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Review

Systemic treatment for oesophageal cancer

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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 patients is poor. This Review will focus on the use of chemotherapy as part of multimodal treatment and for patients with metastatic disease. Randomised phase III trials have, for the most part, failed to demonstrate a survival advantage with the use of chemotherapy. It must be emphasised that many of these phase III trial were underpowered and do not meet today's standards. 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.

Keywords: Oesophageal carcinoma; Chemotherapy; Chemoradiotherapy; Combined modality treatment

1. Introduction

Oesophageal cancer is a highly lethal disease, as reflected by an overall survival rate of 10–20%. Worldwide, almost 400 000 new patients are diagnosed annually and 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], 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].

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

Chemotherapy together with radiotherapy and/or surgery is nowadays frequently integrated into treatment protocols for 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 evidence available from the literature will be 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.

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2. 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 in survival and possible tumour shrinkage allowing 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 pathological response rate of 4–7%, have been reported after cisplatin-based combination chemotherapy [8]. In these studies some authors have concluded that, compared with historical controls, patient outcome is improved after preoperative chemotherapy [9]. Patients who have an objective response to chemotherapy usually have a significant better survival compared with 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: inclusion of only a small number of patients, use of chemotherapy regimes that nowadays are 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 two largest studies conducted, no survival benefit was found in the Intergroup study [19], while in the Medical Research Council (MRC) study [21], a significant survival benefit was demonstrated for 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 also received two postoperative courses of chemotherapy. The overall rate of clinical response (19%) to preoperative chemotherapy was surprisingly low. Survival after two 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 of published and unpublished studies comparing chemotherapy followed by surgery versus surgery alone were analysed [22]. 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 five years. Preoperative chemotherapy led to increased toxicity and mortality. Urschel and colleagues [23] 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 treatment-related mortality. No survival benefit was demonstrated in their analysis. 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

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 [12]/1988	SCC	19	20	CP/Vind/BL	Median	9 m	9 m	NS
Nygaard [11]/1992	SCC	56	50	CP/BL	3-year	3%	9%	NS
Schlag [13]1992	SCC	22	24	CP/5FU	Median	10 m	10 m	NS
Maipang [14]/1994	SCC	24	22	CP/Vind/BL	Median	17 m	17 m	NS
Law [17]/1997	SCC	84	85	CP/5FU	Median	16.8 m	13 m	NS
Kok [18]/1997	SCC	84	85	CP/VP	3-year	41%	17%	Significant
Kelsen [19]/1998	SCC/AC	213	227	CP/5FU	Median	14.9 m	16.1 m	NS
Ancona [20]/2001	SCC	48	48	CP/5FU	Median	24 m	25 m	NS
MRC [21]/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; NS, non-significant.

considered to be appropriate in randomised phase III studies for patients with oesophageal cancer.

In only a few trials has the effect of postoperative chemotherapy been investigated. Ando and colleagues [16] 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 two courses cisplatin and vindesine and 100 patients received no adjuvant chemotherapy. The 5-years survival rates were 48.1% and 44.9%, respectively. 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 [24]. Earlier Pouliquen and colleagues [15] 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 for duration of 6–8 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.

3. 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 [25]. This concept has been tested in numerous phase II studies and cisplatin and 5-fluorouracil combined with radiotherapy is the most frequently used regime [26–29]. The limited sample size of most of these studies, the differences in patient selection criteria, the variations in chemoradiotherapy schemes, and the intermingling of both patient with resectable and unresectable tumours makes it difficult to compare these phase II studies with one another. The general conclusion that can be derived from these studies is that preoperative chemoradiotherapy is feasible and that those patients who achieve a complete pathological 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 [30].

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 was a significant survival benefit found [34]. 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 [36] included six randomised studies in their meta-analysis including 764 patients. They 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

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

Author [Ref]/Year	Histology	No. of patients		CT	RT (total dose)	Median survival in months (3-year)		Significance
		CRT	Control			CRT	Control	
Nygaard [11]/1992	SCC	53	50	CP/ BL	35 Gy	8.2 (17%)	7.6 (9%)	NS
Apinop [31]/1994	SCC	35	34	CP/5FU	40 Gy	9.7 (26%)	7.4 (20%)	NS
Le Prise [32]/1994	SCC	41	45	CP/ 5FU	20 Gy	10 (19.2%)	11 (13.2%)	NS
Bosset [33]/1997	SCC	143	139	CP	2×18.5 Gy	18.6 (39%)	18.6 (37%)	NS
Walsh [34]/1996	AC	58	55	CP/5FU	40 Gy	16 (32%)	11 (6%)	$P = 0.01$
Urba [35]/2001	SCC/AC	50	50	CP/5FU/VBL	45 Gy	16.9 (30%)	17.6 (16%)	NS

Ref, reference; CRT, chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; SCC, squamous cell carcinoma; AC, adenocarcinoma; CP, cisplatin; 5FU, 5-fluorouracil; BL, bleomycin; VBL, vinblastine; NS, non-significant.

significant effect on survival was lost when the Walsh study was excluded from the analysis. Kaklamanos and colleagues [37] 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. Treatment mortality increased by 3.4% with chemoradiotherapy (95% CI, −.1% −7.3%) compared with surgery alone. Urschel and colleagues [38] analysed nine randomised trials comparing neoadjuvant chemoradiotherapy and surgery with surgery alone for resectable oesophageal cancer. 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 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 no 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 [39]. A total of 259 patients were randomised and no significant difference in 2-year survival was observed between these two groups. A more or less similar design was followed in a German multicentre study. In this study, 177 patients with squamous cell carcinoma of the oesophagus were treated with three 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 [40]. There was no statistical difference in median survival and 3-year survival between the 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 upon [41–43]. 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 [44].

In a number of phase I and II studies, newer chemotherapeutic agents, such as paclitaxel, docetaxel, irinotecan or biologicals, have been combined with cisplatin or carboplatin and concurrent radiotherapy [45–48]. 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. Organ preservation might be possible in a number of patients, thereby avoiding unnecessary additional surgery, although the appropriate selection criteria to identify such a subgroup of patients are still lacking.

4. Definitive chemoradiotherapy

Patients with potentially resectable oesophageal cancer, but who are 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 in up to 60–80% [49] 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 most 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 two courses of 5-fluorouracil and cisplatin followed by two additional courses was compared with radiotherapy alone [63]. 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) [64]. 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 two arms. A randomised trial involving a total of 221 patients consisting of split-course radiotherapy with or without two courses cisplatin given 3 or 4 days before the start of radiotherapy and four courses afterwards was performed by the European Organisation for Research and Treatment of Cancer (EORTC) [65].

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 [50]/1989	SCC	84	86	MTX	40.5 Gy + 15.75 Gy boost	31	35	NS
Zhou [51]/1991		32	32	CP/5FU	65–75 Gy	77	33	Significant
Hishikawa [52]/1991	SCC	24	25	Futrafur	50–70 Gy ± brachytherapy			NS
Hatlevoll [53]/1992	SCC	46	51	CP/BL	2 × 18.5 Gy	18	29	NS
Lu [54]/1995		30	30	A/CP/5FU	RT 60–70 Gy CRT 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; NS, non-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 [55]/1980	SCC	47	44	BL	50–60 Gy	22	32	NS
Zhang [56]/1984	SCC/AC	48	51	BL	39–73 Gy (mean 63.5Gy)			NS
Andersen [57]/1984	SCC	40	42	BL	55–60 Gy			
Araujo [58]/1991	SCC	28	31	5FU/MMC/BL	50 Gy/25 fr	64	55	NS
Roussel [59]/1994	SCC	110	111	CP	40 Gy	47	31	Significant
Kaneta [60]/1997	SCC	12	12	CP	70–72 Gy	40	24	NS
Slabber [61]/1998	SCC	34	36	CP/5FU	40 Gy	28	20	NS
Cooper [62]/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; fr, fractions; NS, non significant.

No significant difference in overall survival was found, 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 [66]. 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 with 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 [45–48]. 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 [67,68]. 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 [69]. 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 who are poor candidates for surgery can be treated with concurrent chemoradiotherapy. Concurrent chemoradiotherapy leads to a modest gain in overall survival compared with radiotherapy alone at the cost of increased treatment-related toxicity. The radiosensitising effect of biologicals needs to be explored further.

5. 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 [70,71], most patients are palliated by self-expanding metal stent placement or external beam radiation or brachytherapy [72].

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% [73]. In recent years, agents, such as taxanes and irinotecan, have been tested as single agents or in combination with cisplatin, with encouraging response rates [74,75].

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 [76] analysed prognostic factors in patients with advanced oesophageal cancer treated with cisplatin-based combination chemotherapy. 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 [77]. 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 [78–85]. In the study of Nicolaou and colleagues [78] 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 [79] randomised 156 patients to chemotherapy with 5-fluorouracil and cisplatin versus no treatment. No difference in survival was found between the 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 tumour or had irresectable disease. In a randomised phase II study reported by Bleiberg and colleagues [80], patients with squamous cell carcinoma of the oesophagus were randomised to treatment with 5-fluorouracil and cisplatin or cisplatin alone. 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 and colleagues [81], 63 patients were treated with either doxorubicin, methotrexate or 5-fluorouracil. 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) [82,83]. 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 [84], 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. Equivalent efficacy was found, but quality of life was superior with ECF. Tebbut and colleagues [85] 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). 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 [82,84]. 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.

6. 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 [86] estimated that of the 6.4 million people that developed oesophageal cancer during 1973 and 1995, only data from 4388 patients were included in systematic reviews.

What we have learnt so for 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 [76,77]. 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 the benefit outweighs the increased treatment-related toxicity [22,36]. 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 [82,84].

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. However, the key issue is that we need more well designed, adequately powered, randomised trials.

Conflict of interest statement

None declared.

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