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LETTER TO THE EDITOR

Oesophageal cancer staging: a minefield of measurements—author's reply

^{1,2}FRANCESCO GIGANTI, MD, ²ALESSANDRO AMBROSI, PhD, ^{1,2}ANTONIO ESPOSITO, MD,
^{1,2}ALESSANDRO DEL MASCHIO, MD and ^{1,2}FRANCESCO DE COBELLI, MD

¹Department of Radiology and Centre for Experimental Imaging, San Raffaele Scientific Institute, Milan, Italy

²Vita-Salute San Raffaele University, Milan, Italy

Address correspondence to: Dr Francesco Giganti

E-mail: Giganti.fra@gmail.com

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

To the Editor,

We appreciate the letter to the Editor from Borakati, which was written in response to our work “Prospective comparison of MR with diffusion-weighted imaging, Endoscopic Ultrasound, MDCT and Positron Emission Tomography-CT in the preoperative staging of oesophageal cancer: results from a pilot study”.¹

Evidence begins to accumulate regarding the importance of consistent methods in the extrapolation of imaging biomarkers in oncology.²

Therefore, we welcome the comments, and we can provide some additional data in response, as we believe that this will represent an important step forward in the field.

As underpinned by Borakati, it is more difficult to detect superficial tumours than those at a higher stage.

We can provide an additional analysis from the same population ($n = 18$)¹ of the three different techniques for patients grouped as T1–T2 and N0, according to final histology (Table 1).

Endoscopic ultrasound (EUS) has the highest sensitivity (100%), confirming its role in the detection of patients with more aggressive disease (*i.e.* T1–T2 and N+, or at higher stages). Interestingly, the highest negative-predictive value of EUS (100%) shows that this technique has a fundamental role in the prediction of superficial tumours without nodal involvement (T1–T2 and N0).

In terms of specificity, none of the three techniques demonstrate satisfactory results. However, MR shows the highest value (58%), suggesting its potential role in the

detection of superficial tumours without nodal involvement (T1–T2 and N0). MR also has a high negative-predictive value (87%), suggesting its potential added value in the prediction of superficial tumours without nodal involvement (T1–T2 and N0). MR also shows the highest accuracy (67%) and could be seen as a good compromise between all techniques.

However, as already stated in our main article,¹ this is a pilot study and larger studies will need to be carried out before introducing this technique in the standard diagnostic pathway of oesophageal cancer.

As far as molecular imaging is concerned, these are the results from the same population ($n = 18$)¹ using final histology as the reference standard.

For the T1–T2 and N0 subgroup ($n = 12$), the mean apparent diffusion coefficient (ADC) value is $1.76 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ (± 0.51).

For patients with more aggressive disease ($n = 6$), the mean ADC is $1.29 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ (± 0.32).

Interestingly, the difference between these values is close to conventional levels of statistical significance ($p = 0.057$).

For the T1–T2 and N0 subgroup ($n = 12$), the standardized uptake volume (SUV) is 10.50 g cm^{-3} (± 5.80).

For patients with more aggressive disease ($n = 6$), the mean SUV is 13.74 g cm^{-3} (± 5.03).

The difference between these values is not significant ($p = 0.274$).

We concur that a different number of readers is a significant bias that may increase the performance of MR and

Table 1. Performance characteristics of MR, multidetector CT (MDCT) and endoscopic ultrasonography (EUS) in the T1-T2 and NO population, using final histology as the reference standard ($n = 18$)

Pre-operative staging	MR	MDCT	EUS	MR vs MDCT	MR vs EUS	MDCT vs EUS
				<i>p</i> -value	<i>p</i> -value	<i>p</i> -value
Sensitivity	83	83	100	1	0.50	1
Specificity	58	42	25	0.50	0.250	1
Accuracy	67	56	50	1	1	1
PPV	50	42	40	0.367	0.253	0.825
NPV	87	83	100	0.817	0.299	0.292

NPV, negative-predictive value; PPV, positive-predictive value.
Data are percentages and *p*-values are in bold.

multidetector CT (MDCT) when compared with positron emission tomography-CT and EUS.

As already mentioned, this is a limitation of our work and further studies should address this issue.

As far as our pilot study is concerned,¹ two MDCT scans (one in the surgery-only group and one in the chemotherapy/radiotherapy group) and one diffusion-weighted (DW)-MRI scan (in the chemotherapy/radiotherapy group) required the opinion of a third radiologist.

We do agree with Borakati that assessing length and volume is crucial when it comes to tumour delineation for radiotherapy planning.

We previously reported the role of ADC and tumour volume on DW-MRI in the response to neoadjuvant therapy in gastro-oesophageal cancer.³ From the same population that has already been reported,³ we could retrieve data regarding pre- and post-treatment volume on DW-MRI (calculated by planimetry,

i.e. slice by slice) for six patients in the chemotherapy/radiotherapy group.

The mean pre- and post-treatment volumes are 43.18 cm^3 (± 42.85) and 12.67 cm^3 (± 8.55), respectively. They are significantly different ($p = 0.008$).

The mean volume reduction from pre- to post-treatment DW-MRI is 62%.

According to final histology, these patients were classified as T2 ($n = 3$), T3 ($n = 2$) and T4 ($n = 1$).

We strongly encourage further studies including length and volume measurements (*e.g.* by planimetry, using a dedicated software) from different imaging techniques. We also recognize the importance of comparing these parameters with imaging biomarkers such as ADC or SUV.

Different staging modalities have investigated the survival rate of oesophageal cancer.⁴⁻⁷ Owing to the rapid increase in the

Figure 1. Kaplan-Meier curves showing the overall survival rates in the total population ($n = 18$) according to the optimal apparent diffusion coefficient (ADC) cut-off of $1.37 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. Survival time for patients with an ADC value below or equal to this value (*dashed line*) is significantly lower than that of patients above this cut-off (*continuous line*) ($p = 0.002$; median survival: 24 and >49 months, respectively).

application of DW-MRI for the detection and characterization of this tumour, the question of whether imaging parameters from DW-MRI can provide additional information is of utmost importance.

DW-MRI in oesophageal cancer may have an important role in the management of this disease.^{8,9}

We previously reported the role of baseline ADC as a prognostic biomarker for oesophageal cancer.¹⁰

Thus, we were able to retrieve data regarding the survival rate—from the same population that has already been¹⁰ reported—for all the 18 patients included in the present study.¹

Data are updated to December 2013.

Interestingly, we note that an ADC cut-off below or equal to $1.37 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ indicates a negative prognosis (Figure 1). Specifically, survival time for patients with an ADC below or equal to this value is significantly lower than that of patients above this cut-off ($p = 0.002$; median survival for the two subgroups: 24 and >49 months, respectively).

This current finding confirms the potential role of ADC in the risk stratification of oesophageal cancer.

For the sake of completeness, we report that pre-operative T and N staging by MDCT and MR are not significantly

related to the survival rate in the population of our pilot study.¹

Specifically, when the population is divided based on the local invasion (T1–T2 vs T3–T4) and nodal involvement (N0 vs N+) at final histology, we note the following results: T stage ($p = 0.173$) and N stage ($p = 0.871$) for MDCT and T stage ($p = 0.478$) and N stage ($p = 0.426$) for MR.

As we mentioned in our article,¹ our pilot study has several limitations; but, we recognize that a comparison of different imaging techniques in the staging of oesophageal cancer has generated much interest in the scientific community.

It is our hope that many other groups will contribute to the process of publication of data on this topic and will provide useful information for a better understanding of this disease.

Therefore, we welcome discussion through editorials, conference papers and peer-reviewed articles as a way of widening participation in this challenging area of oncological imaging.

Specifically, we welcome this editorial as the beginning of a dialogue that could contribute to the process of delineation and refinement of the application of DW-MRI in the staging of oesophageal cancer.

Yours sincerely,
Francesco Giganti

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