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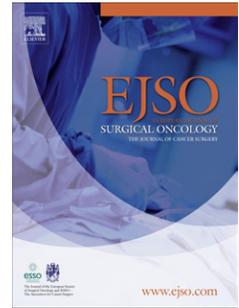
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## The value of post-neoadjuvant therapy PET-CT in the detection of interval metastases in esophageal carcinoma

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**Abstract**

*Background* PET-CT scanning is increasingly applied in the primary work-up of esophageal cancer patients. The additional value of a second PET-CT after completion of neoadjuvant therapy (NT) prior to surgery is presently unclear. Therefore, a consecutive series of esophageal cancer patients underwent PET-CT scanning after completion of NT for evaluation of metastatic disease that became manifest under NT.

*Methods* A consecutive series of patients planned for curative esophagectomy who underwent a PET-CT prior to and after NT were included in this study. The first PET-CT was performed as part of the diagnostic work-up, the second PET-CT was performed after completion of NT and prior surgery. In case of metastatic disease on the post-neoadjuvant therapy PET-CT confirmed by a biopsy, patients were excluded from surgical resection.

*Results* Between November 2008 and July 2010 a total of 50 patients underwent first and second PET-CT scanning. Confirmed metastatic disease on the second PET-CT was present in 4/50 patients (8%). These patients were excluded from resection. A false-positive diagnosis concerning a pulmonary lesion was present in 1 patient (2%); this infiltrate had disappeared on follow up imaging.

*Discussion* This study showed development of metastatic disease during NT detected by PET-CT in 8% of esophageal cancer patients, suggesting an additional value of a second PET-CT in order to prevent unnecessary surgical resections.

**Key words: PET-CT, interval metastases, esophageal carcinoma, neoadjuvant therapy, diagnosis**

## Introduction

Esophageal carcinoma is known for its early dissemination; at least half of the patients have locally advanced or metastatic disease at the time of diagnosis.<sup>1</sup> In order to select patients for a potentially curative esophagectomy accurate staging is essential. Current staging techniques to establish the M-stage according to the American Joint Committee on Cancer (AJCC) include computed tomography (CT), positron emission tomography (PET) and integrated PET-CT.<sup>2,3</sup> In comparison with conventional techniques like CT, PET-CT has repeatedly been shown to be the most accurate for the identification of metastatic disease.<sup>4,5</sup>

In case of potentially curable disease neoadjuvant therapy is increasingly applied in order to improve postoperative survival rates.<sup>6</sup> Several studies have described <sup>18</sup>F-Fluorodeoxyglucose (FDG) PET in the prediction of response to neoadjuvant therapy. These studies evaluate the change in standard uptake value (SUV) between the start of neoadjuvant treatment and the SUV at an early stage during therapy.<sup>7,8</sup> Differentiation between responders and non-responders is of importance for identification of patients without response to neoadjuvant therapy in whom chemoradiation could be withheld; hereby, serious side effects and a delay of surgical therapy could be prevented. Patients with a complete response could undergo definitive curative chemoradiotherapy without resection instead of neoadjuvant therapy followed by resection. Unfortunately, the present studies on response prediction show conflicting results.

Studies on PET-CT after completion of neoadjuvant therapy are scarce.<sup>9</sup> Currently, restaging prior to surgery is not the standard of care. However, in consequence of the duration of preoperative therapy and the following weeks until surgery, neoadjuvantly treated patients have an extended period until esophagectomy during which systemic disease could become manifest.

In our center, all esophageal cancer patients undergo PET-CT scanning as part of diagnostic staging. Furthermore, all patients with potentially curable esophageal carcinoma treated with neoadjuvant therapy undergo a second PET-CT after completion of chemoradiotherapy. The aim of this study was to evaluate the additional value of PET-CT after neoadjuvant therapy in the detection of metastatic disease after chemoradiotherapy in patients with esophageal carcinoma.

## Methods

### *Patients*

All patients planned for curative esophagectomy who underwent a post-NT but preoperative PET-CT were included in this study. Preoperative staging consisted of endoscopy with biopsy, external ultrasonography of the neck and endoscopic ultrasonography (both including fine needle aspiration (FNA) on indication). Furthermore, PET-CT scanning was performed in all patients. Clinical staging was performed according to the 6<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC).<sup>2</sup> All patients were discussed during a multidisciplinary meeting. In case of tumor stage II-IVa patients were considered eligible to receive neoadjuvant therapy followed by esophagectomy.

### *Neoadjuvant therapy*

Chemoradiotherapy consisted of 50.4 Gy in 1.8 Gy fractions 3-D conformal radiotherapy combined with two cycles of cisplatin (100mg/m<sup>2</sup>) and 5-FU (4 days of continuous infusion of 1000mg/m<sup>2</sup>) in week 1 and 5. Surgical resection was scheduled 8-10 weeks after completion of neoadjuvant therapy.

### *PET-CT imaging*

Patients underwent PET-CT scanning (Siemens, 16 slice CT and a lutetium oxyorthosilicate (LSO) based PET detector) prior to and six weeks after completion of neoadjuvant chemoradiotherapy. Patients were instructed to fast for at least 4-6 hours prior to the injection of FDG and blood glucose levels were measured. After a resting period of at least 45 minutes post injection the imaging starts from the top of the head to the middle of the thigh. The PET detector collects emission data in a 3D mode. Emission scans lasted 3-5 minutes per bed depending on the body weight. Scans were corrected for decay, scatter and randoms and reconstructed using ordered subset expected maximization (OSEM) with 4 iterations and 16 subsets and followed by a 5mm full width at half maximum (FWHM) Gaussian reconstruction filter. Transmission scans consisted of a diagnostic quality iodine contrast-enhanced CT (120 Kev, 140Ma, pitch 1.25, 5mm reconstructed slices to match PET section thickness, supine position) of the whole scanning range. All studies were interpreted by both an experienced nuclear physician and a radiologist. A consensus report was made.

The first PET-CT took place as part of the preoperative work-up; the second PET-CT was evaluated as a possible indicator of response to NT, and for the presence of metastatic disease that could have progressed to a detectable stage during NT.

In case of histologically proven or otherwise obvious metastatic disease as detected on the post-NT PET-CT patients were excluded from surgical resection.

## Results

Between November 2008 and July 2010 a total of 50 patients who were planned for an esophageal resection underwent neoadjuvant chemoradiotherapy followed by a post NT PET-CT. Patient characteristics are listed in Table 1.

All patients were evaluated as having no distant metastases on their first PET-CT. All patients underwent a second PET-CT after completion of neoadjuvant treatment and were still considered fit for esophagectomy at the time of their restaging PET-CT. The median interval between completion of chemoradiotherapy and the second PET-CT was 6 weeks (range: 2 - 10.5 weeks). In 5/50 patients (10%) the second PET-CT was suspect for metastatic disease that became manifest during chemoradiotherapy. One of these five patients had a pulmonary lesion suspect for pneumonia, however pulmonary metastases could not be excluded. This patient was treated with antibiotics after which a complementary CT showed the pulmonary lesion had disappeared and this patient underwent a surgical resection. The second patient had developed a suspect lesion at the iliac crest bone. In the third patient, a suspect lesion of the right scapula was present on PET-CT after neoadjuvant therapy. Both patients underwent biopsy of the suspect lesion, which proved to be metastases of the primary tumor. The fourth patient had several lesions on the second PET-CT that were suspect for skeletal and liver metastases, which could also be seen on the CT-images alone. In this patient, no biopsy was performed since the presence of disseminated metastases was considered to be obvious. Finally, a lesion in the upper lobe of the right lung was seen in the fifth patient. Wedge resection was performed by video assisted thoracic surgery (VATS) and it proved to be malignant on histopathological examination. The pulmonary lesion in this patient could also be seen on the CT-images alone.

The median interval between baseline staging and detection of metastases that had developed during chemoradiotherapy was 155 days [IQR: 90-160].

Patients who were excluded from surgical resection based on metastatic disease on post NT PET-CT are described in Table 2. The PET-CT's of these patients are shown in Figure 1.

Forty-six patients underwent a transhiatal or transthoracic esophageal resection however in one patient, a peritonitis carcinomatosa was peroperatively identified.

## Discussion

This study shows that of all neoadjuvantly treated patients with esophageal carcinoma planned for esophagectomy, 8% presented with metastatic disease on PET-CT after preoperative chemoradiotherapy. In 2 of these 4 patients, metastatic disease was also visible on CT alone.

Accurate patient selection is essential since metastatic disease implicates curative treatment is no longer possible.<sup>10</sup> Initial staging includes a thorough search for metastatic disease however when patients are treated with neoadjuvant therapy with an extended interval until resection, routine restaging is currently not the standard of care.

Several other studies have described post neoadjuvant therapy metastases with an incidence of 8-17%.<sup>9,11-13</sup> The primary outcome in four of these studies was response to neoadjuvant therapy and the diagnosis of interval metastases was an accidental finding. Detailed description of the cases is lacking and the studies are small.<sup>11-13</sup> Only one study determines the utility of PET-CT for detecting interval metastases as primary outcome.<sup>9</sup> This of Bruzzi et al study retrospectively reviewed PET-CT scans of 85 patients who underwent neoadjuvant chemoradiotherapy and detected interval metastases in 7 patients (8%). All seven patients presented with adenocarcinoma of the esophagus stage IIB or III. Our study shows a corresponding incidence of metastatic disease in 8% of patients after neoadjuvant chemoradiotherapy. All patients were diagnosed with adenocarcinoma of the distal esophagus and in all patients the nodal status was N1 prior to chemoradiotherapy. Considering the corresponding findings between the study of Bruzzi et al and our results the development of metastatic disease could be associated with the initial nodal status. If TNM-stage is identified as a risk factor for the development of interval metastases, post NT PET-CT could be applied only in patients with TNM-stages associated with a high risk of developing interval metastases.

In half of the patients with metastatic disease after completion of chemoradiotherapy (4%), metastases could have been diagnosed with CT alone. However, it is not possible to predict the location of possible metastases in advance. The skeletal metastases in this study were not visible on CT alone, therefore PET should always be a part of post NT restaging.

A disadvantage of performing a second PET-CT after completion of chemoradiotherapy is the possibility of a false-positive result, requiring further diagnostic evaluation. The false-positive rate in this study was only 2% indicating a small number of patients would undergo further evaluation without consequences. Furthermore, redundant complementary diagnostic investigations do not outweigh the prevention of a palliative resection.

In conclusion, this study shows that metastatic disease is present on post neoadjuvant therapy PET-CT in 8% of patients with esophageal carcinoma. A PET-CT after completion of neoadjuvant therapy should be performed routinely prior to esophagectomy to prevent palliative resections.

ACCEPTED MANUSCRIPT

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**Table 1 Patient characteristics of 50 patients planned for neoadjuvant therapy followed by esophagectomy**

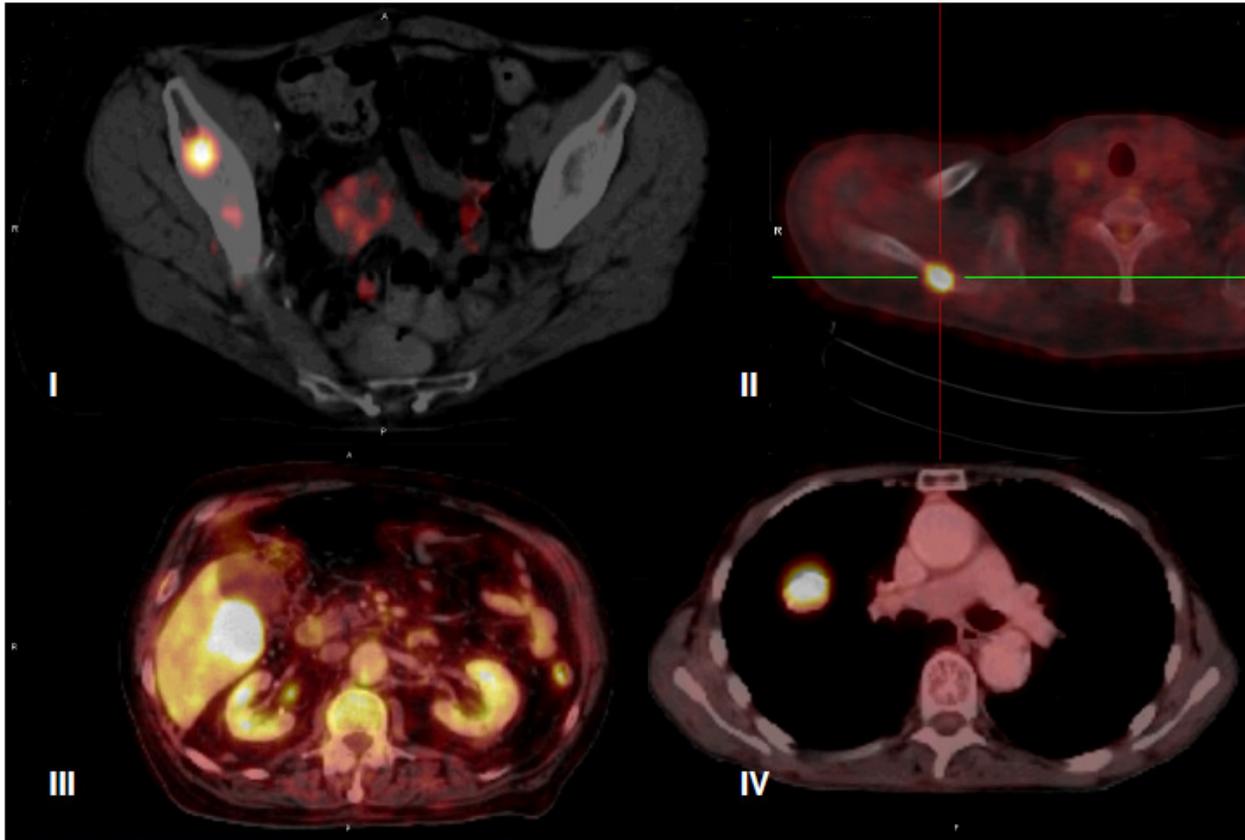
|                                | <b>n (%)</b> |
|--------------------------------|--------------|
| <b>Male</b>                    | 40 (80)      |
| <b>Age median [IQR]</b>        | 61 [56-67]   |
| <b>Tumor location</b>          |              |
| <b>Middle esophagus</b>        | 10 (20)      |
| <b>Distal esophagus</b>        | 28 (56)      |
| <b>GEJ/cardia</b>              | 12 (24)      |
| <b>Histology</b>               |              |
| <b>Adenocarcinoma</b>          | 40 (80)      |
| <b>Squamous cell carcinoma</b> | 9 (18)       |
| <b>Other</b>                   | 1 (2)        |
| <b>Stage</b>                   |              |
| <b>II</b>                      | 21 (42)      |
| <b>III</b>                     | 23 (46)      |
| <b>IVa</b>                     | 6 (12)       |

IQR interquartile range; GEJ gastroesophageal junction

**Table 2 Patients excluded from surgical resection based on M1 on post NT PET-CT**

|                                 | I                | II                 | III              | IV               |
|---------------------------------|------------------|--------------------|------------------|------------------|
| <b>Gender</b>                   | female           | male               | male             | female           |
| <b>Age (years)</b>              | 61               | 57                 | 68               | 59               |
| <b>Initial TNM-stage</b>        | T2N1M0           | T1N1M0             | T3N1M0           | T3N1M0           |
| <b>Histology</b>                | AC               | AC                 | AC               | AC               |
| <b>Tumor location</b>           | distal esophagus | distal esophagus   | distal esophagus | distal esophagus |
| <b>Clinical response to CRT</b> | -                | unknown            | +                | +                |
| <b>SUV on post NT PET-CT</b>    | decrease         | decrease           | decrease         | equal            |
| <b>Location of metastasis</b>   | iliac crest bone | scapula            | liver/skeletal   | pulmonary        |
| <b>Biopsy</b>                   | CT-guided        | Gamme-probe-guided | not performed    | VATS             |

TNM tumor node metastasis; CRT chemoradiotherapy; AC adenocarcinoma; - no response; + response; SUV standard uptake value; CT computed tomography; VATS video assisted thoracic surgery

**Figure 1 Metastases on post-NT PET-CT in four patients**

Location of metastasis after neoadjuvant therapy in four patients: I iliac crest bone; II scapula; III liver; IV lung