

PET/CT imaging and the oligometastatic prostate cancer patient: an opportunity for a curative approach with high-dose radiotherapy?

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Although not curative, androgen deprivation (AD) therapy is presently the first treatment option for patients with recurrent and/or metastatic prostate cancer [1]. Metastatic prostate cancer most frequently becomes resistant to continuous AD after an average treatment time of 2–3 years [2]. Furthermore, long-term AD may induce substantial side effects in patients compromising general health status and quality of life including cognitive and sexual impairment, fatigue, cardiovascular dysfunction, metabolic syndrome, loss of lean body mass, and osteoporosis [3–5]. Intermittent short courses of AD have been proposed as an alternative to continuous AD and tested in several phase II/III trials with the aim of reducing the severity and duration of the above-mentioned side effects and of delaying further the clinical appearance and progression of hormone-independent disease [6, 7]. However, these trials have been unable to show a survival benefit of intermittent compared to continuous AD. Nevertheless, substrata analysis from a pre-PET/CT era randomized trial (RTOG 85-31) that recruited patients between 1987 and 1992 and compared continuous AD plus radiation with radiation alone in patients with pathological node-positive adenocarcinoma of the prostate showed 5-year biochemical control (i.e. PSA <1.5 ng/ml) in 54 % of the combined treatment arm versus 33 % of the radiation-only arm [8]. The 9-year absolute survival rate was 62 % in patients treated with combined treatment [8]. In other words, patients with disease in the

pelvic or paraaortic lymph node regions treated with a combination of AD and curative intent radiotherapy can expect long-term survival despite their metastatic status.

A large majority of patients with early biochemical failure after treatment of their primary tumour with curative intent have no evidence of disease on standard imaging such as bone scan or abdominal CT unless the PSA increases above 20 ng/ml [9]. PET/CT tracers for prostate cancer, including ^{11}C -acetate, ^{11}C -choline and ^{18}F -choline, were developed more than a decade ago and their role as reliable imaging tools for assessing the extension of disease in patients with biochemical failure in an earlier stage has slowly widened [10, 11]. Head-to-head comparisons of these three different tracers are relatively scarce and frequently include only small numbers of patients. We have recently shown with PET/CT that ^{11}C -acetate and ^{18}F -choline produce very similar imaging results in patients with early relapse of prostate cancer [12]. The relapse status of local, regional and distant sites can be properly assessed with these imaging techniques so that the salvage treatment approach can be optimized.

An oligometastatic status is not an uncommon clinical situation in patients with disseminated prostate cancer. Indeed, Harada et al. observed a large proportion of patients with one or two metastases in an autopsy series of 136 patients: 36 % and 32 % of patients had one and two bone lesions, respectively [13]. Only 10 % of patients had four or more bone metastases. As mentioned above, it has been suggested that the number of metastatic lesions in prostate cancer patients may be an important prognosticator. Singh et al. reported that patients with up to five metastases had a 5-year overall survival similar to metastases-free patients and significantly better than patients with more than five metastases (73 % versus 45 %) [14]. The authors concluded that oligometastatic patients may harbour tumours biologically less aggressive with limited metastatic potential and a slow growth rate. These patients may be suitable for more aggressive treatment approaches.

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Although PET/CT imaging techniques with choline or acetate tracers are diagnostic procedures with a potentially higher predictive value than CT and bone scans, their predictive value in patients with low PSA levels (i.e. early relapse scenario) is low. Indeed, during early progression PSA may most frequently be below 4 ng/ml if the failure follows radiotherapy or far below 1 ng/ml if the failure is detected after radical prostatectomy. Such a low PSA level is limiting factor for the detection of the suspected relapse site(s) even with choline or acetate tracers. In a recent study in 156 patients with recurrent prostate cancer after surgery or radiotherapy, PSA levels tended to be significantly lower in patients with a negative PET/CT choline study (median PSA 1.2 ng/ml, range 0.1 – 30.3 ng/ml) than in those with a positive scan (median PSA 4.5 ng/ml, range 0.15 – 296.61 ng/ml) [15]. Scattoni et al. found a relatively low sensitivity of 64 % for nodal metastases with ^{11}C -choline PET/CT imaging in patients with biochemical progression after prostatectomy [16]. Delayed scanning with three-phase ^{18}F -choline PET/CT may improve the positive predictive value of this investigation by better discriminating benign from suspicious inflammatory lymph nodes [17].

Several authors have tried to use the tracing potential of choline and/or acetate PET/CT studies to develop potentially curative treatment strategies for patients with a limited number of metastases. The use of surgery (targeted lymph node resection) or high-dose targeted radiotherapy most frequently combined with AD has been described [18, 19]. In the present issue of EJNMMI, Picchio et al. report on the potential value of PET/CT choline studies for optimizing treatment with high-dose radiation beams of patients with metastatic lymph nodes at relapse. In 42 of 47 patients (90 %) assessed with a PET/CT examination after salvage irradiation they observed a complete or partial metabolic response [20]. Considering the limited sensitivity of PET/CT choline studies, as mentioned above, most of their patients were treated when feasible with extended fields including the entire pelvic or paraaortic lymph node region in the vicinity of the lymph nodes positive on PET/CT, the latter receiving an additional boost dose [20].

Nonetheless, despite the good local response rates after high-dose radiation or salvage lymph-node excision the reported 3-year biochemical progression-free survival figures are relatively modest (<30 – 40 %) [18, 19]. Only patients with a limited number of metastases on PET/CT with choline or acetate at first treatment or at relapse might be candidates for an aggressive treatment strategy that combines limited duration AD (9 – 12 months) with high-dose radiation (>64 Gy) to the tracer positive metastatic lesions. Indeed, we have recently reported on the treatment of patients with oligometastatic prostate cancer (up to four sites) combining AD (median duration 12 months) with high-dose focused radiation to the metastatic sites (lymph node and/or distant sites) detected with choline or acetate PET/CT [21]. The 3-year biochemical-free survival (PSA <1 ng/ml) and clinical failure-free survival in the 50

oligometastatic patients in this study were 54.5 % and 58.6 %, respectively. Furthermore, patients receiving a normalized total dose of >64 Gy showed a significantly better biochemical-free survival (65 % vs. 41.8 % for those receiving ≤ 64 Gy) in the multivariate analysis [21].

While the widely used choline tracers for prostate cancer show good detection rates notably for local recurrences, they appear less specific for lymph node and bone metastases. Indeed, several groups have expressed doubts about the detection of positive lymph node and bone metastases with choline tracers probably because of potential uptake artefacts caused by inflammatory reactions and degenerative bone disease, respectively. Research, notably at the preclinical level, on new radiopharmaceuticals for the detection of prostate cancer has been ongoing in recent years. Recently, the first promising clinical results with bombesin [22–24] and PSMA ligand [25–27] analogues have been reported. These two tracers are among the top currently investigated tracers that recognize gastrin-releasing peptides (GRP) and the PSMA receptors identified in large amount and in a high percentage of prostate cancers. The PSMA ligand MIP-1095 radiolabelled with ^{131}I has already been used therapeutically, and represents a new potential approach to the treatment of disseminated prostate cancer [27].

In summary, despite limited sensitivity and specificity for acetate and choline tracers, patients with oligometastatic prostate cancer may benefit from targeted high-dose irradiation of the suspected lesions associated with a short course of AD. This hypothesis needs to be confirmed in a phase III trial comparing intermittent AD with or without a complement of targeted irradiation. Optimizing the local tumoricidal effect of radiotherapy against gross disease will certainly not cure patients with oligometastatic cancer but may prolong the biochemical and clinical disease-free interval between AD cycles, thus improving the limited efficacy of AD with good quality overall survival. New upcoming tracers such as those recognizing GRP and PSMA receptors may help in the future to better assess the extension status of primary or recurrent disease and to better tailor adapted strategies aiming to optimize the potentially curative treatment of patients with oligometastatic prostate cancer.

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