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Multimodal Treatment of Locally Advanced Esophageal Adenocarcinoma: Which Regimen Should We Choose? Outcome Analysis of Perioperative Chemotherapy Versus Neoadjuvant Chemoradiation in 105 Patients

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Background: The study was done to compare treatment and long-term outcomes of neoadjuvant chemoradiation (neoCRT) and perioperative chemotherapy (periCTX) in patients with surgically treated esophageal adenocarcinoma.
Methods: An analysis of 105 patients with esophageal adenocarcinoma undergoing neoCRT (n = 58) or periCTX (n = 47) and esophagectomy between 2000 and 2012 was carried out.
Results: The overall median survival was 5.97 years. Postoperative morbidity and in-hospital mortality occurred in 74%/7% of the patients the neoCRT group and in 53%/0% of the patients in the periCTX group ($P = 0.03/P = 0.08$). Total or subtotal histological tumor response after neoadjuvant treatment and esophagectomy was found in 59% after neoCRT and 30% after periCTX ($P < 0.01$). Three- and five-year survival rates were 52%/45% for neoCRT and 68%/63% for periCTX ($P = 0.05$). PeriCTX was identified as an independent predictor of survival (RR2.6; 95% CI 1.3–5.1; $P < 0.01$).
Conclusion: A higher rate of histologic response to neoCRT compared to histologic response following the preoperative cycles of periCTX does not translate to a benefit in overall survival. PeriCTX offers a decreased incidence of treatment-related morbidity and mortality and at least equal results in terms of survival compared to neoCRT in patients with locally advanced esophageal adenocarcinoma.
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KEY WORDS: **esophageal cancer; adenocarcinoma; esophagectomy; survival; chemotherapy; chemoradiation**

INTRODUCTION

Esophageal adenocarcinomas are one of the most rapidly increasing tumor entities in the western world [1,2]. Although surgical resection remains the standard for the curative treatment of esophageal adenocarcinoma, different strategies have been developed to improve survival and overall outcome especially for patients with locally advanced tumor stages. The goal of these surgical, chemotherapeutic and radiotherapeutic strategies is not only to increase resectability but also to increase local and systemic tumor control.

Recently, a large randomized-controlled trial (RCT) was able to demonstrate significantly improved survival for neoadjuvant chemoradiation (neoCRT) in patients with adenocarcinoma of the esophagus [3]. Beyond that different protocols of perioperative chemotherapy (periCTX) have been introduced and applied in the recent years as an alternative to neoCRT [4,5]. However, proofs of a clear survival benefit for patients with specifically adenocarcinoma of the esophagus are missing as all successful RCT on periCTX are based on pooled patient collectives including esophageal and gastric adenocarcinoma [4,6]. Therefore, clear evidence for the efficiency of periCTX in terms of survival benefit and improved outcomes for adenocarcinoma of the esophagus is lacking.

For this reason, we conducted this study comparing current protocols of neoCRT and periCTX focused on response to neoadjuvant treatment, treatment outcomes and long-term oncological outcome in patients with locally advanced esophageal adenocarcinoma undergoing neoCRT or periCTX plus esophagectomy.

PATIENTS AND METHODS

This study reports the outcome of 105 consecutive patients with esophageal adenocarcinoma who were treated either with neoCRT or with periCTX and subsequent esophagectomy between January 2000 and April 2012 at our institution. Only patients with histologically proven adenocarcinoma located at the esophagus were included in the study. Informed consent was obtained from all patients before their inclusion in the cancer registry. The study was approved by the Medical Ethics Committee of the University of Freiburg.

Pretherapeutic Work-Up

Pretherapeutic diagnostics included endoscopy with biopsies and computerized tomography (CT) of the thorax and abdomen in all patients. Endoscopic ultrasound (EUS) was used routinely for staging of esophageal tumors if technically possible. In general, lymph nodes were

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preoperatively classified as malignant if >1 cm by CT or EUS. Since 2005, all patients diagnosed with esophageal adenocarcinoma are discussed in the interdisciplinary Tumor Board of our comprehensive cancer center before definitive treatment. Indication for multimodal therapy either by neoCRT or periCTX was given according to our institutional guidelines if the primary tumor invasion of the esophagus exceeded the muscularis propria (T3 and T4 stages) and/or pretherapeutic CT or EUS detected local lymph node involvement (N+ stage) and patients had no other medical contraindication to neoCRT or periCTX. Thus, according to the local guidelines of our comprehensive cancer center, cT3/T4 and/or cN+ esophageal adenocarcinomas with distal extent of tumor at or below the Z-line were treated with periCTX, and those with distal extent of tumor cephalad to the Z-line were treated with neoCRT.

Neoadjuvant Chemoradiation (neoCRT)

NeoCRT was performed with simultaneous radiotherapy (36 Gy; 1.8 Gy/day; days 1–5, weeks 1–4) and chemotherapy with 5-flurouracil (500 mg/m^2 body surface; days 1–5, weeks 1–4) and Cisplatin (20 mg/m^2 body surface; days 1–5, weeks 1 and 4). Beginning in 2011, neoCRT was performed with simultaneous radiotherapy (45 Gy; 1.8 Gy/day; days 1–5, weeks 1–4) and chemotherapy with 5-flurouracil (500 mg/m^2 body surface; days 1–5, weeks 1–4) and Cisplatin (20 mg/m^2 body surface; days 1–5, weeks 1 and 4). The patients were restaged after neoCRT (endoscopy and CT) and resection was performed approximately 4–6 weeks after the end of neoCRT. No adjuvant postoperative radio- or chemotherapeutic treatment was carried out in patients receiving neoCRT.

Perioperative Chemotherapy (periCTX)

PeriCTX was performed according to the protocol suggested by Cunningham et al. with three neoadjuvant cycles preoperative and three adjuvant cycles postoperative of epirubicin (50 mg/m^2 body-surface) by intravenous bolus on day 1, cisplatin (60 mg/m^2 body-surface) intravenously on day 1, and fluorouracil (200 mg/m^2 body-surface) daily for 21 days by continuous intravenous infusion [4]. In one single patient periCTX was carried our with 4 preoperative and 4 postoperative cycles (3 weeks) according to the XELOX protocol with oral capecitabine (1,000 mg/m^2 twice daily on days 1–14 of each cycle) and intravenous oxaliplatin (130 mg/m^2 on day 1 of each cycle). Beginning in 2010, ECF was replaced by the FLOT protocol: patients underwent four 2-week neoadjuvant cycles preoperatively and four 2-week adjuvant cycles postoperatively of doxatel (50 mg/m^2 body-surface) on day 1, folinic acid (200 mg/m^2 body-surface) on day 1, fluorouracil (2,600 mg/m^2 body-surface) on day 1 and oxaliplatin (85 mg/m^2 body-surface) on day 1. The patients were restaged after the neoadjuvant cycles of periCTX (endoscopy and CT) and resection was performed approximately 4–6 weeks after the end of periCTX [5]. All periCTX protocols, were continued postoperatively beginning 4–8 weeks after the operation with either three (ECF) or four (FLOT/XELOX) cycles as described above.

Surgical Therapy

Ninety five percent of the patients were operated by a thoraco-abdominal approach (right-sided thoracotomy, median laparotomy, collar hand-sewn, or intrathoracic stapled anastomosis). The remaining patients (5%) underwent esophagectomy by a transmediastinal approach (laparotomy, no thoracotomy, collar approach with hand-sewn anastomosis). In 96% of the cases, reconstruction was performed by a gastric tube, in the remaining 4% continuity was established by a colon interposition. We routinely performed two-field lymphadenectomy in patients with a thoraco-abdominal approach. In patients with a transmediastinal approach, lymphadenectomy was limited to the lower mediastinum and the D2 abdominal compartment.

Assessment of Clinical Tumor Response

Patients were classified as responders to neoadjuvant treatment if obvious signs of tumor response were found in CT and/or restaging endoscopy 2–4 weeks after completion of neoadjuvant therapy. Endoscopic features of tumor response were regression of tumorous luminal obstruction, macroscopic regression of tumor extension or the endoscopic absence of tumorous lesion in the restaging examination carried out after the neoadjuvant treatment. Computertomographic attributes of tumor response were regression of esophageal wall thickness in the region of esophageal tumor, the regression of local lymph node diameter or the absence of esophageal tumor or enlarged lymph nodes compared to pretherapeutic staging CT.

Assessment of Tumor Regression and Response in Histopathology

Histological regression after neoCRT or the neoadjuvant part of periCTX was determined by a pathologist according to Mandard et al. [7]. Tumor regression (TRG) was classified as grade 1 when no residual tumor cells were found (complete regression), grade 2 in the presence of rare residual cancer cells, grade 3 in case of fibrosis exceeding residual cancer, grade 4 in case of residual cancer exceeding fibrosis and grade 5 in the absence of any regressive changes. Moreover, histological response to neoadjuvant treatment was classified by the pathologist: Total or subtotal tumor response was confirmed in grade 1 + 2 histological regression. Partial response was stated if grade 3 regression was evident. Minimal or no tumor response was described for grade 4 + 5 regression.

Assessment of Lymphatic Spread

The number of tumor-positive lymph nodes and the total number of lymph nodes removed were recorded.

Data Collection and Statistics

The results of our study were gained by retrospective analysis of our prospective esophageal database. Perioperative data and survival information are recorded and entered into an SPSS-database (IBM SPSS for Windows, Version 19). The survival data were systematically obtained from the cancer registry of the Comprehensive Cancer Center of our University hospital. Some single pretherapeutical data were unavailable in a part of the patients especially from the first years of our study (see Table I for numbers). Only patients with complete data for all relevant parameters were included in the final multivariate survival analysis. Proportions were compared using the Chi-square test. Survival was univariately analyzed by the Kaplan–Meier method with a log-rank test for the comparison of subgroups. Multivariate survival analysis was performed by the Cox proportional hazard model (forward selection strategy using a likelihood ratio statistic) including the report of relative risks and their 95%-confidential intervals.

RESULTS

Demographics

Between January 2000 and April 2012, 140 patients underwent esophagectomy for esophageal adenocarcinoma at our institution. After exclusion of patients undergoing surgical resection only (32) and exclusion of patients with insufficient data or lack of follow-up (3), the data of 105 patients were analyzed in this study. There were 96 male and

TABLE I. Demographic, Tumor, and Treatment Characteristics in 105 Patients With Multimodal Treatment of Esophageal Adenocarcinoma

	All (N = 105)	periCTX (n = 47)	neoCRT (n = 58)	*P*-Value
Male sex (n, %)	96 (91%)	43 (92%)	53 (91%)	0.98
Age, years (median, range)	59 (31–78)	62 (31–77)	58 (36–78)	0.08
BMI (median, range)	25.2 (16–37)	25.5 (17–37)	24.6 (16–34)	0.06
Pretherapeutic T stage[a]	n = 95	n = 39	n = 56	0.50
1	1 (1%)	0	1 (2%)	
2	12 (13%)	3 (8%)	9 (16%)	
3	76 (80%)	33 (85%)	43 (85%)	
4	6 (6%)	3 (8%)	3 (5%)	
Pretherapeutic N stage[a]	n = 98	n = 41	n = 57	0.69
N0	24 (25%)	10 (24%)	14 (25%)	
N+	74 (75%)	31 (76%)	43 (75%)	
Postoperative T stage				0.87
0	20 (19%)	8 (17%)	12 (21%)	
1	14 (13%)	7 (15%)	7 (12%)	
2	36 (34%)	17 (36%)	19 (33%)	
3	34 (32%)	15 (32%)	19 (33%)	
4	1 (1%)	0	1 (2%)	
Postoperative N stage				0.24
N0	58 (55%)	23 (49%)	35 (60%)	
N+	47 (45%)	24 (51%)	23 (40%)	
No. of examined lymphnodes				0.86
Median, range	18 (3–42)	19 (3–38)	18 (5–42)	
Resection margin				0.83
Positive	5 (5%)	2 (4%)	3 (5%)	
Negative	100 (95%)	45 (96%)	55 (95%)	
Multimodal therapy				n.a.
FLOT	29 (28%)	29 (61%)		
ECF	17 (16%)	17 (36%)		
XELOX	1 (1%)	1 (2%)		
36 Gy + 5-FU/Cisplatin	47 (45%)		47 (81%)	
45 Gy + 5-FU/Cisplatin	11 (10%)		11 (19%)	

[a]Exact results were unavailable in a few patients.

nine female patients with a median age of 59.0 years. Median postoperative follow-up in the 105 patients was 1.8 years (range 0.22–11.5). Median follow-up was 3.0 years in censored patients and 1.17 years in patients who died.

Tumor and Treatment-Related Data

In the entire group, 58 patients underwent neoCRT (36 Gy + 5-FU/Cisplatin n = 48; 45 Gy + 5-FU/Cisplatin n = 11) and 47 patients periCTX (ECF n = 17; XELOX n = 1; FLOT n = 29). After resection, the postoperative T stages of the analyzed tumors were as follows: pT0 n = 20 (19%); pT1 n = 14 (13%); pT2 n = 36 (34%); pT3 n = 34 (32%) and pT4 n = 1 (1%). Nodal disease was confirmed in 47 patients (45%) by pathological staging and the median number of assessed lymph nodes was 18 (range 3–42). Patients were divided into two groups according to the type of multimodal treatment: NeoCRT and periCTX. The baseline patient and tumor characteristics of the entire collective and of both groups are summarized in Table I. No relevant differences were found between the two groups concerning pre- and post-therapeutic tumor characteristics (Table I). In the neoCRT group (n = 58) the complete neoadjuvant radiochemotherapeutic treatment was completed in 57 patients (97%). In the periCTX group (n = 47), all scheduled preoperative cycles of periCTX were completed in 42 patients (89%). The postoperative cycles of periCTX were begun in 33 patients (70%) and completed without reduction of chemotherapeutic agents or cycles in 26 patients (55%).

The most obvious differences comparing neoCRT and periCTX treatment characteristics were found for postsurgical morbidity and mortality. Compared to periCTX, the overall postoperative morbidity (53% vs. 76%; $P = 0.015$) and especially pulmonary morbidity (21% vs. 52%; $P = 0.001$) were significantly increased in patients after neoCRT (Table II). No significant differences were found comparing 36 Gy + 5-FU/Cisplatin (n = 47 patients) versus 45 Gy + 5-FU/Cisplatin (n = 11 patients) treatment plans concerning postoperative complications (37/47 patients vs. 7/11 patients; $P = 0.247$), pulmonary complications (25/47 vs. 5/11; $P = 0.449$), cardiac complications (5/47 vs. 3/11; $P = 0.167$) and surgical complications (24/27 vs. 6/11; $P = 0.601$). Comparing ECF (n = 17 patients) versus FLOT (n = 29 patients) treatment plans for periCTX no significant differences were seen for postoperative complications (9/17 patients vs. 16/29 patients; $P = 0.562$), pulmonary complications (5/17 vs. 5/29; $P = 0.272$), cardiac complications (1/17 vs. 1/29; $P = 0.614$) and surgical complications (7/17 vs. 10/29; $P = 0.443$). All four operative deaths were in the 36 Gy + 5-FU/Cisplatin neoCRT group with none in the 45 Gy + 5-FU/Cisplatin neoCRT group and none in the periCTX group. Causes of death were pneumonia progressing to ARDS in three patients and sepsis with multisystem organ failure due to anastomotic leakage with mediastinal abscess in one patient (Table II).

Overall Survival After Multimodal Treatment of Esophageal Adenocarcinoma

Of the analyzed 105 patients, 61 were alive and 44 had died at the end of follow-up. The 3- and 5-year overall survival in the entire study collective was 59% and 52% (Table III). The overall median survival (MS) was 5.97 years. A significant improvement of prognosis was found comparing postoperative T stages favoring ypT0–2 stages ($P < 0.001$) and postoperative N stages favoring nodal-negative patients ($P < 0.001$). Five-year survival rates of up to 75% in ypT1 and 79% in yN0 patients were achieved after multimodal treatment of

TABLE II. Postoperative Morbidity and Mortality in 105 Patients After Neoadjuvant Treatment of Esophageal Adenocarcinoma and Esophagectomy

Complication		periCTX (n = 47)	neoCRT (n = 58)	*P*-Value
Pulmonary complications[a]	40 (38%)	10 (21%)	30 (52%)	0.001
Cardiac complications[b]	10 (10%)	2 (4%)	8 (14%)	0.09
Surgical complications	47 (45%)	17 (36%)	30 (52%)	0.08
Anastomotic leakage	13	3	10	
Chylothorax	6	2	4	
Anastomotic stricture	2	0	2	
Wound infection	22	9	13	
Postoperative complications—no. of patients (%)[c]	69 (66%)	25(53%)	44 (76%)	0.015
In-hospital mortality	4 (4%)	0 (0%)	4 (7%)	0.08

[a]Pulmonary complications include respiratory failure with the need for re-intubation, pneumonia, and ARDS.
[b]Cardiac complications include atrial fibrillation and flutter, pericardial effusion, and myocardial infarction.
[c]In 31/69 patients more than one complication occurred.

pretherapeutically locally advanced tumor stages (Table III). Comparing ypT0–2 and ypT3–4 stages, there was a significant survival benefit with 5-year survival rates of 63% versus 26% ($P < 0.001$) for the lower ypT stages (Fig. 1). Moreover the analysis of the data showed an even more distinct difference between postoperatively nodal-negative and nodal-positive patients with 5-year survival rates of 75% vs. 15% ($P < 0.001$; Fig. 1). Furthermore ypN stage (Relative Risk 6.0, $P < 0.001$) could be identified in the multivariate survival analysis as an independent parameter of survival (Table III). Only five patients (5%) in the analyzed collective were treated by transhiatal esophagectomy and five patients (5%) had positive resection margins after esophagectomy. There was no significant disadvantage concerning survival rates for either (5-year survival rates 40% vs. 53% $P = 0.32$ and 30% vs. 54%; $P = 0.34$).

Clinical Response and Histological Response After Neoadjuvant Therapy

Patients who clinically responded to neoadjuvant treatment either after neoCRT or after the neoadjuvant cycles of periCTX had a significant benefit concerning probability of survival compared to patients without signs of clinical response to neoadjuvant treatment (5-year survival rates 59% vs. 19% month; $P \leq 0.001$; Table III). Nevertheless, multivariate survival analysis was not able to confirm clinical response as an independent factor for survival (Table IV). Interestingly, the analysis of histological regression after neoCRT or the neoadjuvant part of periCTX was not able to show significantly-improved survival rates if no or only rare residual tumor cells were found in the specimen (Tumor Regression Grade 1 and 2; $P = 0.09$; Table III). Total or subtotal histological response to neoadjuvant treatment was found in 48 patients (46%), partial response in 16 patients (15%) and only minimal or no histological response in 41 patients (39%) (Table III). Comparing neoCRT and periCTX, a significantly increased rate for total/subtotal response was detected in patients after neoCRT (59% vs. 30%) and a significantly increased rate for only minimal or even no response (55% vs. 26%) was found for patients after periCTX ($P < 0.01$; Table IV).

Comparison of Survival after neoCRT and neoCTX

Although the histological response rate was significantly lower in patients after periCTX, long-term survival was found to be at least equal to neoCRT with a 5-year survival rate of 63% vs. 45% with actually a distinct but not significant advantage in patients after periCTX ($P = 0.05$; Fig. 2). A subgroup comparison of the most well-established protocols (periCTX according the ECF protocol (n = 17) versus neoCRT according the 36 Gy/5-FU protocol (n = 47)) confirmed this distribution with a 5-year survival rate of 59% versus 42%, also with beneficial outcome for periCTX ($P = 0.19$). Interestingly multivariate survival analysis was able to identify periCTX as an independent parameter of survival (Relative Risk 2.6; $P < 0.01$).

DISCUSSION

The prognosis of surgically treated esophageal adenocarcinoma has progressively improved over the last two decades [8,9]. Besides improvement of patient selection, preoperative staging, perioperative critical care and surgical technique, the incremental inclusion of patients with esophageal adenocarcinoma in multimodal treatment protocols is attributed for this improved outcome [8–10]. Multimodal treatment protocols including neoCRT or periCTX are increasingly applied, especially in locally advanced stages [8,11] and have been introduced to national therapeutic guidelines [12]. Although different studies have been carried out comparing either neoCRT or periCTX plus surgery versus surgery alone for esophageal and/or gastric carcinoma, only very limited data comparing neoCRT and periCTX in patients with esophageal adenocarcinoma are available in the literature. For this reason, we conducted the present comparative analysis originating from our institutional experience.

In the past, different studies were able to show an increase in survival rates after combined neoCRT and surgical treatment with 5-year survival rates of 20–47% reported [13–17]. However, the major limitation of most of these trials is a pooled analysis of esophageal adenocarcinoma and squamous cell carcinoma. Recently, the large randomized Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial including 366 patients was able to show a significant improvement of overall survival in patients with esophageal adenocarcinoma or squamous cell carcinoma after neoCRT with 41.4 Gy/carboplatin/paclitaxel and subsequent surgical resection compared to surgery alone [3]. A 5-year survival rate of 47% was reported after neoCRT plus surgery. In this trial, significant survival benefits were found independently for both, esophageal adenocarcinoma and squamous cell carcinoma. This effect was also confirmed by metaanalytical data for esophageal adenocarcinoma [18]. Not only neoCRT but also periCTX has been applied successfully for the treatment of esophageal and gastric adenocarcinoma, although so far no data are available comparing periCTX plus surgery versus surgery alone in patients with exclusively esophageal adenocarcinoma. In recent years, two large randomized multicenter trials (Medical Research Council Adjuvant Gastric Infusional (MAGIC) and Action Clinique Coordonnées en Cancérologie Digestive (ACCORD-07)) were able to find a significant increase in overall survival after cisplatin-based periCTX plus surgery in a pooled collective of patients with gastric or esophageal adenocarcinoma compared to surgery alone [4,6]. These studies reported 5-year survival rates of 36% versus 23% [4] and 38% versus 24% favoring periCTX plus surgery [6].

TABLE III. (A) Univariate Survival Analysis in 105 Patients After Multimodal Treatment of Esophageal Adenocarcinoma; (B) Cox Regression Multivariate Analysis in 105 Patients After Multimodal Treatment of Esophageal Adenocarcinoma

Parameter	n	3-Year survival	5-Year survival	*P*-Value
A: Univariate analysis				
All patients	105	59%	52%	
Gender			0.17	
Male	96	57%	51%	
Female	9	83%	63%	
T-Staging				<0.001
ypT0	20	72%	72%	
ypT1	14	85%	75%	
ypT2	36	64%	54%	
ypT3	34	34%	27%	
ypT4	1	0%	0%	
T-Staging classified				
ypT0–2	70	70%	63%	<0.001
ypT3–4	35	33%	26%	
N-Staging				<0.001
pN0	58	82%	79%	
pN+	47	28%	15%	
Resection margin				0.34
Negative	100	59%	54%	
Positive	5	60%	30%	
Multimodal therapy				0.05
periCTX (all)	47	68%	63%	
neoCRT (all)	58	52%	45%	
Clinical response to neoadjuvant therapy				<0.001
No clinical response	18	29%	19%	
Clinical response	87	65%	59%	
Tumor regression				0.09
Grade 1	19	66%	66%	
Grade 2	29	63%	63%	
Grade 3	16	66%	43%	
Grade 4	28	64%	53%	
Grade 5	13	0%	0%	
Histological response				0.33
Total/subtotal	48	64%	64%	
Partial response	16	66%	44%	
Minimal/no response	41	51%	42%	
No. of examined LNs				0.19
≤5	2	50%	0%	
6–10	15	57%	57%	
11–15	18	83%	75%	
16–20	30	58%	58%	
≥20	40	50%	38%	
No. of positive LNs				<0.001
0	58	82%	79%	
1–2	16	54%	41%	
3–5	17	24%	12%	
>5	14	20%	0%	

Parameter	RR	95% CI	*P*-Value
B: Multivariate analysis			
ypN-Staging	6.0	2.9–12.2	<0.001
periCTX	2.6	1.3–5.1	<0.01
pT0–2 vs. pT3–4			0.08
Clinical response			0.1

In our institution, not only neoCRT but also periCTX protocols are applied in patients with locally advanced esophageal adenocarcinoma with nodal positivity (N+) and/or a local tumor exceeding the muscularis propria (T3/T4) in preoperative diagnostics. In contrast to the randomized trials mentioned above, preoperatively nodal-negative and tumors preoperatively limited to the mucosal, submucosal, and muscular layers were all treated with surgery alone. As T-stage and N-stage are accepted prognostic factors, these lower staged tumors were excluded from analysis and no comparison with patients treated by surgery alone was carried out in the present study. Nonetheless, we were able to reproduce the results of the CROSS trial on neoCRT [3] concerning probability of survival with 3- and 5-year survival rates of 52% and 45% in patients with neoCRT plus surgery. Interestingly, the long-term survival of patients with periCTX plus surgery with 3- and 5-year survival rates of 68% and 63% exceeded the results of the MAGIC and ACCORD-07 trials by far [4,6]. One possible reason for this difference could be the higher rate of margin-negative resections of 96% in our periCTX group compared to 87% in the ACCORD-07 trial [6].

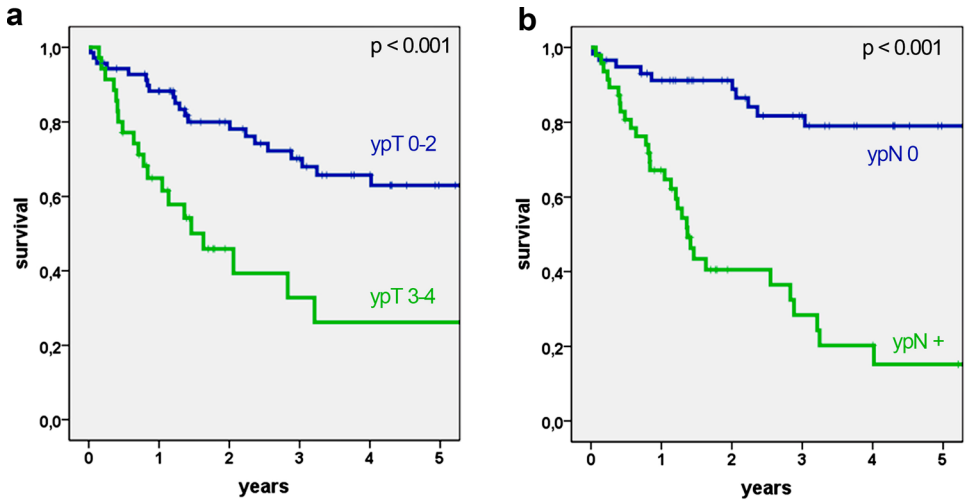

Fig. 1. Actuarial survival in 105 patients after neoadjuvant or perioperative therapy and esophagectomy for esophageal adenocarcinoma: (**a**) Influence of postoperative ypT stage: Comparison of patients with tumor invasion limited to mucosa, submucosa and muscularis propria ypT0–2 (n = 70) and patients with tumor invasion exceeding the muscularis propria ypT3–4 (n = 35). **b**: Influence of postoperative ypN stage: Comparison of patients with tumor-free resected lymph nodes ypN0 (n = 58) and patients with tumor-positive resected lymph nodes ypN+ (n = 47).

TABLE IV. Histologic Response in 105 Patients After Neoadjuvant Treatment for Esophageal Adenocarcinoma

Histologic response	All (n = 105)	periCTX (n = 47)	neoCRT (n = 58)	*P*-Value
Total/subtotal	48 (46%)	14 (30%)	34 (59%)	<0.01
Partial response	16 (15%)	7 (15%)	9 (16%)	
Minimal/no response	41 (39%)	26 (55%)	15 (26%)	

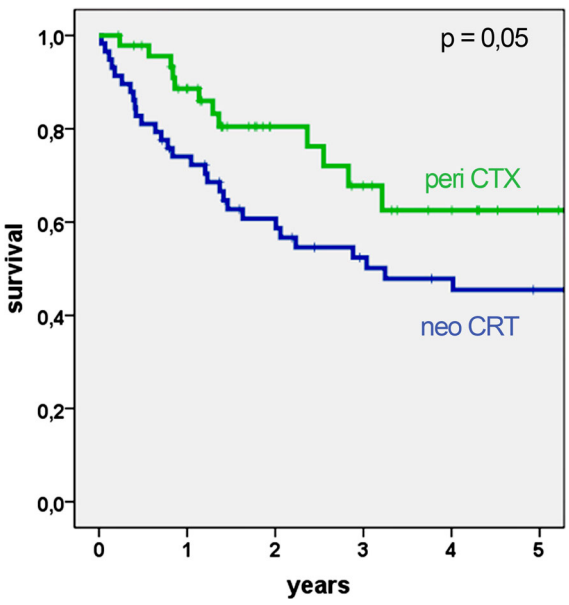

Fig. 2. Actuarial survival in 105 patients after neoadjuvant or perioperative therapy and esophagectomy for esophageal adenocarcinoma: Comparison of patients undergoing neoadjuvant chemoradiation (neoCRT, n = 58) and patients undergoing perioperative chemotherapy (periCTX, n = 47).

Another contributing explanation may be the lower frequency of histological subtypes with poor prognosis, like signet ring cell carcinoma which constitute 6% of all adenocarcinomas of the esophagus opposed to 25% of all gastric adenocarcinomas [19,20].

Although periCTX turned out to be an independent parameter of favorable survival (RR 2.6; $P < 0.01$) and significance for superior long-term compared to neoCRT was nearly reached in univariate analysis ($P = 0.05$), clearly higher rates of minimal or missing histologic tumor response after neoadjuvant treatment were found for periCTX (55% vs. 26%; $P < 0.01$). Though histologic tumor response has been described as a prognostic parameter for neoCRT and periCTX, the impact of this parameter seems to be more relevant in neoCRT than in periCTX [21,22]. To explain this difference, it could be hypothesized that stronger systemic effects of periCTX outbalance the predominantly local effect of neoCRT on the tumor disease and result in a survival benefit.

Consistent with a previous comparative series of neoCRT and periCTX in patients with pooled histotypes of esophageal carcinoma, not only was the rate of pulmonary and cardiac complications increased for neoCRT but also the in-hospital mortality rate of our patients was worse compared to periCTX (0% vs. 7%; $P = 0.08$) [23]. These findings are also consistent with metaanalytical data which showed an increase of treatment morbidity and operative mortality for protocols of neoCRT compared to surgery alone, whereas no differences have been found for periCTX in comparing these outcomes [24,25].

The retrospective and non-randomized character of this study is certainly a limitation of our analysis. Not only the 12-year period of inclusion is a limitation, but also the five different chemotherapeutic and radiochemotherapeutic protocols were different among the patients and impair explanatory power. Despite these facts, our study is apart from a single RCT which was carried out between 2000 and 2005 and closed ahead of schedule without showing significant differences concerning survival—the only comparative analysis on neoCRT versus periCTX in patients with esophageal adenocarcinoma [26]. In our analysis, we were able to reproduce and confirm the recent favorable results of neoCRT plus surgery in patients with esophageal adenocarcinoma detected in the CROSS trial [3]. Furthermore, the results of this study are very encouraging concerning future improvement of long-term survival of esophageal adenocarcinoma, especially by the use of periCTX plus surgery. Therefore, an RCT comparing one of the examined protocols of

periCTX (ECF or FLOT) versus neoCRT in patients with exclusively esophageal adenocarcinoma should be implemented to answer the question whether neoCRT or periCTX should be the preferred neoadjuvant or perioperative modality for patients with esophageal adenocarcionoma.

CONCLUSION

A higher rate of histologic response to neoCRT compared to histologic response following the preoperative cycles of periCTX does not translate to a benefit in overall survival. PeriCTX offers at least equal results in terms of overall survival compared to neoCRT in patients with locally advanced esophageal adenocarcinoma. Postoperative morbidity, especially pulmonary complications, are more frequent after neoCRT than after periCTX. Whether periCTX offers a clear benefit in terms of improvement of survival and reduction of perioperative complications compared to neoCRT should be clarified in an RCT comparing the two regimens.

REFERENCES

1. Walther C, Zilling T, Perfekt R, et al.: Increasing prevalence of adenocarcinoma of the oesophagus and gastro-oesophageal junction: A study of the Swedish population between 1970 and 1997. Eur J Surg 2001;167:748–757.
2. Bosetti C, Levi F, Ferlay J, et al.: Trends in oesophageal cancer incidence and mortality in Europe. Int J Cancer 2008;122:1118–1129.
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al.: Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074–2084.
4. Cunningham D, Allum WH, Stenning SP, et al.: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
5. Homann N, Pauligk C, Luley K, et al.: Pathological complete remission in patients with oesophagogastric cancer receiving preoperative 5-fluorouracil, oxaliplatin and docetaxel. Int J Cancer 2012;130:1706–1713.
6. Ychou M, Boige V, Pignon JP, et al.: Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: An FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715–1721.
7. Mandard AM, Dalibard F, Mandard JC, et al.: Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 1994;73:2680–2686.
8. Makowiec F, Baier P, Kulemann B, et al.: Improved long-term survival after esophagectomy for esophageal cancer: Influence of epidemiologic shift and neoadjuvant therapy. J Gastrointest Surg 2013;17:1193–1201.
9. Ruol A, Castoro C, Portale G, et al.: Trends in management and prognosis for esophageal cancer surgery: Twenty-five years of experience at a single institution. Arch Surg 2009;144:247–254.
10. Siewert JR, Stein HJ, Feith M, et al.: Histologic tumor type is an independent prognostic parameter in esophageal cancer: Lessons from more than 1,000 consecutive resections at a single center in the Western world. Ann Surg 2001;234:360–367.
11. Luketich JD, Pennathur A, Awais O, et al.: Outcomes after minimally invasive esophagectomy: Review of over 1000 patients. Ann Surg 2012;256:95–103.
12. Moehler M, Al-Batran SE, Andus T, et al.: German S3-guideline "Diagnosis and treatment of esophagogastric cancer". Z Gastroenterol 2011;49:461–531.
13. Urba SG, Orringer MB, Turrisi A, et al.: Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305–313.
14. Walsh TN, Noonan N, Hollywood D, et al.: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462–467.
15. Burmeister BH, Smithers BM, Gebski V, et al.: Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: A randomized controlled phase III trial. Lancet Oncol 2005;6:659–668.
16. Lin CC, Hsu CH, Cheng JC, et al.: Concurrent chemoradiotherapy with twice weekly paclitaxel and cisplatin followed by esophagectomy for locally advanced esophageal cancer. Ann Oncol 2007;18:93–98.
17. Tepper J, Krasna MJ, Niedzwiecki D, et al.: Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086–1092.
18. Gebski V, Burmeister B, Smithers BM, et al.: Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. Lancet Oncol 2007;8:226–234.
19. Piessen G, Messager M, Leteurtre E, et al.: Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. Ann Surg 2009;250:878–887.
20. Paraf F, Fléjou JF, Pignon JP, et al.: Surgical pathology of adenocarcinoma arising in Barrett's esophagus. Analysis of 67 cases. Am J Surg Pathol 1995;19:183–191.
21. Schneider PM, Baldus SE, Metzger R, et al.: Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: Implications for response classification. Ann Surg 2005;242:684–692.
22. Mansour JC, Tang L, Shah M, et al.: Does graded histologic response after neoadjuvant chemotherapy predict survival for completely resected gastric cancer? Ann Surg Oncol 2007;14:3412–3418.
23. Luu TD, Gaur P, Force SD, et al.: Neoadjuvant chemoradiation versus chemotherapy for patients undergoing esophagectomy for esophageal cancer. Ann Thorac Surg 2008;85:1217–1223.
24. Urschel JD, Vasan H: A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003;185:538–543.
25. Urschel JD, Vasan H, Blewett CJ: A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2002;183:274–279.
26. Stahl M, Walz MK, Stuschke M, et al.: Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009;27:851–856.