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ORIGINAL ARTICLE

Histopathologic Features are more Important Prognostic Factors than Primary Tumour Location in Gastro-oesophageal Adenocarcinoma Treated with Preoperative Chemoradiation and Surgery

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Abstract The aim of present study was to evaluate the impact of primary tumour location and other factors on the outcome of preoperative chemoradiation followed by surgery in adenocarcinomas of distal oesophagus, gastro-oesophageal junction and stomach. We retrospectively reviewed the institutional patient database. The therapeutic response was re-evaluated as a percentage of residual tumor cells in surgical resection specimens. Overall survival (OS) and disease-free survival (DFS) were assessed. The effect primary tumour location, clinical and pathological TNM stage, and histopathological factors (histological type, grade, angioinvasion, perineural invasion, tumour response) on treatment outcome were evaluated**.** A total of 108 patients underwent preoperative chemoradiation for adenocarcinoma of distal oesophagus, gastro-oesophageal junction or stomach. The median prescribed dose of radiation was 45 Gy. The concurrent chemotherapy consisted of 5-fluorouracil +/− cisplatin +/− taxanes. R0 resection was achieved in 80 patients (74%). The complete response was observed in 19%. The median follow-up was 50.8 months. Three-year and 5-year OS and DFS were 36.2% and 25.3%; and 28.1% and 23.7%, respectively. Pretreatment T-stage, pathological N-stage, radicality of resection, histological subtype, grade, angioinvasion and perineural invasion, were identified as statistical significant OS predictors in univariate analysis; pathological N-stage, radicality of resection and angioinvasion, in multivariate analysis. The primary tumor location did not influence the prognosis. The pathologic response to chemoradiation had borderline significance. In conclusion, no prognostic impact of primary tumour location, in contrast to other investigated factors, was evident in the present study. The most important predictors of prognosis were angioinvasion status and pN–stage.

Keywords Gastric cancer · Gastro-oesophageal junction cancer · Distal oesophageal cancer · Preoperative chemoradiation · Prognostic factor

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Introduction

The role of concurrent chemoradiation in the treatment of cancer of distal oesophageal, gastro-oesophageal junction (GEJ) and gastric adenocarcinomas is, in general, still not clear. Historically, chemoradiation was used in the pre-

operative setting for oesophageal adenocarcinomas, as clinical trials and meta-analyses confirmed the benefit of pre-operative chemoradiation compared to surgery alone in oesophageal cancer [1, 2]. Unfortunately, most of these clinical trials enrolled both patients with squamous cell carcinomas and adenocarcinomas. The clear benefit of pre-operative chemoradiation and surgery compared to surgery alone in a subgroup of patients with adenocarcinoma of distal oesophagus, including GEJ, was reported recently in the CROSS trial [3]. An alternative to the neoadjuvant approach in distal oesophageal and GEJ adenocarcinomas is a combination of pre-operative and post-operative chemotherapy based on the results of two phase III studies, i.e. MAGIC and FNCLCC/FFCD trials. Both of these trials enrolled patients with adenocarcinomas of distal oesophagus, gastroesophageal junction and stomach, demonstrating a survival benefits compared to surgery alone.

The standard neoadjuvant approach for localized gastric cancer is chemotherapy alone in combination with surgery and post-operative chemotherapy based on the results of MAGIC and FNCLCC/FFCD trials, mentioned above [4, 5]. The chemoradiation is administered in gastric cancer usually in a postoperative setting, based on the results of the SWOG 9008/INT 0116 randomized trial [6].

Unfortunately, there are currently no data from prospective randomized trials demonstrating an effect of pre-operative chemoradiation in gastric cancer. This approach in gastric cancer was tested in single arm phase I/II studies, including multicentric RTOG 9904 trial [7]. The published data are encouraging with substantial rates of pathological complete responses. Currently, a randomised phase III trial TOPGEAR is investigating pre-operative chemoradiation versus pre-operative chemotherapy in resectable gastric cancer [8].

Pre-operative chemoradiation has been used also at our institution for more than 15 years and the preliminary results in the first cohort of patients with gastric cancer were published earlier [9–11]. Furthermore, the pre-operative chemoradiation regimen in gastric cancer patients was almost identical as in oesophageal cancer patients. Therefore, this offered a possibility to compare the treatment outcome in patients treated by pre-operative chemoradiation in all three locations and to evaluate the influence of other factors on the treatment results.

The aims of this retrospective study included the analysis of the response rate (RR), disease free survival (DFS), overall survival (OS) in patients with locally and/or regionally advanced adenocarcinomas of distal oesophagus, gastro-oesophageal junction and stomach treated by concurrent chemoradiation in preoperative setting and to analyze the prognostic effect of the primary site, clinical and pathological staging, histopathology type and other histopathological factors (tumor grade, angioinvasion and perineural invasion, and extent of treatment response).

Methods and Materials

We retrospectively reviewed data from patients with locally and/or regionally advanced (T3-T4 and/or N+ M0) histologically verified adenocarcinomas of distal oesophagus (tumours with the centre 1 cm and more above the squamocolumnar junction, corresponds to Siewert I type), gastro-oesophageal junction (cardial and subcardial tumorus with the centre not more than 5 cm bellow the squamocolumnar junction, corresponds to Siewert II and III) and stomach. The clinical staging was based on pre-treatment computed tomography. Endosonography was used in cases the lymph nodes were not considered to be suspicious or to specify cT-stage to exclude T1-T2N0M0 clinical stages. All patients were considered to have resectable tumour without distal metastases and underwent preoperative chemoradiation with the aim of subsequent curative surgery. The required minimal prescribed pre-operative radiation dose for inclusion in the present analysis was 40 Gy.

Pre-treatment and post-operative pathological TNM classification was performed according to International Union Against Cancer (UICC) TNM classification of malignant tumors, 7th edition [12].

The histopathological grade was classified in pretreatment tumour biopsies. The Lauren type of tumour was assigned based on evaluation of both specimens, pretreatment and post-operative. The angioinvasion and perineural invasion status were evaluated in definitive biopsies postoperatively. The pathological response rate was based on the assessment of the percentage of residual tumor cells (RTC) in relation to the grossly identifiable tumour bed of the primary tumor site. Five grade scale (I-V) of tumour response was used (RTC: 0%, ≤1%, 2–10%, 11–50% and 51–100%). This evaluation is consistent with the methods used in clinical trials published earlier [13–15]. The slides were assessed separately by two pathologists with expertise in gastrointestinal tumours (J.L. and A.R), and all discordant cases were reviewed under a double-headed microscope until a consensus was reached.

Statistical Analysis

Descriptive statistics was used to characterize the patient cohort, including median, mean, and 95% confidence interval for continuous data, and absolute and relative frequencies for categorical data. Kaplan-Meier analysis and log-rank test were used for survival analysis. Univariate and multivariate Cox regression analyses were used to study the association between patient/tumour/treatment characteristics and survival. Relationship between tumor location and other independent factors was also analyzed using the chi-square test. A p-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using the NCSS 8

statistical software program (NCSS, Keysville, Utah) by biomedical statistician (I.S.).

Results

Patients

A total of 108 patients who underwent between January 2000 and March 2014 chemoradiation for potentially resectable adenocarcinoma of distal esophagus, gastro-oesophageal junction or stomach in the pre-operative setting were identified. Histological specimens of the primary tumour were retrospectively revised by pathologists at our institution.

Radiotherapy

The prescribed dose of radiotherapy ranged from 40 to 50.4 Gy, with the median prescribed dose being 45 Gy. Higher dose of 50.4 was prescribed usually in adenocarcinomas of distal oesophagus, the dose of 45 Gy was prescribed in tumors of GEJ and stomach. The dose of 40 Gy was used historically with conventional techniques of radiotherapy.

The clinical target volume (CTV) for gastric cancer encompassed the stomach and regional lymph nodes. In GEJ and distant oesophageal tumors CTV was extended to include oesophagus 4 cm above gross tumor volume and, on the contrary, distant parts of stomach were excluded in these cases.

The radiotherapy technique in the cohort evolved in time from conventional (two opposed anterior-posterior fields with shielding of part of kidneys) to conformal radiotherapy and intensity modulated radiotherapy (IMRT). IMRT is a standard technique in these indications at our institution since 2009.

Concurrent Chemotherapy

The concurrent chemotherapy was administered in all 108 patients. 5-fluorouracil in continuous infusion (200 mg/m^2/day) was used in all patients. In 80 patients (74%) weekly regimen of cisplatin (25–40 mg/m^2) was administered and in 7 patients, docetaxel or paclitaxel were added to 5-fluorouracil and cisplatin.

Surgery

R0 resection was achieved in 80 patients (74%). To achieve R0 radicality, various surgical approaches were used – from resection of distal oesophagus or proximal gastrectomy through subtotal gastrectomy to total or extended total gastrectomy (including the resection of abdominal part of oesophagus up to the level of hiatus). The choice of procedure was up to the operating surgeon in all cases. As a main surgical approaches, proximal gastrectomy +/− distal oesophagectomy were used in gastrooesophageal junction and distal oesophageal tumours, and total gastrectomy was done in gastric tumours. For reconstruction of upper gastrointestinal tract, two methods were used – direct oesophagogastroanastomosis using 21 mm circular stapler after proximal gastrectomy and resection of distal oesophagus or reconstruction with excluded Roux-en-Y jejunal loop following any subtotal and total gastrectomy (mostly using 25 mm circular stapler for anastomosis).

The resection was classified as R1 in three patients. The tumor was unresectable in 23 patients (13 cases were gastric tumours, 7 cases were tumours of gastroesophageal junction, and 3 unresectable tumours were located in distal oesophagus), mostly because of peritoneal dissemination. Two patients did not undergo the surgery. One patient with gastric cancer died before the surgery because of sepsis. The other patient (adenocarcinoma of distal oesophagus) refused surgery.

The group of patients with radical resection was in statistical analyses compared with all other patients with R1 resection or no resection at all („radicality of resection“).

The resection was classified as R1 in three patients. The tumor was unresectable in 23 patients (13 cases of gastric carcinoma, 7 cases of carcinoma of gastroesophageal junction, and 3 cases of carcinoma of distal oesophagus), mostly because of peritoneal spread. Two patients did not undergo surgery. One patient with gastric cancer died before the surgery because of sepsis. The other patient (adenocarcinoma of distal oesophagus) refused surgery.

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All patient, tumour and treatment characteristics are summarized in Table 1.

Histopathological Analysis

Seventy-nine of eighty R0 resected samples were available for the retrospective pathological evaluation. The pathological complete response (grade I) was noted in 20 cases (19% of all 108 patients). All post-chemoradiation response grades in R0 resected patients are summarized in Table 2.

Adjuvant Chemotherapy

Adjuvant chemotherapy was used as a standard treatment since 2008 in patients who underwent curative resection and were in good performance status after the surgery, mostly in gastric and gastrooesophageal junction carcinomas. The indication was not influenced by tumour response after chemoradiation.

Table 1 Patient and tumour characteristics (A). Treatment characteristics (B)

Patient and tumour characteristics	Number of patients	
	Absolute	Relative
Gender		
Male	88	81%
Female	20	19%
Age		
median 62.5 years (range 28–80)		
Primary location		
Distal oesophagus	24	22%
Gastro-oesophageal junction	39	36%
Stomach	45	42%
Pre-treatment clinical stage		
T2N1M0	20	19%
T2N2M0	2	2%
T3N0M0	15	14%
T3N1M0	43	40%
T3N2M0	14	13%
T3N3M0	2	2%
T4N0M0	2	2%
T4N1M0	7	6%
T4N2M0	3	3%
Angioinvasion		
Absent	55	51%
Present	32	30%
Not evaluable	21	19%
Perineural invasion		
Absent	74	69%
Present	13	12%
Not evaluable	21	19%
Grading		
Grade 1	4	4%
Grade 2	40	37%
Grade 3	63	58%
Not evaluable	1	1%
Lauren type		
Intestinal	68	63%
Diffuse	24	22%
Mixed	10	9%
Not evaluable	6	6%
Radiotherapy dose		
40 Gy in 20 fractions	25	23%
41.40 Gy in 23 fractions	1	1%
45 Gy in 25 fractions	66	61%
50.4 Gy in 28 fractions	16	15%
Radiotherapy technique		
AP/PA fields	46	43%
3D–CRT	19	17%
IMRT	43	40%
Concurrent chemotherapy		
5-fluorouracil	108	100%
Cisplatin	80	74%
Paclitaxel or docetaxel	7	6%
Radicality of resection		
R0	80	74%
R1	3	3%
Unresectable disease	23	21%
No surgery	2	2%
Adjuvant chemotherapy (following R0 resection)		
Yes	34	31%
5-fluorouracil-based	31	29%
Cisplatin or taxane-based	3	3%
No	46	43%

Abbreviations: AP/PA = anteroposterior and posteroanterior; 3D–CRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy.

Overall, adjuvant chemotherapy was administered in 34 patients (31%), including 19 patients with gastric carcinoma (42%), 15 patients with gastro-oesophageal junction carcinomas (38%), and in one patient with carcinoma of distal oesophagus (4%). The adjuvant treatment was based on 5-fluorouracil in 31 patients, and cisplatin- or taxane-based in 3 patients.

Post-Treatment Follow-Up

Patients with unresectable disease underwent palliative treatment or best supportive care according to their performance status, extent of the disease and current recommendations of systemic palliative treatment. The same approach applied in patients with recurrence of the disease during follow-up.

Among eighty patients who underwent R0 resection recurrence was observed in 37 cases (46%). In all but two cases the disease recurred only as distant metastases (liver metastases, lung metastases, peritoneal and pleural spread, or other locations). In two cases synchronous local and distant recurrence was observed. In three cases second primary malignancy was identified (in two cases urinary bladder cancer and in one case pancreatic cancer).

Results of Survival

The median follow-up of surviving patients was 50.8 months (range 7–165 months). Three-year and 5-year OS was 36.2% (95% CI 26.3–46.0%) and 25.3% (95% CI

Table 2 Assessment of pathological tumour response

Grade of pathological tumour response	Proportion of residual tumour cells	Classification of tumour response	Number of patients	
			Absolute	Relative (n = 108)
I	0%	Complete pathological response	20	19%
II	≤1% (isolated tumor cells)	Near complete pathological response	24	22%
III	2–10%,	Partial pathological response	16	15%
IV	11–50%	Moderate pathological response	8	7%
V	51–100%	Minimal or no pathological response	11	10%
NA	Not Available	No resection/No tissue available	29	27%

15.9–34.7%), respectively; and 3-year and 5-year DFS was 28.1% (95% CI 19.0–37.2%) and 23.7% (95% CI 14.8–32.7%), respectively (Fig. 1).

Prognostic Factor Assessment

Factors identified as statistically significant predictors of survival with the log-rank test included pretreatment cT-stage (OS and DFS), pathological N-stage (OS and DFS), radicality of resection (OS), Lauren tumour type (OS), tumor grade (OS), angioinvasion (OS and DFS) and perineural invasion (OS and DFS). Cox regression univariate analysis revealed as a significant predictor of survival pre-treatment cT-stage (OS and DFS), pathological N-stage (OS and DFS), number of positive lymph nodes (OS and DFS), radicality of resection (OS), Lauren tumor type (OS), tumor grade (OS), angioinvasion (OS and DFS) and perineural invasion (OS). Cox regression multivariate analysis confirmed the statistically significant effect of pretreatment cT-stage on DFS, pathological N-stage on DFS and OS, radicality of resection on OS and angioinvasion status on OS.

Neither age (≤ 65 years versus >65 years) nor gender affected survival. Similarly, primary tumor site, dose of radiotherapy or radiotherapy technique did not affect the prognosis. The pathological response grade after chemoradiation (Grade I-II vs Grade III-V) had borderline significance (p = 0.08). In case of comparison of complete pathological response versus anything less than complete pathological response (Grade I vs. Grade II-V) the impact on prognosis was not statistically significant.

We did not note an impact of adjuvant chemotherapy on DFS (p = 0.51) or OS (p = 0.70), although adjuvant chemotherapy was indicated mainly in gastric cancer patients.

Detailed data are reported in Table 3. The impact of primary tumour site on DFS and OS is presented in Fig. 2 (a-b). The impact of other factors (Lauren histopathologic type, tumour grade, presence of angioinvasion and perineural invasion) on 5-year OS is shown in Table 4. Because we revealed no influence of primary tumour location on treatment outcomes, we

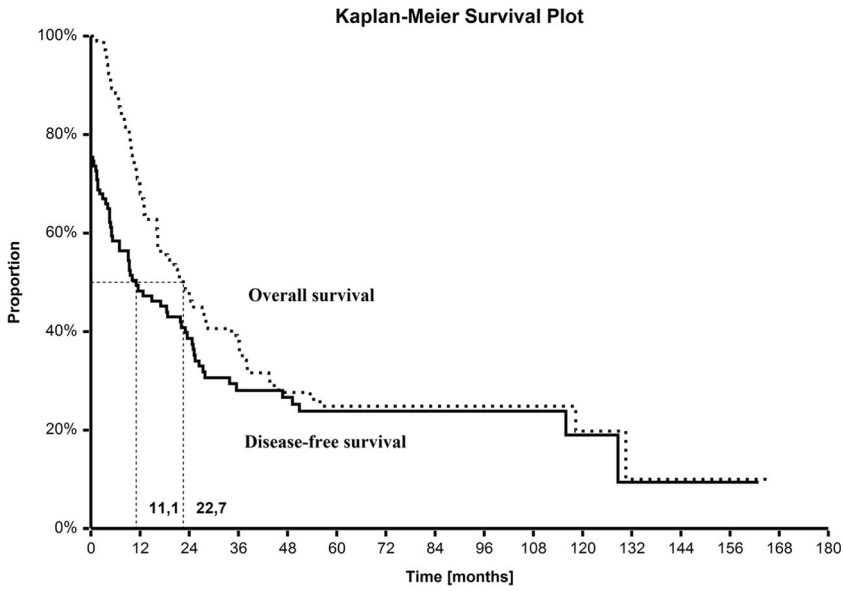

Fig. 1 Overall survival and disease-free survival (n = 108)

Table 3 Factors impact on the survival

Logrank test	DFS	OS
Gender	ns	ns
Tumour location	ns	ns
cT stage	$p = 0.015$	$p = 0.002$
	T3/T2 HR 1.92, 95% CI 1.05–3.51	T3/T2 HR 2.32, 95% CI 1.34–3.99
	T4/T3 HR 2.41, 95% CI 0.53–10.91	T4/T3 HR 1.97, 95% CI 0.80–4.00
	T4/T2 HR 5.05, 95% CI 0.68–37.70	T4/T2 HR 3.95, 95% CI 1.40–11.14
cN stage	ns	ns
ypT stage	ns	ns
ypN stage	$p = 0.002$	$p = 0.0006$
	ypN1/ypN0 HR 2.84, 95% CI 1.09–7.39	ypN1/ypN0 HR 2.48, 95% CI 1.00–6.19
Radical resection	-	$p < 0.0001$ No/Yes HR 3.81, 95% CI 1.82–7.98
Lauren subtype	ns	$p = 0.028$ Diffuse/Intestinal HR 1.73, 95% CI 0.99–3.02
Tumour grade	ns	$p = 0.03$ Grade 2/Grade 1 HR 1.65, 95% CI 0.51–5.40 Grade 3/Grade 2 HR 1.57, 95% CI 0.97–2.53 Grade 3/Grade 1 HR 2.83, 95% CI 1.14–7.01
AI	$p = 0.0005$	$p = 0.0001$
	Yes/No HR 2.59, 95% CI 1.32–5.07	Yes/No HR 2.88, 95% CI 1.51–5.50
PNI	$p = 0.049$	$p = 0.031$
	Yes/No HR 2.03, 95% CI 0.80–5.16	Yes/No HR 2.09, 95% CI 0.85–5.12
Cox regression univariate	DFS	OS
Age	ns	ns
Gender	ns	ns
Tumour location	ns	ns
cT stage	$p = 0.009$	$p = 0.0006$
	RR 2.15, 95% CI 1.21–3.83	RR 2.09, 95% CI 1.37–3.17
cN stage	ns	ns
ypT stage	ns	ns
ypN stage	$p = 0.006$	$p = 0.013$
	ypN1 RR 2.90, 95% CI 1.36–6.21	ypN1 RR 2.55, 95% CI 1.21–5.36
	ypN2 RR 1.90, 95% CI 0.71–5.09	ypN2 RR 1.68, 95% CI 0.63–4.45
	ypN3 RR 5.38, 95% CI 1.76–16.43	ypN3 RR 6.20, 95% CI 2.24–17.17
Number of positive LN	$p = 0.013$	$p = 0.0026$
	RR 1.07, 95% CI 1.02–1.14	RR 1.09, 95% CI 1.03–1.14
No radical resection	-	$p < 0.0001$ RR 4.50, 95% CI 2.61–7.75
Lauren subtype	ns	$p = 0.03$ RR 1.75, 95% CI 1.06–2.93
Tumour grade	ns	$p = 0.03$ RR 1.62, 95% CI 1.05–2.51
AI	$p = 0.0008$	$p = 0.0001$
	RR 1.65, 95% CI 1.23–2.22	RR 1.75, 95% CI 1.32–2.33
PNI	ns	$p = 0.036$ RR 1.46, 95% CI 1.03–2.07
RT dose	ns	ns
RT technique	ns	ns
Response grade	ns	ns
Cox regression multivariate	DFS	OS
Age	ns	ns

Table 3 (continued)

Logrank test	DFS	OS
Gender	ns	ns
Tumour location	ns	ns
cT stage	$p = 0.020$	ns
cN stage	ns	ns
ypT stage	ns	ns
ypN stage	$p = 0.034$	$p = 0.010$
Number of positive LN	ns	ns
No radical resection	-	$p = 0.017$
Lauren subtype	ns	ns
Tumour grade	ns	ns
AI	ns	$p = 0.016$
PNI	ns	ns
RT dose	ns	ns
RT technique	ns	ns
Response grade	ns	ns

Abbreviations: DFS = disease-free survival; OS = overall survival; HR = Cox-Mantel hazard ratio; RR = risk ratio; 95% CI = 95% confidence interval; AI = angioinvasion; PNI = perineural invasion, LN = lymph nodes, RT = radiotherapy.

evaluated the rate of factors that affected the prognosis in the present analysis for each location. The subgroup of gastric cancer was associated with higher rate of histopathological grade 3, diffuse or mixed Lauren type and positive angioinvasion status (in details - Table 5).

Discussion

For locally and/or regionally advanced distal oesophageal and GEJ adenocarcinoma current standard of care includes perioperative chemotherapy plus surgery [4, 5], or pre-operative chemoradiation plus surgery [3]. Standard of care based on phase III randomized clinical trials for locally and/or regionally advanced gastric cancer also admits perioperative chemotherapy plus surgery [4, 5], or surgery plus post-operative chemoradiation [6]. The pre-operative chemoradiation has been so far not widely used in all gastric cancer because of an absence of phase III randomized trial data. A randomised phase III trial TOPGEAR trial is currently comparing pre-operative chemoradiation versus pre-operative chemotherapy in resectable gastric cancer [8].

Until now, the only phase III randomized clinical trial for these tumours that compared preoperative chemotherapy plus surgery alone to the same regimen with radiation (dose of 30 Gy) and concomitant cisplatin and etoposide before surgery for GEJ adenocarcinomas was the German trial reported by Stahl et al. Unfortunately, this trial was closed prematurely because of slow patient recruitment ($n = 126$). Nevertheless, this trial demonstrated encouraging results in terms of pathological complete response rate (2% vs. 15.6%) and 3-years overall survival (27.7% vs. 47.4%; $p = 0.07$) [16].

Another randomized phase II trial of Burmeister et al., randomized 75 patients with adenocarcinoma of oesophagus or GEJ to preoperative chemotherapy (cisplatin and 5–fluorouracil) or the same preoperative chemotherapy combined with radiotherapy (dose of 35 Gy). There was statistically significant increase of pathologic complete response rate (0% vs. 13%; $p = 0.02$), but not in DFS and OS (5-y OS 36% vs. 26%; $p = 0.6$) [17].

For gastric cancer, there is an experience from single-arm single-institution or multi-institutional studies [18–24]. The most of these trials reported promising results, mainly in terms of pathological complete response rate. These data seem encouraging compared to data from large prospective clinical trials that used pre-operative chemotherapy [4, 5] and did not report similar response rates. On the other hand, there is no evidence that higher complete response rate in chemoradiation trials is associated with better overall survival compared to pre-operative chemotherapy without radiation.

The present retrospective clinical study confirmed a relatively high rate of pathological complete response (19%). Furthermore, near complete response (isolated vital tumor cells) was observed in additional 22% of patients. Previous clinical trials reported complete response rates after preoperative chemoradiation in gastric and GEJ cancer ranging from 7 to 26% [7, 14, 16, 19, 21–29]. The published pathological complete response rates after chemoradiation in oesophageal cancer are higher than in gastric cancer but, most of these trials evaluated both patients with adenocarcinomas and squamous

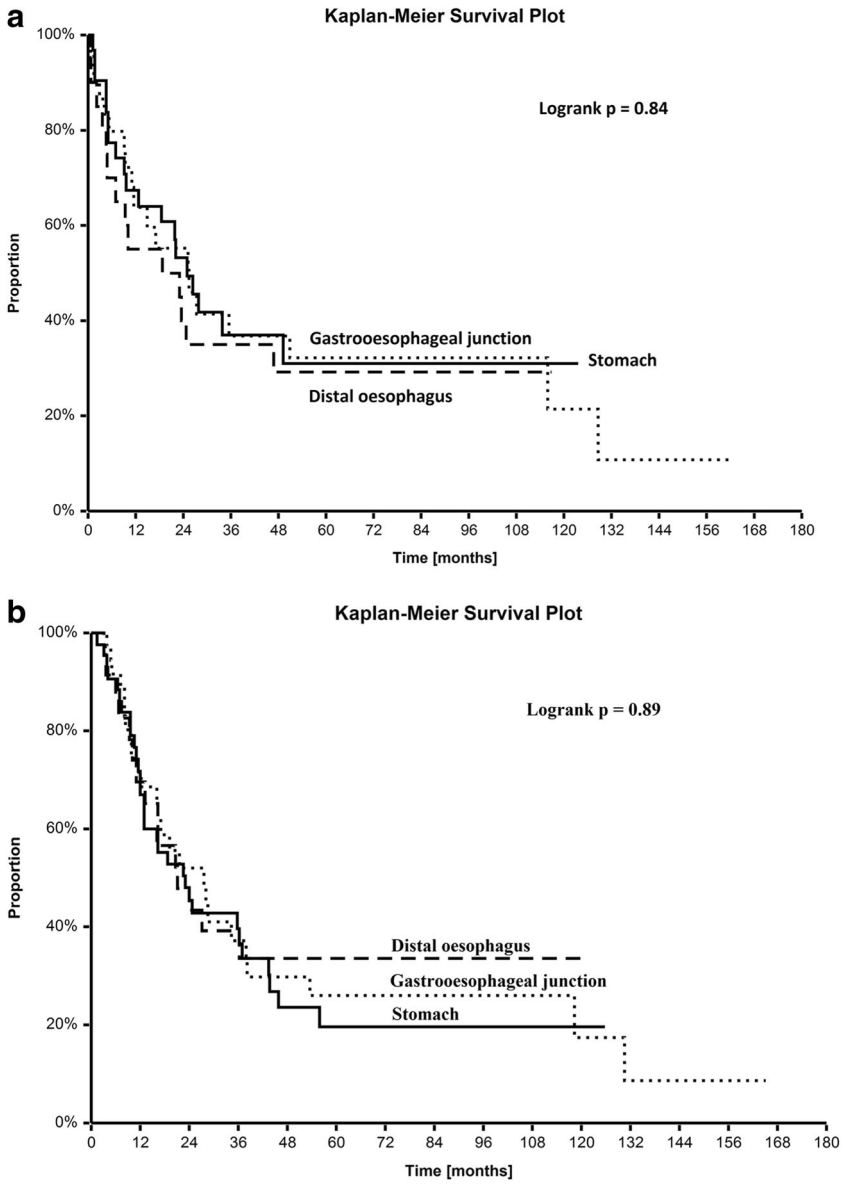

Fig. 2 Disease-free survival according to primary tumour origin (**a**) (n = 108). Overall survival according to primary tumour site (**b**) (n = 108)

cell carcinomas [3, 30]. Phase II trial ACOSOG Z4051 included only patients with locally advanced adenocarcinoma of distal esophagus and used preoperative RT plus concurrent docetaxel, cisplatin and panitumumab. The pathologic complete response rate was 33.3% among patients who underwent surgery and 27.7% in all enrolled patients [31].

Disease free survival and overall survival in the present study are shorter compared to the MAGIC trial [4]. This could be explained by patient selection in a prospective randomized trial like MAGIC. Many patients in the present study had borderline resectable disease and the institutional protocol did not include a diagnostic laparoscopy in patients without a suspicion of peritoneal dissemination. Therefore in some patients the disease was found to be unresectable during surgery after the chemoradiation. In comparison with other trials that used preoperative chemoradiation, including RTOG 9904 trial [7], the R0 resection rate and survival showed comparable results, although the disease-free survival and overall survival substantially depends on patient inclusion criteria in each trial.

In the statistical sub-analysis we focused on comparison of treatment results for three principal tumour locations and also on other putative prognostic factors that included pre-treatment clinical and post-treatment pathologic staging, grade of response, tumour type and grade, and angioinvasion and perineural invasion. Present data indicate that the primary site of adenocarcinoma has not impact on the prognosis. Further statistical analysis of tumour and treatment characteristics for primary sites (stomach versus distal oesophagus + GEJ) showed the presence of more negative prognostic factors in gastric cancer patients.

The important point for the discussion is a possible effect of adjuvant chemotherapy on the treatment outcome. In the

Table 4 Overall survival according to histological findings

		Median OS [m]	5-year OS [%] (95%CI)	Logrank test significance level
Lauren subtype	intestinal	28.0	32.7% (20.2–45.1)	$p = 0.028$
	diffuse + mixed	16.0	11.1% (0.00–24.7)	
Tumour grade	grade 1	34.3	50.0% (1.00–99.0)	$p = 0.03$
	grade 2	36.2	37.0% (19.7–54.3)	
	grade 3	18.8	17.0% (6.37–27.7)	
Angioinvasion	absent	43.6	41.6% (26.6–56.6)	$p = 0.0001$
	present	12.9	14.6% (0.12–29.2)	
Perineural invasion	absent	36.2	35.5% (22.8–48.2)	$p = 0.031$
	present	12.9	11.1% (0.00–31.0)	

Abbreviations: OS = overall survival.

present study, adjuvant treatment was administered in 42% of patients with gastric primary, and in 38% of patients with gastrooesophageal junction primary. With the exception of one patient, the patients with distal oesophageal primary were not treated with adjuvant chemotherapy as adjuvant chemotherapy is not a standard approach in oesophageal cancer. Adjuvant chemotherapy was not associated with any benefit nor in whole group of patients nor in subgroups of gastric and gastrooesophageal junction cancer. Furthermore, although adjuvant chemotherapy regimens demonstrated survival benefit in gastric cancer in Asian clinical trials, the benefit of adjuvant chemotherapy in Western countries is still considered ambiguous [32]. Therefore, we consider the impact of adjuvant chemotherapy on the conclusions of the present study is marginal, if any.

In contrast to the absence of an effect of the primary tumour site on prognosis, more differences were found in subanalyses for other parameters. This study confirmed that the pre-treatment clinical T-stage had statistically significant effect on overall survival, but pretreatment clinical N-stage had no such effect. This could be explained by an uncertainty regarding regional lymph node evaluation. In contrast, the pathological N-stage (univariate and multivariate analysis), as well as number of positive lymph nodes (univariate analysis), were statically significant prognostic factors for OS. Of note, pathological N-stage was found to be a predictor of survival in previously published papers [14, 15]. Obviously, in patients treated in the neoadjuvant setting pathological N-stage reflects not only the initial extent of the disease, but also response to therapy. The present study also noted that Lauren tumour type (univariate analysis), histological grade (univariate analysis), perineural invasion (univariate analysis) and angioinvasion (univariate and multivariate analysis) may significantly affect the prognosis.

Recently, Budgwell et al. published retrospective study in 192 gastric cancer patients, who underwent diagnostic laparoscopy, pre-operative chemoradiation and gastrectomy and reported age ≥ 65 years, male sex, R1 status and pN1, pN2 and pN3 status as statistically significant negative prognostic factors [33].

Table 5 Proportion of tumor or treatment characteristics in subgroups of gastric cancer and distal oesophageal/ gastrooesophageal junction cancer

Tumour or treatment parameter	Stomach ($n = 45$)	Distal oesophagus or gastrooesophageal junction ($n = 63$)	Chi-square significance level
Stage			
T2	7/45 (15.6%)	15/63 (23.8%)	$p = 0.325$
T3	31/45 (68.8%)	43/63 (68.3%)	
T4	7/45 (15.6%)	5/63 (8.9%)	
ypN0	14/35 (40.0%)	36/55 (65.5%)	$p = 0.031$
Histopathological grade:			
Grade 1	0/45 (0%)	4/62 (6.4%)	$p = 0.002$
Grade 2	10/45 (22.2%)	30/62 (48.4%)	
Grade 3	35/45 (77.8%)	28/62 (45.2%)	
Radical R0 resection	31/45 (68.9%)	52/63 (82.5%)	$p = 0.097$
Lauren type: diffuse + mixed	23/45 (51.1%)	10/57 (17.5%)	$p = 0.0003$
Angioinvasion	18/34 (52.9%)	14/53 (26.4%)	$p = 0.012$
Perineural invasion	5/34 (14.7%)	8/53 (15.1%)	$p = 0.960$

Several prior trials reported that pathological complete response after preoperative chemoradiation was associated with better overall survival [7, 15, 19, 23, 30]. The present study did not confirm these results. The improvement of overall survival in patients with pathological complete response rate was not statistically significant, although a trend toward significance was evident when the cutoff of 1% of residual tumor cells was used. Relatively low number of patients with pathological complete response in the present cohort may explain this lack of statistical significance.

Conclusions

The present retrospective study suggests that preoperative chemoradiation in patients with gastric adenocarcinoma is associated with similar survival results compared to distal oesophageal and gastrooesophageal junction adenocarcinoma. The histological type (according Lauren classification), grade, absence/presence of angioinvasion and perineural invasion, pretreatment clinical T-stage (but not pretreatment clinical N-stage), and pathological ypN-stage can predict patient prognosis better than the primary tumour location. The effect of pathologic response grade on overall survival was not statistically significant in the present study.

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Compliance with Ethical Standards

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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