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EDITORIAL COMMENTARY

Evaluation of neck node response after radiotherapy: minimizing equivocal results

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About two-thirds of patients with head and neck squamous cell carcinoma (HNSCC) originating from the mucosal linings of the upper aerodigestive tract present with advanced stage disease. If the primary tumour is located in the pharynx or larynx, patients are generally treated with radiotherapy with or without chemotherapy. In patients with functionally unresectable HNSCC (resectable but high morbidity of surgical treatment expected) who are treated with this nonsurgical treatment, salvage surgery is kept in reserve in case residual disease occurs.

The decision to perform a neck dissection following (chemo)radiotherapy is clear when patients have proven residual nodal disease in the neck. However, distinguishing between residual metastasis and radiotherapy sequelae is difficult in most patients with a residual neck mass, since posttreatment induration and fibrosis make accurate clinical assessment difficult. Because no reliable clinical parameters are available to predict pathological neck status after (chemo)-radiotherapy, routine planned neck dissection is performed in many institutions. The integration of planned neck dissection into the multidisciplinary management of patients with locoregionally advanced head and neck cancer treated with concomitant chemoradiotherapy is highly effective in controlling residual neck nodal disease. However, in the majority of neck dissection specimens, no viable tumour cells are found. Moreover, neck dissection after radiotherapy is associated with a significant risk of wound healing problems and shoulder morbidity. On the other hand, late recurrences in the neck are rarely surgically salvageable and are associated with an increased risk of metastatic spread to distant sites. Therefore, early detection of residual neck disease after (chemo)radiotherapy is important [1–4].

There is a tendency to perform neck dissections after (chemo)radiotherapy only if indicated by posttreatment diagnostic evaluation of the neck (physical examination, imaging and/or cytological evaluation) [1–4]. Van der Putten et al. [5] reported on 129 patients with neck recurrence out of 540 HNSCC patients who underwent neck dissection after chemoradiotherapy because of clinical suspicion of neck recurrence. In this series a planned neck dissection would have been unnecessary in 76 % of the patients with N2/N3 disease. In patients with N0/N1 neck the number of unnecessary neck dissections would be even higher (92.8 %) [5].

For more individualized salvage neck treatment after (chemo)radiotherapy, the head and neck surgeon needs a reliable selection tool with clear results. For improved survival, high sensitivity is needed: residual neck disease should be detected early. Delaying a neck dissection allows more time for both cancer progression and radiation-induced fibrosis, which may hamper the feasibility of a neck dissection and increase surgical complications. To avoid unnecessary salvage neck dissections, a high negative predictive value is necessary. Since the head and neck surgeon only wants to know if a salvage neck dissection should be performed, equivocal test results are not useful.

Although different imaging modalities have been investigated [6], ^{18}F-FDG PET/CT seems to be the most promising

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diagnostic technique for response assessment following (chemo)radiotherapy. Unfortunately, it is not yet established how these PET/CT scans should be performed and interpreted for optimal use in clinical practice. This is illustrated by the wide variation in sensitivity (25 – 100 %) and negative predictive value (14 – 100 %) [7, 8]. It must be emphasized that because of the low incidence (less than 10 %) of residual disease due to improved (chemo)radiotherapy, high negative predictive values can be obtained relatively easily nowadays. The reported apparent variability of the operational characteristics of ^{18}F-FDG PET in this setting may be related to, for example, the included patient spectrum, the timing of PET after therapy, PET positivity criteria, and the definition of the reference test (e.g. methods and duration of follow-up).

PET imaging obtained too soon after radiotherapy has been associated with a high rate of false-positive findings due to postradiotherapy soft tissue effects, and false-negative findings because of the residual viable cancer cells not having sufficient time to repopulate to a level that can be detected by PET. If the time interval between the end of therapy and PET scanning increases the negative predictive value improves. In a meta-analysis of the diagnostic performance of posttreatment ^{18}F-FDG PET imaging in head and neck cancer, Gupta et al. [9] found that the sensitivity of PET scans performed 12 or more weeks after radiotherapy was significantly higher than that of scans performed within 12 weeks. Recently, Leung et al. [10] sought to determine the optimal timing of the first posttreatment ^{18}F-FDG PET scan after chemoradiotherapy and found that PET/CT scans obtained within 7 weeks after treatment were less accurate than scans obtained at later time points. Furthermore, the accuracy of these scans did not differ significantly whether they were obtained between 7 and 10 weeks, between 11 and 14 weeks, or after 15 weeks or more [10]. The optimal timing is still a matter of debate, particularly because of the better chance of salvage when residual disease is diagnosed in a timely manner. An interval between 8 and 12 weeks after the end of treatment is generally accepted.

^{18}F-FDG uptake can be evaluated quantitatively and qualitatively. Qualitative assessment of the metabolic rate of glucose by dynamic scanning to obtain the rate of glucose consumption is not feasible in daily clinical practice. Semiquantitative assessments include standardized uptake values (SUV), of which maximum SUV (SUVmax) is most often used, metabolic tumour volume and total lesion glycolysis. Visual assessment is commonly used, but standardized criteria are lacking. Different Likert scales have been investigated. As can be done with continuous data (e.g. SUV), such ordinal scales enable determination of the best dichotomization, e.g. considering equivocal results positive or negative. ROC curves seam be useful for determining the optimal cut-off values, but sensitivity and specificity are not equally important in this clinical problem. An unnecessary neck dissection outweighs missing residual disease which potentially compromises survival. The same holds true for finding a significant difference for each criterion within a scoring system. It is only a prerequisite for further determination of the best dichotomized categorization for use in daily clinical practice.

Several SUVmax cut-off values ranging from 2.0 to 3.0 have been reported [11–15]. Each of these cut-off values was considered optimal in the series in which it was reported. Besides patient population, acquisition protocol, definition of region of interest and the reconstruction algorithm used in the different institutions may affect the choice of the best cut-off value to detect residual neck disease after (chemo)radiotherapy. Guidelines for standardization of PET imaging and quantification of ^{18}F-FDG uptake have been developed [16]. However, too often publications fail to provide sufficient details on the imaging methodology to assess whether quantitative data can be compared with the results of other studies. Finally, any data-driven threshold for test positivity requires prospective external validation. The obvious potential added value of quantification (e.g. by avoiding observer variation) can only be exploited and capitalized upon after standardization of the methodology of the technique.

For qualitative PET interpretation several Likert scores have been used. Sjövall et al. [17] used the five-point Deauville scale as applied in malignant lymphoma (relating residual uptake to mediastinal blood pool and liver uptake). Marcus et al. [18] recently proposed the five-point "Hopkins scale" based on intensity (similar to the Deauville scale, but using the jugular vein rather than the mediastinal blood pool), adding a description of aspects of residual uptake (focal or diffuse). Krabbe et al. [19] graded the confidence of image interpretation using a five-point scale (*0* definitely no tumour, *1* probably no tumour, *2* equivocal, *3* probably tumour, and *4* definite tumour). Schouten et al. [20] used a similar system based on aspect and intensity. The different qualitative scoring systems are thus based on focal uptake assessed in relation to adjacent tissue, internal jugular vein, mediastinum or liver uptake [17, 18, 21].

Baseline PET imaging may be useful in PET reading for evaluating treatment response [22]. Another option for improving response evaluation might be to repeat PET scans during follow-up. Although in the study by Sjövall et al. [17] this seemed not to improve the response evaluation, in the study by Krabbe et al. [19] the detection of residual neck disease improved. Preliminary data [20] have indicated that a combination of ^{18}F-FDG PET and DW-MRI may be an attractive option for optimizing the decision making to perform a neck dissection following chemoradiotherapy. Sjövall et al. [17] conclude that a Likert scale seems to satisfy the

requirements for a common qualitative way of assessing PET scans and also the reporting of PET results in the evaluation of head and neck cancer. Consensus regarding qualitative assessment would facilitate PET reporting in clinical practice and enable comparative studies between patients and institutions.

For malignant lymphoma the Deauville five-point scoring system was developed. It was subsequently compared with other interpretation systems and found to be accurate and reproducible. It was validated in an international multicentre study and was accepted as a standard reporting criterion in clinical practice and for clinical trials [23, 24]. Sjövall et al. [17] made the first step in this process of improving response evaluation in head and neck cancer by comparing different interpretation systems. However, larger series preferably in multicentre collaborative studies are needed to compare different test positivity criteria, and to be able to comprehensively study the potential impact of other variables (e.g. timing, tumour subtype, reference standards etc.), and ultimately to validate the proposed taxonomy.

Compliance with ethical standards

Conflicts of interest None.

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