Editorial Commentary

Can PET-CT improve the staging and outcome of patients with muscle-invasive bladder cancer?

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Patients with non-metastatic muscle-invasive bladder cancer (MIBC) receive neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC). Alternatively, patients are treated with trimodality therapy. For locally advanced MIBC, adjuvant immunotherapy is further indicated (1,2). Despite treatment intensification over time, the prognosis remains poor with overall survival at 5 years of <60% (3). Lack of improvement in outcome might be due to an inaccurate staging of patients at the time of diagnosis. According to guidelines, conventional imaging [i.e., computed tomography (CT) and magnetic resonance imaging (MRI)] is recommended for the primary staging of patients with MIBC, and fluorodeoxyglucose-positron emission tomography-CT (FDG-PET-CT) can be used to guide treatment, although its value is still highly debated (2).

Multiple trials have shown that PET-CT has a higher diagnostic accuracy than CT or MRI for local and distant staging of MIBC patients (4-6).

A systematic review reported a pooled sensitivity of 58% [95% confidence interval (CI): 51–64%] and specificity of 89% (95% CI: 82–94%) for lymph node staging with PET-CT/MRI. For distant metastases, a pooled sensitivity and specificity for PET-CT/MRI of 89% (95% CI: 61–98%) and 95% (95% CI: 80–99%), respectively was found. Within this systematic review, no radiotracer outperformed another (4).

Fibroblast activation protein (FAP) is a type II transmembrane serine protease that is upregulated on fibroblasts at sites of active tissue remodeling. High expression of FAP is also found in solid tumors which makes it an attractive target for molecular imaging (7-9). Hagens *et al.* suggested that FAP inhibitor (FAPI) radiotracers are more accurate for local and distant staging of patients with genitourinary cancers. However, the overall level of evidence remains low (10). Although ^{68}Ga-FAP-PET can potentially refine the staging of MIBC patients, some words of caution should be made.

First, while immunohistochemical studies showed high expression of FAP in urothelial cancer, FAP is not specific for urothelial carcinomas. FAP overexpression is seen in different other tumor types, such as gastrointestinal malignancies, as well as several benign conditions (7-9).

Second, like other tracers, FAP-targeting radiotracers are excreted through the urinary tract which hampers the visualization of primary tumors in the bladder and upper urinary tract. Also, the superiority of FAPI-based PET radiotracers over other tracers for lymph node staging and detection of bone metastases is still unclear.

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In the study of Koshkin *et al.*, the potential of ^{68}Ga-FAP-2286 PET imaging in the staging of MIBC is further explored (11). The authors concluded that the largest advantage of ^{68}Ga-FAP-2286 PET is the earlier detection of smaller lesions (i.e., lymph nodes <1 cm) compared to conventional imaging. The authors also suggest that ^{68}Ga-FAP-2286 PET outperforms FDG-PET-CT due to an improved tumor-to-background ratio and finer resolution of nodal disease.

Although recognized by the authors, it is important to point out that this is a small study in a heterogeneous MIBC patient group, including patients with metastatic and localized disease. In the localized MIBC group, histological confirmation of disease was aimed for but was only reported in 4 out of 7 patients with positive ^{68}Ga-FAP-2286 PET scan, resulting in a sensitivity of ^{68}Ga-FAP-2286 PET of 57%. Also, in the recent paper of Unterrainer *et al.*, the sensitivity of ^{68}Ga-FAPI-46 PET/CT was 57% (12). This is comparable but not superior to the sensitivity data reported with other PET-CT tracers (both ^{18}F-FDG or C11-choline). It is unclear whether the remaining 6 patients with negative ^{68}Ga-FAP-2286 PET imaging in the localized cohort had pathological confirmation of absence of nodal invasion.

In the presented study, ^{68}Ga-FAP-2286 PET was performed before NAC and two patients had no evidence of disease (pathological T0N0M0) after NAC and surgery (11). It would have been interesting to have a ^{68}Ga-FAP-2286 PET during and after completing NAC to see whether imaging would have become negative afterward. Imaging might have an important role in the treatment management of MIBC patients and could be used to distinguish patients who benefit from NAC from those who do not.

It has been suggested that patients with residual disease at RC after NAC have worse overall survival and cancer-specific survival when compared to matched patients who did not receive NAC (13,14). Predicting tumor response on NAC enables us to determine whether a patient should be referred for early RC, and whether a patient is an optimal candidate for bladder-preserving therapies, such as trimodality therapy. The value of PET-CT and MRI in predicting treatment response has been studied and promising results have been reported for both imaging modalities although further research is needed (15,16).

Finally, in this study of Koshkin *et al.*, discordancy between conventional imaging and Ga-FAP-2286 PET CT was seen in 8 out of 13 patients (62%) in the localized MIBC group, resulting in a change in treatment plan in 3 of them (38%) (11).

Undoubtedly, better imaging modalities will lead to better risk classification of MIBC patients. But, as for other tumor types, it is unclear how additional information, from PET-CT, should be incorporated into the treatment approach of our MIBC patients. The EFFORT study is an ongoing Belgian multicentric trial that evaluates the impact of treatment intensification based on ^{18}F-FDG-PET-CT (17). Patients included in the EFFORT trial are all non-metastatic MIBC patients on conventional imaging and are treated radically. All patients receive an ^{18}F-FDG-PET-CT before and after NAC. Based on ^{18}F-FDG-PET-CT patients are classified as truly non-metastatic (group 1), oligometastatic (group 2) or polymetastatic (group 3). For the latter two groups treatment intensification is performed with a metastasis-directed therapy or initiation of adjuvant immunotherapy for patients categorized in groups 2 and 3 respectively (17). This trial is still in the recruiting phase. Results are awaited to evaluate the impact of more precise imaging modalities and treatment adjustments on oncological outcomes.

To conclude, although this study adds to the literature evaluating the potential of PET-CT imaging in the staging of MIBC, further prospective trials are eagerly awaited to define the place of FAPI-PET-CT in staging and treatment management.

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