Langenbecks Arch Surg (2013) 398:177–187
DOI 10.1007/s00423-012-1001-1

REVIEW ARTICLE

Multimodal treatment of esophageal cancer

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Received: 22 August 2012 / Accepted: 3 September 2012 / Published online: 13 September 2012
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Abstract
Background The treatment of localized esophageal cancer has been debated controversially over the past decades. Neoadjuvant treatment was used empirically, but evidence was limited due to the lack of high-quality confirmatory studies. Meanwhile, data have become much clearer due to recently published well-conducted randomized controlled trials and meta-analyses.
Methods Neoadjuvant and perioperative platinum fluoropyrimidine-based combination chemotherapy has now an established role in the treatment of stage II and stage III esophageal adenocarcinoma and cancer of the esophagogastric junction. Neoadjuvant chemoradiation is now the standard of care for treating stage II and stage III esophageal squamous cell cancer and can also be considered for treating esophageal adenocarcinoma.
Results Patients with esophageal squamous cell cancer treated with definitive chemoradiation achieve comparable long-term survival compared with surgery. Short-term mortality is less with chemoradiation alone, but local tumor control is significantly better with surgery.
Conclusion This expert review article outlines current data and literature and delineates recommendable treatment guidelines for localized esophageal cancer.

Keywords Esophageal cancer · Neoadjuvant · Chemotherapy · Chemoradiation · Response

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Pathogenesis and epidemiology of esophageal cancer

What we call esophageal cancer is not a homogenous disease. An important distinction has to be made between squamous cell cancer and adenocarcinoma of the esophagus, while other histologies are much rarer.

Esophageal squamous cell cancer (ESCC)

According to its physiologic epithelial layer, ESCC can occur in all parts of the esophagus. Carcinogenesis is mostly triggered by exogenous agents. While in the Western hemisphere, alcohol and tobacco abuse are prevalent, in Asia the consumption of nitrosamines plays a more dominant role. Important for treatment decisions is the fact that due to its specific pathogenesis in the Western world, many patients with ESCC have concomitant diseases that are associated with alcohol and tobacco consumption such as chronic obstructive pulmonary disease, liver cirrhosis and synchronous cancers of the lung or head and neck region [1].

Esophageal adenocarcinoma (EAC)

EAC mostly develops via metaplasia of the epithelium of the distal esophagus (so called Barrett's mucosa). This is induced by chronic gastro-esophageal reflux [2, 3]. Esophageal metaplasia is found in up to 90 % of patients with

EAC. Persons with Barrett's esophagus seem to have a 125-fold increased risk to developing EAC, although this number has been called into question by recent observations [4].

Epidemiology

Esophageal cancer is the eighth most common form of cancers worldwide. Overall incidence rates are 2-fold higher in less-developed compared with more-developed regions, being highest in Asia. Survival is universally poor. ESCC comprises the majority of cases worldwide. In contrast to ESCC, EAC predominantly occurs in more developed countries, with the rate of rise in incidence exceeding the rate of decline of ESCC in several Western countries [5]. A steep increase in the incidence of EAC has been observed between 1973 and 2001. Recent observations indicate that today a plateau may have been reached [6]. Similarly, for all other adenocarcinomas located at the esophago-gastric junction — that in the current (7th) edition of the TNM classification are classified as esophageal cancers [7] — a rise in incidence has been reported [8].

Pathologic anatomy and classification

The probability of lymphatic spread and its direction depends on the depth of infiltration and on the localization of the primary tumor. Usually, the first site of lymph node metastases is locoregional. This means that in proximal and mid-thoracic cancers (mostly ESCC) mediastinal lymph nodes are often involved whereas cancers of the distal parts of the esophagus (mostly EAC) metastasize along the gastric cardia and the lesser gastric curvature. In more advanced stages, EAC can also metastasize to the upper mediastinum and ESCC can spread down to the celiac axis.

In the 7th edition of the TNM classification [7], two specific changes have been implemented: First, all adenocarcinomas of the esophago-gastric junction (AEG), that for clinical purposes have been classified as AEG type I, II and III (Fig. 1) [9], are now classified as to the anatomical extent according to the TNM of esophageal tumors. It is important to note that this decision has been taken in order to simplify the classification and to improve the comparability of study cohorts. Especially for choosing the best surgical approach, Siewert's classification remains relevant: usually, AEG type I is treated by esophagectomy and mediastinal lymph node dissection while AEG type III is treated by transhiatal extended gastrectomy. For AEG type II there exist unequal expert recommendations.

A second major change concerns the N status. While before 2010 the difference between involved and non-involved lymph nodes (pN1 or pN0) was the only distinction that was made, now a sub-categorization takes into account the number of involved lymph nodes (LN) with pN1=1–2 LN, pN2=3–6 LN, and pN3>6 LN. Moreover, the former classification of M1a lymphatic (which described lymph node metastases at the celiac axis) has been abandoned. In a retrospective analysis of a large cohort of almost 3,000 patients the prognostic value of these changes has been validated [10]: For primarily resected patients a good discrimination of the different lymph node categories could be shown. In comparison to the former classification system, the prognosis of patients with N3 tumors was comparable to the former M1 lymphatic category.

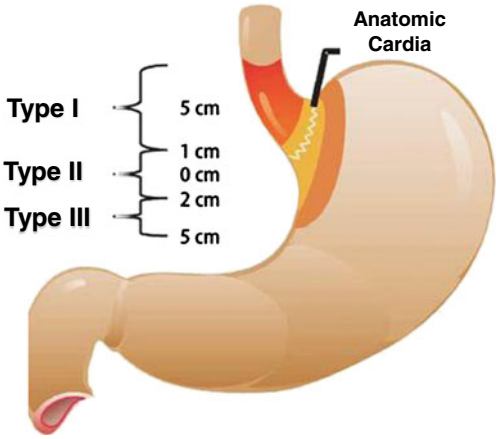

Fig. 1 Classification of adenocarcinoma of the esophago-gastric junction according to Siewert et al. [9]

The rate of lymph node involvement correlates with the T-category and is relevant for the prognosis and for treatment planning. It is of particular importance to exclude patients from sole endoscopic resection of "early cancer" who may have lymphatic spread (L1 or pN+). A differentiation must be made between mucosal (T1m) and submucosal (T1sm) cancer and the sub-categorization of submucosal infiltration in thirds according to the Japanese classification (sm1, sm2, sm3) has also gained importance. While both ESCC and EAC have practically no lymph node metastases as long as they are limited to the mucosal layer, the frequency of lymph node metastases ranges from 10 % to 20 % in sm1 cancers to 50–60 % in sm3 cancers. There is a trend towards deeper submucosal infiltration and therefore more lymphatic spread in ESCC [11]. A stage dependent comparison of lymphatic spread for tumors categorized T2 or greater does not show differences between ESCC and EAC. While it is clear that tumors that infiltrate beyond the mucosal layer must not be treated by endoscopic resection, the value of multimodal treatment in T1b and T2 categories is still debated.

Distant metastases often concern the liver and the peritoneum; in proximal cancers lung metastases are also often found. As mentioned above, classification of involved celiac lymph nodes as M1a has been left in the 7th TNM edition,

because the prognosis of this condition was shown to be better than with other distant sites. Celiac lymph nodes can be dissected when performing an esophagectomy. Therefore, lymph node metastases at this site should not preclude patients from resection.

The topographic relation of the esophageal cancer to the tracheo-bronchial system is of major therapeutic relevance, as tumors located at the level of the trachea or bifurcation may infiltrate the tracheal wall which precludes radical surgical resection.

For cancers of the upper esophageal third, the distance from the proximal esophageal sphincter is important and should always be assessed and documented in tumors with a proximal location. The more proximal the location, the less probable is the chance that a tumor can be removed with preservation of the larynx or the swallowing functions. Clear cut-offs cannot be given. The experience and expertise of the surgical team matter. Due to the clinical data that will be outlined later, surgical treatment of upper third esophageal cancer has been replaced in most centers in favor of definitive chemoradiation.

Diagnostic work-up and staging

A sophisticated diagnostic work-up and staging must be performed in order to allow for an accurate treatment choice. The recommended standard procedures are listed in Table 1.

Of utmost importance is the exclusion of Stage IV (M1 category), because in this situation surgical therapy cannot be routinely recommended and treatment goals are palliative. In order to exclude distant metastases, a high-resolution and high-quality computed tomography (CT) of the thorax and abdomen should be performed. For proximal tumors, the CT should include the neck region. Magnetic resonance tomography does not yield better results and is therefore not routinely recommended. Ultrasound of the thorax and abdomen helps to identify metastases and effusions but cannot replace CT. Much discussion is about the routine use of positron emission tomography. According to the current literature, the diagnostic benefit of whole-body positron emission tomography is limited if a "state-of-the-art staging" has been performed. Therefore, its routine implementation in daily clinical practice is at least questionable [12]. Bone scans are not a recommended routine staging procedure and should be limited to patients with specific bone associated symptoms or findings. In case of ascites in non-liver cirrhosis patients, laparoscopy should be performed to exclude peritoneal carcinomatosis.

Following the exclusion of distant metastases, appropriate staging of the primary tumor is of interest as the selection of the adequate primary treatment is based on it. This is most reliably performed by means of endoscopic ultrasound [13, 14]. Its average accuracy for T staging is 84 % (range 60–90 %) while for nodal staging it is 77 % (range 50–90 %) [15]. If the tumor cannot be passed endoscopically and accordingly cannot be investigated with endoscopic ultrasound, a T3 or T4 category must be assumed. In proximal and mid-esophageal tumors, tracheo-bronchoscopy including multiple biopsies and brush cytology examinations from the tracheal mucosa is recommended to rule out tumor infiltration, indicating that the tumor is not resectable and has an enhanced risk of causing esophago-tracheal fistula.

The question of tumor infiltration into other adjacent organs can usually be answered with a high-quality spiral CT. As with current CT technology multiple reconstruction

Table 1 Diagnostic work-up in esophageal cancer: (a) basic diagnostic work-up and (b) additional investigations according to the results of (a) and in particular situations

Investigation	Aim/indication
(a)	
Endoscopy+biopsy	Localization, tumor extension, histologic confirmation
Endoscopic ultrasound	T category (N with limitations)
Abdominal ultrasound	Liver metastases and ascites
High-resolution computed tomography (CT) of the thorax and abdomen	Local extension, distant metastases, pleural effusion, ascites
Ultrasound (US) or CT of the neck	If indicated, especially in proximal tumors
(b)	
Bronchoscopy+biopsy	Indicated in tumors adjacent to the trachea/carina
Laparoscopy+biopsy+laparoscopic US	Suspicion of peritoneal carcinomatosis/liver metastases
Thoracoscopy	Suspicion of pleural carcinomatosis/lung metastases
Positron emission tomography	Suspicion of distant metastases
Bone scintigraphy	Suspicion of bone metastases
Contrast swallow	Suspicion of esophago-tracheal fistula
Endoscopic "lifting sign"	Mucosa-/submucosal infiltration
Chromoendoscopy	Suspicion of early cancer or multifocality

techniques can be done, contrast swallow X-ray investigations are no longer necessary and the indication is limited to the exclusion of fistulas in particular cases.

The distinction between mucosal and submucosal infiltration is important if endoscopic resection is considered, but this goes beyond the scope of this article.

The pathological N-status is difficult to predict. The major clinical criterion is lymph node size. However, according to morphometric investigations in resection specimen, the correlation between lymph node size and lymph node involvement is only weak [16]. In a treatment concept that includes radical lymphadenectomy, the pre-operative assessment of the lymph node status is thought to be of minor importance because these lymph nodes will be completely removed anyway. This does also include lymph nodes located at the celiac axis. Suspicion of celiac lymph node involvement should therefore not preclude patients from esophagectomy. Nevertheless, if a presumed positive lymph node status is considered as an important criterion for indicating neoadjuvant treatment, if no other criteria are met, clinical estimation of the N category becomes more weight and unevitable diagnostic inaccuracies may lead to inaccurate treatment decisions.

Preoperative risk analysis

Esophagectomy is associated with a significant perioperative morbidity and mortality. Peri-operative treatment led to increased morbidity in some studies. This should be well recognized, as many patients with esophageal cancer have relevant concomitant diseases. Due to alcohol and tobacco consumption many patients with ESCC suffer from pulmonary and hepatic impairment. Patients with EAC are more often obese and have concomitant cardiovascular disease. These and other risks must be carefully assessed. If possible they must be treated and corrected before the start of any treatment. In case of remaining and severe functional impairment, patients must be excluded from surgery or combined chemoradiotherapy. Scores that are composed of the most relevant medical risk factors have been established for clinical practice [16–20].

Briefly, liver cirrhosis in stages Child B and C, prevalent alcohol abuse with the risk of postoperative withdrawal syndrome and chronic obstructive pulmonary disease leading to severe impairment of the lung function or gas exchange have been established as the most critical risk factors. If these factors together with cardiovascular, renal and metabolic disorders are carefully checked and controlled, highly experienced multidisciplinary treatment teams can keep the perioperative mortality including preoperative treatment below 5 %.

Indications for surgical treatment

Surgery offers a curative potential in localized esophageal cancer without distant metastases. In very early stages, i.e., in cancers limited to the mucosal layer, endoscopic resection is an accepted alternative to surgery [11, 21]. In intermediate stages (T1b and T2 categories), primary surgical resection is the treatment of choice. In locally advanced categories (T3 and resectable T4), surgery is part of a multimodal treatment strategy and usually follows neoadjuvant chemotherapy or chemoradiation (Fig. 2).

Radical and transthoracic esophagectomy is the surgical technique of choice. A prospective randomized study performed in the Netherlands proved a better survival for this approach compared with less radical transhiatal resection in adenocarcinoma of the esophagus [22, 23].

Limited resection techniques like distal esophagectomy combined with limited lymphadenectomy and reconstruction according to Merendino may be performed as an alternative to endoscopic resection in patients with distal adenocarcinoma with mucosal infiltration. In clinical practice, the Merendino procedure is not often performed as most patients with very early tumors are referred to expert centers for endoscopic resection. Due to a 30 % rate of lymph node metastases in carcinomas infiltrating the submucosal layer, Merendino's procedure cannot be recommended in cancers infiltrating beyond the mucosal layer [24, 25].

Details concerning endoscopic and surgical resection techniques are not the scope of this article but can be found in other expert review articles [26–30].

Perioperative treatment

Despite the optimization of surgical treatment and the formation of high-volume centers, the outcome following resection for esophageal cancers remains unsatisfactory [31]. This is in part due to the specific disease biology. In addition, the location of esophageal cancer in a narrow anatomic compartment hampers removal of the tumor with wide and safe resection margins. Therefore, preoperative (neoadjuvant) therapy has been established in order to tackle systemic disease as early as possible in the course of treatment and to shrink tumors in order to improve their resectability. Meanwhile, neoadjuvant chemotherapy and neoadjuvant combined chemoradiation have a proven benefit and can be recommended in locally advanced stages [32]. Definitive chemoradiation without surgery is an alternative treatment option for patients who cannot undergo surgery. In the following paragraphs, the current knowledge on the different strategies will be outlined.

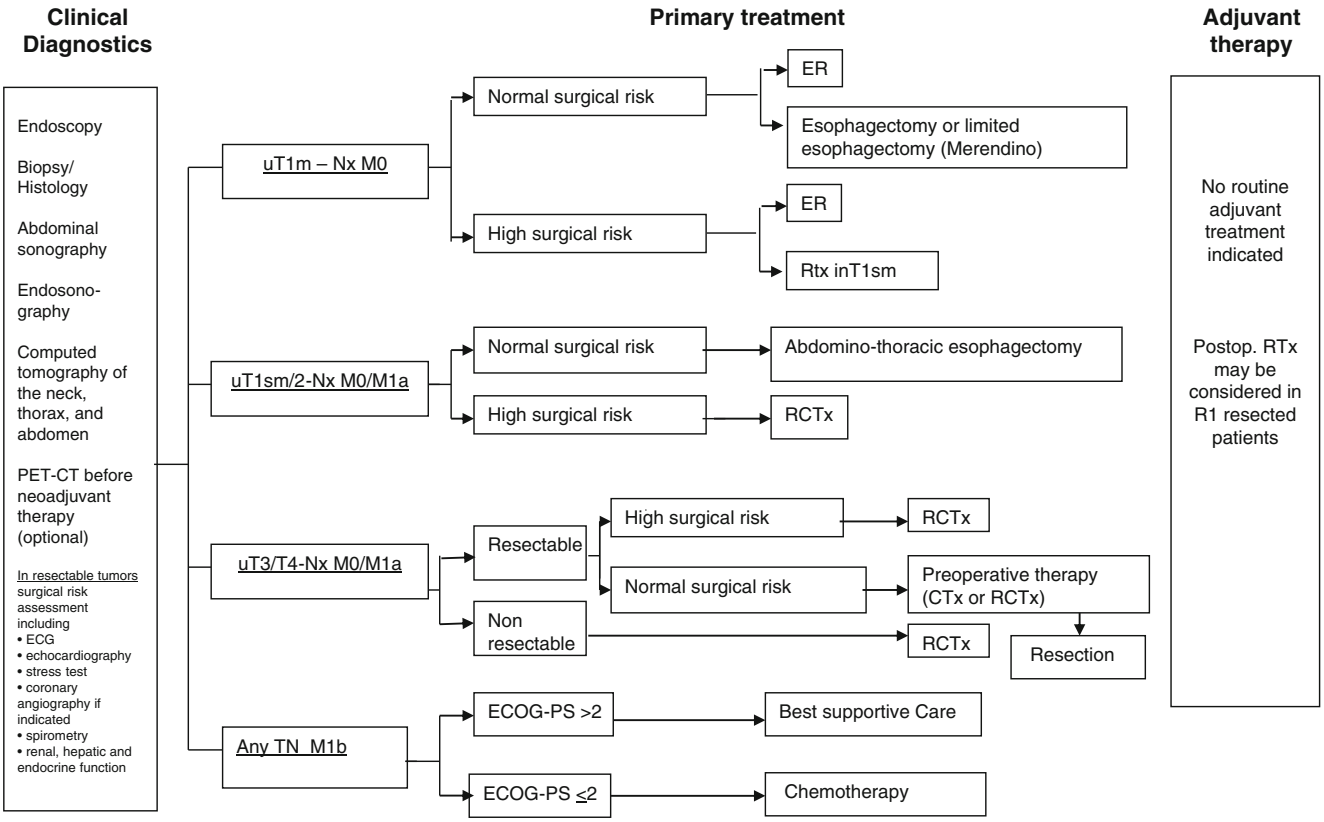

Fig. 2 Flow chart of the diagnostic and therapeutic management of esophageal cancer

Neoadjuvant radiation without chemotherapy

Six fully published studies and one Cochrane review on published and unpublished studies have been performed to prove the benefit of neoadjuvant radiation without chemotherapy in resectable esophageal cancer [33, 34]. Clinical response to neoadjuvant radiation was observed in two thirds of the patients, but a significantly improved survival was reported in only one study [35]. Two studies reported a worse outcome in the patients who had received neoadjuvant radiation. A Cochrane review on 1,147 patients presenting mostly data on ESCC patients who were randomized to neoadjuvant radiation or esophagectomy alone, concludes that neoadjuvant radiation led to a relative risk reduction for the endpoint death of 11 %; hazard ratio (HR) 0.89; 95 % confidence interval (CI) 0.78–1.01. The absolute survival difference was 2 % after 2 years and 4 % after 5 years. This result is neither clinically compelling nor statistically significant [35]. Neoadjuvant radiation alone followed by surgery is therefore not a recommended approach to treat esophageal cancer.

Neoadjuvant chemotherapy without radiation

Ten fully published studies have been performed to investigate neoadjuvant chemotherapy without radiation. Two large studies included patients with ESCC and EAC [36, 37] while some smaller studies focused on either of these two histological subtypes. Newer studies focusing on patients with EAC show a significant survival benefit for patients undergoing neoadjuvant chemotherapy with cisplatin and 5-fluorouracil (5-FU) for 6–8 weeks [37, 38]. A recently published meta-analysis over 2,062 patients who were randomly assigned to receive neoadjuvant chemotherapy or surgery alone shows a significant survival improvement for patients undergoing neoadjuvant chemotherapy with a relative risk reduction of 13 % (HR 0.87; 95 % CI, 0.79–0.96; p=0.005), resulting in an absolute difference in the 2-year survival of 5.1 %. While the difference was not statistically significant for patients with ESCC (HR 0.92; 95 % CI, 0.81–1.04, p= 0.18), significance was reached in the subgroup of patients with adenocarcinoma (HR 0.83; 95 % CI, 0.71–0.95, p=0.01) [32].

In conclusion, it was shown that neoadjuvant chemotherapy is effective in patients with localized esophageal cancer. The effectiveness is unsatisfactory in patients with ESCC, while in patients with EAC neoadjuvant chemotherapy leads to a significant and clinically meaningful survival improvement without compromising the safety of surgical resection.

Neoadjuvant chemoradiation

In recent years, neoadjuvant chemoradiation has been the most commonly investigated approach in the treatment of resectable esophageal cancer. Investigators have studied new drug combinations, targeted drugs, novel radiation techniques and different sequences of combining chemotherapy and radiation. Despite all efforts, a clear reference treatment has yet to be established.

Meta-analyses came to the conclusion that combined neoadjuvant chemoradiation confers a significant improvement in overall survival and local tumor control. The most recent meta-analysis included 1,932 patients from 13 randomized trials [32]. The HR for the reduction of the overall mortality was 0.78 in favor of chemoradiation (95 % CI, 0.70–0.88; $p=0.002$), resulting in an absolute 2-year survival difference of 8.7 %. The benefit for patients with ESCC and patients with EAC was in the same range.

The recently published Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) is a prospective randomized controlled trial comparing surgery alone with neoadjuvant chemoradiation followed by surgery [39]. It is the largest ever performed study investigating neoadjuvant chemoradiation in esophageal cancer. The straightforward study methodology and the quality of the results are compelling. CROSS shows a significant survival benefit for neoadjuvant treatment. Postoperative mortality was not increased in the tri-modality arm. CROSS certainly defines a new standard of care for the management of localized ESCC, which consisted of weekly carboplatin plus paclitaxel combined with radiation 41.1 Gy followed by surgery. For adenocarcinoma, the results from CROSS are less clear than for ESCC. The benefit associated with neoadjuvant chemoradiation in EAC was in the same range as shown for neoadjuvant chemotherapy without radiation in some other studies. Therefore, the debate, if chemotherapy alone or chemoradiation should be used as neoadjuvant treatment in localized EAC is not yet over.

In conclusion, neoadjuvant chemoradiation has proven efficacy in localized esophageal carcinoma that holds true for both common histologic subtypes. Neoadjuvant chemoradiation augments the postoperative morbidity and mortality, according to some but not all studies.

Choice of the neoadjuvant treatment

The choice of neoadjuvant treatment can be seen differentially for ESCC and EAC, taking into consideration the different localization of these two tumor entities, but also their different pathogenesis and biology.

For patients with ESCC, neoadjuvant chemotherapy does not seem to be effective enough, while neoadjuvant chemoradiation improves the survival, albeit potentially at the expense of increased postoperative morbidity [32, 40]. In patients with EAC, neoadjuvant chemotherapy as well as neoadjuvant chemoradiation revealed to be effective. There are no sufficiently powered studies thus far to compare these two approaches. In smaller studies, there is a trend in favor of neoadjuvant chemoradiation. However, the postoperative 90-day mortality following neoadjuvant chemoradiation was as high as 10 % in a recently published study performed at German university and large community hospitals [41]. The authors of the recent meta-analysis conclude that until now “a clear advantage of neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy has not been established” [32].

Patient selection

(1) Patients with tumors that are not resectable (e.g., T4b category with infiltration into the tracheal wall) should not undergo resection and are therefore no candidates for neoadjuvant treatment.
(2) Patients with locally advanced tumors with uncertain R0 resectability (most T3 tumors) should receive neoadjuvant treatment. In squamous cell cancer, neoadjuvant chemoradiation is the treatment of choice. In adenocarcinoma, neoadjuvant chemotherapy or chemoradiation can be recommended.
(3) Patients with tumors with highly probable R0 resectability (most T2 and T1b cancers) should undergo primary resection. Within clinical studies or well-documented center standards, these patients may also be eligible for neoadjuvant treatment.

The predictability of complete (R0) resection depends mainly on the T category. In cT3 tumors, especially when the location of the tumor is in the upper or mid-thoracic mediastinum, the chance for an R0 resection is only about 50 %.

Due to the marked complication rate of esophagectomy and the co-existing morbidity of many patients who are diagnosed with esophageal cancer, especially those with ESCC, the functional capacity and organ functions of patients planned for multimodality treatment have to be checked thoroughly. Only patients with adequate physical and psychological resources are acceptable candidates for multimodality treatment of esophageal cancer including surgery.

Complications

No significant increase in postoperative complications and mortality was reported following neoadjuvant chemotherapy

without radiation. However, during cisplatin plus 5-FU-based chemotherapy severe (grade 3) and life threatening (grade 4) adverse events occur in 32 % of the treated patients. The pre-operative death rate is 1.1–2.1 % [42–44].

Three meta-analyses report on significantly increased postoperative morbidity and mortality following neoadjuvant chemoradiation [40, 44, 45]. However, the post-operative mortality was not increased when studies with single radiation doses of >2 Gy were not included [40]. The potential deleterious effects of neoadjuvant chemoradiation are only partly understood. Radiation in higher doses causes a disruption of the alveolar diffusion capacity and thereby deteriorates the pulmonary gas exchange. As a consequence, post-operative respiratory insufficiency occurs more often in irradiated patients [46]. Therefore, current concepts of pre-operative radiation treatment confine the target volumes to a necessary extent, limiting especially the exposure of the lungs. In this context, currently available techniques of intensity-modulated radiation treatment planning may have additional beneficial.

In the recently published CROSS trial, post-operative mortality following pre-operative chemoradiation with carboplatin-paclitaxel and 41.4 Gy was not increased compared to the surgery alone arm [39].

Treatment protocols

In the largest study ever performed, a significant survival benefit for neoadjuvant therapy was demonstrated. Patients were treated with two cycles of cisplatin 80 mg/m^2 on day 1 (infusion over 4 h) plus 5-FU 1,000 mg/m^2/day on days 1–4 (infusion over 24 h/day). Cycle two was given after 3 weeks [37]. Resection was performed 3–5 weeks after the start of the second cycle. Other chemotherapy regimens including taxanes, anthracyclines and other compounds have been investigated in smaller studies but have not yet proven to be superior.

An optimal chemoradiation regimen is difficult to be identified in view of the heterogeneity of data and publications. Outside of clinical trials radiation should be conventionally fractionated. Single doses are <2 Gy. There is some experience with hyperfractionated and accelerated radiation protocols. But they are not standard in the pre-operative treatment of esophageal cancer. In Europe, 40–45 Gy are standard in the pre-operative setting. Some centers administer additional doses up to 50 Gy in smaller target volumes. In North America, 50 Gy is regarded as an accepted pre-operative radiation dose. Higher doses may lead to severe pulmonary impairment. Concomitant cisplatin and continuous infusion with 5-FU are typically given as radiosensitizers and to treat systemic disease. In order to circumvent cisplatin-specific adverse effects, cisplatin was substituted for oxaliplatin with promising preliminary results [47–49]. A randomized phase III study in France was just reported at the American Society of Clinical Oncology 2012 meeting in Chicago but did not show clear superiority of oxaliplatin and 5-FU over cisplatin plus 5-GU [50]. In the recently presented CROSS trial, weekly carboplatin plus paclitaxel in combination with radiation (41.1 Gy) revealed as a feasible regimen with high efficacy especially in ESCC [39].

The delay between the end of chemoradiation and surgery is usually 4–8 weeks, but randomized studies assessing the optimal time point are lacking. Therefore, evidence-based recommendations cannot be given. While usually within 6 weeks a clinically perceivable regeneration of the skin and mucous membranes is ongoing, the risk for developing pneumonitis is highest in this time frame [51]. In our own experience, a delay of 4–8 weeks between the end of chemoradiation and esophagectomy revealed feasible and is recommended. According to current retrospective literature, a longer delay than this has no disadvantages [52].

Assessment and prediction of response to treatment

A series of recent studies assessed response during and after neoadjuvant treatment. This topic has gained interest, as histopathological response after neoadjuvant treatment has revealed as a prognostic marker [53–57]. Standard clinical investigations like CT and endoscopic ultrasound performed during and after neoadjuvant treatment revealed as inaccurate for assessing the response and predicting the patients' prognosis [58–60]. Often these methods cannot differentiate between tumor, scar or post-therapeutic edema. Additional information can be retrieved using metabolic imaging, especially 18 F-fluordeoxyglucose positron emission tomography (FDG-PET) [60–62]. However, FDG-PET cannot detect microscopic residual disease. Therefore, it should not be argued that a negative post-therapeutic PET should deter patients from surgery that is otherwise indicated. Meanwhile, studies clearly show that tumors that do not respond metabolically to neoadjuvant therapy have a very poor prognosis, even following radical and complete resection. The best therapeutic strategy for metabolic non-responders is not yet clear.

There is promising data concerning early metabolic response assessment by doing sequential FDG-PETs. An early decrease of the standard uptake value (SUV) 2 weeks after the start of neoadjuvant chemotherapy allows to predict later histopathologic response with a high accuracy [63, 64]. Meanwhile, it was demonstrated in a prospective interventional study that data obtained by early metabolic response assessment can be used to guide neoadjuvant treatment in locally advanced EAC [65]. These compelling results could unfortunately not be confirmed during neoadjuvant chemoradiation [66, 67], presumably due to the specific effects of

radiation on tumor, stroma and surrounding healthy tissue. The early metabolic response assessment is not a routinely recommended investigation during neoadjuvant treatment, but it is certainly one of the most intriguing topics of clinical investigation in current upper gastrointestinal oncology.

Quality of life

During neoadjuvant therapy, patients with esophageal cancer often sustain impairment of their health-related quality of life (HRQL). This is more pronounced during neoadjuvant chemoradiation than during neoadjuvant chemotherapy. Following neoadjuvant treatment, but before surgery, HRQL returns to baseline levels. Six weeks after surgery, patients reported marked reductions in physical and social functions and increase in fatigue, nausea and emesis, pain, dyspnea, appetite loss, and coughing. Recovery of HRQL is not hampered by preoperative treatment, and fewer problems with postoperative nausea, emesis, and dysphagia are reported by patients who have undergone neoadjuvant treatment compared with patients who have undergone surgery alone. These results support the use of neoadjuvant treatment before surgery from a quality of life perspective [68]. Interestingly, despite the major psychosocial and physiological impacts of the disease, more than 50 % of mid- and long-term survivors of the Ivor–Lewis procedure for esophageal cancer have a HRQL similar to that of the healthy reference population [69]

Conclusions for perioperative treatment

Neoadjuvant therapy in locally advanced esophageal cancer is an established standard of care, as now there is sufficient prove of efficacy. In ESCC, combined chemoradiation on the basis of platinum and 5-FU or platinum and paclitaxel revealed a reasonable feasibility and good efficacy. In EAC, neoadjuvant treatment is also widely used and has proven efficacy. To date there is not yet sufficient evidence that chemoradiation is significantly superior compared with chemotherapy alone. Both methods can be applied and are recommended. In the context of clinical investigation, response-adapted algorithms may gain importance.

Definitive chemoradiation

Concomitant chemoradiation has shown superiority compared to radiotherapy alone regarding local tumor control, relapse-free survival and overall survival [70]. There is an improvement of about 8 % after 2 years, if radiation therapy and chemotherapy are applied simultaneously and not sequentially.

In order to assess an optimal radiation dose study RTOG 94–05 compared 50.4 and 64.5 Gy, both given in combination with cisplatin (75 mg/m^2 day 1) and 5-FU (1,000 mg/m^2 days 1–4, repeated in week 5 of radiation therapy) [71]. The higher radiation dose failed to show superiority compared to the lower dose with regards to local tumor control, overall survival and relapse-free survival. On the other hand, acute adverse effects and treatment-associated deaths were significantly more common with the higher dose. Therefore, the regimen from RTOG 85–06 that was published in 1992 is still regarded as a kind of reference regimen consisting of 50.4 Gy radiation dose (conventional fractioning 1.8–2.0 Gy/day) combined with cisplatin 1 × 75 mg, and 5-FU 4 × 1,000 mg, week 1+5 of radiation treatment and week 9+13 [72]. In many experienced centers, variations of this protocol have been developed and higher radiation doses are applied in smaller target volumes.

In case of contraindications against any chemotherapy, radiation is sometimes used alone. Of note, to our current knowledge, radiation without concomitant chemotherapy is a treatment without curative potential in esophageal cancer.

Radiochemotherapy versus surgery

Three randomized studies compared the results of definitive radiotherapy (in two studies in combination with concomitant chemotherapy) and surgical resection in patients with ESCC [73]. One can conclude that a significant survival advantage of surgical treatment of ESCC was not proven in these studies, although in one small German multicenter study a strong trend towards a better survival was shown with a 3-year survival difference of 31 % with surgery compared to 24 % with chemoradiation [74]. Regarding local tumor control, all randomized studies show a significant advantage in favor of surgical treatment. Therefore, surgical resection remains a treatment with a proven value and should be recommended in patients without contraindications and willing to take the risk of postoperative morbidity and mortality.

Until now, there are scarce data on the efficacy of definitive chemoradiation in EAC. Therefore, chemoradiation alone is not a proven and established alternative to surgery in EAC.

Clinical research

In order to make multimodality treatment more efficacious and to improve further the outcome of patients with esophageal cancer, the following clinical research directions are currently being investigated:

Integration of radiation therapy into treatment of esophagogastric junction adenocarcinoma

The randomized phase II/phase III Trial of Preoperative Therapy for Gastric and Esophagogastric Junction

Adenocarcinoma (Top Gear Study) is now open and is allocating patients to perioperative chemotherapy (arm A) versus perioperative chemotherapy combined with radiation (arm B) (http://www.australiancancertrials.gov.au/search-clinical-trials/search-results/clinical-trials-details.aspx?TrialID=83497&ds=1). This global study has been initiated by the Australian Gastrointestinal Trials Group (AGITG) and is also supported by the National Cancer Institute of Canada (NCIC) and the European Organization of Research and Treatment of Cancer (EORTC). This trial is designed to give a definitive answer, if chemotherapy alone or chemoradiation is the preferred treatment in adenocarcinoma of the esophago-gastric junction. As a further step, better planning of radiation volumes using modern imaging techniques may improve further the efficacy of radiation and reduce its adverse effects. Several national trials are being currently conducted [75].

Integration of targeted drugs into the multimodal treatment of esophageal cancer

Another way of trying to improve outcome is the detection of relevant biomarkers and drug targets for better treatment of esophageal cancer. Members of the growth factor receptor tyrosine kinase families such as EGFR, HER2 and cMet, are currently being investigated as promising candidates [7–79]. A couple of trials investigate the monoclonal anti-EGFR-antibodies cetuximab or panitumumab and the anti-HER2-specific antibody trastuzumab in the perioperative therapy of esophago-gastric cancer. Before integrating these compounds into clinical practice, the results of these clinical trials and the accompanying biomarker studies should be awaited.

Response prediction and early response evaluation by metabolic imaging

Some groups have assessed the value of metabolic imaging during neoadjuvant treatment of esophageal cancer [65–67]. Multicenter studies are still lacking but plans have been discussed intensively within the EORTC [80]. The U.S. Cancer and Leukemia Group B and the National Cancer Institute have now opened a randomized phase II multicenter study investigating the role of PET response monitoring during induction chemotherapy in the trimodality treatment of esophageal cancer (trial CALGB 80803; http://clinicaltrials.gov/ct2/show/NCT01333033).

Conflicts of interest None.

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