Is there any role for surgery in the multidisciplinary treatment of esophageal cancer?

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Due to the poor prognosis of patients after unimodal therapy like surgical resection or radiotherapy multidisciplinary treatment is regarded as standard of care in localized esophageal cancer. Within the last decade phase III trials investigating the curative potential of radiochemotherapy alone have challenged surgery to be an indispensible part of curative therapy. Nevertheless, surgical resection does play an important role in the multidisciplinary treatment. But its role is limited to subgroups of patients with a distinct clinical situation. Today it appears that particularly patients with adenocarcinomas of the lower esophagus and esophagogastric junction and those patients with squamous cell carcinomas not responding to induction chemo- or radiochemotherapy benefit from surgery. Patient selection according to their individual operative risk is most important to guide multidisciplinary therapy. Early molecular or diagnostic markers to predict response to chemo- or radiotherapy and also recurrence despite complete surgical resection are urgently needed.

Key words: chemoradiotherapy, esophageal cancer, multidisciplinary treatment

introduction

At least in western countries the majority of patients present with locally advanced tumors at diagnosis. In this situation long-term survival rates will not exceed 20% (intention-to-treat) even the in most experienced centers worldwide [1]. Therefore, multidisciplinary treatment instead of primary surgery is regarded as an international standard in localized esophageal cancer. In the USA combined chemoradiation without surgery has been preferred in clinical practice since the mid-1990s [2]. Recently, European trials also challenged the indispensible use of surgery within multimodal treatment concepts. So, we have to deal with the question of whether surgery still plays a role in the multidisciplinary treatment of esophageal cancer.

treatment of adenocarcinomas

According to the current UICC classification (7th edition) adenocarcinomas (ACs) of the esophagogastric junction are now defined as esophageal cancers [3]. This makes it somewhat more complicated to discuss treatment options in esophageal AC. Nevertheless, it can be concluded from the literature that curative therapy in localized tumors should include surgical resection. This is caused by the fact that prospective data on curative therapy without surgery are very limited in AC. This is true for trials investigating definitive chemoradiotherapy compared with radiotherapy alone, which included only 10% of patients with AC [4]. This is also true for studies comparing preoperative with definitive chemoradiotherapy [5, 6]. However, from the limited data we have, we can not conclude that AC may respond less well to radiotherapy or chemotherapy and therefore will be treated differently from squamous cell carcinomas (SCCs) at times [7].

In conclusion, there is a clear role for surgery in localized ACs of the esophagus and future studies have to address the question of which adjunctive therapy should be added to surgical resection in which clinical situation.

treatment of SCCs

From the RTOG trial we know that combined radiochemotherapy is superior to radiotherapy alone with regard to long-term survival in localized esophageal cancer [8]. This has been also proved by a meta-analysis [4] and the vast majority of patients treated within those phase III trials had SCCs. Beside that, numerous trials investigated the role of preoperative chemotherapy or radiochemotherapy (Table 1) in SCC [9–12]. Of note, most of these trials did not prove superiority of multimodal therapy compared with surgery alone, mostly due to the limited number of patients randomized into these studies. A couple of meta-analyses have been carried out and almost all of them proved multidisciplinary treatment to increase overall survival (Table 2) [13–15]. Particularly in those meta-analyses dealing with preoperative radiochemotherapy it appears that the advantage of combined treatment modality increases with the patient’s risk, e.g. with increasing tumor stage at diagnosis.

What can we conclude from these trials with regard to our question of the role of surgery in esophageal SCC? First, a relevant number of patients will die of surgery (10%–15% of those patients with SCC after preoperative radiochemotherapy); second, at least 40% of the patients will develop distant...
metastasis leading to death even after complete tumor resection and multimodal treatment; third, ~25% of those patients coming to surgery after preoperative radiochemotherapy reveal complete pathohistologic remission in the resected specimen, which makes it unlikely that they would benefit from surgery.

This prompted European groups to prospectively investigate the role of surgery in locally advanced SCC of the thoracic esophagus. The German Oesophageal Cancer Study Group [5] primarily randomized patients for preoperative radiochemotherapy (40 Gy) followed by surgical resection or definitive radiochemotherapy (at least 65 Gy) without surgery. All patients started with the same induction chemotherapy and received one course of chemotherapy concurrently with the first 8 days of radiation therapy. In this equivalence study 2-year overall survival was the primary endpoint and its difference <15% between treatment arms. The hypothesis was that optimized radiochemotherapy may offer equivalent survival with lower treatment-related mortality. At a median observation time of 6 years the overall survival at 2 years proved equivalent between the two treatment arms. The survival rate was 39.9% in the operative group and it reached 35.4% in the non-surgery group, respectively (for δ = −0.15; P = 0.007). Equivalence was also shown for median and 3-year survival and treatment arm was not predictive of survival in a Cox regression analysis. The overall treatment–related mortality was significantly inferior for patients with surgery (12.8% compared with 3.5%). On the other hand, freedom from local tumor progression was significantly improved by surgery [hazard ratio (HR) 2.1; 95% confidence interval (CI) (1.3–3.5); P = 0.003] and patients with surgery were less likely to die of esophageal cancer. Tumor response to induction chemotherapy proved to be an independent prognostic factor and responders had a very high probability of surviving 3 years (58% compared with 55%) regardless of the treatment group. Moreover, in the group of responders to induction chemotherapy there was no difference in local tumor control between treatment arms (HR 1.63 (95% CI 1.04–2.55); P = 0.03). This difference may be due to different definitions of tumor response in these two trials.

A French multicenter trial (FFCD 9102) [6] randomized patients who showed a radiographic response to induction radiochemotherapy to proceed either with radiochemotherapy (45 Gy) followed by surgery or with radiochemotherapy (66 Gy) without surgery. This trial also looked for equivalence between treatment groups and the difference in 2-year overall survival should be <10%. The survival difference was 6.2% in favour of the non-surgical group in the intention-to-treat analysis. Therefore, in this biologically preselected group of patients (treatment responders) the study was able to rule out that definitive radiochemotherapy may be inferior to radiochemotherapy plus surgery. This was in part due to a significantly increased treatment–related mortality in patients with surgery (9% compared with 1%). Unlike the German trial (with regard to responders) there were significantly more locoregional relapses after chemoradiation [HR 1.63 (95% CI 1.04–2.55); P = 0.03]. This difference may be due to different definitions of tumor response in these two trials.

A more recent publication evaluated those 192 patients of the French study group who were not randomized into the 9102 study because they did not show a tumor response to induction radiochemotherapy [16]. The overall survival of these non-responders was significantly inferior compared with the responders in the FFCD 9102 study (median survival times 11.5 compared with 18.9 months; P = 0.002). However, even in the group of non-responders 112 patients were operated on and 80 of them (71%) had complete tumour resection. The median survival of those non-responders undergoing salvage surgery was comparable to that of responders having surgery within the randomized trial (median survival times 17.3 compared with 17.7 months).

What can we conclude from these European studies in patients with locally advanced SCC? It appears that induction

### Table 1. Preoperative radiochemotherapy plus surgery versus surgery alone in SCC: phase III trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (n)</th>
<th>Patients with AC</th>
<th>R0 resection</th>
<th>PCR</th>
<th>MS (Mo)</th>
<th>OS (%/at years)</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF/40Gy+S</td>
<td>58</td>
<td>100</td>
<td>Not available</td>
<td>25</td>
<td>16</td>
<td>32/3</td>
<td>Walsh [9]</td>
</tr>
<tr>
<td>S</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6/3</td>
<td></td>
</tr>
<tr>
<td>CFV/45Gy+S</td>
<td>50</td>
<td>76</td>
<td>45</td>
<td>24</td>
<td>17</td>
<td>30/3</td>
<td>Urba [10]</td>
</tr>
<tr>
<td>S</td>
<td>50</td>
<td></td>
<td>45</td>
<td></td>
<td></td>
<td>16/3</td>
<td></td>
</tr>
<tr>
<td>CF/35Gy+S</td>
<td>128</td>
<td>63</td>
<td>80</td>
<td>9</td>
<td>22</td>
<td>Not available</td>
<td>Burmeister [11]</td>
</tr>
<tr>
<td>S</td>
<td>128</td>
<td></td>
<td>59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF/50Gy+S</td>
<td>30</td>
<td>75</td>
<td>Not available</td>
<td>40</td>
<td>54</td>
<td>39/5</td>
<td>Tepper [12]</td>
</tr>
<tr>
<td>S</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td>16/5</td>
<td></td>
</tr>
</tbody>
</table>

*Independently of histology.
C, cisplatin; F, 5-fluorouracil; V, vinblastin; PCR, pathohistologic complete remission; MS, median survival time; S, surgery.

### Table 2. Rate of postoperative mortality in patients with or without preoperative radiochemotherapy: data from meta-analyses

<table>
<thead>
<tr>
<th>Author</th>
<th>HR (with 95% CI) and long rank P value comparing operative mortality after preoperative versus primary surgery</th>
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</thead>
<tbody>
<tr>
<td>Urschel 2003</td>
<td>1.72 (0.96–3.07); P = 0.07</td>
</tr>
<tr>
<td>Fiorica 2004</td>
<td>2.10 (1.18–3.73); P = 0.01</td>
</tr>
<tr>
<td>Stuschke 2004</td>
<td>1.80 (1.10–2.90); P = 0.02</td>
</tr>
</tbody>
</table>
Chemo- or radiochemotherapy allows for selecting patients who will not have a survival benefit from additional surgery compared with dose-intensified radiochemotherapy (>65 Gy) alone. So, the role of surgery in this situation is limited to reducing the local progression rate by ~30% and the need for interventions against dysphagia by ~20%, respectively [6]. This has to be weighed against an increase in the early treatment-related death rate of 5%–10%. In contrast, there obviously is a role for surgery in those patients without tumour response to induction chemotherapy. Without surgery their prognosis is very poor (median survival time ~6 months, 2-year survival rate <10%) [5, 6]. If these patients are able to undergo early salvage surgery (after a limited dose of preoperative radiochemotherapy, e.g. <51 Gy) their prognosis seems to significantly improve although the postoperative mortality has to be considered. The question is how best to define response to induction therapy. Can we easily rely on esophagograms and dysphagia like the French group did or do we need more complicated scores including endoscopy and CT scans as were used in the German trial? Or should we use more modern diagnostic tools like positron emission tomography?

In conclusion, the role of surgery in SCC of the esophagus appears to be limited to a subgroup of operable patients having resectable intrathoracic carcinomas that show in vivo resistance to chemo- or radiochemotherapy.

**predictive markers for guidance of treatment**

These considerations lead us to the question of whether we have predictors to guide the treatment of localized esophageal cancer. Several groups defined scores for judging the risk of a patient dying after esophagectomy with or without preoperative therapy [17]. Patient selection proved an important factor in reducing postoperative mortality and therefore, these risk scores may currently be the most important tool for selecting patients for different multidisciplinary concepts.

What about molecular markers? Candidates for predicting response to radiochemotherapy may be genes and corresponding proteins regulating the cell cycle like p53, cyclin D1 and c-myc, or enzymes that may be associated with resistance to chemo- or radiotherapy. However, these potential markers have usually been investigated retrospectively so far, and consequently the results with regard to their predictive value are contradictory [18, 19].

FDG-PET scanning before surgery seems to be significantly correlated with pathologic tumor stage and outcome in patients with resectable SCC [20]. However, this method has not been established for predicting response or resistance to multidisciplinary treatment.

In conclusion, there are currently no predictive markers available to guide multidisciplinary treatment in localized esophageal cancer, particularly those of squamous cell histology. Surgical resection still plays an important role in the multidisciplinary treatment of esophageal cancer. But its role is limited to subgroups of patients with a distinct clinical situation. Today it appears that particularly patients with ACs of the lower esophagus and esophagogastric junction and those patients with SCCs not responding to induction chemo- or radiochemotherapy will benefit from surgery.

**disclosures**

The author has no conflict of interest to disclose.

**references**