Editorial

PET-guided treatment algorithms in oesophageal cancer: the promise of the near future!

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Although the implementation of neoadjuvant multimodality strategies resulted in pathologic downstaging, improvement of resection rates and a decrease in recurrent disease, 5-year survival rates of oesophageal carcinoma are still below 50% (1). The most common reason for treatment failure is the development of distant metastases, also after trimodality therapy, consisting of chemoradiotherapy followed by oesophagectomy. This means that the patient must have been harboured micrometastases during the neoadjuvant chemoradiotherapy already. In order to destroy these micrometastases, additional induction chemotherapy before trimodality therapy has been investigated all over the world. It is not completely clear whether the addition of induction therapy results in a survival benefit (2-5). Nevertheless, two potential benefits have been reported: an increase of the nutritional status of patients due to less problems of dysphagia and an upfront identification of patients with a poor response for which neoadjuvant chemoradiotherapy might by unbeneficial and even harmful. To identify these poor responding patients an imaging technique which accurately differentiates responders from non-responders is needed. The study of van Rossum *et al.*, recently published in the European Journal of Nuclear Medicine and Molecular Imaging (6), investigated whether ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography and computed tomography (PET/CT) has the potential to reliably measure response to induction chemotherapy and to upfront predict pathologic response before start of neoadjuvant chemoradiotherapy. In this study, 70 patients with an oesophageal adenocarcinoma out of a prospectively acquired database of 132 patients were eligible for analysis. Thirty-nine percent of patients showed a poor pathologic response, compared to a good pathologic response in 61% of patients. More aggressive tumour characteristics, such as higher T-stage, signet ring cell adenocarcinoma and poor differentiation grade and also comorbidities, such as cardiac disease, diabetes mellitus, chronic obstructive pulmonary disease and smoking at diagnosis, were observed more frequently in the poor response group. The relative change in tumour FDG-uptake after induction chemotherapy as compared to the baseline value, expressed in total lesion glycolysis (ΔTLG, which is the multiplication of SUV_{mean} and the metabolic tumour volume), was significantly correlated to pathologic response ($P<0.01$), with a high discriminatory ability (AOC 0.74). The most optimal cut-off value of ΔTLG to discriminate between responders and non-responders was –26%. In 25 patients, a ΔTLG was measured above this value and in 45 patients below this

value, which corresponded with a poor pathologic response of 72% *vs*. 20% in the group with a poor *vs*. a good metabolic response. Progression-free survival was significantly better for the metabolic responders as compared to the metabolic non-responders (P=0.02), however, no overall survival benefit could be detected (P=0.18). This threshold resulted in a sensitivity of 67%, a specificity of 84%, an accuracy of 77%, a PPV of 72% and a NPV of 80% to predict a poor pathologic response. Due to the use of FDG-PET the baseline overall prevalence of good pathologic response increased from 61% to 80% in the group with metabolic response and overall prevalence of poor pathologic response increased from 39% to 72% in the group with poor metabolic response. This increase enables the treating physician to upfront decide, on the one hand, to omit preoperative chemoradiotherapy and to prevent the patient from a toxic, ineffective treatment and, on the other hand, to encourage the patient with a good metabolic response to proceed with the intensive trimodality treatment. FDG-PET, however, can only aid in the decision for neoadjuvant treatment intensification or modification, since it apparently is only an indicator for tumour biology and a predictor of treatment failure, and not a predictor of overall survival in this stage of the disease. Due to conflicting results of the efficacy of the three-step treatment strategy in phase I–II studies (2-5), this treatment approach has not yet been investigated in a phase III trial. The efficacy of treatment approaches can be underestimated if applied in unselected patient populations. In our opinion, many potentially effective treatments for specific patient groups never reached the final implementation phase. This is due to the fact that no upfront selection took place to provide the treatment to the right patient who might really benefit from it and not to the patient who might not. Therefore, nowadays, in the era of personalized medicine, it is of utmost importance, to find (imaging) biomarkers that are able to select the right patient for the right treatment. In the study of van Rossum *et al.* (6) this imaging biomarker was FDG-PET, which significantly increased the predictive value of response to trimodality treatment. It provided much-needed knowledge to help to make relevant individualized treatment decisions in the near future. The study of van Rossum *et al.* (6) confirmed the results of previous studies which studied smaller patient cohorts (7-9), and also found a significant correlation between metabolic response and histopathologic response (7-11). The current study showed a higher predictive value, probably due to the use of a newer generation PET-scanner, with higher sensitivity and intrinsic resolution as compared to previous studies (7-9). In our opinion, the time is ripe to perform a prospective study, using PET-CT to tailor treatment according to the responsiveness on induction chemotherapy and to evaluate whether these image-based decisions result in a survival benefit. Several other prospective trials, evaluating the benefit of image guided treatment decisions have been performed. The first studies that realized this concept were the MUNICON (Metabolic response evalUatioN for Individualization of neoadjuvant Chemotherapy in oesOphageal and oesophagogastric adeNocarcinoma) -1 and -2 trials (12,13). These trials prospectively confirmed that FDG-PET is able to identify responders to induction chemotherapy already after two weeks of treatment. Both trials showed that the continuation of neoadjuvant chemotherapy in metabolic responders resulted in a favourable outcome. The MUNICON-1 trial demonstrated that outcome was not affected when a metabolic non-responder discontinued preoperative chemotherapy in order to switch immediately to surgery as compared to continuation of preoperative chemotherapy (12). Such an image-guided treatment concept saves time and reduces unnecessary side effects and costs. MUNICON-2, however, showed that the poor prognosis of metabolic non-responders could not be improved by addition of neoadjuvant radiation therapy, which indicates the dismal tumour biology of these tumours (13). A third trial which used a personalized response-adapted treatment concept is the Cancer and Leukemia Group B trial 80803 (14). This trial is based on findings of a retrospective study in 38 patients, which demonstrated that median progression-free survival increased when PET non-responders changed chemotherapy regimen during radiation as compared to continuation of the same chemotherapy regimen as used during induction chemotherapy (15) (*Figure 1*). In the 80803 trial, FDG-PET based decisions were also made on the choice of chemotherapy regimen used for preoperative chemotherapy. Participants randomly assigned to treatment group A were treated with FOLFOX6 (5FU and oxaliplatin) chemotherapy. Patients in group B were treated with carboplatin and paclitaxel. After completing 6 weeks of the assigned chemotherapy, participants underwent PET/CT. Metabolic responders remained on their assigned treatment. Non-responders switched to the other treatment during their radiation therapy treatment. This trial is recently

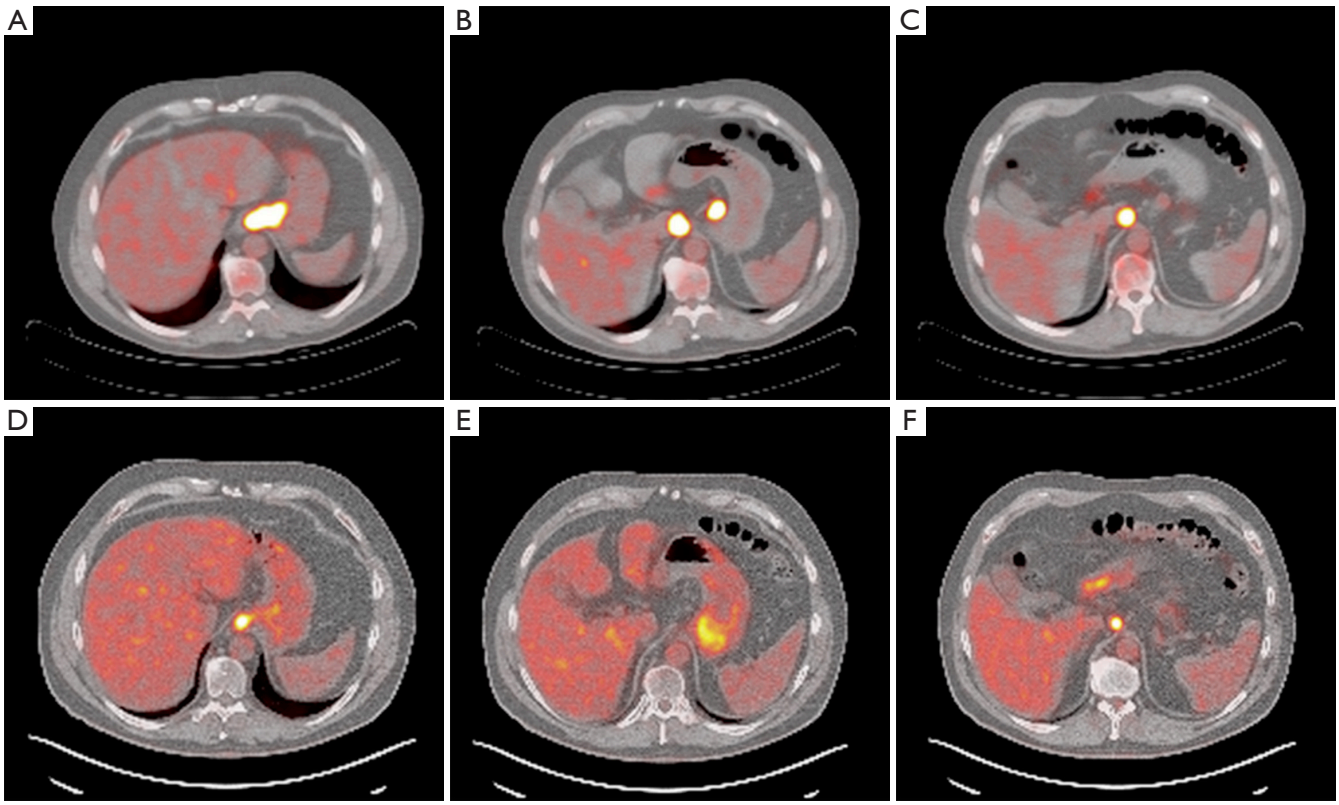

Figure 1 Example of ^{18}FDG-PET/CT based response monitoring. This figure shows the ^{18}FDG-PET/CT scans of a 51-year-old man with a cT2/3N1 moderately differentiated intestinal type Her2Neu negative adenocarcinoma of the distal oesophagus which was treated with induction chemotherapy consisting of capecitabine and oxaliplatin. The first FDG-PET/CT (A–C) was performed after induction chemotherapy and the second scan (D–F) was performed after chemoradiotherapy with carboplatin and paclitaxel. The pre-chemoradiation PET/CT showed a strong FDG-avid primary tumour on the gastroesophageal junction (A) and two FDG-avid lymph nodes in the gastrohepatic ligament of 19 and 12 mm in diameter (B,C). The second PET/CT was performed preoperatively, one month after completion of chemoradiotherapy. This scan showed partial metabolic response. Tumour metabolic activity at the gastroesophageal junction decreased considerably (D), the metabolically active lymph node in the small gastric curvature disappeared (E) and the right precrural lymph node decreased in size (from 19 to 14 mm) as well as in metabolic activity. Subsequently, a transhiatal oesophagectomy with gastric pull-up was performed. The post-resection specimen of the gastroesophageal junction showed a residual tumour with a diameter of 2.2 cm reaching the muscularis propria, without lymphangio invasion and perineural growth and with tumour free resection margins. Two lymph nodes out of 18 showed tumour localisation. Currently, 2 months after surgery, the patient is in good condition without evidence of disease recurrence. It is however known, that patients with FDG-avid lymph nodes after neoadjuvant treatment have a poor prognosis [hazard ratio for recurrence 2.11 (P=0.02) for FDG avid lymph nodes] (16). FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

closed and results are currently awaited. Hopefully, the results of this trial confirm the feasibility of a PET-guided treatment algorithm. Such algorithms are the promise of the near future. By using such image-based treatment algorithms, the choice of therapy, its intensity, and its duration might become better adjusted to the individual patient's tumour biology.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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