



# Oligorecurrent prostate cancer limited to lymph nodes: getting our ducks in a row

## Nodal oligorecurrent prostate cancer

Andrei Fodor<sup>1</sup> · Andrea Lancia<sup>2</sup>  · Francesco Ceci<sup>3</sup> · Maria Picchio<sup>4</sup> · Morten Hoyer<sup>5</sup> · Barbara Alicja Jereczek-Fossa<sup>6,7</sup> · Piet Ost<sup>8</sup> · Paolo Castellucci<sup>9</sup> · Elena Incerti<sup>4</sup> · Nadia Di Muzio<sup>1</sup> · Gianluca Ingrosso<sup>2</sup>

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### Abstract

**Purpose** Oligorecurrent prostate cancer with exclusive nodal involvement represents a common state of disease, amenable to local therapy. New radio-labeled tracers have enriched the possibility of cancer detection and treatment. In this review, we aim to illustrate the main nuclear medicine diagnostic options and the role of radiotherapy in this setting of patients.

**Methods** We performed a PubMed search referring to the PRISMA guidelines to analyze the performance of PSMA- and choline-PET in detecting oligorecurrence limited to lymph nodes, and to review the main studies supporting either ablative stereotactic body radiotherapy or regional lymph node irradiation in this clinical setting.

**Results** PSMA-PET has shown higher efficacy in the diagnosis of nodal lesions if compared with choline-PET. More specifically, for PSA  $\leq 2$  ng/ml, the median detection rate of choline-PET ranges from 19.5 to 44.5%, whereas PSMA ranges from 51.5 to 74%. SBRT achieves high local control rates positively affecting progression-free survival (PFS), with androgen deprivation therapy (ADT)-free survival ranging from 25 to 44 months and with low toxicity rates (0–15%). Prophylactic nodal irradiation shows 3-year PFS rates ranging from 62 to 75%, but with a potential higher risk of toxicity. However, the chosen treatment option needs to be tailored on the single patient.

**Conclusions** Newer PET/CT radio-labeled tracers have increased disease detection in oligorecurrent prostate cancer patients. Growing evidence of their impact on metastasis-directed therapy encourages the use of the most advanced radiotherapy techniques in the clinical management of such patients.

**Keywords** Oligorecurrent · Prostate cancer · Radiotherapy · Choline · PSMA · SBRT

✉ Andrea Lancia  
andrea.lancia.dr@gmail.com

<sup>1</sup> Department of Radiation Oncology, San Raffaele Scientific Institute, Milan, Italy

<sup>2</sup> Department of Radiotherapy, Tor Vergata General Hospital, Viale Oxford 81, 00133 Rome, Italy

<sup>3</sup> Department of Molecular and Medical Pharmacology, Ahmanson Translational Imaging Division, University of California at Los Angeles (UCLA), Los Angeles, USA

<sup>4</sup> Unit of Nuclear Medicine, San Raffaele Scientific Institute, Milan, Italy

<sup>5</sup> Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

<sup>6</sup> Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy

<sup>7</sup> Department of Radiation Oncology, European Institute of Oncology, Milan, Italy

<sup>8</sup> Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium

<sup>9</sup> Nuclear Medicine Unit, University of Bologna, S. Orsola Hospital Bologna, Bologna, Italy

## Introduction

Oligorecurrent prostate cancer limited to lymph nodes may be a very favorable clinical condition, which can be diagnosed using both functional and/or morphologic imaging modalities, such as Positron Emission Tomography (PET) [1] and whole-body Magnetic Resonance Imaging (MRI) [2]. Metastasis-directed therapy, administered with curative intent, could represent the appropriate therapeutic strategy in this clinical setting [3–10]. This treatment option might improve the overall survival, retard disease progression, and the onset of endocrine therapy, which can have a detrimental effect on patients' quality of life. One of the main issues in everyday clinics is that we are currently nowhere near the detection of minimal disease. In this setting, prostate cancer-specific PET radiotracers will help to delineate a new scenario in the therapy of oligometastatic prostate cancer. New imaging tools, such as Prostate Specific Membrane Antigen (PSMA)-PET, are going to improve the diagnosis and treatment decision-making [11–14].

The aim of the present work is to highlight the nuclear medicine diagnostic options and radiotherapy as a treatment modality in patients affected by hormone-sensitive oligorecurrent prostate cancer limited to lymph nodes.

## Materials and methods

We reviewed the current literature and gave an overview report on PET and radiotherapy options in patients affected by oligorecurrent prostate cancer limited to lymph nodes. Concerning PET, several radiotracers including  $^{11}\text{C}$ -choline,  $^{18}\text{F}$ -choline,  $^{18}\text{F}$ -fluciclovine, and  $^{68}\text{Ga}$ -PSMA are available in recurrent prostate cancer diagnosis [1, 7, 13–15]. We limited the scope of our search to choline- and PSMA-PET because of the current availability of data in the literature about these tracers and because of their wide clinical use in Europe [15].

We performed a PubMed literature search according to the preferred reporting items and meta-analysis (PRISMA) guidelines [16]. We identified articles published within the last 10 years, up to September 30th 2017, using Medline search with the following selection criteria: English language, full papers, diagnosis of oligorecurrent prostate cancer limited to lymph nodes with choline- and/or PSMA-PET, and treatment of oligorecurrent prostate cancer limited to lymph nodes with radiotherapy. The following Medline terms were used: prostate cancer, lymph node metastasis, lymph node recurrence, oligometastatic prostate cancer, oligorecurrent prostate cancer, positron

emission tomography, PET, choline-PET,  $^{11}\text{C}$ -choline or  $^{18}\text{F}$ -choline-PET, prostate-specific membrane antigen PET, PSMA-PET, metastasis-directed radiotherapy, stereotactic radiotherapy, stereotactic body radiotherapy, radiosurgery, stereotactic ablative radiotherapy, regional lymph node radiotherapy, and prophylactic lymph node radiotherapy. Two authors (A.L. and G.I.) independently performed the study selection. Disagreements were resolved by consensus with two authors (P.O. and A.F.). We reviewed the full version of each article.

## Results

### Nuclear medicine diagnostic options

In the following sections, we discuss the role of choline-PET and PSMA-PET in patients affected by oligorecurrent prostate cancer limited to lymph nodes.

### Choline-PET

$^{11}\text{C}/^{18}\text{F}$ -choline Positron Emission Tomography/Computed Tomography (PET/CT) is the most studied PET diagnostic modality to evaluate prostate cancer patients, particularly in the context of restaging following rising PSA. A meta-analysis (12 studies,  $n$  patients = 1055) demonstrated that choline-PET/CT showed pooled per-patient sensitivity and specificity of 85 and 88%, respectively, in detecting metastases in the setting of biochemical relapse [1], being a useful diagnostic tool for guiding tailored treatments when a definitive diagnosis of recurrence cannot be achieved with conventional imaging modalities [3, 4]. On the other hand, it showed a low sensitivity (33%) in detecting lymph node metastases, while its specificity remained high (92%) [17].

With the aim of analyzing the anatomical patterns of recurrence in patients affected by biochemical relapse after primary treatment, De Bruycker et al. [18] identified 625 lesions in 208 patients who underwent choline-PET, and defined them as “low volume” and “high volume” patients considering the number of detected metastases (respectively, having three or less metastases and more than three). The median PSA value at the time of choline-PET was 11.3 ng/ml in the “low volume” cohort and 13.8 ng/ml in the “high volume” group. Seventy percent of the metastases were located at the nodal stations (50% in the pelvic region). Pathological confirmation was available only in 69 (33%) patients, whereas in the remaining 139, the diagnosis of metastasis was based on clinical data (i.e., continued increasing PSA and lesion progression, PSA decrease, and iconographic metastasis regression after therapy) [18]. In the series by Graziani et al. [19], with a median PSA value at the time of positive choline-PET of 2.1 ng/ml in 2337

patients, a lymph node involvement was described in 64% (1497) of the cases. When looking at the site of prostate cancer recurrence, we can argue that, according to data in the literature, lymph node recurrence is the most dominant failure pattern outside the prostatic fossa [18–21]. Hence, a lymph node metastasis-directed therapy could be a useful treatment option to delay disease progression.

Currently, according to the EAU (European Association of Urology)–ESTRO (European Society for Radiotherapy and Oncology)–SIOG (International Society of Geriatric Oncology) guidelines on prostate cancer, choline-PET/CT is the recommended imaging tool for restaging patients in the setting of oligorecurrence [10], but the new tracer  $^{68}\text{Ga}$ -PSMA demonstrates higher accuracy for disease detection in patients with biochemical relapse.

### PSMA-PET

Novel imaging approaches to measure the expression of the prostate specific membrane antigen have been recently introduced. PSMA, the Glutamate Carboxypeptidase II (GCP II), is a membrane bound metallopeptidase physiologically expressed in several tissues. Although the function of GCP II in prostate remains unclear, it is well known that this protein is over expressed in 90–100% of prostate cancer lesions [11]. As a consequence, due to its selective over expression, PSMA is a reliable tissue marker for prostate cancer and is considered an ideal target for tumor-specific imaging and therapy [12]. The precise localization of the catalytic site of PSMA in extracellular domain allowed for the development of small, highly specific urea-based inhibitors that are internalized inside the cell after ligand binding [11]. A variety of PET probes targeting this peptide receptor have been introduced [13] and these agents are undergoing extensive clinical evaluations [14, 22]. Furthermore, PSMA inhibitors can be radio-labeled with diagnostic ( $^{68}\text{Ga}$  or  $^{18}\text{F}$ ), or therapeutic nuclides ( $^{177}\text{Lu}$  or  $^{225}\text{Ac}$ ), to be used for radio ligand therapy (RLT) [23]. Initial results attest to a high accuracy for disease detection in patients with biochemical recurrence [14, 22]. More specifically, PSMA-based imaging has shown in a prospective study a better performance compared with the well-established direct competitor as choline-PET/CT [24]. This novel imaging procedure showed the best performance in patients in the early stages of the biochemical recurrence, namely, those with low-PSA levels [14]. According to a recent meta-analysis evaluating a total of 736 recurrent patients over 12 studies, a detection rate of 65% was calculated in patients in the range of PSA comprised between 0.2 and 2 ng/ml [25]. Based on the few studies concerning histological validation, PSMA has a high diagnostic accuracy, with per-lesion sensitivity and specificity of 80 and 97%, respectively; per-patient sensitivity and specificity are 86% in both cases [17].

As patients with biochemical recurrence are still potentially curable, the ability to precisely localize recurrence site(s) is critically important as it facilitates their stratification into the best therapeutic approach that encompasses salvage radiation therapy, metastasis-directed therapy, and medical treatment or combination therapies [3]. Recently, Calais et al. [26] performed an intention-to-treat analysis in a cohort of 270 recurrent prostate cancer patients with PSA < 1 ng/ml and suitable for salvage radiotherapy. Authors evaluated how often salvage radiotherapy based on consensus contouring guidelines fails to cover PSMA-expressing disease, thus assessing the potential impact of  $^{68}\text{Ga}$ -PSMA-PET/CT on treatment volume definition. Forty-nine percent of patients had a positive  $^{68}\text{Ga}$ -PSMA-PET/CT, with 19% having at least one PSMA-positive lesion for which there was no uniform consensus in the delineation of their clinical target volumes (CTVs) and 12% of them having extra-pelvic PSMA-positive lesions. On one hand, this multicenter post hoc analysis highlighted the importance of PSMA-based imaging to address salvage therapy. On the other hand, these results justify a randomized prospective trial to determine whether  $^{68}\text{Ga}$ -PSMA-PET/CT can improve outcomes in patients with prostate cancer and early biochemical recurrence. Finally, the impact of this novel imaging procedure on the clinical management was evaluated in some recent studies [27, 28]. The data were concordant in assessing a valuable impact of  $^{68}\text{Ga}$ -PSMA-PET/CT in salvage treatment planning, which ranges from 40 to 76% in different cohort of recurrent patients. Emmett et al. [29] analyzed data on 164 patients with biochemical failure after radical prostatectomy treated with PSMA-informed salvage radiotherapy. The authors concluded that PSMA is independently predictive of treatment response to salvage radiotherapy, and patients with a negative-PSMA-PET/CT who underwent radiotherapy to the prostatic bed had a better biochemical outcome compared with those not treated [29]. In conclusion, PSMA-based PET imaging already proved higher accuracy compared to direct PET imaging competitors and conventional radiological imaging. Therefore, salvage therapies guided by this highly accurate imaging procedure could significantly affect patient management.

### Radiotherapy

The new available nuclear medicine imaging tools to detect minimal disease make metastasis-directed therapy appealing in prostate cancer. In the following sections, we discuss the radiotherapy treatment options in patients affected by oligorecurrent prostate cancer limited to lymph nodes.

## Ablative stereotactic body radiotherapy

In oligorecurrent prostate cancer, it is possible to utilize SBRT to deliver ablative doses of radiation ( $\geq 5$  Gy per fraction for biologically effective doses of at least 80 Gy assuming  $\alpha/\beta$  of 3 Gy) [3, 30]. Several studies have shown that it is possible to obtain local control rates near to 100% with dose fractionation schedules varying from 5 to 11 Gy per fraction to a total dose of 25–50 Gy [3, 30]. SBRT seems to be a useful tool in patients with a limited number of metastases (less than three or five) [3, 30–35], and the subgroup with oligorecurrence confined to lymph nodes might benefit most from this treatment modality, which positively impact on disease control and may defer palliative androgen deprivation therapy (ADT) [5, 30, 34]. SBRT is a non-invasive treatment delivered on outpatient basis, with a low-toxicity profile ranging from 0 to 15% [3, 30].

Several retrospective studies investigated the impact of SBRT on nodal recurrence after primary treatment. In an analysis of a multicenter cohort, Ost et al. reported the pattern of relapse after SBRT in 72 patients with oligorecurrent nodal prostate cancer [5]. No patient had neoadjuvant or concomitant ADT. Median PSA at the time of SBRT was 3.4 ng/ml [interquartile (IQR), 1.6–7.7], 76% of cases had a single nodal involvement, and 73% of oligorecurrent metastases occurred in the pelvic region. With a median follow-up of 3 years, they found a 3- and 5-year progression-free survival (PFS) of 34 and 13%, respectively, and the median ADT-free survival was 44 months. The majority of relapses (68%) after SBRT were found to be in nodal regions, addressing the presence of undetectable micrometastases that seems to cause mainly oligoprogression rather than widespread disease. This progression pattern might give the possibility of a repeated SBRT strategy, similar to what has been described for brain metastases and the use of stereotactic radiosurgery. Likewise, the combination of prophylactic regional nodal irradiation and ablative boost to the nodal lesion could also represent an appropriate treatment.

A recent systematic review [30] analyzed 211 patients, collected from nine studies, and treated with SBRT for 270 lymph nodes. Of the total cohort, 162 (76.7%) patients were treated with SBRT for pelvic node oligorecurrence. Choline-PET/CT was the most used staging modality, and was performed at a median PSA value of 4.2 ng/ml (range 1.77–16). With a median follow-up of 21.9 months (range 4.4–36), local control was achieved in 98.1% of patients, and median PFS (defined as biochemical and/or radiological progression) was 22.5 months (range 11–30). The median ADT-free survival was 32.8 months (range 25–44). In the retrospective study by Jereczek et al. [35], the analysis on 94 patients who underwent salvage SBRT (93% Linac-based, 7% with Cyberknife) for 124 lymph node metastases showed that after a median follow-up of 18.5 months, the 2-year local

control and PFS were 84 and 30%, respectively. The median PSA value at the time of SBRT was 3.5 ng/ml (IQR 1.6–6.1), and 60.5% of irradiated lymph nodes were located in the pelvic region. At multivariate analysis, age above 75 years, ADT up to 12 months, and pelvic lymph node involvement were correlated with longer PFS. Pre-SBRT PSA value  $> 10$  had a negative impact on biochemical control. It seems that also a Gleason score  $\geq 8$  might be correlated with a worse biochemical control [32].

## Regional lymph node irradiation

Prophylactic regional lymph node irradiation could represent a therapeutic option in the management of nodal oligorecurrent prostate cancer patients, despite relatively few studies on this issue have been published in the literature [36–38]. This treatment strategy after salvage lymph node dissection results in a significant delay of nodal relapse within the treated region compared with surgery only (5-year relapse-free survival of 70.7 vs 26.3%,  $p < 0.0001$ ) [39].

Wurschmidt et al. [36] treated 19 recurrent prostate cancer patients with salvage whole-pelvis radiotherapy based on choline-PET findings. Median PSA at the time of choline-PET was 1.9 ng/ml. A total dose ranging from 45 to 50.4 Gy was delivered to the pelvic lymph nodes, with a boost of 66.6 Gy delivered to the PET-positive nodes. Three-year biochemical relapse-free survival (b-RFS) was 49% with a median survival of 28.3 months; 3-year distant relapse-free survival (DRFS) was 75%. Schick et al. [37] reported the outcome of 43 patients treated with radiotherapy for nodal metastases. More specifically, 26 patients received regional lymph node irradiation (21 for pelvic node metastases and 5 for pelvic and extra-pelvic) at a median total dose of 50.4 Gy with a median boost dose of 65 Gy to the choline-PET-positive nodes, in combination with 1 year of ADT. At 3 years, b-RFS was 54.5% and clinical failure-free survival (defined as the time from radiotherapy to the development of new metastases) was 58.6%.

In 81 patients with biochemical relapse (78 post-surgical, 3 after radical radiotherapy) and positive lymph nodes at 11-carbon-choline-PET/CT, Fodor et al. [38] treated in-field radiotherapy-naïve patients with regional (pelvic and/or lombo-aortic) irradiation at a median dose of 51.8 Gy/28 fractions with simultaneous integrated boost (SIB) up to 65.5 Gy on positive nodes. Patients previously irradiated to the same volume were treated on the corresponding lymph node chain with high doses, without SIB. Twelve months of ADT were prescribed in all except 20 patients, and 22 were already castration-resistant. PSA response at 3 months was registered in 91.4% of patients. Three-year overall survival was 80%, local control was 90%, and clinical relapse-free survival (local and distant) was 62%. Again, a low number

of positive nodes, and pelvic-located recurrence were positive prognostic factors.

## Discussion

### Recommendation on the most suitable diagnostic procedure

In the setting of biochemical recurrence after primary treatment, data in the literature suggest that PSMA has the potential to overcome the limitations of choline-PET at PSA levels < 2 ng/ml [24, 25, 40]. More specifically, two studies (one prospective and the other retrospective) demonstrated a higher detection rate (histologically verified) of local relapses, secondary lymph nodes, and bone lesions revealed by PSMA compared with choline-PET, which is more evident at low-PSA value (< 1 ng/ml) [24, 40]. In a recent review, ten studies on choline-PET and six on PSMA-PET were compared based on PSA cut-off values [15]. Median choline and PSMA detection rate at PSA < 1 ng/ml were 19.5% (range 7–44%) and 51.5% (range 29–67%), respectively. For PSA ranging from 1 to 2 ng/ml, choline-PET had a median detection rate of 44.5% (range 29–81%), whereas the median PSMA value was 74% (range 46–93%). Finally, for PSA > 2 ng/ml, the median values were 76% (range 54–89%) and 90.5% (range 71–93%) for choline and PSMA, respectively.

About the comparison of PET findings with histology, data on PSMA revealed its high diagnostic accuracy (per-lesion specificity of 97% and sensitivity of 80%; per-patient specificity and sensitivity both of 86%) [25], whereas choline has a high specificity (92%) but a low sensitivity (33%) in detecting lymph node metastases [17]. Further studies on histological validation are still necessary.

In conclusion, PSMA-PET represents a very promising tool in patients affected by biochemical recurrence showing a PSA value < 2 ng/ml, to better guide a potentially curable local treatment.

### Recommendation on the most suitable radiotherapy scenario

Metastasis-directed radiotherapy in oligorecurrent prostate cancer patients could be the optimal salvage treatment in a subset of patients, or it might postpone palliative ADT and, therefore, preserve the quality of life. Although a recent post hoc analysis of the STAMPEDE trial evidenced, with a short median follow-up (17 months) and a low event rate, the positive impact of adding radiotherapy to ADT in patients with newly diagnosed nonmetastatic prostate cancer with pelvic nodal involvement [41], no randomized trials data are currently available. Concerning oligorecurrent prostate cancer

patients with exclusive nodal involvement, to date, only retrospective works have been published in the literature analyzing the role of radiotherapy in this setting. Two different strategies are available, individual lymph node ablative irradiation, or prophylactic extended node irradiation combined with a boost to positive nodes. SBRT achieves high local control rates positively affecting PFS, with ADT-free survival ranging from 25 to 44 months and with low toxicity rates (0–15%) [30]. Prophylactic nodal irradiation shows 3-year PFS rates ranging from 62 to 75% [36–38]. Although delivered with intensity-modulated technique using image guidance, the main drawback of extended nodal irradiation could be the potential increase of toxicity. Based on surgical series [17, 42], regional irradiation could be the more appropriate salvage local treatment due to occult micrometastatic disease in neighboring lymph nodes. To date, choline-PET has been the most established imaging tool to evaluate patients affected by biochemical recurrence [1] and to guide irradiation [3, 30–35], but PSMA-PET shows a better performance [15, 24, 25]. This imaging procedure is improving treatment selection by detecting oligorecurrent disease in an early stage or by upstaging an apparent oligorecurrent disease. Finally, novel biomarkers and genomic profiling will further lead to a precise selection of patients with low burden of disease who could be treated only with localized ablative radiotherapy, potentially obviating the need of regional prophylactic nodal irradiation and postponing the start of systemic therapy.

In conclusion, the chosen treatment option needs to be tailored on the single patient. Randomized trials [4, 43] will help the physician in decision-making. With a median follow-up of 3 years, data from the STOMP trial [44] show that oligometastatic prostate cancer patients (with up to three extracranial metastases) treated with metastasis-directed therapy have a longer ADT-free survival compared with the surveillance subgroup. OLIGOPELVIS [43] trial prospectively investigates the impact of pelvic radiotherapy in terms of overall survival, PFS, ADT-free survival, and quality of life in patients with oligorecurrence confined to lymph nodes, compared with standard of care.

## Conclusions

Prostate cancer patients with oligorecurrence confined to lymph nodes represent a very early metastatic setting. Advances in molecular imaging will have a pivotal role in the definition of this state of disease [45], which could be amenable of local curative therapy. Although currently supported by a weak level of evidence, metastasis-directed therapies in this subgroup of patients reduce disease burden, delay clinical progression, and retard the onset of ADT.

**Authors contribution** AF, AL, and GI made substantial contributions to conception and design of the study. AF, AL, GI, FC, NDM, EI, MP, and PC participated in drafting the article and revised it critically for important intellectual content. PO, BAJF, MH, and GI gave the final approval of the version to be submitted and any revised version.

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### Compliance with ethical standards

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Informed consent** For this type of study, formal consent is not required.

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