European Journal of Radiology 85 (2016) 540–545

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Prognostic value of volumetric PET parameters in unresectable and metastatic esophageal cancer

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ARTICLE INFO

Article history:
Received 11 December 2015
Received in revised form 5 January 2016
Accepted 6 January 2016

Keywords:
Oesophageal cancer
F18-PET/CT
Outcome analysis
Metabolic tumor volume
SUV

ABSTRACT

Purpose: To assess the prognostic value of volumetric parameters measured with PET/CT in patients with advanced or metastatic esophageal cancer (EC).
Materials and methods: We identified 71 patients (33 adenocarcinoma [AC] and 38 squamous cell carcinoma [ESCC]) with unresectable or metastatic EC who had PET/CT prior to palliative treatment. Volumetric parameters (metabolic tumor volume [MTV], total lesion glycolysis [TLG], tumor length [TL]) as well as maximum and mean standardized uptake (SUVmax, SUVmean) were obtained from ^{18}F-FDG PET/CT studies. The correlation between overall survival (OS) and established clinical parameters was assessed using a Cox proportional hazards model.
Results: ESCC patients had higher SUVmax and SUVmean compared to AC ($p = 0.002$ and $p < 0.001$, respectively). There was an association of lower SUVmax and SUVmean with metastatic compared to locally advanced tumors (e.g., median SUVmax stage IV: 14.9, 95% confidence interval [95% CI 4.4–35.5] vs. stage IIIA-C: 23.3 [9.2–40.6], $p = 0.017$). TL, MTV and TLG showed an association to OS for all patients and for the subgroup of AC patients (AC; TL: Hazard ratio [HR] 3.23, [95% CI 1.03–10.11], $p = 0.044$; MTV: HR 3.16, [95% CI 1.08-9.23], $p = 0.035$). There was no correlation between PET parameters and survival in ESCC patients. Clinical nodal status was the only clinical variable associated to OS (HR 2.45 [95% CI 1.26–4.75], $p = 0.008$) in AC patients. In a multivariate analysis, nodal status and MTV remained as independent factors associated to OS (N: HR 9.98, [95% CI 1.28–78.11], $p = 0.028$; MTV: HR 1.02, [95% CI 1.01–1.03], $p = 0.003$).
Conclusions: MTV predicted poor OS in patients with advanced AC. No PET parameters were associated to OS in ESCC patients.

1. Introduction

Among cancers of the gastrointestinal tract, esophageal squamous cell carcinoma (ESCC) and adenocarcinoma of the esophago-gastric junction (AEG, here AC) as defined by Siewert and Stein [1] still represent tumors with poorest prognosis and outcome. With the prevalence of this condition increasing over the last 25 years [2,3], more than 18,000 cases are expected to occur in the United States every year with a yearly mortality of about 15,000 [4,5].

Since up to 65% of patients are metastatic or inoperable at the time of diagnosis [4], many patients will be directed to non-surgical treatment which consists mainly of radiochemotherapy (RCHT) or chemotherapy (CHT) alone, with an expected 5-year survival of 15% [4]. Besides several established clinical prognostic factors for long-term survival [6], only few imaging features exist, which are accepted markers for poor prognosis [7]. In order to better plan which patients might benefit from intensified treatment, the establishment of novel markers to correctly predict prognosis is required.

F18-FDG PET/CT has become the standard in the evaluation of patients with EC, since it has been shown that significantly more

Abbreviations: AC, adenocarcinoma; AEG, adenocarcinoma of the the esophago-gastric junction; CI, confidence interval; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; Gy, gray; HR, hazard ratio; IQR, interquartile range; MTV, metabolic tumor volume; PET, positron emission tomography; RCHT, radiochemotherapy; TL, tumor length; TLG, total lesion glycolysis; SUV, standardized uptake value.

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http://dx.doi.org/10.1016/j.ejrad.2016.01.002
0720-048X/

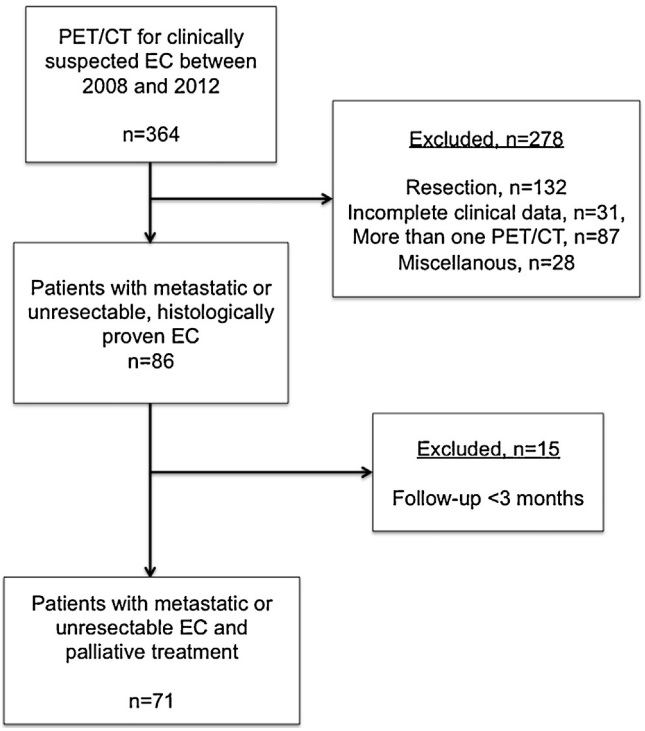

Fig 1. Flow chart of the patient selection process for this study. EC, esophageal cancer (includes esophageal squamous cell cancer and cancer of the gastro-esophageal junction).

distant metastases can be detected compared to CT alone [8]. Most commonly, maximum standardized uptake value (SUVmax) is used to predict outcome in localized or metastatic EC. However, over the last years, the concept of volumetric parameters has emerged that have the potential to better mirror the true tumor biology [9]. With the use of both the metabolic tumor volume (MTV) as well as total lesion glycolysis (TLG; derived from MTV and mean SUV of the entire mass), not only the tumor volume, but also the FDG avidity of the entire tumor is displayed [10]. In several reports this has been shown to correlate with survival [9–13]. However, in many of these studies, the intent to treat is not clearly defined, hence patients with both curative and palliative intent were included. This leads to sometimes-conflicting results between studies, and it is yet unclear, if volumetric parameters can be used to assess prognosis in patients with advanced EC.

Thus, the purpose of this study was to determine the value of volumetric PET-CT parameters on survival in comparison to SUVmax and clinical parameters in patients with advanced or metastatic EC.

2. Materials and methods

2.1. Patients

The local institutional review board approved the study (blinded), and written informed consent was obtained for PET/CT exams.

From our PET/CT database, we identified 364 patients who were examined for an esophageal or gastro-esophageal junction tumor staging between 2008 and 2012 (for semantic purposes, those two groups will be referred to as EC from now on). After exclusion of all patients with a different pathology other than esophageal adeno- or squamous cell carcinoma, exclusion of all patients resected in curative intent and patients with a short follow-up, we identified 71 patients who underwent RCHT or CHT for advanced or metastatic EC at our institution. The patient selection process is summarized in Fig. 1.

Treatment consisted of chemotherapy (CHT) in 55 patients and (chemo)-radiotherapy (RCHT) in 34 patients. Eighteen patients received both CHT and RCHT, sequentially. Chemotherapy regimens varied considerably between patients but could be grouped in 4 cohorts: Cisplatin 80 mg/m^2 and 5-fluoruracil 1000 mg/m^2 q21d, CF-regimen (n = 22); Cisplatin 75 mg/m^2 and 5-fluoruracil 750 mg/m^2 q21d (DCF) or Epirubicin 50 mg/m^2, Oxaliplatin 130 mg/m^2 and Capecitabine 625 mg/m^2 q21d, EOX-regimen (n = 18); Monotherapy with 5-FU/capecitabine (n = 2); combination of various regimens (n = 29).

Median radiation dose was 60 Gy (interquartile range, IQR 45.6–60 Gy).

The treatment decision was made during an interdisciplinary tumor board and only patients with unresectable disease or metastases were considered for non-surgical treatment. In 4 patients, medical reasons or decreased general performance status was the reason for palliative treatment.

Clinical staging was performed according to the 7th edition of the American Joint Committee on Cancer classification [14]. For nodal stage, no differentiation between the numbers of positive nodes was made; all clinically node-positive patients were set to be N+.

Patient follow-up was performed by the responsible department at our institution or by the referring physician.

2.2. ^{18}F-FDG-PET/CT protocol

A 64-row multi-detector PET/CT system (Biograph TruePoint64; Siemens, Erlangen, Germany) was used for all ^{18}F-FDG-PET/CT examinations. Patients were instructed to fast at least 4 h before imaging; the glucose cutoff level tolerable for the scan was 150 mg/dL. PET was performed 50–60 min after injection of 300 MBq of ^{18}F- FDG, with 3 min per bed position. TrueX algorithm was used for reconstruction of PET images, with 4 iterations per 21 subsets, a 5-mm slice thickness, and a 168 × 168 matrix.

For the CT protocol, patients were recommended to drink 1000–1500 mL of water immediately before the scan, for better distension of the lumen, which has been shown to enhance the visibility of the esophageal wall [15]. A contrast-enhanced scan of the neck, chest, and abdomen was performed after the injection of 2 mL/kg Iomeron 300® (Bracco, Milan, Italy, maximum 150 mL) at a flow rate of 4 mL/s, followed by a saline flush (50 mL). Scan delay for the arterial phase was 30 s (covering esophagus, upper abdomen), followed by a portal venous phase of the abdomen with a delay of 60 s. Section collimation was 64 × 0.6 mm, slice thickness was 3 mm with 2 mm increments, and a 512 × 512 matrix was used. Coronal and sagittal reconstructions were performed with a 3–5 mm slice thickness. The duration of the entire PET/CT was approximately 20 min.

2.3. Image analysis

Two attending physicians (radiology and nuclear medicine) read the images after acquisition and clinical decisions were based upon that report.

For the purpose of this investigation, an additional analysis of FDG PET images was performed on a Leonardo clinical workstation with TrueD® software (Siemens, Erlangen, Germany). Two radiologists and a resident (blinded) reviewed the PET volumetric images. Maximum SUV (SUVmax), mean SUV (SUVmean), tumor length (TL) and MTV on PET images were measured. An ellipsoid-shaped volume of interest (VOI) was manually drawn around the primary tumor that included the entire lesion in the axial, sagittal, and coronal planes, Fig. 2. Regional lymph nodes were not included in the VOI, as well as adjacent FDG-avid organs, such as the liver and the heart [16,17].