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EDITORIAL COMMENTARY

Predicting tumour response to chemoradiotherapy in oesophageal cancer by early interim ^{18}F-FDG PET: where do we stand and where should we go?

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Oesophageal cancer is a disease with a dismal prognosis and high mortality. There were an estimated 482,000 new cases and 407,000 patients died of the disease worldwide in 2008 [1]. Concurrent chemotherapy and radiotherapy is now considered the neoadjuvant treatment of choice in patients with operable oesophageal cancer, as has been demonstrated by the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial [2]. However, not all patients benefit from this treatment. In the CROSS trial, as much as 39 % of patients had no histopathological tumour regression (tumour regression defined as <10 % viable tumour cells in the resected specimen). Yet, toxicity due to chemotherapy occurs in 11–90 % and there is also a risk of radiation-induced complications [2, 3]. In patients who respond insufficiently, inefficient chemoradiotherapy should be discontinued, and surgery should not be delayed. On the other hand, patients who respond favourably may benefit from additional preoperative treatment and surgery may be delayed or even refrained from. Therefore, there is a need for a method which can differentiate responders from non-responders early in the course of neoadjuvant treatment. In clinical practice, integrated ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) already has a well-established role in the diagnosis and staging of oesophageal cancer [4]. The change in ^{18}F-FDG uptake at PET performed before and after the start of neoadjuvant therapy may be used to predict which tumours respond to treatment.

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To date, there are only a few published prospective studies investigating the value of ^{18}F-FDG PET in early prediction of tumour response to neoadjuvant therapy in oesophageal cancer. Two subsequent studies in independent study populations by researchers from Munich demonstrated that early metabolic tumour response, as measured by ^{18}F-FDG PET, is correlated to histopathological response and better overall survival (OS) [5, 6]. However, these studies [5, 6] were performed in patients who only received neoadjuvant chemotherapy, whereas concurrent chemoradiotherapy is now considered the standard neoadjuvant treatment [2]. Increased ^{18}F-FDG uptake caused by radiation-induced inflammation may limit the use of ^{18}F-FDG PET, because ^{18}F-FDG PET is unable to distinguish whether tracer uptake is associated with inflammatory cells or residual viable tumour cells [7, 8]. To our knowledge, there are only three published prospective studies [7–9] in which the predictive value of early interim ^{18}F-FDG PET in patients who received concurrent neoadjuvant chemoradiotherapy has been investigated. These studies all demonstrated an association between a decrease in tumour standardized uptake value (SUV) 14 days after start of neoadjuvant treatment and histopathological tumour response [7–9]. The study by Wieder et al. [7], in 38 patients with squamous cell carcinoma, also found an association between metabolic tumour response and OS. In contrast, the study by Malik et al. [8], in 37 patients with adenocarcinoma, did not find a significant association.

The study by Cuenca et al. [10] in the present issue of the *European Journal of Nuclear Medicine and Molecular Imaging* adds further evidence that early interim ^{18}F-FDG PET may be used to predict tumour response to chemoradiotherapy. Cuenca et al. [10] retrospectively analysed 59 patients with locally advanced oesophageal cancer (T3/T4, N1 M1a) who underwent an integrated ^{18}F-FDG PET/CT scan before and 5 weeks after the beginning of chemotherapy

(2 weeks after the beginning of radiotherapy at 20 Gy). After 40 Gy and three cycles of 5-fluorouracil (FU)/cisplatin, patients' eligibility for surgery was discussed in a multidisciplinary team meeting, taking into account medical status and favourable tumour response, as shown by CT and oesophagogastroscopy. A relatively small group of 19 patients subsequently underwent surgical resection of the tumour. The authors describe a significant correlation between OS and reduction of tumour SUV (2-year OS of 62 % for responders vs 27 % for non-responders, at a cut-off level of ≥50 % SUV regression for metabolic tumour response). Cuenca et al. [10] also demonstrate that this finding remained significant for patients who were exclusively treated with chemoradiotherapy (n=40). For patients who underwent subsequent surgery, there also was a difference in OS, but it did not reach statistical significance. This may be related to the small number of operated patients, which is one of the limitations of the study. Furthermore, considering the high and increasing incidence of adenocarcinoma in the Western world, the inclusion of mainly patients with squamous cell carcinoma (n=41) could have influenced the results. As shown by the authors [10], the metabolic response was higher in adenocarcinoma than in squamous cell carcinoma and they also found a different optimal cut-off value of SUV regression for the definition of metabolic response. Another study limitation is the inclusion of mainly patients with highly locally advanced tumours, which limits the generalizability of the results to patients with less advanced TN stages.

What is next? Can we use early interim ^{18}F-FDG PET to guide decisions on (dis)continuing or prolonging chemoradiotherapy and subsequent surgery in clinical practice? Much research work still needs to be done. The studies published so far were all single-centre studies with relatively small sample sizes, comprising patients with squamous cell and adenocarcinoma, and there were differences in the chemoradiotherapy regimen [7–9]. In addition, PET acquisition methods and ways of image analysis were not uniform. Future studies may follow existing recommendations [11, 12] to standardize the method for evaluation of metabolic tumour response. Last, it has not been investigated yet at which time point during chemoradiotherapy interim ^{18}F-FDG PET should be performed and there is no consensus yet on the optimum threshold to differentiate responders from non-responders. A well-designed multicentre trial and standardization from international centres by way of collaboration are required to explore potential causes of heterogeneity and to definitively establish its value. If the predictive value will turn out to be sufficiently high, randomized trials are warranted to determine whether treatment decisions based on early assessment of metabolic tumour response by ^{18}F-FDG PET can improve outcome for patients with oesophageal cancer.

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