Editorial

Challenges in assessing response of oesophageal cancer to neoadjuvant therapy, and the potential of composite PET-CT and multimodal metrics

John M. Findlay[1,2], Kevin M. Bradley[3], Richard S. Gillies[1], Nicholas D. Maynard[1], Mark R. Middleton[4]

[1]Oxford OesophagoGastric Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [2]NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, UK; [3]Department of Radiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [4]Department of Oncology, University of Oxford, Oxford, UK

Correspondence to: Mr. John M. Findlay. Oxford OesophagoGastric Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. Email: john.findlay@oncology.ox.ac.uk.

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We read with interest Dr. Włodarczyk and Professor Kużdżał's appraisal of the potential for composite positron emission tomography-computed tomography (PET-CT) metrics to improve the assessment of oesophageal cancer to neoadjuvant therapy, in particular that of a new metric we recently described: metabolic nodal response (mNR) (1,2).

Our colleagues highlight the goal of precision oncology for oesophageal cancer: tailoring therapies to patients. At present, whilst neoadjuvant therapy improves survival for patients overall (3), this is not necessarily true for patients individually. Unfortunately, those with relatively chemo- and radio-resistant tumours may actually come to harm, as ultimately futile therapy merely delays surgery and risks toxicity. However, in the absence of markers to identify these patients we are forced to continue with well-intentioned but largely imprecise oncology.

The reasons precision oncology has largely failed to translate *in vitro* reports to *in vivo* success (other than relatively isolated therapies targeted to individual gene mutations and copy numbers) are numerous (4). These include highly complex molecular interactions in individual cancer cells (genetic, epigenetic, transcriptomic, proteomic), compounded by cellular interactions, tumour microenvironment, clonal heterogeneity, and tumour evolution during therapy (5). As a consequence, the effect sizes of these markers tend to be limited, and certainly an insufficient basis on which to decide whether to give or omit specific therapies (6).

We are therefore forced to rely on surrogates of response, such as metabolic response using serial ^{18}F-FDG PET-CT. As our colleagues discuss, Lordick *et al.* notably described interval assessment of oesophageal cancer during neoadjuvant chemotherapy, aborting or continuing therapy on the basis of whether the primary tumour demonstrated a metabolic response on PET-CT, as evidenced by a reduction in avidity alone (7). This approach has yet to be adopted for a number of reasons, including concerns regarding the inherent limitations of PET-CT to accurately reflect the viability and metastatic potential of tumour cells, as well as the pragmatic but somewhat arbitrary dichotomisation of response (which in reality occupies a spectrum). In the paper our colleagues discuss, we assessed the relative performance of a number of additional PET-CT metrics in a cohort of patients with oesophageal cancer receiving neoadjuvant chemotherapy. We found that whilst composite spatial-avidity metrics of metabolic tumour response (mTR; such as metabolic or tumour glycolytic volume) appeared to have greater predictive accuracy than avidity alone, this was by no means a perfect surrogate for pathological tumour response (pTR). We noted that the primary tumour and nodal tumour often responded differently, and subsequently found mNR (but not mTR) to be an independent predictor of prognosis, once pTR

was considered (1). This makes sense, as logically response of the primary tumour to neoadjuvant therapy is relevant primarily in terms of facilitating a clear (R0) resection, and secondarily as a surrogate of therapy sensitivity of any occult metastases. However, the primary tumour overall may be very different to the metastatic clones responsible for these metastases, in contrast to nodal tumour. We therefore believe that mNR provides valuable surrogate information regarding the phenotype of these metastatic clones, which crucially are responsible for the vast majority of post-operative recurrences.

However, beyond the limitations in our study discussed by our colleagues, we acknowledge mNR to suffer the same failings as mTR: unphysiological thresholding of responses, and not infrequent disagreement between metabolic and pathological response. Further complicating issues are the subjectivity inherent in pTR assessment (8), and whether a homogenous microscopic assessment truly reflects the different phenotypes within a cancer. Indeed, we previously reported a novel concept of genetic response of oesophageal adenocarcinoma to neoadjuvant chemotherapy (as evidenced by next generation sequencing). This was generally concordant with pathological response, but with some notable exceptions suggesting some tumours exhibit a profound response, followed by rapid overgrowth by a marginal clone which was not captured using traditional radiological or pathological response assessment (5).

Ultimately, assessment of these many facets of response in parallel may allow us to quantify response better during therapy (e.g., serial biopsy with molecular assessment of the primary tumour and circulating DNA, along with cross-sectional and functional response using PET-CT). However, until we have the ability to do so, as our colleagues suggest both composite avidity-spatial PET-CT metrics of the primary tumour plus mNR may better be able to direct therapy for patients in clinical trials.

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Footnote

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