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EDITORIAL COMMENTARY

Do we have to withdraw antiandrogenic therapy in prostate cancer patients before PET/CT with [^{11}C]choline?

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Androgen deprivation therapy (ADT) is a frequent treatment used in patients with prostate cancer (PCa). ADT can be used as neoadjuvant therapy before radical prostatectomy to decrease the rates of local recurrence and positive margins, as primary treatment for PCa, and as adjuvant therapy after radical prostatectomy, in a continuous or intermittent regimen [1, 2]. ADT can be performed with different drugs, including gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, antagonists of the androgen receptor, and 5α-reductase inhibitors [1, 2]. ADT leads to depletion of testosterone levels, inactivation of the androgen receptor, or both (i.e. castration) [2]. As normal prostate cells as well as PCa cells are initially dependent on testosterone for replication and growth, many cancer cells will senesce in response to the onset of the biochemical castration state [2]. In spite of castration, many patients will experience an increase in PSA and ultimately will develop metastases (i.e. androgen-independence or hormonal resistance) [1, 2].

In the current issue of the *EJNMMI*, Fuccio et al. report their results concerning the effect of ADT on the uptake of [^{11}C]choline in 14 PCa patients who were scanned twice with PET/CT [3]. Patients were initially scanned due to biochemical failure after radical prostatectomy. Patients had never taken antiandrogenic drugs at the time of the first PET/CT scan. In 13 of the 14 patients the first [^{11}C]choline PET/CT scan was positive. After the first PET/CT scan, all patients received ADT (GnRH agonists in 12 patients, bicalutamide in 2 patients) for a minimum period of 6 months. The second [^{11}C]choline PET/CT scan was positive in only 5 of the 14 patients. All nine patients with a negative PET/CT scan after ADT initially had a positive PET/CT scan. [^{11}C]choline uptake disappeared for skeletal and extraskeletal lesions. In all these nine patients, PSA after ADT either reverted to undetectable levels or showed a substantial decrease in comparison to the baseline scan. The patient with a negative initial scan showed a positive second scan, representing a false-negative. The remaining four patients showed some increase in PSA levels as well as progression on the PET/CT scan indicating rapid evolution to hormone resistance. The authors correctly concluded that an inhibitory effect of ADT on [^{11}C]choline uptake occurred only in patients with hormone-sensitive PCa [3].

To the best of our knowledge, DeGrado et al. were the first to report an inhibitory effect of ADT on the uptake of radiolabelled choline in vivo in their initial evaluation of [^{18}F]fluorocholine [4]. These authors described the case of a 59-year-old man with untreated locally advanced PCa that displayed [^{18}F]fluorocholine uptake in the primary tumour and in several skeletal metastases. The lesions were still visible 2 months after ADT, but the intensity of uptake decreased by more than 60% [4]. De Waele et al. reported a similar case of a 57-year-old man with PCa at initial staging who displayed focal [^{11}C]choline uptake in the prostate and in multiple iliac lymph nodes [5]. After 6 months of therapy with leuprorelin and flutamide [^{11}C]choline uptake was no longer visible [5].

The study by Fuccio et al. [3] has the merit of having addressed with a sufficient sample size a timely relevant scientific question. Many studies with PET/CT and radiolabelled choline have either provided insufficient information about the ADT status of the patients or mixed hormone-sensitive patients with hormone-resistant patients

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and failed to report separate results for the two subgroups [6–10]. The results obtained by Fuccio et al. further extend previous in vitro and in vivo studies [11–13]. Hara et al. showed that androgen depletion reduces the uptake of tritiated choline in androgen-dependent LNCaP cells but not in androgen-independent PC-3 cells [11]. Similar results have been reported by Emonds et al. in a paper also published in the current issue of the *EJNMMI* [12]. These authors reported that androgens induced a time-dependent stimulation in [^{11}C]choline uptake in androgen-sensitive PC346C cells but had no effect in androgen-independent PC-3 cells [12]. Giovacchini et al. assessed the effect of neoadjuvant ADT in a small group of six patients treated with the androgen receptor antagonist bicalutamide (median treatment of 4 months) [13]. In the whole group, prostate SUV_{max} after therapy was significantly reduced compared to the baseline value, with a mean decrease of 45%. Visually, the metabolically active area was smaller after ADT than at baseline [13]. Several mechanisms could account for the decrease in [^{11}C]choline SUV_{max} after ADT, including a reduction in prostate volume (i.e. partial volume effect), atrophy of glandular cells with loss of the prostatic metabolites choline, creatine and citrate, reduced proliferation rate, downregulation of the expression of genes involved in lipid metabolism, including the choline transporter or choline kinase activity [13–18].

In summary, in vitro and in vivo studies provide strong evidence that the uptake of radiolabelled choline will be significantly reduced by ADT in patients with hormone-sensitive PCa [3–5, 11–13]. The results obtained with neoadjuvant ADT have implications for the use of [^{11}C]choline PET/CT in the initial staging of PCa, even though this indication for the use of [^{11}C]choline PET/CT remains debated [13, 19, 20]. In patients undergoing [^{11}C]choline PET/CT during initial staging, the scan should be performed before initiating ADT, or alternatively ADT should be interrupted in good time before the scan.

Different considerations apply to patients who develop biochemical failure during ADT, i.e. patients with hormone-resistant PCa. In this group of patients there are currently no available data derived from paired studies. However, useful information has been obtained from cross-sectional studies including a relatively large number of hormone-sensitive and hormone-resistant patients in which the two groups were contrasted either semiquantitatively or by appropriate statistical analysis (logistic regression) [21, 22].

A first study carried out in 358 patients with PCa found that [^{11}C]choline PET/CT scans are more frequently positive in hormone-resistant patients than in hormone-sensitive patients (56% vs. 44%, respectively) [21]. This is in contrast to the notion that ADT substantially impairs [^{11}C]choline uptake in hormone-resistant patients. Moreover, hormone resistance was a significant predictor of a positive [^{11}C]choline PET/CT scan in univariate analysis. This finding could be attributed to the greater aggressiveness of the disease and/or to the greater prevalence of other predictive factors (i.e. more advanced pathological stage, higher PSA levels, etc.) in the group of hormone-resistant patients with PCa. Similar findings were obtained by Castellucci et al. in 102 patients with PSA levels below 1.5 ng/ml [22]. Other studies that have shown a positive detection rate of the technique in both subgroups of patients, consistently showed higher percentage values in hormone-resistant patients than in hormone-sensitive patients [21, 23–26]. Overall, these results suggest that in patients who develop biochemical failure during ADT, ADT itself does not significantly affect the uptake of [^{11}C]choline in sites of disease recurrence. On the contrary, hormone-resistant patients who develop biochemical failure are more likely to show a positive [^{11}C]choline PET/CT scan than hormone-sensitive patients [21, 22, 25].

Fuccio et al. also comment in the Discussion that on the basis of their results "it may be suggested that the withdrawal of ADT before execution of [^{11}C]choline PET/CT could increase the detection rate and the intensity of choline uptake in metastatic lesions, therefore increasing the sensitivity of the [^{11}C]choline PET/CT scan" [3]. We would like to comment on this statement. Although ADT withdrawal in hormone-resistant patients could increase [^{11}C]choline uptake, the cross-sectional studies discussed above [21–26] suggest that this effect is likely to be modest. It is, however, of little importance if ADT withdrawal induces a slight increase in [^{11}C]choline uptake in some metastatic lesions. As Fuccio et al. [3] imply, the real question that needs to be addressed is whether ADT withdrawal induces a significant increase in the positive detection rate of the technique, i.e. whether it substantially decreases the number of false-negative scans. A conclusive answer to this question could be obtained only by an ad hoc defined paired study. A suitable study design would require an initial [^{11}C]choline PET/CT scan at the time of biochemical progression, then fast withdrawal of antiandrogenic drugs and acquisition of a second [^{11}C]choline PET/CT scan during pharmacological wash-out. The two paired studies should be performed with the shortest possible interval between them to avoid any progression of the disease. Castration testosterone levels are reached over 2–4 weeks after ADT, with variations depending on the drug used [1]. In the absence of strong evidence for an inhibitory effect of ADT in patients with hormone-resistant PCa, prolonged withdrawal of ADT in oncological patients experiencing progression of disease may be ethically questionable. Moreover, since 56% to 85% of hormone-resistant patients would be expected to have a positive [^{11}C]choline/[^{18}F]fluorocholine PET/CT scan [21, 23–26], systematic ADT withdrawal in all patients before PET/CT would be useless in the majority.

In summary, we feel that at the present time there is insufficient evidence to support the withdrawal of ADT on a regular basis before [^{11}C]choline (or [^{18}F]fluorocholine) PET/CT scanning in patients with hormone-resistant PCa. In addition to further ad hoc clinical data, a deeper understanding of the biochemical mechanisms underlying the inhibition of uptake of radiolabelled choline by ADT is required.

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