Can 68GA-PSMA or radiolabeled choline PET/CT guide salvage lymph node dissection in recurrent prostate cancer?

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EDITORIAL COMMENTARY

Can ^{68}GA-PSMA or radiolabeled choline PET/CT guide salvage lymph node dissection in recurrent prostate cancer?

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In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Pfister et al. [1] evaluate the performance of ^{18}F-fluoroethylcholine (^{18}F-FEC) and ^{68}Ga-PSMA PET/CT in patients undergoing salvage lymph node dissection (sLND) for recurrent prostate cancer (PCa). The introduction of novel imaging modalities and tracers has increased the detection of oligometastatic PCa recurrence, potentially justifying the use of sLND rather than a systemic approach. The present study is premised on the notion that radiopharmaceutical agents can be useful for guiding surgical procedures in cases of predominant nodal recurrence of PCa. This is a topic of great interest to urologists, radiologists and nuclear medicine physicians. What evidence must we consider for the use of sLND? Could extended LND rather than sLND during radical prostatectomy (RP) improve patient survival? What is the best imaging modality for ensuring appropriate treatment?

These closely related questions are important because they prompt us to examine the value of clinical trials in the area of sLND in PCa. The literature is lacking in both randomized trials comparing sLND with a control group treated with current best practice and prospective case–control studies evaluating the impact of PET imaging for the detection of lymph node metastases before or after RP. The "scientific run" to the best imaging modality and highest-performing tracer is justified only if they provide a survival benefit and improved quality of life for patients with oligometastatic PCa.

In addressing this issue, therefore, key points to consider in the design of future studies include (1) selection of the patient population, (2) previous therapies and ongoing androgen therapy, (3) extension of sLND, (4) the definition of endpoints and outcomes, (5) a comparison of different imaging modalities in the same population, and (6) whom to randomize—for example, the patients, the surgeons, or the imaging technologists?

In the study by Pfister et al. [1], 66 patients were retrospectively evaluated: 38 underwent ^{18}F-FEC and 28 underwent ^{68}Ga-PSMA PET/CT prior to sLND. Differences between the two populations must be considered, including demographic characteristics, primary treatments, and follow-up management. In our opinion, the *selection of patients* is the key driver for the trial. Only patients with well-defined treatment of the primary tumor should be included.

The extension of lymphadenectomy during RP should be defined, even though the role of pelvic lymph node dissection remains one of the most controversial areas in the management of clinically localized PCa. However, recent advances in our understanding of tumor biology and the introduction of a new PCa classification system [2] should enable better stratification of patients and should provide information about the best treatment strategy.

Any systemic or combination therapy should be avoided before sLND procedures. This is of pivotal importance, given the potential effects of hormone or radiation therapy on PET/CT performance. In our experience, patients with hormone-sensitive PCa and those with castration-resistant cancer

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undergoing androgen deprivation therapy and treatment with new anti-hormonal agents (e.g. abiraterone acetate or enzalutamide), respectively, demonstrate a significant reduction in radiolabeled choline PET/CT uptake in the lymph nodes after the administration of drugs (Fig. 1). In addition, careful selection of the time from primary treatment to sLND and the PSA cutoff before salvage surgery is critical, because they will affect the sensitivity and specificity of nuclear imaging modalities. In the study by Pfister et al. [1], PSA values ranged from 0.04 to 8.4 ng/mL, with a median of 2.7 and 2.35 ng/mL, respectively, for ^{18}F-FEC and ^{68}Ga-PSMA. However, PSA alone cannot predict a positive PET/CT, because the sensitivity and specificity of radiolabeled choline in these patients is increased in cases of low PSA doubling time and high PSA velocity [3].

Accuracy is a frequent *endpoint* in diagnostic studies. However, a series of *different outcomes* should be addressed in PCa patient candidates for sLND. For example, the current literature shows that some patients benefit from sLND, with approximately 9–19 % remaining free from biochemical recurrence, and approximately 26–34 % remaining free from clinical recurrence [4, 5]. However, these data indicate that the benefit of sLND in the majority of cases is prolonging survival and/or postponing hormone therapy, but not achieving a complete cure. Indeed, whether these patients would have died from PCa without the removal of the lymph node metastases is unknown. Information about the site of nodal relapse may be suboptimal, particularly for sacral and retroperitoneal regions. Extended retroperitoneal lymph node dissection is likely the only approach for limiting the effect of the Will Rogers phenomenon. The risk of surgical complications is obviously also an ethical concern. Although Pfister et al. [1] reported no data about site/region accuracy for either ^{18} F-FEC or 68Ga-PSMA PET/CT, reports available in the literature indicate that the accuracy of radiolabeled choline for the detection of retroperitoneal lymph node recurrence ranges from 20 to 40 % [6–8], thus guiding the use of extended sLND in only a small percentage of patients.

Another important issue is the *comparison of different imaging modalities*, such as diffusion-weighted magnetic resonance imaging (DW-MRI) and PET/CT with radiolabeled choline or ^{68}Ga-PSMA, in the same population. The study by Pfister et al. [1] was performed in different study populations. Although patient characteristics were similar, certain biological tumor features would have affected the accuracy of both radiopharmaceutical agents. Most published papers, however, have discussed the performance of DW-MRI in lymph node staging in PCa before primary treatment. The reliability of the technique for detecting clinical lymph node relapse after primary treatment is still unknown, and therefore warrants further investigation [3].

Finally, several *medical reasons* can be considered as confounders, both surgical (i.e. individual surgical volume, expertise and commitment to performing sLND) and imaging issues (i.e. blinded analysis, reading experience and reproducible methodology).

In conclusion, while a prospective randomized trial may provide definitive answers to the abovementioned "clinical questions" concerning the role of sLND, conversely, it could lead to misleading conclusions. Therefore, it is extremely important to adopt different treatment regimens by considering the biology and behavior of PCa. In this regard, careful patient

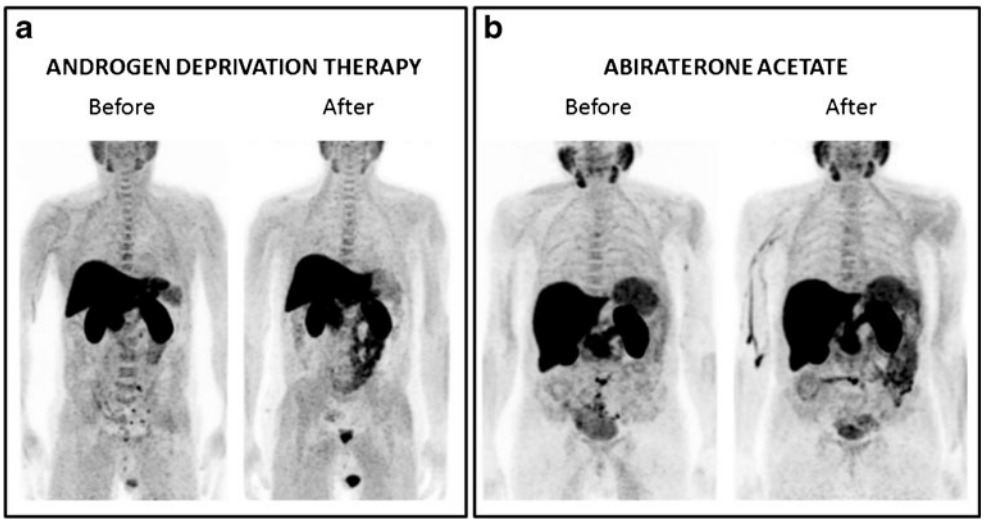

Fig. 1 **a** A 67-year-old man with PCa treated by radical prostatectomy and lymph node dissection (pT3bN1; GS: 9; positive margins). Serial monthly PSA (0.56 ng/mL->2.37 ng/mL->3.03 ng/mL) demonstrated biochemical failure, with significant uptake of ^{18} F-fluoroethylcholine in the abdominal-pelvic lymph node on PET/CT images (*left*), and thus treatment with LH-RH agonists was started. Six months after the start of treatment, PET/CT was negative (*right*). **b** A prostate cancer patient with increased PSA level (36.80 ng/mL) during hormone therapy. Significant uptake of choline at the lumbar lymph nodes was demonstrated (*left*). The patient was treated with abiraterone acetate. A PET/CT with ^{18} F-fluoroethylcholine (*right*) 3 months after the start of therapy showed a good metabolic response (PSA: 12.97 ng/mL)

selection, novel biomarkers, and developments in nuclear medicine will certainly help in resolving these issues.

Compliance with ethical standards

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Conflict of interest There are no potential conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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