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Prognostic role of early 18-FDG PET/CT during neoadjuvant chemotherapy for resectable adenocarcinoma of the esophagus and esophagogastric junction

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We prospectively investigated whether metabolic response assessed by 18F-fluorodeoxyglucose positron emission tomography combined with computed tomography (PET/CT) early in the course of neoadjuvant chemotherapy is predictive of survival in patients with adenocarcinoma of the esophagus and esophagogastric junction. PET/CT was performed before and in the third week after the initiation of the first cycle of neoadjuvant chemotherapy, which consisted of epirubicin, cisplatin, and 5-fluorouracil or capecitabine. The metabolic response was defined as a relative decrease in the peak standardized uptake value (SUL) of the tumor by ≥35% or total lesion glycolysis (TLG) by ≥66%. The associations of metabolic response with overall survival (OS) and disease-free survival (DFS) were investigated using Kaplan-Meier curves and multivariable Cox regression analysis. Among 126 recruited patients, the early metabolic response was assessed in 107 patients (90 of them underwent surgical resection). The five-year OS and DFS rates of all patients were 28% and 27%, respectively. No difference was found in OS (p=0.10 for SUL, p=0.08 for TLG) or DFS (p=0.50 for SUL, p=0.20 for TLG) between metabolic responders and non-responders. Post hoc analysis of the patients with a follow-up PET/CT within 16 days showed that metabolic response reflected by SUL predicted OS (p=0.03). We concluded that metabolic response assessed by PET/CT after the first cycle of neoadjuvant chemotherapy does not predict survival in patients with adenocarcinoma of the esophagus and esophagogastric junction. However, proper timing of the follow-up PET/CT may affect the prognostic ability of the early metabolic response.

Key words: adenocarcinoma of the esophagus and esophagogastric junction, neoadjuvant chemotherapy, FDG-PET/CT, early metabolic response, overall survival, disease-free survival

The incidence of adenocarcinoma of the esophagus and esophagogastric junction (AEG) has been rising substantially in recent decades, especially in the Western world, where it has become the predominant type of esophageal cancer [1]. The cure rates of locally advanced tumors after surgery alone are disappointing, with 5-year survival rates rarely exceeding 25% [2, 3]. Neoadjuvant therapy followed by surgery has been established as a standard of care for locally advanced resectable esophageal cancer [4]. For AEG, perioperative chemotherapy has been shown to be beneficial compared to surgery alone, as evidenced by randomized trials [3, 5]. However, the response to chemotherapy is not uniform, and only the responders seem to benefit from preoperative treatment [6, 7]. Non-responders most likely do not benefit from neoadjuvant therapy but are still exposed to its toxicity, causing surgery or other more effective treatment to be delayed, which might negatively affect their long-term survival [6]. The early prediction of response to chemotherapy could be of great value for a tailored approach to induction regimens. Measuring changes in tumor metabolism using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) during the course of neoadjuvant treatment for esophagogastric cancer yielded promising results for the early identification of non-responses [8, 9]. Weber and Ott with co-workers (i.e., the Munich group) found that a decrease in the maximum standardized uptake value (SUVmax) by more than 35% from baseline as early as 14 days after the start of induction chemotherapy in AEG was predictive of a histopathological response and survival [8, 9]. Subsequently, two prospective non-randomized trials (MUNICON I, II) were conducted by the Munich group, in which the treatment regimens were modified early in the course of neoad-

juvant chemotherapy: in MUNICON I, PET non-responders proceeded to early surgery, while in MUNICON II, PET non-responders received neoadjuvant radiochemotherapy [10, 11]. Both studies showed worse prognosis in metabolic non-responders irrespective of treatment. The threshold of early metabolic response set by the Munich group has been widely accepted, although few studies have validated this approach in a prospective setting.

We recently published the results of a prospective clinical trial evaluating the ability of repeated FDG-PET combined with computed tomography (PET/CT) to predict the histopathological response to neoadjuvant chemotherapy for AEG early in the course of treatment [12]. The aim of the present study was to evaluate the association of early metabolic response with long-term survival.

Patients and methods

The present study reports a secondary aim of the prospective clinical trial, which was primarily designed to evaluate the association of early metabolic response and histopathological response [12]. This study took place at the 3rd Department of Surgery and Department of Oncology, First Faculty of Medicine, Charles University in Prague, and at PET centrum, Na Homolce Hospital, Prague, Czech Republic. The scientific protocol was approved by the local ethics committee and by the State Institute for Drug Control, Czech Republic. The trial was registered in the European Clinical Trials Database under EudraCT number 2011-001856-12. Informed consent to participate in a clinical study was obtained from each recruited patient. The English translation of the Informed Consent Form (the original form is in the Czech language) is available upon request.

Patients. Eligibility criteria for patient inclusion comprised histologically proven adenocarcinoma of the esophagus or esophagogastric junction (Siewert type I–III), clinical stage cT2-4a, cN0-3, and cM0 (according to the 7th edition of the UICC TNM classification system) [13] based on pre-treatment spiral CT and endoscopic ultrasound, World Health Organization performance status of 0–1 and medical condition allowing combined multimodality treatment. Eligible patients were included in the study after providing written informed consent. The exclusion criteria included age over 75 years, diabetes mellitus with a glycemic level over 10 mmol/l, distant organ metastases on baseline PET/CT, and FDG non-avid tumor on baseline PET/CT.

Metabolic response assessment. The study protocol included two PET/CT scans for each patient: one at baseline (PET1) and one in the third week of the first cycle of neoadjuvant chemotherapy (PET2). All scans were acquired with the same scanner (Biograph 40 TruePointTrueV HD PET/CT scanner, Siemens). The PET Response Criteria in Solid Tumors (PERCIST 1.0) recommendations were used to maintain reproducibility [14].

The mean ± standard deviation (SD) dose of FDG given to the patients was 4.00±0.31 MBq/kg of body weight, with a mean ± SD difference in the dose between PET1 and PET2 of 1.6±4.9%. The median accumulation times on PET1 and PET2 were 75 min (IQR, 70–82 min) and 75 min (IQR, 69–81 min), respectively.

Two PERCIST 1.0 parameters were used for the quantitative analysis of FDG uptake in the primary tumor: the peak standardized uptake value normalized to lean body mass (SUL_{PEAK}, abbreviated SUL hereinafter) and the total lesion glycolysis of the primary tumor (TLG) [14]. SUL was measured in a circular region of interest (ROI) with a radius of 0.6 cm around the hottest spot in the tumor. TLG was calculated from the average standardized uptake value in the metabolic tumor volume (MTV), covering the entire metabolically active primary tumor mass, multiplied by this MTV. The MTV was automatically delineated by the software at the threshold level derived from the average standardized uptake value of the liver parenchyma. Details on the methodology of scanning and data acquisition have been published previously [12, 15, 16].

The early metabolic response of the tumor to chemotherapy was measured as a relative change (percent) in FDG uptake between PET1 (SUL1 and TLG1) and PET2 (SUL2 and TLG2) and was expressed as ΔSUL and ΔTLG using the following formula: $\Delta SUL=[(SUL1-SUL2)/SUL1]\times100$. The measurement for PET2 was performed in the most active intra-tumor area, which may not have been exactly the same as the intra-tumor area in PET1. The metabolic response was defined as a relative decrease in SUL of at least 35% [9, 10] and/or a relative decrease in TLG of at least 66%, according to our previous study [12].

Perioperative chemotherapy. Chemotherapy included three preoperative and three postoperative cycles of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) intravenously on day 1 plus a continuous infusion of fluorouracil (200 mg/m^2/day) with a portable infusion pump for 21 days (ECF) or oral capecitabine (1,000 mg/m^2 twice a day) for 14 days (ECX) in a 21-day cycle [5, 17]. The details of the chemotherapy regimen and its modifications in our cohort of patients have been described previously [18]. The adjuvant therapy regimen was altered in some patients depending on the final pathological stage and postoperative performance status of the patients.

Surgery and pathology. Surgery was performed 3–6 weeks after the completion of chemotherapy unless it was contraindicated or refused by the patient. Patients with resectable disease underwent either a transthoracic esophagectomy with gastric pull-up reconstruction (Ivor Lewis procedure) or a total gastrectomy depending on the location and extent of the tumor. The details of our surgical technique for the Ivor Lewis procedure have been described previously [19]. Abdominal lymph node dissection was performed during all radical operations, and infracarinal mediastinal lymphadenectomy was added to transthoracic esophagectomy.

Pathological staging was performed using the 7th edition of the Union for International Cancer Control (UICC) TNM classification system [13]. The absence of tumor cells within 1 mm within the edge of the tissue specimen was regarded as R0 resection. The tumor regression grade (TRG) according to Mandard was used to define tumor response to chemotherapy [20]. Patients found to have the unresectable disease during explorative surgery were considered histopathological non-responders.

Follow up. After the completion of therapy, the patients were followed clinically every 3 months for the first two years and then every 6 months. Contrast-enhanced CT and endoscopy were performed in 6-month intervals during the first two years and yearly thereafter, for at least 5 years. Survival was calculated from the start of neoadjuvant chemotherapy. Disease-free survival (DFS) represented the time to the first recurrence or death from unknown reasons. Patients who died from a non-malignant reason without documented relapse were censored on the date they were last seen or the date of death.

Statistical analysis. All analyses were performed using R software, version 3.2.2. The data are shown as the median with interquartile range (IQR) for continuous variables and count (percentage) for categorical variables. Comparisons between groups were performed using the Student's t-test or Mann-Whitney U test for continuous variables and χ^2-test for categorical variables. Disease-free and overall survival curves were constructed with the Kaplan-Meier method and compared with the log-rank test. Univariable Cox proportional hazards regression analysis was used to assess the impact of the clinical, metabolic, and pathological variables at baseline on recurrence and survival. Multivariable Cox regression analyses were used to determine independent prognostic markers. Two models of multivariable analyses were created. In the first model (model No. 1), the predictive significance of metabolic response was adjusted for possible confounding pre-treatment factors: age, clinical stage, and baseline SUL and TLG values. In the second model (model No. 2), the clinical, metabolic, and pathological variables that were significant in the univariable analysis were entered into a multivariable Cox proportional hazards model. All statistical tests were two-sided, and a p-value <0.05 was considered significant.

Results

Between January 2009 and April 2015, 148 patients were recruited into the study. After the baseline PET/CT, twenty-two patients were excluded (21 patients with distant metastases, one patient with an FDG non-avid tumour). Five patients from the study group had disease progression during neoadjuvant treatment as determined by repeated imaging and did not undergo surgery. Another three patients did not proceed to surgery due to having a poor performance status after chemotherapy, and one patient discontinued treatment prematurely, so 117 patients proceeded to surgery. Nineteen patients from the study group did not have a second PET/CT scan according to the protocol due to logistical reasons or their deteriorated condition, so the early metabolic response was assessed in 107 patients.

Surgery. Of the 117 patients who underwent surgery, 16 were found to have unresectable cancer during the surgical exploration (8 patients had metastatic disease and 8 patients had unresectable tumors), 10 patients underwent total gastrectomy (those with Siewert type III tumors), and 91 patients underwent Ivor Lewis esophagectomy. There was a median of 20 (range 2–55) resected lymph nodes, and tumor-free margins (R0) were achieved in 87 out of 117 surgical patients (74%). No patient was pathologically found to have a complete tumor response. One surgical patient died due to postoperative complications 19 days after surgery, and another patient committed suicide 75 days after surgery (30-day surgical mortality 1%, 90-day surgical mortality 2%). The patient and tumor characteristics are shown in Table 1.

Perioperative therapy. Preoperatively, epirubicin was omitted in one patient, and cisplatin was replaced by oxaliplatin in two patients. One or two cycles of chemotherapy were omitted in six patients. The chemotherapy regimen was postponed in 39 patients (31%), and a reduced dose of cytostatics was administered to 7 patients.

All three cycles of postoperative ECF or ECX chemotherapy were administered to 68 (54%) patients; 4 patients received two and 7 patients received only one postoperative cycle of the same treatment. In three patients, postoperative chemotherapy was changed to the FOLFOX regimen. Six patients received adjuvant concomitant chemoradiotherapy based on cisplatin and fluorouracil. Twent patients received additional radiotherapy after postoperative ECF/ECX chemotherapy, and one patient received postoperative radiotherapy alone. Non-resected patients received either palliative chemotherapy of various types or palliative chemoradiation. Altogether, adjuvant (or palliative in non-resected patients) radiotherapy was administered to 27 (21%) patients. No adjuvant therapy was administered to 25 (20%) patients.

Follow-up. The median follow-up time for the surviving patients was 63 months (range 30–107 months). During follow-up, 91 patients died. Six patients died from non-malignant causes without cancer relapse, and in ten patients, the recurrence status was unknown. Eighty patients were diagnosed with disease recurrence (locoregional, metastatic, or both). The estimated 5-year OS and DFS rates of the study group (n=126) were 28% and 27%, respectively. There was a significant difference in OS between resected patients and non-resected patients (median survival 27.9 months vs. 11.2 months, log-rank $p<0.001$).

Metabolic response and survival. The metabolic response was evaluated in 107 patients having PET2 at a median of 16 days (range 12–22 days) after the start of chemotherapy but always prior to the second cycle. One patient was excluded from ΔTLG analysis due to an excessively low baseline rate of

Table 1. Patient and tumor characteristics in all patients and in metabolic responders versus non-responders.

Parameter	All patients		SUL responders		SUL non-responders		p-value	TLG responders		TLG non-responders		p-value
	n=126	(%)	n=51	(%)	n=56	(%)		n=46	(%)	n=60	(%)	
Age, median (range)	60 (27–75)		60 (35–68)		62 (27–75)		0.155	60 (27–74)		63 (35–75)		0.139
Male gender	115	91	44	86	53	95	0.249	40	87	57	95	0.262
Tumor location							0.806					0.804
Siewert I	41	33	20	39	19	34		18	39	21	35	
Siewert II	64	51	23	45	25	45		20	43	31	52	
Siewert III	16	13	7	14	5	9		5	11	7	12	
unknown	5	4	1	2	7	13		3	7	1	2	
Clinical staging							0.191					0.173
T2N0	5	4	4	8	1	2		2	4	3	5	
T2N+	10	8	7	14	3	5		7	15	3	5	
T3/4N0	31	25	11	22	14	25		13	28	12	20	
T3/4N+	80	63	29	57	38	68		24	52	42	70	
Grading							0.739					0.200
G1/2	52	41	23	45	19	34		23	50	19	32	
G3/4	46	37	22	43	23	41		17	37	27	45	
unknown	28	22	6	12	14	25		6	13	14	23	
Surgical radicality							0.731*					0.273*
R0	87	69	38	75	39	70		36	78	40	67	
R1	14	11	6	12	7	13		4	9	9	15	
surgical exploration	16	13	6	12	6	11		5	11	7	12	
no surgery	9	7	1	2	4	7		1	2	4	7	
Pathological T-stage							0.468					0.526
T1	6	5	3	6	3	5		4	9	2	3	
T2	19	15	12	24	7	13		10	22	9	15	
T3	71	56	26	51	34	61		24	52	36	60	
T4	5	4	3	6	2	4		2	4	2	3	
unknown	25	20	7	14	10	18		6	13	11	18	
Pathological N-stage							0.105					0.086
N0	39	31	22	43	12	21		21	46	13	22	
N1	29	23	12	24	15	27		8	17	18	30	
N2	23	18	7	14	12	21		7	15	12	20	
N3	10	8	3	6	7	13		4	9	6	10	
unknown	25	20	7	14	10	18		6	13	11	18	
M-stage**							0.582					0.776
M0	112	89	48	94	50	89		43	93	54	90	
M1	14	11	3	6	6	11		3	7	6	10	
Lymph vascular invasion							0.189					0.123
Yes	44	35	15	29	23	41		13	28	25	42	
No	57	45	29	57	23	41		27	59	24	40	
unknown	25	20	7	14	10	18		6	13	11	18	
Histopathological response							1					0.117
TRG 1	0	0	0	0	0	0		0	0	0	0	
TRG 2/3	29	23	13	25	14	25		16	35	11	18	
TRG 4/5	88	70	37	73	38	68		29	63	45	75	
unknown	9	7	1	2	4	7		1	2	4	7	

Notes: TRG-tumor regression grade [20]; *a difference in R0 resectability between responders and non-responders; **based on clinical staging (patients not operated) and pathological staging (operated patients)

total lesion glycolysis in the primary tumor (TLG1=0.24). The metabolic activity of the tumor significantly decreased after the first cycle of chemotherapy from a median SUL1 of 7.51 (IQR, 5.12–11.16) to a median SUL2 of 4.81 (IQR, 3.44–6.29) ($p<0.0001$) and from a median TLG1 of 153.35 (IQR, 53.12–324.01) to a median TLG2 of 52.07 (IQR, 18.65–112.11) ($p<0.0001$). The corresponding median ΔSUL was 33.5% (IQR, 11.74–48.37), and the median ΔTLG was 59.16% (IQR, 34.58–85.29). There were 51/107 (48%) metabolic responders according to SUL (ΔSUL ≥35%) and 46/106 (44%) metabolic responders according to TLG (ΔTLG ≥66%). Thirty-three patients (31%) were metabolic responders in terms of both metabolic parameters.

There were no significant differences in pre-treatment and postoperative variables between metabolic responders and non-responders, Table 1.

Analysis of survival according to metabolic response was performed in a group of 107 patients with relevant metabolic response assessment. Nineteen patients who failed to have PET2 according to the protocol were not included. There was no significant difference in OS between metabolic responders and non-responders in terms of both SUL (median 29.8 vs. 19.1 months, log-rank p=0.10) and TLG (median 31.4 vs. 18.4 months, log-rank p=0.08). Similarly, no significant difference was found in DFS between metabolic responders and non-responders in terms of both metabolic parameters (median 19.0 vs. 15.5 months for SUL, log-rank p=0.5 and median 19.0 vs. 14.0 months for TLG, log-rank p=0.2) (Figures 1A–1D).

When adjusted for possible confounding pre-treatment covariates (age, clinical stage, baseline metabolic activity SUL1/TLG1) in the multivariable Cox regression analysis

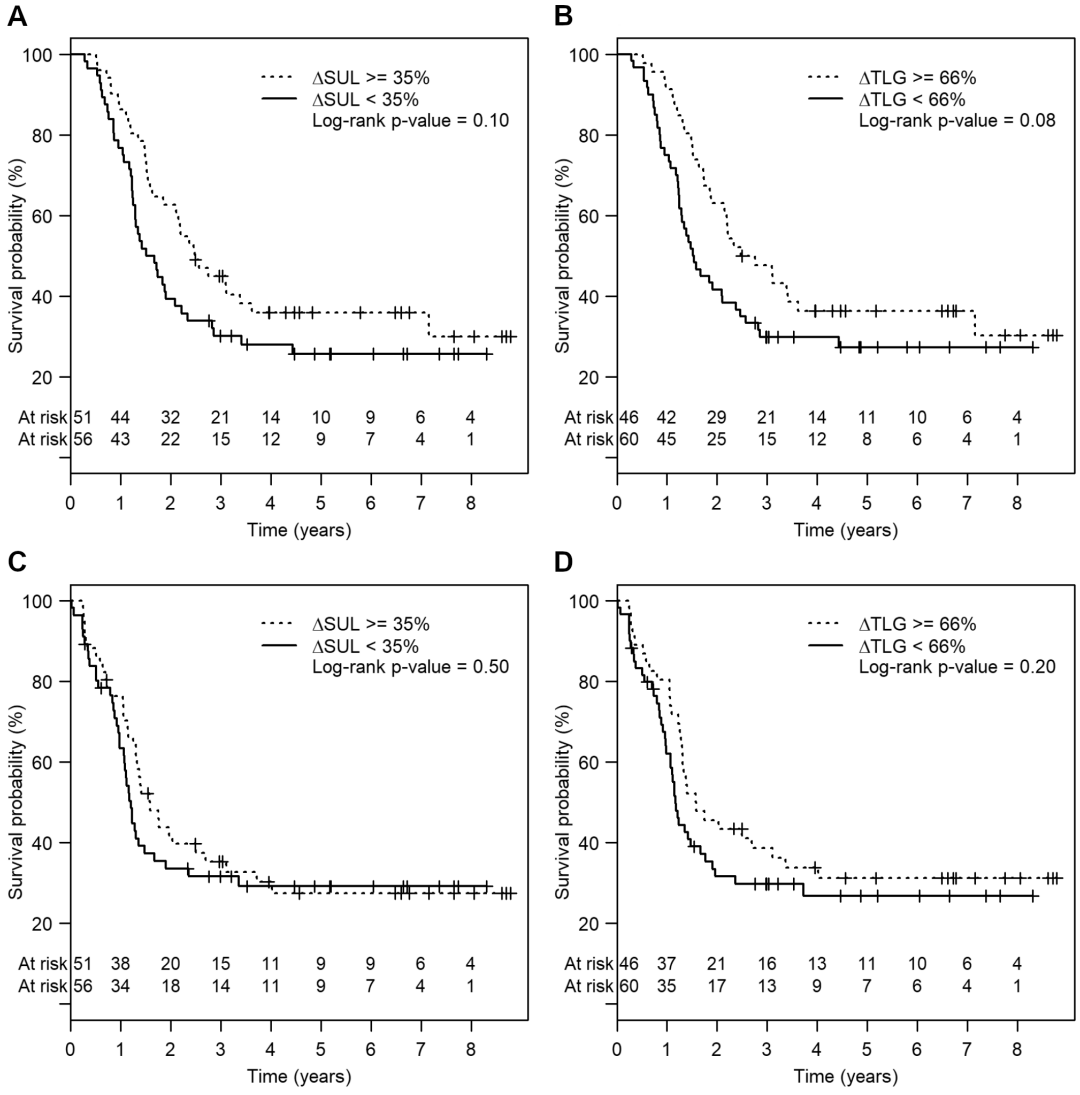

Figure 1. Kaplan-Meier survival curves according to the metabolic response in 107 study patients. A) OS according to ΔSUL; B) OS according to ΔTLG; C) DFS according to ΔSUL; D) DFS according to ΔTLG

(model No. 1), the hazard ratios (HRs) for OS for metabolic responders were 0.74 (95% confidence interval (CI), 0.46–1.20; p=0.22) and 0.71 (95% CI, 0.42–1.18; p=0.18) for SUL and TLG, respectively. Similar results were found with multivariable model No. 1 for DFS: HR of 0.92 (95% CI, 0.57–1.46; p=0.73) according to SUL and HR of 0.83 (95% CI, 0.50–1.38; p=0.47) according to TLG.

The results of the univariable and multivariable (model No. 2) Cox regression analyses in the population of resected patients (90 patients) are shown in Table 2. Only pathological N-stage was found to be independently predictive of OS (p=0.0002) and DFS (p=0.01).

Post hoc subgroup analysis. We performed a post hoc analysis of a subgroup of patients who had a second PET/CT within 16 days after the start of chemotherapy. The aim was to compare our study with earlier studies [9, 10], in which early follow-up PET was performed 14 days after the start of neoadjuvant chemotherapy. Fifty-five patients had their PET2 on days 12–16 (median 14 days, IQR 14–15 days) after the start of chemotherapy. In this subgroup of patients, metabolic responders according to SUL had significantly better OS than non-responders (p=0.03, Figure 2). Such a significant difference was not found in DFS (log-rank p=0.65). Better OS or DFS was not found between metabolic responders and non-responders according to TLG (p=0.08 and 0.16, respectively). Multivariable Cox regression analysis comprising only pre-surgical variables (model No. 1) showed that metabolic response according to SUL was significantly associated with improved OS (HR 0.43, 95% CI 0.19–1.00; p=0.048). However, multivariable analysis comprising all

Table 2. Univariable and Multivariable Cox proportional hazards regression analysis (model No. 2) of overall and disease-free survival in resected patients (n=90).

Risk factor	Overall survival						Disease-free survival					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value
Gender (Female-ref. vs. Male)	3.13	[0.76; 12.87]	0.113				2.17	[0.68; 6.97]	0.193			
Age (continuous)	1.01	[0.98; 1.04]	0.446				1	[0.97; 1.03]	0.990			
Tumor location (Siewert type I-ref.)												
Siewert type II	0.73	[0.42; 1.27]	0.265				1.07	[0.61; 1.87]	0.821			
Siewert type III	1.01	[0.41; 2.47]	0.985				0.95	[0.36; 2.54]	0.921			
LVI (No vs. Yes)	2.11	[1.24; 3.60]	0.006			0.797	2.54	[1.48; 4.36]	0.001			0.4
cN stage (N0 vs. N+)	1.29	[0.71; 2.36]	0.409				1.44	[0.77; 2.67]	0.253			
cT stage (T 1/2 vs. T3/4)	1.55	[0.73; 3.28]	0.250				1.75	[0.79; 3.86]	0.168			
c Stage Group (cT2N0 - ref.)												
cT2N1+	1.29	[0.26; 6.40]	0.756				3.05	[0.37; 25.39]	0.302			
cT3/4N0	1.55	[0.35; 6.93]	0.566				3.43	[0.45; 26.43]	0.236			
cT3/4N1+	2	[0.48; 8.31]	0.340				4.42	[0.61; 32.22]	0.143			
ypN stage (N0 vs. N1-3)	4.81	[2.41; 9.63]	<0.0001	4.44	[2.00; 9.81]	0.0002	3.68	[1.93; 7.03]	<0.0001	2.67	[1.25; 5.71]	0.01
ypT stage (T1/2 vs. T3/4)	1.95	[1.01; 3.77]	0.048			0.955	2.15	[1.08; 4.27]	0.029			0.848
Grading (G1/2 vs. G3/4)	1.95	[1.13; 3.36]	0.016			0.071	1.86	[1.08; 3.21]	0.027			0.143
TRG (TRG1-3 vs. TRG4/5)	2.04	[1.08; 3.87]	0.028			0.148	2.36	[1.22; 4.59]	0.011			0.06
Resection (R0 vs. R1/2)	2.71	[1.41; 5.20]	0.003			0.129	2.59	[1.36; 4.95]	0.004			0.173
Postop. CT (No vs. Yes)	0.73	[0.36; 1.50]	0.395				0.88	[0.42; 1.86]	0.738			
Postop. RT (No vs. Yes)	1.36	[0.80; 2.32]	0.256				1.58	[0.61; 4.13]	0.347			
SUL1 (continuous)	1.02	[0.97; 1.07]	0.463				1.02	[0.98; 1.08]	0.345			
SUL2 (continuous)	1.04	[0.98; 1.11]	0.179				1.04	[0.98; 1.11]	0.187			
TLG1 (continuous)	1	[1; 1]	0.254				1	[1; 1]	0.469			
TLG2 (continuous)	1.00	[1; 1]	0.241				1	[1; 1]	0.348			
ΔSUL% (continuous)	0.99	[0.99; 1]	0.135				1	[0.99; 1.001]	0.378			
ΔTLG% (continuous)	1	[0.99; 1]	0.555				1	[1; 1]	0.801			
Metabolic response ΔSUL (Non-responder vs. Responder)*	0.71	[0.42; 1.19]	0.189				0.9	[0.53; 1.52]	0.693			
ΔTLG (Non-responder vs. Responder)**	0.68	[0.40; 1.16]	0.160				0.8	[0.47; 1.36]	0.407			

Notes: HR-hazard ratio; CI-95% confidence interval; ref.-reference; LVI - lymph vascular invasion; TRG-Mandard tumor regression grade, SUL1; TLG1-baseline FDG glucose uptake values, SUL2; TLG2-FDG glucose uptake values after the first cycle of neoadjuvant chemotherapy, ΔSUL%; ΔTLG%-metabolic response as a continuous variable; *metabolic response defined as ΔSUL ≥ 35% [9]; **metabolic response defined as ΔTLG ≥ 66% [12]

known covariates, including post-surgical variables (model No. 2), did not confirm the independent predictive significance of metabolic response according to SUL (HR 0.47, 95% CI 0.09-2.42; p=0.36). No independent predictor of OS was found by model No. 2 of multivariable analysis in this subgroup of patients.

Discussion

In this prospective study, we did not demonstrate that the early metabolic response assessed by PET/CT after the first cycle of neoadjuvant chemotherapy predicted OS or DFS in patients with adenocarcinoma of the esophagus and EG junction. However, our data suggest the importance of the accurate timing of early follow-up PET/CT.

The rationale for evaluating the metabolic response early in the course of neoadjuvant therapy is that this evaluation creates an opportunity to alter the therapeutic regimen in non-responders to improve their prognosis. The Munich group pioneered the early evaluation of metabolic response and early alteration of neoadjuvant treatment in metabolic non-responders in gastroesophageal cancer [8–11]. Their threshold of early metabolic response (ΔSUV ≥35%) used in the MUNICON I and II studies [10, 11] has been widely adopted by researchers, although it has never been validated in randomized trials.

Several studies evaluating the early response to neoadjuvant chemoradiotherapy yielded conflicting results [21–26]. In most studies, the early response was not associated with histopathological response or survival. The metabolic effect of acute radiation esophagitis interfering with the metabolic response of the tumor itself may be one of the reasons for the conflicting outcomes [26]. In contrast, studies that assessed the metabolic response after induction chemotherapy followed by neoadjuvant chemoradiation found significantly longer survival in metabolic responders compared to non-responders [27–30]. Only one study concerning squamous cell carcinoma of the esophagus did not confirm this association [31].

Very few authors, apart from the Munich group, have evaluated the early metabolic response during the course of neoadjuvant chemotherapy without radiotherapy in gastroesophageal carcinoma. Schneider et al. studied the metabolic response (ΔSUV ≥35%) of a group of 30 patients 14 days after the start of neoadjuvant chemotherapy in gastric cancer [32]. The early metabolic response did not sufficiently predict the overall histopathological response but reliably identified histopathological non-responders and was associated with a significantly better overall survival. Vihervaara et al. evaluated the metabolic response of a group of 42 patients with gastroesophageal cancer (mostly gastric cancer) during or after the completion of the second cycle of chemotherapy (out of a total of three cycles), at an average of 35 days after the start of chemotherapy [33]. In contrast, they found no association between metabolic response and histopathological response or overall survival. Won et al. in their prospective study of twenty patients with gastric cancer, switched neoadjuvant therapy in early PET non-responders from ECX to docetaxel and irinotecan, while PET responders continued the ECX regimen [34]. The 2-year DFS rates were not different between the groups. It is questionable whether this was due to the change in chemotherapy in patients with a predicted worse prognosis (non-responders) or whether the early metabolic evaluation incorrectly predicted a group of patients who should have had a worse prognosis. Nevertheless, the authors suggested that changing chemotherapy regimens in PET non-responders might lead to improved outcomes compared to historical controls. Finally, Barbour et al. recently published a prospective randomized trial (DOCTOR) of a cohort of 124 patients with AEG, where PET non-responders to one cycle of neoadjuvant cisplatin and 5-fluorouracil (CF) were randomized to either the addition of docetaxel (DCF) or DCF plus radiotherapy with 45 Gy, while PET responders continued with the second cycle of CF [35]. They found better OS and DFS in early metabolic responders compared to non-responders receiving DCF, although the histopathological response was improved in DCF patients. Contrary to the MUNICON II study, the addition of radiotherapy for PET non-responders improved OS and DFS to be equal to the survival rates of PET responders, and the authors concluded that early PET/CT had the potential to tailor therapy.

We recently published a prospective study evaluating the early metabolic response in patients with adenocarcinoma of the esophagus and EG junction after the first cycle of neoadjuvant chemotherapy in relation to histopathological

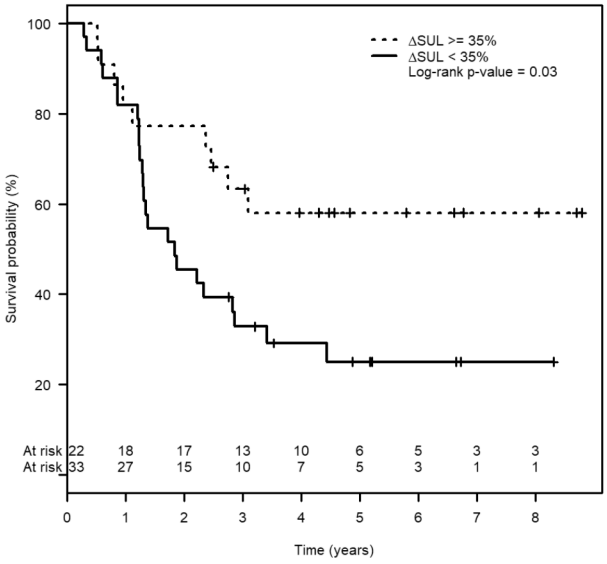

Figure 2. Kaplan-Meier curve of overall survival in the subgroup of 55 patients who underwent follow-up PET/CT within 16 days after the start of neoadjuvant chemotherapy.

response [12]. We followed the PERCIST 1.0 recommendations to standardize the imaging process and methodology of response evaluation [14]. FDG uptake was measured by the SULpeak parameter, which is basically SUVmax normalized to lean body mass, and by the volumetric metabolic parameter total lesion glycolysis (TLG). We did not find a statistically significant correlation between metabolic and histopathological response in 90 patients undergoing resection. The best accuracy for predicting histopathological response was achieved by TLG, with the optimal threshold being a ≥66% decrease in metabolic activity. However, in a post hoc analysis of a subset of 47 patients who had follow-up PET/CT scans approximately 14 days after the start of chemotherapy, we found a correlation between the metabolic response according to TLG, but not SUL, and histopathological response. The details of the differences in metabolic imaging methodology between our prospective study and the original work of the Munich group are discussed in detail in our previous publication [12].

This paper presents the results of the secondary aim of our prospective study. In the intention-to-treat group, we also included patients who did not undergo surgical resection. During chemotherapy, it was not clear which patients would not undergo resection. A decrease in FDG uptake of at least 35% was chosen to define a metabolic response according to SUL, similar to in the MUNICON studies [9–11] because we did not find any other threshold predicting a histopathological response in our previous analysis. According to the TLG parameter, a decrease of at least 66% was chosen to define a metabolic response because this threshold best predicted histopathological response. The predictive significance of a metabolic response was evaluated using two different Cox regression multivariate analysis models, similar to other published studies [36, 37]. In model No. 1, the predictive significance of the metabolic response was adjusted only by the presurgical variables, which are known at the time of potential alteration of the treatment regimen in non-responders. In contrast, model No. 2 contained only significant variables from the univariate analysis, including pathological data. Model No. 2 provides stronger information on predictive significance but can be used only after surgery when the individualization of neoadjuvant treatment is no longer possible.

In line with our previously published histopathological outcomes, we did not confirm that metabolic responders after the first cycle of chemotherapy had improved OS or DFS compared with metabolic non-responders. However, the time range of PET2 was relatively wide (12–22 days). We did not place extra emphasis on the precise timing of PET2. It was important that the second scan took place before the start of the second cycle. This reflects the situation in clinical practice, where it is sometimes difficult to ensure the precise timing of PET/CT evaluations day-to-day due to logistic reasons or the patient's condition. Thus, we conducted a post hoc analysis of a subgroup of patients who had PET2 within 16 days after the start of therapy. The timing of the PET/CT scans in this subgroup of patients was more comparable to that in previous studies [9–11, 32]. In this subgroup of 55 patients, the early metabolic response according to SUL predicted OS in univariate analysis. However, it did not prove to be an independent predictor of OS in multivariable analysis when all known covariates including post-surgical variables such as resectability and pathological stage were considered. Nevertheless, the metabolic response according to SUL was the only independent predictor of OS out of the variables available after the first cycle of neoadjuvant chemotherapy. A metabolic response according to TLG was not associated with improved survival. This finding is discrepant from our previous finding of the significant association between metabolic and histopathological response. Nonetheless, the univariate analysis did not show that the histopathological response predicted OS or DFS in this subgroup of patients (data not shown). This may explain the discrepant results. Similarly, no correlation between histopathological response to neoadjuvant chemotherapy and survival could be seen in the trial from Barbour et al. [35].

Our study suggests that the accurate timing of early follow-up PET/CT approximately 14 days after the start of chemotherapy may play a role in the ability to predict survival. Our data showed that delaying the follow-up PET/CT by several days resulted in the loss of an association between metabolic response and OS. The cause of this phenomenon is not clear. It can be speculated that in the later phase of the first cycle of chemotherapy, a stromal reaction or early repopulation of tumor cells may increase the initially reduced metabolic activity of the tumor [38]. A lack of standardized timing of the early evaluation of metabolic response can be seen in many studies. Vihervaara et al. performed PET2 on average 35 days after the start of treatment [33]. It can be speculated that the later timing of PET2 could be the reason why the metabolic response did not predict survival. In the original Munich studies, a follow-up PET scan was performed 14 days after the start of treatment [8–10]. However, in the MUNICON II trial [11] and DOCTOR trial [35], the metabolic re-evaluation ranged from 11 to 20 days after starting chemotherapy, very similar to our study. Contrary to our study, both trials demonstrated the ability of early PET/CT to predict survival. Obviously, the question of timing for early metabolic response evaluation is not fully addressed and requires further investigation.

The benefit of our study is that it prospectively analyzed a relatively large group of patients, evaluated two metabolic parameters (SUL and TLG), followed the PERCIST 1.0 methodology of PET/CT scanning and response evaluation to ensure standardization to allow for comparisons of studies and subjected data to multivariate analysis.

However, the conclusions of our study should be interpreted with caution. First, this study presents the results of a secondary aim of a prospective trial in which the size of the investigated patient group was calculated to predict

the histopathological response by PET/CT, not to establish an association with survival. This creates room for a type-I error. Second, survival might have been affected by a longer period of recruitment, dose variation in preoperative chemotherapy, inhomogeneous postoperative chemotherapy, and the selective use of adjuvant radiotherapy. Third, part of the conclusions concerning the timing of follow-up PET/CT was obtained from a post hoc analysis of a subset of patients, which reduces the validity of the findings.

Neoadjuvant chemotherapy in esophageal and gastric cancer is still evolving. The new FLOT regimen [39] is now gaining popularity, and the question arises whether the results of this and other studies can be applied to new therapeutic regimens, including those containing biological therapy.

In conclusion, our study did not confirm that early metabolic response assessed by PET/CT after the first cycle of neoadjuvant chemotherapy predicted OS and DFS in patients with adenocarcinoma of the esophagus and EG junction. However, these results raised questions about the importance of proper timing for the early evaluation of response to treatment. We conclude that acquiring PET/CT images early after the initiation of neoadjuvant chemotherapy cannot yet be considered a suitable tool for individualizing neoadjuvant therapy in patients with adenocarcinoma of the esophagus and EG junction. Further prospective studies, preferably randomized, are needed to more clearly determine the significance of early PET/CT in the setting of contemporary modern treatment of patients with this diagnosis.

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