

Challenges in assessing the response of oesophageal cancer to neoadjuvant therapy, and the role of composite and multimodal metrics

Running title: Challenges in assessing the response of oesophageal cancer to neoadjuvant therapy

John M Findlay<sup>1</sup>, Kevin M Bradley<sup>3</sup>, Richard S Gillies<sup>1</sup>, Nicholas D Maynard<sup>1</sup>, Mark R Middleton<sup>4</sup>

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

Corresponding author:

Mr John M Findlay

Oxford OesophagoGastric Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[john.findlay@oncology.ox.ac.uk](mailto:john.findlay@oncology.ox.ac.uk)

Keywords: oesophageal cancer; positron emission tomography; neoadjuvant chemotherapy; neoadjuvant chemoradiotherapy; response assessment

Conflict of interests: authors declare no conflict of interest

We read with interest Dr Włodarczyk and Professor Kuźdżał'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].

We are therefore forced to rely on surrogates of response, such as metabolic response using serial  $^{18}\text{F}$ -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[6]. 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[2]. This makes sense, as logically response of the primary tumour to neoadjuvant therapy is relevant only in terms of facilitating a clear R0 resection, and as a surrogate of therapy sensitivities of any occult metastases, which are responsible for the vast majority of post-operative recurrences.

We therefore believe that mNR provides valuable extra (surrogate) information regarding the phenotype of metastatic clones. 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[7], 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 of marginal clone which is not captured using traditional radiological or pathological response assessment[5].

Ultimately, assessment of these many facets of response in parallel may allow us to better quantify response 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.

## References

1. Findlay JM, Bradley, K.M, Wang, L., Franklin, J.M., Teoh, E.J., Gleeson, F.V., Maynard, N.D., Gillies, R.S., Middleton, M.R. Predicting pathological response of esophageal cancer to neoadjuvant chemotherapy-the implications of metabolic nodal response for personalised therapy. *Journal of Nuclear Medicine* 2016; In press.
2. Findlay JM, Bradley KM, Wang LM et al. Metabolic nodal response as a prognostic marker after neoadjuvant therapy for oesophageal cancer. *Br J Surg* 2017; 104: 947.
3. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011; 12: 681-692.
4. Morgan G, Aftimos P, Awada A. Current-day precision oncology: from cancer prevention, screening, drug development, and treatment - have we fallen short of the promise? *Curr Opin Oncol* 2016; 28: 441-446.
5. Findlay JM, Castro-Giner F, Makino S et al. Differential clonal evolution in oesophageal cancers in response to neo-adjuvant chemotherapy. *Nat Commun* 2016; 7: 11111.
6. Lordick F, Ott K, Krause BJ et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007; 8: 797-805.
7. MacGregor TP, Maughan TS, Sharma RA. Pathological grading of regression following neoadjuvant chemoradiation therapy: the clinical need is now. *J Clin Pathol* 2012; 65: 867-871.