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EDITORIAL COMMENTARY

Prostate cancer imaging: when the game gets tough, the hard one gets done!

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Recently, in the European Journal of Nuclear Medicine and Molecular Imaging, a paper entitled: "^{68}Ga-PSMA PET/CT in patients with recurrent prostate cancer after radical treatment: prospective results in 314 patients" was published by Caroli et al. [1]. The study was based on a prospective analysis performed in 314 patients affected by prostate cancer who underwent ^{68}Ga-PSMA PET/CT for the biochemical recurrence of disease. Patients with a very early biochemical recurrence (PSA > 0.2 ng/mL) and with a negative/doubtful Choline PET/CT were included. By analyzing the characteristics of the tumor (i.e T-stage, N-stage, PSA value and Gleason score), the authors found that ^{68}Ga-PSMA PET/CT positivity was correlated only with the PSA level, without showing any relationship with the other known biological characteristics of aggressiveness. However, the authors confirmed that ^{68}Ga-PSMA PET/CT is more accurate for PCa restaging than other currently used PET radiotracers.

The correlations among ^{68}Ga-PSMA PET/CT, Choline PET/CT, clinical tumor variables and hormonal therapy are extremely important in order to understand the appropriateness of these imaging modalities in prostate cancer patients.

Clinical features, such as clinical stage, PSA level and Gleason score are usually used for the stratification of the prognosis and therapeutic management of prostate cancer patients. Advanced clinical stage and high Gleason score are associated with a poor prognosis, requiring an aggressive and combined treatments. However, data in literature about the correlation between Gleason Score with Choline PET/CT are controversial. In the study by Cimitan et al. [2], a significant correlation between the detection rate of ^{18}F-Choline PET/CT in accordance with the Gleason score was found, particularly in patients with low PSA levels. Conversely, Giovacchini et al. [3] did not find any correlation between ^{11}C-Choline positivity and Gleason score, at multivariate analysis. Similarly, any correlation between the tumor differentiation and ^{68}Ga-PSMA has been demonstrated [4, 5].

As reported by Meller et al. [6] and Hope et al. [7], the degree of PSMA up-regulation increases with: (1) increasing primary aggressiveness, (2) the appearance of metastases, (3) testosterone withdrawal, by introducing the androgen deprivation therapy (ADT), and (4) transition to castrate resistant status. The introduction of ADT, by increasing the uptake of PSMA, can be considered an advantage and a disadvantage. The advantage is represented by the ability of PSMA PET/CT to recognize more lesions, conversely the disadvantage is the risk of a disease over-stage due to the "flare-phenomenon effect". However, the different biological behavior of Choline and PSMA for ADT raises some comments: (1) choline metabolism is reduced by ADT, probably due to the under-stimulation of the prostate cancer cells, (2) PSMA receptors are increased in case of missing testosterone, probably due to an up-regulation of the receptors, (3) the availability of diverse hormonal therapies (i.e. LH-RH agonists and antagonists; abirateron acetate and enzalutamide) requires further evaluation of these biological effects.

In the study by Caroli et al. [1], the detection rate of ^{68}Ga-PSMA PET/CT was 62.7% in 314 patients with a PSA value, after primary treatments, ranging between 0.03 and 80 ng/mL. In the study by Chondroggianis et al. [8], in 325 patients undergoing ^{18}F-Choline PET/CT with a PSA ranging between 0.5 and 80 ng/mL, detection average was 58.2%, with a high-end value of 70.5% in patients undergoing ADT and 48.9% in patients who did not undergo ADT. The slight difference

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between the detection rate of ^{18}F-Choline PET/CT and ^{68}Ga-PSMA (about 5%) poses some questions about the interchangeability of the radiopharmaceutical agents, particularly for higher PSA levels. However, also Choline showed an increased uptake in castrate resistant condition, with a higher detection rate (increase of about 22%). Nevertheless, similar data are now missing for PSMA.

The final PSA value identified by Caroli et al. [1] for the identification of positive ^{68}Ga-PSMA PET/CT was 1.062 ng/mL, similar to the cut-off value reported for Choline PET/CT [9, 10]. However, as clearly stated by the authors, patients with a PSA value <2 ng/mL and with a GS > 7 and a negative Choline PET/CT would have a positive ^{68}Ga-PSMA PET/CT in 57 and 81% of cases, although the correlation between PSMA with Gleason score was poor [4, 5]. Again, some questions and new data are necessary in order to understand the exact relationship between the aggressiveness of prostate cancer and expression of PSMA. Probably, the presence of low PSA values (< 2 ng/mL) in patients with an undifferentiated disease (GS > 7) and a castrate-resistant prostate cancer represent the condition for the PSMA expression. Also, Choline PET has demonstrated a higher detection rate for patients with low PSA levels and high Gleason score (>7), reaching a value of 46%, but PSMA seems more promising in these subsets of patients. However, aggressive primary tumors with a Gleason Score > 7 tend to display high ^{18}F-FDG uptake [11]. An head-to-head comparison between ^{18}F-FDG and ^{68}Ga-PSMA PET/CT in this category of patients would be of interest.

Like in the majority of published papers, detection rate cannot be considered like the diagnostic performance, in terms of sensitivity and specificity. In fact, detection rate suggests the presence of a higher radiopharmaceutical uptake in some sites more than the target-tissues, independently from the morphological changes. Specifically, PSMA expression has been found in different benign and pathological conditions and also in autonomic nervous system. Therefore, as for the other radiopharmaceutical agent, the interpretation of PSMA imaging should be carefully made, as suggested by Fanti et al. [12]; however, a great attention to the history of patients remains essential. From our preliminary experience, we found that also the preparation of patients who are scheduled for ^{18}F-Choline PET/CT is important. In fact, we found that a prolonged fasting period was associated with higher values of true events than a short period (>10 h vs. 0–5 h) [13]. Thereafter, again, Choline PET/CT is a metabolic imaging, while PSMA provides receptor information, thus not being affected by the fasting.

Most of the cited papers in the study by Caroli et al. [1] were relative to the detection rate of ^{11}C-Choline PET/CT. In the recent meta-analysis by von Eyben et al. [14], the authors found that, although not statistically significant, the detection rate of ^{18}F-Choline was higher than ^{11}C-Choline (25–35% vs. 34–44%; $p = 0.26$), in a subset of patients where PSA levels ranged between 1 and 10 ng/mL. However, the only head-to-head comparison between ^{18}F-Choline PET/CT and ^{68}Ga-PSMA reported a higher detection rate for ^{68}Ga-PSMA than ^{18}F-Choline for a PSA level which ranged between 0.5 and 2 ng/mL (71% vs. 36%). Interestingly, the majority of patients ($n = 27$; 76%) had an aggressive disease (high risk based on the European Association guidelines). No data about the concomitant administration of ADT was reported in this study [15].

Careful analysis of the paper by Caroli et al. [1] raises some comments and opens the door for new discoveries. First, ^{68}Ga-PSMA is more efficient than Choline PET/CT in patients with an early recurrence of disease (PSA > 0.2 ng/mL), independently from the Gleason score, but especially in the castrate resistant condition. Second, PSMA and Choline have different mechanisms of action and, therefore, cannot be considered interchangeably; however, they should be considered complimentary in some clinical conditions (i.e high PSA levels and well/differentiated tumors). Finally, the key message is that the choice of the nuclear medicine imaging for prostate cancer should arrive from the patient clinical history and from a strong collaboration with the clinicians.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals None.

Informed consent Informed consent was not necessary for the present study.

References

1. Caroli P, Sandler I, Matteucci F, De Giorgi U, Uccelli L, Celli M, et al. 68Ga-PSMA PET/CT in patients with recurrent prostate cancer after radical treatment: prospective results in 314 patients. Eur J Nucl Med Mol Imaging. 2018. https://doi.org/10.1007/s00259-018-4067-3.
2. Cimitan M, Evangelista L, Hodolič M, Mariani G, Baseric T, Bodanza V, et al. Gleason score at diagnosis predicts the rate of detection of 18F-choline PET/CT performed when biochemical evidence indicates recurrence of prostate cancer: experience with 1,000 patients. J Nucl Med. 2015;56:209–15.
3. Giovacchini G, Picchio M, Coradeschi E, Bettinardi V, Gianolli L, Scattoni V, et al. Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging. 2010;37:301–9.
4. Einspieler I, Rauscher I, Düwel C, Krönke M, Rischpler C, Habl G, et al. Detection efficacy of hybrid 68Ga-PSMA ligand PET/CT in prostate cancer patients with biochemical recurrence after primary radiation therapy defined by Phoenix criteria. J Nucl Med. 2017;58:1081–7.
5. Afshar-Oromieh A, Holland-Letz T, Giesel FL, Kratochwil C, Mier W, Haufe S, et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Mol Imaging. 2017;44:1258–68.

6. Meller B, Bremmer F, Sahlmann CO, Hijazi S, Bouter C, Trojan L, et al. Alterations in androgen deprivation enhanced prostate-specific membrane antigen (PSMA) expression in prostate cancer cells as a target for diagnostics and therapy. EJNMMI Res. 2015;5:66.
7. Hope TA, Truillet C, Ehman EC, Afshar-Oromieh A, Aggarwal R, Ryan CJ, et al. 68Ga-PSMA-11 PET imaging of response to androgen receptor inhibition: first human experience. J Nucl Med. 2017;58:81–4.
8. Chondrogiannis S, Marzola MC, Ferretti A, Grassetto G, Maffione AM, Rampin L, et al. Is the detection rate of 18F-choline PET/CT influenced by androgen-deprivation therapy? Eur J Nucl Med Mol Imaging. 2014;41:1293–300.
9. Picchio M, Briganti A, Fanti S, Heidenreich A, Krause BJ, Messa C, et al. The role of choline positron emission tomography/computed tomography in the management of patients with prostate-specific antigen progression after radical treatment of prostate cancer. Eur Urol. 2011;59:51–60.
10. Evangelista L, Briganti A, Fanti S, Joniau S, Reske S, Schiavina R, et al. New clinical indications for (18)F/(11)C-choline, new tracers for positron emission tomography and a promising hybrid device for prostate Cancer staging: a systematic review of the literature. Eur Urol. 2016;70:161–75.
11. Jadvar H. Is there use for FDG-PET in prostate cancer? Seminars in Nucl Med. 2016;46:502–6.
12. Fanti S, Minozzi S, Morigi JJ, Giesel F, Ceci F, Uprimny C, et al. Development of standardized image interpretation for 68Ga-PSMA PET/CT to detect prostate cancer recurrent lesions. Eur J Nucl Med Mol Imaging. 2017;44:1622–35.
13. Sanco R, Zappalà M, Arnoldo V, Memo L, Zaramella E, Carraro A, et al. Methods for preparing and acquiring PET/CT exams with 18F-Fluorodeoxyglucose and 18F-Fluoromethycholine. Eur J Nucl Med Mol Imaging. 2015;42:S167.
14. von Eyben FE, Kairemo K. Acquisition with (11)C-choline and (18)F-fluorocholine PET/CT for patients with biochemical recurrence of prostate cancer: a systematic review and meta-analysis. Ann Nucl Med. 2016;30:385–92.
15. Morigi JJ, Stricker PD, van Leeuwen PJ, Tang R, Ho B, Nguyen Q, et al. Prospective comparison of 18F-Fluoromethylcholine versus 68Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. J Nucl Med. 2015;56:1185–90.