*Acta Oncologica*, 2012; 51: 636–644

informa
healthcare

**ORIGINAL ARTICLE**

# Locally advanced esophageal adenocarcinoma: Response to neoadjuvant chemotherapy and survival predicted by [18F]FDG-PET/CT

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**Abstract**

*Background.* [18F]fluorodeoxyglycose-Positron Emission Tomography/Computer Tomography ([18F]FDG-PET/CT) is commonly used in staging of locally advanced esophageal cancer. Its predictive value for response to neoadjuvant therapy and survival after multimodality therapy is controversial. *Methods.* Sixty-six consecutive patients with locally advanced adenocarcinoma of the esophagus or esophagogastric junction underwent surgery after neoadjuvant chemotherapy. Staging was done prospectively with [18F]FDG-PET/CT, before and after completion of neoadjuvant therapy. Pre- and post-therapy maximal standardized uptake values for the primary tumor (SUV1 and SUV2) were determined, and their relative change (SUVΔ%) calculated. Percentage change in SUV1 was compared with histopathologic response (HPR, complete or subtotal histologic remission), disease-free- (DFS) and overall survival (OS). *Results.* Resection with negative margins was achieved in 60 patients. HPR rate was 14 of 66 (21.2%). Median follow-up was 16 months (range 4–72). For all patients, OS probability at three years was 59% and DFS 50%. In receiver operating characteristics (ROC) analysis, HPR was optimally predicted by a $>67\%$ change in baseline maximal SUV (sensitivity 79% and specificity 75%). In univariate survival analysis (Cox regression proportional hazards), HPR associated with improved DFS (HR 0.208, $p=0.033$) but not OS (HR 0.030, $p=0.101$), SUVΔ% $>67\%$ associated with improved OS (HR 0.249, $p=0.027$) and DFS (HR 0.383, $p=0.040$). In a multivariate model (adjusted by age, sex, and ASA score), neither HPR nor SUVΔ% $>67\%$ was predictive of improved OS and DFS. However, SUVΔ% as a continuous variable was an independent predictor of OS (HR 0.966, $p<0.0001$) or DFS (HR 0.973, $p<0.0001$). *Conclusion.* Our results support previous results showing that [18F]FDG-PET/CT can distinguish a group of patients with worse prognosis after neoadjuvant chemotherapy in adenocarcinoma of the esophagus or esophagogastric junction. This information could offer a new independent preoperative marker of prognosis.

Esophageal adenocarcinoma is a lethal malignancy with poor overall five-year survival, 10% to 16% in developed countries [1]. The majority of patients have locally advanced disease at presentation, i.e. the tumor penetrates into the muscular wall or the patient has lymph node metastases, or both. Treatment results remain unsatisfactory regardless of treatment modality – overall five-year survival of locally advanced disease is 15% to 35% after either surgery alone or multimodality therapy [2–4]. Induction therapy is utilized increasingly, and a recent study has shown that patients with a complete histopathologic response (HPR) to neoadjuvant chemo- or radiochemotherapy and R0-resection can have improved five-year survival [5]. However, neoadjuvant therapy may also lead to adverse effects on patients, and surgery may be unnecessarily delayed [6]. A diagnostic modality reliably revealing complete responders is therefore necessary.

Computer tomography (CT), esophagogastroscopy with biopsies and endoscopic ultrasound (EUS) have been insufficiently accurate in assessing response to neoadjuvant therapy as they cannot distinguish tumor scar from active tumor tissue [7–9].

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*(Received 5 August 2011; accepted 20 November 2011)*

ISSN 0284-186X print/ISSN 1651-226X online © 2012 Informa Healthcare
DOI: 10.3109/0284186X.2011.643822

[18F]fluorodeoxyglycose-Positron Emission Tomography ([18F]FDG-PET) has been the most promising method of response evaluation thus far. It measures the uptake of a fluorinated glucose analog (18F-fluorodeoxy-D-glucose; [FDG]) in cells, thus reflecting their metabolic activity. Change in a cell´s metabolic activity rate is thought to act as a surrogate marker of treatment response. In pre-treatment staging, [18F]FDG-PET can identify ypTNM stage IV disease better than CT [7], and when [18F]FDG-PET is combined with EUS, diagnostic accuracy is further improved [10]. [18F]FDG-PET has been shown to identify patients likely to benefit from multimodality therapy for esophageal epidermoid- or adenocarcinoma. In one study, the feasibility of standardized uptake change percentage in guiding treatment protocols is demonstrable [11]. Contradictory findings as to the predictive ability of tumor metabolic changes have emerged as well [12], making the predictive value and optimal timing of [18F]FDG-PET remain controversial. The goal of this study was to evaluate the value of [18F]FDG-PET-CT in prediction of HPR, overall (OS)- and disease-free (DFS) survival after neoadjuvant chemotherapy for locally advanced carcinoma of the esophagus or esophagogastric junction.

## Patients and methods

We reviewed the charts of 66 consecutive patients operated on for adenocarcinoma of the esophagus or esophagogastric junction between 2005 and 2011 at the Division of Thoracic Surgery at Helsinki University Central Hospital. Patients underwent surgery with curative intent after neoadjuvant chemotherapy for locally advanced (T3-4, N0, M0 or T1-4, N1, M0) disease. The institutional review board at Helsinki University Central Hospital approved this study. Patient characteristics are listed in Table I.

Table I. Patient characteristics (n = 66).

| Factor | n (%) |
|---|---|
| Gender | |
| Men | 49 (74%) |
| Women | 17 (26%) |
| Age | |
| Median | 66 |
| Range | 41–79 |
| ASA score | |
| 1 | 18 (27) |
| 2 | 29 (44) |
| 3 | 19 (29) |
| Operation | |
| IL | 32 (49) |
| MIE | 27 (41) |
| TH | 1 (1.5) |
| EX | 6 (9) |
| cTNM | |
| T3N0 | 15 (23) |
| T3N1 | 43 (65) |
| T4N0 | 2 (3) |
| T4N1 | 6 (9) |
| ypTNM | |
| Stage 0 | 9 (14) |
| Stage I | 7 (11) |
| Stage IIA | 15 (23) |
| Stage IIB | 14 (22) |
| Stage III | 15 (23) |
| Stage IV | 6 (9) |
| Tumor regression grade | |
| I | 48 (72) |
| II | 4 (6) |
| III | 6 (9) |
| IV (pCR) | 8 (12) |
| Type of Neoadjuvant | |
| EOX | 53 (80) |
| DCF | 9 (14) |
| ECF | 4 (6) |

cTNM, clinical TNM stage AJCC 2002 [13]; DCF, docetaxel-cisplatin-fluorouracil; ECF, epirubicin-cisplatinol-fluorouracil; EOX, epirubicin-oxaliplatin-cabecitabin; EX, exploration; IL, Ivor Lewis; MIE, minimally invasive esophagectomy; pCR, pathologic complete response; TH, transhiatal; ypTNM, pathologic TNM stage AJCC 2002 after neoadjuvant therapy and surgery [13].

### *Staging*

Patients were preoperatively staged according to AJCC 6th edition guidelines [13]. Staging included endoscopy (EGDS), an iv-contrasted spiral CT-scan of the thorax, abdomen, and pelvis (3–5 mm slice thickness), endoscopic ultrasound (EUS), and [18F]FDG-PET/CT. [18F]-FDG-PET/CT was done prospectively, before and after induction therapy.

### *Neoadjuvant therapy*

Patients were treated with neoadjuvant chemotherapy [14,15], with 53 receiving epirubicin-oxaliplatin-cabecitabine (EOX), four receiving epirubicin-cisplatin-fluorouracil (ECF), and nine, a docetaxel-cisplatin-fluorouracil (DCF) combination. The DCF regimen was used only in the beginning of the study period. Three-week EOX and ECF cycles included an intravenous (iv) bolus of epirubicin (50 mg/m$^2$ of body surface area) on Day 1 and an iv infusion of either oxaliplatin (130 mg/m$^2$) or cisplatin (60 mg/m$^2$) on Day 1. Fluorouracil infusion (200 mg/m$^2$/day) or oral capecitabine (1000–1250 mg/m$^2$/day), were given on Days 1–21. Three cycles were given preoperatively to all but nine patients, who received only two EOX cycles due to unacceptable toxicity. The three-week DCF cycle included an iv infusion of docetaxel (75 mg/m$^2$) on Day 1, cisplatin (75 mg/m$^2$) on Day 1, and fluorouracil infusion (750 mg/m$^2$/day) on Days 1–5. The four preplanned cycles were completed in all nine patients.

No deaths were associated with induction therapy. Median time from last cycle of chemotherapy to the second $^{[18F]}$FDG-PET scan was 15 days (3–39).

*Surgical treatment*

Median time from end of chemotherapy to operation was 52 days (40–130). Our protocol is to operate within four to six weeks after end of the neoadjuvant therapy [16,17]. However, in some cases the interval was prolonged, to allow time for recovery from chemotherapy. En bloc resection with resection of the esophagus and proximal stomach and two-field lymphadenectomy was completed in 59; 27 of these operations were done minimally invasively, with a thoracolaparoscopic approach, and 32 with standard right thoracotomy and laparotomy incisions. One patient underwent transhiatal esophagectomy, and in six patients the operation was discontinued because of disseminated disease confirmed in frozen section biopsies. A minimum of 25 lymph nodes were dissected per person. No operative mortality occurred, and all resected patients (n = 60) had microscopically negative resection margins (R0-resection).

*Patient follow-up*

Our follow-up program includes history, physical examination, laboratory tests, an iv-contrasted CT-scan of the thorax, abdomen, and pelvis (3–5 mm slice thickness) and esophagogastroscopy with biopsies at six-month intervals during the first two years and annually until a five-year follow-up is completed. If recurrence occurs, the patient is referred to an oncologic multidisciplinary team.

*PET acquisition*

Patients were scanned with a dedicated whole-body scanner: 63 at Helsinki University Central Hospital with Philips Gemini GXL 16 PET/CT and three at the Turku PET Center using either GE Advance, Discovery VCT, or Siemens/CTI HR+ -whole-body scanners. Scanning was done from the supra-orbital to the upper mid-thigh, with arms elevated over the head, if possible. After a scout scan, a low-dose CT-scan (50–60 mAs, 120–140 kV) followed, for attenuation correction and for anatomic localization of the emission PET data. Scans were corrected for decay and scatter and reconstructed with ordered subset expectation maximization (OSEM). We visualized the data set in transaxial, coronal, and sagittal slices. Patients fasted for at least six hours and drank one litre of water in the two hours prior to injection. We determined their height and weight and measured the serum glucose level of diabetic patients. If serum glucose level was above 11 mmol/l, the study was rescheduled. Patients rested at least half an hour prior to and one hour after administration of FDG. The dose of FDG was 5 MBq/kg body weight and the scan started one hour after the FDG injection. Standardized uptake values (SUV) were determined with a small fixed-dimension region of interest (ROI), 8 mm in diameter; and the value was determined using the highest activity inside this area. SUV values were calculated after correction of radioactive decay according to the following formula: SUV = ROI activity (MBq/ml)/injected dose (MBq/body weight g). ROIs were drawn at every level where tumor tissue was detectable, and maximal SUV was the highest detectable value inside the tumor. SUV of the primary tumor was determined at baseline and after therapy. Maximal SUV of the pretreatment scan was labeled as SUV1, and the post-treatment scan SUV2. Change percentage (SUV$\Delta$%) was expressed as [(SUV1-SUV2)/SUV1]x100.

*Histomorphologic grading of tumor regression*

Each resected specimen was fixed in formalin and paraffin wax and cut into 5-µm slices. Sections were routinely stained with hematoxylin and eosin. Histopathologic staging analyses were done primarily by independent pathologists blinded to sample coding. Histomorphologic evaluation of the neoadjuvant effect was performed afterwards by a single experienced pathologist (HH), who was blinded to patient data.

Histomorphologic regression evaluation was based on a grading system according to Schneider et al. [18]. Tumor bed specimens were classified as grades I to IV, grade I meaning more than 50% living tumor cells in the tumor bed, grade II, 10% to 50% living tumor cells, grade III, less than 10% and grade IV, no living tumor cells. Grades III to IV were classified as histopathologic responders and grade I to II as the non-responder group.

*Statistical analysis*

All analyses were performed with PASW statistics 18.0 for MAC (SPSS inc. Chicago, Illinois). All quantitative data were expressed as medians (ranges). Distribution of continuous variables was tested with the Kolmogorov-Smirnov one-sample test. Non-parametric data were compared with the independent samples median test. Survival rates were estimated according to Kaplan-Meier. Statistical comparisons between different groups of patients were performed with a log-rank test and the Cox proportional hazards model. Overall- and disease-free survival were calculated

from the date of initiation of neoadjuvant therapy. The endpoint was defined as cancer- or treatment-related death, or first detected recurrence. Significance level was set at $p < 0.05$. The diagnostic accuracy of $^{[18F]}$FDG-PET/CT was calculated by the receiver operating characteristics (ROC) test. The area under the ROC curve (AUC) provides a measure for the accuracy of a diagnostic test. It ranges from 0.5 (random guessing) to 1.0 (perfect test). The optimum cut-off value for differentiation of responding and non-responding tumors was defined by the point of the ROC curve with minimum distance from the 0% false positive rate and the 100% true positive rate. In addition, 95% confidence intervals (CI) for these parameters were calculated by use of the F distribution. Positive and negative predictive values for each threshold value identified by ROC analysis were calculated by standard formulas.

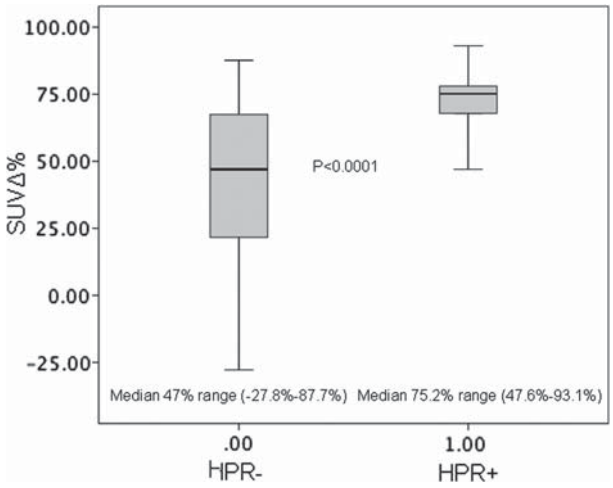


Figure 1. Independent samples Median test-stem and leaf plot. Median change in SUVΔ% (maximum standardized uptake value percentage change after neoadjuvant therapy) in histopathologic responders and non-responders.

## Results

### *Association of SUVΔ% and HPR*

SUVΔ% was significantly ($p < 0.0001$) more prominent in histopathologic responders than in non-responders (Figure 1). An ROC test was run to evaluate how change in tumor maximal SUV predicts HPR (Table II and Figure 2). A decrease of 67% in maximal SUV was the optimal cut-off value differentiating between histopathologic responders and non-responders. Cut-off values used by other authors were also tested [3,4] (Figure 2).

### *Survival analysis*

Three patients were excluded from survival analysis because of another simultaneous malignancy (two metastatic intestinal neuroendocrine tumors and one lymphoma). OS was 59% at three years and DFS 50% at three years. Median follow-up was 16 months (range 4–72). In univariate analysis, the Cox regression proportional hazards regression test (Table III) SUVΔ% > 67% and HPR were both associated with improved DFS (Figures 3 and 4), but only SUVΔ% > 67% was associated with improved OS with statistic significance (Figures 5 and 6). Other variables predictive of improved OS or DFS were ypTNM stage < 2b and male gender. SUVΔ% was dichotomized according to optimal cut-off value of histopathologic response prediction. Neither pre- or post-neoadjuvant maximal SUV's of the primary tumor were predictive of OS or DFS in this analysis. HPR and SUVΔ% were also tested with the Cox regression proportional hazards regression model in a multivariate setting, adjusted by age, sex and ASA score (Tables IV and V). It appeared that neither HPR or SUVΔ% > 67% could retain significance when predicting OS or DFS. Therefore we tested SUVΔ% also as a continuous variable, which made it an independent predictor of both OS and DFS. And when testing lower cut-offs for SUVΔ% (35% and 0%), independent predictive ability remained strong. Male gender was also associated independently with improved OS and DFS, and that result remained in all models.

## Discussion

Results of this study suggest that $^{[18F]}$-FDG-PET/CT is useful for assessing treatment response to neoadjuvant chemotherapy of esophageal adenocarcinoma.

Table II. ROC analysis of SUVΔ% and histopathologic response prediction.

| CUTOFF | SE | SP | PPV | NPV | AUC (95%CI) | p |
|---|---|---|---|---|---|---|
| 67% | 79% | 75% | 46% | 93% | 0.810 (0.702–0.919) | < 0.0001 |
| 50%[a] | 93% | 58% | 37% | 97% | NL | NL |
| 35%[b] | 100% | 33% | 29% | 100% | NL | NL |

AUC, area under curve; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics; SE, sensitivity; SP, specificity; SUVΔ%, percentage change in maximal SUV after neoadjuvant therapy.
[a]author Port et al. [19].
[b]author Lordick et al. [11].

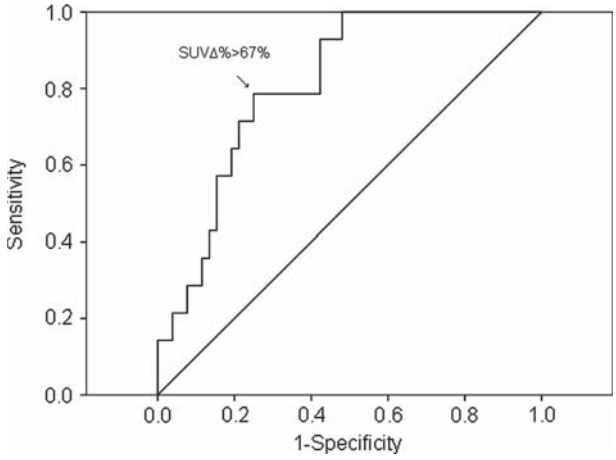


Figure 2. ROC curve analysis for prediction of histopathologic response by SUVΔ% (maximum standardized uptake value percentage change after neoadjuvant therapy). Arrow denotes optimal point of separation at 67% decrease in SUVΔ%. ROC, receiver operating characteristics.

Our most important finding was that SUVΔ% as a continuous variable was a stronger predictor of survival than was HPR, and it was also an independent predictor of survival. This suggests that risk of death or of recurrence rises the less that the patient shows regression of metabolic activity of the primary tumor after induction chemotherapy. Moreover, when the second [18F]FDG-PET scan failed to show any sings of metabolic regression, or when metabolic activity rose, our patients had a dismal prognosis (n = 8). None of those patients survived more than two years after the beginning of neoadjuvant treatment, and none had a recurrence-free period lasting more than one year.

Secondarily, our chosen cut-off (SUVΔ% > 67%) identified histopathologic responders at a 79% true negative and 75% true positive rate. When using a lower cut-off of SUVΔ% (35%) [11], the true negative rate became 100%, but the true positive rate was only 33%. A lower cut-off could select all histopathologic responders, but also a significant number of false positives. Therefore, accuracy for [18F]FDG-PET was not enough to identify patients having complete or major histopathologic remission for clinical use. Thirdly, gender appeared as an independent risk factor, women having clearly worse prognosis.

The feasibility of [18F]FDG-PET-CT in predicting response to neoadjuvant chemotherapy in esophageal adenocarcinoma, was presented in the MUNICON II trial by Lordick et al. [11]. They have shown how 35% regression of tumor FDG metabolism during neaodjuvant chemotherapy can serve to guide patients into either a neoadjuvant and surgery-, or a surgery-only group. Their cut-off value of 35% had a sensitivity of 100% and specificity of 58%. Our results of ROC analysis are in line with these, as when the same cut-off was tested with our data, sensitivity was 100%, but specificity remained poor. However, in MUNICON II, histopathologic response appeared as a stronger predictor of survival than was metabolic response in univariate analysis. Patients with a metabolic and histopathologic response survived better than did patients with a metabolic but no histopathologic response (HR 4.55, 95% CI 1.37–15.04, p = 0.004). However, the survival of patients with a metabolic but no histopathologic response was not significantly better than was the survival of patients with no metabolic response (HR 1.21, 95% CI 0.56–2.63, p = 0.549). In the MUNICON II study, the second PET scan was done during treatment, and no multivariate analysis was done. In an earlier study by the same group [16], 65 patients with locally advanced adenocarcinoma of the esophagogastric junction were

Table III. Cox regression univariate analysis of association of essential risk factors, long-term-, and disease-free survival among patients with locally advanced esophageal adenocarcinoma undergoing surgery after neoadjuvant chemotherapy.

| | Overall survival | | Disease-free survival | |
|---|---|---|---|---|
| Variable | HR (95% Cl) | p | HR (95% Cl) | p |
| Age | 0.969 (0.929–1.010) | 0.139 | 0.971 (0.937–1.007) | 0.116 |
| Gender (M) | 0.407 (0.166–0.999) | 0.050 | 0.383 (0.173–0.849) | 0.018 |
| HPR+ | 0.030 (0.000–1.983) | 0.101 | 0.208 (0.049–0.881) | 0.033 |
| ASA < 3 | 0.356 (0.199–1.786) | 0.131 | 0.415 (0.143–1.204) | 0.106 |
| ypStage < 2b | 0.213 (0.070–0.643) | 0.006 | 0.293 (0.122–0.704) | 0.006 |
| SUVΔ% > 67 | 0.249 (0.073–0.856) | 0.027 | 0.383 (0.153–0.959) | 0.040 |
| SUVΔ% > 35 | 0.192 (0.077–0.476) | < 0.0001 | 0.116 (0.075–0.370) | < 0.0001 |
| SUVΔ% > 0 | 0.140 (0.052–0.379) | < 0.0001 | 0.139 (0.049–0.376) | < 0.0001 |
| SUVΔ% | 0.973 (0.959–0.986) | < 0.0001 | 0.974 (0.962–0.987) | < 0.0001 |
| SUV1 | 0.935 (0.852–1.026) | 0.157 | 0.966 (0.898–1.039) | 0.352 |
| SUV2 | 1.043 (0.970–1.122) | 0.252 | 1.035 (0.969–1.108) | 0.303 |

ASA, American Society of Anesthesiologists physical status classification [31]; CI, confidence interval; HPR, histopathologic response; HR, hazard ratio; SUV1 and SUV2, pre- and postneoadjuvant maximum standardized uptake values; SUVΔ%, Maximum standardized uptake value percentage change after neoadjuvant therapy; ypTNM, Tumor, node and metastasis staging according to AJCC 2002 after neoadjuvant therapy and surgery [13].

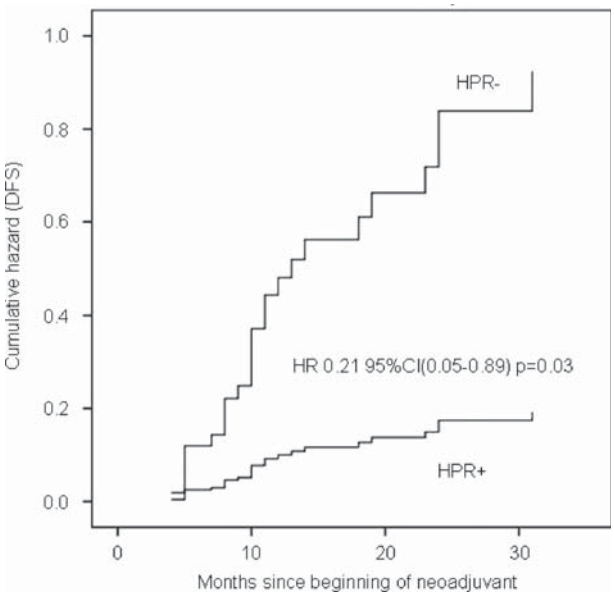


Figure 3. Cox regression proportional hazards univariate analysis of effect of HPR after neoadjuvant therapy on OS. OS, overall survival.

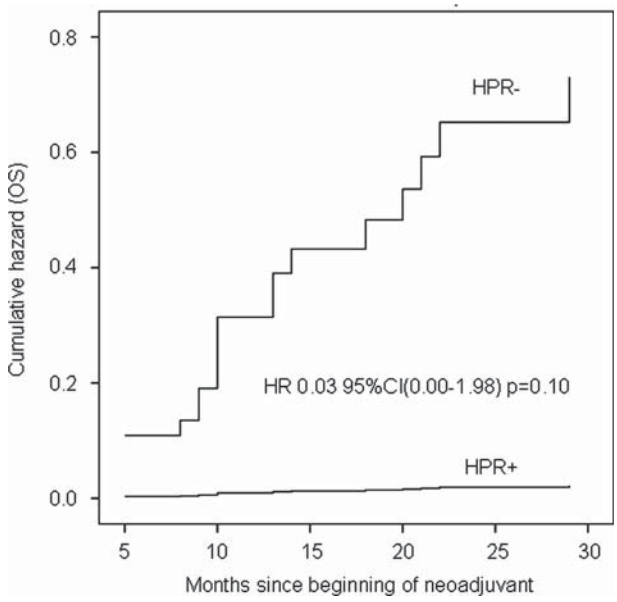


Figure 5. Cox regression proportional hazards univariate analysis of effect of percentage change > 67% (SUVΔ%) of maximal SUV of the primary tumor after neoadjuvant therapy on OS. OS, overall survival.

operated on after neoadjuvant chemotherapy. Cox regression multivariate analysis revealed a metabolic response (SUVΔ% > 35%) as the only independent predictor of event-free survival of patients with complete (R0) resection (histopathologic response, ypN, and ypT categories in the same model). This supports our results, as we had only R0 resections among patients in this study and we also tested the same cut-off. A study similar to ours was that of Port et al. [19] who reviewed 62 patients (51 adenocarcinomas and 11 epidermoid carcinomas of the esophagus) with surgery after neoadjuvant chemotherapy. They defined the optimal cut-off of SUVΔ% for histopathologic response prediction as 50% and reported a sensitivity of 90% and specificity of 47.1%. When we tested the same cut-off, sensitivity was 93% and specificity 58%, a result similar to Port's [18]. As in our study, the decrease in tumor metabolic activity was significantly correlated with improved survival, regardless of pathologic downstaging, and it was an

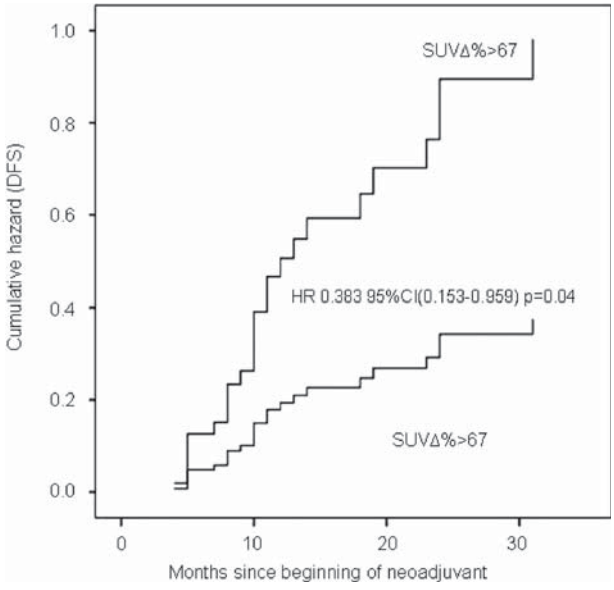


Figure 4. Cox regression proportional hazards univariate analysis of effect of HPR after neoadjuvant therapy on DFS. DFS, disease-free survival; HPR, histopathologic response.

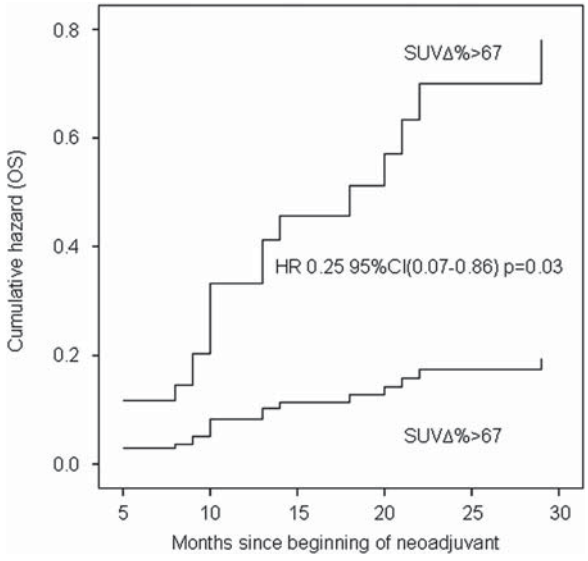


Figure 6. Cox regression proportional hazards univariate analysis of the effect of percentual change > 67% (SUVΔ%) of maximal SUV of the primary tumor after neoadjuvant therapy on DFS. DFS, disease-free survival.

Table IV. Cox regression multivariate analysis of association of multiple risk factors and poor long-term overall survival among patients with locally advanced esophageal adenocarcinoma undergoing surgery after neoadjuvant chemotherapy.

| | Overall survival | | | |
|---|---|---|---|---|
| | Model 1. | | Model 2. | |
| Variable | HR (95% Cl) | p | HR (95% Cl) | p |
| Age | 0.967 (0.919–0.10.17) | 0.192 | 0.959 (0.911–1.011) | 0.119 |
| Sex (M) | 0.301 (0.114–0.796) | 0.016 | 0.168 (0.054–0.523) | 0.002 |
| HPR+ | >0.0001 (0–3.88E254) | 0.966 | >0.0001 (0–9.06E179) | 0.959 |
| ASA<3 | 0.741 (0.240–2.289) | 0.602 | 0.761 (0.252–2.300) | 0.628 |
| SUVΔ%>67% | 0.313 (0.088–1.113) | 0.073 | NL | |
| SUVΔ%>35% | NL | | 0.146 (0.049–0.436) | 0.001 |
| | Model 3. | | Model 4. | |
| Age | 0.952 (0.903–1.004) | 0.069 | 0.942 (0.889–0.998) | 0.042 |
| Sex (M) | 0.208 (0.072–0.602) | 0.004 | 0.156 (0.050–0.483) | 0.001 |
| HPR+ | >0.0001 (0–4.08E227) | 0.963 | >0.0001 (0–1.65E274) | 0.969 |
| ASA<3 | 0.861 (0.269–2.754) | 0.800 | 0.936 (0.300–2.920) | 0.909 |
| SUVΔ%>0% | 0.109 (0.034–0.349) | <0.0001 | NL | |
| SUVΔ% | NL | | 0.966 (0.949–0.984) | <0.0001 |

ASA, American Society of Anesthesiologists physical status classification [31]; CI, confidence interval; HPR, histopathologic response; HR, hazard ratio; SUVΔ%, Maximum standardized uptake value percentage change after neoadjuvant therapy; ypTNM, Tumor, node and metastasis staging according to AJCC 2002 after neoadjuvant therapy and surgery [13].

independent predictor of survival in Cox regression multivariate survival analysis (the same model with cTNM and pTNM). The technique and protocol of $^{[18F]}$FDG-PET/CT in Port's [19] and Lordick's [11] studies were similar to ours.

$^{[18F]}$FDG-PET/CT results are more controversial when chemoradiochemotherapy is used rather than chemotherapy [12,20–24]. Wieder et al. have reported on 38 patients having surgery after preoperative radiochemotherapy for esophageal squamous cell carcinoma [25]. In predicting histopathologic response, they reported high sensitivity (93%) and specificity (88%) for a 30% decrease in SUV in a second PET scan two weeks after the start of neoadjuvant therapy. Both the metabolic and the histopathologic response were significantly correlated with survival. Javeri et al. [26] studied retrospectively 151 patients with esophageal adenocarcinoma operated on after neoadjuvant chemoradiation. They found that the greater the decline of SUVΔ% as a continuous variable (HR 0.99, 95% CI 0.987–0.998, $p = 0.01$), the longer the OS of patients with esophageal adenocarcinoma. The same is predicted by our results (HR 0.966, 95% CI 0.949–0.984, $p < 0.0001$).

Table V. Cox regression multivariate analysis of the association of multiple risk factors and poor long-term disease-free survival among patients with locally advanced esophageal adenocarcinoma operated on after neoadjuvant chemotherapy.

| | Disease-free survival | | | |
|---|---|---|---|---|
| | Model 1. | | Model 2. | |
| Variable | HR (95% Cl) | p | HR (95% Cl) | p |
| Age | 0.975 (0.934–1.018) | 0.211 | 0.985 (0.916–1.002) | 0.063 |
| Sex (M) | 0.338 (0.143–0.801) | 0.014 | 0.167 (0.062–0.451) | <0.0001 |
| HPR+ | 0.308 (0.069–1.384) | 0.125 | 0.508 (0.106–2.420) | 0.359 |
| ASA<3 | 0.493 (0.163–1.493) | 0.211 | 0.493 (0.166–1.469) | 0.205 |
| SUVΔ%>67% | 0.498 (0.192–1.289) | 0.151 | NL | |
| SUVΔ%>35% | NL | | 0.114 (0.043–0.300) | <0.0001 |
| | Model 3. | | Model 4. | |
| Age | 0.953 (0.908–1.000) | 0.049 | 0.958 (0.914–1.003) | 0.069 |
| Sex (M) | 0.235 (0.090–0.613) | 0.002 | 0.232 (0.092–0.585) | 0.002 |
| HPR+ | 0.340 (0.075–1.534) | 0.160 | 0.501 (0.107–2.358) | 0.382 |
| ASA<3 | 0.756 (0.242–2.356) | 0.629 | 0.605 (0.202–1.816) | 0.370 |
| SUVΔ%>0 | 0.115 (0.037–0.357) | <0.0001 | NL | |
| SUVΔ% | NL | | 0.973 (0.958–0.987) | <0.0001 |

ASA, American Society of Anesthesiologists physical status classification [31]; CI, confidence interval; HPR, histopathologic response; HR, hazard ratio; SUVΔ%, Maximum standardized uptake value percentage change after neoadjuvant therapy; ypTNM, tumor, node and metastasis staging according to AJCC 2002 after neoadjuvant therapy and surgery [13].

Malik et al. [22] recently presented data on 37 patients with esophageal AEG who were operated on after neoadjuvant chemoradiotherapy. In their prospective report, a 26.4% decrease in SUV in their second PET scan showed no correlation with response or with survival. Sensitivity was 62.5% and specificity 71.4% for predicting histopathologic response. A prospective analysis by Vallböhmer et al. [12] analyzed 119 patients with esophageal carcinoma (66 epidermoid and 53 adenocarcinomas). HPR was the best indicator of survival, but they could find no association between SUVs and survival or HPR.

Radiation-induced esophagitis has been considered as a major factor causing confusion regarding the lower accuracy of $^{[18F]}$FDG-PET/CT after radiochemotherapy [12,22,27]. Our study and studies done with chemotherapy only, are therefore not directly comparable to studies done with radiochemotherapy only. Moreover, comparing studies is difficult since SUV measurement is not standardized across different centers, and the SUV definition itself is subject to several sources of error including patient size, measurement duration, plasma glucose concentration, recovery coefficients, partial volume, and ROI (region of interest) selection [28]. Other possible sources of bias are different study protocols, different cut-off values to define metabolic response, and different histopathologic scoring systems. In studies done after chemotherapy [11,19], including ours, metabolic response is also an independent prognostic factor in patients with R0 resection. This was not apparent in studies done after neoadjuvant chemoradiotherapy, where metabolic response is not predictive of survival [12,21,23]. It is intriguing to speculate that metabolic response recorded from the area of a tumor after neoadjuvant chemotherapy may also reflect systemic control of the disease. When tumor response evaluation occurs after neoadjuvant chemoradiotherapy, we cannot judge whether the response is achieved by radiation only or also by chemotherapy. This could in part explain why after neoadjuvant chemoradiotherapy, metabolic response is not a reliable prognostic marker.

A systematic review comprising a total of 849 patients with esophageal cancer was conducted by Kwee [29]. It showed significant heterogeneity in both sensitivity and specificity of $^{[18F]}$FDG-PET in predicting tumor response to neoadjuvant therapy ($p < 0.0001$). Pooled estimates for sensitivity were 67% (95% CI 62%–67%) and specificity 68% (95% CI 64%–73%). Area under a summary ROC curve was 0.7815. Our results are in line with these estimates. Their conclusion was that overall accuracy is still insufficient for $^{[18F]}$FDG-PET to guide neoadjuvant therapy decisions

Our female patients had significantly worse prognosis, which is in contrast to published results of demographic studies [30]. Males and females had no significant differences in age ($p = 0.936$), ASA score ($p = 0.918$), SUV$\Delta$% ($p = 0.889$) or HPR ($p = 0.682$). However, females were more often of ypTNM stage $>$ 2a ($p = 0.028$), which clearly explains this statistical difference. This is most likely coincidental, as the number of patients was small.

A weakness of our study is our retrospective collection of data and limited follow-up, especially in the histopathologic-responder group. This can contribute to HPR's losing significance in a multivariate model. Strengths of our study are quality preoperative staging and follow-up protocols including all treated patients. An experienced specialist also reviewed histopathologic and metabolic data. All patients underwent surgery by the same experienced team, R0-resection was achieved in 60 of 66 patients, and a high number of lymph nodes were dissected in all operations.

Our own results support other results showing that $^{[18F]}$FDG-PET/CT can differentiate a group of patients with a worse prognosis after neoadjuvant chemotherapy in esophageal adenocarcinoma. This information offers a new and independent preoperative marker of prognosis that can prove useful when balancing risks of surgery against expected benefit. Results of post-treatment measurement of metabolic response might also help in choosing patients with a worse prognosis for future experimental trials. The overall value of $^{[18F]}$FDG-PET remains to be defined in multicenter randomized trials.

## Acknowledgements

The authors thank Mrs. Yvonne Sundström for her skillful technical and secretarial assistance. This study was supported by Helsinki University Central Hospital Research Funds (EVO). We have no conflict of interest to declare.

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