Review Article

Neoadjuvant treatment in esophageal cancer—established treatments and new developments reviewed

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Abstract: As the majority of patients experiences locoregional relapse and/or distant metastasis even after radical resection of esophageal cancer, many efforts have been made and are ongoing to identify the optimal multimodality treatment strategy. The true benefit and harm of neoadjuvant therapy including chemotherapy, radiotherapy or the combination, is still difficult to interpret given the heterogeneity in patient and tumor characteristics. Nonetheless, neoadjuvant chemoradiation with weekly carboplatin and paclitaxel (the CROSS regimen) is considered standard of care for squamous cell carcinoma in Europe. Definitive chemoradiation is considered an equal alternative in the United States. For adenocarcinoma, preoperative chemoradiation with a platinum and 5FU or the CROSS regimen and peri-operative chemotherapy with a platinum and 5FU or the FLOT (fluorouracil, leukovorin, oxaliplatin and docetaxel) regimen are all options. New developments in systemic anti-tumor therapy will most likely involve dual anti-HER2 inhibition or novel anti-HER2 antibody-drug conjugates for adenocarcinoma. Immunotherapy monotherapy in an unselected patient population does not seem to be as effective in esophageal cancer as it is in other cancer types. However, when we can correctly identify the subset of patients which does benefit from this treatment by employing new predictive markers, or find an effective synergistic combination of immunotherapy with chemotherapy and/or radiotherapy, immunotherapy could still improve patient outcome in the future.

Keywords: Chemotherapy; chemoradiotherapy; esophageal cancer; neoadjuvant; radiotherapy

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Introduction

Radical surgery is thus far seen as the most effective treatment to cure oesophageal cancer. However, several studies are ongoing that try to select patients who may not need resection after neoadjuvant treatment (1-4). Historically, 5-year survival rates after oesophagectomy did not exceed 20–40% (5,6). However, these number should be interpreted with caution as perioperative mortality has decreased and staging and patient selection has improved. Nonetheless, there is a need to improve locoregional control and prevent the development of distant metastases after surgery alone. Hence, multimodality treatment regimens were developed to improve outcome. These multimodality regimes mainly consist of radical surgery in combination with pre-operative and/or postoperative chemotherapy and/or radiotherapy.

There are several mechanisms by which these (neo) adjuvant therapies may improve survival. Down-staging of the tumor by neoadjuvant therapy could result in a higher likelihood of achieving a tumor-free resection margin. Micrometastases could be eliminated pre- or postoperatively by applying systemic chemotherapy. Finally, improvement of tumor-related symptoms and signs such as dysphagia and cachexia may lead to a better condition of the patient prior to major surgery. On the other end, serious adverse events

due to preoperative treatment could interfere with planned surgery or postoperative treatment could lead to treatment-related morbidity and even mortality in a period when the patient is vulnerable.

Data on the benefit and harm of neoadjuvant therapy including chemotherapy, radiotherapy or the combination thereof, are still conflicting. The different treatment regimes, tumor location (proximal, mid or distal esophagus or junction) and histology (squamous versus adenocarcinoma) hamper comparisons across studies (7). Several meta-analyses of randomized controlled trials have been published, but even these are hard to interpret given the heterogeneity of included studies. This lack of clear scientific evidence results in the application of different therapies across the world and sometimes even within countries.

In this review, we discuss the pivotal trials and meta-analyses on neoadjuvant radiotherapy, chemotherapy and chemoradiation for esophageal cancer. We also address recent developments in this field, including the addition of targeted therapies, immune therapy and the option to entirely omit surgical resection. Lastly, we will highlight some ongoing debates in the field.

Neoadjuvant radiotherapy

The added value of neoadjuvant radiotherapy for resectable esophageal cancer was analyzed in a 2005 Cochrane review (8) of five randomized studies including mainly patients with squamous cell carcinoma (86% of the study population) (9-13). Of note, some of these trials date back to the 80's, and a variety of radiation regimens were given (varying from 20 to 40 Gy given in 10 to 20 fractions over a period of 1 to 4 weeks). This limits the translation of these data into today's practice. A moderate benefit from preoperative radiotherapy was reported (HR 0.89), which was not statistically significant and neoadjuvant radiotherapy without administering chemotherapy is not considered standard-of-care (14,15).

Neoadjuvant chemotherapy

In 2015, a a meta-analysis of 10 trials studying the value of preoperative chemotherapy in resectable thoracic esophageal cancer was published (16). The MAGIC-study was not included in this meta-analysis because the authors were unable to identify the outcomes for patients with esophageal cancer form this trial that largely included patients with gastric cancer (74%). For the primary outcome of survival, there was a significant benefit for the neoadjuvant chemotherapy group (HR 0.88, 95% CI, 0.80–0.96) compared to the surgery alone group. Of note, this study did not discriminate between adeno- and squamous cell carcinoma. Studies including squamous cell cancer seemed to drive the observed survival advantage with preoperative chemotherapy. Also, some low-quality studies weighted heavily on the observed effect on survival.

We will discuss the largest trials included in this review individually, with an arbitrary cut-off at 200 included patients (*Table 1*).

In the US, a large randomized study including 467 patients was performed to show the possible benefit of preoperative chemotherapy consisting of three pre-operative and, in the absence of disease progression to preoperative chemotherapy, two postoperative cycles of cisplatin and fluorouracil (17). No difference was seen in overall survival even at long term follow-up (6). A similar regimen of only two preoperative cycles of cisplatin and fluorouracil before surgery was tested against surgery alone in the OEO2 MRC trial (18) including 802 patients. A small but statistically significant survival benefit was seen in the chemotherapy group (HR 0.84), corresponding with an increase in 5-year survival from 17.1% to 23.0%. Noteworthy, survival in the surgery arm was poor in this study compared to other studies (5,6). There was no difference in effect size between adeno- and squamous cell carcinoma.

The different outcomes of these two large trials using similar pre-operative chemotherapy regimens are puzzling. The US study used a higher dose of cisplatin (100 *vs.* 80 mg/m^2) and more cycles (three pre-operative instead of two cycles, and when feasible postoperative cycles). Perhaps this more intense chemotherapy regimen affected patient's condition too much to be combined with optimal and timely surgery. This is reflected by the lower percentage of patients proceeding to a surgical resection in the chemotherapy arm (80%) than the surgery arm (96%). Patients in the OEO2 trial had worse outcomes than patients in the US trial regardless of the study arm. A median survival of 13 months in the surgery and 16.8 in the chemotherapy arm were reported for the OEO-2 study. Patients in the surgery arm of the US trial did remarkably well, at a median overall survival of 16.1 months. It should be noted that an unknown number of patients with positive resection margins did get postoperative radiotherapy. Perhaps this could have made up for ineffective preoperative chemotherapy and as such narrowed a difference in efficacy between the chemotherapy

Table 1 Neoadjuvant chemotherapy for esophageal cancer

Trial	Trial name	Year	Pre-operative chemotherapy regimen	Post-operative chemotherapy regimen	AC, SCC or both	# of patients	Primary endpoint	mOS (months)	5-year survival rate (%)	HR
Kelsen *et al.*	RTOG 8911	1998	3× cisplatin/ fluorouracil	2× cisplatin/ fluorouracil	Both	467	OS	15 *vs.* 16	NR	1.07
Allum *et al.*	OEO2	2009	2× cisplatin/ fluorouracil	None	Both	802	OS	NR	23 *vs.* 17*	0.84*
Cunningham *et al.*	MAGIC	2006	3× cisplatin/ flourouracil/ epirubicin	3× cisplatin/ flourouracil/ epirubicin	AC	503	OS	NR	36 *vs.* 23*	0.75*
Schuhmacher *et al.*	EORTC 40954	2010	2× cisplatin/ fluorouracil	None	AC	144	OS	64 *vs.* 52	NR	0.84
Ychou *et al.*	ACCORD 07	2011	3-4× cisplatin/ fluorouracil	3-4× cisplatin/ flourouracil	AC	224	OS	NR	38 *vs.* 24*	0.69*
Al-Batran *et al.*	FLOT4	2019	4× flourouracil/ leukocorin/ oxaliplatin/ docetaxel	4× flourouracil/ leukocorin/ oxaliplatin/ docetaxel	AC	716	OS	50 *vs.* 35*	45 *vs.* 36*	0.77*
Boonstra *et al.*		2011	4× cisplatin/ etoposide	None	SCC	169	OS	16 *vs.* 12*	26 *vs.* 17*	0.71*

Randomized phase 3 trials reporting on 200 or more patients are depicted. *, outcomes that reached prespecified statistical significance. NR, not reported; HR, hazard ratio; AC, adenocarcinoma; SCC, squamous cell carcinoma; mOS, median overall survival.

and the surgery arm.

Below, we will also discuss studies according to histological type to reveal possible differences in effect of chemotherapy between adenocarcinoma and squamous cell carcinoma.

Adenocarcinoma

For gastric cancer, the MAGIC study has long dictated the standard-of–care for gastric cancer (19). In this British study published in 2006, 503 patients with resectable cancer of the stomach, gastro-esophageal junction or distal esophagus were randomized to surgery alone or surgery plus three preoperative and three postoperative cycles of epirubicin, cisplatin and fluorouracil. At 5 years, survival in the chemotherapy-arm was improved by 13% (23% *vs.* 36%, HR 0.75). Approximately one quarter of the patients in this study had cancer of the lower esophagus or GOJ and the effect of chemotherapy was similar regardless of tumor site (P for interaction = 0.25). Of note, less than half of patients could complete the full postoperative chemotherapy regimen.

Afterwards, it was shown that replacement of iv fluorouracil with oral capecitabine was non-inferior in the metastatic setting. Hence, capecitabine was commonly administered in the resectable setting as well (20). In 2019, the MAGIC regimen was replaced by the so-called FLOT schedule (consisting of four preoperative and four postoperative cycles of fluorouracil, leucovorin, oxaliplatin and docetaxel) based on the FLOT4 trial. This randomized study showed an increased median overall survival in the FLOT group as compared to the MAGIC group (50 *vs.* 35 months) (21). In the FLOT4 trial, patients with cancer of the stomach and gastroesophageal junction were included, including Siewert types I–III. However, cancers of the distal esophagus without involvement of the junction were not included.

The European Organisation for Research and Treatment of Cancer (EORTC) undertook a trial looking to compare neoadjuvant chemotherapy with cisplatin and fluorouracil with surgery alone in patients with adenocarcinoma of the stomach and GOJ. The trial was stopped for poor accrual after 144 patients were randomized. Radical resection rate was higher in the chemotherapy arm, but this did not

translate into an increased survival (HR 0.84) (22).

A French trial published in 2011 looked at the value of peri-operative chemotherapy for adenocarcinoma of the distal esophagus, gastroesophageal junction and stomach (23). Among 224 patients, three pre-operative and three postoperative cycles of cisplatin and fluorouracil chemotherapy offered an overall survival benefit compared to surgery alone (5-year overall survival 38 *vs.* 24%). There was also a higher rate of radical resections (R0) for patients that received perioperative chemotherapy (84 *vs.* 73%). This study was however hampered by the fact that in 2011 the standard-of-care in most European countries was already based on the MAGIC study. Hence, cisplatin/fluorouracil peri-operative chemotherapy was not widely adopted in clinical practice, but has remained part of standard of care in the United Kingdom based on the results of the OEO2 trial.

Squamous cell carcinoma

A Dutch trial looked at the value of preoperative cisplatin and etoposide added to surgery in 169 patients with squamous cell carcinoma of the thoracic esophagus (24). Notably, 33% of theoretically eligible patients were not included into the study for unknown reasons, raising the possibility of inclusion bias. Thirty of the 85 patients in the chemotherapy group indeed received four cycles of chemotherapy because of a clinical response to the preoperative chemotherapy. Pre-operative chemotherapy improved survival outcomes, with a 2-year survival of 42 *vs.* 30%, respectively and a better median survival (16 *vs.* 12 months, HR 0.71). No detailed information on chemotherapy toxicity was available.

Neoadjuvant chemoradiation

The possible benefit of neoadjuvant radiation combined with chemotherapy has been assessed in several meta-analyses. Some of these studies were hampered by a lack of qualitative interpretation of the individual studies and/or flaws in the analysis (7). The meta-analysis published in 2009 by Jin *et al.* was of high quality, but was still limited by the quality of the data of the original trials (25). We discuss this and another meta-analysis that had a different conclusion.

Jin *et al.* included eleven randomized studies published between 1992 and 2008. Most (seven) studies included only SCC, one study only AC and three studies included both histologic subtypes. Both sequential and concurrent chemoradiation was applied. All studies used cisplatin as part of the chemotherapy backbone, often combined with fluorouracil, but in varying dosages and schedules. The radiotherapy dosage and fractination also varied widely, from 2- to 5-week schedules and from 20 to 50.4 Gy. The study group included 1308 patients (range, 56–282). Overall, there was a statistically significant benefit in 1-, 3- and 5-year survival in the neoadjuvant chemoradiation group (HR 1.28, 1.78 and 1.46, respectively). In a subgroup analyses, no benefit was seen from sequential chemoradiation while concurrent chemoradiation did show a beneficial effect on overall survival. When only patients with SCC were analyzed, no statistically significant effect on survival was seen. The beneficial effect on survival was probably driven by two relatively small studies from the US, which does raise questions on the external validity of the data. Less patients treated with neoadjuvant chemoradiotherapy underwent oesophagectomy and postoperative mortality was higher in the CRT group (even up to 23.5% in the earliest study published in the eighties). However, patients treated with neoadjuvant CRT were more likely to have a radical resection.

Gebski *et al.* performed a meta-analysis of ten randomized trials on neoadjuvant chemoradiotherapy and eight on neoadjuvant chemotherapy versus surgery alone (26). In this meta-analysis, all-cause mortality was lower in the neoadjuvant chemoradiation group (13% absolute difference in survival at 2 years). While the effect seemed stronger for adenocarcinoma, it was also statistically significant for squamous cell carcinoma.

These conflicting results of the two meta-analyses show the difficulty in drawing conclusions on the overall value of neoadjuvant chemoradiation in the older studies included in the analyses.

We will discuss the biggest trials (100 or more patients) included in the aforementioned meta-analyses as well as the phase 3 randomized controlled trials that have been published after 2009 (*Table 2*).

In Australia, the effect of preoperative chemoradiation with radiotherapy (35 Gy) and one cycle of cisplatin and fluorouracil was investigated in 256 patients with resectable esophageal cancer, irrespective of histological subtype (27). While the patients that underwent surgery only did have a higher rate of irradical resection and more positive lymph nodes, no difference was seen in overall survival. There was a benefit of preoperative chemoradiation in the patients with SCC, but this was a subgroup analysis for which the

Table 2 Neoadjuvant chemoradiotherapy for esophageal cancer

Trial	Trial name	Year	Chemotherapy regimen	Radiotherapy regimen	AC, SCC or both	# of patients	Primary endpoint	mOS (months)	5-year survival rate (%)	HR
Urba *et al.*		2001	1x cisplatin/ flourouracil/ vinblastin	30×1.5 Gy	Both	100	OS	18 *vs.* 17	NR	NR
Burmeister *et al.*		2005	1x cisplatin/ fluorouracil	15×3.0 Gy	Both	256	OS	22 *vs.* 19	NR	0.89
van Hagen *et al.*	CROSS	2012	5x carboplatin/ paclitaxel	23×1.8 Gy	Both	366	OS	49 *vs.* 24*	47 *vs.* 33	0.66*
Mariette *et al.*	FFCD 9901	2014	2× cisplatin/ fluorouracil	25×1.8 Gy	Both	195	OS	NR	NR	1.09
Walsh *et al.*		1996	2× cisplatin/ fluorouracil	15×2.6 Gy	AC	113	OS	16 *vs.* 11*	NR	NR
Nygaard *et al.*		1992	2× bleomycin/ cisplatin	20×1.75 Gy	SCC	186	NR	NR**	NR	NR
Bosset *et al.*		1997	2× cisplatin	10×3.7 Gy	SCC	282	OS	19 *vs.* 19	NR	1.0
Lee *et al.*		2004	2× cisplatin/ fluorouracil	38×1.2 Gy	SCC	101	OS	28 *vs.* 27	NR	0.88
Cao *et al.*		2009	2× cisplatin/ flourouracil/ mitomycin	20×2.0 Gy	SCC	473	NR	NR&	NR	NR
Yang *et al.*	NEOCRTEC-5010	2018	2× cisplatin/ vinorelbin	20×2.0 Gy	SCC	451	OS	100 *vs.* 42*	NR	0.71*

Randomized phase 3 trials reporting on 100 or more patients are depicted. All studies concerned concurrent pre-operative chemoradiation. *, outcomes that reached prespecified statistical significance. **: 2×2 factorial design, radiotherapy alone or chemoradiation *vs.* surgery alone statistically significant longer OS; chemoradition *vs.* surgery alone not significant; &, 3-year survival rate was statistically superior at 74% *vs.* 53%. NR, not reported; HR, hazard ratio; AC, adenocarcinoma; SCC, squamous cell carcinoma; mOS, median overall survival.

study was not primarily powered.

A North-American study randomized 100 patients to surgery plus or minus intensive preoperative chemoradiation consisting of 45 Gy radiation combined with one cycle of fluorouracil (administered on each day of the three-week cycle), cisplatin (administered on ten days of the three-week cycle) and vinblastine (administered on ten days of the three-week cycle) (28). No significant difference was seen in median overall survival between the treatment arms. Three-year survival was numerically improved in the chemoradiation arm (30% *vs.* 16%), but the study was underpowered.

Since the publication of the meta-analysis by Jin *et al.* in 2009 (25), three additional trials have been published on all-type histology esophageal cancer. In early-stage esophageal cancer (stage I or II), preoperative chemoradiation consisting of 45 Gy irradiation and two cycles of cisplatin and fluorouracil did not result in increased 3-year overall survival compared to surgery alone (29). A higher postoperative mortality rate was seen in the chemoradiation group (11.1% *vs.* 3.4%).

In 2012, the Dutch CROSS trial was published. In this study, 366 patients with cancer of the esophagus or gastro-esophageal junction, staged as cT1N1M0 or cT23N01M0, were randomized to surgery alone or surgery plus chemoradiation with weekly carboplatin (AUC2) and paclitaxel (50 mg/m^2) for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions). The R0 resection rate was higher in the chemoradiation group (92% *vs.* 69%), and median OS was 49.4 *vs.* 24.0 months (HR 0.657). Pathological complete response was achieved in 23% of adenocarcinoma patients and 49% of squamous

cell carcinoma patients. The treatment was well-tolerated with 7% grade 3–4 toxicity (30). After longer follow-up, the survival benefit remained and was even bigger in squamous cell carcinoma (HR. 0.48) compared to adenocarcinoma (HR 0.73). After this publication, the CROSS regimen was adopted as the standard-of-care in large parts of the world.

Adenocarcinoma

In 2013, an effort was undertaken to perform a meta-analysis comparing perioperative chemotherapy plus resection with surgery alone based on individual patient data of patients with adenocarcinoma of the esophagus, junction and stomach (31). Based on eight randomized trials, an absolute survival benefit of 9% at 5 years was seen for perioperative chemotherapy. The treatment effect seemed more pronounced in tumors of the gastro-esophageal junction. In tumors of the junction and esophagus, combined chemoradiotherapy was more beneficial than chemotherapy alone.

In 1996, a relatively small study was published on 113 patients with adenocarcinoma of the esophagus or junction who underwent pre-operative chemoradiation with two cycles of cisplatin/fluorouracil and surgery or surgery alone (32). Median survival was superior in the chemoradiation arm, at 16 *vs.* 11 months in the surgery arm. Three-year survival was also increased significantly (32% *vs.* 6%), while 1- and 2-year survival were not.

Squamous carcinoma

Three large trials investigated neoadjuvant treatment in squamous cell carcinoma and were included in the 2009 meta-analysis (25).

In a Norwegian study published in 1992, 186 patients with resectable squamous cell esophageal cancer were randomized to four treatment groups; surgery alone, pre-operative chemotherapy with cisplatin and bleomycin plus surgery, pre-operative radiation (35 Gy) plus surgery or pre-operative chemotherapy (bleomycin and cisplatin), radiation (35 Gy) plus surgery. A pooled analysis of the radiotherapy groups versus those without showed a higher three-year survival rate in the groups receiving radiotherapy. On the other hand, comparison of the groups receiving pre-operative chemotherapy *vs.* those without did not show a beneficial effect on survival. The study was not powered to compare the individual treatment arms (13). These results are in line with the hypothesis that especially squamous carcinoma is sensitive to radiation , which was also seen in the Australian study (27). From the CROSS data, we know that 49% of patients with squamous cell carcinoma have a pathological complete response (pCR) after neoadjuvant chemoradiation, as opposed to 23% of the adenocarcinoma patients (30).

In 1997, a French trial (33) randomized 282 patients with stage I or II squamous cell cancer of the esophagus to neoadjuvant chemoradiotherapy (two one-week courses of radiotherapy and cisplatin) plus surgery or surgery alone. The addition of chemoradiotherapy did not improve overall survival, despite more curative resections. Postoperative mortality was higher in the chemoradiotherapy group (12% *vs.* 3.6%) mainly due to respiratory insufficiency and mediastinal infection or sepsis.

In 2004, a Korean study was performed which looked at the benefit of preoperative chemoradiation with a higher radiation dose of 45.6 Gy combined with two cycles of cisplatin and fluorouracil followed by surgery versus surgery alone in 101 patients (34). A relatively high number of patients in the preoperative chemoradiation arm did not undergo esophagectomy, mostly due to patients' refusal to undergo surgery. *Post aut propter*, no significant difference in overall survival was seen between the two groups.

A study looking at an alternative chemoradiation schedule was published in 2018 and thus not included in the meta-analysis (35). A total of 451 patients with cT1-4N1M0 or cT4N0M0 squamous cell carcinoma of the esophagus were randomized to neoadjuvant chemoradiation (consisting of two cycles of vinorelbine and cisplatin plus 40Gy concurrent irradiation) followed by surgery or surgery alone. The primary endpoint of overall survival was improved in the chemoradiation group (median 100 *vs.* 42 months). However, concern was raised over the overlapping 95% confidence intervals and apparent lack of constant ratio of the hazards between the chemoradiation and the surgery alone group over time. Thus, the benefit of chemoradiation may be smaller (36). Of note, in this study, peri-treatment mortality was somewhat increased in the chemoradiation group (2.2% *vs.* 0.4%), but not as marked as in previous studies.

A Chinese study randomized 473 patients to four different treatment arms: preoperative radiotherapy, preoperative chemotherapy (consisting of mitomycin, cisplatin and fluorouracil), preoperative chemoradiotherapy (using the same cytotoxic agents) or surgery alone (37). Given the design and number of included patients, the power to detect smaller differences in survival was suboptimal, and

no formal power calculation or definition of the primary endpoint were presented in the manuscript. One-year survival did not differ between the groups, while three-year survival was better in the chemoradiotherapy (74%) and radiotherapy group (69%) than in the chemotherapy (57%) or surgery alone group (53%). The suboptimal quality of the study design and report complicates the interpretation and implementation of these data.

Guidelines

The European Society for Medical Oncology (ESMO) issued a clinical practice guideline in 2016 (14). This guideline recommends different strategies for locally advanced adeno and squamous cell carcinoma (cT3–4 or cN1–3 M0). In squamous cell cancer, there is level I evidence and a grade A recommendation to prefer neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy, as the former results in higher rates of radical resection and better local tumor control and survival. The CROSS regimen is recommended as standard of care. In adenocarcinoma, both preoperative chemoradiation with a platinum and 5FU or carboplatin/paclitaxel and perioperative chemotherapy (8–9 weeks of the combination of a platinum and a fluoropyrimidine pre- and postoperatively) are considered standard-of-care (I, A). The NCCN guideline offers slightly different advice (15) in adenocarcinoma; preoperative chemoradiation is preferred but both preoperative and peri-operative chemotherapy as considered alternatives.

Very recently, the ASCO published a guideline on the treatment of locally advanced esophageal cancer, which recommends neoadjuvant chemoradiation or chemotherapy (FLOT) for adenocarcinoma patients, with the caution to be aware of possibly more severe postoperative complications with chemoradiation compared with chemotherapy (38). No specific chemotherapy backbone is recommended in case of chemoradiation. For squamous cell carcinoma, neoadjuvant chemoradiation or definitive chemoradiation is recommended.

New developments: targeted therapy

As our knowledge on the molecular drivers of various cancers increases, new drugs that target specific driver genes, commonly termed targeted therapy, have been developed. The theoretical advantage of targeted therapy is a lower toxicity profile together with a different mechanism of action thereby possibly overcoming chemotherapy resistance.

EGFR-targeted treatment

In 2018, a European study was published that looked at the benefit of cetuximab, an EGFR-inhibitor (39). The control arm in this study consisted of neoadjuvant chemotherapy (two cycles of docetaxel and cisplatin), neoadjuvant chemoradiation (45 Gy plus 5 weekly cycles of docetaxel and cisplatin) and surgery. Cetuximab was administered weekly in the neoadjuvant setting and for 3 months fortnightly postoperatively. Progression-free survival was not statistically significant different between the study arms (2.9 *vs.* 2.0 years). The interpretation of this study results is hampered by the fact that the control arm is not a treatment scheme commonly used in daily clinical practice.

The addition of another anti-EGFR antibody, panitumumab, to peri-operative ECC (epirubicin, cisplatin and capecitabine) was tested in 160 patients with gastric or esophagogastric junction cancer in a German randomized phase II study. The primary endpoint was the histological non-response rate after neoadjuvant chemotherapy, defined as the rate of ypT3–4 resection specimens. This rate was not decreased by the addition of panitumumab, nor were there significant differences in PFS or OS (3-year OS 49% with panitumumab *vs.* 62% without) (40). In the Dutch phase II PACT study, panitumumab was added to neoadjuvant chemoradiation (CROSS regimen) in resectable esophageal cancer patients. The primary endpoint, aiming at a pCR of 40% or more, was not met (pCR was 22%) in the intention to treat population (41). A randomized phase III trial on the addition of panitumumab to EOC (epirubicin, oxaliplatin, capecitabine) was terminated prematurely and did not show an increased OS at the cost of more toxicity (42). The addition of cetuximab was also tested in two phase III trials in combination with definitive chemoradiation, which both failed to show a positive effect. In the SCOPE1 trial, survival was even worse in the cetuximab-treated patients likely due to excess toxicity resulting in less intense treatments (43,44). EGFR-inhibitors therefore do not seem the way to move forward in this field.

HER2-targeting treatment

HER2, also known as EGFR2, has been studied as a target for treatment in esophageal and gastric adenocarcinoma in the primary and the metastatic setting. In breast cancer, the anti-HER2 monoclonal antibody trastuzumab as well

as other HER2-targeting agents such as pertuzumab, lapatinib and antibody-drug conjugates such as T-DM1, have been very successful. The effect of HER2-inhibition is unfortunately not as strong in esophageal cancer. Approximately 15–34% of esophageal or esophagogastric junction adenocarcinomas are HER2-positive (45-48), with a higher incidence in junction carcinomas. HER2-positivity is not a strong prognostic factor (48), unlike in breast cancer. In a small study of 66 esophageal squamous cell carcinomas, 11% was HER2-positive and this was associated with poorer survival (49).

The addition of trastuzumab to neoadjuvant therapy has been explored in several studies.

A phase III randomized study (NCT01196390) looked at the addition of trastuzumab to neoadjuvant chemoradiation according to CROSS in HER2-positive adenocarcinoma of the esophagus or junction. The study completed accrual at the end of 2019. The first presentation of the data after median follow-up of five years showed no survival benefit when trastuzumab was added to neoadjuvant chemoradiation (50).

A combination of anti-HER2 drugs has been studied in the Dutch TRAP study (51). Some 40 patients were treated with neoadjuvant chemoradiation according to CROSS plus trastuzumab and pertuzumab. The combination was well-tolerated, and showed promising PFS and OS data. Exploratory biomarker analyses suggested that high HER2 expression and Grb7-overexpression (a growth-factor binding protein) could be used to identify patients that may benefit from double anti-HER treatment (51). These results should of course be confirmed in a randomized phase III study. In the German PETRARCA randomized phase II study, trastuzumab and pertuzumab were combined with peri-operative FLOT for HER2-positive resectable esophagogastric adenocarcinoma. Unfortunately, this trial closed prematurely after the results from the JACOB trial (52), which looked at the same regimen but in the metastatic setting. This study was negative. Despite the limited sample size, pathological complete response rate (the primary endpoint) was significantly higher in the trastuzumab/pertuzumab arm (35% *vs.* 12%) as well as the rate of nodal negative resection specimens (68 *vs.* 39%). This impressive increase did come at the cost of increased toxicity, mainly diarrhea and leucopenia (53).

New development; immunotherapy

Tumor cells can escape the immune system by modulating T cell receptors activity resulting in an immune system tolerant to the tumor cells (54). The aim of immunotherapy in cancer treatment is to reverse this inhibition on T cells, resulting in an immune response to tumor cells and thereby apoptosis.

In the metastatic setting, various immunotherapy agents have been studied in first line and beyond and in differing combinations. Thus far, results have been disappointing (55-57), especially when compared to the successes achieved in treatment of melanoma and lung cancer. Efforts are ongoing with these and novel immunotherapy agents, in the primary and metastatic setting. Results could also be improved with better patient selection, perhaps moving beyond the currently used markers such as microsatellite instability (MSI) and PD-L1 expression.

Ongoing debates: adenocarcinoma of the gastro-esophageal junction

In both the CROSS and the FLOT trial, adenocarcinoma of the esophagus and junction were included. Thus, there is ongoing debate on the most optimal neoadjuvant therapy for these tumors. The ESOPEC trial has been initiated in Germany to compare the CROSS and FLOT regimen in lymph node positive and cT2-4aNx adenocarcinoma of the esophagus and junction, with overall survival as primary endpoint (58). Similarly, the Neo-AEGIS trial is recruiting patients in the United Kingdom and other European countries with lymph node positive and cT2-3Nx adenocarcinoma of the junction only, to be randomized between CROSS and FLOT (59). These studies are targeted to complete accrual mid-2023 and beginning of 2024, respectively, and these results are eagerly awaited.

Ongoing debates: chemoradiation for SCC

In China, there is reluctance to treat squamous cell carcinoma of the esophagus with neoadjuvant chemoradiation because of a perceived increased risk for postoperative mortality (29,60). However, mortality rates were rather high decades ago where centralization of surgery and minimally invasive surgery was not yet implemented and suboptimal chemotherapy regimens were administered. The CMISG1701 trial is currently recruiting patients with cT3–4aN0–1M0 squamous cell carcinoma of the esophagus, to compare neoadjuvant chemoradiotherapy (40 Gy irradiation combined with four weekly cycles of cisplatin plus paclitaxel) with neoadjuvant chemotherapy

(two 3-weekly cycles of cisplatin plus paclitaxel), both followed by minimally invasive esophagectomy (61). Accrual is planned to be complete at the end of 2021.

Ongoing debates: definitive chemoradiation as an alternative

In the ESMO guideline, definitive chemoradiation is recommended as a alternative treatment (II, B) in patients who are not fit for surgery. Definitive chemoradiation is alos recommended as the preferred treatment option for cervically located tumors (III, B). In the United Kingdom, the option of definitive chemoradiation is discussed as a treatment option alongside neoadjuvant chemoradiation plus resection in all patients with resectable non-metastatic SCC of the esophagus, according to the NICE guideline (62). The NCCN guideline offers again slightly different advice; definitive chemoradiation should be reserved for patients with unresectable disease or those who decline surgery (15). The difference in recommendation is probably the result of the additional toxicity seen from definitive chemoradiation; while resection of a very proximal esophageal tumor necessitates laryngo-pharygectomy which is associated with quite some morbidity. Therefore, in most centers definitive chemoradiation is the preferred option for proximally located esophageal tumors.

Conclusions

Many different multimodality treatments have been developed and tested with the aim to improve the outcome of esophageal cancer patients, which unfortunately remains dismal. In large parts of the world, neoadjuvant chemoradiation according to CROSS is considered standard-of-care, while in other countries chemoradiation with platinum/5FU is preferred. For adenocarcinoma, peri-operative chemotherapy with FLOT is also a valid option. Improvements may come from a combination of HER-2 targeting agents with chemotherapy or immunotherapy, provided that there is adequate patient selection, which should probably move beyond MSI and PD-L1 expression. More personalized medicine could also be achieved by better selection of those patients in need of esophageal resection after neoadjuvant treatment, and naturally, those patients who do not need resection, as cure has been reached by the neoadjuvant treatment alone, or distant metastases develop shortly thereafter.

Altogether, new study designs accommodating more accurate patient selection and perhaps pre-operative treatment intensification in patients with a poor response to first line neoadjuvant treatment, are needed to improve the prognosis of this challenging disease.

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Footnote

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