Choosing the Best Treatment for Esophageal Cancer

Criteria for Selecting the Best Multimodal Therapy

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Abstract

The best multimodal therapy in esophageal cancer comprises neoadjuvant radiochemotherapy in patients with adenocarcinoma or squamous cell carcinoma whereas neoadjuvant chemotherapy is only appropriate for patients with adenocarcinoma. However, the 2-year survival benefit by this induction therapy compared to surgery alone is only 5–9 %. Targeted drugs seem to be promising in order to improve the response rate. The choice of the best multimodal therapy by response prediction seems only to be possible in patients during chemotherapy for adenocarcinoma, whereas during neoadjuvant radiochemotherapy a response prediction by FDG–PET is not possible. The principle item of multimodal therapy is still transthoracic en bloc esophagectomy which should be performed in high volume centers in order to guarantee stable and good results.

Contents

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1 Introduction

Multimodal therapy is a combination of different treatment modalities for one disease. In esophageal cancer therapy with curative intent, surgery is still the principle item whereas chemotherapy and/or radiotherapy are additional treatment modalities. If the best treatment for esophageal cancer should be chosen it is obvious that primarily the best surgery has to be applied. This is characterized by

- low perioperative morbidity and mortality,
- high rate of R0 resection,
- adequate lymphadenectomy,
- appropriate type of reconstruction with high quality of life and
- surgery performed in high volume centers.

Surgery after neoadjuvant treatment is difficult because of scar and adhesions in the dissection plains due to shrinkage of the primary tumor or destruction and fibrosis of the lymph nodes.

2 Postoperative Mortality

The latest metaanalysis by Sjöquist shows a range of postoperative mortality after neoadjuvant radiochemotherapy from 13 studies with 1,932 patients between 0 and 17 % compared to the control groups with surgery alone between 0 and 19 %. Postoperative mortality after induction chemotherapy based on the same metaanalysis of 10 studies with 2,062 patients was between 2 and 15 % in the intervention group compared to 0–10 % in the group with surgery alone (Sjöquist 2011). The comparison of the mortality rates between the intervention group and the control group in this metaanalysis shows no clear difference between both strategies. Our own data in 655 patients with transthoracic en bloc esophagectomy for cancer with gastric pull-up and high intrathoracic esophagogastrostomy show the results of Table 1.

During the performance of cis-Platin 5 FU-based chemotherapy severe (grade 3) or life threatening (grade 4) toxicities were observed in 31 % and preoperative mortality in 1–2 % of the treated patients (Urschel 2002; Malthaner and Fenlon 2003). Some metaanalysis about neoadjuvant radiochemotherapy, however, showed an elevated postoperative morbidity and mortality (Urschel 2003; Kaklamanos 2003; Malthaner 2004; Fiorica 2004; Grear 2005; Gebski 2007; Jin 2009). In these meta-analysis especially, an elevated rate of pulmonary complications and anastomotic insufficiency was reported and by this an increased mortality. In this context, the single dosage and also the total dosage of radiotherapy are of great importance. Postoperative mortality was no more significantly elevated if radiotherapy studies

Table 1 Own results of 655 patients with esophagectomy for cancer (radiochemotherapy (RTX/CTX)): 5-FU-Cisplatin

	Without RTX/CTX	With RTX/CTX
T category	pT1–pT3	cT3
n	286	362
morbidity	34 %	35 %
30-day mortality	2.7 %	2.2 %
R0-resection	94 %	94 %

with single dose of more than 2 Gy were excluded (Fiorica 2004). The total dosage of preoperative radiotherapy should be limited to 45 Gy as a higher dose can lead to an increased rate of complications and mortality (Semrau 2009). However, the latest published metaanalysis of Sjöquist did not show an elevated postoperative mortality after neoadjuvant radiochemotherapy (Sjöquist 2011). In our own group of 362 patients after neoadjuvant radiochemotherapy and esophagectomy, the postoperative mortality was also not elevated compared to surgery alone (Table 1).

The time interval between neoadjuvant therapy and surgery is also important. Mostly an interval of 4–6 weeks is used. In case of an earlier operation, disadvantages can develop because of the remaining edema or inflammation of the tissue or not completely established regression of the tumor. If the time interval between neoadjuvant therapy and surgery is too extended a new onset of cancer growth can develop and surgical dissection can be difficult by the fibrosis after radiation. Ruol showed in a retrospective analysis that an interval of up to 90 days after neoadjuvant therapy of squamous cell carcinoma of the thoracic esophagus does not lead to a prognostic disadvantage (Ruol 2010).

3 R0-Resection

Another important issue for defining best surgery is a high rate of R0 resection.

The rate of R0 resection in our patient group with neoadjuvant radiochemotherapy was 94 % which was not different to the patient group with surgery alone. (Table 1) Our results compare favorably with the literature which f. e. in the metaanalysis of Jin showed a R0-resection rate of only 77 % (Jin 2009).

4 Lymphadenectomy

The extent of lymphadenectomy has important consequences on prognosis. We could show in an analysis of several international centers of esophageal surgery in 2,166 patients without induction therapy and more than 5-year follow-up that the prognosis is correlating with the number of resected lymph nodes (Peyre 2008). This is not only true for patients with infiltrated lymph nodes but also for patients with N0 category. In our

own analysis of pN0 patients, the number of resected lymph nodes also had an effect on survival (Bollschweiler 2006). This is probably due to an effect on micrometastasis. The favorable effect of adequate lymphadenectomy is also demonstrated by the comparison of the less radical transhiatal esophagectomy versus radical transthoracic esophagectomy in adenocarcinoma of the esophagus. Omloo reported from the Dutch prospective randomized trial comparing both kinds of surgery a significant survival benefit for the group of patients with radical transthoracic esophagectomy (Omloo 2007). Therefore, best surgery in the frame of multimodal treatment should include an adequate abdominal and thoracic lymphadenectomy.

5 Multimodal Treatment

Our own data on patients with pT3 esophageal carcinoma and R0 resection without neoadjuvant treatment show a 5-year survival rate of 20 % which is similar to the results of the literature. As this outcome is not satisfying, it is agreed today that patients with cT3 or resectable cT4 esophageal cancer should receive neoadjuvant treatment. However, if the survival curves of patients with pT2 and also pT1 sm3 esophageal adenocarcinomas are considered, these are also not completely satisfying. The 5-year survival rate of patients with pT1 sm3 and pT2 were both 50 % (Hölscher et al. 2011). This is due to the high rate of lymph node metastasis which in pT1 sm3 carcinoma was already 56 %. Therefore, there is a current discussion on the indication for multimodal therapy. Considering the mentioned data, it could be appropriate to favor induction therapy also in patients with pT2 or even pT1 sm3 carcinoma.

The best type of surgery has been defined above. As for multimodal therapy also the best additional modalities should be applied. This means the question if the therapy should be performed in a neoadjuvant or adjuvant setting and if this modality should be radiotherapy, chemotherapy, or combined radiochemotherapy.

6 Adjuvant Therapy

Adjuvant treatment after R0 resection of esophageal carcinoma could not show a survival benefit in randomized studies for locally advanced esophageal cancer by radiotherapy alone, chemotherapy alone, or radiochemotherapy. The same is true for additive therapy after R1 or R2 resection. For these reasons, currently there is no indication for adjuvant or additive therapy after esophagectomy.

7 Neoadjuvant Radiotherapy

Neoadjuvant radiotherapy alone followed by esophagectomy in locally advanced esophageal cancer has been analyzed in six randomized trials (Fok 1993; Launois 1981; Gignoux 1987; Wang 1989; Nygard 1992; Arnott 1992). A clinical response on induction therapy was only found in one-third of the patients. Only in one of six

studies a significant survival benefit could be achieved. Two studies even showed an inferior survival of the patients after neoadjuvant radiotherapy. A metaanalysis of 1,147 patients of five randomized studies mostly with squamous cell carcinoma reported a non-significant survival benefit of only 4 % after 5 years (Arnott 1992). Because of these reasons neoadjuvant radiotherapy alone is not appropriate for advanced esophageal carcinoma.

8 Neoadjuvant Chemotherapy or Radiochemotherapy

To answer this question it is most appropriate to report the results of the latest metaanalysis of Sjöquist from 2011 (Sjöquist 2011). This analysis comprised ten randomized controlled trials with the comparison between neoadjuvant chemotherapy plus surgery versus surgery alone. This trial included 2,062 patients. Further 13 randomized controlled trials comparing neoadjuvant radiochemotherapy plus surgery versus surgery alone, with a total of 1,932 patients were analyzed. Concerning neoadjuvant chemotherapy the result of the metaanalysis is a 2-year overall-survival benefit of 5.1 % after induction therapy which is significant. The difference for patients with squamous cell carcinoma was not significant whereas the benefit for those with adenocarcinoma was significant. Concerning neoadjuvant radiochemotherapy plus surgery this group showed a significant 2-year overall-survival benefit of 8.7 % compared to surgery alone. The prognostic advantage was similar for patients with adenocarcinoma or squamous cell carcinoma.

Because of these results the choice of neoadjuvant treatment has to be differentiated between patients with squamous cell carcinoma or adenocarcinoma. In squamous cell carcinoma only radiochemotherapy is effective. In adenocarcinoma, neoadjuvant chemotherapy and also neoadjuvant radiochemotherapy are effective. There are no sufficiently large randomized trials with a direct comparison of both treatment modalities. Smaller studies like the one from Stahl and from Burmeister show a higher effectiveness of neoadjuvant radiochemotherapy compared to neoadjuvant chemotherapy in adenocarcinoma of the esophagus (Stahl 2009; Burmeister 2011). Based on the latest metaanalysis of Sjöquist no definitive advantage for neoadjuvant radiochemotherapy compared to chemotherapy is evident for adenocarcinoma. However, in patients with squamous cell carcinoma neoadjuvant radiochemotherapy should be performed as chemotherapy alone is not sufficiently effective.

Our own study showed that the histological type of esophageal cancer might affect the response to neoadjuvant radiochemotherapy and subsequent prognosis (Bollschweiler 2009). This study comprised 297 patients with cT3 or resectable cT4 esophageal cancer. A total of 154 had squamous cell carcinoma and 143 adenocarcinoma. The rate of radiochemotherapy was 65 %. All patients had transthoracic esophagectomy with a median number of resected lymph nodes of 27. The 30-day mortality rate was 3.2 % in patients with squamous cell carcinoma and 2.8 % in those with adenocarcinoma. The rate of response was defined by the percentage of residual vital tumor cells according to histology (Schneider 2008). Minor response was more than 10 % vital tumor cells and major response less than 10 % vital tumor

cells. The first interesting result was that in patients with squamous cell carcinoma the relation between minor and major response was 49–51 % whereas in adenocarcinoma this was 71–29 % ($p = 0{,}01$). This means that patients with adenocarcinoma had a less good response of only one-third compared to squamous cell carcinoma with about half of the patients. However, those patients with squamous cell carcinoma and major response had a 5-year survival rate of only 30 % compared to the patients with adenocarcinoma and major response of about 70 %.

The best results can be achieved in those patients with complete response. According to our own multicenter trial these patients with ypT0 N0 M0 R0 have a 5-year overall-survival rate of 55 % and a disease free survival rate of 70 % (Vallböhmer 2010).

9 Response Prediction

The survival benefit for patients after neoadjuvant therapy is only approved for patients with good response to induction therapy. Non-responder have not only no survival benefit but also an unnecessary investment of time and can suffer from side effects by treatment. In our own studies, we could show that lymph node status and histomorphologic tumor regression are very important prognostic factors after radiochemotherapy of esophageal carcinoma (Schneider et al. 2008; Bollschweiler 2010). Because of this background great efforts were started to predict the response to neoadjuvant therapy. Clinical examinations like endoscopy with biopsy, endosonography, and computed tomography have only a minor significance in response prediction after neoadjuvant therapy (Schneider 2008). A response prediction by FDG-PET two weeks after start of induction therapy seems to be possible after neoadjuvant chemotherapy of esophageal adenocarcinoma (Lordick 2007). In neoadjuvant radiochemotherapy, however, an early prediction of response during the induction therapy is not possible (Vallböhmer 2009; van Heijl 2011). Concerning response prediction by biomarkers from biopsy only retrospective results are currently available. Prospective studies are urgently needed.

10 Targeted Drugs in Multimodal Therapy

In order to select the best multimodal therapy targeted drugs have been applied. These drugs block specific tumor signal transduction pathways and have been analyzed in the treatment of adenocarcinomas of the esophagus (Bang 2010). In a prospective multicentric phase I/II study, it was shown that the monoclonal EGFR antibody Cetuximab which is added to the conventional neoadjuvant radiochemotherapy can affect a significant increase of histopathologic response (Ruhstaller 2011). In this study, the induction therapy was tolerated very well. However, another phase II study with addition of Cetuximab to neoadjuvant radiochemotherapy of locally advanced adenocarcinoma had to be stopped because of a high rate of side

effects (Gibson et al. 2010). Because of these controversial results targeted drugs currently should only be applied in prospective studies. The amplification of MET Proto-Oncogen defines a small aggressive subgroup of adenocarcinoma of the esophagus and the gastroesophageal junction with evidence for a good response on the MET inhibitor Crizotinib (Lennerz 2011). Therefore, targeted drugs seem to be promising in order to contribute to the selection of the best multimodal therapy.

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