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Oligometastatic Disease in Prostate Cancer: Advances in Diagnosis and Treatment

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Abstract

Prostate cancer (PC) is the second most common cancer in men and the fifth leading cause of death in men worldwide in 2012 [1]. Oligometastatic disease is defined as the presence of five or fewer metastatic or recurrent lesions that could be treated by local therapy to achieve long-term survival or cure [2]. Androgen deprivation therapy is currently the accepted treatment of metastatic PC. However, the identification of oligometastatic disease in PC with the improvements in diagnostic imaging has lead to early treatment of these isolated metastases showing some benefit [3]. In this chapter, we aim to discuss the newer modalities used in the identification of oligometastatic disease in PC and the advances in treatment.

Keywords: Oligometastases, prostate cancer, diagnosis, treatment

1. Introduction

Although oligometastases forms a recent vogue in prostate cancer, the concept of ‘oligometastases’ was originally described by Hellman and Weichselbaum in 1995 [4]. They theorised that metastases occurred as a ‘metastatic progression’ from localised disease to widespread systemic disease [5]. As such, in some patients with limited metastases, they described an ‘oligometastatic state’ which occurs as a transitional state between localised and systemic disease [5]. Therefore, rather than classifying all metastatic prostate cancer in to a universal cohort with poor outcomes, this defined a group of patients who could be identified and treated with potentially favourable results.

1.1. Definitions

The nomenclature in 'oligometastases' is often used interchangeably and can be sometimes confusing. The term 'oligometastasis' usually refers to metastases (from tumours early in the chain of progression) limited in number and location because the facility for metastatic growth has not been fully developed and the site for growth is restricted, while 'oligometastatic disease' is defined as solitary or few detectable metastatic lesions (<5 metastases) that are usually confined to a single organ [5]. Although sometimes oligometastases can refer to synchronous or metachronous disease, it should be stressed that the key feature determining the behaviour of oligometastases is its metastatic potential. As such, 'true oligometastases' are defined as oligometastases with limited metastatic potential, while 'induced oligometastases' occur following successful systemic treatment have more extensive malignant capacities and were spared from eradication by pharmacological means, local immunological conditions or from the development of resistant clones [6].

In prostate cancer, induced oligometastases can be further divided into those with a rising PSA following primary therapy who has oligometastases on imaging or those with castrate-resistant prostate cancer (CRPC) with a rising PSA level and image-detected oligometastases [7].

2. The evidence for treatment of oligometastases

Treatment of liver metastases in colorectal cancer, lung metastases from a variety of cancers and adrenal metastases in lung cancer have demonstrated improved survival and in some cases even cure; forming the basis of treating oligometastases in cancers [6]. Currently, androgen deprivation therapy is the optimal treatment for widespread metastatic prostate cancer. Studies have demonstrated that those men on androgen deprivation therapy for ≤ 3 metastases had much superior outcomes compared to those with larger number of metastases [8, 9]. A further study demonstrated that men with prostate cancer who developed ≤ 5 metastatic sites had better survival than those with > 5 lesions [10]. With the recent shift, the landscape of prostate cancer diagnostics and treatments has changed significantly offering the opportunity to accurately identify and treat the oligometastases. Treatment of oligometastases in prostate cancer can offer better local cancer control and reduce the systematic metastatic potential and its complications by reducing seeding of established metastases control of the overall disease burden and perhaps even cure [7]. In addition, the treatment of oligometastatic disease in prostate cancer delays the need for androgen deprivation and its associated systemic side effects.

3. Biology of oligometastases

As described in Paget's 'seed and soil' hypothesis, metastases occur due to an interaction between the tumour cell and the targeted organ, which supports the secondary growth of the

primary tumour cells [6, 11]. This is a complex and selective process which promotes tumour growth by tumour diversity due to the genetic instability of the tumour cells due to the telomere erosion, mutations in tumour-suppressor and DNA-repair genes, and intrinsic tumour metabolism (aerobic glycolysis) that is toxic to surrounding normal cell and suppression of the host immunity [6]. A number of genes contribute to this metastatic process such as metastasis 'initiation' genes; metastasis 'progression' genes and metastasis 'virulence' genes by altering cell adhesion, intravasation, survival in the circulation, extravasation, seeding in a distant site, invasion, and development of the appropriate microenvironment in host organs and provides a selective advantage of the primary tumour cells to be preserved and amplified during tumour progression [6]. As such, these primary tumour cells that have limited capability in one or more of the necessary biological requirements for metastasis form the basis of oligometastases [6].

4. Advances in imaging modalities: identification of oligometastases in prostate cancer

4.1. The conventional modalities: computed tomography (CT) and skeletal scintigraphy (^{99m}Tc -MDP bone scan)

CT of the abdomen and pelvis forms the main modality of staging patients with intermediate or high-risk disease generating valuable information of local advancement, lymph node and bony involvement of prostate cancer [12] (**Figure 1**). Studies have demonstrated its specificity and positive predictive value up to 100%, but its sensitivity remains poor [13]. As such, CT is gradually being superseded by MRI and the combination PET/CT in recurrent prostate cancer and oligometastatic disease.



Figure 1. The CT scan of the abdomen and pelvis demonstrates a pelvic lymph node denoted by the white arrow.

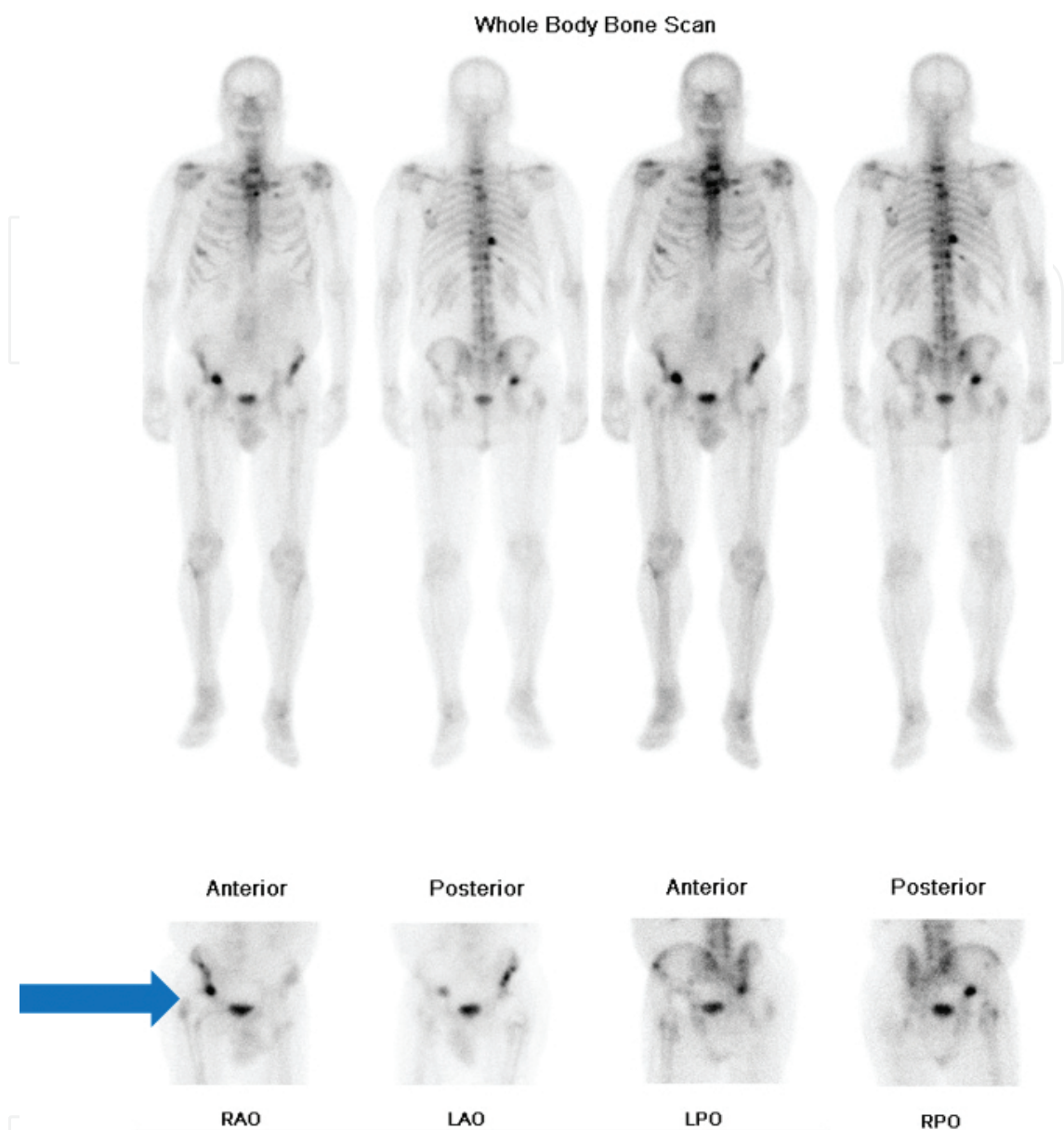


Figure 2. The isotope bone scan demonstrates uptake at the right acetabulum (blue arrow) with several areas of focal uptake in the axial skeleton, in the ribs and in the left scapula.

^{99m}Tc -methylene diphosphonate (MDP) bone scan is the main imaging modality used to assess the burden of skeletal disease in patients with PC in intermediate or high-risk PC or those with symptoms of bony metastases [12] (**Figure 2**). However, bone scintigraphy can be non-specific and can show increase bone uptake in degenerative joint disease, benign fractures and inflammation in addition to metastases [14]. However, further functional and anatomical details can be obtained by integrating the SPECT/CT along with skeletal scintigraphy. While the negative predictive value of the bone scan is estimated between 87 and 100% in the literature, its diagnostic yield is highly dependent on the PSA level and clinical stage [12]. As such bone scans have a poor yield in the early detection of prostate cancer recurrences post-definitive treatment.

4.2. The newer imaging modalities

4.2.1. Multi-parametric magnetic resonance imaging (MP-MRI)

MP-MRI forms an integral role in diagnosis of prostate cancer and localisation for prostatic biopsy. In addition, it is a very useful tool in determining extra prostatic extension, lymph nodes or bony metastases in prostate cancer.

A number of studies have demonstrated promising results in detecting local recurrences post-radical prostatectomy using MP-MRI. In patients with biochemical recurrence post-radical prostatectomy, MP-MRI can help determine loco-regional relapse and small amounts of healthy residual glandular tissue, scar/fibrosis and granulation tissue, and it may even enable assessment of the aggressiveness of nodule recurrence by means of ADC values and help identify tumour deposits and target treatment [15]. One study demonstrated sensitivities and specificities of 84–88 and 89–100%, respectively in detection of recurrences post-radical prostatectomy using MP-MRI [16].

One of the limitations of MRI is the poor detection of pelvic lymph nodes at PSA levels <0.5 ng/mL, threshold usually used for salvage therapy. One of the main reasons for this being that 70% of lymph-node metastases in prostate cancer is <8 mm [17]. In 2008, a meta-analysis of 24 studies demonstrated that both CT and MRI scans were both poor at detecting pelvic lymph-node metastases and there were no differences between the modalities [18]. In fact, they concluded that reliance on either CT or MRI will misrepresent the patient's true status regarding nodal metastases, and thus misdirect the therapeutic strategies offered to the patient [18]. However, there have been significant advances in better anatomical imaging since the introduction of MP-MRI scans and technology such as lymphotropic nanoparticle-enhanced MRI can improve the lymph-node detection as well as for biopsy targeting and guidance of salvage treatment [19].

The increasing use of whole body MP-MRI may be the future of staging patients with oligo-metastatic prostate cancer, as this can also be used to detect bony metastases with good accuracy [20]. However, this technology is currently mainly limited due to cost and needs further validation.

4.2.2. Positron emission tomography (PET) scan

Positron emission tomography (PET) scan is a functional scan which commonly uses ¹⁸F-labeled sodium fluoride (¹⁸F-NaF) and ¹⁸F-labeled 2-fluoro-2-deoxy-Dglucose (¹⁸F-FDG) as a radiotracer to detect a metabolic process associated with PC and is fused with a CT to determine the anatomic location of this process. Despite the role of ¹⁸F-FDG PET/CT in detecting occult metastatic disease in men with biochemical recurrence, and the high detection rates of osseous metastases with ¹⁸F-NaF PET/CT compared to standard imaging [21], they are still not recommended as first-line imaging modalities due to poor sensitivities in at low PSA levels and in high-grade tumours [12, 22–24].

A recent meta-analysis by Evangelista et al. concluded that Choline PET and PET/CT represent high sensitivity and specificity techniques for the detection of loco-regional and distant

metastases in prostate cancer patients with recurrence of disease demonstrating a pooled sensitivity of 85.6% and a pooled specificity of 92.6% for all sites of disease (prostatic fossa, lymph nodes and bone) [25]. They further demonstrated a pooled sensitivity of 100% (95% CI 90.5–100%) and pooled specificity of 81.8% (95% CI 48.2–97.7%) for lymph-node metastases [25]. In accordance, majority of the studies investigating recurrent oligometastatic prostate cancer utilised Choline PET as the imaging modality of choice [26].

4.2.3. Prostate specific membrane antigen PET/CT (PSMA PET/CT)

^{68}Ga -PSMA-ligand PET/CT utilises the prostate specific membrane antigen which is significantly upregulated in prostate cancer. Although the data for PSMA PET/CT scan in recurrence of prostate cancer is limited, the early results have been promising. ^{68}Ga -PSMA-PET improves detection of lymph nodes, bone or visceral metastases compared with standard imaging (Figures 3 and 4). One study demonstrated a specificity of 98.9% and sensitivity 65% for detection of pelvic lymph-node disease in prostate cancer with PSMA PET, much better than standard imaging modalities [27]. Furthermore, PSMA-PET-MRI or PSMA-PET-CT enables a complete staging procedure to be performed by a single examination compared with the standard staging combination of CT and bone scan.

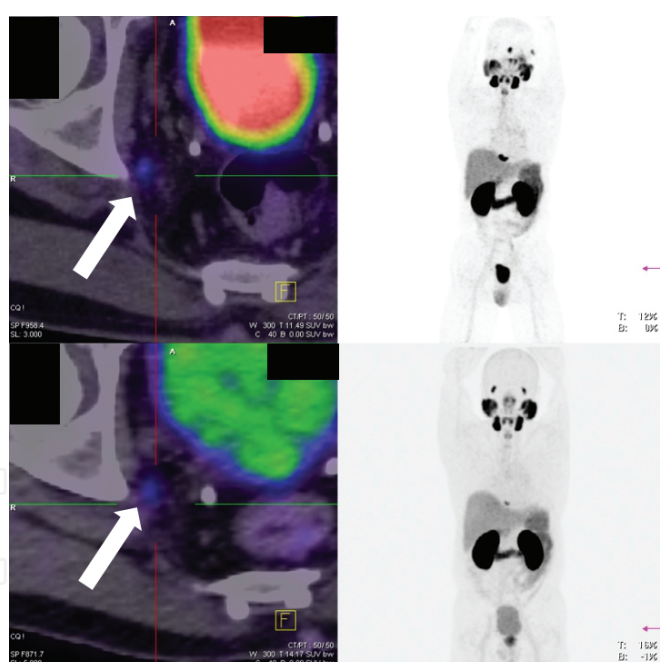


Figure 3. The PSMA PET scan demonstrates uptake of the tracer in an internal iliac node denoted by the white arrow.

One study using data from 319 patients showed a sensitivity, specificity, negative predictive value and positive predictive value of PSMA PET/CT of 76.6, 100, 91.4 and 100%, respectively, in the detection of recurrent prostate cancer [28]. The PSMA detection of recurrent prostate cancer improved with higher PSA levels and the use of androgen deprivation therapy [28]. A further study of 248 patients replicated the accuracy of PSMA-PET with an overall detection

rate of 89.5% with a mean PSA value of 1.99 ng/ml [29]. As such, PSMA PET/CT is increasingly being used in studies focussed on oligometastatic disease and may form the cornerstone in detection and management of oligometastatic disease.

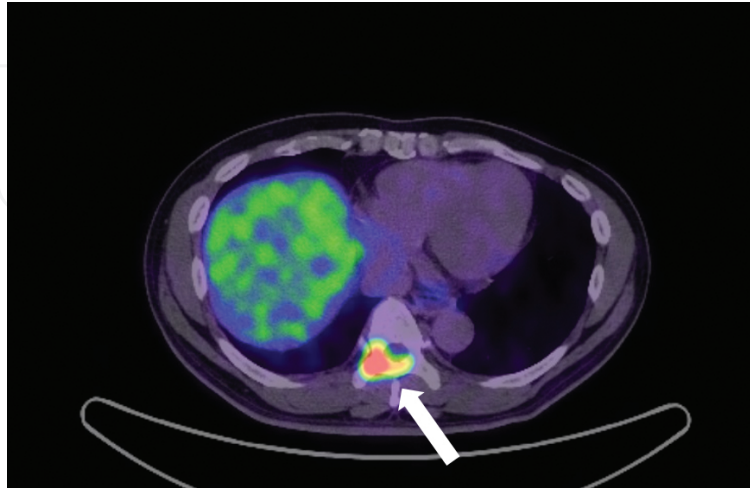


Figure 4. The PSMA PET scan demonstrates uptake of the tracer in a spine at the T9 level denoted by the white arrow.

5. Advances in treatment: treatment of oligometastatic prostate cancer

The conventional treatment of metastatic prostate cancer of androgen deprivation therapy is associated with a number of systemic side effects most importantly cardiovascular disease, and a large majority of patients will develop resistance to androgen deprivation. As such, metastases directed treatment of oligometastatic disease provides opportunity to select and treat this group of patients, delay the need for androgen deprivation or perhaps even cure.

5.1. Synchronous oligometastatic prostate cancer

5.1.1. Radical prostatectomy

Based on the responses seen by cytoreductive therapy in other cancers such as ovarian, breast and renal cell carcinoma, a few recent studies have investigated the role of radical prostatectomy in metastatic prostate cancer. Using the SEER database of 8185 men with stage IV M1 prostate cancer, Culp et al. demonstrated that a reduction in cancer specific mortality in men undergoing radical prostatectomy or brachytherapy [30]. They demonstrated a 44.8% improvement in 5-year overall survival and 27.1% improvement disease-specific survival in this cohort undergoing radical prostatectomy compared with those who did not have surgery or radiotherapy [30]. However, there were a few significant limitations in this study including the use of systemic therapy. A further study by Engel et al. replicated these findings using the Munich Cancer registry data demonstrating an improved survival in those who underwent a radical prostatectomy in the presence of lymph-node metastases [31]. While these results

appear to be promising, in the absence of prospective randomised controlled study data, radical prostatectomy for oligometastatic disease should be currently considered experimental.

5.2. Recurrent disease: oligometastases after primary curative therapy

5.2.1. Salvage lymph-node dissection

Salvage lymph-node dissection in the setting of oligometastatic prostate cancer is limited to a number of cohort studies, with the largest being 59 patients [32]. Recently, a systematic review combined the results of these smaller series and reported on the results of 151 patients undergoing salvage pelvic, retroperitoneal or pelvic and retroperitoneal lymph-node dissection for oligometastatic disease [26]. Majority of the studies performed an open salvage lymph-node dissection with a median two positive nodes removed with 49 patients receiving post-operative prophylactic nodal irradiation and adjuvant ADT in 54% [26].

In the reported largest series with the longest follow-up of 59 patients undergoing salvage lymph-node dissection for oligometastatic prostate cancer, Suardi et al. reported a 8-year biochemical recurrence free survival rate of 23% and an overall 8-year clinical recurrence free survival of 38% and cancer specific mortality free survival rate of 81% [32]. They found that the PSA level at salvage LND, biochemical recurrence and the presence of retroperitoneal lymph-node metastases all influenced clinical recurrence post-operative clinical recurrence [32]. Jilg et al., in their study of 47 patients undergoing salvage LND, reported a clinical progression-free survival of 25.6% and cancer specific survival of 77.7% at 5 years [33]. Notably, the initial disease recurrence post-salvage lymph-node dissection occurred again in lymph nodes in 47–59% in these studies [26].

A large proportion of patients (55%) undergoing salvage lymph-node dissection developed complications with the majority being Clavien grade ≤ 2 [26]. The most common complications were lymphorrhoea (13%), fever (17%), ileus (10%), and a lymphocele requiring drainage (8%). Grade 3a complications were observed in 11% of the patients. Only one case of grade 3b complication (lymphocele requiring surgical drainage) was reported [26].

The current role of salvage lymph-node dissection in oligometastatic disease remains experimental and more robust long-term data are needed prior to being utilised as an established treatment modality in this setting.

5.2.2. Stereotactic radiotherapy (SBRT)

SBRT is external beam radiotherapy which is used to deliver a high dose of radiation very precisely to an extra cranial target within the body, as a single dose or a small number of fractions, thus reducing the amount of normal tissue irradiated and potentially offering complete ablation of all tissue in the treated area [34]. Therefore, it is a less invasive alternative to surgery in treating lymph-node recurrence and bony metastases in prostate cancer.

Similar to salvage lymph-node dissection, the evidence is based on small cohort studies. In one of the larger studies of 50 men with recurrence, post-definitive therapy for Schick et al.

demonstrated that a short duration androgen deprivation with and high-dose irradiation to the metastatic lesions median follow-up of 31 months (range 9–89) the 3-year biochemical relapse-free survival, clinical failure-free survival, and overall survival rates were 54.5, 58.6 and 92%, respectively [35]. In a contrasting large cohort of 50 patients receiving SBRT with a median follow up of 2 years, Decaestecker et al. reported a 35% progression free survival at 2 years [36]. The differences in progression-free survival rates are attributed to the use of adjuvant ADT and prophylactic nodal irradiation used in the study by Schick, offering better progression-free survival [31]. A further interesting observation between the studies was the pattern of first progression where, 75% presented with oligometastases in the series of Decaestecker et al. compared with only 10% in the series of Schick et al. The recurring patents then went on to receive second or third course of SBRT in the former study [36]. A short PSA doubling time before SBRT predicted worse PFS in the study by Decaestecker et al. [36]. A recent retrospective series of 19 men who had biochemical recurrence post-local therapy for prostate cancer with oligometastases (≤ 3 metachronous metastases) demonstrated a 21 months' median distant progression-free survival with 3- and 5-year DPFS of 31 and 15%, respectively [37]. Also importantly, this study demonstrated a delay of androgen deprivation by 28 months [37].

A further study by Tabata et al. demonstrated overall survival rates of up to 90.5% in patients receiving radiotherapy for oligometastatic disease of the bones with long-term pain control in oligometastatic disease and no spinal cord compression or pathological fractures occurring at the radiated sites [38]. CyberKnife-based stereotactic ablative radiotherapy is newer modality being utilised in oligometastatic disease with early studies also demonstrating good local control and relatively good PSA response [39].

The toxicity rates of SBRT six studies were reviewed in their analysis by Ost et al. [26]. Sixteen per cent of patients had late complications with the majority being grade 2 toxicity, mainly gastrointestinal in 8.5%, with one case of grade 3 toxicity (macroscopic haematuria) [26].

6. Conclusion

The concept of oligometastases in prostate cancer offers a newer approach to patients with the presence of five or fewer metastatic or recurrent lesions that could be treated by local therapy to achieve long-term survival or cure. Furthermore, it offers the advantage of delaying the need for androgen deprivation therapy and its associated side effects. Treatment of oligometastatic prostate cancer relies on early diagnosis in order to offer the best outcomes for these patients. Therefore, improvements in prostate cancer diagnostics such as choline PET, whole-body multi-parametric MRI, PSMA PET can provide early identification of this group of patients, while surgical and targeted radio-ablative techniques can deliver advanced therapeutics to the targeted regions. While the future management strategies appear promising for oligometastatic prostate cancer, it currently remains experimental.

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