


# Postoperative follow-up programs improve survival in curatively resected gastric and junctional cancer patients: a propensity score matched analysis

Leila Sisic<sup>1</sup> · Moritz J. Strowitzki<sup>1</sup> · Susanne Blank<sup>1</sup> · Henrik Nienhueser<sup>1</sup> · Sara Dorr<sup>1</sup> · Georg Martin Haag<sup>2</sup> · Dirk Jäger<sup>2</sup> · Katja Ott<sup>3</sup> · Markus W. Büchler<sup>1</sup> · Alexis Ulrich<sup>1</sup> · Thomas Schmidt<sup>1</sup> 

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## Abstract

**Background** To date there is no evidence that more intensive follow-up after surgery for esophagogastric adenocarcinoma translates into improved survival. This study aimed to evaluate the impact of standardized surveillance by a specialized center after resection on survival.

**Methods** Data of 587 patients were analyzed who underwent curative surgery for esophagogastric adenocarcinoma in our institution. Based on their postoperative surveillance, patients were assigned to either standardized follow-up (SFU) by the National Center for Tumor Diseases (SFU group) or individual follow-up by other physicians (non-SFU group). Propensity score matching (PSM) was performed to compensate for heterogeneity between groups. Groups were compared regarding clinicopathological findings, recurrence, and impact on survival before and after PSM.

**Results** Of 587 patients, 32.7% were in the SFU and 67.3% in the non-SFU group. Recurrence occurred in 39.4% of patients and 92.6% within the first 3 years; 73.6% were treated, and of those 17.1% underwent resection. In recurrent patients overall and post-recurrence survival (OS/

PRS) was influenced by diagnostic tools ( $p < 0.05$ ), treatment ( $p \leq 0.001$ ), and resection of recurrence ( $p \leq 0.001$ ). Standardized follow-up significantly improved OS (84.9 vs. 38.4 months,  $p = 0.040$ ) in matched analysis and was an independent positive predictor of OS before and after PSM ( $p = 0.034/0.013$ , respectively).

**Conclusion** After PSM, standardized follow-up by a specialized center significantly improved OS. Cross-sectional imaging and treatment of recurrence were associated with better outcome. Regular follow-up by cross-sectional imaging especially during the first 3 years should be recommended by national guidelines, since early detection might help select patients for treatment of recurrence and even resection in few designated cases.

**Keywords** Gastric cancer · Esophageal cancer · Follow-up · Recurrence · Prognosis

## Abbreviations

SFU	Standardized follow-up
PSM	Propensity score matching
OS	Overall survival
PRS	Post-recurrence survival
PET	Positron emission tomography
CT	Computerized tomography
AEG	Adenocarcinoma of the esophagogastric junction
UICC	Union Internationale Contre le Cancer
NCT	National Center for Tumor Diseases Heidelberg
THG	Transhiatal extended gastrectomy
MRI	Magnetic resonance imaging
CTx	Chemotherapy
CRTx	Chemoradiotherapy
RTx	Radiotherapy
HR	Hazard ratio
CI	Confidence interval

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✉ Thomas Schmidt  
thomas.schmidt1@med.uni-heidelberg.de

<sup>1</sup> Department of Surgery, University Hospital Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

<sup>2</sup> Department of Medical Oncology, National Center for Tumor Diseases (NCT), University Hospital Heidelberg, 69120 Heidelberg, Germany

<sup>3</sup> Department of Surgery, RoMed Hospital Rosenheim, 83022 Rosenheim, Germany

## Introduction

It is generally accepted that the recurrence rate after resection of esophagogastric adenocarcinoma ranges from 1.9 to 50.5% in the literature depending on the tumor stage [1–6], histopathological subtype [7], and type of and response to perioperative treatment [8–11]. Despite the relatively broad worldwide agreement on preoperative staging, perioperative multimodal treatment concepts, and surgical strategies, little consensus has been reached regarding postoperative follow-up [12–15]. Often no national guidelines concerning postoperative patient surveillance exist, and if available, no clear specifications are given on the interval, duration, and mode of follow-up. Surveillance strategies vary from only symptom-based examinations [14–16] to detailed follow-up plans [17, 18] even including regular PET-CT scans in eastern countries [19–21]. European, British, and German guidelines, for example, do not recommend standardized and structured follow-up after gastric cancer resection at all [14–16].

However, a recently published report of the European Registration of Cancer Care (EURECCA) on clinical pathways for esophagogastric adenocarcinoma revealed that in clinical reality many European centers follow more sophisticated surveillance plans including regular cross-sectional imaging and examination of tumor markers [22], even though practice guidelines advocate otherwise. Regular follow-up seems justified, as it not only serves the purpose of detecting recurrent disease, but also offers other important advantages: detection and management of postoperative complications and nutritional issues, psychological support for patients, and data collection for research [23]. The need for more than symptom-driven surveillance is also reflected by the Charter Scaligero on follow-up after gastrectomy for cancer, which was developed by a panel of experts during the 10th International Gastric Cancer Congress in Verona. The Charter states that follow-up should be adapted to the stage of disease, should consist of clinical review and cross-sectional imaging with or without upper gastrointestinal endoscopy, and should be discontinued after 5 years [24].

Many have questioned the oncological benefit of regular surveillance after resection of esophagogastric adenocarcinoma because therapeutic options for recurrent disease are limited, and treatment for recurrence generally consists of palliative chemotherapy. Nowadays probably more attention should be paid to the early diagnosis of mostly asymptomatic recurrence, since—given an adequate performance status—both oncological and surgical treatment has become more aggressive over the last decade even in the palliative setting, including, e.g., triplet combination chemotherapy with more effective but also potentially

more toxic agents [25–27], antibodies such as trastuzumab [28] and ramucirumab [29], resection of metastatic disease [30–35], and resection of peritoneal spread with intraperitoneal chemotherapy [36–39].

To date, there is no evidence that standardized follow-up after curative treatment of esophagogastric adenocarcinoma improves the long-term prognosis [23, 40–42]. However, so far not one randomized controlled study evaluating intensive follow-up is available in the literature. Data addressing this problem are limited, retrospective, and of varying quality. Studies comparing intensive vs. less intensive or symptom-driven surveillance could not detect a difference in overall survival, but as there was significant heterogeneity between groups with respect to treatment modalities, age, and tumor stage [43–45], no valid conclusion can be drawn from these results.

Besides the key question whether an intensive follow-up is generally beneficial, at least for a subgroup of patients, it is even more controversial which diagnostic means should be employed during postoperative surveillance and in which intervals [23, 40, 41, 46–49]. Most studies report the highest probability of recurrence during the first 2 years after surgery, whereas relapse after more than 5 years in gastric cancer is reported to be extremely rare [3, 24, 42, 50, 51].

The aim of this retrospective exploratory study was the analysis of two different follow-up programs with respect to their influence on overall survival and survival after recurrence. Second, the effect of the type of diagnostics applied and the type of treatment of recurrence on outcome was analyzed.

## Patients and methods

### Study design and patient population

A total of 972 patients with adenocarcinoma of the stomach or esophago-gastric junction (AEG type I, II, or III according to the Siewert classification) underwent surgery at the University of Heidelberg, Department of Surgery, between 2001 and 2014. Three hundred eighty-five patients were excluded from the analysis because of palliative surgery ( $n = 68$ ), presence of distant metastases (M1,  $n = 174$ ), incomplete resection (Rx/R1,  $n = 93$ ), and postoperative death (in-hospital and/or 90-day mortality,  $n = 50$ ). Clinicopathological and follow-up data of the remaining 587 patients were collected in a prospective database and analyzed retrospectively. A flow chart of the patient selection process is presented in supplementary Fig. 1.

## Pretreatment staging

Staging consisted of upper endoscopy with biopsies and a CT scan of the chest and upper abdomen for all patients. Examinations were performed either on an outpatient basis or in the radiological department and endoscopy unit of our institution. Clinical tumor stage and tumor localization were evaluated according to the 7th edition of the UICC staging system. Patients diagnosed before 2010 were reclassified according to the 7th edition of the UICC staging system. The cN category only differentiated between nodal-negative (cN0) and nodal-positive (cN+) disease according to lymph node diameter, shape, and contrast enhancement.

## Neoadjuvant treatment

Two hundred fifty-one patients (42.8%) received neoadjuvant treatment. Neoadjuvant treatment consisted of chemotherapy in the majority of cases (95.2%). Details on neoadjuvant treatment regimens are listed in supplementary Table 1. Patients received treatment on an outpatient basis by either the National Center for Tumor Diseases Heidelberg (NCT) or other treating oncologists.

## Surgery

The surgical approach to tumor resection was chosen depending on tumor localization. Most patients with AEG I underwent a right abdominothoracic en-bloc esophagectomy with a two-field lymphadenectomy (Ivor-Lewis procedure). Patients with AEG III or proximal gastric cancer received a transhiatal extended gastrectomy (THG) with extended D2 lymphadenectomy including left retroperitoneal lymphadenectomy. AEG II patients were treated like either an AEG I or III tumor depending on tumor extension into the esophagus. For tumors in the middle or distal third of the stomach, the standard procedure was a total gastrectomy with D2 lymphadenectomy. In distal tumors, a subtotal gastrectomy was preferred because of quality of life if an adequate proximal resection margin was given. Other surgical procedures included: esophago-gastrectomy ( $n = 10$ ), Merendino procedure ( $n = 6$ ), transmediastinal esophagectomy ( $n = 6$ ), and pancreaticoduodenectomy with total gastrectomy ( $n = 5$ ).

## Histopathology and postoperative staging

Resection specimens were histologically examined in the Department of Pathology. Histopathologic work-up included extent of the primary tumor, regional lymph node spread, presence of distant metastases [(y)pTNM categories

according to the UICC classification, 7th edition, 2010], R category, tumor differentiation (grading), and growth pattern according to Laurén.

## Adjuvant treatment

Adjuvant treatment was administered in the form of perioperative treatment if patients had undergone neoadjuvant treatment. A postoperative adjuvant treatment without previous neoadjuvant therapy was only recommended as an individual treatment decision. Treatment was administered on an outpatient basis by either the NCT or other treating oncologists.

## Follow-up

Patients were followed on an outpatient basis in the NCT according to a standardized protocol every 3 months during the first 2 years, every 6 months during the 3rd and 4th year, and after 12 months in the 5th year. Structured follow-up was completed 5 years after surgery, and further examinations were based on clinical symptoms. Follow-up examinations included a CT scan every other visit alternating with abdominal sonography and endoscopy every 12–18 months. In the non-SFU group patients underwent individual follow-up by other physicians. At discharge no specification for postoperative follow-up was given, and symptom-driven examinations were recommended according to the German S3 guidelines. Physicians organized follow-up according to their personal discretion. The choice between follow-up at our institution or by other physicians was at the discretion of the patients. The choice of follow-up data of these patients was obtained by contacting their treating physician and/or the patients themselves. Complete follow-up information was available for all patients. The length of follow-up was calculated from the date of first diagnosis till the last review of patients in February 2017 or time of death. The median follow-up time for surviving patients ( $n = 337$ ) was 64.5 months.

## Propensity score matching

To reduce the effects of selection bias and confounding factors in survival comparison, propensity score matching (PSM) was performed to create comparable groups. Propensity scores were estimated using a multivariable logistic regression model with the follow-up groups as the dependent variables and potential confounders [age, tumor localization, (y)pT category, (y)pN category, neoadjuvant treatment, adjuvant treatment] as covariates. One-to-one matching without replacement was performed using a 0.0 caliper width [52]. This allowed us to generate 121 score-matched pairs with either standardized or individual

follow-up, which were used in subsequent analyses as indicated.

### Statistical analysis

Overall survival (OS) was calculated from time of diagnosis till death or last follow-up date. Post-recurrence survival (PRS) was defined as the interval from diagnosis of recurrence till death or last follow-up. Survival rates were estimated using the Kaplan-Meier method. Differences in survival among groups were calculated using the log-rank test. Prognostic factors were evaluated in a univariate and multivariate analysis using the Cox regression model. To compare categorical variables, we used the  $\chi^2$  test. The Mann-Whitney *U* test was used to compare continuous variables. All tests were two-sided, and a *p* value <0.05 was considered as statistically significant. Analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Patient demographics, tumor characteristics, and treatment

The median age at time of diagnosis was 63 (range 27–90) years; 313 patients (53.3%) were diagnosed with esophageal or junctional and 274 (46.7%) with gastric adenocarcinoma. Detailed information on patient demographics, tumor characteristics, and treatment is summarized in Table 1.

One hundred ninety-two patients (32.7%) underwent standardized follow-up (SFU group) and 395 patients (67.3%) individual follow-up (non-SFU group). Baseline characteristics showed significant heterogeneity between groups: the SFU group was associated with fewer patients aged  $\geq 70$  years, more advanced cT, cN, and (y)pT categories, and more frequent administration of neoadjuvant and adjuvant treatment.

To create comparable groups propensity score matching (PSM) was performed. Analysis of heterogeneity after PSM between 121 patients with standardized and 121 patients with individual follow-up revealed almost equal distribution of age, tumor localization, diagnosis, (y)pT and (y)pN category, and neoadjuvant and adjuvant treatment. Furthermore, no statistically significant difference between the SFU and non-SFU group could be observed with respect to the remaining baseline characteristics (Table 1).

### Survival

Upon last follow-up, 250 of 587 patients (42.6%) had died. Cause of death was mostly tumor-related (80.0%; *n* = 200);

other causes were tumor-unrelated (9.6%; *n* = 24), secondary malignancies (2.4%; *n* = 6), or unknown (8.0%, *n* = 20). Median OS from time of diagnosis for all patients was 93.8 (95% CI 71.4–116.3) months. The estimated 3- and 5-year OS rate was 66.2 and 55.7%.

### Influence of intensified follow-up on survival

The median follow-up time for surviving patients was 60.5 months in the SFU (*n* = 113) and 68.5 months in the non-SFU group (*n* = 224) (*p* = 0.871).

No significant difference regarding overall survival comparing all patients (*n* = 587) with standardized (SFU, *n* = 192) and individual (non-SFU, *n* = 395) follow-up (median OS: SFU not reached vs. non-SFU 89.9 months; *p* = 0.490; Fig. 1a) could be observed.

Subgroup analyses showed a beneficial effect of standardized follow-up on OS for patients with locally advanced tumors [(y)pT3/4, median OS 45.6 vs. 35.2 months, *p* = 0.096; supplementary Fig. 2a] and lymph node metastases [(y)pN1/2/3, median OS 44.2 vs. 34.0 months, *p* = 0.097; supplementary Fig. 2b], but failed to reach statistical significance.

However, survival analysis of matched patients (*n* = 242) revealed significantly improved overall survival for patients with standardized follow-up (median OS: SFU 84.9 vs. non-SFU 38.4 months, *p* = 0.040; Fig. 1b).

There was no significant difference with respect to post-recurrence survival between the SFU and non-SFU group before and after PSM (median PRS: SFU 10.0/9.1 vs. non-SFU 6.0/5.8 months; *p* = 0.147/0.325, respectively).

### Univariate and multivariate analysis for overall survival

Besides standardized follow-up, which improved the prognosis in the matched patient collective only, age under 70 years as well as lower cT, cN, (y)pT, and (y)pN categories was associated with improved OS in univariate analysis of all and matched patients. Additionally, tumor localization at the stomach and resection by subtotal gastrectomy were significant positive prognostic factors before PSM (Table 2).

Multivariate Cox regression analysis included the following factors: follow-up, age, gender, diagnosis, grading, Laurén classification, cT category, cN category, neoadjuvant treatment, surgery, (y)pT category, (y)pN category, and adjuvant treatment.

Independent positive prognosticators for OS of all and matched patients were: age under 70 years, lower (y)pN category, and standardized follow-up. cT category was an independent prognostic factor before PSM, whereas cN

**Table 1** Baseline characteristics of patients with individual (non-SFU) and standardized follow-up (SFU) before and after propensity score matching

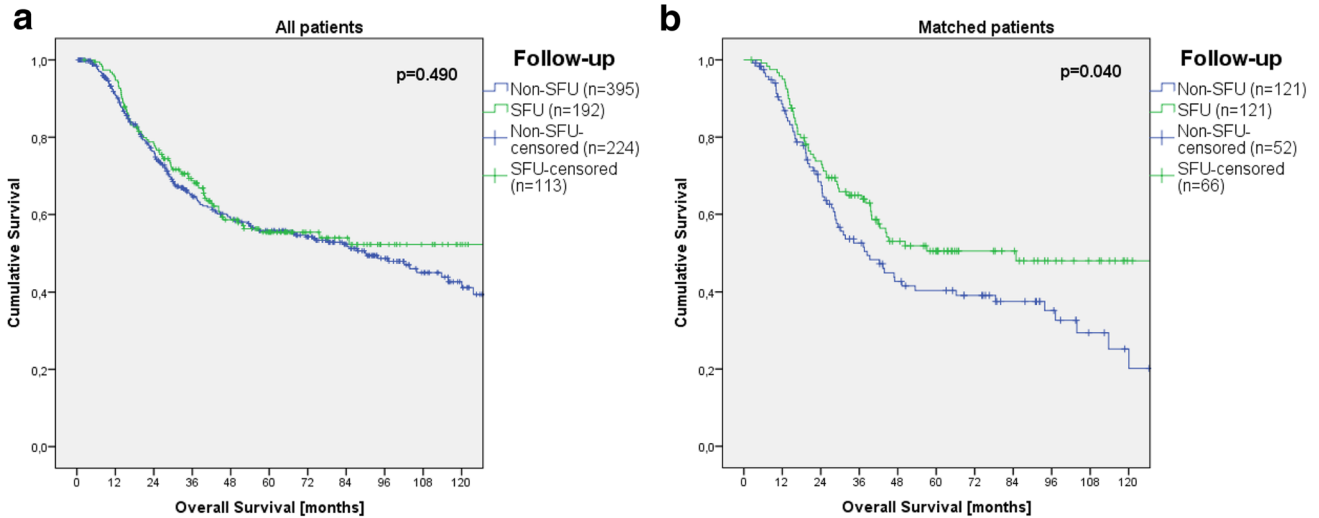
	All patients ( <i>n</i> = 587)				<i>p</i>	Matched patients ( <i>n</i> = 242)				<i>p</i>
	Non-SFU ( <i>n</i> = 395)		SFU ( <i>n</i> = 192)			Non-SFU ( <i>n</i> = 121)		SFU ( <i>n</i> = 121)		
	<i>n</i>	%	<i>n</i>	%		<i>n</i>	%	<i>n</i>	%	
Age at diagnosis (years)					<b>0.001</b>					1.000
≤45	32	8.1	11	5.7		3	2.5	3	2.5	
46–69	223	56.5	140	72.9		88	72.7	88	72.7	
≥70	140	35.4	41	21.4		30	24.8	30	24.8	
Gender					0.947					0.228
Male	287	72.7	139	72.4		96	79.3	88	72.7	
Female	108	27.3	53	27.6		25	20.7	33	27.3	
Localization					0.523					1.000
Esophagus/EGJ	207	52.4	106	55.2		71	58.7	71	58.7	
Stomach	188	47.6	86	44.8		50	41.3	50	41.3	
Diagnosis					0.883					0.987
AEG I	84	21.3	44	22.9		31	25.6	30	24.8	
AEG II	97	24.6	47	24.5		31	25.6	33	27.3	
AEG III	26	6.6	15	7.8		9	7.4	8	6.6	
Gastric cancer	188	47.6	86	44.8		50	41.3	50	41.3	
Grading					0.101					0.646
Low grade (G1/2)	146	37.0	57	29.7		44	36.4	41	33.9	
High grade (G3/4)	234	59.2	125	65.1		71	58.7	75	62.0	
Missing data	15	3.8	10	5.2		6	5.0	5	4.1	
Laurén classification					0.108					0.171
Intestinal	211	53.4	91	47.4		73	60.3	63	52.1	
Non-intestinal	152	38.5	88	45.8		39	32.2	49	40.5	
Missing data	32	8.1	13	6.8		9	7.4	9	7.4	
cT category					<b>&lt;0.001</b>					0.418
cT1	49	12.4	8	4.2		4	3.3	7	5.8	
cT2	120	30.4	36	18.8		27	22.3	30	24.8	
cT3	185	46.8	124	64.6		77	63.6	68	56.2	
cT4	18	4.6	18	9.4		7	5.8	12	9.9	
Missing data	23	5.8	6	3.1		6	5.0	4	3.3	
cN category					<b>&lt;0.001</b>					0.585
cN0	214	54.2	66	34.4		48	39.7	53	43.8	
cN+	159	40.3	121	63.0		68	56.2	65	53.7	
Missing data	22	5.6	5	2.6		5	4.1	3	2.5	
Neoadjuvant treatment					<b>&lt;0.001</b>					1.000
Primary surgery	268	67.8	68	35.4		54	44.6	54	44.6	
Neoadjuvant treatment	127	32.2	124	64.6		67	55.4	67	55.4	
Type of neoadjuvant treatment					0.522					0.247
Chemotherapy	119	93.7	120	96.8		61	91.0	65	97.0	
Chemoradiotherapy	6	4.7	3	2.4		4	6.0	2	3.0	
Radiotherapy	2	1.6	1	0.8		2	3.0	0	0.0	
Surgery					0.510					0.352
Subtotal gastrectomy	106	26.8	40	20.8		28	23.1	25	20.7	
Total gastrectomy	92	23.3	43	22.4		26	21.5	21	17.4	
THG	88	22.3	47	24.5		25	20.7	33	27.3	
Ivor Lewis procedure	91	23.0	53	27.6		34	28.1	39	32.2	
Other	18	4.6	9	4.7		8	6.6	3	2.5	
(y)pT category					<b>0.019</b>					0.995

**Table 1** (continued)

	All patients ( <i>n</i> = 587)				Matched patients ( <i>n</i> = 242)					
	Non-SFU ( <i>n</i> = 395)		SFU ( <i>n</i> = 192)		Non-SFU ( <i>n</i> = 121)		SFU ( <i>n</i> = 121)		<i>p</i>	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
(y)pT0	18	4.6	11	5.7	6	5.0	6	5.0		
(y)pT1	101	25.6	28	14.6	20	16.5	20	16.5		
(y)pT2	70	17.7	29	15.1	18	14.9	18	14.9		
(y)pT3	183	46.3	108	56.3	66	54.5	64	52.9		
(y)pT4	23	5.8	16	8.3	11	9.1	13	10.7		
(y)pN category									0.138	1.000
(y)pN0	198	50.1	78	40.6	58	47.9	58	47.9		
(y)pN1	63	15.9	37	19.3	20	16.5	20	16.5		
(y)pN2	56	14.2	37	19.3	13	10.7	13	10.7		
(y)pN3	78	19.7	40	20.8	30	24.8	30	24.8		
Adjuvant treatment									<b>&lt;0.001</b>	1.000
Not administered	286	72.4	94	49.0	67	55.4	67	55.4		
Administered	109	27.6	98	51.0	54	44.6	54	44.6		
Type of adjuvant treatment									<b>0.046</b>	0.235
Chemotherapy	93	85.3	92	93.9	49	90.7	51	94.4		
Chemoradiotherapy	16	14.7	6	6.1	5	9.3	3	5.6		

Bold values indicate a significance-level of *p* < 0.05

SFU standardized follow-up, EGJ esophagogastric junction, AEG adenocarcinoma of the esophagogastric junction, THG transhiatal extended gastrectomy



**Fig. 1** Influence of standardized follow-up (SFU) on overall survival **a** before and **b** after propensity score matching (PSM)

category was an independent prognostic factor after PSM (Table 3).

**Recurrence**

Of 587 patients, 231 (39.4%) developed recurrence; 82.2% of all recurrences (*n* = 190) were diagnosed within the first 24 months and 92.6% within 36 months after surgery; 43.3% of patients (*n* = 100) were asymptomatic

when recurrence was detected. Recurrence rate and risk for recurrence were increased in case of proximal tumor localization, advanced (y)pT category, and advanced (y) pN category (all *p* < 0.001) (supplementary Table 2). Diagnosis of recurrence was made by cross-sectional imaging (CT or MRI) in the majority of cases (82.3%), and histological confirmation was possible in 43.3% (*n* = 100). Most patients (82.7%) relapsed in the form of distant recurrence, while less than one third (28.1%) showed locoregional

**Table 2** Univariate Cox regression analysis for overall survival before and after propensity score matching

	All patients ( <i>n</i> = 587)				Matched patients ( <i>n</i> = 242)			
	<i>n</i>	HR	95% CI	<i>p</i>	<i>n</i>	HR	95% CI	<i>p</i>
Follow-up				0.490				0.040
Non-SFU	395	1			121	1		
SFU	192	0.91	0.70–1.19		121	0.69	0.49–0.99	
Age at diagnosis (years)				<0.001				<0.001
≤45	43	1			6	1		
46–69	363	0.97	0.57–1.66		176	0.90	0.28–2.86	
≥70	181	1.66	0.96–2.86		60	2.03	0.63–6.56	
Gender				0.194				0.893
Male	426	1			184	1		
Female	161	0.83	0.62–1.10		58	0.97	0.64–1.47	
Localization				<0.001				0.079
Esophagus/EGJ	313	1			142	1		
Stomach	274	0.60	0.46–0.77		100	0.72	0.50–1.04	
Diagnosis				0.001				0.290
AEG I	128	1			61	1		
AEG II	144	1.05	0.75–1.47		64	0.95	0.59–1.51	
AEG III	41	1.14	0.69–1.86		17	1.23	0.62–2.43	
Gastric cancer	274	0.62	0.45–0.86		100	0.72	0.46–1.13	
Grading				0.177				0.954
Low grade (G1/2)	203	1			85	1		
High grade (G3/4)	359	1.20	0.92–1.56		146	0.99	0.69–1.43	
Laurén classification				0.729				0.447
Intestinal	302	1			136	1		
Non-intestinal	240	1.05	0.81–1.36		88	0.86	0.59–1.26	
cT category				<0.001				0.008
cT1	57	1			11	1		
cT2	156	3.04	1.51–6.15		57	3.14	0.75–13.27	
cT3	309	5.02	2.56–9.85		145	5.08	1.24–20.77	
cT4	36	6.81	3.05–15.20		19	6.65	1.48–29.96	
cN category				<0.001				0.003
cN0	280	1			101	1		
cN+	280	1.63	1.26–2.11		133	1.75	1.20–2.54	
Neoadjuvant treatment				0.232				0.634
Primary surgery	336	1			108	1		
Neoadjuvant treatment	251	1.17	0.91–1.51		134	1.09	0.76–1.56	
Surgery				<0.001				0.123
Subtotal gastrectomy	146	1			53	1		
Total gastrectomy	135	1.63	1.09–2.45		47	1.46	0.81–2.65	
THG	135	2.26	1.55–3.30		58	1.61	0.94–2.75	
Ivor Lewis procedure	144	1.92	1.30–2.83		73	1.60	0.95–2.71	
Other	27	2.92	1.64–5.19		11	2.92	1.24–6.88	
(y)pT category				<0.001				<0.001
(y)pT0	29	1			12	1		
(y)pT1	129	0.55	0.26–1.18		40	0.97	0.32–2.97	
(y)pT2	99	1.23	0.60–2.55		36	1.19	0.39–3.63	
(y)pT3	291	2.01	1.03–3.94		130	2.13	0.78–5.83	
(y)pT4	39	3.95	1.84–8.48		24	3.86	1.29–11.58	
(y)pN category				<0.001				<0.001
(y)pN0	276	1			116	1		

**Table 2** (continued)

	All patients (n = 587)				Matched patients (n = 242)			
	n	HR	95% CI	p	n	HR	95% CI	p
(y)pN1	100	1.63	1.10–2.40		40	1.49	0.87–2.56	
(y)pN2	93	2.87	2.02–4.09		26	2.53	1.47–4.36	
(y)pN3	118	5.05	3.66–6.95		60	3.63	2.36–5.58	
Adjuvant treatment				0.766				0.179
Not administered	380	1			134	1		
Administered	207	0.96	0.73–1.26		108	0.78	0.54–1.12	

Bold values indicate a significance-level of  $p < 0.05$

HR hazard ratio, CI confidence interval, SFU standardized follow-up, EGJ esophagogastric junction, AEG adenocarcinoma of the esophagogastric junction, THG transhiatal extended gastrectomy

**Table 3** Multivariate Cox regression analysis for overall survival before and after propensity score matching

	All patients (n = 587)				Matched patients (n = 242)			
	n	HR	95% CI	p	n	HR	95% CI	p
Age at diagnosis (years)								
≤45 (reference)	43	1		<b>0.001</b>	6	1		<b>&lt;0.001</b>
46–69	363	1.32	0.75–2.33	0.330	176	1.43	0.44–4.61	0.555
≥70	181	2.20	1.23–3.93	<b>0.008</b>	60	3.34	1.01–11.12	<b>0.049</b>
cT category								
cT1 (reference)	57	1		<b>&lt;0.001</b>	NA			
cT2	156	2.42	1.15–5.13	<b>0.021</b>				
cT3	309	3.78	1.81–7.88	<b>&lt;0.001</b>				
cT4	36	5.36	2.19–13.12	<b>&lt;0.001</b>				
cN category								<b>0.043</b>
cN0 (reference)	NA				101	1		
cN+					133	1.56	1.01–2.39	
(y)pN category								
(y)pN0 (reference)	276	1		<b>&lt;0.001</b>	116	1		<b>&lt;0.001</b>
(y)pN1	100	1.41	0.93–2.16	0.109	40	1.33	0.75–2.35	0.324
(y)pN2	93	2.25	1.52–3.32	<b>&lt;0.001</b>	26	2.12	1.13–3.98	<b>0.019</b>
(y)pN3	118	3.69	2.60–5.23	<b>&lt;0.001</b>	60	2.95	1.82–4.77	<b>&lt;0.001</b>
Follow-up								
Non-SFU (reference)	395	1			121	1		
SFU	192	0.72	0.53–0.97	<b>0.034</b>	121	0.61	0.42–0.90	<b>0.013</b>

Bold values indicate a significance-level of  $p < 0.05$

Factors included: follow-up, age, gender, diagnosis, grading, Laurén classification, cT category, cN category, neoadjuvant treatment, surgery, (y)pT category, (y)pN category, adjuvant treatment

HR hazard ratio, CI confidence interval, SFU standardized follow-up, NA not applicable

recurrence. The most frequent pattern of distant recurrence was distant lymphatic spread (36.4%), followed by peritoneal recurrence (30.7%), liver (25.5%), lung (12.1%), and bone metastases (10.0%). Less frequent sites (<5%) included the brain, soft tissue, adrenal, and ovarian metastases. In 101 patients (43.7%), recurrence was detected at multiple sites (supplementary Fig. 3).

One hundred seventy patients (73.6%) were treated for recurrence, while 61 patients did not receive any treatment for recurrence at all (26.4%). Treatment of recurrence was mostly with palliative intent (85.3%). Twenty-nine of the patients who received treatment (17.1%) underwent

resection of recurrence with or without additional treatment; 141 patients (82.9%) received only chemotherapy (CTx), chemoradiotherapy (CRTx), radiotherapy (RTx), or any combination of these treatment modalities. Details on time of diagnosis, diagnostic means for detection, patterns, and treatment of recurrence are listed in Table 4.

Eighty-three patients (43.2%) in the SFU group and 148 (37.5%) in the non-SFU group developed recurrence ( $p = 0.180$ ). No significant differences between the SFU and non-SFU group could be detected regarding time of diagnosis, symptoms, diagnostic means for detection, and pattern of recurrence, except for liver metastases, which



**Table 4** Time of diagnosis, diagnostic means for detection, pattern, and treatment of recurrence in patients with individual (non-SFU) and standardized follow-up (SFU)

	Non-SFU ( <i>n</i> = 148)		SFU ( <i>n</i> = 83)		Total ( <i>n</i> = 231)		<i>p</i>
Interval till recurrence							0.362
<12 months	76	51.4%	52	62.7%	128	55.4%	
12–24 months	42	28.4%	20	24.1%	62	26.8%	
24–36 months	17	11.5%	7	8.4%	24	10.4%	
>36 months	13	8.8%	4	4.8%	17	7.4%	
Symptomatic recurrence							0.276
No	53	35.8%	47	56.6%	100	43.3%	
Yes	53	35.8%	34	41.0%	87	37.7%	
Missing data	42	28.4%	2	2.4%	44	19.0%	
Diagnostic means							0.336
Clinically/sonography	13	8.8%	5	6.0%	18	7.8%	
Endoscopy	5	3.4%	2	2.4%	7	3.0%	
Imaging (CT or MRI)	88	59.5%	65	78.3%	153	66.2%	
Imaging and endoscopy	26	17.6%	11	13.3%	37	16.0%	
Missing data	16	10.8%	0	0.0%	16	6.9%	
Cross-sectional imaging							0.247
No	18	12.2%	7	8.4%	25	10.8%	
Yes	114	77.0%	76	91.6%	190	82.3%	
Missing data	16	10.8%	0	0.0%	16	6.9%	
Histologically confirmed							0.311
No	67	45.3%	48	57.8%	115	49.8%	
Yes	65	43.9%	35	42.2%	100	43.3%	
Missing data	16	10.8%	0	0.0%	16	6.9%	
Pattern of recurrence							
Locoregional	45	30.4%	20	24.1%	65	28.1%	0.129
Distant	117	79.1%	75	90.4%	192	83.1%	0.586
Lymphatic	50	33.8%	34	41.0%	84	36.4%	0.621
Peritoneal	45	30.4%	26	31.3%	71	30.7%	0.703
Liver	46	31.1%	13	15.7%	59	25.5%	<b>0.002</b>
Lung	13	8.8%	15	18.1%	28	12.1%	0.077
Bone	15	10.1%	8	9.6%	23	10.0%	0.704
Brain	8	5.4%	2	2.4%	10	4.3%	0.220
Adrenal	3	2.0%	5	6.0%	8	3.5%	0.154
Soft tissue	4	2.7%	3	3.6%	7	3.0%	0.806
Ovarian	4	2.7%	3	3.6%	7	3.0%	0.806
Other	2	1.4%	1	1.2%	3	1.3%	0.855
Multiple sites	69	46.6%	32	38.6%	101	43.7%	0.056
Missing data	15	10.1%	0	0.0%	15	6.5%	
Treatment of recurrence							<b>0.001</b>
No	50	33.8%	11	13.3%	61	26.4%	
Yes	98	66.2%	72	86.7%	170	73.6%	
	Non-SFU ( <i>n</i> = 98)		SFU ( <i>n</i> = 72)		Total ( <i>n</i> = 170)		<i>p</i>
Therapy of recurrence							
Intention of treatment							0.135
Palliative	87	88.8%	58	80.6%	145	85.3%	
Curative	11	11.2%	14	19.4%	25	14.7%	
Resection of recurrence							0.767
No (CTx/CRTx/RTx only)	82	83.7%	59	81.9%	141	82.9%	

**Table 4** (continued)

	Non-SFU ( <i>n</i> = 98)		SFU ( <i>n</i> = 72)		Total ( <i>n</i> = 170)		<i>p</i>
Yes ( $\pm$ CTx/CRTx/RTx)	16	16.3%	13	18.1%	29	17.1%	0.300
Type of therapy							
Resection	6	6.1%	9	12.5%	15	8.8%	
Resection + CTx/CRTx/RTx	10	10.2%	4	5.6%	14	8.2%	
CTx only	59	60.2%	46	63.9%	105	61.8%	
CRTx/RTx ( $\pm$ CTx)	23	23.5%	13	0.0%	36	21.2%	

Bold values indicate a significance-level of  $p < 0.05$

SFU standardized follow-up, CT computed tomography, MRI magnetic resonance imaging, CTx chemotherapy, CRTx chemoradiotherapy, RTx radiotherapy, + and / or  $\pm$  with or without

were more frequent in the non-SFU group (31.1 vs. 15.7%,  $p = 0.002$ ). Patients in the SFU group were more likely to receive treatment for recurrence than patients in the non-SFU group (86.7 vs. 66.2%;  $p = 0.001$ ). However, there was no difference with respect to type of treatment (Table 4).

### Diagnosis, pattern, and treatment of recurrence and survival

Of 231 patients with recurrence, 200 had died at last follow-up. Cause of death was tumor-related in all cases ( $n = 200$ ). For patients with recurrence, median overall survival from time of diagnosis was 24.2 (95% CI 21.3–27.2) months, and median post-recurrence survival was 7.1 (95% CI 5.2–9.0) months.

OS and PRS were considerably improved by treatment or recurrence (Fig. 2a, b), surgical resection of recurrence (Fig. 2c, d), and especially resection combined with CTx and/or CRTx and/or RTx (Fig. 2e, f). Additionally, improved OS and PRS were linked to asymptomatic recurrence (supplementary Fig. 4a, b), diagnostic means for detection of recurrence (supplementary Fig. 5a, b), and particularly detection of recurrence by cross-sectional imaging (supplementary Fig. 5c, d). Survival analyses for patients with recurrent disease regarding factors associated with the diagnosis, pattern, and treatment of recurrence are summarized in Table 5.

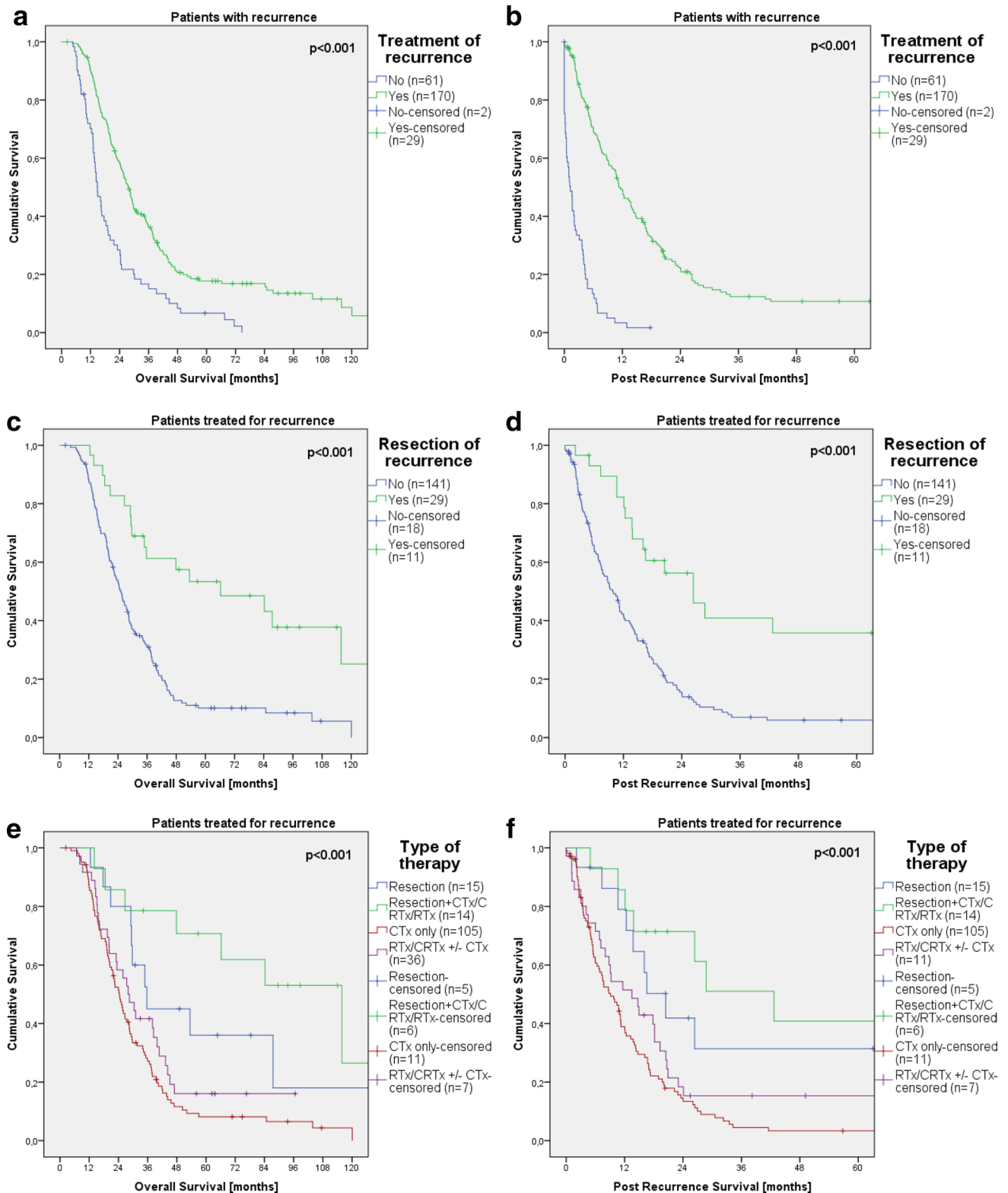
Multivariate analysis for PRS identified symptomatic (HR 1.73,  $p = 0.005$ ) and peritoneal recurrence (HR 1.54,  $p = 0.040$ ) as negative independent prognosticators, while resection of recurrence significantly improved PRS (HR 0.36,  $p < 0.001$ ) (supplementary Table 3).

### Discussion

In the absence of randomized controlled trials, the discussion on the need, schedule, and recommended examinations for follow-up after resection of esophagogastric cancer has been completely controversial worldwide [12–15, 24].

Our study is the first one to compare intensive follow-up by a specialized center with individual follow-up of other physicians after reducing heterogeneity between groups by propensity score matching. We could show that patients are likely to benefit from standardized surveillance by a specialized center after complete resection of esophagogastric adenocarcinoma if baseline characteristics are comparable between groups. The lack of survival benefit from intensive follow-up in our entire patient collective can be explained by more advanced (y)pT and (y)pN categories in the SFU group. Patients with more advanced tumor stages are more likely to be subjected to intensive follow-up than patients with early stage disease [43, 44, 46]. We believe that this selection bias could explain why other series failed to show a beneficial effect of intensive postoperative surveillance on survival [43–45]. Besides, even general practitioners or other outpatient physicians seem to frequently arrange cross-sectional imaging during follow-up for patients with esophagogastric cancer. Apparently most patients in Germany receive relatively intensive surveillance including cross-sectional imaging despite the German guidelines not recommending any regular follow-up examinations in esophagogastric cancer at all [16, 22]. This might be symptomatic of another reason for regular follow-up, namely the patients' wishes. Nowadays, patients are well informed and probably not satisfied with reassessment only in case of clinical symptoms. It seems as if repeated follow-up examinations do not lead to discomfort but rather reassurance of the patients. Furthermore, the literature confirms that early asymptomatic diagnosis of recurrence is associated with improved prognosis [53, 54].

According to our data, cross-sectional imaging seems to be the most effective examination technique for detection of recurrence. In our series, mostly CT scans were performed, and recurrence was rarely discovered by endoscopy. Since—as in our analysis—the most frequent pattern of recurrence after R0 resection of esophagogastric adenocarcinoma is distant and only a small percentage of patients show local relapse [4, 42, 55], cross-sectional



**Fig. 2** Influence of treatment of recurrence on **a** overall survival, **b** post-recurrence survival; influence of resection of recurrence on **c** overall survival, **d** post-recurrence survival; influence of type of treatment for recurrence on **e** overall survival, **f** post-recurrence survival

**Table 5** Influence of diagnosis, pattern, and treatment of recurrence on overall and post-recurrence survival

	<i>n</i>	Events	mOS	95% CI	<i>p</i>	mPRS	95% CI	<i>p</i>
Interval till recurrence (months)					<b>&lt;0.001</b>			0.262
<12	128	118	15.2	13.7–16.6		6.9	4.8–8.9	
12–24	62	53	27.5	23.5–31.6		6.8	1.8–11.8	
24–36	24	17	44.2	42.5–45.9		11.2	0.0–22.8	
>36	17	12	74.6	53.7–95.5		9.1	3.8–14.4	
Symptomatic recurrence					<b>0.026</b>			<b>&lt;0.001</b>
No	100	83	27.5	23.6–31.5		13.8	10.4–17.2	
Yes	87	80	20.1	14.8–25.4		4.5	2.9–6.2	
Diagnostic means					<b>0.010</b>			<b>0.042</b>
Clinically/sonography	18	17	19.4	3.9–34.9		3.7	1.8–5.5	
Endoscopy	7	6	12.4	11.2–13.7		2.2	1.7–2.7	
Imaging (CT or MRI)	153	132	24.4	19.5–29.3		9.1	6.4–11.9	
Imaging and endoscopy	37	29	39.9	26.1–53.7		11.1	5.0–17.3	
Cross-sectional imaging					<b>0.011</b>			<b>0.007</b>
No	25	23	22.1	5.1–27.9		3.7	2.6–4.7	
Yes (CT or MRI)	190	161	28.5	22.8–29.2		9.2	6.8–11.6	
Histologically confirmed					<b>0.007</b>			0.091
No	115	102	22.1	17.9–26.3		6.8	4.0–9.6	
Yes	100	82	28.5	24.8–32.2		10.7	7.9–13.4	
Locoregional recurrence					0.127			0.626
No	151	130	23.3	19.9–26.8		7.3	4.2–10.3	
Yes	65	55	31.1	22.2–39.9		9.1	5.1–13.1	
Distant recurrence					0.191			0.190
No	24	19	35.9	21.9–49.9		14.8	9.5–20.0	
Yes	192	166	24.2	20.9–27.6		7.5	5.4–9.6	
Peritoneal recurrence					<b>0.004</b>			<b>&lt;0.001</b>
No	145	121	27.5	23.3–31.7		11.1	7.8–14.5	
Yes	71	64	20.4	13.5–27.3		6.0	4.2–7.7	
Multiple sites					0.248			<b>0.013</b>
No	115	97	25.8	21.7–30.0		12.1	9.0–15.2	
Yes	101	88	22.6	17.6–27.6		6.0	3.9–8.2	
Treatment of recurrence					<b>&lt;0.001</b>			<b>&lt;0.001</b>
No	61	59	14.9	12.3–17.4		1.2	0.5–2.0	
Yes	170	141	27.5	24.7–30.4		11.2	9.0–13.4	
Intention of treatment					<b>0.001</b>			<b>&lt;0.001</b>
Palliative	145	126	25.6	22.2–28.9		10.0	8.0–12.0	
Curative	25	15	47.9	22.3–73.5		26.4	18.8–34.0	
Resection of recurrence					<b>&lt;0.001</b>			<b>&lt;0.001</b>
No (CTx/CRTx/RTx only)	141	123	25.2	21.6–28.9		9.8	7.3–12.3	
Yes (±CTx/CRTx/RTx)	29	18	66.2	17.3–115.2		26.4	15.6–37.2	
Type of therapy					<b>&lt;0.001</b>			<b>&lt;0.001</b>
Resection	15	10	35.7	25.4–46.1		20.5	13.0–27.9	
Resection + CTx/CRTx/RTx	14	8	115.8	60.7–171.0		42.7	19.2–66.2	
CTx only	105	94	24.4	21.2–27.6		9.1	6.2–12.1	
CRTx/RTx (±CTx)	36	29	28.0	21.2–34.8		13.5	6.7–20.3	

Bold values indicate a significance-level of  $p < 0.05$

*mOS* median overall survival, *mPRS* median post-recurrence survival, *CT* computed tomography, *MRI* magnetic resonance imaging, *CTx* chemotherapy, *CRTx* chemoradiotherapy, *RTx* radiotherapy, + and /= or ± with or without

imaging is more likely to detect recurrence, and the role of routine endoscopy for postoperative surveillance seems to be limited. In this respect, our findings are in line with recent reviews of the literature [23, 40] and studies of other high-volume centers [42, 45, 56, 57]. Moreover, local recurrence is very likely to present with symptoms. A large series at Memorial Sloan-Kettering Cancer Center with 1147 patients could show that 65% of local recurrences were initially suspected because of symptoms and only 1% of asymptomatic recurrences were detected by endoscopy [57]. We thus suggest that postoperative surveillance should be based mainly on cross-sectional imaging, whereas routine endoscopy during follow-up should be reserved for patients with high risk of local recurrence, for example, in case of unclear or positive resection margins (Rx or R1), though it should be performed in a timely manner in case of local symptoms.

In our patient collective, more than 50% of patients relapsed within 1 year, 80% of patients within 2 years, and more than 90% within 3 years after curative resection. Comparable results have been reported previously in esophagogastric adenocarcinoma [42]. Since only a small percentage of patients will recur more than 3 years postoperatively, and the probability of relapse after more than 5 years is extremely low [3, 24, 50], intensive follow-up should be performed for a minimum of two and maximum of 3 years after surgery, followed by a subsequent de-escalation and discontinuation of surveillance after 5 years.

Our analyses as well as previous studies have shown that the risk for recurrence increases with advanced stage of disease [58–61]. Indeed, for early gastric cancer thousands of follow-up examinations would be necessary to detect relapse as the incidence is very low [1, 2]. For these cases, the cost-benefit ratio seems to be unfavorable. On the other hand, in case of locally advanced and nodal-positive esophagogastric adenocarcinoma, intensive follow-up after resection should be more effective, since the probability of relapse is far higher [3–5]. It thus seems reasonable to adapt the intensity of surveillance according to tumor stage.

The lack of curative treatment options for the vast majority of patients with recurrent disease has been frequently used as an argument against regular surveillance after resection of esophagogastric adenocarcinoma. However, our results indicate a strong survival benefit by treatment of recurrent disease. Part of this survival advantage surely is due to the fact that only patients with a good performance status will receive treatment for relapse, while those with poor general status and hence limited prognosis will not. Yet, this certainly does not account for the entire effect of treatment on survival in our collective. Even though the majority of patients received palliative treatment, mostly in the form of chemotherapy, various randomized controlled trials have shown that palliative chemotherapy improves the outcome in esophagogastric cancer

[27, 62, 63]. We could show that patients followed by a specialized center according to a standardized protocol receive treatment after relapse more frequently than those with individual follow-up. Our results indicate that earlier detection of asymptomatic recurrence and hence better performance status might enable a larger proportion of patients to receive treatment with a beneficial effect on prognosis.

The fact that resection of recurrence improved survival is a classical selection bias and therefore not surprising.

Resection of recurrence led to major improvement of prognosis and even long-term survival, especially when combined with further treatment modalities. Since surgical resection was possible only in a small percentage of selected patients with either isolated local recurrence or circumscribed metastatic disease, the detected survival benefit by resection of relapse probably is caused by selection bias to a relevant extent. However, some smaller series have described an improved and even long-term outcome after resection of local recurrence [64–67] and metachronous liver metastases [68–74] of gastric adenocarcinoma as an individual treatment strategy for a small and highly selected subset of patients. Thus, considering the lack of other curative treatment options, surgical treatment should be attempted whenever resection of recurrent lesions seems feasible and performance status is adequate. As in primary esophagogastric adenocarcinoma, surgical resection embedded in multimodal treatment plans seems to offer the best chance of re-cure.

Limitations of the study are the retrospective, non-randomized, and single-center design. Moreover, since the SFU and non-SFU groups were heterogeneous, comparison of prognosis between the two groups has to be interpreted carefully. Even though propensity score matching was performed, remnant heterogeneity between groups cannot be excluded. Besides, despite the considerable sample size of the entire study population, it might still be too small for adequate subgroup analyses.

Despite all limitations, this study strongly supports an intensified standardized follow-up in curatively resected esophagogastric cancer patients. Prospective randomized controlled data on this topic are needed. However, international expert opinion states that attaining high-grade evidence for standardized follow-up by randomized controlled trials is improbable [24]. As long as no prospective data are available, we suggest that all patients should be subjected to an intensified standardized surveillance protocol after curative resection of esophagogastric adenocarcinoma. In summary, we propose postoperative follow-up visits including scheduled cross-sectional imaging as follows: for locally advanced [(y)pT3/4] and/or nodal positive disease [(y)pN1/2/3]: every 3 months during the first 2 years, every 6 months during the 3rd and 4th year, and every 12 months during the 5th year;

for locally limited tumors (pT0/1/2) and nodal negative disease (pN0): every 6 months during the first 3 years and every 12 months during the 4th and 5th year. After complete tumor resection, routine endoscopy is not necessary, but endoscopic examinations should be performed in case of local symptoms.

## Conclusion

Intensive follow-up by a specialized center was associated with improved overall survival in a large propensity score-matched patient collective after complete resection of esophagogastric adenocarcinoma. Cross-sectional imaging seems to be the diagnostic modality of choice for postoperative follow-up. Moreover, the treatment and especially the resection of recurrence were associated with improved survival, treatment being offered significantly more often to patients followed by a specialized center. Since more than 90% of relapses occur within the first 3 years after surgery, we recommend intensive follow-up by cross-sectional imaging during this time period, whereas routine endoscopy is not required. Follow-up should be stage-adapted, gradually decreased in intensity, and discontinued after 5 years. Early detection of asymptomatic recurrence might allow for a larger proportion of patients to receive treatment and could even facilitate resection of recurrence potentially resulting in repeated cure with long-term survival in a small subgroup of selected patients. National practice guidelines should be modified accordingly.

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## Compliance with ethical standards

**Human rights** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

**Informed consent** Informed consent or substitute for it was obtained from all patients for being included in the study.

**Conflict of interest** The authors declare that they do not have any commercial interest in the subject of study. GM Haag reports fees for advisory role from Sanofi, Roche, Taiho, Nordic, Lilly, Pfizer, honoraria from Roche, travel grants from Amgen, Ipsen and Celgene; research funding is provided by Nordic and Taiho Pharmaceuticals. There is no relationship to the submitted work.

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