



Multimodality imaging for early assessment of head and neck patients during induction chemotherapy: a reliable future option?

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Wong and coauthors recently published on Journal of Nuclear Medicine (1) an interesting article regarding how 18-F-FDG-PET/CT and DW-MRI seem to be useful for early response assessment to radical chemo-radiotherapy (RT-CT) in head and neck squamous cell carcinoma (HNC) after one cycle of induction chemotherapy (IC). This paper faces several well recognized uncertainties regarding the optimal treatment strategy for locally advanced HNC.

The current role of IC in the primary treatment of locally advanced HNC still remains an object of debate. To date, no consensus regarding the usefulness of IC in the context of multimodality treatment for HNC exists. The rationale behind the adoption of IC is based on two main clinical hypotheses: (I) the disease shrinkage and the subsequently radiation therapy (RT) volumes reduction can allow more effective and less toxic RT; (II) multiple-agents up-front chemotherapy can impact on distant metastases and overall survival. Nevertheless, these assumptions showed a conflictual relationship with the “evidence-based oncology”. According to current recommendations, in regard to RT volumes extension, pre-induction primary site and loco-regional metastatic nodes, as well as radiation doses, should not be modified irrespectively to the IC-response (2). Moreover, modern RT is commonly able to sculpt the radical radiation dose to the patient’s head and neck anatomy, regardless of the extent of the disease. In fact, it is well recognized how RT advances for HNC allow radiation oncologists to optimize clinical outcomes and tolerability profile by means of: (I) static and rotational intensity-modulated RT techniques for a better dose

conformation to tumor target reducing dose to OARs (3-6); (II) image guided on-board RT-technology minimizing daily patients’ positioning uncertainties (7).

Thus, starting from these arguments, when treatment volume (and consequently toxicity) reduction is the main end-point, IC seems to be not so strictly essential in HNC treatment strategy. Moreover, if clinical outcome is the definitive objective, most of the available published experiences lack to demonstrate a clear advantage of IC when compared to concomitant cisplatin-based chemotherapy. The real value of the studies exploring IC has been largely debated by the scientific community due to several biases in the methodology procedure and/or study-design, statistical power and heterogeneity of patients population (8). Furthermore, a recent update of MACH-NC meta-analysis, globally confirmed the better impact of platinum based concomitant RT-CT when compared to multi-agents IC before RT (9). Conversely, the magnitude of the benefit of IC seems to be confined only to the locally advanced laryngeal cancer, in the specific setting of organ preservation, as demonstrated by three randomized phase III trials (10-12).

The role of IC is largely debated also for locally advanced oropharyngeal cancer, especially for the HPV-positive tumors where their potential higher sensitivity to antineoplastic therapies is opening the hypothesis of a de-intensification of therapeutic regimens. On the other hand, the response to IC would act as an *in vivo* predictive marker of treatment responsiveness and, thus, it could led to identify patients in which a reduction of the radiation doses could be taken into account in a treatment scenario shaped to each

patient. In this sense, to optimize the ongoing process of personalized oncology, other predictive factors of response could be useful in the selection criteria for IC, including multimodality imaging. In that direction, to predict response to RT-CT, Wong and colleagues investigated on the early assessment (after one cycle) of IC using 18F-FDG-PET/CT and DW-MRI (1). In their experience, the 18F-FDG-PET/CT “metabolic tumor volume (MTV)” and the “tumor lesion glycolysis (TLG)” acquired before and after one cycle of IC were found as early predictors of response to subsequent chemo-RT. On the contrary, DW-MRI failed to provide further biologic informations.

In HNC, the impact of 18F-FDG-PET/CT has been investigated in several setting such as pre-treatment staging, RT planning-strategy and to monitor response after treatment (13). Some authors reported that adding 18F-FDG-PET/CT to morphologic-imaging flow-chart did not significantly modify clinical management (14-16). Conversely, in four prospective trials the treatment management was influenced by 18F-FDG-PET/CT in approximately 30% of HNC patients (17-20). The usefulness of 18F-FDG-PET/CT in RT-planning is under investigation: the main criticisms remain specific technical gaps related to visual operator-interpretation or variability of gross tumor volume definition (21,22). In the monitoring of response after treatment 18F-FDG-PET/CT-guided surveillance resulted in fewer neck dissections and subsequently surgical complications, as demonstrated in a randomized, controlled trial recently published by Mehanna *et al.* on *New England Journal of Medicine* (23). Lastly, semi-quantitative evaluation is of great interest in the nuclear-medicine environment: MTV, a volumetric measurement of tumor cells with increased 18F-FDG uptake, could help to predict the therapeutic response and prognosis in several settings as well as the TLG, a derivative metabolic parameter of global metabolic activity (24).

In the study by Wong *et al.* (1), patients with favorable metabolic response after one cycle of IC, defined as a reduction of MTV >55% or TLG >60%, could be considered for radiation de-intensification, especially for HPV-positive oropharyngeal patients. According to Authors (1), IC could be interrupted in case of early MTV or TLG progression.

It remains to explore if the biological residual volume contains resistant cellular clones, early selected after the administration of the cytotoxic drugs. In this case, the natural history of HPV-positive oropharyngeal tumor could be iatrogenically impaired and the radiation dose de-intensification could be a suboptimal treatment. The limitations of the analysis by Wong *et al.* (1) including the

sample size (20 patients analyzed) and the limited follow-up (median, 14 months) do not permit any conclusive interpretation of the data. Anyway, the study by Wong and colleagues (1) is clinically relevant and it could open a new scenario of personalization in oncology selecting oropharyngeal patients suitable to IC by means of molecular imaging parameters.

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Footnote

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