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EDITORIAL

The potential of FDG-PET in the detection of occult lymph node metastasis: importance of patient selection and reference standard

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In patients with head and neck squamous cell carcinoma the presence of lymph node metastases is one of the most important prognostic factors. It is obvious that the patients with clinically manifest lymph node metastases require treatment of the neck. Therefore, the detection of lymph node metastases is of utmost importance. A meta-analysis showed that conventional imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and especially US-guided fine needle aspiration cytology (USgFNAC), are more reliable than palpation [1]. Positron emission tomography (PET) imaging with F-18-fluorodeoxyglucose (18F-FDG) is a functional modality that has been used increasingly for staging head and neck cancer. Modern PET–CT imaging equipment combines both anatomic and functional imaging, potentially providing more accurate diagnosis and improved patient management. Here, the CT scan is used for attenuation correction of the PET images as well as for anatomic localisation; most scanners can provide state-of-the-art contrast-enhanced CT (CECT) (and not just the low-dose CT [ld-CT] required for attenuation correction) together with PET in a single scan session.

Kyrzas et al. [2] found in another meta-analysis that 18F-FDG-PET has a good performance in the pre-treatment evaluation of the presence of lymph node metastases in HNSSC patients: pooled sensitivity of 79 % (95 % confidence interval (CI) 72–85 %) and pooled specificity of 86 % (95 % CI 83–89 %). In studies in which both 18F-FDG-PET and conventional diagnostic tests were performed, sensitivity and specificity of 18F-FDG-PET were 80 % (95 % CI 72–87 %) and 86 % (95 % CI 82–90 %), respectively, while for conventional diagnostic tests these figures were 75 % (95 % CI 65–83 %) and 79 % (95 % CI 72–85 %), respectively [2]. In 167 patients, Roh et al. [3] compared pre-operative PET or PET–CT (only ld-CT) with CT or MRI for the detection of (occult and evident) lymph node metastases (per neck): sensitivity 90–91 % and 76–77 %, and the specificity 87–88 % and 81–83 %, respectively. No difference between PET only and PET–CT in accuracy was found [3].

However, the detection of occult lymph node metastases is the most important problem. The meta-analysis of Kyrzas et al. showed that 18F-FDG-PET detected only 50 % (95 % CI 37–63 %) of the occult lymph node metastases, reiterating the inability of imaging tests to document microscopic disease. The specificity was 87 % (CI 76–93 %)[2]. Krabbe et al. [4] found for the detection of occult metastases by FDG-PET a sensitivity of 50 %, a specificity of 97 %, negative predictive value of 88 % and a positive predictive value of 80 %. In 18F-FDG-PET studies addressing HNSCC patients with a clinically negative neck sensitivity and specificity were quite variable. Brouwer et al. [5] showed that PET studies applying routine histopathological work-up reported much higher sensitivities to detect occult lymph node metastases than those using serial step sectioning and immunohistochemistry as the reference (gold) standard (67–100 % vs. 0–40 %) [5]. Routine histopathological examination can miss micrometastases in up to 15.2 % [6] through which some

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false-negative findings may be incorrectly scored true negative. Since single tumour cells and micrometastases can also be missed by histopathological examination using step serial sectioning and immunohistochemistry, long term observation of the neck is even a better reference standard. It is important to realize that sensitivity is dependent on the reference standard used.

Additional explanations for heterogeneity may flow from differences in patient selection and inclusion criteria: not unexpectedly, studies reporting low sensitivity tend to have included patients with clinically as well as ultrasonographically negative necks, whereas higher sensitivities are reported if patients were included who were clinically negative but who more often had radiological evidence of lymph node metastases [7]. Therefore, it is of utmost importance that in clinical studies the definition of the clinically or radiologically negative neck is described in detail.

Jeong et al. [8] showed that PET–CT (ld-CT) was more accurate than PET alone and CECT alone for the conducting cervical lymph node evaluation in 47 HNSCC patients with and without clinical lymph node metastases who were scheduled for neck dissection(s): sensitivity of 91.8 %, 80.3 % and 90.2 %, and specificity 98.8 %, 92.8 % and 93.9 %, respectively. Whereas ld-CT is used for attenuation correction, CECT may be helpful for the localisation of increased 18F-FDG uptake, e.g. differentiation between uptake in lymph nodes and brown fat, increasing 18F-FDG-PET specificity. Ng et al. [9] showed that for the detection of subclinical lymph node metastases the visual correlation of 18F-FDG-PET with CE CT/MRI has been reported to be more accurate than 18F-FDG-PET alone. In 134 patients with oral squamous cell carcinoma they found a sensitivity of 51.4 %, which is increased to 57.1 % after visual correlation with CT/MRI. This increment stemmed from the correction of false-negative 18F-FDG-PET results caused by necrotic nodes [9]. Ozer et al. [10] recently reported a sensitivity of 57 % and specificity of 82 % for the detection of occult metastasis by 18F-FDG-PET–CT in 112 patients with clinically negative neck according to physical examination, CT and/or MRI [10]. Unfortunately, CT scanning (ld-CT or CECT) was not defined. The study in the present issue of *European Archives of Otorhinolaryngology* shows a sensitivity of 84.2 % and a specificity of 76.5 % of 18F-FDG-PET–CT in the detection of occult lymph node metastasis [11]. In interpreting these figures one should keep in mind the above discussed important aspects of chosen definition of clinically negative neck (patient selection), imaging technique (ld-CT or CECT) and reference standard (routine histopathological examination of neck dissection specimen, step serial sectioning and immunhistochemistry of all lymph nodes in neck dissection specimen or clinical follow-up).

Although 18F-FDG-PET and 18F-FDG-PET–CT may have the best accuracy for detecting occult cervical lymph node metastases in the clinical N0 neck, they are still not sufficiently reliable to avoid elective treatment of the neck. This can also be theoretically expected because of the limited resolution of the current PET scanners. Nevertheless, 18F-FDG-PET may provide important information about involvement of lymph nodes and be of value in treatment planning in head and neck cancer.

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