a maximum of eight courses in case of ongoing response.

Pretreatment and follow-up evaluation

Pretreatment evaluation included a detailed history taking, a physical examination and routine blood examinations. All patients underwent a baseline computed tomography (CT) of the chest and the upper abdomen. After discontinuation of treatment follow-up visits were done every three months to document late toxic effects, disease progression and survival.

Evaluation of response and toxicity

Patients were evaluable for response after two courses of chemotherapy. Evaluation of response was done every other course of chemotherapy. However, if tumor progression was found at any time after randomization, it was recorded as progressive disease. Tumor response was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST) [11]. The duration of response was measured from the time of complete or partial response until the first date of recurrent or progressive disease. Stable disease was measured from the start of treatment until the criteria for progression were met. Progression free and overall survival was documented from the time of patient randomization until tumor progression or death.

Quality of life assessment

Quality of life was measured using the EORTC QLQ-C30 (version 3.0) and QLQ-OES18 [12, 13]. Questionnaires were filled in before therapy, after every other cycle, and after completion of chemotherapy. Patients with missing forms were excluded from the analysis of the absent assessment point. Scores were calculated according to the guidelines, yielding a range of 0-100. A higher score for a functional scale represents a higher level of functioning. A higher score for a symptom scale/item represents a higher level of symptomatology/problems [14]. Because high drop-out rates result in more favorable scores among the remaining patients, comparisons were only made between baseline and after the second course, and between baseline and after stopping chemotherapy.

Statistical analysis

An optimal two-stage design for phase II trials as described by Simon was used [15]. In the first stage, a total of 13 patients were included and at least four responses were required to continue to the second stage. In the second stage, 30 additional patients were included to a total sample size of at least 43. Thirteen responses were needed to conclude with a 95% confidence that the response rate was greater than 40%. Statistical differences in quality of life at different time points were determined using the t-test. All tests were two sided at the .05 level of significance. The SPSS statistical package (version 12.0; SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

Patient Characteristics

From April 2003 to October 2005 fifty-one patients were included in this study. The baseline characteristics are summarized in Table 1. The majority of the patients was male (86%) and most of them had adenocarcinoma (88%).

Toxicity of and adherence to chemotherapy

The median number of treatment cycles was four (range 1-8). Apart from progression of disease or end of protocol, reasons for stopping chemotherapy were toxicity (22%), patient's request (4%), and clinical deterioration (2%). The dose of capecitabine was reduced in 5 patients (10%), due to diarrhea (n=3) or hand foot syndrome (n=2). In 4 pa-

Table 1. Baseline characteristics

Characteristic	Number (%)
Gender	
Male	44 (86)
Female	7 (14)
Age (years)	
Median	60
Range	31-76
WHO	
0	20 (39)
1	30 (59)
Missing	1(2)
Weight loss (%)*	
< 5%	17 (33)
5-10%	17 (33)
> 10%	13 (26)
Missing	4 (8)
Histology	
Adenocarcinoma	45 (88)
Squamous cell carcinoma	4 (8)
Undifferentiated carcinoma	2 (4)
Prior chemoradiotherapy/chemotherapy	
Yes	6 (12)
No	45 (88)
Prior surgery	
Transhiatal esophagectomy	17 (33)
Laparotomy, without resection	4 (8)
Sites of metastases	
Lymph nodes	37
Liver	23
Lung	16
Locoregional recurrence	8
Other	8

tients the administration of capecitabine was prematurely interrupted due to diarrhea. The dose of oxaliplatin was reduced in three patients, due to painful paresthesia.

Hematological toxicity is summarized in Table 2. Apart from one case each of grade 3 neutropenia and grade 3 anemia, no grade 3 or 4 hematological toxicities were observed. In the latter patient analysis showed an undetectable haptoglobin, and an increased LDH and bilirubin, indicating hemolysis, which has been described in relation to oxaliplatin administration [16].

Non-hematological toxicity is summarized in Table 2. Eighteen patients were hospitalized during treatment. In eight patients this was directly related to the treatment (dehydration caused by anorexia, nausea, vomiting, and/or diarrhea (n=6), grade 4 lethargy (n=1), observation for one night in hospital after laryngopharyngeal dysesthesia (n=1)). In two patients the hospitalization was possibly related to the treatment (venous thromboembolism). The eight other hospitalizations were due to disease related problems,

Table 2. Hematological and non-hematological toxicities

	Grade				
	0	1	2	3	4
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Anaemia	7 (14)	36 (70)	7 (14)	1 (2)	-
Leucopenia	43 (84)	6 (12)	2 (4)	12 (22.6)	1 (1.9)
Neutropenia	45 (88)	-	5 (10)	1 (2)	-
Thrombocytopenia	31 (61)	15 (29)	5 (10)	-	-
Nausea	9 (18)	29 (57)	10 (19)	3 (6)	-
Vomitus	21 (41)	20 (39)	6 (12)	4 (8)	-
Anorexia	36 (71)	10 (19)	4 (8)	1 (2)	-
Diarrhea	23 (45)	23 (45)	4 (8)	1 (2)	-
Lethargy	6 (12)	30 (59)	12 (23)	2 (4)	1 (2)
Hand foot syndrome	42 (82)	3 (6)	4 (8)	2 (4)	-
Polyneuropathie (sensory)	4 (8)	34 (67)	11 (21)	2 (4)	-
Polyneuropathie (motor)	47 (92)	1 (2)	1 (2)	2 (4)	-
Hyperbilirybinemia	39 (76)	8 (16)	3 (6)	1 (2)	-

such as dysphagia requiring esophageal stenting, jaundice, ileus, pericarditis, fever and tumor related bleeding.

Response

Forty-nine patients were evaluable for response. No complete responses were seen. Nineteen patients (39%) achieved a partial response, 21 patients (43%) had stable disease, and nine patients (18%) had disease progression. The median duration of response was 5.3 months (range 2-18).

Survival

All 51 patients were evaluable for survival. At the date of evaluation (April 15th, 2006) 43 patients have died. The median survival time for all patients was 8 months (95% CI 6-9 months, range 2 to 27 months). The one year overall survival was 26%; the two-year overall survival was 7%.

Quality of life (QoL)

Hundred-forty-one of 165 expected questionnaires were completed (85%). Four patients were excluded because QoL data were not obtained before the start of treatment. The scores of the responders were not different from the scores of the non-responders.
From 41 patients we obtained the QLQ-C30 questionnaires at baseline and after the second course, from 39 patients the OES18 questionnaires at these time points. Although the physical functioning score declined significantly from 85 to 78 (p=0.04), the emotional functioning score improved significantly from 61 to 73 (p=0.003). The other functional scores did not change. The sleeping score of the EORTC QLQ-C30 decreased significantly from 34 to 16 (p=0.006), indicating improvement of sleeping. The pain score from the EORTC QLQ-OES18 decreased significantly from 16 to 9 (p=0.045), indicating less pain. The score for dry mouth increased significantly from 5 to 14 (0.005). No significant changes were seen in the other symptom scores.

From 33 patients we obtained the QLQ-C30 questionnaires at baseline and after stopping chemotherapy, from 31 patients the OES18 questionnaires at these time points. Scores on the physical functioning scale declined from 88 to 78 (p=0.02), but scores on the emotional functioning scale improved from 60 to 71 (p= 0.02). From the symptom scales of the EORTC QLQ-C30, the sleeping score decreased significantly from 34 to 17 (p=0.03), indicating less symptoms. However, the fatigue score increased significantly from 30 to 43 (p=0.003), indicating more fatigue. From the symptom scales of the EORTC QLQ-OES18, the pain score decreased significantly form 15 to 7 (p=0.02), indicating less pain. The dry mouth score increased significantly from 5 to 20 (p=0.01), indicating worsening of complaints from a dry mouth. No significant changes were seen in the other symptom scores.
The global QoL score was 63 at baseline and 62 after the second course and after stopping chemotherapy.

DISCUSSION

Our study showed no major hematological toxicity, except for grade 3 anemia in one patient and grade 3 neutropenia in another patient. Grade 3 or 4 non-hematological toxicity was uncommon as well. However, in 22% of the patients toxicity was the reason for stopping the chemotherapy (grade 2 toxicity in 7/11 patients and grade 3 or 4 in 4/11 patients). The most (in more than 85% of the patients) reported toxicities were constitutional, namely lethargy and polyneuropathy, but these were of mild to moderate intensity. Other frequently (in more than 50% of the patients) reported toxicities were gastrointestinal (nausea, vomiting and diarrhea), which were also generally of mild to moderate intensity. These toxicities were comparable to that found in the study of Cassidy et al. [10] in patients with metastatic colorectal cancer, as were the reasons for withdrawal from therapy. In one other phase II study the combination of oxaliplatin and capecitabine was tested as first-line treatment in patients with metastatic adenocarcinoma of the esophagus, gastro esophageal junction and gastric cardia [17]. Grade 3 and 4 gastrointestinal toxicity and lethargy were more common in this study, neurological and hematological toxicities were not mentioned. The toxicity prompted a dose-reduction of capecitabine to 825 mg/m2, because of four treatment-related deaths. An explanation for this difference in toxicity can not be found, because the baseline characteristics of the patients enrolled in both studies seem to be comparable. However, this regional differences in mainly gastrointestinal tolerability for fluoropyrimidines between the United States and the rest of the world have been described before [18]. In another phase II study performed in 54 patients with advanced gastric cancer [19], the toxicity of this regimen was comparable to the toxicity in our trial.
Our study showed an median overall survival of 8 months, which is in line with the results from other studies performed at our institution in patients with metastatic or local-regional unresectable esophageal cancer [20]. However, the 1 year survival in our study was slightly worse compared to that observed in previous studies at our institution (26% vs. 33%). This might be explained by the fact that in our study more patients with poor prognostic factors such as liver metastases were included (45% versus 23%).

Improving or maintaining quality of life and achieving symptom relief are important goals in the management of patients with metastatic esophageal cancer. In this study patients reported an improvement in emotional well-being after two courses of chemotherapy as well as after stopping the chemotherapy. This is intriguing, because the physical functioning scores declined significantly over the same period. The reason for this decline in the physical functioning scores is most probably caused by the increase of fatigue, which was stated more frequently after stopping chemotherapy (median after 4 courses). This increase in fatigue score may be due to the treatment, but in about half of the patients, the treatment was stopped due to disease progression, which can also lead to a higher level of fatigue. The improvement of emotional well-being during chemotherapy can not be easily comprehended. Possibly, a better way of coping with the diagnosis of incurable cancer throughout time leads to this improvement. Secondly, the very act of undergoing treatment, may also lead to an improvement of emotional well-being. It has been described that the QoL improves during chemotherapy, despite considerable toxicity [21]. Besides, it is well known that patients are willing to undergo treatments that have small benefits with major toxicity [22].

Overall, the global QoL score at baseline did not change over time. In the study of Ross et al [5] the global QoL scores were maintained with epirubicin/ cisplatin/ 5-fluorouracil, but declined with mitomycin/cisplatin/5-fluorouracil. In that study the QoL scores declined over time, but the follow-up of questionnaires was longer than in our study (up to one year after treatment). In the study of Webb et al. [6] the global QoL scores were maintained and showed no difference between arms at 12 weeks *(P* = .71), but at 24 weeks the difference became more pronounced *(P* = .04), with the epirubicin/cisplatin/5-fluorouracil scores maintained and the 5-fluorouracil/adriamycin/ methotrexate scores lower.

In conclusion, our study shows that the activity of the combination of oxaliplatin 130 mg/m2 intravenously on day 1 and capecitabine 1000 mg/m2 orally twice daily on days 1-14 in a 21-day cycle is comparable to other chemotherapy regimens in metastatic or local-regional unresectable esophageal cancer. The frequency of grade 3/4 toxicity was low and the quality of life was maintained during the treatment. Because this treatment is probably less toxic than cisplatin-based therapy, with preservation of quality of life during treatment, and because it can be given on an outpatient basis, this regimen is a viable treatment option in patients with advanced esophageal cancer.

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Chapter 7

Summary and future perspectives

SUMMARY

Oesophageal cancer is a highly lethal disease, as reflected by an overall survival rate of 10-20%. This is due to the fact that most patients who present with complaints, such as dysphagia, have either locally advanced or metastatic disease. Even after surgery with curative intent, overall survival remains poor. In approximately two-third of the patients local recurrences and/or distant metastases are detected within five years of follow-up. Explanations for this high number of local recurrences and metastases are that tumour spread to lymph nodes occurs rather early in tumorigenesis due to the presence of a submucosal lymph node plexus [1] and the presence of lymph node metastases is very strong adverse prognostic factor. Furthermore, approximately 30% of the oesophageal resections are microscopically irradical [2-4].

Chemotherapy is nowadays frequently used in the treatment of oesophageal cancer. The goal of preoperative and postoperative chemotherapy is a reduction of local recurrences and lymphatic and/or distant spread, with improvement in survival. Besides, preoperative chemotherapy can lead to possible tumour shrinkage allowing an increased radical resectability rate. Chemotherapy in combination with radiotherapy can be used as a part of a multimodality treatment or as definitive treatment. Theoretically, chemotherapy and radiotherapy can interact in several ways. Both treatment modalities may be active against different tumour cell populations; the chemotherapy may be effective against micrometastases, while radiation is active locoregionally. Moreover, chemotherapy may synchronise cells in a vulnerable phase for radiotherapy. Preoperative chemoradiotherapy can induce considerable tumour shrinkage and thereby increase the number of radical resections. Many studies have reported that after chemoradiotherapy in 10–28% of the patients no tumour cells are found in the resection specimen (pathological complete response (pCR)) [5-9]. Several studies have shown that a pCR is associated with a better prognosis [10, 11].

Chemotherapy can also be used in the treatment of patients with metastatic disease. Palliative chemotherapy may result in local and distant tumour and symptom control and this may result in a survival benefit as well.

Chapter 2 is a review article that focussed on the use of chemotherapy alone or as part of combined modality treatment in patients with oesophageal cancer. The evidence available from the literature was used to discuss whether chemotherapy can be considered as an integral part of standard treatment or should still be considered experimental with its impact on survival and quality of life unproven or unknown. The conclusion that can be derived is that it is feasible to administer chemoradiotherapy preoperatively and that chemotherapy and radiotherapy can be combined as definitive treatment. Although there are indications that preoperative chemotherapy or preoperative chemoradiotherapy may have an impact on survival, the precise extent, if any, is still unknown. It is also unknown whether the benefit outweighs the increased treatment-related toxicity. The uncertain impact of preoperative chemotherapy or chemoradiotherapy is caused by the fact that most performed phase III studies are underpowered or flawed by a poor design.

The evidence that chemotherapy may be beneficial for patients with metastatic disease can be derived from only two trials in which both patients with oesophageal and gastric cancer were treated. The most important conclusion that can be derived from

this overview of the literature concerning the treatment with chemotherapy or chemoradiotherapy is that most of these studies are feasibility studies, phase 2 studies and underpowered phase 3 studies.

In **Chapter 3** a phase 2 study is reported in which the safety and efficacy of an outpatient preoperative chemoradiotherapy regimen, consisting of five weekly courses of carboplatin and paclitaxel and concurrent 23 daily radiotherapy fractions for 54 patients with resectabel oesophageal cancer. Fifty-three patients (98%) completed the preoperative treatment. The treatment was well tolerated by the patients. Grade 3-4 toxicities were: neutropaenia 15%, thrombocytopaenia 2%, and oesophagitis 7.5%. The pathological complete response rate was 25%. All patients had an R0-resection (microscopically radical). At the time of analysis the median overall survival had not yet been reached. The estimated 3-year survival rate was 56%. A major advantage of this treatment regimen is that it can be given on an outpatient basis. A multicentre randomised phase 3 trial with this regimen followed by surgery versus surgery alone in now ongoing in the Netherlands.

Chapter 4 describes the results of a quality of life analysis in 54 patients with oesophageal cancer treated with curative intent by neoadjuvant chemoradiotherapy followed by oesophagectomy. Because of the trade-off between the potentially negative quality of life effects and the uncertain favourable survival effect of neoadjuvant chemoradiotherapy in these patients, the health-related quality of life was assessed for up to one year postoperatively in patients treated with preoperative chemoradiotherapy with a non-cisplatin based outpatient regimen followed by surgery. Patients undergoing this treatment completed standardized health related quality of life questionnaires. Differences in generic and condition-specific health related quality of life scores over time were analysed, using a linear mixed effects model. The generic quality of life was assessed with the quality of life core questionnaire (QLQ-C30) from the European Organisation for Research and Treatment of Cancer (EORTC). The condition-specific health related quality of life was assessed with a site-specific questionnaire for oesophageal cancer (OES18) from the EORTC. Mean scores of most health related quality of life scales deteriorated significantly during neoadjuvant chemoradiotherapy. The largest deterioration was observed for physical and role functioning scales. Postoperatively, most mean health related quality of life scores improved until recovery to baseline level. The emotional functioning score showed a different pattern; it was worst at baseline, and increased over time during chemoradiotherapy and postoperatively. The dysphagia and pain scores worsened considerably during chemoradiotherapy, restored to baseline three months postoperatively, and were even significantly better one year postoperatively. The time of assessment of the health related quality of life after chemoradiotherapy (one week after finishing the treatment) might have influenced the results, because at this time point the toxicity of chemoradiotherapy is at maximum. Given the discrepancy found between the seriousness of toxicity assessed by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) and by the symptom scales and items of the QLQ-C30 and OES18 questionnaires, one can conclude that health related quality of life assessment gives additional information on toxicities of chemoradiotherapy regimens.

After chemoradiotherapy several histological changes in the resected specimen can be identified. On the basis of the histological changes, the grade of tumour regression can be defined. Regression of the primary tumour can range from the absence of regressive changes to a total response with no vital residual tumour cells (complete pathological response). In **Chapter 5** an overview is given from the Rotterdam experience with neoadjuvant carboplatin and paclitaxel concurrent with radiotherapy in 67 patients with resectable oesophageal cancer. The residual tumour cells after preoperative treatment were determined, and the effect of specific pathologic and clinical findings to overall survival was correlated. In 60% of the patients a good response to chemoradiotherapy was seen (<10% vital tumour cells in the resected specimen). A complete pathological response was found in 24% of the patients. The proportion of patients with tumour infiltration into the adventitia (T3) was significantly higher before treatment than after treatment. This applied for nodal involvement as well. When vital tumour cells were left in the oesophageal wall after chemoradiotherapy, the tumour was graded more frequently as poorly differentiated than before treatment. This might be explained by the fact that poorly differentiated tumour cells may be more resistant to the cytotoxic insult caused by neoadjuvant therapy. On the other hand, a complete pathological response was more frequently found in pre-treatment poorly differentiated tumours. Achieving a complete pathological response did result in an obvious trend toward a survival benefit. The presence of nodal metastasis as assessed by EUS was significantly associated with a worse survival, in contrast to the presence of nodal metastasis after CRT as assessed by pathological analysis.

In **Chapter 6** the results of a phase 2 study with palliative chemotherapy are reported. In this study we assessed the safety and efficacy of the combination of oxaliplatin and capecitabine in a 21-day treatment cycle as first-line therapy in 51 patients with advanced cancer of the oesophagus, oesophagogastric junction or cardia. In addition, the effects of this schedule on the patients' well being were evaluated by a quality of life analysis on these patients during the treatment. Grade 3 neutropaenia was seen in one patient and anaemia in another. No grade 4 haematological toxicities were observed. Grade 4 non-haematological toxicity (lethargy) occurred in one patient (2%). Grade 3 non-haematological toxicity was seen in 14 (27%) patients (nausea, vomiting, anorexia, diarrhoea, polyneuropathy, lethargy, hand-foot syndrome, and hyperbilirubinaemia). Despite the fact that grade 3 or 4 toxicity was uncommon, toxicity was the reason for stopping the treatment in 22% of the patients. The overall response rate was 39%. The median overall survival was 8 months. In the quality of life analysis, the emotional well being improved during treatment, but the physical functioning scores declined. The fatigue score on the symptom scales increased. Overall, the global quality of life score did not change during treatment. Because this treatment can be given on an outpatient basis, and is probably less toxic than cisplatin-based therapy and preserves quality of life during treatment, it might be a viable treatment option in patients with advanced oesophageal cancer.

FUTURE PERSPECTIVES

Theoretically, there are several ways to improve the high mortality rate of oesophageal cancer. First, reducing the incidence of oesophageal cancer could lower the total number of patients diagnosed yearly with this devastating disease. Secondly, by improving the selection of patients who might benefit from surgical treatment, the survival resected patients might increase. Finally, the development of better diagnostic and treatment approaches can ameliorate the prognosis of patients with oesophageal cancer.

Reducing the incidence of owsophageal cancer

Until the 1970s the incidence of squamous cell carcinoma exceeded the incidence of adenocarcinoma of the oesophagus in the Western world. Tobacco smoking and alcohol abuse are the main risk factors for the development of squamous cell cancer of the oesophagus. Although there are no known intervention trials studying the impact of the cessation of smoking on the incidence of this type of oesophageal cancer, cessation of smoking is believed to be an important prevention measure. Unfortunately, of the smokers who try to quit only a minority succeeds [12]. Maybe, the introduction of new pharmacotherapies to treat nicotine dependency can have a beneficial effect [13]. In Linxian China, the oesophageal cancer mortality rate is extremely high. There is a suspicion that the population's chronic deficiencies of micronutrients are etiologically involved. Therefore, randomized, placebo-controlled nutrition intervention trials were performed to test the effect of vitamin and mineral supplements for 6 years in lowering the incidence rate of cancer. Results from the General Population Trial showed that those who received the β-carotene-vitamin E-selenium combination had a 13% reduction in cancer mortality, and a 4% decrease in deaths from oesophageal cancer, after a relatively short period of follow-up [14]. Results from the Dysplasia Trial showed that supplementation reduced the likelihood of having oesophageal dysplasia after both 30 and 72 months of intervention [14]. With dysplasia being a premalignant lesion, the effect of the nutrition intervention on mortality might therefore increase in the future.
Over the last decades there has been a substantial increase in the incidence of adenocarcinomas of the lower third of the oesophagus in Western countries. Adenocarcinomas of the oesophagus are associated with obesity [15], gastro-oesophageal reflux disease [16], and Barrett's metaplasia [17-19]. Oesophageal cancer arising from a Barrett's oesophagus is thought to arise within the 'Barrett's metaplasia-low grade dysplasia-high grade dysplasia-carcinoma sequence'. While only 0.2-2% of the patients with Barrett's oesophagus will eventually develop oesophageal cancer [20, 21], there is still an increased risk. Besides, the detection of these premalignant lesions by random biopsies is troubled by sampling error and by the intra- and interobserver variation of histological assessment. New developments in both endoscopy technique and tissue sampling might improve early diagnosis of high grade dysplasia and cancer [22]. In addition, the presence of genetic alterations in metaplastic and dysplastic Barrett's epithelium might be used in the future surveillance of patients with Barrett's oesophagus, since these molecular markers could identify a subset of patients with an increased risk of malignant degeneration. For example, patients with an increase of tetraploid or aneuploid cell populations in Barrett's epithelium, were found to be at a higher risk for developing invasive carcinoma during follow-up (RR 7.5) [23].

For those patients diagnosed with Barrett's metaplasia, prevention of progression to oesophageal cancer is an important goal. Whether the interventions that inhibit the development of inflammatory mediators and reduce acid reflux and bile exposure may offer a cost-effective and widely applicable treatment option is currently being investigated in the AspECT trial. In this phase III trial patients with a Barrett's oesophagus circumference of 3 cm or greater are randomised to receive continuous low- or high-dose proton pump inhibitor therapy with or without aspirin.

Development of novel diagnostic strategies

Even after surgery with curative intent, the overall survival after an oesophagectomy remains poor. The identification of those patients who may or may not benefit from surgery is therefore of utmost importance. Positron emission tomography (PET) has become a major diagnostic tool for the detection of mediastinal lymph nodes and extrathoracic metastases in non-small cell lung cancer [24]. However, the diagnostic yield of a PET-scan to improve the selection of patients with oesophageal cancer for potentially curative surgery is limited after "state-of-the art" staging [25, 26]. On the other hand, a PET-scan might be a useful diagnostic tool that allows for accurate prediction of tumour response early during chemoradiotherapy. Data suggest that metabolic changes in tumour tissue as measured by FDG-PET predict response better than EUS or a CT-scan [27]. Whether a PET-scan predicts early in the treatment the non-response to neoadjuvant chemoradiotherapy in patients with potentially curable oesophageal cancer is currently being investigated in the NEOPEC-trial in the neoadjuvant arm of a randomized multicentre Dutch trial comparing neoadjuvant chemoradiotherapy followed by surgery versus surgery alone (see below).

The stage of the disease as expressed in the TNM staging system [28], is one of the most important prognostic factors for patients with oesophageal cancer. Lagarde et al. showed that besides TNM staging, the number of positive lymph nodes or the positive/negative lymph node ratio, extracapsular lymph node involvement, radicality of oesophagectomy, and tumour size are important prognostic factors as well [29]. In some other tumour types the presence of prognostic features may influence subsequent treatment decisions, such as the administration of adjuvant chemotherapy in case of nodal involvement in breast and colorectal cancer, or the start of palliative chemotherapy in case of a high PSA doubling time in prostate cancer. For oesophageal cancer up till now, no such treatment decisions are linked to the presence of prognostic factors. However, molecular pathology has revealed a vast number of genes and molecules, which are related to tumour invasion and metastasis, and in that way also to prognosis. In patients with breast cancer, overexpression of the HER2/neu protein is associated with an aggressive behaviour of the tumour [30]. Trastuzumab, a humanized monoclonal antibody against the extracellular domain of HER2, has been shown to benefit patients with HER2-positive breast cancer [31, 32]. Several prognostic factors of genes and molecules in adenocarcinoma of the oesophagus have been established, like HER2/neu, TGF-β, p53, COX2, E-cadherin, β-catenin, UPA, MMP-1, DNA aneuploidy, and >50% promotor hypermethylation. The targeting of these pathways may enhance the therapeutic options for patients with this type of cancer [33].

Recently, it has become possible to detect, enumerate, and characterise circulating tumour cells (CTCs) reliably [34]. Potential applications of this are: establishing prognosis,

serving as a marker to assess treatment-induced anti-tumour activity, detecting recurrent disease, elucidating prognostic and predictive factors, and exploring biological processes (dissemination, drug resistance, and therapy-induced cell death). Likely, the detection, enumeration and characterization of CTCs will form a valuable attribution to medical oncology in terms of research and patient management purposes in the near future.

Development of novel therapeutic approaches

Oesophageal surgery is associated with considerable peri-operative morbidity and mortality, especially in low-volume hospitals [35]. The concentration of oesophageal surgery in high volume hospitals may have a positive effect on the morbidity and mortality. Another important reason to centralize the treatment of patients with oesophageal cancer is the presence of multidisciplinary consultations teams in most of these high volume hospitals.

A conclusion concerning neoadjuvant chemoradiotherapy of the review article in this thesis was that the role of preoperative chemoradiation is still unclear. Recently, a meta-analysis showed a significant 2-year survival benefit for preoperative chemoradiotherapy and, to a lesser extent, for preoperative chemotherapy in patients with carcinoma of the oesophagus [36]. However, because this meta-analysis is based on mostly inadequately performed and underpowered phase 3 studies, the strength of the conclusions of such meta-analyses is questionable. Yet, the concept of neoadjuvant chemoradiotherapy remains very appealing. Therefore, and because of the favourable results from our phase 2 study with neoadjuvant carboplatin and paclitaxel with concurrent radiotherapy followed by oesophagectomy, we are currently involved in a randomised phase 3 trial with this preoperative chemoradiotherapy regimen followed by surgery versus surgery alone (CROSS-trial). This study has, up to now, included more than 300 patients.

Many questions remain concerning the optimal radiation dose and schedule and chemotherapy schedule. By the use of newer chemotherapeutic agents, such as taxanes and irinotecan, weekly or continuous administration of chemotherapy together with concurrent radiotherapy, hyperfractionated radiotherapy schedules, an improvement in treatment outcome might be achieved. Targeted therapy with a cyclooxygenase -2 inhibitor, vascular endothelial growth factor inhibitors, epidermal growth factor receptor blockers or mammalian target of rapamycin inhibitors are attractive means for combining with radiotherapy or chemotherapy alone, or with chemoradiotherapy [37].

As stated, oesophageal surgery is associated with considerable peri-operative morbidity and mortality. Apart from the severe physical impact, an oesophageal resection also has a major psychological and social effect [38-41]. An alternative, organ preserving, treatment regimen consisting of continuing chemoradiotherapy in patients responding to preoperative chemoradiation, thereby avoiding unnecessary additional surgery is an attractive treatment option. This strategy seems to be a reasonable treatment option with a comparable survival rate to surgery according to two studies [42, 43], albeit that the locoregional recurrence rate was higher in patients treated with definitive chemoradiation. However, appropriate selection criteria to identify patients who will respond to chemoradiotherapy would allow us to maximize the therapeutic benefit and to minimize toxicity. In order to prevent unnecessary toxicity, it would even be better to be able to predict response to chemoradiotherapy before start of the treatment. Sev-

eral molecular markers have been tested for their potential to predict therapy response [44]. The authors found an association between the response of patients with Barrett's adenocarcinoma to neoadjuvant chemotherapy with 5-fluorouracil and cisplatin and the expression levels of methylenetetrahydrofolate reductase (MTHFR), caldesmon (actinomyosin regulatory protein), and multidrug resistance protein 1 (MRP1), in part with a sensitivity of >90%. Further investigation is needed to develop diagnostic tools that may predict response to preoperative chemoradiotherapy by analyzing routine biopsies from tumour tissue.

The effect of oesophageal surgery with or without preoperative therapy on the quality of life of patients with oesophageal cancer is frequently not very well highlighted. Because health related quality of life assessments give additional information on toxicities of chemoradiotherapy regimens, and in order to investigate the possible effect of neoadjuvant chemoradiotherapy on an impaired and/or delayed recovery of health related quality of life after surgery, a quality of life analysis is performed with the above mentioned phase 3 study as well. Results from that study can be used to inform patients about what to expect from this multimodality treatment for resectable oesophageal cancer and hence contribute to the process of shared decision making about treatment choice.
For the many patients who present with metastatic disease or who relapse after surgery or definitive chemoradiotherapy no curative options are available. For these patients palliation of dysphagia and of symptoms such as pain and fatigue are important goals. Especially in this patient group improving or maintaining quality of life is extremely important. However, current standards for analyzing quality of life and symptom control in randomized controlled trials are poor. Definition of a palliative endpoint, with an a priori hypothesis, is essential; defining the proportion of patients with palliative response is preferred. A checklist could raise standards of reporting in future randomized controlled trials [45].
Placement of a self-expanding metal stent, external beam radiotherapy, intraluminal radiotherapy (brachytherapy), and laser therapy are commonly used palliative modalities to treat dysphagia [46]. Few studies have been performed to compare these treatment options. There are no studies comparing the effect of chemotherapy and other palliative treatments on symptom control (e.g. dysphagia). In one study the use of single-dose brachytherapy was compared with metal stent placement for the palliation of dysphagia in patients with oesophageal cancer [47]. Despite slow improvement, single-dose brachytherapy gave better long-term relief of dysphagia than metal stent placement. Since brachytherapy was also associated with fewer complications than stent placement and, moreover, since the effects of single dose brachytherapy on health related quality of life compared favourably to those of stent placement for the palliation of oesophageal cancer [48], it is recommended as the primary treatment for palliation of dysphagia from oesophageal cancer.
The results from the phase II trial studying the effect of the treatment with oxaliplatin and capecitabine of patients with metastatic or locally advanced oesophageal cancer in this thesis showed that palliative chemotherapy can maintain quality of life during treatment and might even improve symptoms (pain). The effect of chemotherapy on survival is unclear, mainly due to a lack of randomised trials. The conclusions from the

Cochrane Review concerning the use of chemotherapy for metastatic carcinoma of the oesophagus and gastro-oesophageal junction are that there is a need for well designed, adequately powered, phase III trials comparing chemotherapy versus best supportive care for patients with metastatic oesophageal cancer [49]. Chemotherapy agents with promising response rates and tolerable toxicity are cisplatin, 5-fluorouracil (5-FU), paclitaxel and anthracyclins. Future trials comparing palliative treatment modalities should assess quality of life with validated quality of life measures as well.

The increasing knowledge of the molecular biology of cancer and the development of new diagnostic tools and targeted agents offer new challenges and opportunities for the treatment of patients with oesophageal cancer and the development of more tailor made treatment strategies with the best benefit for our patients.

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Samenvatting

SAMENVATTING

Slokdarmkanker is een zeer dodelijke ziekte, gezien de algemene overleving van 10-20%. Dit is het gevolg van het feit dat de meeste patiënten die zich presenteren met klachten zoals dysfagie al een vergevorderd of uitgezaaid stadium van de ziekte hebben. Ook na een oesofagusresectie met curatieve intentie, treedt er bij ongeveer éénderde van de patiënten binnen vijf jaar een ziekterecidief op in de vorm van een lokaal recidief en/of metastasen. Een verklaring voor dit grote aantal recidieven is het feit dat de tumor al in een vroeg stadium uitzaait naar de lymfklieren ten gevolge van de aanwezigheid van een submucosale lymfklierplexus en het feit dat de aanwezigheid van lymfkliermetastasen een slechte prognostische factor is. Daarnaast is een oesofagusresectie tot in 30% van de gevallen niet radicaal.
Chemotherapie wordt tegenwoordig frequent gebruikt in de behandeling van slokdarmkanker. Het kan voor of na een oesofagusresectie gegeven worden met als doel een ziekterecidief ten gevolge van occulte lymfklier- of afstandsmetastasen te elimineren om zo de overleving te verbeteren. Preoperatieve chemotherapie kan daarnaast de tumor doen krimpen, waardoor de kans op een radicale resectie vergroot wordt. Chemotherapie in combinatie met radiotherapie kan gebruikt worden als onderdeel van 'multimodality' behandeling of als definitieve behandeling. Er is een interactie van chemotherapie en radiotherapie op verschillende niveaus. Beide hebben antikanker activiteit; chemotherapie kan effectief zijn tegen micrometastasen, terwijl radiotherapie locoregionaal werkt. Chemotherapie is bovendien in staat om cellen tijdens de celdeling in een bepaalde fase te houden, waarin de cellen beter gevoelig zijn voor radiotherapie. Het doel van preoperatieve chemoradiotherapie is afname van de tumorgrootte om zo de kans op een radicale resectie te vergroten. Veel studies hebben gerapporteerd dat na chemoradiotherapie bij 10-28% van de patiënten geen tumorcellen meer in het resectiepreparaat kunnen worden teruggevonden (complete pathologische respons (pCR)). Verscheidene studies hebben aangetoond dat zo'n pCR is geassocieerd met een betere prognose.
Chemotherapie kan ook gebruikt worden in de behandeling van patiënten met gemetastaseerde ziekte. Het doel van deze behandeling is controle van de locale tumor en van de afstandsmetastasen, zodat er symptoomvermindering optreedt. Een bijkomend voordeel van deze behandeling zou een toename van de levensverwachting kunnen zijn.

In **Hoofdstuk 2** werd een overzicht gegeven van het gebruik van chemotherapie alleen of als onderdeel van een gecombineerde behandeling (met radiotherapie en/of operatie) bij patiënten met slokdarmkanker. Beschikbaar bewijs uit de literatuur werd gebruikt om te bediscussiëren of chemotherapie beschouwd kan worden als integraal onderdeel van de behandeling van patiënten met slokdarmkanker of dat het effect op overleving en kwaliteit van leven nog niet duidelijk is. De conclusie van het overzichtsartikel was dat de combinatie van chemotherapie met bestraling zonder veel problemen gegeven kan worden voor een slokdarmoperatie of goed gebruikt kan worden als definitieve behandeling voor slokdarmkanker. Hoewel er aanwijzingen zijn dat preoperatieve chemotherapie of chemoradiotherapie enig effect kan hebben op de overleving, is de grootte van dit effect, als het er al is, nog niet duidelijk. Tevens is het nog niet duidelijk of de eventuele voordelige effecten op de overleving opwegen tegen de nadelige ef-

fecten van deze behandeling. Het onzekere effect van preoperatieve chemotherapie of chemoradiotherapie wordt veroorzaakt door het feit dat de meeste fase 3 onderzoeken op dit gebied niet van voldoende grootte zijn of gekenmerkt worden door een slechte opzet. Het bewijs dat chemotherapie nuttig kan zijn bij patiënten met gemetastaseerd slokdarmkanker kan uit slechts twee studies geconcludeerd worden. Een beperking van deze twee studies is het feit dat zowel patiënten met slokdarmkanker als patiënten met maagkanker werden behandeld.
De belangrijkste conclusie die uit dit overzicht van de literatuur kan worden getrokken is dat met betrekking tot de rol van chemotherapie in de behandeling van patiënten met slokdarmkanker er voornamelijk fase 2 studies en fase 3 studies van onvoldoende grootte zijn gepubliceerd.

In **Hoofdstuk 3** werd een fase 2 studie besproken, waarin het effect en de bijwerkingen van een poliklinisch preoperatief chemoradiotherapie schema werd beschreven bij 54 patiënten met een resectabel oesofaguscarcinoom. De behandeling bestond uit vijf wekelijkse toedieningen van paclitaxel en carboplatin gelijktijdig met 23 bestralingen op werkdagen. De behandeling werd voltooid door 98% van de patiënten en werd goed verdragen. De belangrijkste hematologische toxiciteit bestond uit een graad 3 neutropenie bij 15% van de patiënten. De belangrijkste niet-hematologische toxiciteit was een graad 3 oesofagitis bij 7,5% van de patiënten. Bij 13 van de 52 (25%) patiënten die geopereerd werden, kon in het resectiepreparaat geen tumorcellen meer worden teruggevonden. Bij alle patiënten kon een microscopisch radicale operatie plaatsvinden. Ten tijde van het analyseren van de overlevingsdata was de mediane algemene overleving nog niet bereikt. De geschatte 3-jaars overleving was 56%. Het grote voordeel van dit schema is, is dat het poliklinisch kan worden toegediend. Een gerandomiseerde fase 3 studie waarin deze preoperatieve behandeling gevolgd door operatie wordt vergeleken met operatie alleen bij patiënten met een resectabel oesofaguscarcinoom wordt nu in meerdere ziekenhuizen in Nederland uitgevoerd.

Hoofdstuk 4 beschrijft de resultaten van een kwaliteit van leven analyse gedurende preoperatieve chemoradiotherapie en na operatie bij 54 patiënten met een resectabel oesofaguscarcinoom. Gezien de afwegingen tussen de mogelijke negatieve effecten op de kwaliteit van leven en de onzekere positieve effecten op overleving van preoperatieve chemoradiotherapie gevolgd door een oesofagusresectie, werd in dit onderzoek de kwaliteit van leven beoordeeld tot één jaar na de operatie bij patiënten met een resectabel oesofaguscarcinoom. Op gezette tijden werden gestandaardiseerde vragenlijsten afgenomen. Het verschil in algemene kwaliteit van leven scores en de ziekte specifieke kwaliteit van leven scores over de tijd werd geanalyseerd. Voor de beoordeling van de algemene kwaliteit van leven werd de hoofdvragenlijst voor kwaliteit van leven (QLQ-C30) van de Europese Organisatie voor Onderzoek en Behandeling van Kanker (EORTC) gebruikt. Voor de ziekte specifieke kwaliteit van leven werd de ziektespecifieke vragenlijst (OES-18) van de EORTC gebruikt. De gemiddelde kwaliteit van leven scores daalden significant gedurende de preoperatieve chemoradiotherapie. De grootste daling werd gezien voor fysiek en rol functioneren. Na de oesofagusresectie verbeterden de gemiddelde scores weer tot uitgangsniveau. Het emotioneel functioneren was slecht bij aanvang van de behandeling, maar verbeterde over de tijd significant. De scores

voor dysfagie en voor pijn verslechterden aanzienlijk tijdens de chemoradiotherapie, maar deze waren drie maanden na de operatie weer op uitgangsniveau en één jaar postoperatief zelfs beter dan bij aanvang van de behandeling. Het tijdstip waarop het effect van de chemoradiotherapie op de kwaliteit van leven werd beoordeeld (één week na staken van de chemoradiotherapie) kan een effect gehad hebben op de uitkomst van de analyse, aangezien op dat moment de toxiciteit van de behandeling het grootst is. Gezien het feit dat er een forse discrepantie bestond tussen gemeten toxiciteit met behulp van de National Cancer Institute Common Toxicity Criteria (NCI-CTC) en de symptomen gemeten met behulp van de kwaliteit van leven vragenlijsten (QLQ-C30 en OES-18), moet geconcludeerd worden dat kwaliteit van leven analyses extra informatie geven over de bijwerkingen van chemoradiotherapie schema's.

Na preoperatieve chemoradiotherapie kunnen in het uitgenomen slokdarmpreparaat diverse histologische veranderingen worden gezien; soms worden er zelfs helemaal geen tumorcellen meer in het resectiepreparaat teruggevonden (complete pathologische respons). Daarnaast is het mogelijk de mate van respons op chemoradiotherapie te kwantificeren. In **Hoofdstuk 5** wordt een overzicht gegeven van deze histologische veranderingen na preoperatieve chemoradiotherapie met paclitaxel en carboplatin gecombineerd met radiotherapie bij 67 patiënten met een resectabel oesofaguscarcinoom. Tevens werden deze histologische veranderingen samen met klinische karakteristieken gecorreleerd met overlevingsdata. Bij 60% van de patiënten trad een goede respons op na chemoradiotherapie (<10% tumorcellen over in het uitgenomen slokdarmpreparaat). Bij 24% was sprake van een complete pathologische respons. Ook bleek uit de resectiepreparaten dat de uitbreiding van de tumor in de slokdarmwand significant minder was dan voor de behandeling en dat er bij minder patiënten lymfkliermetastasen konden worden gevonden. De tumor in het resectiepreparaat werd vaker als slecht gedifferentieerd geclassificeerd dan voor start van de behandeling. Dit lijkt niet het gevolg te zijn van het 'uitselecteren' van slecht gedifferentieerde tumoren, aangezien tumoren die preoperatief als slecht gedifferentieerd waren beoordeeld, significant vaker een complete pathologische respons lieten zien. Er bleek een duidelijke trend te bestaan tot een betere overleving voor patiënten die een complete pathologische respons hadden. De aanwezigheid van lymfkliermetastasen bij onderzoek met endo-echografie was significant geassocieerd met een slechter overleving, in tegenstelling tot de aanwezigheid van lymfkliermetastasen in het resectiepreparaat na chemoradiotherapie.

In **Hoofdstuk 6** werden de resultaten van een fase 2 studie beschreven, waarin de veiligheid en werking van de combinatie van oxaliplatin en capecitabine in een 3-wekelijks schema is beoordeeld als eerstelijns behandeling van 51 patiënten met een gemetastaseerd of lokaal vergevorderd oesofaguscarcinoom, junction tumor of cardiacarcinoom. Tevens werden de effecten van dit schema op het welbevinden van de patiënten getest met behulp van een kwaliteit van leven analyse gedurende de behandeling. De belangrijkste hematologische toxiciteit bestond uit een graad 3 anemie bij 2% en een graad 3 neutropenie bij 2% van de patiënten. De belangrijkste niet-hematologische toxiciteit bestond uit een graad 4 lethargie en verscheidene graad 3 bijwerkingen (misselijkheid, braken, anorexie, diarree, polyneuropathie, lethargie, handvoetsyndroom en een hyperbilirubinemie) bij 27% van de patiënten. Ondanks deze relatief lage frequentie van

graad 3 en 4 toxiciteit, werd de behandeling bij 22% van de patiënten gestaakt omwille van voor de patiënt onacceptabele bijwerkingen. Het responspercentage was 39%. De mediane overleving was 8 maanden. De kwaliteit van leven analyse liet een achteruitgang van het fysiek functioneren zien, evenals een verslechtering van de vermoeidheidsscores. Het emotionele functioneren verbeterde gedurende de behandeling. De algemene kwaliteit van leven score veranderde niet gedurende de behandeling. Omdat deze behandeling poliklinisch kan worden gegeven en mogelijk minder bijwerkingen heeft dan cisplatin bevattende chemotherapieschema's én aangezien de kwaliteit van leven gewaarborgd blijft gedurende de behandeling, kan dit schema als een bruikbare behandelingsoptie worden beschouwd voor patiënten met een gemetastaseerd of lokaal vergevorderd oesofaguscarcinoom.

TOEKOMSTIGE ONTWIKKELINGEN

Theoretisch zijn er verschillende manieren om de hoge mortaliteit van slokdarmkanker te verbeteren. Ten eerste kan een reductie van de incidentie van slokdarmkanker het aantal patiënten dat jaarlijks met deze verwoestende ziekte gediagnosticeerd wordt verlagen. Ten tweede kan de overleving geopereerde patiënten vergroot worden door een betere selectie van patiënten die baat hebben bij een chirurgische behandeling. Als laatste kan de prognose van patiënten met slokdarmkanker verbeterd worden door de ontwikkeling van betere diagnostische mogelijkheden en behandelingen.

Vermindering incidentie slokdarmkanker

Tot de jaren zeventig was in de westerse wereld de incidentie van het plaveiselcel carcinoom van de slokdarm groter dan die van het adenocarcinoom. Roken en alcoholgebruik zijn de belangrijkste risicofactoren voor de ontwikkeling van het plaveiselcel carcinoom van de slokdarm. Hoewel er geen bekende studies bestaan die het effect van het stoppen met roken op de incidentie van dit type slokdarmkanker hebben onderzocht, wordt aangenomen dat het stoppen met roken een belangrijk preventief effect heeft. Helaas slaagt slechts een minderheid van de rokers er in te stoppen. Misschien dat de introductie van nieuwe medicamenten om nicotine verslaving te bestrijden een positief effect heeft. In Linxian in China is de mortaliteit ten gevolge van slokdarmkanker zeer hoog. Vermoedelijk heeft dit te maken met de chronische deficiëntie van micronutriënten onder de bevolking. Om die reden zijn gerandomiseerde, placebogecontroleerde voeding-interventie studies verricht om het effect van vitamine en mineralen supplementen gedurende 6 jaar op vermindering van de incidentie van slokdarmkanker te beoordelen. De resultaten van de 'General Population Trial' toonden dat die patiënten die de combinatie van β-caroteen-vitamine E-selenium kregen een 13% reductie hadden in kanker mortaliteit, en een 4% daling in het aantal overledenen ten gevolge van slokdarmkanker. De resultaten van de 'Dysplasia Trial' toonden dat de supplementen de kans op het krijgen van dysplasie in de slokdarm na zowel 30 als 72 maanden verminderden. Aangezien dysplasie een voorstadium is voor slokdarmkanker kan het effect van voeding-interventie op sterfte in de toekomst dus nog wel groter worden.
In de laatste decennia heeft er in westerse landen een sterke toename plaatsgevonden in de incidentie van adenocarcinomen van het laatste éénderde gedeelte van de

slokdarm. Adenocarcinomen van de slokdarm zijn gerelateerd aan overgewicht, gastro-oesofageale reflux ziekte en Barrett's metaplasie. Adenocarcinomen van de slokdarm die ontstaan uit een Barrett's slokdarm, ontwikkelen zich waarschijnlijk via de 'Barrett's metaplasie-laaggradige dysplasie-hooggradige dysplasie-carcinoma' volgorde. Hoewel slechts 0.2-2% van de patiënten met een Barrett's slokdarm slokdarmkanker krijgt, is dit toch een verhoogd risico. Daarom lijkt screening en surveillance endoscopie met weefsel biopten bij patiënten met Barrett's metaplasie een aantrekkelijke strategie om de incidentie van slokdarmkanker te verminderen. Echter, de huidige screening en surveillance richtlijnen voor Barrett's slokdarm en de daaraan verwante neoplasie worden niet ondersteund door sterk bewijs. Eén van de redenen hiervoor is dat endoscopische herkenning van premaligne afwijkingen moeilijk kan zijn. Daarnaast wordt de vaststelling van deze premaligne lesies door middel van willekeurige biopten bemoeilijkt door 'sampling error' en door de intra- en interobserver variatie bij histologische beoordeling. Nieuwe ontwikkelingen op het gebied van zowel endoscopie technieken als van weefsel verzameling kan de vaststelling van hooggradige dysplasie en vroeg carcinomen verbeteren. Daarnaast kunnen de aanwezige genetische veranderingen in metaplastisch en dysplastisch Barrett's epitheel in de toekomst gebruikt worden voor de surveillance van patiënten met een Barrett's slokdarm, aangezien deze moleculaire markers een categorie patiënten kan identificeren met een verhoogd risico op maligne ontaarding. Zo hebben bijvoorbeeld patiënten met een verhoogd aantal tetraploïde of aneuploïde celpopulaties in Barrett's epitheel, een verhoogd risico op het ontwikkelen van een invasief carcinoom gedurende follow-up (RR 7.5). Voor patiënten met Barrett's metaplasie is het voorkomen van slokdarmkanker een belangrijk doel. Of het onderdrukken van de ontstekingsverschijnselen en de zure en gallige reflux een kosten effectieve en makkelijk toepasbare behandeling is wordt op dit moment onderzocht in de AspECT studie. In deze fase 3 studie worden patiënten met een Barrett's oesofagus met een grootte van 3 cm of meer gerandomiseerd tussen continue lage of hoge dosis proton pomp remming met of zonder aspirine.

Ontwikkeling van nieuwe diagnostische strategieën

Zelfs na een in opzet curatieve operatie, blijft de overleving van patiënten met slokdarmkanker slecht. Het identificeren van die patiënten die wel of niet kunnen profiteren van een operatie is daarom uitermate belangrijk. Positron emissie tomografie (PET) is een belangrijk diagnostische middel geworden bij het niet-kleincellig longcarcinoom voor de detectie van mediastinale lymfklieren en metastasen op afstand. De waarde van een PET-scan om een betere selectie voor een curatieve operatie van patiënten met slokdarmkanker te krijgen, is beperkt als patiënten adequaat gestadiëerd zijn. Aan de andere kant kan een PET-scan wel een waardevol diagnostisch instrument zijn voor een accurate voorspelling van respons op chemoradiotherapie vroeg in de behandeling. Er zijn aanwijzigen dat de metabole veranderingen in tumorweefsel, zoals die gemeten worden met een FDG-PET scan, de respons beter voorspellen dan een endo-echografie of een CT-scan. Of een PET-scan vroeg in de behandeling het niet responderen op neoadjuvante chemoradiotherapie kan voorspellen in patiënten met mogelijk curabel slokdarmkanker, wordt op dit moment onderzocht in de NEOPEC-studie in de neoadjuvante arm van een Nederlandse multicenter studie die neoadjuvante chemoradiotherapie gevolgd door chirurgie vergelijkt met chirurgie alleen (zie hieronder).

Het stadium volgens de TNM classificatie is één van de meest belangrijke prognostische factoren voor patiënten met slokdarmkanker. Lagarde et al. toonden aan dat naast de TNM stagering ook het aantal positieve lymfklieren of de positieve/negatieve lymfklier ratio, extracapsulaire uitbreiding van lymfklieren, de radicaliteit van de slokdarmresectie en de tumor grootte belangrijke prognostische factoren zijn. Bij sommige andere tumor types spelen de aanwezigheid van prognostische factoren een rol in de beslissingen omtrent de vervolgbehandeling, zoals adjuvante chemotherapie in het geval van positieve lymfklieren bij borst- en dikke darmkanker of de start van palliatieve chemotherapie in het geval van een hoge PSA verdubbelingtijd in prostaatkanker. Voor slokdarmkanker zijn er nog geen behandeling consequenties verbonden aan de aanwezigheid van prognostische factoren. Echter, de moleculaire pathologie heft een aantal genen en moleculen ontdekt, die gerelateerd zijn aan tumor invasie en de ontwikkeling van metastasen. Op die manier zijn zij ook gerelateerd aan de prognose. In patiënten met borstkanker is de overexpressie van het HER2/neu eiwit geassocieerd met een agressief gedrag van de tumor. Trastuzumab, een gehumaniseerd monoklonaal antilichaam tegen het extracellulaire domein van HER2, is effectief in patiënten met HER2-positiev borstkanker. Voor het adenocarcinoom van de slokdarm zijn verschillende prognostische factoren van genen en moleculen vastgesteld, zoals HER2/neu, TGF-β, p53, COX2, E-cadherin, β-catenin, UPA, MMP-1, DNA aneuploïdie, en >50% promotor hypermethylatie. Gerichte therapie tegen deze 'pathways' kan het therapeutische arsenaal voor patiënten met dit soort kanker vergroten.
Onlangs is het mogelijk gebleken om betrouwbaar circulerende tumor cellen (CTCs) te detecteren, te tellen en te karakteriseren. Mogelijke toepassingen hiervan zijn: het vaststellen van de prognose, het dienen als een marker om behandeling geïnduceerde antitumor activiteit te meten, het detecteren van recidief ziekte, het ophelderen van prognostische en predictieve factoren en het onderzoeken van biologische processen (disseminatie, geneesmiddelen resistentie, en therapie geïnduceerde celdood). Waarschijnlijk zal de detectie, het tellen en de karakterisatie van CTCs op korte termijn een waardevolle aanvulling zijn binnen de medische oncologie in termen van onderzoek en patiëntenzorg.

Ontwikkeling van nieuwe therapeutische mogelijkheden

Slokdarmoperaties kennen een aanzienlijke peri-operatieve morbiditeit en mortaliteit, voornamelijk in ziekenhuizen waar weinig van dit soort operaties worden uitgevoerd. Het concentreren van slokdarmoperaties in zogenaamd hoog-volume ziekenhuizen kan een positief effect hebben of de morbiditeit en mortaliteit. Een andere belangrijke reden om de behandeling van patiënten met slokdarmkanker te centraliseren is de aanwezigheid van multidisciplinaire consultatieve teams in de meeste van deze hoog-volume ziekenhuizen.
Een conclusie aangaande neoadjuvante chemoradiotherapie van het review artikel in dit proefschrift was dat de rol van preoperatieve chemoradiatie nog steeds onduidelijk is. Recent is er een meta-analyse gepubliceerd die een significant 2-jaars overlevingsvoordeel liet zien voor preoperatieve chemoradiotherapie en, in mindere mate, voor preoperatieve chemotherapie in patiënten met slokdarmkanker. Aangezien deze meta-analyse gebaseerd is op voornamelijk inadequaat uitgevoerde en kleine fase 3 studies, is de waarde van de conclusies van zulke meta-analyses twijfelachtig. Het concept van

neoadjuvante chemoradiotherapie blijft echter aantrekkelijk. Om deze reden en vanwege de gunstige resultaten van onze fase 2 studie met neoadjuvant carboplatin en paclitaxel concurrent met radiotherapie gevolgd door een slokdarmresectie, doet ons centrum op dit moment mee aan een gerandomiseerde fase 3 studie met dit preoperatieve chemoradiotherapie schema gevolgd door operatie versus operatie alleen. Deze studie heeft tot op heden meer dan 300 patiënten geïncludeerd.
Er blijven nog veel vragen omtrent de optimale dosering voor bestraling, het bestralings- en chemotherapieschema. Met het gebruik van nieuwe chemotherapeutische middelen, zoals taxanen en irinotecan, wekelijks of continue toediening van chemotherapie tegelijk met radiotherapie, gehyperfractioneerde radiotherapie schema's, kunnen mogelijk betere behandelresultaten worden geboekt. 'Targeted therapy' met een cyclooxygenase -2 remmer, 'vascular endothelial growth factor' remmers, 'epidermal growth factor' receptor blokkers of remmers van de 'mammalian target of rapamycin' zijn aantrekkelijke benaderingen om met radiotherapie of chemotherapie alleen te combineren of met chemoradiotherapie.
Zoals gezegd, gaat een slokdarmresectie gepaard met een aanzienlijke peri-operatieve morbiditeit en mortaliteit. Naast de forse lichamelijk gevolgen heeft een slokdarmresectie ook grote psychologische en sociale effecten. Een alternatieve, orgaansparende behandeling bestaande uit het continueren van de chemoradiotherapie bij patiënten die responderen op preoperatieve chemoradiatie is een aantrekkelijke behandeloptie, omdat je op die manier een onnodige aanvullende operatie vermijdt. De behandelstrategie lijkt een geschikte behandeloptie te zijn met een overleving die vergelijkbaar is met de overleving na een operatie volgens twee studies, alhoewel in de groep die behandeld was met definitieve chemoradiotherapie meer locale recidieven optraden. Er zijn dan echter wel geschikte selectie criteria nodig om de patiënten die zullen responderen op de chemoradiotherapie te identificeren. Op die manier kun je het therapeutische voordeel zo groot mogelijk maken en de toxiciteit zo klein mogelijk. Om onnodige toxiciteit te voorkomen, zou het zelf beter zijn om de respons op chemoradiotherapie voor start van de behandeling te voorspellen. Verschillende moleculaire markers zijn getest op de mogelijkheid om respons op therapie te voorspellen. In een studie werd een verband gevonden tussen de respons van patiënten met een Barrett's adenocarcinoma op neoadjuvante chemotherapie met 5-fluorouracil and cisplatin en de expressie van methylenetetrahydrofolate reductase (MTHFR), caldesmon (actinomyosin regulatory protein), en multidrug resistance protein 1 (MRP1), met sensitiviteit van >90%. Meer onderzoek is nodig om diagnostische hulpmiddelen te ontwikkelen die de respons op preoperatieve chemoradiotherapie kunnen voorspellen door middel van het analyseren van de biopten die uit het tumorweefsel genomen zijn.

Het effect van een slokdarmresectie met of zonder preoperatieve behandeling op de kwaliteit van leven van patiënten met slokdarmkanker wordt vaak onderbelicht. Omdat gezondheid gerelateerde kwaliteit van leven beoordeling extra informatie geeft over de toxiciteit van een chemoradiotherapie schema, en om de mogelijke gevolgen van neoadjuvante chemoradiotherapie op een verminderd of vertraagd herstel van gezondheid gerelateerde kwaliteit van leven na een slokdarmresectie te beoordelen, wordt ook een kwaliteit van leven onderzoek uitgevoerd in de boven genoemde fase 3 studie. De resultaten van die studie kunnen gebruikt worden om patiënten te informeren over zij

kunnen verwachten van deze 'multimodality' behandeling en op die manier kunnen de resultaten bijdragen in het proces van het kiezen voor een behandeling door behandelaar en patiënt.
Voor de vele patiënten met gemetastaseerde of gerecidiveerde slokdarmkanker zijn geen curatieve behandelmogelijkheden voorhanden. Voor deze patiënten is palliatie van dysfagie en van andere symptomen zoals pijn en vermoeidheid zeer belangrijk. Juist in deze groep patiënten is het verbeteren of het behouden van kwaliteit van leven zeer belangrijk. Echter, op dit moment zijn de standaarden voor het analyseren van kwaliteit van leven en van symptoom controle in gerandomiseerde. Het definiëren van een palliatief eindpunt, met een a-priori hypothese, is essentieel; het is gewenst het aantal patiënten met palliatieve response te definiëren. Een 'checklist' kan behulpzaam zijn om de standaarden van toekomstige gerandomiseerde studies te vergroten.
Het plaatsen van een 'self-expanding' metalen stent, uitwendige radiotherapie, intraluminale radiotherapie (brachytherapie), en laser therapie zijn vaak gebruikte palliatieve mogelijkheden om dysfagie te behandelen. Er zijn maar weinig studies verricht die deze behandel mogelijkheden met elkaar vergelijken. Er zijn geen studies die het effect van chemotherapie vergelijken met het effect van andere palliatieve behandelingen op symptoomcontrole (bijvoorbeeld dysfagie). In een studie is het gebruik van 'single-dose' brachytherapie vergeleken met het plaatsen van een metalen stent ter palliatie van dysfagie in patiënten met slokdarmkanker. Ondanks langzame verbetering gaf 'single-dose' brachytherapie betere lange termijn verbetering van dysfagie dan plaatsing van een metalen stent. Aangezien brachytherapie gepaard ging met minder complicaties dan stent plaatsing en aangezien, nog belangrijker, het effect van 'single dose' brachytherapie op gezondheid gerelateerde kwaliteit van leven gunstiger is dan van stent plaatsing voor de palliatie van slokdarmkanker, wordt 'single-dose' brachytherapie aanbevoelen als eerste behandeling van dysfagie ten gevolge van slokdarmkanker.
De resultaten van de fase 2 studie die het effect van de behandeling met oxaliplatin en capecitabine van patiënten met gemetastaseerd of lokaal vergevorderd slokdarmkanker onderzocht in dit proefschrift, toonden aan dat palliatieve chemotherapie in staat is om de kwaliteit van leven gedurende de behandeling kan behouden en mogelijk zelfs symptomen kan verlichten (pijn). Het effect van chemotherapie op overleving is onduidelijk, voornamelijk ten gevolge van het gebrek aan gerandomiseerde studies. De conclusies van de Cochrane Review betreffende het gebruik van chemotherapie bij patiënten met gemetastaseerde slokdarmkanker of kanker van de slokdarm-maagovergang zijn dat er een grote behoefte is aan goed uitgevoerde fase 3 studies van voldoende grootte die chemotherapie vergelijken met goede palliatieve zorg bij patiënten met gemetastaseerde slokdarmkanker. Cytostatica met mogelijke goede respons percentages en acceptabele toxiciteit zijn cisplatin, 5-fluorouracil (5-FU), paclitaxel en antracyclines. Toekomstige studies die palliatieve behandel mogelijkheden vergelijken moeten ook kwaliteit van leven beoordelen met behulp van gevalideerde kwaliteit van leven vragenlijsten.

De toegenomen kennis van de moleculaire biologie van kanker en de ontwikkeling van nieuwe diagnostische mogelijkheden en 'targeted' middelen bieden nieuwe uitdagingen en kansen voor de behandeling van patiënten met slokdarmkanker en de ontwikkeling van meer therapie op maat met het beste resultaat voor onze patiënten.

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En nu is het echt af: Hakuna Matata!!!!!!!

Rotterdam, juni 2008

CURRICULUM VITAE

Esther van Meerten werd op 27 oktober 1971 geboren te Rotterdam. In 1990 behaalde zij haar VWO-gymnasiumdiploma aan de Rijksscholengemeenschap te Oud-Beijerland. Aansluitend ging zij geneeskunde studeren aan de Erasmus Universiteit te Rotterdam. In december 1997 behaalde zij haar artsexamen met lof. Zij werkte in 1998 als AGNIO interne geneeskunde in het voormalige Zuiderziekenhuis (tegenwoordig Medisch Centrum Rijnmond Zuid, locatie Zuider). In januari 1999 startte zij met de opleiding tot internist in datzelfde ziekenhuis (opleider dr. A. Berghout). Vanaf januari 2003 werd de opleiding voortgezet in het Erasmus MC (opleider prof.dr. H.A.P. Pols). In januari 2004 startte zij met de opleiding voor het aandachtsgebied interne oncologie (opleider prof. dr. G. Stoter) op de centrumlocatie van ditzelfde ziekenhuis. In de zomer van 2004 begon zij aan de onderzoeken die werden beschreven in dit proefschrift. Vanaf september 2006 is zij werkzaam als staflid van de afdeling interne oncologie op de locatie Daniel, sinds jaunari 2008 in vast dienstverband.

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