Commentary

# Diagnostic performance of [18F] fluorodeoxyglucose PET/CT and diffusion-weighted magnetic resonance imaging for the evaluation of treatment response to induction chemotherapy followed by definitive chemoradiotherapy in locally advanced head and neck squamous cell carcinoma

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Recently, functional imaging such as fluorine-18 fludeoxyglucose integrated with computed tomography (18F-FDG-PET/CT) or diffusion-weighted magnetic resonance imaging (DW-MRI) represent an area of highly active research in oncology. DW-MRI is an advanced imaging modality that records the molecular diffusion of protons to further assess tissue carácter, providing the opportunity to differentiate post-treatment tumour recurrence from chemoradiotherapy-induced local tissue changes (1). In the case of PET/CT, besides providing useful diagnostic information regarding pretreatment staging (2,3) and post-treatment follow-up (4), intensity of FDG uptake is emerging as a valuable predictive factor regarding treatment outcome (5).

In this context, Wong *et al*. (6) have recently reported the results of a small prospective study (20 patients) with previously untreated locoregionally advanced (stage III–IVb) head and neck cancer squamous cell carcinoma (HNSCC) including the oropharynx (n=18) and hypopharynx/larynx (n=2). There were 12 (60%) human papillomavirus (HPV)-positive HNSCC.

The primary endpoint of the study was to analyze the predictive value of early assessment [after one cycle of induction chemotherapy (IC)] with 18F-FDG-PET/CT and DW-MRI for subsequent response to definitive chemoradiotherapy.

The IC regimen administered consisted of two cycles of 3 weekly TPF [docetaxel (75 mg/m$^2$) day 1/cisplatin (75 mg/m$^2$) day 1/5-fluorouracil (1,000 mg/m$^2$) days 1–4]. Three weeks after IC, patients proceeded to 6 weeks of definitive radiotherapy to a total dose of 65 Gy in 30 fractions (using intensity-modulated radiotherapy with a simultaneous integrated boost), with concomitant chemotherapy [cisplatin (100 mg/m$^2$) or carboplatin (AUC5) days 1 and 29].

Patients underwent 18F-FDG-PET/CT and DW-MRI at baseline (pretreatment) and 2 weeks following each cycle of IC. Again, response was assessed 3 months after finishing chemoradiotherapy with, MRI, 18F-FDG-PET/CT and clinical examination including nasendoscopy. Patients were definitively classified in two groups: responders and non-responders (with evidence of persistent disease at 3 months after the completion of chemoradiotherapy).

The changes in 18F-FDG-PET/CT and DW-MRI functional parameters from baseline were compared between the first and second IC cycles. Functional imaging

parameters such as metabolic tumor volume (MTV), total lesion glycolysis (TLG) or apparent diffusion coefficient (ADC) were analysed to see if they were useful early predictive biomarkers for ultimate response to subsequent chemoradiotherapy.

Regarding treatment outcomes, there were 15 responders and 5 non-responders. At the time of analysis, all responders remained alive and disease-free, whereas all non-responders had locoregional failure (four non-responders had died by the time of analysis).

Responders showed a significantly greater mean reduction in MTV and TLG after first IC cycle than non-responders. These authors also found a clear association between MTV or TLG response and HPV status.

In addition, a combination of pre-treatment TLG 40% <300 g and TLG 40% reduction >60% after first IC cycle gave an improved sensitivity and specificity of 93% and 80% in predicting complete remission compared to individual parameters.

There was no significant difference in the changes from baseline between first and second IC cycles for all PET parameters, indicating that most metabolic response or non-response to IC was evident soon after the first cycle, with no significant change following a subsequent cycle.

On the other hand, regarding DW-MRI data, the mean ADC following the first IC for primary tumor was higher in responders than non-responders but this result was not found statistically significant (P=0.089). Lymph nodes in responders also showed a greater, but not statistically significant increase in ADC after the first IC cycle than non-responding patients. Similarly, there was no significant difference in the magnitude of ADC changes between the first and second course of IC.

Interestingly, other commonly used clinical parameters such as T stage, N stage and tumor grade were not found statistically significant factors predicting response to chemoradiotherapy (6).

More importantly, there was a significant difference in the anatomical changes for both primary tumor and lymph nodes between the first and second course of IC (with remarkable additional change after the second cycle of IC). This fact further supports that biological changes after IC measured by functional imaging are usually evident before morphological changes (7) occur. Therefore, this confers a potential advantage over conventional imaging or clinical examination for early response assessment.

In order evaluate the results obtained by Wong *et al.* (6), in the context of the current management of locoregionally advanced HNSCC, it is also important to briefly review the following issues.

Prior to the turn of the century, surgery followed by postoperative radiotherapy or radiotherapy alone were common standard approaches for locally advanced HNSCC. Several trials of chemoradiotherapy compared to radiotherapy alone finally culminated in meta-analyses concluding that chemoradiation resulted in improved overall survival compared to radiotherapy alone (8). Moreover, a phase III trial showed improved overall survival for the use of radiotherapy and cetuximab compared to radiotherapy alone (9). Currently, chemoradiotherapy is supported by multiple trials, and therefore, it has become the primary mode of therapy for patients who are candidates for this therapy (10). In addition, despite contradictory evidence regarding its overall survival benefit, IC remains a standard-of-care in organ sparing approaches, especially in laryngeal cancer and appears to reduce distant failure rates in HNSCC (11-13).

Although patients with advanced disease are submitted to intensive treatment combinations (radical radiotherapy or surgery or both, with or without chemotherapy) locoregional failure occurs in almost 30–40% of cases (14), threatening patients' survival and seriously impairing their quality of life. Despite careful evaluation of the traditional clinical factors such as tumor stage, lymph node involvement, and anatomic subsite, it is not possible to reliably predict the outcome after a selected treatment. The identification of pretreatment factors that could potentially predict outcome is therefore of great interest. That is precisely why there is increasing current interest in the metabolic imaging of cancers as shown by Wong *et al.* (6).

Identification of pretreatment prognostic factors to supplement conventional TNM staging could help to detect high-risk subpopulations of patients who might benefit from treatment intensification. Some authors have explored the role of pretreatment PET (15,16) or MRI (17) metabolic parameters and prognosis at the end of the radical chemoradiotherapy. However, the study performed by Wong *et al.* (6) is one step ahead of previous studies.

These authors (6) propose the identification of patients who will fail treatment, especially early during the course of treatment, allowing changes in patient management strategies. For instance, those patients exhibiting unfavorable metabolic response could be considered for surgery instead of continuing another IC cycle or concurrent chemoradiotherapy. This issue is especially interesting in patients presenting with larynx carcinoma.

 

However, in the population studied by Wong *et al*. only 2/20 patients had larynx/hypopharynx carcinoma, and therefore there is not enough number of patients to definitively address this issue.

Regarding radiotherapy dosimetry in the non-responders (in relation to the area where persistent disease was identified on post-chemoradiotherapy imaging), Wong *et al*. (6) found that there was significant overlap between persistent disease and MTV after the first IC cycle. More interestingly, Wong *et al*. found that most metabolic response or non-response to IC was evident soon after the first IC cycle, with no significant change following a second cycle. This issue has relevant clinical applicability for guiding treatment individualization. On one hand, this indicates that residual MTV after the first IC cycle, represents a more 'aggressive' tumor area and it could be, therefore, a potential biological target volume for radiotherapy dose escalation. On the other hand, those patients presenting favorable metabolic response after the first IC cycle, could be considered for radiotherapy dose reduction (especially considering HPV-positive patients).

To the best of our knowledge, although there are other studies that have evaluated response assessment with 18F-FDG-PET/CT after IC in HNSCC (18-20), this is the first study in HNSCC to provide full longitudinal 18F-FDG-PET/CT and DW-MRI data (both imaging tools at the same time) following each cycle of IC. These findings provide the basis for a future interventional study using functional imaging parameters to stratify patients. Nevertheless, although Wong *et al*. (6) show promising results, the study population is small and the results are still preliminary. Hopefully, long-term follow-up including more patients will show us more definitive conclusions.

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