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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Is Preoperative Chemotherapy Followed by Surgery the Appropriate Treatment for Signet Ring Cell Containing Adenocarcinomas of the Esophagogastric Junction and Stomach?

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Background. Recent data suggest primary resection as the preferable approach in patients with signet ring cell gastric cancer (SRC). The aim of our retrospective exploratory study was to evaluate the influence of SRC on prognosis and response in esophagogastric adenocarcinoma treated with neoadjuvant chemotherapy.

Methods. A total of 723 locally advanced esophagogastric adenocarcinomas (cT3/4 N any) documented in a prospective database from two academic centers were classified according to the WHO definition for SRC (more than 50 % SRC) and analyzed for their association with response and prognosis after neoadjuvant treatment.

Results. A total of 235 tumors (32.5 %) contained SRC. Median survival of SRC was 26.3 compared with 46.6 months ($p < 0.001$) for non-SRC. SRC were significantly associated with female gender, gastric localization, advanced ypT and R1/2 categories, and lower risk of surgical complications and anastomotic leakage (each $p < 0.001$). Clinical (21.1 vs. 33.7 %, $p = 0.001$) and histopathological response (less than 10 % residual tumor: 16.3 vs. 28.9 %, $p < 0.001$) were significantly less frequent in SRC. Clinical response ($p = 0.003$) and complete histopathological response (pCR) (3.4 %) ($p = 0.003$) were associated with improved prognosis in SRC. Clinical response, surgical complications, ypTN categories, but not SRC were independent prognostic factors in forward Cox regression analysis in R0 resected patients. Risk of peritoneal carcinomatosis was increased ($p < 0.001$), while local ($p = 0.015$) and distant metastases ($p = 0.02$) were less frequent than in non-SRC.

Conclusions. Prognosis of SRC is unfavorable. Although response to neoadjuvant chemotherapy is rare in SRC, it is associated with improved outcome. Thus, chemotherapy might not generally be abandoned in SRC. A stratification based on SRC should be included in clinical trials.

Preoperative chemotherapy followed by resection is the European recommended standard of care for the treatment of locally advanced gastric cancer.[1,2] However, one recent well-designed, but underpowered randomized phase III trial with high surgical standards showed similar outcomes for patients with primary resection compared with those with preoperative chemotherapy.[3] Although a recent meta-analysis failed to prove a significant survival benefit for chemoradiotherapy compared with chemotherapy in adenocarcinomas of the esophagogastric junction, the addition of radiotherapy is currently discussed within studies to increase response rates, especially after the results of the CROSS study.[4,5]

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It has become clear that not all patients benefit equally from preoperative treatment in esophagogastric cancer. Clinical as well as histopathological nonresponders have a worse outcome than patients who respond to chemotherapy.[6–10] Both clinical and histopathological response have been reported to be associated with localization, Laurén classification, and tumor grading.[8,10,11]

The subgroup of patients with signet ring cell carcinoma (SRC) attracted attention over the last years because of growing incidence, young age at diagnosis, and unfavorable outcome.[12–14] Until now, this group received identical chemotherapy compared with other gastric cancer entities, and no prospective intervention studies with stratification based on signet ring cell type adenocarcinoma have been reported to date. In contrast to the present oncological guidelines stands a recent recommendation from the FREGAT working group.[15] Here, primary resection without preoperative chemotherapy is proposed for patients with SRC containing gastric cancer because of an absence of cytostatic or cytotoxic effect in this subgroup and a significantly impaired prognosis. Data describing signet ring cell differentiation in the neoadjuvant setting are rare, although poorer response rates have been reported for SRC containing gastric cancer in small patient populations.[16,17] More literature is available on diffuse-type gastric cancer, as which SRC is commonly classified, and chemotherapy.[18] Diffuse-type carcinomas treated with chemotherapy are reported to have worse prognosis, lower response rates, and an association with distal localization.[19,20] Furthermore, the rate of free peritoneal tumor cells at the time of resection is significantly increased compared with intestinal type gastric cancer, possibly explaining the short time to recurrence and the high rate of peritoneal carcinomatosis.[21]

Our retrospective exploratory study aims to evaluate the prognosis of SRC compared with non-SRC after neoadjuvant chemotherapy and, secondly, to establish prognostic factors within the group of SRC patients with special emphasis on their response classification to define whether these patients should in fact be excluded from preoperative treatment in the future.

PATIENTS AND METHODS

Patients and Staging

A total of 925 patients with locally advanced esophagogastric adenocarcinomas were treated with neoadjuvant therapy from 1987 to 2011 in two academic centers. There were 723 patients included in this analysis; reasons for exclusion are shown in Fig. 1. All patients had histopathologically proven esophagogastric adenocarcinoma, a

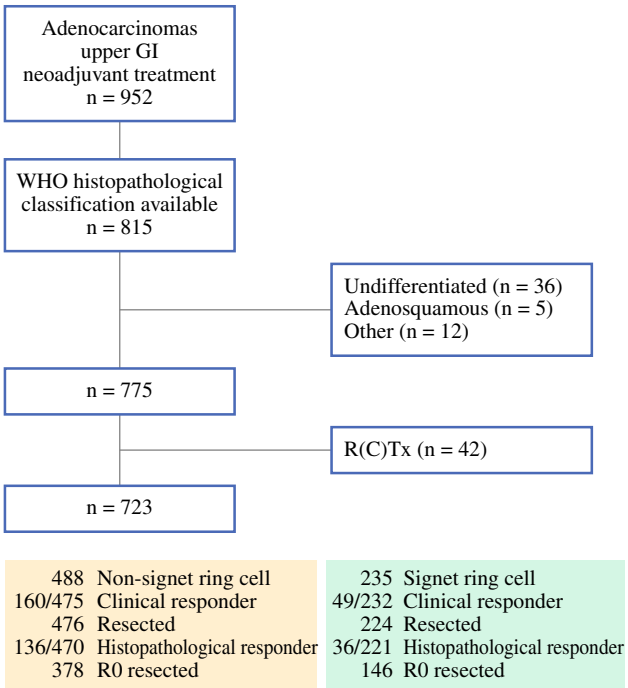

FIG. 1 Patient population

Karnofsky index >80, were staged cT3/4, N any, cM0/x, and underwent preoperative chemotherapy.

Pretherapeutic staging included an endoscopy and a multidetector CT scan with intravenous (IV) contrast for all patients; both were repeated after the end of chemotherapy. The different chemotherapy regimens applied are shown in Table 1. The study was approved by the institutional review board.

Surgery

Resections were performed according to tumor localization and local standards. AEGI were treated either by a transthoracic or transhiatal esophagectomy with gastric pull-up and intrathoracic or cervical anastomosis with a two-field lymphadenectomy. AEGII/III were treated by a transhiatal extended gastrectomy and extended D2 lymphadenectomy including left retroperitoneal lymphadenectomy, or abdominothoracic esophagectomy and intrathoracic anastomosis, where there were positive proximal frozen section resection margins.[7,22,23] Tumors of the middle and distal gastric third were treated with total or subtotal gastrectomy and D2 lymphadenectomy.[9,24]

Clinical Response Evaluation

Clinical response was assessed by the interdisciplinary tumor board of the respective university hospital based on combined evaluation of endoscopy and CT scan after

TABLE 1 Patient characteristics

	Signet ring cell		Non-signet ring cell		*p* value
Gender					
Male	146	(62.1 %)	426	(87.3 %)	<0.001
Female	89	(37.9 %)	62	(12.7 %)	
Chemotherapy regimens divided in 4 main groups					
+platinum	169	(71.9 %)	330	(67.6 %)	
+epirubicin	29	(12.3 %)	42	(8.6 %)	0.016
+taxane	28	(11.9 %)	102	(20.9 %)	
Other	9	(3.8 %)	14	(2.9 %)	
Chemotherapy regimens with and without taxane					
With taxane	28	(11.9 %)	102	(20.9 %)	0.003
Without taxane	207	(88.1 %)	386	(79.1 %)	
Localization					
AEG I	23	(8.8 %)	199	(40.8 %)	
AEG II	43	(18.3 %)	160	(32.8 %)	
AEG III	33	(14.0 %)	59	(12.1 %)	<0.001
Middle third	56	(23.8 %)	29	(5.9 %)	
Distal third	50	(21.3 %)	27	(5.5 %)	
Total	30	(12.8 %)	14	(2.9 %)	
Laurén classification					
Intestinal	0		387	(80.6 %)	
Diffuse	177	(75.3 %)	12	(2.5 %)	
Mixed	47	(20.0 %)	55	(11.5 %)	<0.001
Not applicable	11	(4.7 %)	26	(5.4 %)	
Histology					
Intestinal	0		387	(80.6 %)	
Non-intestinal	235	(100 %)	93	(19.4 %)	<0.001
Clinical response					
Nonresponder	183	(78.9 %)	315	(66.3 %)	
Responder	49	(21.1 %)	160	(33.7 %)	0.001
Operation					
No	11	(4.7 %)	12	(2.5 %)	
Yes	224	(95.3 %)	476	(97.5 %)	0.118
Type of operation					
Subtotal gastrectomy	18	(8.0 %)	8	(1.7 %)	
Total gastrectomy	107	(47.8 %)	69	(14.5 %)	
Transhiatal ext. GE	66	(29.5 %)	175	(36.8 %)	
Transhiatal EE	7	(3.1 %)	73	(15.3 %)	
Transthoracic EE	25	(11.2 %)	149	(31.3 %)	<0.001
Explorative laparotomy and biopsy	1	(0.4 %)	1	(0.2 %)	
Other			1	(0.2)	
Complications ($n = 224$ operated SRC, 476 other)					
No	151	(36.5 %)	263	(63.5 %)	
Yes	73	(25.5 %)	213	(74.5 %)	0.002
Surgical complications					
No	172	(67.4 %)	300	(63.0 %)	
Yes	52	(32.6 %)	176	(37.0 %)	<0.001
Anastomotic leakage ($n = 223$ SRC, 475 other with anastomosis)					
No	208	(93.3 %)	393	(82.7 %)	
Yes	15	(6.7 %)	74	(17.3 %)	<0.001
ypT (UICC 7th)					
0	8	(3.6 %)	25	(5.3 %)	
1	10	(4.5 %)	43	(9.1 %)	
2	12	(5.4 %)	82	(17.3 %)	<0.001
3	123	(55.2 %)	284	(59.8 %)	
4	70	(31.4 %)	41	(8.6)	
Not applicable (biopsy)	1		1		
ypN (UICC 7th)					
0	75	(33.6 %)	181	(38.1 %)	
1	34	(15.2 %)	90	(18.9 %)	
2	37	(16.6 %)	85	(17.9 %)	0.072
3	77	(34.5 %)	119	(25.1 %)	
R category					
0	146	(65.2 %)	378	(79.4 %)	
1	61	(27.2 %)	65	(18.3 %)	<0.001
2	17	(7.6 %)	11	(2.3 %)	
Histopathological response ($n = 222$ resected SRC, 470 other)					
Nonresponder 2 + 3	185	(83.3 %)	334	(71.1 %)	
Responder 1a + 1b	37	(16.7 %)	136	(28.9 %)	<0.001
Nonresponder 3	123	(55.4 %)	225	(47.9 %)	
Nonresponder 1b + 2	91	(41.0 %)	221	(47.0 %)	
Responder 1a	8	(3.6 %)	24	(5.1 %)	0.380
30-day mortality					
No	220	(96.9 %)	460	(96.4 %)	
Yes	7	(3.1 %)	17	(3.6 %)	0.743
In-hospital mortality					
No	209	(92.1 %)	440	(92.2 %)	
Yes	18	(7.9 %)	37	(7.8 %)	0.936

Number of patients can vary because not all data are available for every patient. Missing data are not listed separately

AEG adenocarcinoma of the esophagogastric junction, *GE* gastrectomy, *EE* esophagectomy

neoadjuvant treatment before resection. Responders were defined to display at least a partial response in both endoscopy (less than 75 % residual tumor) and CT scan (decrease of more than 50 % of wall diameter).

Histopathological Workup and Response Evaluation

Resected specimens were worked up in a highly standardized manner and analyzed histopathologically by experienced pathologists (R.L., W.W.). Histologic typing of tumors was performed according to the World Health

Organization (WHO) classification. The WHO definition of SRC was based on the resected specimen or the pretherapeutic biopsy in cases where there was a complete histopathological response (pCR). The histopathological staging ypTNMR was done according to UICC Seventh. The scoring system of Becker et al.[24] was applied for classification of regression (regression 1a, no residual tumor; regression 1b, <10 % residual tumor; regression 2, 10–50 % residual tumor; regression 3, >50 % residual tumor).

Statistical Analysis

Statistical analyses were performed using PASW Statistics software (version 18.0; SPSS, Inc., Chicago, IL). Quantitative values are expressed as mean ± standard deviation, median, and range. The χ^2 test was used for comparison of frequencies. Survival curves were estimated according to the Kaplan–Meier method. The log-rank test was used for comparison of survival curves. Multivariate analysis was done stepwise by forward and backward Cox regression analysis. Overall survival was calculated from diagnosis to death, time to recurrence from resection to recurrence. All statistical tests were conducted two-sided, and a p value <0.05 was considered statistically significant. No imputation of missing data was planned; the analysis was done at the full cases population.

RESULTS

Of 723 adenocarcinomas, 235 were classified as poorly cohesive adenocarcinomas, signet ring cell type with more than 50 % signet ring cells. Of the 235, 59 had an additional WHO classification component. Further patient characteristics are shown in Table 1.

Association of SRC with Clinicopathological Factors

SRC were significantly associated with female gender, diffuse Laurén classification, an increase from proximal to distal, more advanced ypT-categories, lower probability of an R0 resection (all $p < 0.001$), but not with more advanced ypN categories ($p = 0.072$). Both clinical (49 of 232 (21.1 %)) and histopathological response (37 of 222 (16.7 %)) were significantly less frequent than in the other WHO histopathological classifications (both $p < 0.001$). Overall complication rate ($p = 0.003$), surgical complication rate ($p < 0.001$), and rate of anastomotic leakage ($p = 0.001$) were also statistically lower. Associations are presented in detail in Tables 2 and 3.

Influence of Clinicopathological Factors on Prognosis Within the Analyzed Groups

The median survival for all patients was 36.7 ± 2.7 months (range, 31.3–42.2 months). Survival was significantly associated with WHO histopathological

TABLE 2 Prognostic factors: association of prognosis in patients with and without signet ring cell cancer with localization and type of resection

	Signet ring cell component[a]			No signet ring cell component[b]		
	n	Median survival (months)	95 % CI	*n*	Median survival (months)	95 % CI
Localization						
AEG I	23	19.7 ± 2.7	14.4–24.9	199	44.2 ± 6.3	31.9–56.5
AEG II	43	28.3 ± 4.9	18.6–38.0	160	49.2 ± 7.2	35.1–63.3
AEG III	35	16.9 ± 3.3	10.4–23.4	59	63.9 ± 17.0	30.6–97.1
Middle third	48	37.1 ± 7.9	21.7–52.6	28	Not reached	
Distal third	31	30.2 ± 4.0	22.4–38.0	27	38.3 ± 24.5	0.0–86.4
Total	31	21.4 ± 4.7	12.2–30.6	15	17.1 ± 1.3	14.6–19.5
Type of resection						
No resection	12	14.5 ± 1.5	11.6–17.5	14	8.0 ± 1.9	4.273–11.727
Subtotal GE	18	Not reached		8	20.3 ± 6.7	7.196–33.460
Total GE	107	32.1 ± 4.7	23.0–41.3	69	107.8	
Transhiatal extended GE	66	25.5 ± 3.6	18.6–32.5	175	42.4 ± 6.2	30.2–54.6
Transhiatal EE	7	13.3 ± 3.9	5.7–20.9	73	35.6 ± 9.1	17.9–53.4
Transthoracic EE	25	19.7 ± 2.4	14.9–24.5	149	53.9	

AEG adenocarcinoma of the esophagogastric junction, *GE* gastrectomy, *EE* esophagectomy

[a] Localization: $p = 0.024$. Type of resection $p < 0.001$

[b] Localization: $p = 0.018$. Type of resection $p < 0.001$

TABLE 3 Prognostic factors within the various analyzed groups

Factor	*p* value, log-rank test		
	All	R0	Signet ring cell
Gender	0.284	0.238	0.898
SRC, yes/no	<0.001	0.02	–
Chemotherapy			
4 groups	0.042	0.420	0.420
Taxane, yes/no	0.009	0.155	0.938
SRC vs SRC + other WHO versus rest	0.001	0.053	0.114
Grading G1/2 versus 3/4	<0.001	0.015	–
Localization			
(AEG I/II/III/GC)	0.019	0.042	0.024
(AEG I–III/GC)	0.144	0.501	0.183
Lauren (int/diff/mixed/uncl.)	<0.001	0.010	0.247
Clinical response			
(R/NR)	<0.001	<0.001	0.003
(PR/MR/NC/PD)	<0.001	<0.001	<0.001
Type of operation (STG/TG/THG/TH EE/TT EE)	0.014	0.382	<0.001
Complications, yes/no	0.007	0.022	0.002
Surgical complications	0.006	0.005	0.001
Leakage, yes/no	0.018	0.059	0.063
ypT (0/1/2/3/4)	<0.001	<0.001	<0.001
ypN (0/1/2/3/4)	<0.001	<0.001	<0.001
R category	<0.001	–	<0.001
Regression			
(1a + b vs 2 + 3)	<0.001	<0.001	0.104
(1a vs 1b vs 2 vs 3)	0.004	<0.001	0.001
(1a vs 1b + 2 + 3)	<0.001	0.001	0.003

SRC signet ring cell containing carcinoma, *AEG* adenocarcinoma of the esophagogastric junction, *R* response, *NR* nonresponse, *PR* partial response, *MR* minor response, *NC* no change, *PD* progressive disease, *STG* subtotal gastrectomy, *TG* total gastrectomy, *THG* transhiatal extended gastrectomy, *TH EE* transhiatal esophagectomy, *TT EE* transthoracic esophagectomy, *GE* gastrectomy, *EE* esophagectomy

classification (Fig. 2a) ($p = 0.002$). The prognosis of SRC with a median survival of 26.3 ± 2.3 months (range, 21.8–30.8 months) was significantly worse compared with other adenocarcinomas with 46.6 ± 4.4 months (range, 39.9–55.3 months) (Fig. 2b) ($p < 0.001$). Of the 235 patients with SRC, 59 had a mixed histopathological WHO classification tumor. The survival of these patients was statistically not significantly improved with 28.3 ± 5.2 months (range, 18.2–38.4 months) compared with patients with only SRC with 23.3 ± 2.6 months (range, 18.2–28.5 months) ($p = 0.114$). Further prognostic factors for the whole patient population are shown in Table 3.

Localization and type of resection influenced prognosis in patients with and without SRC significantly (Table 2). Resections for signet ring cell cancer were less frequently extended to the esophagus. Surgical complications had stronger prognostic relevance for patients with signet ring cell cancer ($p = 0.001$) than in the patients with differing WHO classification ($p = 0.044$). ypT category, ypN category, and exact clinical (Fig. 2c) and histopathological response (Fig. 2d) had strong prognostic impact in both subgroups (all $p < 0.001$). The application of different chemotherapy regimens (Table 3), but especially the addition of taxanes influenced prognosis, but not in R0-resected patients or SRC (Fig. 2e; Table 3).

Among the completely resected patients, the presence of signet ring cells was still a prognostic factor ($p = 0.020$). The other significant prognostic factors are well known and accepted, as localization divided into AEGI, II, III, and gastric cancer, Laurén classification, grading, clinical response for both the less and the more differentiated group, complications, surgical complications, ypT category, ypN category, and histopathological regression irrespective of type of classification (see Table 3).

Within the subgroup of SRC, basically these identical factors had prognostic influence apart from Laurén classification and histopathological regression classification with responders defined as having less than 10 % residual tumor (regression grade 1a/b). For patients with signet ring cell carcinomas either the classification into precise histopathological subgroups of tumor regression (Fig. 2d) or the classification into complete versus incomplete response are of prognostic relevance (Table 3).

Independent Prognostic Factors Within the Analyzed Groups

Independent prognostic factors among the completely resected patients were clinical response, surgical complications, the ypT category, and the ypN category. All factors were confirmed by forward and backward Cox regression analysis. The backward analysis revealed the presence of signet ring cells as an additional independent prognostic factor (Table 4).

Within the SRC subgroup, forward and backward Cox regression identified surgical complications, the ypN category, and the *R* category as independent prognostic factors (Table 5).

Patterns of Recurrence

Of the 524 patients with complete resection, 250 suffered from recurrence. The risk of recurrence was not different for patients with or without SRC ($p = 0.845$).

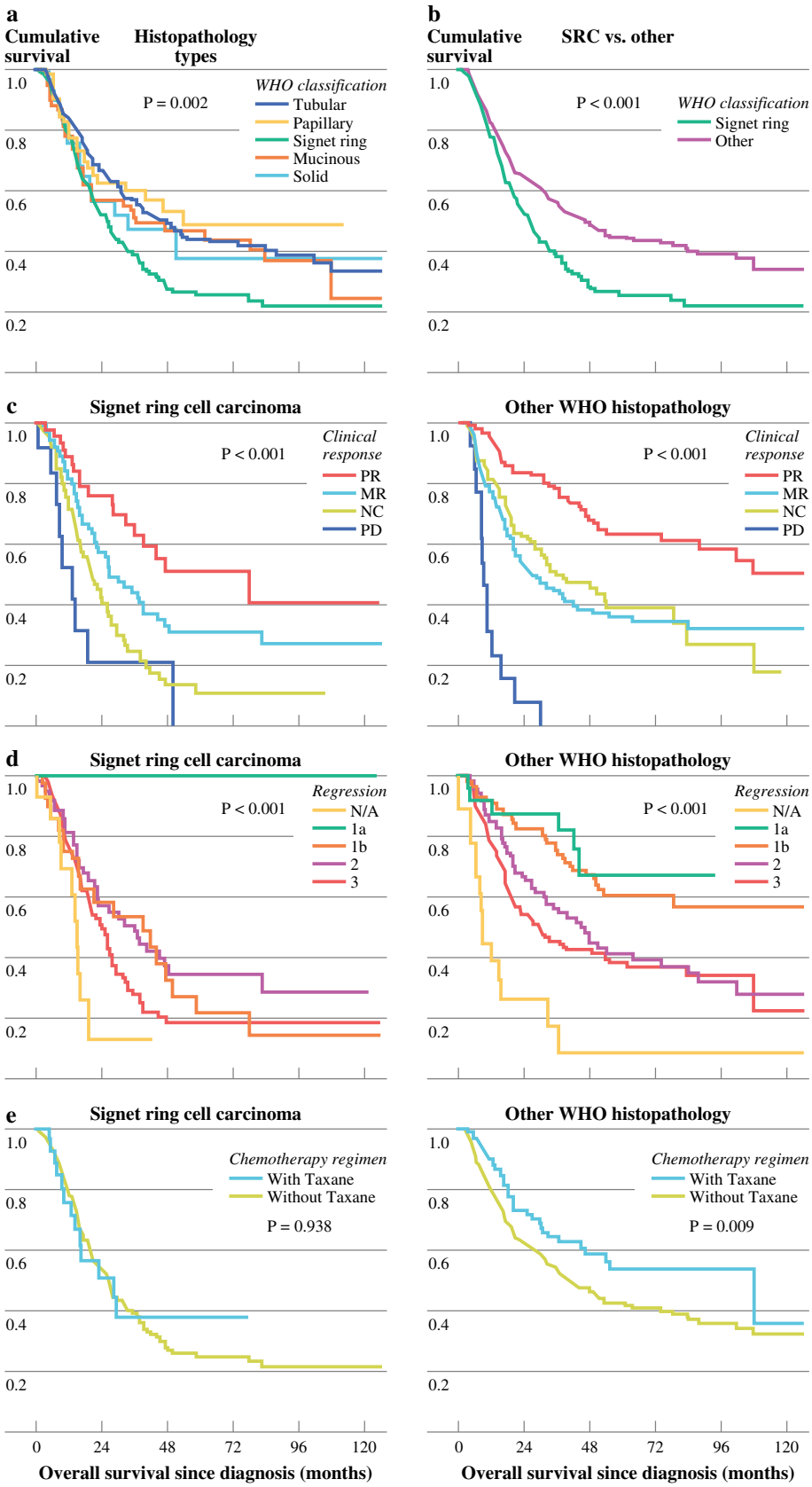

FIG. 2 Survival curves. **a** Overall survival based on log-rank test, according to WHO classification. **b** Overall survival based on log-rank test, signet ring cell classification versus rest. **c** Overall survival based on log-rank test, signet ring cell containing tumors versus rest; according to clinical response evaluation. *PR* partial response, *MR* minor response, *NC* no change, *PD* progressive disease. **d** Overall survival based on log-rank test, signet ring cell containing tumors versus rest; according to histopathological response evaluation. *N/A* no regression score available, *1a* no residual tumor, *1b* <10 % residual tumor, *2* 10–50 % residual tumor, *3* >50 % residual tumor. **e** Overall survival based on log-rank test, signet ring cell containing tumor versus rest; according to chemotherapy with and without taxane

TABLE 4 Multivariate analysis: all R0 resected patients (215 events) including localization, presence of signet ring cells, Laurén classification, clinical response (R/NR), complications, surgical complications, ypT, ypN, regression (1a/1b vs 2/3)

Factor	Forward Cox regression analysis		
	p value	RR	95 % CI
Clinical response	0.009	0.644	0.462–0.897
Surgical complications	0.007	1.465	1.108–1.937
ypT	<0.001	1.426	1.182–1.721
ypN	<0.001	1.379	1.224–1.554
Signet ring cell cancer[a]	0.02	0.679	0.490–0.940

[a] Additional factor in backward Cox regression analysis

TABLE 5 Multivariate analysis: signet ring cell cancer (128 events) including clinical response, complications, surgical complications, ypT, ypN, R, regression (1a/1b vs 2/3)

Factor	Forward Cox regression analysis[a]		
	p value	RR	95 % CI
Surgical complications	<0.001	0.470	0.318–0.693
ypN			
ypN3		1	
ypN0	0.002	0.461	0.286–0.744
ypN1	0.001	0.363	0.198–0.664
ypN2	0.212	0.728	0.442–1.199
R category			
R2		1	
R0	<0.001	0.172	0.088–0.335
R1	0.001	0.326	0.167–0.637

[a] All factors were confirmed by backward cox regression analysis

However, patterns of recurrence were different. Patients with SRC had less frequent local recurrence ($p = 0.015$) and distant metastases ($p = 0.022$), but more frequent peritoneal carcinomatosis ($p < 0.001$).

Time to recurrence or death after complete resection was not statistically different between patients with SRC (20.1 ± 3.7) and without (31.7 ± 8.3) ($p = 0.285$).

DISCUSSION

This is to our knowledge the largest series evaluating the influence of an SRC component on response and prognosis after preoperative chemotherapy in adenocarcinomas of the esophagogastric junction and stomach. Median survival and clinical and histopathological response rates were significantly impaired for patients with SRC. Whereas standard clinical response evaluation can be applied in SRC, histopathological response classification should be appraised differently, as only complete histopathological response (regression grade 1a), which is extremely rare, appears to improve prognosis meaningfully. Although clinical and complete histopathological response significantly influenced prognosis in patients with SRC, neither are independent prognostic factors within this subgroup.

Recently the French FREGAT working group proposed abandoning perioperative chemotherapy in gastric cancer with SRC because of the lack of cytostatic effect of the applied chemotherapy and worse prognosis compared with primarily resected patients. However, the survival data presented in this retrospective multicenter study were poor with a median survival of 14.0 months in the surgery alone group and 12.8 months in the group with additional perioperative chemotherapy ($p = 0.043$); the Kaplan–Meier curves of the two groups crossed after about 12 months.[15] Furthermore, an inclusion bias cannot be ruled out, as 41 % of the group treated with additional chemotherapy underwent an extended resection to neighboring organs compared with only 28 % in the primarily resected group ($p = 0.001$), unless this fact might be attributed to progression during chemotherapy. Our patients with SRC generally underwent less-extensive surgical procedures, most likely because of their more distal localizations. The median survival of 26.3 months in our study for patients with SRC after chemotherapy is superior to the data after primary resection in the French study, which cannot be explained by the different chemotherapy regimens applied, or by the long study periods, only by a different patient selection. Most patients had platinum-based regimes in both studies; in our study chemotherapy was administered preoperatively rather than perioperatively, and overall less epirubicin was used.[1,2,7,25–27] The inclusion of AEG I is also not responsible for the comparatively better prognosis, because median survival of AEG I with SRC was no longer compared with the other localizations, in contrast to large series of neoadjuvantly treated or primary resected AEG I.[11,28] Complete resection rates are nearly identical with 65.9 % after primary resection, 62.3 % after perioperative chemotherapy in the French study, and 65.2 % in our study for SRC. Admittedly, the complete resection rates are relatively frustrating compared with larger series with preoperative/perioperative chemotherapy not stratified for WHO histopathology with 79–84 % complete resection rates.[1–3] Problems with clear resection margins most frequently do not occur luminally, but at the circumferential resection margin, which is known to be associated with aggressive tumor biology, locally advanced tumor categories, and diffuse Laurén classification.[29–31] The problem of a positive circumferential resection margin cannot be solved by more radical surgery. Preoperative chemoradiotherapy might be more effective to increase complete resection.[32,33] Residual tumor after chemotherapy is often localized in the deeper portion of the gastric wall, so that a histopathological response with less than 10 % residual

tumor does not necessarily lead to a "downcategorizing" of the tumor.[24,34] The patients with complete histopathological response in our study are all alive without recurrence comparable to the data of Chirieac et al.[32] which demonstrates the benefit of preoperative treatment for a tiny subgroup. This highlights the demand for more effective treatment regimens to increase pathological complete responses. Triple chemotherapy regimens or the inclusion of radiotherapy for junctional tumors increased histopathological complete response rates to up to 20 %, but with conflicting results in SRC.[32,35,36] The addition of biologicals might be another option.[37]

Surprisingly, standard clinical response evaluation by endoscopy and CT scan after neoadjuvant treatment could reliably identify patients with clinical response and subsequent favorable prognosis, although it was deemed more difficult than in intestinal-type gastric cancer because of the different growth patterns and a less endoluminal tumor fraction.[7] Admittedly, endoscopy and CT scan were always assessed by experienced investigators, but evaluated prospectively preoperatively without knowledge of the histopathological report. Clinical response was even an independent prognostic factor within the whole patient group, but lost its significance within the subgroup of SRC. In this subgroup, no therapy-related factors, but only established prognostic factors such as surgical complications, R category, and ypN category, which both are accepted to be improved by neoadjuvant chemotherapy, were prognostically relevant.[30,38]

A general problem for treatment stratification of SRC is the definition of SRC itself. Since adenocarcinomas are often a mixture of different components, which might with further imponderability also variably be influenced by chemotherapy, the World Health Organization defined signet ring cell carcinomas as an adenocarcinoma in which the predominant component consists of isolated or small groups of malignant cells containing intracytoplasmic mucins, possibly generating an interobserver variability even between experienced pathologists.[39] A further influencing factor that should be considered is the concordance of the pretherapeutic biopsy and the final histopathological workup after resection, especially in SRC. An astonishingly high agreement is reported with an accuracy of 92.5 % in a retrospective analysis with special emphasis on SRC, but only 11.4 % of the patients were treated with preoperative chemotherapy, whereas the experienced group from Cologne reported an agreement in 74 % of biopsy and resected specimen in untreated patients.[40–43]

In summary, SRC after neoadjuvant treatment had a significantly worse survival than all other WHO histopathological classifications with 26.3 months median survival; however, this is still longer than 17.6 months for a retrospective unpublished primary resected cohort of 97 patients with SRC staged cT3/4 any N and M0/x from Heidelberg in the respective period. Both clinical and complete histopathological responses are rare, but, if present, associated with significantly improved prognosis. However, none were independent prognostic factors within the SRC subgroup. A general exclusion of SRC from neoadjuvant chemotherapy seems unjustified at the moment, because a small subgroup seems to profit, and no randomized study showing a general survival benefit for SRC after primary resection only exists so far. More effective preoperative therapy strategies for SRC, identification of predictive markers for response, and trial stratification according to SRC component are warranted in the future.

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