The Current Evidence in Support of Multimodal Treatment of Locally Advanced, Potentially Resectable Esophageal Cancer

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Abstract

Background: Treatment of locally advanced resectable esophageal cancer is challenging. In the past three decades surgical treatment has become safer, chemotherapy more powerful and radiation techniques more precise. Today’s stage-dependent treatment relies on modern diagnostic tools such as multidetector helical CT, high-frequency endoscopic ultrasound, PET, image fusion techniques and MRI. Specialists cooperate on multidisciplinary tumor boards that follow transparent decision trees based on the newest evidence. Methods: Results of recent randomized controlled trials are examined with emphasis on their reliability and comparability. Results: Patients with esophagogastric cancer undergoing neoadjuvant chemotherapy, perioperative chemotherapy and neoadjuvant radiochemotherapy plus esophagectomy had a higher R-0 resection rate, fewer involved lymph nodes and better overall survival than with esophagectomy alone. While perioperative morbidity and mortality were not remarkably enhanced by neoadjuvant chemotherapy, several trials showed an increase of mortality after neoadjuvant radiochemotherapy. Adenocarcinoma seems to respond better to chemotherapy than squamous cell cancer, and squamous cell cancer seems to respond better to radiochemotherapy than adenocarcinoma. Conclusion: On the basis of the results of randomized trials, preoperative treatment of esophageal cancer shows a survival benefit and should be recommended as the standard treatment strategy in advanced esophageal cancer. While preoperative radiochemotherapy is the standard for advanced squamous cell cancer, both chemotherapy and radiochemotherapy may be adopted for neoadjuvant/perioperative treatment of adenocarcinoma depending on the patient’s general condition. Markers to predict response are urgently needed since only responders benefit from multimodal treatment and nonresponders suffer potential harm when surgery is delayed.
preoperative radiotherapy showed no benefit compared to surgery alone. With that lesson learned, preoperative polychemotherapy and radiochemotherapy regimens were designed. Soon it was obvious that only patients with a definite histopathologic response had a survival benefit, while nonresponders seemed to have a worse prognosis, even in comparison with patients who only had surgery [2, 3]. This in turn made the identification of markers predictive for response a central target of research.

The current evidence for preoperative treatment of esophageal cancer is based on recently published results of randomized multicenter trials. Clinical trials on esophageal adenocarcinoma frequently include cardia and gastric cancers as well, usually in an even higher proportion than true esophageal cancer [4–6]. These studies generally deal with perioperative or neoadjuvant chemotherapy. Other studies include esophageal adenocarcinoma and squamous cell cancer when evaluating neoadjuvant chemotherapy or radiochemotherapy [7, 8]. However, differences in inclusion criteria (i.e. staging) and therapeutic regimen make it difficult to compare those trials and to draw useful conclusions for clinical practice. This review aims to describe and interpret recently published trials on multimodal treatment of resectable esophageal cancer.

Methods

Recent reports of randomized trials evaluating multimodal treatment of esophageal cancer are reviewed.

Results

Chemotherapy Followed by Resection versus Surgery Alone

Two large randomized controlled trials recruited esophageal cancer patients exclusively and compared the benefit of neoadjuvant chemotherapy with resection alone [2, 7]. While the US Intergroup Trial 113 [2] with 440 patients did not show a notable survival benefit, the larger MRC trial [7] found an absolute benefit of 9% in survival rate after 3 years (43 vs. 34%) and later a 6% benefit in the 5-year follow-up (23 vs. 17%). Both trials are characterized by a low rate of R-0 resection (Intergroup 113: 63 and 59%; MRC 60 and 53%). Complete resection rates in advanced esophageal cancer are reported to be distinctly higher after radiochemotherapy (POET 71%, CROSS 92%) [8, 9]. Complete response was a rare result of neoadjuvant chemotherapy with 4% (complete histopathological response) for the MRC trial and 7% for the Intergroup 113 trial (complete radiological response) [2, 7].

Interestingly, patients received only 2 cycles of Cis/FU in the MRC trial and 3 cycles in the Intergroup 113 trial. The scheduled cisplatin dose was 80 mg/m² in the MRC and 100 mg/m² in the Intergroup trial plus postoperative chemotherapy as facultative addition to the preoperative protocol. However, only 70% of the Intergroup 113 patients were treated per protocol while 90% received the complete protocol medication in the MRC trial. Obviously, the Intergroup 113 regime was more toxic, nullifying the putative positive effect of the higher protocol dose.

The 30-day mortality rate after surgery in both arms (10%) shows that the MRC trial might not be suitable for the present situation since postoperative hospital death rates in centers now are reported to be lower than 5%.

In addition to these two studies, two further multicenter trials applied perioperative chemotherapy for esophagogastric adenocarcinoma. The majority of patients suffered from gastric or esophagogastric junction tumors; the proportion of esophageal cancers was 15% in the MAGIC trial and 11% in the French ACCORD trial [4, 6]. Survival results were almost identical and showed a significant survival benefit in the perioperative treatment arms. Five-year survival rates were 36% (MAGIC) and 38% (ACCORD) in the treatment arm and 23% (MAGIC) and 24% (ACCORD) in the surgery-only group [4, 6]. Remarkably, only 50% (ACCORD) and 66% (MAGIC) were able to receive postoperative therapy, while almost all of the patients received the preoperative cycles [4, 6]. Keeping the negative results of adjuvant treatment studies in mind, this observation raises the question whether postoperative continuation of chemotherapy has any effect, especially in patients without any signs of response to the neoadjuvant treatment. It appears that postoperative chemotherapy should be given to patients with a clinical and/or pathohistological response to preoperative chemotherapy who are in good condition after surgery.

A further study conducted in Germany that included patients with AEG II, AEG III and stomach cancer showed similar results [5]. However, due to low accrual this study was closed prematurely, which may explain the marginal statistical significance of differences in overall survival.

In all, these randomized trials provide broad evidence that preoperative polychemotherapy does not elevate either morbidity or mortality. Neoadjuvant chemotherapy might be disadvantageous in nonresponders and
some argue that valuable time may be lost until surgery; however, progressive disease prevented only 2.7–5.8% of patients from undergoing surgery [5, 6]. Regarding survival, some groups have shown that nonresponders tend to have poorer survival than patients who underwent primary resection without neoadjuvant treatment [2, 3].

Radiochemotherapy Followed by Resection versus Resection Alone

Recently, the first large-scale randomized trial (CROSS trial) comparing neoadjuvant radiochemotherapy with surgery was published after earlier preliminary studies which included less than 120 patients [10, 11]. While hospital mortality was identical for both arms (4%), the R-0 resection rate and rate of free lymph nodes were impressively higher in the treatment group, and the survival benefit of neoadjuvant radiochemotherapy was significant [8]. The overall complete histopathological response rate was 29%, 43% for squamous cell cancers and 23% for adenocarcinoma. The survival benefit was larger with squamous cell cancers than with adenocarcinoma [8].

However, a meta-analysis [12] reported that pooling the data of numerous studies on neoadjuvant radiochemotherapy indicated an almost doubled surgical mortality rate after radiochemotherapy plus surgery compared with surgery alone (odds ratio: 1.78; 1.14–2.78; 6.6 vs. 3.8%). Although some groups recently were able to prevent increased hospital death after radiochemotherapy and surgery [8], the risk for death after this multimodal procedure obviously is elevated, reaching 10% or more in some studies [13, 14].

Neoadjuvant Radiochemotherapy versus Neoadjuvant Chemotherapy

Comparing neoadjuvant radiochemotherapy and neoadjuvant chemotherapy in uT3/uT4 adenocarcinomas of the esophagus and cardia, Stahl et al. [9] found favorable results after trimodal treatment: while the R-0 rate was similar in both groups, the rate of negative lymph nodes and complete histopathological response was clearly higher after radiochemotherapy followed by an absolute survival benefit of 19% after 3 years (chemotherapy: 28%; radiochemotherapy: 47%) [9]. But again, this benefit was won at the cost of elevated postoperative hospital mortality (chemotherapy: 3.8%; radiochemotherapy: 10.2%; n.s.) [9]. This trial also indicated a survival benefit with neoadjuvant radiochemotherapy for esophageal and esophagogastric junction adenocarcinoma, and may play a role in fit patients.

Neoadjuvant Radiochemotherapy plus Resection versus Definitive Radiochemotherapy

The fact of notable morbidity and mortality after surgery has fed the discussion on the omission of esophagectomy, especially in squamous cell cancer, and two randomized studies have focused on this question. In a German trial, T3/T4 squamous cell cancers were treated with induction chemotherapy followed by neoadjuvant radiochemotherapy and surgery or definitive radiochemotherapy without resection [14]. Local tumor control as well as overall survival was better in the surgery arm [14]. When only patients who responded to pretreatment were randomized, as has been done in France, the survival benefit of neoadjuvant radiochemotherapy plus esophagectomy over definitive radiochemotherapy alone vanished [13], though local tumor control remained better after surgery.

Randomized Predictive Marker Trial in Neoadjuvant Treatment of Esophageal Cancer

The first and as yet only randomized predictive marker trial for esophageal cancer was recently closed in Austria (PANCHO trial); the results are expected during 2014. In the pilot trial a very high correlation was found between p53 mutations in forceps biopsies and nonresponse to Cis/FU chemotherapy. This effect was followed by a remarkable impact on survival [unpubl. data].

Discussion

Several recent trials have shown the survival benefit of multimodal treatment on esophageal cancer. National and international guidelines already include preoperative treatment protocols and tumor boards have put this knowledge into clinical practice [1]. Still, there are some details on treatment of esophageal cancer that need to be worked out. In discussing published trials, their differences must be borne in mind with regard to histological tumor type, tumor localization, staging tests, and composition and timing of treatment modalities, as well as surgical technique. Furthermore, we have to be aware that pretreatment staging is only an estimate and limits our intention to administer a treatment tailored to the stage of the disease. N-staging, which is a strong predictor of survival, still presents an unsolved problem.

Is Surgery Dispensable in Complete Clinical Response?

Clinical response evaluation is much more difficult than the gold standard of response evaluation based on histopathological evaluation of tumor regression. Histo-
pathological evaluation is closely correlated with survival. There are indications that the accuracy of CT, endoscopic ultrasound and FDG-PET is too low to allow these clinical methods to be accepted for identification of complete response. At the moment, surgery plus histopathological evaluation is the only way to assess complete response. On its basis, definitive chemoradiation alone is currently recommended only for high-risk patients and those with potentially noncuratively resectable tumors, as well as for patients who refuse radical surgery [1].

For squamous cell cancer there is one randomized trial with selection of responders that has indicated surgery improves local tumor control but may not prolong survival significantly after preoperative chemoradiation when compared with definitive high-dose radiochemotherapy [13]. However, hospital mortality in the surgical arm was 9%, which demonstrates the elevated risk for triple modality treatment [13]. Therefore, definitive radiochemotherapy is an acceptable alternative to radiochemotherapy and esophagectomy in unfit patients [1].

**Which Patients Should Not Be Selected for Neoadjuvant (Radio)Chemotherapy?**

Several studies and a meta-analysis have indicated an increased postoperative risk after neoadjuvant radiochemotherapy and resection [12, 15]. Patients with limited capacity to tolerate complications should not be selected for a trimodal procedure. A pretherapeutic risk score has been developed to select patients for preoperative radiochemotherapy. Since preoperative chemotherapy does not elevate either morbidity or mortality, this procedure without radiation may be the alternative strategy in patients with advanced esophageal cancer and unfavorable comorbidities.

**Do Patients with cT2N0 Tumors Benefit from Multimodal Treatment or Is It Overtreatment?**

Primary resection (endoscopic resection for mucosal cancers, surgical resection for submucosal cancers) is recommended for node-negative early cancers without preoperative chemotherapy or radiotherapy since the prognosis is good after complete resection. However, the MRC, ACCORD and MAGIC trials also included a remarkable proportion of T1 and T2 tumors [4, 6, 7]. It is debatable whether multimodal treatment is justified for clinically staged T2N0 tumors. The data are not sufficient to give an evidence-based answer based on subgroup analysis. This seems to be more a question of accurate staging, as we know that lymphatic involvement is expected in up to 60% of patients with T2 staging. Even clinically staged N0 still bears a considerable risk of node involvement. Additionally, histopathological evaluation may also miss micrometastases, though micrometastatic node involvement has a prognostic impact. Accordingly, neoadjuvant chemotherapy or radiochemotherapy may also be recommended for the cT2N0 situation [1] in fit patients.

**How Can We Identify Responders?**

This is one of the most important questions. While neoadjuvant treatment improves survival in a cohort, it can potentially harm nonresponders. It is evident that nonresponders do not benefit from neoadjuvant therapy, but lose time to surgery and are exposed to treatment-induced toxicity. The pANCHO trial is expected to shed light on this topic.

In summary, treatment of esophageal cancer remains a highly challenging interdisciplinary task that should have a well-defined structure and standardized procedures. Every patient with an esophageal malignancy or a lesion suspicious for malignancy should be presented to an interdisciplinary tumor board [1].

**Disclosure Statement**

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**References**


