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ORIGINAL ARTICLE

The Role of Continuing Perioperative Chemotherapy Post Surgery in Patients with Esophageal or Gastroesophageal Junction Adenocarcinoma: a Multicenter Cohort Study

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Abstract

Purpose The aim of this cohort study was to assess the benefit that patients with lower esophageal or gastroesophageal junction (E/GEJ) adenocarcinoma receive by continuing perioperative chemotherapy post-surgery.

Methods Three hundred twelve patients underwent radical tumor surgical resection after preoperative chemotherapy. Chemotherapy was mainly ECX (epirubicin, cisplatin, capecitabine). Propensity score matching (PSM) was used to compare continuation of chemotherapy post-surgery vs. no postoperative treatment.

Results Two hundred ten patients (67.3%) had GEJ and 102 (32.7%) lower esophageal adenocarcinoma. Microscopically clear surgical margins (R0), according to the Royal College of Pathologists, were achieved in 208 patients (66.7%). In total, 225 patients (72.1%) continued perioperative chemotherapy post-surgery. PSM was used to create two patient groups, well-balanced for basic epidemiological, clinical, and histopathological characteristics. The first included 148 patients who continued perioperative chemotherapy after surgery and the second 86, who did not receive postoperative treatment. The first group had non-significantly different median time-to-relapse (TTR 22.2 vs. 25.7 months, $p = 0.627$), overall survival (OS 46.1 vs. 36.7 months, $p = 0.199$), and post-relapse survival (15.3 vs. 8.7 months, $p = 0.122$). Subgroup analysis showed that only patients with microscopically residual disease after surgery (R1 resection) benefited from continuation of chemotherapy post-surgery for both TTR (hazard ratio [HR] 0.556, 95% CI 0.330–0.936, $p = 0.027$) and OS (HR 0.530, 95% CI 0.313–0.898, $p = 0.018$).

Conclusions Continuation of perioperative chemotherapy post-surgery was not associated with improved outcome in patients with E/GEJ adenocarcinoma. Patients with microscopically residual disease post-surgery might receive a potential benefit from adjuvant chemotherapy.

Keywords Esophageal–gastroesophageal junction adenocarcinoma · Perioperative chemotherapy · Adjuvant chemotherapy · Propensity score matching analysis · Prognosis

Introduction

Esophageal cancer is one of the most common and lethal cancers worldwide;[1] 5-year survival stubbornly remaining below 20%.[2] Squamous cell carcinoma (SCC) and adenocarcinoma represent the main histological subtypes of esophageal cancer and are widely accepted as distinct disease entities, due to different epidemiological, clinical, and molecular characteristics. For example, SCC is more common in Asia, while adenocarcinoma is more prevalent in the Western World. SCC usually involves the upper and middle esophagus, while adenocarcinoma is more common in the lower esophagus and gastroesophageal junction (E/GEJ). Additionally, a recent

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study demonstrated that adenocarcinoma has a molecular profile similar to the subtype of gastric adenocarcinoma with chromosomal instability.[3] Current treatment guidelines describe and study these two subtypes separately due to the different biology and higher radio-sensitivity of SCC as compared to adenocarcinoma.[4,5]

Surgery represents the cornerstone of curative treatment of E/GEJ adenocarcinoma, while the introduction of neoadjuvant/adjuvant chemotherapy and chemoradiotherapy has improved the outcome of this disease.[6–8] In the UK, perioperative chemotherapy is considered one of the standard therapeutic options, based on the landmark randomized MAGIC trial showing an improvement of 5-year overall survival (OS) from 23 to 36% with the addition of perioperative epirubicin/cisplatin/5-fluorouracil (ECF) chemotherapy to surgery.[6] Nevertheless, only 25% of the patients had E/GEJ cancer in this study. Recently, the FLOT4 randomized trial demonstrated a further benefit for 5-year OS from 36 to 45% with perioperative 5-fluorouracil/leucovorin/oxaliplatin/docetaxel (FLOT) chemotherapy versus (vs.) ECF.[9] Notably, in this trial more than half of the patients had GEJ adenocarcinoma and about one third of those having radical surgery did not start adjuvant chemotherapy, mostly due to postoperative morbidity, while less than half managed to complete the entire course of allocated adjuvant chemotherapy.[9] Therefore, the role of adjuvant chemotherapy has been questioned by many experts in the field of upper gastrointestinal tumors in favor of preoperative chemo (radio) therapy.[7,8,10]

The aim of this study was to evaluate whether patients with resectable E/GEJ adenocarcinoma benefit by continuation of perioperative chemotherapy postoperatively.

Materials and Methods

This multicenter cohort study included consecutive patients with upper gastrointestinal adenocarcinoma, who started perioperative chemotherapy from July 2009 to January 2017 in three tertiary referral centers (The Christie Hospital NHS Foundation Trust, Manchester; The Mid Yorkshire Hospitals NHS Trust, Wakefield; and St James's University Hospital, Leeds, UK) and were operated in centers of the Greater Manchester and Leeds regions from November 2009 to March 2017. The inclusion and exclusion criteria for this study are summarized in Table 1.

All patients underwent transthoracic esophageal resection, or extended gastrectomy when the tumor was deemed resectable through this approach. Following resection, all tumor specimens were assessed by specialist gastrointestinal pathologists. The status of surgical resection margin (R margin) was classified according to the Royal College of Pathologists (RCPath) criteria into R0 (negative) and R1 (microscopically positive).[11] We defined as infiltrated R margin the case when tumor cells are observed at the edge of the resection margin and close R margin the case when tumor cells are detected within 1 mm from the edge of the resection margin. Lymph node ratio (LNR) was defined as the number of lymph nodes infiltrated by cancer divided by the number of harvested lymph nodes in the surgical specimen. Data were collected retrospectively from case notes and pathology reports were reviewed. All cases were re-classified according to the Eighth Edition of the American Joint Committee on Cancer staging (AJCC8) of the esophagus or GEJ into neoadjuvant pathological stage groups (ypTN).[12]

Patients were classified into those who received at least 1 cycle of adjuvant chemotherapy and those who did not continue chemotherapy postoperatively due to postoperative morbidity or patient's decision. Patients who progressed or died within the first 3 months postoperatively were excluded from the study, because adjuvant chemotherapy was not expected to have influenced their already very poor prognosis. The standard chemotherapy regimen used was ECX (epirubicin 50 mg/m^2 on day 1, cisplatin 60 mg/m^2 on day 1, and capecitabine 650 mg/m^2 on days 1–21). Patients who were unable to swallow tablets received ECF (epirubicin 50 mg/m^2 on day 1, cisplatin 60 mg/m^2 on day 1, and 5-fluorouracil 200 mg/m^2 on days 1–21). Patients with renal dysfunction (glomerular filtration rate < 40 ml/min) received EOX (epirubicin 50 mg/m^2 on day 1, oxaliplatin 130 mg/m^2 on day 1, capecitabine 650 mg/m^2 on days 1–21) or ECarboX (epirubicin 50 mg/m^2 on day 1, carboplatin AUC 5 on day 1, capecitabine 650 mg/m^2 on days 1–21). Patients with cardiac dysfunction (left ventricular ejection fraction < 50%) were treated with MCX (mi-

Table 1 Inclusion and exclusion criteria

	Included	Excluded
Interventions	• At least one cycle (maximum 3) of neoadjuvant chemotherapy followed by surgery with curative intent	• Surgery with non-curative intent • Neoadjuvant or adjuvant radiotherapy
Histopathology results	• Histological confirmation of adenocarcinoma • Lower esophagus or Siewert type I-II tumors	• Proximal, mid-esophagus or Siewert type III tumors • Squamous cell carcinoma
Postoperative outcome	• No evidence of macroscopic tumor postoperatively	• Tumor relapse or death within the first 3 months postoperatively

Table 2 Comparison of basic characteristics between patients who received neoadjuvant and adjuvant chemotherapy and those who were treated only with neoadjuvant chemotherapy

		Adjuvant chemotherapy					Total	
		Yes		No				
Basic characteristics	Subgroups	*N*	%	*N*	%	*p* value	*N*	%
Age (years)	< 65	106	47.1	42	48.3	0.900	148	47.4
	≥ 65	119	52.9	45	51.7		164	52.6
Sex	Male	191	84.9	77	88.5	0.472	268	85.9
	Female	34	15.1	10	11.5		44	14.1
Primary site	Lower esophagus	66	29.3	36	41.4	0.045	102	32.7
	GEJ	159	70.7	51	58.6		210	67.3
Type of operation	Transthoracic esophageal resection	199	88.4	80	92.0	0.419	279	89.4
	Extended gastrectomy	26	11.6	7	8.0		33	10.6
T stage	ypT0	11	4.9	9	10.3	0.444	20	6.4
	ypT1	30	13.3	11	12.6		41	13.1
	ypT2	28	12.4	13	14.9		41	13.1
	ypT3	144	64.0	50	57.5		194	62.2
	ypT4	12	5.3	4	4.6		16	5.1
N stage	ypN0	94	41.8	35	40.2	0.227	129	41.3
	ypN1	55	24.4	19	21.8		74	23.7
	ypN2	45	20.0	13	14.9		58	18.6
	ypN3	31	13.8	20	23.0		51	16.3
AJCC8 stage	I	53	23.6	22	25.3	0.139	75	24.0
	II	40	17.8	13	14.9		53	17.0
	IIIA	12	5.3	8	9.2		20	6.4
	IIIB	83	36.9	22	25.3		105	33.7
	IVA	37	16.4	22	25.3		59	18.9
Lymph node ratio	0%	94	41.8	35	40.2	0.540	129	41.3
	1–19%	72	32.0	24	27.6		96	30.8
	≥ 20	59	26.2	28	32.2		87	27.9
Histological differentiation	Pathological complete response	9	4.0	9	10.3	0.085	18	5.8
	Well	15	6.7	2	2.3		17	5.4
	Moderate	81	36.0	30	34.5		111	35.6
	Poor	120	53.3	46	52.9		166	53.2
Lymphovascular invasion	No	124	55.1	45	51.7	0.614	169	54.2
	Yes	101	44.9	42	48.3		143	45.8
R margins (RCPath criteria)	Negative	156	69.3	52	59.8	0.111	208	66.7
	Positive	69	30.7	35	40.2		104	33.3
Positive margin (RCPath criteria)	All margins negative	156	69.3	52	59.8	0.169	208	66.7
	CRM	61	27.1	27	31.0		88	28.2
	Proximal margin	7	3.1	6	6.9		13	4.2
	Distal margin	0	0.0	1	1.1		1	0.3
	CRM + Distal margin	1	0.4	1	1.1		2	0.6
Distance from R margin	> 1 mm	156	69.3	52	59.8	0.258	208	66.7
	0.1–1 mm (close margins)	37	16.4	20	23.0		57	18.3
	0 mm (infiltrated margins)	32	14.2	15	17.2		47	15.1
N of neoadjuvant chemotherapy cycles	1	0	0.0	5	5.8	< 0.001	5	1.6
	2	5	2.2	13	14.9		18	5.8
	3	220	97.8	69	79.3		289	92.6
Total		225	100	87	100		312	100

AJCC8 stage post-neoadjuvant pathology stage according to the 8th edition of the American Committee on Cancer staging, *CRM* circumferential resection margin, *GEJ* gastroesophageal junction, *R margin* surgical resection margin, *RCPath* Royal College of Pathologists

tomycin 7 mg/m^2 on alternate cycles, cisplatin 60 mg/m^2 on day 1, capecitabine 650 mg/m^2 on days 1–21). Finally, patients who wanted to avoid alopecia underwent chemotherapy with modified FOLFOX (oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, 5-fluorouracil 400 mg/m^2, and 5-fluorouracil 2400 mg/m^2 48 h infusion, all started on day 1).

The current study was performed as part of a clinical audit approved by the Audit Department of the Christie NHS Foundation Trust (CE15/1604). All procedures were conducted in accordance with the Helsinki Declaration, as revised in 2013.[13]

Statistical Analysis

Statistical analysis was performed using statistical package SPSS® version 22.0 (SPSS, Chicago, IL, USA). Cases were

Table 3 Basic characteristics independently associated with continuation of perioperative chemotherapy post surgery

Basic characteristics	Subgroups	OR	95% CI		*p* value
			Lower	Upper	
Age (years)	≥ 65 vs. < 65	1.000	0.578	1.730	0.999
Sex	Female vs. male	1.474	0.636	3.412	0.365
Primary site	GEJ vs. lower esophagus	1.528	0.864	2.702	0.145
Type of operation	Extended gastrectomy vs. transthoracic esophageal resection	1.170	0.445	3.076	0.750
T stage	ypT3–4 vs. ypT0–2	2.399	1.167	4.934	0.017
N stage	ypN2–3 vs. ypN0–1	0.783	0.401	1.530	0.475
Histological differentiation	Poor vs. pCR-well-moderate	1.037	0.591	1.819	0.899
Lymphovascular invasion	Yes vs. no	0.897	0.480	1.679	0.734
R margins (RCPath criteria)	Positive vs. negative	0.461	0.231	0.918	0.028
N of cycles of neoadjuvant chemotherapy	3 vs. 1–2	12.909	4.483	37.169	0.001

95% CI 95% confidence intervals, *GEJ* gastroesophageal junction, *OR* hazard ratio, *pCR* pathological complete response, *R margin* surgical resection margin, *RCPath* Royal College of Pathologists

classified according to baseline characteristics, namely age (≥ 65 vs. < 65 years), sex (male vs. female), primary tumor site (GEJ vs. esophagus), type of surgery (transthoracic esophagectomy vs. extended gastrectomy), T stage (ypT0 vs. ypT1 vs. ypT2 vs. ypT3 vs. ypT4a), ypN stage (ypN0 vs. ypN1 vs. ypN2 vs. ypN3), LNR (0 vs. 1–19 vs. 20–100%), tumor histological differentiation (well/moderate vs. poor), lymphovascular invasion (LVI) (yes vs. no), and R margin status (R0 vs. R1, type of positive margin, infiltrated vs. close R margin vs. R0). The baseline characteristics of patients who received and those who were not treated with adjuvant chemotherapy were compared by chi-square test.

Propensity score matching (PSM) was used to construct two well-balanced groups of patients, where the effect of adjuvant chemotherapy will be assessed.[14] Initially, a propensity score was calculated for each patient using a logistic regression model, fitted for the delivery or not of adjuvant chemotherapy according to the following covariates: age ≥ 65 vs. < 65 years, male vs. female sex, primary tumor site, type of operation, ypT0–2 vs. ypT3–4, ypN0 vs. ypN1 vs. ypN2–3, pathological complete response (pCR) and well-moderately vs. poorly differentiated histology, present vs. absent LVI, and R0 vs. R1. Then, 2:1 matched study groups were created using the nearest-neighbor (greedy) matching without replacement, with a caliper set at 0.20.

We assessed the effect of adjuvant chemotherapy on time-to-relapse (TTR) and overall survival (OS) in the two groups of patients that were selected by PSM. Survival curves were constructed by the Kaplan-Meier method, and survival comparisons were performed using the log-rank test. TTR was defined as the time from the date of surgery until the date of disease relapse and OS as the time from the date of operation until the date of death from any cause. Cox proportional hazards models were used to assess the prognostic significance of continuing chemotherapy postoperatively for each patient subgroup.

All statistical comparisons were two-sided and differences were considered statistically significant for a p value < 0.05. Due to the retrospective nature of the study, as well as the application of PSM to select the matched study groups for analysis, no formal sample size calculation was performed.

Results

In total, 312 eligible patients were included in the analysis. Adjuvant chemotherapy was initiated in 225 patients (72.1%). Of them, 213 patients (94.6%) received at least one postoperative cycle of ECX, while the rest had received other regimens (five ECarboX, three EOX, two MCX, one ECF, one FOLFOX). One hundred fifty-seven patients (69.8%) completed 3 cycles of adjuvant chemotherapy, 48 (21.3%) received 2 cycles, and 20 (8.9%) 1 cycle. Two hundred seventy-nine patients (89.4%) underwent two-stage transabdominal and transthoracic resection of the esophagus, while 33 (10.6%) underwent extended total gastrectomy. The median number of harvested lymph nodes was 19 (range, 3–75). Of 143 LVI positive patients, 120 (83.9%) had infiltrated lymph nodes, while among 169 LVI negative patients 63 (37.3%) had positive lymph nodes (chi-square, $p < 0.001$).

Table 2 describes the basic characteristics of patients who were treated with neoadjuvant and adjuvant chemotherapy and of those who received only neoadjuvant chemotherapy without continuing chemotherapy postoperatively. Notably, patients with lower esophageal primaries received statistically less postoperative chemotherapy. Also, those who did not complete 3 cycles of neoadjuvant chemotherapy were less likely to continue chemotherapy postoperatively. Factors independently associated with

Table 4 Comparison of basic characteristics between patients who received neoadjuvant and adjuvant chemotherapy and those who were treated only with neoadjuvant chemotherapy, after propensity score matching

		Adjuvant chemotherapy					Total	
		Yes		No				
Basic characteristics	Subgroups	*N*	%	*N*	%	*p* value	*N*	%
Age (years)	< 65	66	44.6	42	48.8	0.587	108	46.2
	≥ 65	82	55.4	44	51.2		126	53.8
Sex	Male	130	87.8	76	88.4	1.000	206	88.0
	Female	18	12.2	10	11.6		28	12.0
Primary site	Lower esophagus	53	35.8	36	41.9	0.403	89	38.0
	GEJ	95	64.2	50	58.1		145	62.0
Type of operation	Transthoracic esophageal resection	132	89.2	79	91.9	0.650	211	90.2
	Extended gastrectomy	16	10.8	7	8.1		23	9.8
T stage	ypT0	8	5.4	9	10.5	0.543	17	7.3
	ypT1	20	13.5	11	12.8		31	13.2
	ypT2	24	16.2	12	14.0		36	15.4
	ypT3	84	56.8	50	58.1		134	57.3
	ypT4	12	8.1	4	4.7		16	6.8
N stage	ypN0	59	39.9	35	40.7	0.272	94	40.2
	ypN1	35	23.6	19	22.1		54	23.1
	ypN2	32	21.6	12	14.0		44	18.8
	ypN3	22	14.9	20	23.3		42	17.9
AJCC8 stage	I	39	26.4	22	25.6	0.432	61	26.1
	II	19	12.8	13	15.1		32	13.7
	IIIA	10	6.8	8	9.3		18	7.7
	IIIB	52	35.1	21	24.4		73	31.2
	IVA	28	18.9	22	25.6		50	21.4
Lymph node ratio	0%	59	39.9	35	40.7	0.676	94	40.2
	1–19%	47	31.8	23	26.7		70	29.9
	≥ 20	42	28.4	28	32.6		70	29.9
Histological differentiation	Pathological complete response	7	4.7	9	10.5	0.126	16	6.8
	Well	12	8.1	2	2.3		14	6.0
	Moderate	54	36.5	30	34.9		84	35.9
	Poor	75	50.7	45	52.3		120	51.3
Lymphovascular invasion	No	76	51.4	45	52.3	0.893	121	51.7
	Yes	72	48.6	41	47.7		113	48.3
R margins (RCPath criteria)	Negative	91	61.5	52	60.5	0.890	143	61.1
	Positive	57	38.5	34	39.5		91	38.9
Positive margin (RCPath criteria)	All margins negative	91	61.5	52	60.5	0.642	143	61.1
	CRM	49	33.1	26	30.2		75	32.1
	Proximal margin	7	4.7	6	7.0		13	5.6
	Distal margin	0	0.0	1	1.2		1	0.4
	CRM + Distal margin	1	0.7	1	1.2		2	0.9
Distance from R margin	> 1 mm	91	61.5	52	60.5	0.944	143	61.1
	0.1–1 mm (close margins)	30	20.3	19	22.1		49	20.9
	0 mm (infiltrated margins)	27	18.2	15	17.4		42	17.9
N of neoadjuvant chemotherapy cycles	1	0	0.0	5	5.8	< 0.001	5	2.2
	2	3	2.0	13	15.1		16	6.8
	3	145	98.0	68	79.1		213	91.0
Total		148	100	86	100		234	100

AJCC8 stage post-neoadjuvant pathology stage according to the 8th edition of the American Committee on Cancer staging, *CRM* circumferential resection margin, *GEJ* gastroesophageal junction, *R margin* surgical resection margin, *RCPath* Royal College of Pathologists

continuation of perioperative chemotherapy post-surgery were the completion of 3 cycles of preoperative chemotherapy, the absence of microscopically residual disease (R0 resection), and more deeply invasive primary tumors (ypT3–4), as described in Table 3. PSM resulted in the selection of two groups of patients, the first including patients who received both neoadjuvant and adjuvant chemotherapy and the second including patients who received only neoadjuvant chemotherapy. Both groups were well-balanced for basic characteristics, as described in Table 4, with the exception of early discontinuation of neoadjuvant chemotherapy, which was much more common in those patients who did not receive adjuvant chemotherapy.

At a median follow-up time of 45.3 months (range, 3.4–81.5), 140 patients (44.9%) had relapsed and 146 (46.8%) had died. Of the latter, 23 (15.8%) died without known tumor

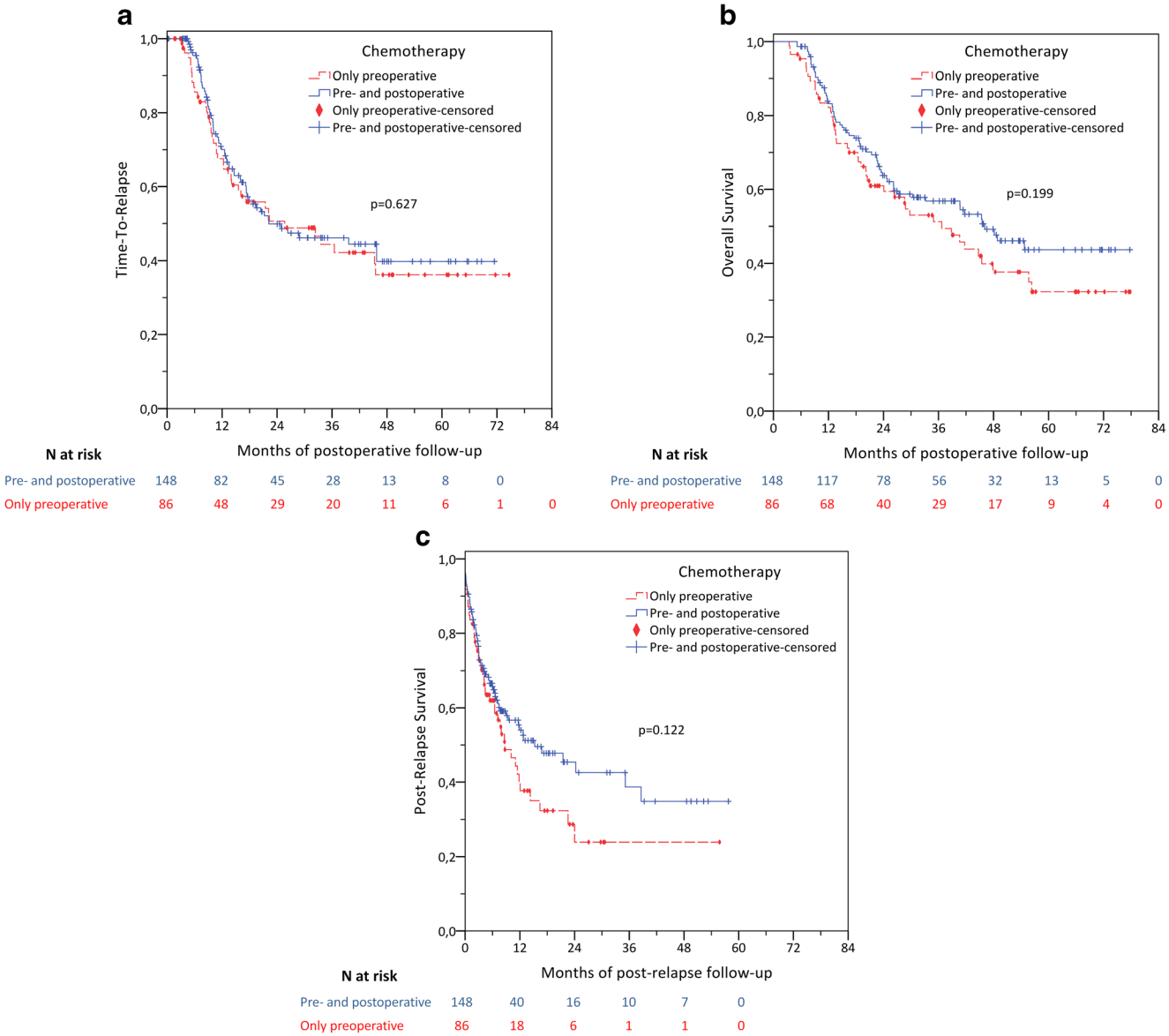

Fig. 1 Survival curves for time-to-relapse, overall, and post-relapse survival of patients treated with pre- and postoperative chemotherapy vs. only preoperative chemotherapy after propensity score matching (**a**, **b**, and **c**, respectively)

relapse. Median TTR was 24.9 months (95% CI 18.1–31.7) and median OS was 45.4 months (95% CI 37.1–53.7). Post-relapse survival was 12.7 months (95% CI 9.2–16.2). Patients treated with neoadjuvant and adjuvant chemotherapy, compared to those who did not continue their chemotherapy post-surgery, had similar TTR (24.9 [95% CI 18.5–31.3] vs. 22.3 [95% CI 5.2–39.4] months, respectively, $p = 0.574$) and only a trend for longer OS (48.2 [95% CI 38.6–57.7] vs. 36.7 [95% CI 24.4–49.0] months, respectively, $p = 0.077$). Also, those who received pre- and postoperative chemotherapy had statistically longer post-relapse survival (15.3 months, 95% CI 7.4–23.1) compared to those who received chemotherapy only before operation (8.7 months, 95% CI 4.9–12.5, $p = 0.045$). Of patients who received both neoadjuvant and adjuvant chemotherapy, 13/98 (13.3%) died without known tumor relapse, while among patients who were treated only with neoadjuvant chemotherapy, a non-significantly higher proportion (10/48, 20.8%) died without reported tumor relapse (chi-square test, $p = 0.239$). After PSM, the groups of patients who continued their chemotherapy postoperatively compared to those who received only neoadjuvant chemotherapy had again similar TTR (22.2 [95% CI 4.1–40.3] vs. 25.7 [95% CI 8.6–42.8] months, respectively, $p = 0.627$, Fig. 1a) and non-significantly longer OS (46.1 [95% CI 35.1–57.0] vs. 36.7 [95% CI 24.5–48.9] months, respectively, $p = 0.199$, Fig. 1b). Finally, those who received pre- and postoperative chemotherapy retained a trend for longer post-relapse survival (15.3 months, 95% CI 5.7–24.8) compared to those who received chemotherapy only before operation (8.7 months, 95% CI 4.9–12.5, $p = 0.122$, Fig. 1c).

Table 5 Impact of receiving neoadjuvant and adjuvant chemotherapy compared to those who were treated only with neoadjuvant chemotherapy on time-to-relapse within each subgroup in the propensity score-matched population and statistical interaction between adjuvant chemotherapy and basic characteristics

		Time-to-relapse				
		HR	95% CI		*p* value	*p* value
Basic characteristics	Subgroups		Lower	Upper	for subgroups	for interaction
Age (years)	< 65	0.688	0.402	1.178	0.173	0.155
	≥ 65	1.227	0.685	2.199	0.492	
Sex	Male	0.909	0.598	1.382	0.655	0.987
	Female	0.893	0.290	2.751	0.844	
Primary site	Lower esophagus	0.857	0.435	1.688	0.655	0.863
	GEJ	0.926	0.571	1.502	0.756	
Type of operation	Transthoracic esophageal resection	0.971	0.644	1.465	0.889	0.189
	Extended gastrectomy	0.390	0.104	1.466	0.164	
T stage	ypT0–2	1.693	0.585	4.898	0.331	0.095
	ypT3–4	0.663	0.433	1.015	0.059	
N stage	*ypN0*	*0.349*	*0.129*	*0.945*	*0.038*	0.340
	ypN1	1.491	0.638	3.482	0.357	
	ypN2–3	0.823	0.488	1.388	0.465	
AJCC8 stage	I–IIIA	0.556	0.243	1.269	0.163	0.419
	IIIB–IVA	0.839	0.531	1.328	0.454	
Histological differentiation	pCR-well-moderate	0.845	0.440	1.621	0.612	0.968
	Poor	0.874	0.533	1.431	0.592	
Lymphovascular invasion	No	0.825	0.427	1.594	0.567	0.978
	Yes	0.846	0.517	1.384	0.505	
R margins (RCPath criteria)	Negative	1.349	0.727	2.502	0.343	*0.029*
	Positive	*0.556*	*0.330*	*0.936*	*0.027*	
N of cycles of neoadjuvant chemotherapy	1–2	0.031	0.000	12.584	0.257	0.964
	3	0.979	0.634	1.512	0.925	

Statistically significant results are marked in italics

AJCC8 stage post-neoadjuvant pathology stage according to the 8th edition of the American Committee on Cancer staging, *95% CI* 95% confidence intervals, *GEJ* gastroesophageal junction, *HR* hazard ratio, *pCR* pathological complete response, *R margin* surgical resection margin, *RCPath* Royal College of Pathologists

The impact of continuing chemotherapy postoperatively vs. no adjuvant treatment on prognosis of each subgroup of patients with different basic characteristics is described in Table 5 for TTR and Table 6 for OS. Importantly, continuation of chemotherapy postoperatively did not affect TTR or OS of those patients who had completed all the 3 cycles of the preoperative chemotherapy. Moreover, only patients with R1 margin seemed to fare better with adjuvant chemotherapy for both TTR and OS. Additionally, a statistically significant interaction for TTR was observed between the status of R margin and adjuvant chemotherapy, which still remained ($p = 0.017$) when only patients who had completed 3 cycles of neoadjuvant chemotherapy were selected. The respective survival curves are shown in Fig. 2 (a–d). In contrast, neither patients with AJCC8 stages I–IIIA nor those with stages IIIB–IVA had better outcome with adjuvant chemotherapy (respective survival curves shown in Fig. 3). However, patients with deeply invasive tumors (ypT3–4) tended to fare better with adjuvant chemotherapy, while paradoxically, only patients with tumor-free lymph nodes tended to have better prognosis when receiving adjuvant chemotherapy compared to patients with positive lymph nodes who did not seem to derive any benefit from adjuvant chemotherapy.

Discussion

The present study showed that continuing perioperative chemotherapy postoperatively might not improve patient outcome. The study question was based on the fact that a significant portion of the patients on perioperative chemotherapy for gastric/GOJ cancer do not receive the adjuvant part of the treatment.[6,9] Early disease progression or death, patient preference, previous toxicity, or surgical complications commonly contribute to that. An interim analysis of TOPGEAR

Table 6 Impact of receiving neoadjuvant and adjuvant chemotherapy compared to only with neoadjuvant chemotherapy on overall survival within each subgroup in the propensity score-matched population and statistical interaction testing between adjuvant chemotherapy and basic characteristics

		Overall survival				
		HR	95% CI		*p* value	*p* value
Basic characteristics	Subgroups		Lower	Upper	for subgroups	for interaction
Age (years)	< 65	0.684	0.399	1.172	0.167	0.428
	≥ 65	0.906	0.538	1.525	0.711	
Sex	Male	0.752	0.506	1.115	0.156	0.520
	Female	1.067	0.328	3.470	0.914	
Primary site	Lower esophagus	0.912	0.498	1.670	0.765	0.571
	GEJ	0.716	0.444	1.153	0.169	
Type of operation	Transthoracic esophageal resection	0.823	0.557	1.216	0.328	0.413
	Extended gastrectomy	0.543	0.152	1.942	0.348	
T stage	ypT0–2	1.131	0.486	2.632	0.775	0.248
	ypT3–4	*0.626*	*0.412*	*0.952*	*0.028*	
N stage	ypN0	0.438	0.192	1.003	0.051	0.553
	ypN1	1.265	0.561	2.852	0.571	
	ypN2–3	0.708	0.428	1.171	0.178	
AJCC8 stage	I–IIIA	0.687	0.335	1.412	0.307	0.965
	IIIB–IVA	0.685	0.440	1.067	0.094	
Histological differentiation	pCR-well-moderate	0.712	0.375	1.351	0.299	0.755
	Poor	0.800	0.504	1.269	0.344	
Lymphovascular invasion	No	0.852	0.464	1.563	0.604	0.519
	Yes	0.675	0.419	1.086	0.105	
R margins (RCPath criteria)	Negative	0.965	0.557	1.671	0.900	0.153
	Positive	*0.530*	*0.313*	*0.898*	*0.018*	
N of cycles of neoadjuvant chemotherapy	1–2	0.032	0.000	16.029	0.277	0.457
	3	0.828	0.552	1.243	0.362	

Statistically significant results are marked in italics

AJCC8 stage post-neoadjuvant pathology stage according to the 8th edition of the American Committee on Cancer staging, *95% CI* 95% confidence intervals, *GEJ* gastroesophageal junction, *HR* hazard ratio, *pCR* pathological complete response, *R margin* surgical resection margin, *RCPath* Royal College of Pathologists

randomized trial showed that only 65% of patients in the perioperative chemotherapy arm completed the postoperative part of ECF/ECX.[15] In this trial, approximately 22% of patients experienced grade 3 or higher postoperative complications, thus representing the main reason of not receiving adjuvant chemotherapy. Postoperative complications after curative surgery for gastric cancer decrease the likelihood of patients to receive adjuvant chemotherapy, affecting adversely their overall outcome.[16] Therefore, it is plausible to prefer to administer preoperative chemotherapy or chemoradiotherapy instead of postoperative treatment, especially in E/GEJ adenocarcinoma which was under-represented in SWOG/INT-0116 clinical trial[17] and nearly absent in randomized trials of adjuvant chemotherapy from Far East.[18,19]

Current evidence from prospective randomized clinical trials does not answer the question as to whether postoperative chemo (radio) therapy offers any survival benefit in patients with E/GEJ adenocarcinoma. What has been proven is only that preoperative chemo (radio) therapy[7,8] or perioperative chemotherapy[6] is superior to surgery alone. In addition, OE05 clinical trial demonstrated that 4 cycles of preoperative ECX were no better than 2 cycles of cisplatin-5-fluorouracil with respect to survival in patients with E/GEJ adenocarcinoma and thus it was concluded that offering more chemotherapy before surgery does not improve patient outcome.[20] Currently, the TOPGEAR trial is investigating the impact of treatment intensification by adding preoperative chemoradiotherapy to perioperative chemotherapy.[15] The only trials that are expected to answer to the question of whether postoperative treatment is necessary in E/GOJ patients who have already received preoperative treatment are the NEO-AEGIS clinical trial which is comparing the MAGIC and CROSS regimens,[21] and the ESOPEC trial which is comparing the new standard of care (FLOT) to the CROSS protocol.[22] Their results are awaited and might change our institutions' current standard which is perioperative chemotherapy in E/GEJ adenocarcinoma.

Therefore, to our knowledge, the only evidence available to answer the above question arises from retrospective studies.

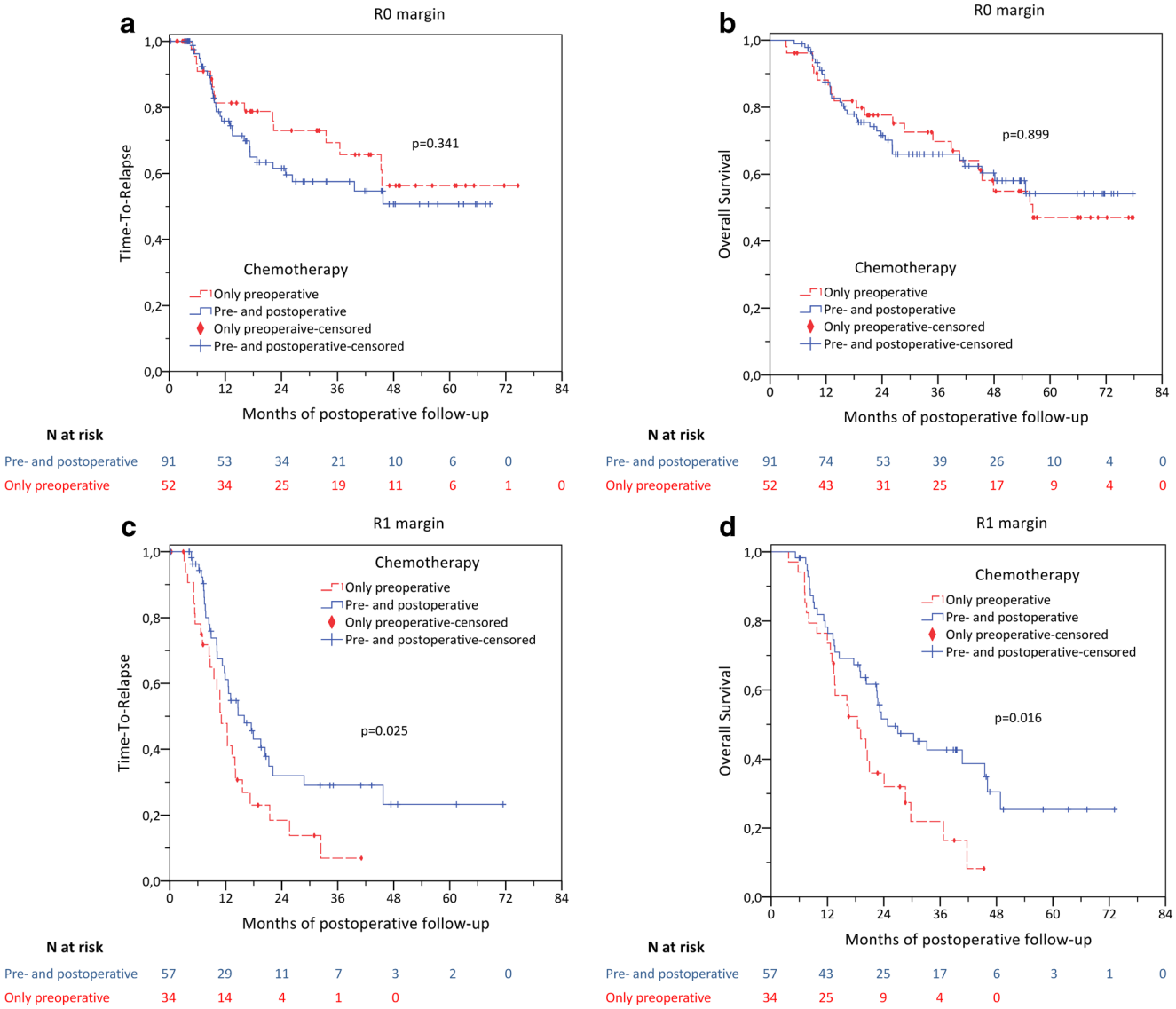

Fig. 2 Survival curves for time-to-relapse and overall survival of patients (propensity score-matched population) treated with pre- and postoperative chemotherapy vs. only preoperative chemotherapy and who underwent R0 (**a** and **b**, respectively) and R1 margin resection (**c** and **d**, respectively)

The largest analysis to date included 1694 patients with lymph node positive esophageal adenocarcinoma, from the US National Cancer Database, who underwent esophagectomy without neoadjuvant treatment.[23] Patients who received postoperative chemotherapy had improved survival, while the addition of radiotherapy to chemotherapy did not improve outcome. However, the studies main weakness is that the database included cases from multiple centers, with no information on the type of chemotherapy given. In contrast, determining whether receiving the postoperative part of perioperative chemotherapy makes any difference in patient outcome is addressed by only a few small studies. In 66 patients treated with perioperative ECF chemotherapy for gastroesophageal adenocarcinoma, patients who continued their chemotherapy postoperatively had statistically longer survival.[24] Luc et al. demonstrated comparable results in a trial of 110 patients with similar characteristics.[25] A larger study of 134 esophagogastric cancer patients treated with perioperative ECF, EOX, or FLOT showed that the benefit from continuing chemotherapy post surgery might be limited to those harboring ypN positive tumors with poor histological regression.[26] In contrast, Saunders et al. demonstrated the opposite results: only patients with esophagogastric adenocarcinoma with Mandard tumor regression grade 1–3 benefited by continuing perioperative ECX/ECF/EOX post surgery.[27] Finally, Sisic et al. demonstrated a potential benefit of receiving the postoperative part of treatment only with FLOT chemotherapy or in tumors with non-intestinal histology.[28]

Strength of the above studies is that they include relatively homogeneous populations treated with standard chemotherapy

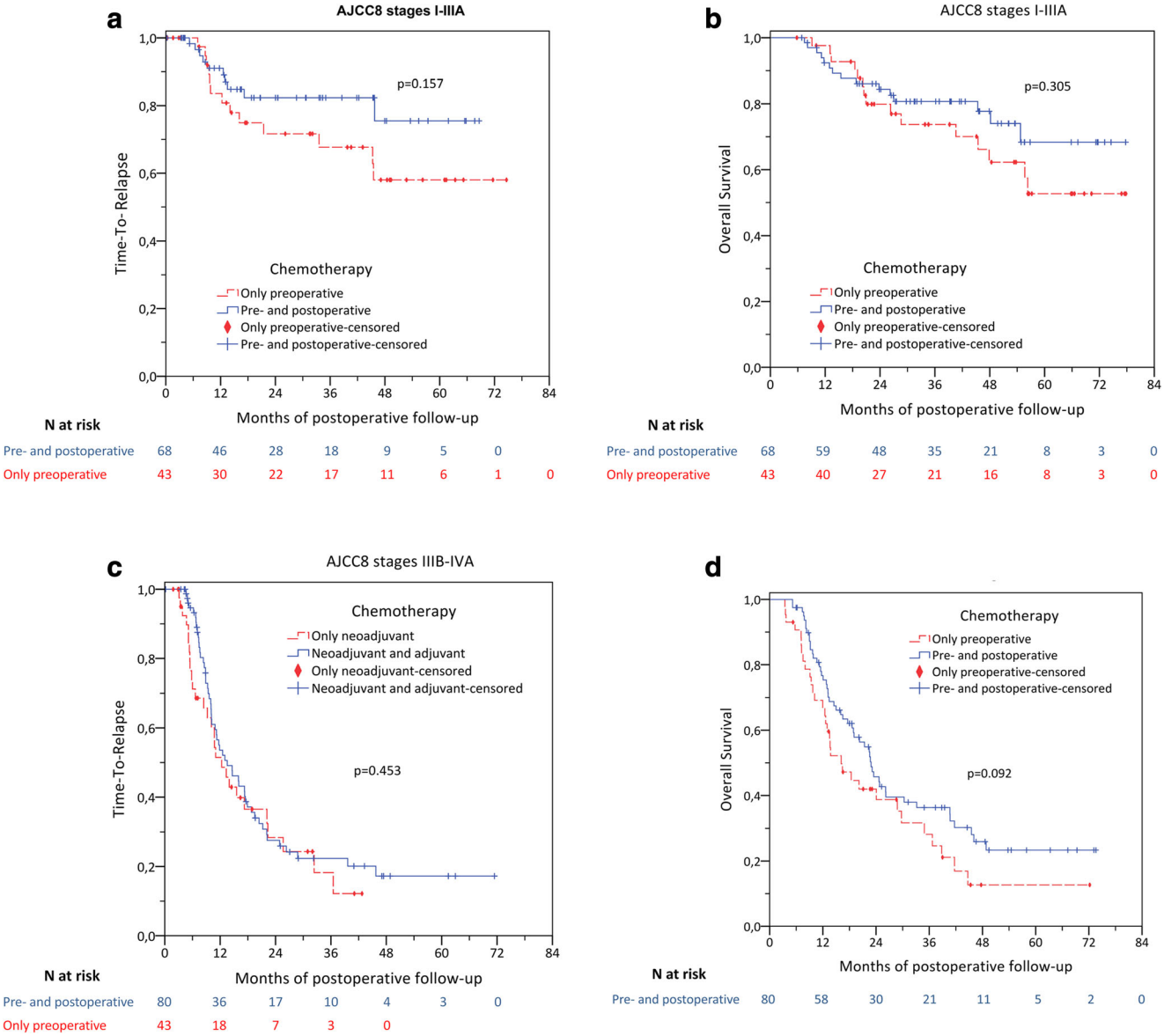

Fig. 3 Survival curves for time-to-relapse and overall survival of patients (propensity score-matched population) treated with pre- and postoperative chemotherapy vs. only preoperative chemotherapy and who had AJCC8 post-neoadjuvant pathology stages I–IIIA (**a** and **b**, respectively) and IIIB–IVA (**c** and **d**, respectively)

regimens. However, in our opinion, the fact that they did not use PSM analysis makes their interpretation less convincing. PSM analysis is considered as the standard statistical method to compare different treatments in retrospective populations, by creating groups of patients with well-balanced baseline characteristics, which might have prognostic significance.[14] PSM analysis is not, however, a substitute for prospective randomized trials, as it cannot balance groups for unknown prognostic factors as randomization can do. Thus, selection bias might be still unavoidable with this method.

Another concern with these trials is that they include, in the same analysis, patients with gastric and E/GEJ adenocarcinoma. The risk of microscopic residual disease is much higher after surgical resection of E/GEJ tumors compared to gastric tumors,[29,30] due to the proximity of the circumferential resection margin (CRM) to the E/GEJ tumors. In contrast, the stomach is an intraperitoneal organ, thus in gastric tumor surgery there is no CRM unless it extends to the GEJ. ESMO and NCCN guidelines[4,31,32] have a distinct chapter for esophageal and gastric adenocarcinoma, implying that they may require different treatment approaches.

Our study is the first to show that continuation of perioperative chemotherapy post-surgery might benefit only patients with R1 resections (by RCPath criteria), even though they were less likely to receive postoperative chemotherapy. Patients with infiltrated surgical margins are considered having microscopic residual disease. Therefore they are at high risk of developing tumor recurrence and thus adjuvant

treatment might reduce this risk. Although no direct evidence from randomized trials exists that adjuvant treatment improves disease outcome in R1 cases, especially in the case where neoadjuvant treatment has already been administered, large retrospective studies showed a potential benefit from adjuvant chemotherapy[30] and chemoradiotherapy.[33] However, both these studies included heterogeneous populations, with regard to histological subtype and treatment. Park et al.[34] and Qiu et al.[35] demonstrated improved disease outcome with postoperative chemotherapy but not radiotherapy in retrospective analyses of 71 and 124 patients, respectively, with esophageal SCC. Finally, Gertler et al.[36] showed that 15/83 patients who underwent an R1 surgery for GEJ adenocarcinoma and received postoperative treatment, mostly chemoradiotherapy, demonstrated a trend for improved survival compared to those who did not receive any adjuvant treatment. Therefore, to our knowledge, the present study was the first to demonstrate a survival benefit from continuing the same chemotherapy regimen postoperatively in patients with microscopically involved margins. Importantly, we did not administer postoperative radiotherapy in any patient with positive resection margins as there is no evidence from randomized trials that this treatment can offer additional benefit especially when neoadjuvant chemotherapy has already been offered.

Of interest, patients who continued their perioperative chemotherapy post-surgery had statistically better post-relapse survival. This difference might be explained by the fact that patients who did not receive adjuvant chemotherapy might have been less fit to receive chemotherapy post-relapse, although this was not recorded. Another explanation could be that these patients might had experienced higher toxicity during neoadjuvant chemotherapy or had declined to complete neoadjuvant treatment, thus precluding them from receiving chemotherapy postoperatively as well as post-relapse.

Our study has several strengths that should be highlighted. All patients were treated in a relatively short period of time with a relatively homogeneous treatment. More specifically, all patients had E/GEJ adenocarcinoma, all patients received at least 1 cycle of neoadjuvant chemotherapy, the vast majority having 3 cycles of neoadjuvant ECX. Also, patients who relapsed or died within the first 3 postoperative months were excluded, because these patients might be considered to have lost the opportunity to benefit from adjuvant chemotherapy. In addition, no patient received radiotherapy pre- or post-surgery according to routine local practice regarding the treatment of E/GEJ adenocarcinoma. Potential weaknesses are the relatively small sample size and the retrospective nature of the study. Also, there was still some heterogeneity in the current cohort, as a small number of patients did not undergo a transthoracic operation and did not receive ECX. We believe that these small minorities cannot significantly influence the results; instead, their exclusion might have put the study in additional risk of unknown selection bias. Finally, not all patients who started adjuvant chemotherapy managed to complete 3 cycles. Due to sample size restrictions, these patients were analyzed as a single group.

Conclusions

In conclusion, the present study was not able to demonstrate a benefit in survival by continuing perioperative ECX-based chemotherapy post-surgery. However, subgroup analysis and statistical interaction testing showed that patients with involved surgical margins (by RCPath criteria) might derive some benefit. In our opinion, these findings are important, due to the lack of definitive evidence on how to treat these patients. Undoubtedly, prospective studies are required for confirmation.

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Compliance with Ethical Standards

Conflict of Interest None.

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