· Advances in Medical Sciences · Vol. 54(2) · 2009 · pp 158-169 · DOI: 10.2478/v10039-009-0044-1

Surgery within multimodal therapy concepts for esophageal squamous cell carcinoma (ESCC): the MRI approach and review of the literature

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Received 18.08.2009
Accepted 16.10.2009
Advances in Medical Sciences
Vol. 54(2) · 2009 · pp 158-169
DOI: 10.2478/v10039-009-0044-1

ABSTRACT

Background: Radical esophagectomy with lymphadenectomy remains the only curative therapy for patients with resectable esophageal squamous cell cancer (ESCC), however, combined treatment modalities may improve survival. Based upon more than 1300 consecutive esophageal resections, we present our current multidisciplinary ESCC approach with analysis in the context of recently published RCTs.

Methods: Subject to tumor staging, patients with resectable ESCC receive either a neoadjuvant radiochemotherapy (uT3N+) or are referred to primary surgery (uT1/2N0). By Medline searches (1997-2009), all published RCTs containing multimodal ESCC therapy concepts were identified and a systematic review was generated.

Results: From July 2007 to June 2009, 62 patients with ESCC were treated in our department (40 multimodal treatment concept, 21 primary surgery, 1 definite radiochemotherapy). The R0 resection rate was 78%, in hospital mortality 4.8%. 60% of patients showed a good response to neoadjuvant treatment. 18-month follow-up data revealed absence of tumor recurrence in 7 patients (18%). Our approach is aligned to the current published literature including 12 studies in this review. In line with our institutional experience, neodjuvant radiochemotherapy tends to improve overall survival and increases the likelihood of R0 resection. However, postoperative morbidity and mortality rates are increased. Adjuvant treatment failed to demonstrate any improvement in prognosis. For palliation, concurrent radiochemotherapy is the treatment of choice.

Conclusion: The MRI approach can be aligned to the most recent published data. Surgical resection remains the principle treatment for patients with resectable ESCC. Although multimodal therapy concepts tend to improve survival rates, postoperative morbidity and mortality rates are increased.

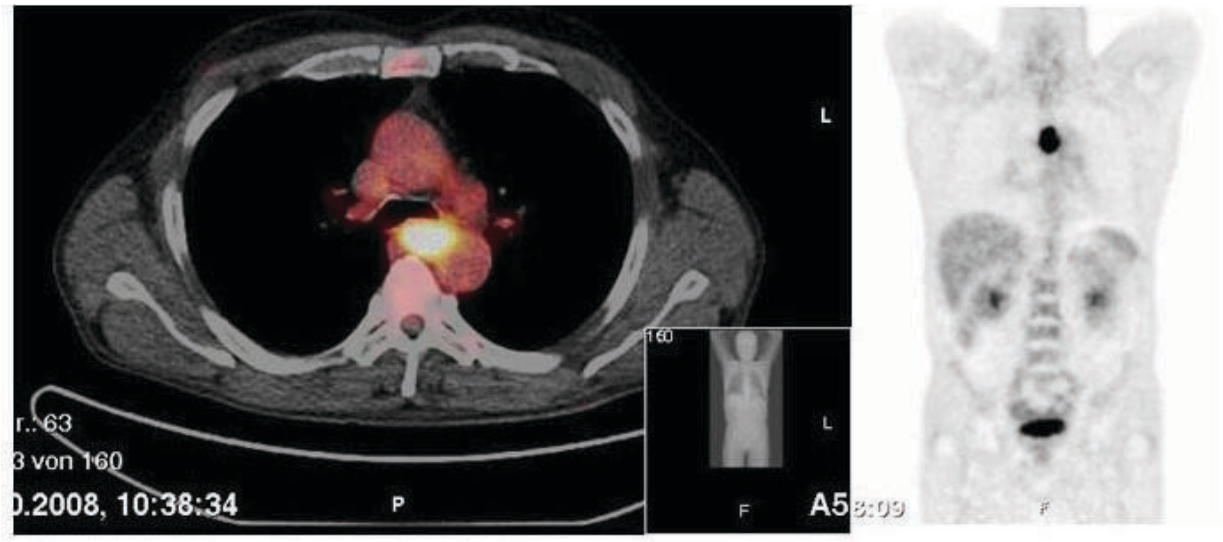
Key words: squamous cell cancer, esophagus, multimodal therapy, surgery, survival

INTRODUCTION

The prognosis of patients with esophageal squamous cell cancer (ESCC) is still not satisfying but has improved during the last years, with long-term survival rates between 5 and 20% [1]. The key prognostic factor remains curative resection with proper lymphadenectomy, however, considerable postoperative morbidity hampers this therapeutic approach [2]. Therefore, esophageal surgery has become the domain of specialized high-volume centers [3].

Multimodal treatment concepts have been investigated in esophageal cancer for years, however, the combination with the best outcome for ESCC has still to be defined [4]. The introduction of neoadjuvant radiochemotherapy followed by surgery yielded promising results for a subgroup of patients, particularly those who respond well to neoadjuvant therapy [5,6]. Two meta- analyses showed a significant advantage for the combined treatment regarding local tumor control and disease-free survival for patients with locally advanced resectable esophageal cancer [7,8]. However, there is an ongoing discussion on substantial increase in treatment related morbidity and mortality [9]. For patients with unresectable disease, combined radiochemotherapy is the treatment of choice [10]. The recent implication of response monitoring concepts

Figure 1. **FDG-PET ([18F]-deoxyglucose Positron emission tomography) response evaluation: increased metabolic uptake of primary tumor on day one of neoadjuvant treatment (beginn of neoadjuvant radiochemotherapy). Increased tracer uptake of the primary tumor site.**



by PET-CT may further tailor neoadjuvant therapy to patients who profit most depending on whether they respond or non-respond to multimodal therapy [11]. On the other hand patients who do not respond get earliest effective therapy without the risk of further tumor progression due to ineffective therapy.

Based upon the knowledge of over 1300 consecutive esophageal resections for cancer in our institution, with over 70% of patients receiving neoadjuvant treatment, the aim of this study is the presentation of the current MRI institutional approach for the treatment of patients with ESCC, as well as a review of the literature to summarize the results of recently published data in order to estimate the survival effect of different treatment modalities.

MATERIAL AND METHODS

The surgical department of the "Klinikum rechts der Isar, Technical University Munich, Germany (MRI)" is a high volume centre for esophageal surgery in Germany with 100-150 esophageal resections annually [12]. Each year, approximately 35 patients with ESCC are resected in curative intend. In the past years, the main focus of the surgical department was the treatment of patients with esophageal cancer and cancer of the esophageal-gastric junction [12].

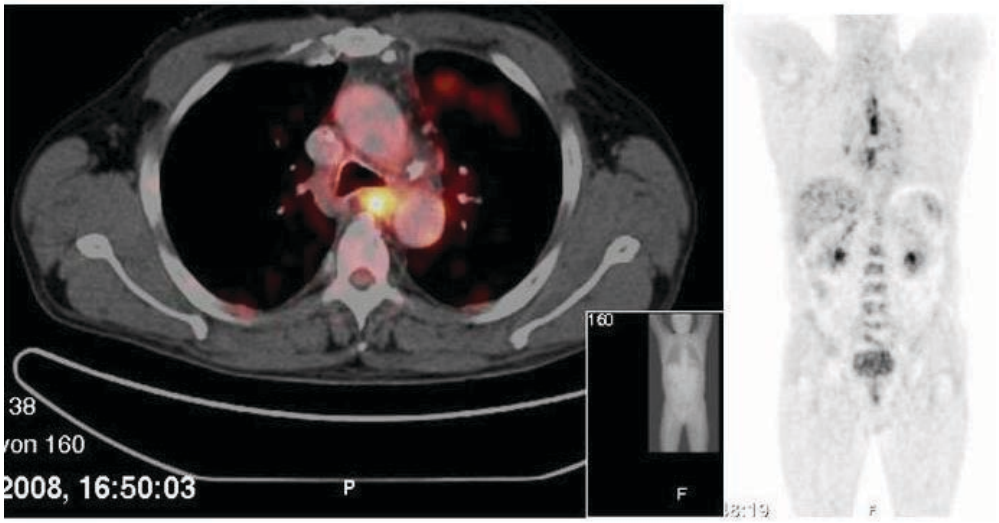
From July 2007 to June 2009, 62 patients with histological confirmed ESCC were operated in our department. Within a multidisciplinary multimodal treatment concept, patients with suspected ESCC receive a meticulous tumor staging including esophago-gastro-duodenoscopy, endoscopic ultrasound, bronchoscopy, spiral-CT of neck, thorax and abdomen and FDG-PET ([18F]-deoxyglucose Positron emission tomography). Furthermore, a functional diagnostic work-up including ECG, echocardiography, test of pulmonary function and laboratory sampling with tumor marker assessment (SCC) is performed. Each patient is discussed in our interdisciplinary cancer conference [13], consisting of specialists of gastroenterology, radiotherapy, oncology, radiology, pathology and surgery, for determination of the most promising individual treatment approach.

Based on these findings, patients with localized disease (uT3N+, absence of regional/distant organ metastasis) receive 2 cycles of neoadjuvant radiochemotherapy [14] within clinical trials (OE-7 trial) and early metabolic tumor response monitoring by FDG-PET after 14 days *(Fig. 1 and 2*). Radiation is given in daily doses of 1.8 Gy up to a total dose of 45 Gy (days 1-5, 8-12, 15-19, 22-26, 29-33). Concomitant chemotherapy consists of 5-FU (doses of 180-225 mg/m^2; days 1-5, 8-12, 15-19, 22-26, 29-33), Oxaliplatin (doses of 45-50 mg/m^2; day 1, 8, 22, 29) and the investigational drug Cetuximab (doses of 400/250 mg/m^2; day -15, -8, 1, 8, 15, 22, 29).

Four to six weeks after the end of neoadjuvant treatment, abdomino-thoracic resection with 2-field lymphadenectomy (paraesophageal, paracardial, left gastric and celiac lymph nodes) and gastric conduit in the posterior mediastinum is performed for tumors located in the middle and distal part of the esophagus. For tumors located in the upper part of the esophagus either a gastric conduit or colon interposition is performed. Cervical esophagus reconstruction after curative resection is done by a free jejunal graft interposition. Before surgery, a second risk analysis is performed to ensure the medical operability of each patient. Postoperatively, the patients are kept under surveillance in our specialized intensive-care unit for several days before admittance for further convalescence to the normal ward.

In case of early tumor stages (uT1/2N0), patients are referred directly to surgery, whereas patients with advanced

Figure 2. **FDG-PET ([^{18}F]-deoxyglucose Positron emission tomography) response evaluation: decreased metabolic uptake of primary tumor on day 14 of neoadjuvant treatment (after 2 weeks of neoadjuvant radiochemotherapy). Decreased tracer uptake of the primary tumor site.**



or disseminated disease (uT4 or M1) or severe co-morbidity, that do not qualify for a surgical approach, receive a definite radiochemotherapy consisting of 5-FU, Cisplatin and a radiation dose up to 54 Gy. No adjuvant chemotherapy is routinely applied.

Besides the histopathologic tumor assessment according to the UICC classification [15], the regression type after neoadjuvant treatment is determined using the classification of Becker et al. [16]. Patients with regression grade I, representing <10% vital tumor cells in the histologic specimen, are classified as responders to neoadjuvant treatment, where as patients with regression grade II (10-50% vital tumor cells) and grade III (>50% vital tumor cells) are classified as intermediate- and non-responders to neoadjuvant therapy.

The majority of patients is referred to our out-patient cancer therapy center for tumor follow-up quarterly in the first-, biannual in the second-, and yearly in the third postoperative year. Follow-up examination includes physical examination, laboratory samples including tumor marker SCC, abdomen sonography, chest x-ray, esophago-gastro-duodenoscopy and computed tomography of neck, thorax and abdomen according to the guidelines of the European Society for Medical Oncology for GI-tumors [17].

In the current manuscript, we compare our MRI institutional approach for treatment of patients with ESCC to the current evidence, conducting a comprehensive search of the published literature through the MEDLINE database (1997-2009) using the medical subject heading term esophageal squamous cell carcinoma. The number of studies was specified by using the terms chemotherapy, radiotherapy, radiochemotherapy and surgery. We reviewed all abstracts to obtain full text articles of potentially relevant studies addressing the issue of multimodal therapy concepts for ESCC.

The following inclusion criteria were used for the review: (1) published studies with full text articles, (2) pathologic diagnosis of invasive squamous cell cancer of the esophagus, (3) multimodal therapy concepts (neoadjuvant chemotherapy or radiochemotherapy, surgery and definite radiochemotherapy) and (4) patient survival as outcome measurement. To obtain a general overview of treatment modalities for ESCC, also non-randomized and retrospective studies were included. Twelve studies met the selection criteria and were used in our analysis. Characteristics of these studies are shown in *Tab. 1*.

Outcomes assessed in the review included overall survival, rate of complete (R0) resection, overall morbidity and mortality and overall cancer recurrence. Survival rates were obtained from the individual trials using the most reliable data available (raw data). Complete resection was defined as microscopically complete R0 resection. For morbidity and mortality, 30- day margins were used. Overall cancer recurrence was defined as any type (local, regional, distant), or combination of types of cancer recurrence.

RESULTS

The MRI approach to patients with ESCC

From July 2007 to June 2009, 387 patients with esophageal carcinoma and carcinoma of the esophago-gastric junction (AEG I/II) were discussed in our interdisciplinary cancer conference. While 190 of these patients were surgically treated in curative intend, the rest of the patients had either just begun neoadjuvant treatment, revealed disseminated disease by time of diagnosis or suffered from recurrent disease and were therefore referred to a palliative treatment concept. 62 of the 190 surgically treated patients (33%) had histologically confirmed ESCC, consisting of 44 man and 18 women.

Table 1.Characteristics of analyzed studies.

Author/ Year	Accrual period; Inclusion criteria; Trial design	Pat.	Interventions	R0 resect. rate [%]	Median survival [%]	Survival rate [%]					p	Comment
						1 yr.	2 yr.	3 yr.	4 yr.	5 yr.		
Ancona [19] 1997	1983-1991; ESCC,uT4N+ M0; prospective, non-randomized	163	Cisplatin/5-FU + + abdomino-thor. esophagectomy, gastric tube	33	23	75	46	33	29	29	n.s.	R0 Resect., Mortality postOP 11.8 vs. 8.3 %
		587	abdomino-thor. esophagectomy, gastric tube	6.6	22	68	44	30	27	24		
Ancona [20] 2001	1992-1997; ESCC, uT3N+ M0; RCT	47	Cisplatin/5-FU + + abdomino-thor. esophagectomy, gastric tube	37	25	75	55	44	42	34	n.s.	Overall morbidity 37.5% vs. 39% (n.s.), overall mortality 4.2%, 3- and 5 yr. surv. rates (R0 resect.) significant better with neo. CTx
		47	abdomino- thor. esophagectomy, gastric tube	35	24	75	55	41	38	22		
MRC [18] 2002	1992-1998; 31% ESCC (69% Adeno Ca); RCT	123 (400)	Cisplatin/5-FU + + abdomino-thor. esophagectomy, gastric tube	60	16.8	59	43	35	28	26	n.s.	Survival rates for overall collective, similar for ESCC
		124 (402)	abdomino- thor. esophagectomy, gastric tube	54	13.3	54	34	27	20	15		
Matsuyama [21] 2007	1999-2003, ESCC, uT3 N+, effect on lymph-node micro metastases; retrospect. non-random.	75	Cisplatin/Adriamycin/5-FU + + abdomino-thor. esophagectomy, gastric tube	--	--	78	70	--	--	--	n.s.	Survival rates accord. clin. response; neoadj. CTx can eradicate microme-tastases
		32	abdomino-thor. esophagectomy, gastric tube	--	--	78	30	--	--	--		
Bosset [22] 1997	1989-1995; ESCC, uT3N0; RCT	143	Cisplatin/37 Gy + abdomino-thor. esophagectomy, gastric tube	--	18.6	66	48	36	28	24	n.s.	Overall morbidity 33% vs. 26% (n.s.), Mortality + disease free survival sign. higher in comb. treatment group
		139	abdomino- thor. esophagectomy, gastric tube	--	18.6	66	44	36	28	24		
Heise [23] 2001	1986-1999, ESCC, uT3/4 Nx; prospect. non-random.	33	Cisplatin/5-FU (Etoposid/Leucovorin) + 40 Gy + + abdomino-thor. esophagectomy, gastric tube (21% transhiatal)	82	20.3	70	41	30	29	26	n.s.	Mortality 6% vs. 12% (n.s.); sign. longer 2-/5- year survival rate after combined treatment for pT3N1
		170	abdomino-thor. esophagectomy, gastric tube (34% transhiatal)	70	13.9	62	33	24	20	17		

Table 1.Characteristics of analyzed studies. (continued)

Bedenne [24] 2007	1993-2000; ESCC,uT3N+; RCT	129	Cisplatin/5-FU + 46 Gy + sur-gery (mostly abd.-thor. eso-phagectomy)	75	17.7	70	34	30	22	--	n.s.	6- month mortal-ity sign. higher for combined treatment (16 vs. 6%)
		130	Cisplatin/5-FU + add. 20 Gy (total 66 Gy)	--	19.3	68	40	29	20	--		
Hsu [25] 2008	1999-2004; ESCC, uT3N+; retrospective, non-random.	83	Cisplatin/5-FU or Cisplatin/ Paclitaxel + 36 Gy + abd.-thor. esophagectomy, gastric tube	96	30	--	--	47	--	--	n.s.	3-yr. LPFS sign. improved (71% vs. 39%) , 3-yr. DFS n.s.
		44	Cisplatin/5-FU or Cisplatin/ Pacli-taxel + 60 Gy	--	30	--	--	40	--	--		
Laterza [26] 1999	1987-1998; ESCC,uT3N+; single arm, uncontrolled, Phase II	111	Cisplatin/5-FU + + 30 Gy + + abd. thor. esophagec-tomy	61	14	--	32	--	--	18	n.s.	--
Adham [27] 2000	1987-1997; ESCC,uT3N+; single arm, prospective	55	Cisplatin/5- FU + + 36 Gy + + abd.thor. esophagectomy	84	14	61	--	39	--	33	n.s.	--
Stahl [29] 2005	1994-2002; ESCC,uT3/4 N+ M0; pros-pective, phase III	86	Cisplatin/5-FU/ Leucovorin/ Eto-posid + 40 Gy + abd.thor. esophagectomy	82	16.4	--	40	--	--	--	n.s.	2-year LPFS sign. higher in surgical group (64.3 vs. 40.7%)
		86	Cisplatin/5-FU/ Leucovorin/ Etoposid + 65 Gy	--	14.9	--	35	--	--	--		
Murakami [28] 2007	1999-2001; ESCC,uT3N+; retrospective	385	Cisplatin/5-FU + 60 Gy	--	--	--	--	--	--	--	--	Treatment of choice for T1carcinoma

The mean age was 66 ± 9.0 years. In 25 patients, the tumor was located above the tracheal bifurcation, in 15 patients ad bifurcationem and in 22 patients beneath the tracheal bifurcation. By endosonography and computed tomography, five patients were staged T1N0, two patients T1N1, 7 patients T2N0 and three patients T2N1. The majority of patients (n=37) had localized ESCC staged T3N1. Six patients suffered from distant metastases by time of diagnosis and one patient was staged T4N1M1. Due to an endoscopic tumor perforation, one patient did not receive a further tumor staging. In none of the patients, a tumor infiltration of the larynx or tracheo-bronchial system was detectable by panendoscopy and bronchoscopy.

After completion of tumor assessment and discussion in our interdisciplinary cancer conference, 2 patients received neoadjuvant chemotherapy (FLOT-scheme), whereas 38 patients received standard neoadjuvant radiochemotherapy and one patient definite radiochemotherapy. 21 patients were assigned for primary surgical resection.

In five patients, dose reduction of the neoadjuvant chemotherapy regime was necessary due to haematologic toxicity, however, no treatment related severe morbidity or death was observed during this course of treatment. In the multimodal treatment group (n=40), surgery was performed 3-4 weeks after the end of neoadjuvant therapy.

55 of 62 patients were resected in curative intend (88.7%). In 35 patients, resection of the esophagus and proximal stomach was performed by a right thoracic and abdominal approach with 2-field lymphadenectomy (Ivor –Lewis procedure) and primary reconstruction, where as 20 patients received a total thoracic esophagectomy with reconstruction in a second step. Seven patients (11.3%) with disseminated disease, which revealed during restaging or intraoperatively, received palliative procedures such as explorative thoracotomy (n=2), explorative laparotomy (n=4) and explorative laparoscopy (n=1).

For reconstruction, a gastric conduit with intrathoracic stapled anastomosis was carried out in 45 patients, where as only three patients received a colon interposition. In the group of patients with total esophagectomy (n=20), 13 patients were reconstructed until time of writing, with 12 patients receiving

a gastric conduit and one patient a colon interposition. The mean operation time was 4.3 ± 2.1 hours.

Complete tumor resection (R0 resection) was possible in 48 of 62 patients (78%). Excluding patients with explorative/palliative procedures (n=7), in which no tumor resection was performed, the R0 resection rate of the remaining 55 in curative intend resected patients increased to 87%. The R0 resection rate in the group of patients within the multimodal treatment concept was slightly lower compared to surgery alone (78% vs. 81%), however, in the surgery only group most patients had early tumor stages (uT1/2N0) and smaller tumor masses. Postoperative surgical and medical morbidity was in an average range, with 60% of the patients developing at least one complication, which was mainly pulmonary infection and cardiac arrhythmia. Morbidity rates of patients within the multimodal treatment concept were higher compared to surgery alone (63% vs. 52%), however, the difference was not statistically significant. Mean hospital stay was 28.5 days, in hospital mortality 4.8% (n=3: two patients with primary surgery, one patient with neoadjuvant therapy).

Pathohistological data were available from all resected patients (n=55). The mean number of examined lymph nodes was 13 (range 2 to 30 lymph nodes). No viable tumor was present in 17 specimens (31%), where as in 21 specimens (38%) cancer was confined to the esophageal wall with tumor free lymph nodes. In 17 specimens (31%), the tumor showed lymph node involvement.

Regression analysis revealed a good tumor response to neoadjuvant treatment in 22 patients (60%; regression grade 1: <10% residual tumor cells), 9 patients had a median response (20%; regression grade 2: 10-50 % residual tumor cells) and 7 patients were classified as non-responders (19%; regression grade 3: >50% residual tumor cells).

Follow-up data was assessed in 42 of 62 patients (71%), three patients had died during hospital stay already. At the time of writing, 8 patients had been seen for 3-month follow up, 5 patients for 6-month follow-up, 10 for 9-month follow-up, 9 for 12-month follow-up and 7 for 18-month follow-up in our cancer therapy centre. The remaining 20 patients were either seen for follow-up by their GP (n=13), were operated less than 3 months ago by the time of writing (n=4) or had died before 3-month follow-up (n=3). Six patients (15%) had developed recurrent cancer 12 months after surgery (local recurrence (n=1), distant recurrence (n=3), local + distant recurrence (n=1)). Although not statistically significant, patients with good response to neoadjuvant treatment (regression grade 1 and 2) were less likely to develop cancer recurrence compared to non-responders to neoadjuvant treatment (40 vs. 60%). 7 patients (18%) had no signs of tumor recurrence 18-month after surgery, five of them were treated within the multimodal treatment concept.

Review of the literature

The review of the literature revealed twelve trials restricted to ESCC only, with exception of the MRC trial that also included patients with esophageal adenocarcinoma (n=555) [18]. Overall data of 3347 patients were analyzed including 2587 men and 542 women, in two trials no gender data were available. The median patient age was 59 years. We identified four trials with 1753 patients that compared neoadjuvant chemotherapy followed by surgery with surgery alone [18-21], two studies with 485 patients comparing neoadjuvant radiochemotherapy followed by surgery with surgery alone [22,23] and two studies with 386 patients that compared neoadjuvant radiochemotherapy followed by surgery with definite radiochemotherapy [24,25]. In two trials, the outcome after neoadjuvant radiochemotherapy followed by surgery (111 patients [26], 55 patients [27]) was evaluated. In one study respectively, the outcome after definite radiochemotherapy (385 patients [28]) and neoadjuvant chemotherapy followed by radiochemotherapy and surgery compared to neoadjuvant chemotherapy followed by radiochemotherapy alone (172 patients [29]) was assessed.

Neoadjuvant chemotherapy followed by surgery versus surgery alone

Four trials of neoadjuvant chemotherapy followed by surgery compared with surgery alone are presented in *Tab. 1*. The chemotherapy regime consisted of 2 cycles cisplatin/5-FU [18-20] or the combination of cisplatin/adriamycin and 5-FU [24] administered 3-4 weeks prior to surgery. In one trial, the reference group of patients treated with surgery alone was retrospectively selected using the same inclusion criteria as for the treatment group [19], one study assessed the data for both treatment arms retrospectively [21]. In contrast, there are two controlled clinical trials where patients were randomly assigned to either treatment arm [18,20]. Median survival after neoadjuvant chemotherapy was identical with median survival after primary surgery. Noteworthy, there was a marked difference of median survival between different trials but not different treatment modalities. Statistical analysis did not result in any significant differences with regard to one year survival after inclusion of preoperative chemotherapy followed by surgery versus surgery alone within a multidisciplinary treatment concept.

Until December 2005, 3 meta-analyses were published comparing neoadjuvant chemotherapy and surgery with surgery alone for patients with esophageal carcinoma. However, data are not limited to patients with ESCC.

Urschel et al. [30] found a lower rate of esophageal resection but a higher rate of complete R0 resection in the combined treatment group (Odds ratio 0.71, p=0.001). However, a survival benefit could not be demonstrated (3 year survival: odds ratio 0.77, p=0.48) for the neoadjuvant chemotherapy and surgery group (11 RCTs, n=1976 patients).

In 1996, Bhansali et al. [31] carried out a meta-analysis to assess the effect of chemotherapy on survival in patients

with esophageal cancer. In total, 3250 patients were analyzed. Again, no significant survival benefit for the combined treatment modality was noted (12 RCTs).

Only the meta-analysis of Malthaner et al. [32]) revealed survival advantages for patients treated with neoadjuvant chemotherapy plus surgery at three, four and five years, which reached significance only at 5 years compared to surgery alone (p=0.02). However, in contrast to other studies, the overall rate of resections and the rate of complete R0 resections did not differ between the combined treatment and surgery alone group (11 RCTs, n=2051 patients).

Neoadjuvant radiochemotherapy followed by surgery versus surgery alone

Two trials of neoadjuvant radiochemotherapy followed by surgery compared with surgery alone are presented in *Tab. 1* [22,23]. In the study by Bosset et al. [22], neoadjuvant therapy consisted of two cycles chemotherapy with Cisplatin/5-FU switched to three cycles of Cisplatin/Leucovorin/ Etoposid/5-FU and radiotherapy with a total dose of 37 Gy, where as in the study by Heise et al. [23] neoadjuvant chemotherapy consisted of two cycles Cisplatin only and radiotherapy with a total dose of 40 Gy. Surgery was performed 3-4 weeks after the end of neoadjuvant treatment. Addition of radiochemotherapy followed by surgery did not improve survival when compared to surgery alone.

The benefit of neoadjuvant radiochemotherapy for esophageal cancer has been extensively studied. Until December 2005 three meta-analyses were published, however, data are not limited to ESCC as patients with adenocarcinoma of the esophagus were also included.

Urschel et al. [8] reported an improved 3-year survival (Odds ratio 0.66, p=0.016) and reduced loco-regional cancer recurrence (Odds ratio 0.38, p=0.0002) for patients treated with neoadjuvant radiochemotherapy and surgery compared with surgery alone, associated with a lower rate of esophageal resection, but a higher rate of complete (R0) resection (Odds ratio 0.53, p=0.007). There was a non-significant trend toward increased treatment mortality (Odds ratio 1.63, p=0.053) with neoadjuvant radiochemotherapy (9 RCTs, n=1116 patients).

Fiorica et al. [33] stated, that radiochemotherapy followed by surgery significantly reduced three year mortality compared with surgery alone (Odds ratio 0.53, p=0.03), however, postoperative mortality was significantly increased by neoadjuvant treatment (Odds ratio 2.1, p=0.01; 6 RCTs, n=764 patients).

This positive effect was not longer present in the study of Greer et al. [34] who reported a small, non-statistically significant trend towards an improved long-term survival for patients treated with neoadjuvant radiochemotherapy and surgery (Odds ratio 0.86, p=0.07; 6 RCTs, n=738 patients).

Neoadjuvant radiochemotherapy followed by surgery versus definite radiochemotherapy

Two trials of neoadjuvant radiochemotherapy followed by surgery versus definite radiochemotherapy are presented in *Tab. 1*. In the study by Bedenne et al. [24], the neoadjuvant regimen consisted of two cycles chemotherapy before and three cycles chemotherapy after randomization with Cisplatin/5-FU and concurrent radiotherapy with 46 Gy (and additionally 20 Gy) to a total of 66 Gy. The median survival was 17.7 months after neoadjuvant therapy followed by surgery and 19.3 months after neoadjuvant therapy followed definite radiochemotherapy. However, this trial included only responders to neoadjuvant therapy for unknown reasons. Two-year local control rate was 66.4% in the surgical arm and 57.0% in the radiochemotherapy arm. The need for stents was lower in the surgery arm but the 3-month mortality rate was higher upon surgery (9.3% vs. 0.8%).

In the study by Hsu et al. [25] the neoadjuvant regimen consisted of either cisplatin/5-FU or cisplatin/paclitaxel and concurrent radiotherapy with 36 Gy (and additionally 24 Gy) to a total of 60 Gy. Again, no statistically significant difference of three year survival was detected between the two groups (47% vs. 40%).

In two single arm studies published in 1999 by Laterza et al. (26) and in 2000 by Adham et al. [27], 166 patients with ESCC treated with neoadjuvant radiochemotherapy (cisplatin/5-Fu + 30/36 Gy) followed by surgery were analyzed. The morbidity rate associated with neoadjuvant treatment ranged between 37% and 54.5%, the postoperative mortality rate was 10.3% and 7.3%. Complete (R0) resection was achieved in 61.2% and 83.6% of cases. The 5- year survival rates were 36.5% and 33%, good responders to neoadjuvant treatment (downstaging) showed 5- year survival rates of 34.9% and 53% compared to non-responders (10.7% and 0%). In the report by Adam et al. [27], the overall survival rates were significantly higher in the responder group (1-,3-,5-years: 68%, 54% and 48% compared to the non-responder group: 32%/7.6%/none).

Two recently published trials from Germany [29] and Japan [28] evaluated the outcome of ESCC by adding respectively excluding surgery to/from the multimodal therapy. In the randomized controlled trial by Stahl et al. [29], 172 eligible patients were equally randomized to either induction chemotherapy (three courses cisplatin, 5-FU, leucovorin, etoposid) followed by radiochemotherapy (cisplatin, etoposid, 40 Gy) followed by surgery, or the same induction chemotherapy followed by definite radiochemotherapy (at least 65 Gy) without surgery. The postoperative morbidity rate reached 70% with a mortality rate of 12.8% in the surgical group compared to 3.5% in the radiochemotherapy group. Complete (R0) resection was achieved in 82% of patients. Median survival was 16.4 months in the surgical group and 14.9 months in the radiochemotherapy group. There was a strong tendency in improved 3-year survival in the surgical group (31.3% vs. 24.4%) but this finding was not statistical significant. In contrast, freedom from local progression (LPFS)

was significantly better in the surgery group (64.3% vs. 40.7%) than in the radiochemotherapy group. Clinical tumor response, once again, revealed to be a single independent prognostic factor for overall survival.

In the multicenter trial from Japan published by Murakami et al. in 2007 [28], 385 patients with ESCC receiving definite radiochemotherapy (Cisplatin, 5-FU, 60 Gy) were retrospectively analyzed. Compared to former studies, the utilization of radiochemotherapy had remarkably increased (61% vs. 35% in 1997), however, it was significantly less in T1 cases. For this tumor entity, radiotherapy seems to be the treatment of choice according to the study data.

In 2005, Arnott et al. [35] published a meta-analysis to assess the potential benefit from adding radiotherapy prior to surgery (5 RCTs, n=1147 patients) compared to patients treated with surgery alone. No concomitant chemotherapy was administered. For patients with ESCC, a tendency of survival benefit of 3% at 2 years and 4% at 5 years was noted, although, this result was statistically not significant (p=0.062).

The role of adjuvant therapy in treatment of ESCC

The role of adjuvant therapy of ESCC is addressed in a number of clinical trials [36-40]. However, as most of these trials included both adenocarcinoma and squamous cell cancer, detailed data for ESCC is difficult to obtain. Zhang et al. [41] conducted a meta-analysis comprising a total of 1000 patients with esophageal cancer (ESCC and Adenocarcinoma) in 2008. The results indicated that adjuvant chemotherapy did not significantly improve survival. Only for patients with N+ category, a positive trend towards better survival was found but did not reach significance (OR 0.76, CI 0.538-1.083).

DISCUSSION

During the last two decades diagnostic as well as therapeutic approaches for patients with esophageal squamous cell carcinoma have changed fundamentally [42]. The introduction of more accurate staging methods allows selection of those patients who are optimal candidates for surgery and who may profit most from interdisciplinary therapy. With the concept of metabolic tumor response monitoring during neoadjuvant therapy, tailoring of treatment can be achieved to patients who benefit most without losing time until definitive therapy. The sobering reality of long term survival rates still below 20% underline the obvious need for multidisciplinary treatment approaches, which were addressed in a number of recent clinical trials [43-46].

Surgical resection with radical esophagectomy and lymphadenectomy is currently the only well established curative treatment modality for patients with non metastatic resectable ESCC (cT1-3 N0-1 M0) if the patient is fit to undergo major surgery [47], as a complete (R0) resection of the esophagus and regional lymph nodes are essential for detailed pathological staging and improved prognosis with regard to long-term survival [48]. Surgery alone results in overall 5-years survival rates of 20-30% [12,49]. In the case of a R0 resection, 5-year survival rates can be as high as 42% [49]. Whether laparoscopic and/or thoracoscopic esophagectomy will be able to improve survival cannot be determined currently, as long term follow up data are rare. Short term results however, are promising [50]. Surgical outcome may be better in the case of extended lymphadenectomy in patients with ESCC, however, there is no conclusive evidence so far. As lymph node involvement in patients with ESCC impacts not only additive/adjuvant treatment plans but also prognosis, a preferably high number of lymph nodes should be dissected. The Ivor-Lewis procedure seems superior compared to the transhiatal approach [51]. The extend of lymphadenectomy for cancer of the thoracic esophagus has been classified by the Consensus Conference of the International Society for Diseases of the Esophagus (ISDE) as a standard, extended, total or 3-field lymphadenectomy [52]. In our institution and may other centers in the western world, the Ivor- Lewis approach with a 2-field lymphadenectomy (extended mediastinal lymphadenectomy and lymph node dissection of the upper abdominal compartment) is the most frequently performed procedure [12], whereas in Japan, 3-field lymphadenectomy is frequently performed [53]. Importantly 3-field lymphadenectomy achieves higher rate of R0 resections, which may also translate in better oncological outcome [54-56].

For reconstruction after esophagectomy a gastric conduit may be the primary choice [57]. Alternatively reconstruction using the colon can be performed as well. No difference is seen between hand suture vs. stapler anastomosis even so stapled technique may result in slightly more strictures [57-59]. Long term patency is likely improved with colon interposition when compared to gastric conduits. The later may have the advantage of better vascularization and less anastomotic leakages with equivalent late foregut function and quality of life for both conduits [60,61]. In case a complete (R0) resection is accomplished, the posterial mediastinal route may lead to fewer postoperative complications.

The high number of noncurative resections with positive margins requires preoperative therapy to increase the likelihood of curative resection [62]. Traditionally patients with solid tumors undergo surgical tumor removal followed by adjuvant chemotherapy depending upon final histology. For patients with ESCC this approach is not as attractive, since severe preexistent medical co-morbidity often precludes adjuvant therapy [63]. The value of adjuvant therapy in ESCC was tested in several trials [36-40] but there was no evidence that adjuvant therapy improves prognosis or quality of life for these patients. The concept of preoperative therapy was analyzed in several randomized controlled trials and meta-analyses. Clearly, most of these trails were underpowered to show a benefit for the individual hypothesis tested.

Whether preoperative chemotherapy improves survival or not is controversial. The meta-analysis by Urschel et al.

[30], did not support any survival benefit, whereas an older Cochrane review reported an improvement in 5-year survival after neoadjuvant chemotherapy [32]. No survival benefit was detectable upon neoadjuvant radiotherapy [35]. The value of preoperative radiochemotherapy was studied in 9 randomized trials including. Two meta-analyses reported improved 3-year survival upon preoperative radiochemotherapy [8,33].

Despite these promising developments, it is noteworthy that neoadjuvant therapy increased the risk of surgery and surgical morbidity. In two trials preoperative radiochemotherapy was associated with an increase in postoperative mortality rates [22,23]. It is therefore still debatable, whether the small survival benefit outweighs the higher mortality caused by such a treatment [30,64].

For definitive radiochemotherapy Bedenne et al. [24] reported similar survival after neoadjuvant therapy followed by surgery vs. definite radiochemotherapy. However, this trial included only responders to neoadjuvant therapy for unknown reasons. Another controlled clinical trial by Stahl et al. [29] also reported comparable median and 3-years survival rates for surgery and definite radiochemotherapy. However, although these studies were carefully planned and conducted, the trial by Bedenne lacked to demonstrate the results of non-responders and the trial by Stahl, most likely, did not include enough patients to demonstrate a survival benefit for surgery. Therefore, data concerning outcome and overall survival of definite radio(chemo)therapy for resectable ESCC patients are still preliminary. For palliation in turn (cT4, non operable patient, high co-morbidity), concurrent radiochemotherapy might be the treatment of choice [10]. However, this concept achieves local tumor control in terms of dysphagia rather than benefiting survival time.

In summary, surgical resection is presently the treatment of choice for patients with resectable ESCC if they are fit to undergo resection. Although multimodal therapy concepts tend to improve survival rates by tumor downstaging, especially for patients with complete (R0) resection [20], postoperative morbidity and mortality rates are still higher compared to surgery alone [22]. Patients surviving for 3 years or longer are less likely to develop tumor recurrence after neoadjuvant radiochemotherapy [65]. Future trials should continue to assess multimodal treatment concepts for this patient population to investigate dose escalation of radiochemotherapy and thereby reducing the risk of postoperative morbidity and mortality. In addition, the impact of neoadjuvant radiochemotherapy on tumor response and complete (R0) resection rates should be further investigated [6], as complete histopathological response is discussed as an independent positive prognostic factor for ESCC [11].

ACKNOWLEDGEMENTS

The authors indicate no potential conflicts of interest.

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