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Perioperative EOX treatment in operable locally advanced gastroesophageal adenocarcinoma: Prediction of tumor response by FDG –PET and histopathology

Hanna Vihervaara[a,*,1], Annika Ålgars[b,1], Jukka Kemppainen[c], Jari Sundström[d], Raija Ristamäki[b], Paulina Salminen[a]

[a] Turku University Hospital, Department of Digestive Surgery, Finland
[b] Turku University Hospital, Department of Oncology, Finland
[c] Turku University Hospital, Department of Clinical Physiology and Nuclear Medicine and Turku PET Centre, Finland
[d] Turku University Hospital, Department of Pathology, Finland

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ABSTRACT

Purpose: The aim of this retrospective single-center analysis was to evaluate the feasibility of fluorine-18 fluorodeoxyglucose (FDG)-PET imaging in evaluating metabolic response of preoperative chemotherapy in the treatment of locally advanced operable gastroesophageal adenocarcinoma and to investigate the association between histopathologic and FDG-PET response and overall survival.

Methods: Patients with locally advanced adenocarcinoma of distal esophagus, gastroesophageal junction or stomach were assessed for the study during 2008–2012. After evaluation with endoscopy, computed tomography and FDG-PET, patients with clinical stage II or III disease were assigned for perioperative EOX (epirubicin-oxaliplatin-capecitabine) treatment targeted at three cycles both pre- and postoperatively, if possible. Metabolic response was evaluated by repeated FDG-PET during or right after the second chemotherapy cycle. Becker tumor regression grade (TRG) was used to evaluate histopathologic response. For statistical purposes, the clinically significant cut-off for tumor maximum standardized uptake value (SUV_{max}) change (SUVδ%) was set at −35%.

Results: 54 patients were included in the study. 53 PET images were obtained before chemotherapy, 11 (21%) of those were PET negative. A major metabolic response was detected in 19 patients and major histopathologic response in 14 patients. No statistically significant association was observed between SUVδ% and histopathological responses. Median overall survival (OS) time of the patients was 49.9 months. No association between OS and PET response was found in our study. The administration of all six cycles of perioperative EOX was associated with improved OS.

Conclusions: Follow-up PET during or right after second preoperative chemotherapy cycle did not assist in identifying patients with favorable histopathological response or OS.

1. Introduction

Worldwide almost 1.4 million people are diagnosed with gastroesophageal cancer every year resulting in over one million deaths annually [1]. In Europe the relative 5-year survival for gastric cancer is 25% and for esophageal cancer it is less than 15% [2]. Despite margin negative R0 resection in locally advanced disease, the survival rate is still unsatisfactory. The MAGIC trial showed that perioperative chemotherapy improves progression-free survival (PFS) and overall survival (OS) in resectable gastroesophageal adenocarcinoma [3]. Currently perioperative chemotherapy is used as standard treatment in locally advanced operable gastroesophageal adenocarcinoma at many institutions.

Inefficient neoadjuvant treatment delays surgery and makes patients more vulnerable to adverse events. The MUNICON trial showed that a fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) -guided treatment algorithm could be useful when tailoring multimodal treatment of adenocarcinoma of the oesophagogastric junction by evaluating early metabolic response after initiation of neoadjuvant chemotherapy [4]. Ott et al. identified three different

* Corresponding author. Turku University Hospital, Hanna Vihervaara, P.O. Box 52, 20520, Turku, Finland.
E-mail address: hanna.vihervaara@tyks.fi (H. Vihervaara).
[1] Equal author contribution.

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metabolic groups: metabolic responders and non-responders with either FDG-avid tumors or FDG non-avid tumors. Better OS and major histopathologic response in gastric cancer was predicted by PET in FDG-avid tumors and an unfavorable outcome was shown in FDG non-avid tumors [5].

The aim of our retrospective single-center analysis was to evaluate both the feasibility of FDG-PET imaging in predicting tumor response to perioperative chemotherapy in the treatment of locally advanced operable gastroesophageal cancer and the association of histopathologic response to FDG-PET imaging response.

2. Patients and methods

2.1. Patient population

All patients diagnosed with locally advanced gastroesophageal adenocarcinoma eligible for chemotherapy have been evaluated for perioperative epirubicin-oxaliplatin-capecitabine (EOX) therapy at Turku University Hospital since 2007. The diagnoses were histologically confirmed and the clinical stage of the disease was initially evaluated by computed tomography (CT) of the chest and abdomen and/or FDG-PET-CT. In patients presenting with clinical stage II and III gastroesophageal adenocarcinoma without contraindications for perioperative EOX-therapy, initiation of EOX therapy was undertaken. Contraindications for perioperative chemotherapy included distant metastasis, esophageal or gastric obstruction untreatable with self-expanding metallic stent or active tumor hemorrhage, age above 80 or below 18 and inability to commit to perioperative chemotherapy. All patients were evaluated individually taking into account possible other comorbidities that could have had an effect on the eligibility for perioperative EOX therapy. All consecutive patients with biopsy proven locally advanced adenocarcinoma of distal esophagus, cardia or stomach assigned for perioperative EOX treatment from January 2008 to December 2012 were included in our retrospective study. PET imaging data and histopathologic responses were retrospectively re-assessed by investigators (J.K. and J.S., respectively). This retrospective study protocol was approved by the institutional ethical review board of Turku University Hospital.

2.2. The administration of chemotherapy

The chemotherapy regimen was modified according to the REAL-2 study: continuous intravenous infusion of fluorouracil was replaced by peroral capecitabine and cisplatin by the less nephrotoxic oxaliplatin [6]. The perioperative EOX regimen consisted of three preoperative and three postoperative cycles of intravenous epirubicin 50 mg/m^2 on day 1, oxaliplatin 130 mg/m^2 on day 1 and capecitabine 625 mg/m^2 twice daily for 21 days. Peroral capecitabine of the third preoperative cycle was ceased after 14 days. All patients underwent a baseline PET-CT prior to the initiation of the EOX treatment. A control PET-CT (PET_2) was performed during or right after second preoperative EOX cycle assuming the tumor was PET positive at baseline imaging. The median PET_2 imaging timeline was 15 days from the first day of second chemotherapy cycle i.e. during the third week of second chemotherapy cycle (range day 6 – day 26). Chemotherapy was not ceased during the imaging. Four patients had their second PET scan right after the second chemotherapy cycle (two at day 22 one at day 24 and one at day 26). After PET_2 the decision to proceed to third chemotherapy cycle or surgery was made in a multidisciplinary meeting. If the metabolic activity of the tumor had increased in the control PET scan, perioperative treatment regimen was discontinued and surgical treatment was ensued. If the tumor uptake was decreased or unchanged, a third preoperative cycle was administered. In case of a baseline PET negative tumor, three preoperative EOX cycles were scheduled. Three cycles of postoperative EOX therapy were recommended taking into account both the metabolic and histopathologic responses and individual patient tolerance for the preoperative treatment. Postoperative chemotherapy was initiated six to ten weeks after surgery.

Table 1
Patient characteristics (n = 54).

	n (%)	n (range)
Age (years)		
Median	65	
Range	40–76	
Sex		
Male	33 (61.1)	
Female	21 (38.9)	
Type of surgery according to tumor site and median number of lymph nodes removed		
Distal esophagus, n = 8		
Esophageal resection a.m. Iwor-Lewis	8 (100)	9 (0–35)
Gastroesophageal junction, n = 12		
Total gastrectomy	9 (75)	14 (9–24)
Esophageal resection a.m. Iwor-Lewis	3 (25)	11 (4–27)
Stomach, n = 34		
Total gastrectomy	31 (91.2)	18 (5–49)
Subtotal gastrectomy	1 (2.9)	11
Laparotomy	2 (5.9)	
Histology of primary tumor		
Intestinal adenocarcinoma	21 (38.9)	
Diffuse adenocarcinoma	29 (53.7)	
Mixed type carcinoma	3 (5.6)	
Unknown	1 (1.8)	
Clinical preoperative stage of disease*		
Stage II	39 (72.2)	
Stage III	15 (27.8)	
Performance status at start of chemotherapy		
Z = 0	12 (22.2)	
Z = 1	34 (63)	
Unknown	8 (14.8)	
ypStage of disease		
Stage 0	2 (3.7)	
Stage I	12 (22.2)	
Stage II	17 (31.5)	
Stage III	19 (35.2)	
Unknown	4 (7.4)	
Extent of surgery		
R0	41 (75.9)	
R1	9 (16.7)	
R2	1 (1.85)	
Unknown	1 (1.85)	
No resection performed	2 (3.7)	

* = staging performed by PET-CT, CT, endoscopy.

2.3. Surgery

Surgery was performed one to two weeks after completion of preoperative chemotherapy. Complete removal of the tumor with lymphadenectomy was performed. Both the extent of the lymphadenectomy and the required resection type were evaluated by each individual surgeon in accordance with the tumor type and location. At the time of the study the extent of the lymphadenectomy was not thoroughly standardized; the majority of lymphadenectomies were D1 or D1 + [7]. The types of surgery and the number of removed lymph nodes are shown in Table 1. The resection was evaluated radical (R0) if no macroscopic (R2) or microscopic (R1) residual tumor were present.

2.4. Imaging and image analysis

If the clinical stage was estimated to be stage II or III by endoscopy

and/or CT, FDG-PET-CT was performed either right after the endoscopy or in some patients after initial CT imaging. The first FDG-PET-CT was performed before the initiation of preoperative chemotherapy. If there was no sufficient FDG tumor uptake, repeated PET scan was considered unnecessary. For FDG positive tumors, PET_2 was performed after the second cycle of preoperative EOX treatment.

Whole body ^{18}F-FDG-PET/CT scan was performed with Discovery STE or VCT (General Electric Medical Systems, Milwaukee, WI, USA). Intravenous injection of ^{18}F-FDG (4 Mbq/kg) was administered after minimum of six hours of fasting. For every patient the second PET/CT scan was performed with the same device as the reference scan. Low-dose PET/CT (kV 120, Smart mA range 10–80) from skull base to mid-thigh was performed 50–60 min after the injection. The median imaging time from injection was for PET_1 52 min (range 48–77) and for PET_2 51 min (range 47–66). PET images were corrected for dead time, decay, and photon attenuation. PET images were reconstructed in 3D mode with 128 × 128 matrix size using ML-OSEM reconstruction algorithm. Imaging analysis was performed using ADW 4.5 workstation. The maximum standardized uptake value (SUV_{max}) was measured and the percentage change (SUVδ%) was calculated according to the formula $SUV\delta_{max} = [(SUV2_{max} - SUV1_{max})/SUV1_{max}] * 100$. PET positivity was defined as any metabolic activity exceeding normal physiological activity. All PET-CT scans were retrospectively re-reviewed by experienced nuclear medicine physician (J.K.).

2.5. Histopathological analysis

All the microscopic specimens were re-evaluated by a pathologist experienced in histopathology of gastric carcinomas (J.S). Tumor specimens were classified according to Lauren's classification into adenocarcinomas of intestinal and diffuse type [8]. In addition, an additional category including both of these components was classified as mixed type adenocarcinoma. ypTN (pathological data following systemic therapy) stage was determined and the number of lymph nodes detected was recorded according to TNM classification, 7th edition [9]. Histologic tumor regression was defined by tumor regression grade (TRG) described by Becker [10]: TRG Ia-b with no or less than 10% of vital tumor cells left, TRG II with 10–50% of vital tumor cells left and TRG III with more than 50% of vital tumor cells left. According to the Becker grade the patients were divided into responding (TRG Ia-b) and non-responding (TRG II-III) groups.

2.6. Statistical analysis

Statistical analysis was performed with the SAS 9.4 and Enterprise Guide 6.1 programs (SAS Institute Inc, Cary, NC). Kaplan-Meier, Log-rank test and Cox proportional hazards regression model were used for univariate survival analysis. OS was calculated from the onset of EOX therapy until death of any cause. TTR (time to recurrence) was calculated from the onset of EOX therapy until disease recurrence, including both distant and locoregional recurrences as well as death from same malignancy.

The cut-off for SUV-value change in PET-CT images after the second preoperative EOX cycle was set at −35% in accordance with previous publications in this field [4]. Limit for progression was set at 20% increase in SUV-value. In addition, ROC-analysis was performed to evaluate possible better cut-off values for the SUV-change observed in the PET images. However, more optimal cut-off values could not be identified when the effect of SUV change on long term follow-up status of the patients (disease free *vs* recurrent disease; alive *vs* died of disease), surgical resection status (R0 *vs* R1/R2) were calculated. P-values < 0.05 were considered statistically significant. All statistical tests were two-sided.

3. Results

3.1. Patient characteristics

Between January 2008 and December 2012, 54 patients were assigned for perioperative treatment of gastro-esophageal adenocarcinoma at the Turku University Hospital. The patient characteristics are presented in Table 1. The majority (61%) of the patients were male, 63% of the tumors were located in the stomach with diffuse adenocarcinoma being the most common histological subtype, and 72% of the patients had clinical stage II disease.

3.2. PET and tumor histology

A total of 53 PET images were obtained before the EOX treatments and in 11 of these the tumor was PET negative (21%). The median tumor standardized uptake value (SUV_{max}) before the treatment (SUV_1) was 6.0 (range 2.5–32.4). For all patients that were PET-positive at baseline (n = 42), a control PET-CT to evaluate response to therapy was performed. After two EOX cycles, the SUV_2 median was 4.1 (range 2.5–31.0) and the difference between SUV1 and SUV2 was statistically significant ($p < 0.0001$). The median SUVδ% was −30.2%. A major metabolic response (SUVϱ% > 35%, median 60%, range 35.7%–87.5%) was detected in 19 patients. A more detailed description of PET negative and positive findings is shown in Fig. 1 (histology) and in Fig. 2 (localization of tumor). Fig. 3 shows PET-positive and PET-negative images before EOX therapy and the follow-up images during or after second EOX cycle. A major histopathologic response (less than 10% of viable cancer cells in tumor bed) was seen in 14 patients out of 53 (26%). One patient with unverified histopathological diagnosis was excluded from the analysis. No statistically significant association was observed between SUVδ% and histopathological responses (Spearman, r = 0.12, p = 0.44; Fisher's exact test, p = 0.7) We tested the association between SUVδ% and histopathological response in the subgroups of patients with intestinal type adenocarcinoma and patients with R0 surgery performed, but no statistically significant association was found within these groups either (intestinal type adenocarcinoma subgroup of patients: Spearman r = −0.17, p = 0.5, Fisher's exact test p = 0.7; R0 subgroup of patients: Spearman r = 0.16, p = 0.34, Fisher's exact test p = 0.9).

Eight patients had PET-positive lymph nodes detected in their baseline PET-CT scans. Six of these patients had also histologically confirmed lymph node metastasis in their postoperative pathology report. Only three of the patients with initially PET-positive lymph node status had PET-positive lymph nodes detected also in their response PET-CT scan. Two out of these three patients had histologically detected node positive disease in their final pathology report.

3.3. Chemotherapy

After histopathologically confirmed diagnosis of gastroesophageal adenocarcinoma EOX treatment was initiated within a medium of 35 days (range 12–69 days). Out of the 54 patients, 45 (83%) completed three cycles of preoperative EOX treatment and 9 (17%) patients received only 2 cycles. The reasons for not completing all three cycles were: progression in PET-CT (3), adverse events and no change in tumor in CT or PET imaging (4), unclear pathological diagnosis (1) and heart condition (1). For one patient the initial histopathological diagnosis of adenocarcinoma remained uncertain and after the second EOX cycle no repeated tumor biopsy could be performed due to excellent tumor response to EOX therapy leaving no tumor tissue to be identified for biopsies.

Significant hematologic adverse events associated to preoperative chemotherapy included grade 3 thrombocytopenia (4% of the patients) and grade 3–4 neutropenia (35% of the patients). Two neutropenic infections requiring intravenous antimicrobial therapy were detected

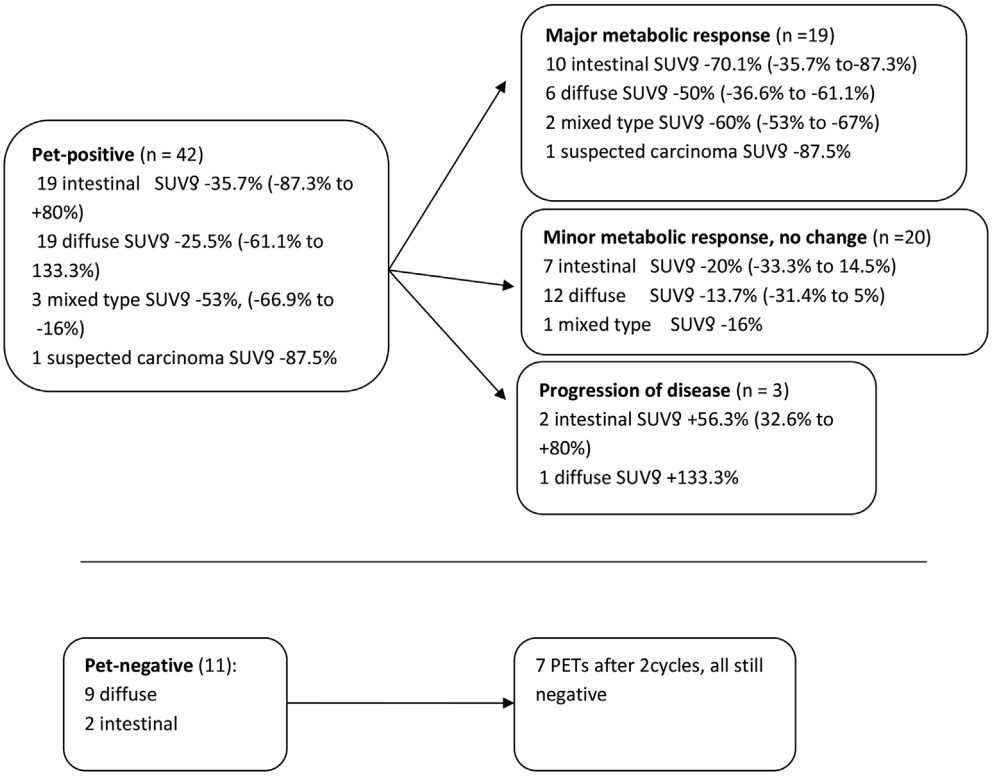

Fig. 1. Distribution of PET-positive and -negative tumors and their SUVϑ% median (range) between the first and second PET-CT scan.

during chemotherapy. There were no chemotherapy related deaths.

Altogether 23 out of 54 patients (43%) received all six cycles of perioperative chemotherapy. Postoperative EOX treatment was initiated for 35 patients (65%). Of those, 27 (77%) completed all three postoperative cycles, 6 (17%) completed two cycles and 2 (6%) patients received only one cycle. Of the 19 patients who did not receive post-

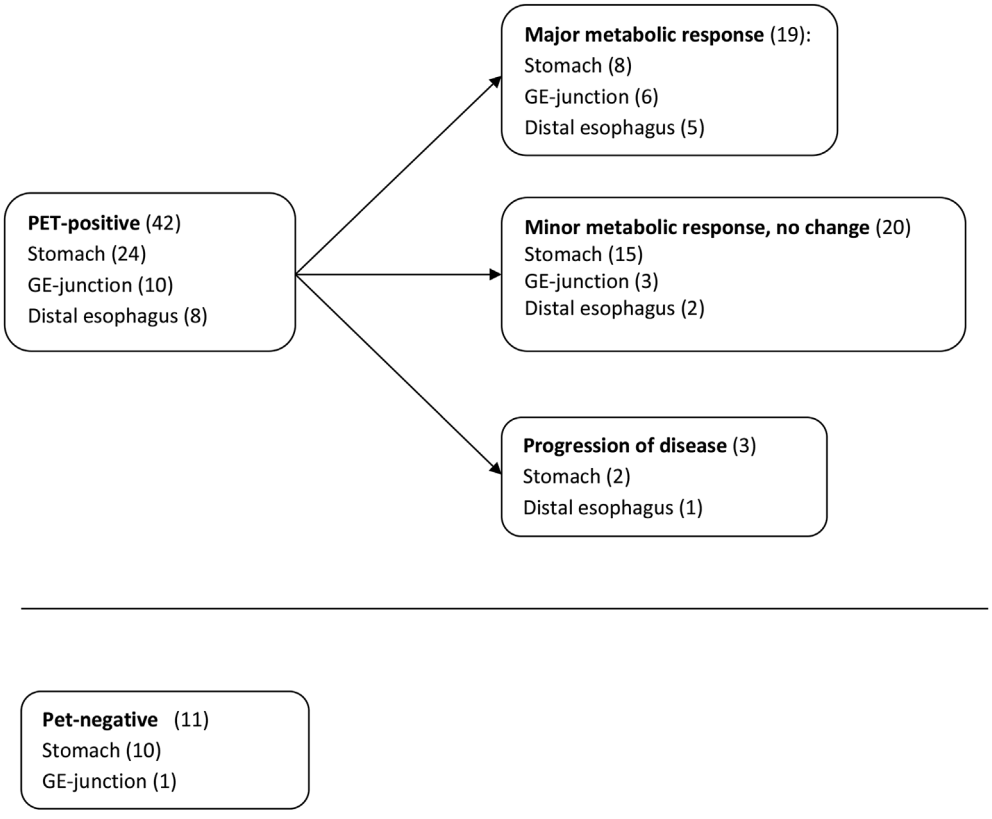

Fig. 2. Distribution of tumor localization in PET-positive and negative findings.

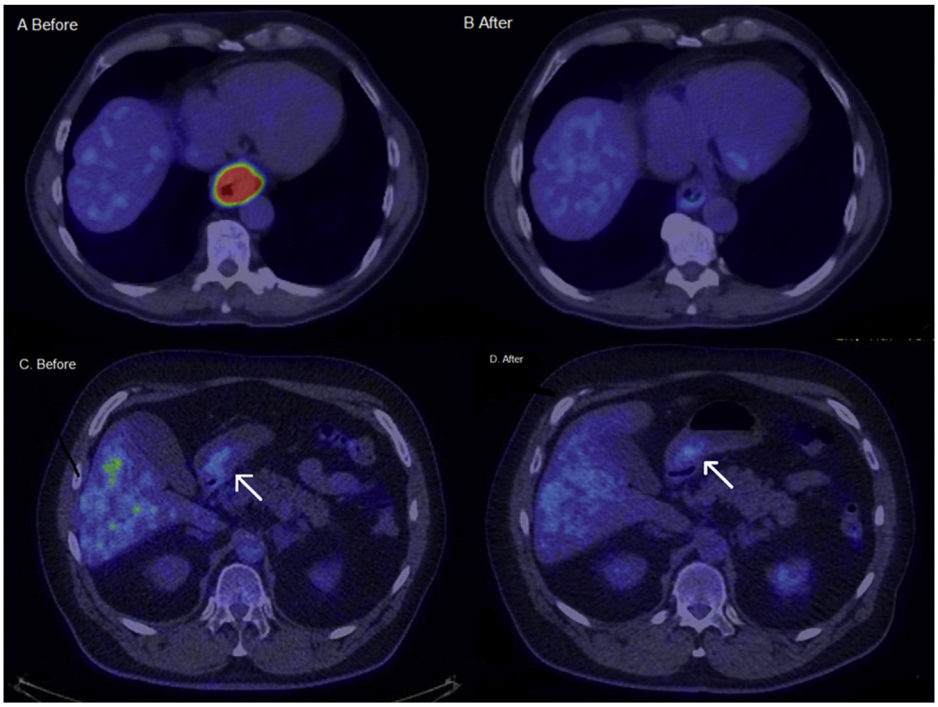

Fig. 3. FDG-PET images from metabolic responders and non-responders. A. Distal esophageal carcinoma of intestinal type, SUV_{max} 21.9 B. Major metabolic response after two cycles of chemotherapy, SUV_{max} 4.5, $\delta SUV_{max}\%$ −79% C. Diffuse gastric carcinoma in antrum, SUV_{max} 4.4 D. Metabolic non-responder after two cycles of EOX treatment, SUV_{max} 4.4, $\delta SUV_{max}\% = 0$.

operative EOX treatment, 13 (68%) patients received some other postoperative chemotherapy regimen (docetaxel-capecitabine, n = 6; single capecitabine, n = 2; docetaxel-capecitabine-trastuzumab, n = 1; chemoradiation, n = 4). Out of 35 patients receiving postoperative EOX, three patients received additional radiotherapy due to R1 resection. The reasons for not receiving postoperative EOX therapy were: no tumor regression detected in pathological examination of the tumor specimen (6), disease progression in PET-CT during preoperative EOX therapy (3), margin positivity (2), postoperative complications (2), no PET response and adverse effects (1), early cancer metastasis and death (2), toxic effects of preoperative EOX treatment (1), misunderstanding in the perioperative regimen (1) and reason not known (1). Dose reduction was needed for 65% (24/35) of the postoperatively EOX treated patients. EOX regimen was initiated at a median of 41 days post-surgically (range 24–125 days).

3.4. Surgery

The type of surgery and extent of nodal dissection are described in detail in Table 1. Out of the 52 patients operated on with radical intention, 41 (79%) underwent R0 resection. Median number of lymph nodes removed was 16 (range 0–49). Nodal status of the 52 surgically treated patients was as follows: ypN0 26 (50%), ypN1 6 (11%), ypN2 13 (25%), ypN3a 5 (10%) and ypNx 2 (4%). Two patients underwent only explorative laparotomy due to an inoperable tumor and in the other patient the second PET scan showed progression of the disease. The other patient had a PET positive intestinal tumor with no major metabolic response detected.

Postoperatively 16 patients experienced altogether 17 early (< 30 days after surgery) complications: intra-abdominal abscess (5), anastomotic leakage (4), fluid collection in the pleural cavity (2), bile leakage after concomitant cholecystectomy (1), acute internal herniation (1), atrial fibrillation (1), seroma (1), urinary tract infection (1), ileus (1). No surgery related mortality was reported. Late postoperative complications (> 30 days after surgery) included duodenum stump leakage (2), wound infection (1), abdominal abscess (1), anastomosis stricture (1) and strangulation (1). All four infectious complications occurred during postoperative chemotherapy.

3.5. Follow-up, survival and recurrence

Kaplan-Meier survival curves for time to recurrence and overall survival are shown in Fig. 4. The median follow up time was 38.9 months (range 4.8–77.9 months). During follow-up 37% (20/54) of the patients were diagnosed with disease recurrence. At the end of the follow-up period 54% (29/54) of the patients were alive, 43% (23/54) had died of cancer and two patients (4%) had died due to another cause.

No association between TTR and change in SUV value in PET images following second preoperative EOX treatment, or pathological tumor regression grade, gender or age of the patient, location, histology, T-stage, or differentiation grade of the primary tumor was found. Patients with less than six perioperative EOX cycles administered had a shorter median TTR than those who received all planned EOX treatments in the perioperative setting (median not reached vs 45.2 months), but the p-value was only borderline significant (Log-Rank, P = 0.08; Cox, P = 0.09, HR 2.3, 95% CI 0.9–6.0).

The median overall survival (OS) of all the patients included in this study was 49.9 months. The 5 year OS was 78.6% for stage 0-I patients, 65.6% for stage II patients and 14.3% for stage III patients. No association between OS and early PET response was found in our study. T category, histology or location of the primary tumor, gender or age of the patient, histological tumor regression grade did not associate with OS either. Patients who received six cycles of perioperative EOX had an improved OS in comparison to those who were unable to receive or tolerate all planned treatment courses (Log-Rank, P = 0.03; Cox, p = 0.03, HR = 2.6, 95% CI 1.1–6.3; median DFS time not reached vs 41.3 months). 39% of the patients who received 6 EOX cycles had an excellent ECOG performance status (Z = 0). In comparison only 13% of the patients who received less than 6 preoperative EOX cycles had an equal (Z = 0) performance status. Patients with a poor performance status did worse than fit patients, but the difference was only borderline significant (Log-Rank, p = 0.07). Diffuse adenocarcinoma patients with major metabolic response (n = 6) had significantly worse median OS and TTR than diffuse adenocarcinoma patients with minor metabolic response (n = 13), (p = 0.0004 and 0.0001 accordingly). All of these six patients had histologic grade III tumors with a T-stage of at least 3 and five out six patients had lymph node metastasis. Median $SUV1_{max}$

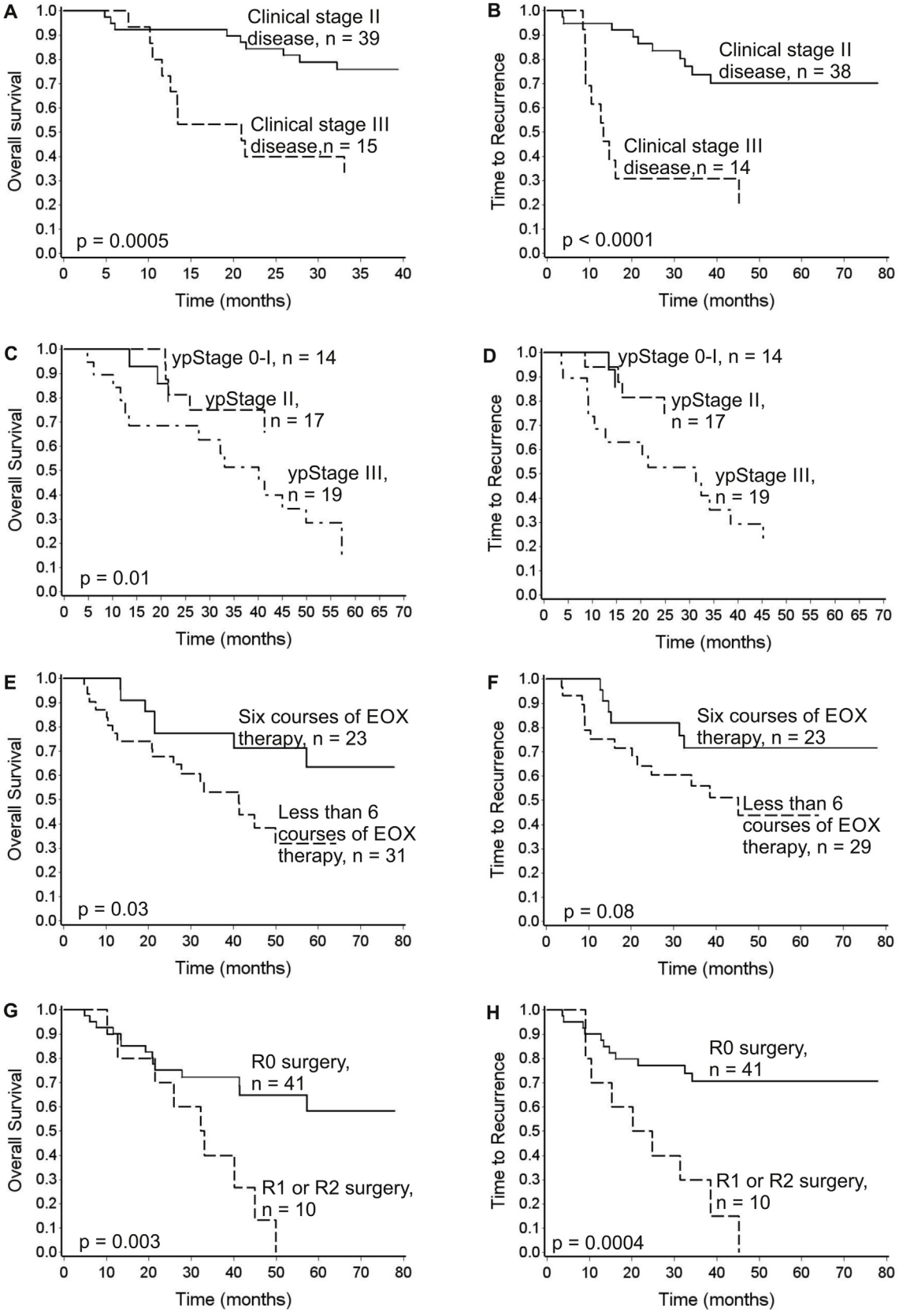

Fig. 4. Kaplan Meier survival curves. Patients with clinical stage II disease have a longer overall survival (OS) **(A)** and time to recurrence (TTR) **(B)** than patients with clinical stage III disease. Postoperative ypStage of the disease associates with OS **(C)** and TTR **(D)**. Patients who receive six courses of perioperative EOX therapy do better in terms of OS **(E)** and TTR **(F)** than patients with less than 6 EOX courses administered. R0 surgery is associated with improved OS **(G)** and TTR **(H)** in comparison to R1 or R2 surgery.

for those 6 patients was 5.7 as it was for intestinal type carcinoma 6.2.

4. Discussion

This current study showed no association between survival benefit and either metabolic response to neoadjuvant chemotherapy evaluated by FDG-PET imaging or histopathologic responses. Contradictory results have been reported regarding the role of metabolic response to neoadjuvant chemotherapy evaluated by FDG-PET imaging on survival in gastroesophageal adenocarcinoma [4,5,11–13]. According to some studies preoperative metabolic response seems to influence survival positively [4,5,11–13], whereas other studies fail to show such an association [12]. Our study was not able to show any survival benefit for patients with major metabolic tumor response during preoperative chemotherapy.

There are many questions concerning the optimal use of FDG-PET in gastroesophageal adenocarcinomas during neoadjuvant chemotherapy: optimal cut off value for metabolic response, optimal timing of the PET imaging after initiation of neoadjuvant therapy and benefits of evaluating metabolic response in gastroesophageal tumors with different histology and locations. The cut off values used for change in SUV vary (35%–67%) between different studies [4,5,11,13]. In our study, we used a cut-off value of 35% decrease in SUV value to separate metabolic responders and non-responders. No correlation between SUVδ% > -35% and OS or TTR was found nor did we find any correlation between SUVδ% and histopathological response. ROC analysis was performed to evaluate other potential cut-off values for SUVδ%, but more accurate cut-off values were not recognized. Early metabolic response with a decrease of 35% or more in SUV has been shown to associate with improved OS in adenocarcinoma of oesophagogastric junction [4,11] and in gastric carcinoma [5]. In contrast, similar to our findings Vallböhmer et al. did not find an association between SUVδ% and survival or histological response in gastric cancer [12].

Timing of the response PET imaging varies from early response evaluation after two weeks of initiation of chemotherapy [4,5,11] to imaging after completion of preoperative chemotherapy [12,13]. Wieder et al. performed a study comparing single and sequential PETs in patients with adenocarcinomas of gastroesophageal junction and reported that early relative decrease (SUVδ% > 35%) in tumor metabolic uptake as well as metabolic change preoperatively after neoadjuvant treatment (SUVδ% > 63%) correlated to histopathological responses [14]. Only early metabolic response was associated with overall survival benefit, a similar trend was seen with later metabolic changes [14]. In our study, metabolic response was measured by PET imaging during the second preoperative chemotherapy cycle at a median of 35 days after the first day of neoadjuvant treatment.

In our analysis, patients with diffuse adenocarcinoma with a major metabolic response did worse than diffuse adenocarcinoma patients with no major metabolic response. To our knowledge this novel finding has not been reported before. However, due to the limited number of patients in this subgroup analysis the clinical relevance of our finding needs to be confirmed in further studies with larger patient numbers. Previously it has been shown that histopathological type may limit the value of FDG-PET imaging: PET positivity of intestinal type tumors is much more common compared to non-intestinal type [15]. In the study of Ott et al., approximately one third of gastric carcinomas were FDG-PET non-avid tumors and 68% of those tumors were non-intestinal type [5]. Vallböhmer et al. were not able to show any benefit of FDG-PET response assessment in advanced gastric cancer: 60% of patients had non-intestinal type tumors [12].

The overall 5-year survival in this study was 59.6% and the 5-year disease free survival 51%. The survival rates of our study are higher than in e.g. the MAGIC study [3] and in the study by Ychou et al. [16] with 5-year survival rates of 36% and 38%, respectively. This difference in OS time could be partially explained by lymph node status as half of the radically operated patients had no metastatic lymph nodes, which is reflected also with the majority (72%) of patients presenting with preoperative clinical stage II. In the MAGIC study [3] and in the study by Ychou et al. [16] no lymph node metastasis were detected in 31.1% of the gastric carcinomas and in 33% of all operated tumors, respectively. In this study, the preoperative clinical stage and postoperative ypStage were clear prognostic factors for OS and TTR, which are already widely recognized predictive factors.

The EOX regimen was carried out safely and metabolic and histopathologic responses guided perioperative chemotherapy. Almost half of the patients received all six cycles of the perioperative regimen. Full completion of chemotherapy was associated with a favorable overall survival. Similar perioperative EOX treatment regimen has been used in the treatment of gastric cancer in Norway [17]. They have implemented the use of ECX (epirubicine, cisplatin, capecitabine)/EOX chemotherapy for gastric adenocarcinoma in their national guidelines since 2007. They reported no survival benefit in their study investigating the effect of the perioperative ECX/EOX treatment in comparison to surgery alone. Their study lacked response assessment during preoperative chemotherapy; instead they performed a CT scan after preoperative chemotherapy. Even though the R0 resection rate was similar to our study (75.9%), 12.2% of the preoperative chemotherapy group patients were not operated at all due to progression of the cancer seen in response CT in contrast to our study with only 3.7% of the patients found to be inoperable at the time of surgery. It remains unclear whether earlier response imaging would have had an effect on the operability rate.

Despite the statistical use of a cut-off value of 35% for the decrease in SUV in our study, the preoperative chemotherapy was discontinued only if the follow-up PET showed progression of the disease. Three patients had a clear progression seen in the second PET scan, two of those patients were not operated radically (one R1-resection and one explorative laparotomy). Out of 54 study patients in only one case (1.8%) PET was not able to identify the patient with inoperable disease. A retrospective study including 100 patients with gastroesophageal adenocarcinomas treated with perioperative chemotherapy without PET or CT response evaluation during the treatment, revealed that 12/100 patients (12%) were found to be inoperable after preoperative chemotherapy [18].

The perioperative chemotherapy was well tolerated. Only two patients had their preoperative chemotherapy ceased because of adverse effects. No chemotherapy related mortality was noted. Preoperative chemotherapy is usually better tolerated than postoperative chemotherapy due to better nutritional and physiological status of the patients. In our study 83% of the study patients were able to tolerate all three preoperative EOX cycles and altogether 50% were given all 6 EOX cycles. In the MAGIC study [3], a total of 86% of patients assigned to perioperative chemotherapy completed preoperative chemotherapy and only 42% completed all six cycles of chemotherapy. In the Norwegian study [17] only 40 out of 90 patients (45%) completed all six perioperative cycles. In our study, fully completed perioperative chemotherapy associated with longer OS, whereas the association with TTR was only borderline significant ($p = 0.08$). The cause for better OS is probably multifactorial. The performance status of patient influences the tolerability of chemotherapy and 85% of patients had a good performance status (Z = 0 or 1). Preoperative chemotherapy may downstage the tumor increasing R0 resections.

A phase 2 trial has been performed with perioperative FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel) therapy in patients with limited metastatic gastric or gastroesophageal junction cancer with promising results [19]. This therapy will probably replace in the future at least part of the perioperative EOX-therapy we have used so far.

The retrospective nature of our study and the relatively small patient number with variability in tumor location need to be taken into account when interpreting the results of this study. The timing of PET response imaging and relatively high portion of gastric

adenocarcinomas might also impact the results. Treatment with perioperative chemotherapy in locally advanced operable gastroesophageal cancer has become standard practice in our hospital, which decreases the risk of feasible patients not being evaluated for perioperative regimen. However, it is likely that at the beginning of the study a few patients have been directed to surgery without preoperative treatment.

These results do not support continuing response PET imaging. However, the relatively high portion of gastric cancers in this study and the timing of response PET may have an impact on the results. Based on earlier literature and our results, we will continue preoperative metabolic response evaluation only with distal esophageal and gastroesophageal junction carcinomas. In our opinion, the wide variability of metabolic behavior of gastric carcinomas supports perioperative chemotherapy without metabolic response evaluation.

In conclusion, follow-up PET during or right after second preoperative chemotherapy cycle did not assist in identifying patients with favorable histopathological response or OS.

The metabolic responses and histopathological responses influenced the treatment of the patients resulting in modifications to the perioperative chemotherapy. The perioperative EOX treatment was well tolerated and receiving all six perioperative EOX cycles was associated with better OS and all cycles should be administered to all eligible patients. Future studies with larger patient numbers and optimized timing of the response PET imaging are needed to assess the value of a PET scan evaluating the metabolic response in patients with gastroesophageal adenocarcinoma.

Disclosures

The authors have no conflicts of interest or financial ties to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2018.11.002.

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