Editorial Commentary

Improved diagnostic accuracy of hybrid positron emission tomography (PET) with tumor-specific radiotracer for head and neck squamous cell carcinoma staging

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We would like to congratulate Lee *et al.* for their recent publication in Clinical Cancer Research, which brings a new insight into the potential future of hybrid positron emission tomography (PET) imaging in head and neck oncology (1).

Current standard imaging for advanced head and neck squamous cell carcinoma (HSNCC) usually includes 18-fluorodeoxyglucose positron emission tomography (18F-FDG-PET), combined with either CT or MRI, which has gained wide application since its first description in clinical oncology by Beyer *et al.* in 2000 (2). Adding hybrid 18F-FDG-PET to the diagnostic and staging process for HNSCC patients results in improved nodal classification and increased detection of distant metastases (3,4). Further, for patients with carcinoma of unknown primary (CUP) of the head and neck, hybrid 18F-FDG-PET is a precious tool for identifying and localizing the primary tumor (5). Finally, an increasing body of evidence indicates that quantification of 18F-FDG uptake can be used as a surrogate marker for tumor aggressiveness, as quantification of 18F-FDG-PET uptake matches with *in vivo* glucose consumption of the tumor, which is inversely correlated with tumor hypoxia and aggressive potential (6-8).

The high sensitivity of hybrid 18F-FDG-PET is both a blessing and a curse, leading to false-positive findings and provoking unnecessary diagnostic workup (9). Since inflammatory changes in the head and neck as well as in the lung are rather frequent in head and neck cancers patients, false-positive findings are encountered in approximately one third of hybrid 18F-FDG-PET scans in this patient population (10). It is therefore intriguing to augment preoperative cross-sectional hybrid imaging with a more specific radiotracer.

In their early-phase clinical study using 89Zr-panitumumab in 14 head and neck cancer patients, Lee *et al.* present a potential advantage of this radiotracer over 18F-FDG by an increased specificity and less false-positive results (1).

Panitumumab is an epidermal growth factor receptor (EGFR) antibody and has been used as a therapeutic agent in several clinical trials in head and neck cancer.

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However, most trials published were negative, and hence panitumumab has no FDA-approved therapeutic indications today (11-14). The use of a PET-able EGFR antibody for diagnostics remains however promising, since EGFR is known to be overexpressed in more than 90% of HSNCCs (15,16). While the radiation burden is a common issue with other 89Zr-based radiotracers used e.g., for immuno-PET, the estimated dose delivered to the patient in the current study was certainly higher than for 18F-FDG, but well within acceptable limits (approximately 10 mSv). The potentially increased specificity seen in their pilot study warrants the following comments:

For the primary tumor, hybrid PET specificity is not a key diagnostic feature, since the tumor itself is typically known already, and even estimates on its size and extension have been made by clinical examination, endoscopy, and cross-sectional imaging, such as MR or CT.

However, a comparably specific radiotracer, such as 89Zr-panitumumab, could potentially prove useful in patients with CUP syndrome, since a certain proportion of primary tumors remain occult even after endoscopy and hybrid 18F-FDG-PET and hence do require ipsilateral palatine and ipsilateral or bilateral lingual tonsillectomy (17). It might be interesting to investigate whether such a specific radiotracer targeting EGFR would be able to identify small hidden primary tumors. Here, both the signal-to-noise-ratio of the radiotracer and the spatial resolution of PET come into play. Notably, the signal-to-noise-ratio of 89Zr-panitumumab was lower compared to 18F-FDG. While the average positron energy of 89Zr is lower compared to 18F [396 *vs.* 635 keV, respectively (18)], its much longer half-life does not only pose logistic problems, but also impacts the signal-to-noise-ratio and therefore image quality.

For the lymph nodes, the potential added value of a more specific hybrid PET exam needs to be analysed separately for each head and neck cancer site.

For advanced stage oral cavity cancer, usually an ipsilateral neck dissection is performed, as access to the neck is necessary for reconstruction and risk of (occult) metastasis is very high (19). There is often a debate as to whether or not perform bilateral neck dissection. Proponents of this method argue that the risk of contralateral nodes is not negligible. These occur in approximately 14% of patients with lateralized oral cavity tumors, according to sentinel lymph node biopsy studies (20). On the other hand, opponents argue that it is more morbid and unnecessary, since postoperative radiotherapy is likely and can be used to cover the contralateral neck nodes as well. In this context, a tumor-specific radiotracer could be of great value, especially since inflammatory changes of nodes are frequent in oral cancer patients due to their dental status and other chronic oral inflammatory conditions.

For oropharyngeal cancer, a specific assessment of the number of nodes is crucial. When discussing the choice of primary treatment in oropharyngeal cancer, the number of nodes is a key information since it may impact treatment recommendations. Single modality surgery is only likely to be feasible if there are 2 or less nodes without extranodal extension. In other words, in presence of multiple pathological nodes, primary chemoradiation will often be favored, especially in HPV-positive disease, since surgery will be followed by adjuvant (chemo)radiation (21). In this context, a radiotracer which can precisely determine the number of metastatic lymph nodes bears great clinical potential. However, it appears cumbersome that the 89Zr-panitumumab uptake of metastatic lymph nodes in the present study was apparently lower both than the uptake of the primary tumor, and lower than their respective 18F-FDG uptake.

For distant disease, false positive lung findings are a common problem well known in CT screening studies such as NSLT and NELSON trials, with false-positive rate of 96.4% and 65%, respectively (22,23). Use of hybrid PET is limited by radiation dose (especially in the screening setting) but studies have shown that hybrid 18F-FDG-PET could improve specificity compared to CT alone (24). 89Zr-panitumumab was found to reduce false-positive findings outside the head and neck compared to 18F-FDG, the absence of distant metastases in the present study precludes a reliable statement on the suitability of 89Zr-panitumumab PET for whole-body staging in head and neck cancer patients. As mentioned correctly by Lee *et al.*, the comparably high liver background may not play a major role in most HNSCC patients. However, HPV-positive oropharyngeal cancers are known for their atypical metastatic pattern, and hence this subgroup should be regarded with caution (25).

In conclusion, tumor-specific hybrid 89Zr-panitumumab PET presents a novel promising development. Its potential added value needs to be confirmed in larger studies before implementation into clinical practice. Additionally, it needs to be benchmarked not only against 18F-FDG, but also against other novel radiotracers on the horizon, particularly the different fibroblast activation protein inhibitor (FAPI)

PET radiotracers that have the potential to raise the bar (26).

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