Clinical Radiology 74 (2019) 865–875

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Review

New concepts in prostate cancer management: the conundrum of managing oligometastatic disease in prostate cancer—through the looking glass darkly

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ARTICLE INFORMATION

Article history:
Received 12 December 2018
Accepted 8 May 2019

The management of oligometastatic prostate cancer continues to stimulate as well as vex cancer professionals since the concept was raised more than two decades ago. The use of regular prostate-specific antigen (PSA) monitoring together with advances in imaging technology such as combined positron-emission tomography (PET)/computed tomography (CT) has enable earlier identification of potential initial spread of disease and recurrence. Recent systematic reviews and trials have supported the feasible and safe delivery of local ablative therapies for oligometastatic lesions with high local control rates and low morbidity. This is very appealing not only to the clinician but hugely to the patient; however, many questions remain as to whether this patient cohort is prognostically and clinically relevant as well as ultimately if local aggressive therapies can alter the natural history of disease progression and benefit these men. This overview examines the issues for identification, treatment, and management of men with oligometastatic prostate cancer.

Introduction

In 1995, Hellman and Weichselbaum[1] raised awareness for a new clinical entity termed oligometastases. This term was coined to describe a limited number of metastasis that could represent the earliest stage of cancer progression before becoming clinically widespread. This straddled the previous concepts for an orderly stepwise contiguous pattern of disease spread that was endorsed within the Halstead principle[2] and that for the systemic hypothesis. The latter scenario implied that the initial measureable cancer status for both primary and regional nodal involvement was simply an early indicator that systemic disease was already present but still microscopic. The oligometastatic state was to sit within this biological spectrum. This oligometastases hypothesis is attractive as it suggests that the disease is not yet widespread and may offer an opportunity that local ablative therapy such as surgery, high-dose radiotherapy, radiofrequency ablation or cryotherapy to oligometastatic lesions could substantially alter the disease's national history. This may even offer long-term remission and intuitively would be a worthy strategy.

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https://doi.org/10.1016/j.crad.2019.05.003
0009-9260/

The concept of treating limited forms of metastatic disease is not new. It has long been recognised that local ablative therapy, such as surgical resection for limited metastases to the lungs and liver from colorectal cancers, can provide local control and even some long-term remissions. A systematic review of lung metastasectomies from 2,925 colorectal cancers cases gathered from modern series reported 5-year survival rates of between 27–68%.[3] Similarly, liver metastasectomies in colorectal cancer have been associated with 28–49% 5-year survival rates in one systemic review.[4] Although the range of 5-year survival rates is wide-ranging, there is still a sizable proportion of patients that have remained controlled and without disease progression. This potential benefit has also been reported for other solid cancers such as soft-tissue sarcomas and renal cancers.[5,6] These studies together with many other non-randomised reports in the literature provide the rationale behind aggressive local ablative therapy alone for oligometastases to limit cancer progression and induce clinical remission.

The traditional approach in these clinical situations as with widespread metastatic prostate cancer is to initiate systemic therapy using androgen-deprivation therapy (ADT). More recently, docetaxel chemotherapy[7] or abiraterone[8] have been added to ADT for initial management of metastatic disease providing improved median survival times with larger benefits demonstrated when there is a greater burden of metastatic disease.

The radical treatment of primary prostate disease when men present with systemic but low metastatic disease burden has also received attention. The rationale for treatment of the primary disease is that the primary may harbour disease clones that can dedifferentiate and mutate into more aggressive sub-clones capable of widespread systemic disease. These concepts would apply similarly to oligometastases with preclinical experimental models suggesting that circulating tumour cells can provide multidirectional self-seeding of other metastases.[9] Recent case reports of genomic lineage tracing from autopsy series[10] are consistent with the hypothesis to eradicate oligometastatic sites of their potential to self-seed castrate resistant disease. This is supported by the results of the STAMPEDE trial reporting an overall survival (OS) benefit for men receiving prostate radiotherapy with newly diagnosed low disease burden metastatic disease.[11] It remains uncertain if this can be fully extrapolated to the use of surgery in the same setting thus this approach remains investigational. The discussion of primary treatment to the prostate is outside the remit of this article and will not be discussed further.

With these reports, it is not surprising that there is considerable interest in the management of oligometastatic disease for prostate cancer. The conundrum for treating physicians is whether to apply systemic therapy for this state of limited metastatic prostate cancer or to consider local ablative therapies as an alternate option or perhaps a multimodality approach in combination with systemic therapies.[12] Currently recommendations are lacking from all major national or international guidelines due to a lack of adequate Level 1 evidence.[13] This overview will evaluate the current status, discuss the issues, and explore the management options for oligometastatic disease in prostate cancer.

Definitions

It is important to define what is meant by oligometastatic prostate cancer so that patient cohorts and treatment outcomes can be properly compared and evaluated. Currently there is no universal consensus definition. Commonly used definitions have been based on the number of metastases whilst other definitions have included both site and size of metastasis.[14,15] Using the number of metastases is simplistic and on face value easy to define. Despite this, there is no consistent number cut-off threshold. Whilst some investigators have included $\leq$10 lesions in their studies,[16] others have selected from a lower range between $\leq$1–5 lesions.[17–21]

An example for the variance in definitions was reported at the 2017 Advanced Prostate Cancer Consensus Conference.[22] The invited panel of 61 international experts from 21 countries did not reach a full consensus for the definition of castration-naive synchronous oligometastatic disease. When specifying a number threshold, 14% of the membership panel voted for $\leq$2 metastases, 66% for $\leq$3 and 20% supported $\leq$5 metastases. For the involvement of anatomical sites, 61% of the membership panel voted to include both bone and/or lymph nodes, 10% preferred only lymph node involvement and 13% wished to include any site including visceral disease. Of note, 10% did not believe that oligometastatic prostate cancer was a clinically meaningful entity.

In addition, the imaging standard for identifying prostate oligometastases has not been defined. Different imaging methods have been used largely guided by availability during the period of the study. In early reports, investigators have used 99m-technetium bone scintigraphy and computed tomography (CT). Later reports have included magnetic resonance imaging (MRI) with functional sequences and positron-emission tomography (PET) with tracers that include sodium fluoride (NaF), fluorodeoxyglucose (FDG), choline and prostate-specific membrane antigen (PSMA). It should be noted that current definitions for oligometastatic disease have not included a genetic classification or biological phenotype nor defined a minimum imaging technique for identification.

There are also many different clinical situations where oligometastatic disease may occur. These scenarios continue to evolve with greater understanding of the disease entity. The following clinical scenarios can be described (see Fig 1):

(1) Synchronous disease: initial presentation of an untreated primary prostate cancer with oligometastatic disease where the patient is still castration naive.[23]
(2) Metachronous disease: the prostate cancer primary has been treated radically and remains controlled with subsequent development of oligometastatic disease. In

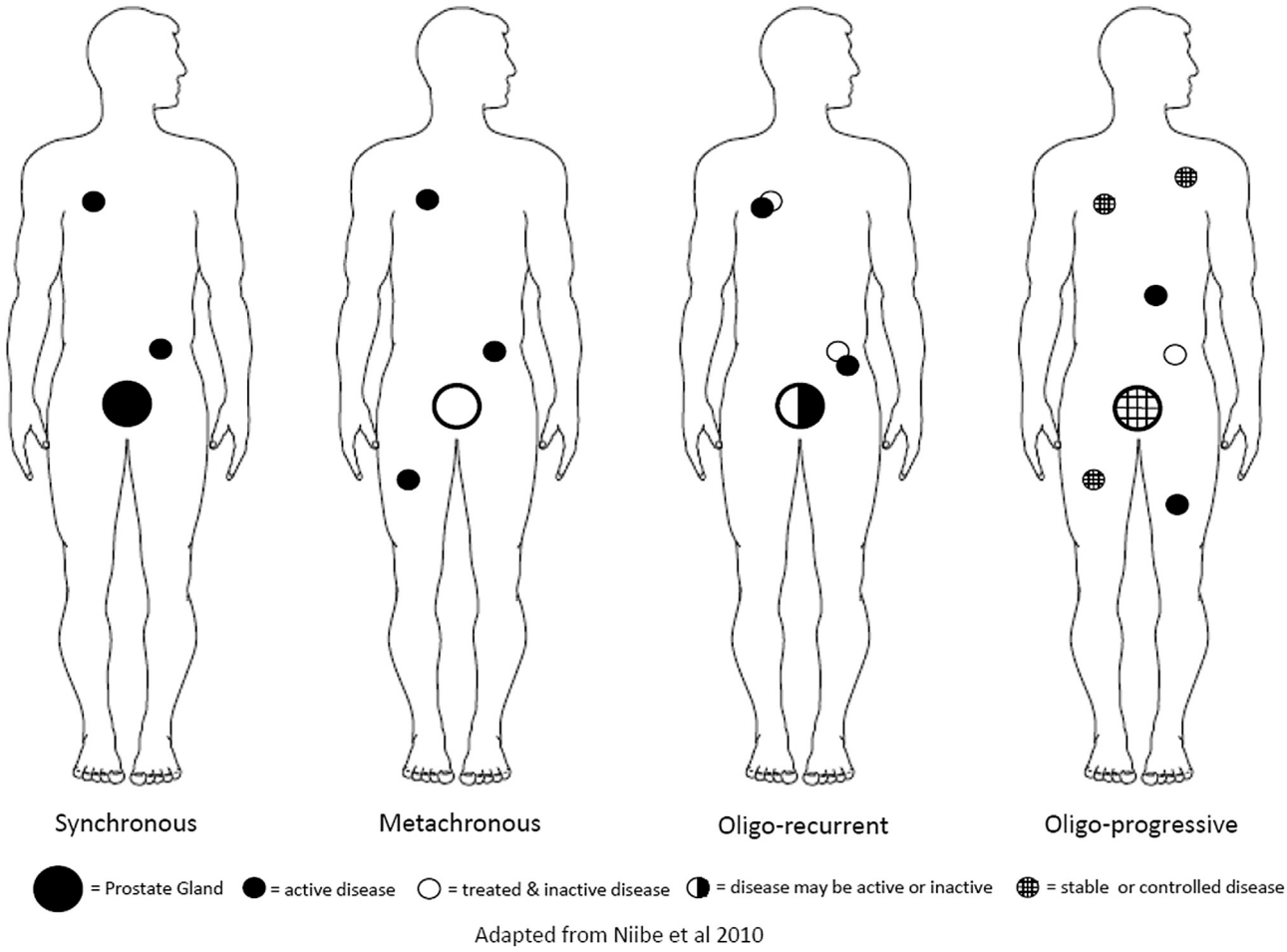

Figure 1 Different potential clinical scenarios for presentation of oligometastatic disease in prostate cancer.

this setting, the patient can be either castration naive or not as they may be receiving first line adjuvant ADT in the latter situation.[23,24]

(3) Oligo-recurrence: whereby there is recurrence of previously treated oligometastases within the vicinity of previous radical therapy such as the high-dose region of previous irradiation or resection. This may also apply to the prostate gland. The patient may be either castration naive or resistant.
(4) Oligo-progressive disease: where widespread metastatic prostate cancer is present and most of the metastases are controlled by systemic therapy apart from a limited number of metastatic lesions that have progressed. Thus there is a mixed response picture. The patient is now castration resistant.[25]

Many of the terms listed above have been used interchangeably in publications that describe oligometastatic disease. This can be confusing. Niibe *et al.*[23] recommended that the oligometastases term should be reserved for synchronous presentations to mirror the situation originally described by Hellman and Weichlbaum.[1] We believe that the term oligometastases would serve better as an overarching term to describe all the different clinical settings listed above as well as any future subcategories. Niibe *et al.*[23] also suggested using the term "oligo-recurrence" for metachronous setting; however, the terms synchronous and metachronous are better self-descriptors of their contemporaneous clinical situations given that there are other emerging clinical sub-groups as listed above. We propose that the term "oligo-recurrence" should be reserved for limited disease re-developing within a previously treated region, as this is a clinical entity we are now noting following ablative treatment. This may suggest radio-resistance of the lesion if ablative radiotherapy was the initial treatment. This is relevant, as it would imply that a different management strategy is needed. Irrespective of these current clinical groupings, future trials will provide data to evolve and refine these sub-groups so that they remain clinically meaningful and guide management strategies.

Identification

Following radical treatment, prostate specific antigen (PSA) testing can provide a relatively reliable surrogate of prostate cancer activity. Elevation of the PSA levels beyond the usual remission threshold levels defined for the different radical treatment techniques can raise suspicion

for disease recurrence.[26] Biochemical PSA relapse can often predate overt symptomatic metastatic disease by several months or years. For example, the threshold for PSA failure post-prostatectomy is 0.2 ng/ml, although a persistently rising PSA below this is also accepted as a sign of treatment failure. Following radical radiotherapy and in the absence of ADT, the international consensus definition for biochemical failure is a PSA level greater than its nadir level post-irradiation + 2 ng/ml.[27] Routine PSA monitoring triggering these PSA thresholds permits re-staging to be initiated in a timely fashion to identify early disease recurrence and this enhances the opportunity to detect oligometastatic disease.

Conventionally, imaging for staging metastases includes bone scintigraphy, CT and MRI. These techniques are widely available and economically accessible. It is well recognised that the bone scintigraphy has limited sensitivity in detecting small-volume bony disease. In a prospective evaluation comparing ^{18}F—NaF, ^{18}F-FDG PET-CT, whole-body diffusion-weighted MRI (WBdwMRI) and bone scintigraphy in patients with breast and prostate cancer, the bone scintigraphy was found to have a sensitivity of only 64.9% for detecting skeletal metastases.[28] For the detection of bone metastases in prostate cancer, other investigators have also reported that NaF PET is more sensitive than bone scintigraphy.[29] This highlights the potential for understaging. Morphological cross-sectional imaging with CT and MRI rely on size and shape criteria to define abnormal disease and are likely to underestimate the extent of disease. Functional imaging using MRI and PET with its disease-specific tracers such as ^{68}GA-PSMA PET-CT can improve cancer detection and better quantify disease extent.[30] Other potential and relevant advantages would be to assess treatment response or provide prognostic biomarker status; however, they are not without their own imaging-related issues and limitations. This has been discussed in depth in the other articles within this special edition and will not be addressed here.

Disease stratification

Selection of the appropriate patient is critical in order to ensure optimal management for the different oligometastatic prostate cancer cohorts. The clinical profile that has been usually assumed to be associated with better prognosis is lower Gleason scores without any adverse histological subtype features with low disease burden and non-visceral disease.[24,31] This is supported by low and/or linear PSA kinetics with long disease-free interval (DFI) suggesting slower disease tempo.[32]

The pragmatic and simplistic selection approach used by many investigators has been to rely on the number of metastatic lesions to triage a possible clinical subset; however, deciding on a reliable cut-off threshold has been difficult as the quality of the data is mostly retrospective and limited. Despite this, some studies have provided guidance. A large single institution retrospective study studied 450 men with biochemically recurrent prostate cancer following radical prostatectomy over a 30-year period where androgen-deprivation therapy was deferred until the development of metastases.[33] They reported on the factors influencing overall survival. They found that the number of metastases $\leq$3 lesions was favourable compared to possessing $\geq$4 metastases and this was an independent multivariate factor. This finding has also been supported by other investigators.[34,35] Other factors such as site and size were more difficult to assess.

A recent systematic review for metachronous oligometastatic prostate disease evaluated 661 men reported within 14 studies.[36] Eligibility for study evaluation was $\leq$5 oligometastases that received treatment irrespective of size and location. The authors described that approximately two-thirds of the men were classified as high-risk cases at initial presentation according to the D'Amico classification[37] and had a median Gleason summed score of 7. The authors could not define a set of disease stratifiers that would be prognostic or predictive. The parameters reviewed included grade, size, type of recurrence, i.e., bone versus nodes versus visceral disease, and location of disease, i.e., regional versus distant disease. This limitation was largely as a result of the small and very heterogeneous retrospective data sets suitable for their review. Therefore, improved stratification will have to await patient outcomes from existing clinical trials with a comparator arm.

In the development of the CORE (A randomised trial of COnventional care versus Radioablation [stereotactic body radiotherapy] in Extracranial oligometastases) trial,[24] the trial committee reviewed the available published studies[38] and settled on a consensus definition for oligometastatic prostate disease in the metachronous setting as the presence of $\leq$3 extra-cranial metastases in two organ systems or less, extra-cranial disease only, size $\leq$6 cm and a DFI of $>$6 months as being potentially representative of a clinical relevant subgroup that may benefit most. Imaging requirements were pragmatic and included bone scintigraphy and CT, but preference was given for using WBdwMRI or PET/CT with either choline or PSMA tracers. This recognised that access to PET/CT would vary from centre to centre and availability would likely change during the course of the trial. The CORE trial also included patients with breast and lung cancer. The recently published phase 2 randomised trial, STOMP utilised $\leq$ 3 extra-cranial metastases diagnosed with choline PET-CT as its main patient criteria.[39] In addition, the trial mandated a negative multiparametric MRI for the prostate gland or prostate bed. Many current prostate oligometastatic studies have used variations of these imaging based morphological stratifiers and none have yet to utilise any genetic or biological criteria.

Treatment outcomes

Several reviews have nicely summarised the outcomes of ablative therapy for oligometastatic prostate cancer.[14,36,38,40] Overall, these reviews remain limited by the quality of the studies utilised. Most of these studies are retrospective single institution reports with small numbers

and used radiotherapy as the main treatment modality. The patient cohorts were heterogeneous with different clinical selection criteria. Imaging reflected the time period of the study. Under-staging of disease extent was likely. Different and non-standard clinical endpoints were used to define disease control, failure, and progression. There was uncontrolled use of systemic therapy in the studies both at initiation and as subsequent therapy. Finally, follow-up was short in many studies. Despite the heterogeneity of the studies, the outcomes appear encouraging.

Although surgery, RFA, and cryotherapy have been used for ablative treatment of oligometastatic disease, most of the published data using these methods have been for other solid cancers such as colorectal and lung cancers with only limited data for prostate cancer. In particular, there are no published series evaluating the use of cryotherapy and RFA solely for prostate oligometastatic disease. Using surgery, the strategy has been directed towards regional pelvic lymph node dissection (pLND). For salvage pLND, several small series reported initial high undetectable PSA rates of up to 59–73% that was not sustained.[31,41,42] Jilq *et al.*[31] reported on 47 men undergoing pLND with half of the cases also receiving adjuvant radiotherapy. At a median follow-up of 35.5 months, the 5-year clinical PFS was 25.6%. Suardi *et al.*[41] reported an 8-year PSA biochemical recurrence-free survival (RFS) of 23% in 59 men with a median follow-up of 81 months. In this study, ADT was given at the discretion of the treating physician with 40% of men yet to receive ADT at 5 years. In a pLND cohort of 52 men evaluated by Karnes *et al.*, 83% of men received adjuvant ADT immediately following surgery.[42] With a short median follow-up of 20 months, the 3-year biochemical RFS was 45.5%. The use of adjuvant ADT will influence the outcome rates. Retroperitoneal dissection has also been reported with reduced clinical RFS rates for cases with involved retroperitoneal disease. In one surgical series, the 5-year clinical RFS rates were reduced from 53% in men without retroperitoneal disease to 11% with retroperitoneal involvement[43]

Most of the published studies on prostate oligometastatic disease have concentrated on the use of stereotactic body radiotherapy (SBRT) as the ablative regime. Using SBRT, local control rates of between 80–100% at 2- to 3-year with PFS rates between 30–64% at 2 years.[36] It is also relevant to note the low rate of both acute and late treatment related side effects for Grade 2 toxicity were low at 2.4% and 1.1% respectively with Grade 3 toxicity limited to one and two cases, respectively.[36] The authors sensibly cautioned that the retrospective assessments and short follow-up may under-report toxicity rates.

Another multi-institutional review attempted to create a more-uniform clinical cohort with fixed inclusion and exclusion selection criteria.[21] This study pooled data from seven larger centre series and evaluated 119 prostate cases defined as having $\leq$3 oligometastases. This cohort included predominantly nodal and bone metastases in 60% and 36%, respectively, with 4% visceral disease. Local control rates were 92% at 5 years. The 3- and 5-year distant metastatic PFS was 31% and 15%, respectively, with a median distant metastatic PFS of 21 months. The authors also reported that a biologically effective dose (BED) of $\leq$100 Gy was associated a higher local recurrence rate compared to when the BED was >100 with 3-year local PFS rates of 79% and 99%, respectively. Late Grade 2 toxicity was 3% and mainly related to gastrointestinal side effects from nodal SBRT. There was no Grade 3 toxicity reported.

Interestingly, the relapses following ablative SBRT were noted to be nodal and oligometastatic in up to 68% of cases.[44] Most of the nodal relapses remained regional. The systematic review by Vilela *et al.*[36] also noted that <6% of cases at first relapse had widespread metastases. This pattern of failure raises several management possibilities. Firstly, oligometastatic relapses offers another ablative opportunity. Subsequent and repeated SBRT has been used with similar local control rates, up to 6% late Grade 2 toxicity and no late Grade 3 toxicity.[32] This level of complications for retreatment is clinically acceptable. Given that the relapses from nodal oligometastatic disease remain regional, this also raises the question whether more aggressive regional treatments upfront would be better such as pLND or irradiation. This strategy would have to balance carefully the potential greater toxicity of a regional approach versus the consequences of second retreatments. This would be relevant for at least two-thirds of nodal cases.[32,44]

Most of the reported studies have limited follow-up between 1–3 years and the impact on survival rates are difficult to estimate. A case-matched analysis to assess the impact on cancer-specific survival (CSS) was undertaken in another pooled multi-institutional study.[45] This retrospective review matched 1,816 cases treated with standard of care (SOC) management using ADT versus 263 cases receiving metastatic-directed therapy (MDT) with either pLND (166 cases) or SBRT (97 cases). The matched ratio was 3:1. This study reported that the MDT approach as associated with improved CSS with a median follow-up of 70 months. The 5-year CSS was 98.6% for MDT and 95.7% for the SOC (p=0.005). Again the limitations remain the retrospective data and lack of standardisation of systemic therapy in the SOC groups.

At the time of writing, two randomised trials have been published assessing the management of metachronous oligometastatic disease. These are the STOMP[39] and the SABR-COMET[46] trials with the latter study being listed only in abstract format. The first study (STOMP) has been published in full and evaluated 66 men with controlled primary prostate cancer presenting with $\leq$3 choline PET/CT identified metachronous oligometastatic disease.[39] This phase 2 trial randomised men to either surveillance versus ablative therapy that could include either SBRT or pLND. The primary endpoint was time to initiation of systemic therapy with ADT. At a median follow-up of 3 years, the median ADT-free survival time was 21 months for the interventional arm versus 13 months for the surveillance arm (HR 0.60, p=0.11). The median PFS was 10 months for the interventional arm versus 6 months for surveillance. There was no Grade 2 toxicity reported.

Although this well-executed randomised study provides the first evidence of potential benefit with pre-defined endpoints and prospective collection of toxicity, there

remain some limitations. It is a small study. The clinical endpoint of ADT-free survival is not standard. The rationale for using the ADT-free survival endpoint was to avoid premature and unnecessary initiation of ADT. ADT has been associated with a multitude of systemic side effects that include adverse metabolic, cardiovascular, and psychological side effects that could affect the patient's health.[47,48] In itself, this surrogate endpoint appears to be clinically relevant. The criteria to initiate ADT in the STOMP trial was the presence of >3 oligometastases even if asymptomatic; however, the initiation of ADT with the development of asymptomatic metastases is still not endorsed universally.

This study did mandate choline-PET/CT to define oligometastatic disease but since its inception, PSMA PET/CT has largely replaced choline-PET/CT. If PSMA PET/CT imaging was used and if it is deemed more sensitive and/or specific in identifying prostate oligometastases than choline PET/CT,[49] then the trial cohorts could be altered. PSMA PET/CT could reduce disease under-staging. Subsequent follow-up with more advanced imaging methods may also affect the decision to initiate ADT thus triggering of ADT may be earlier. This is not a study fault but merely reflective of advancing technology that could date this trial.

The other phase 2 study (SABR-COMET) randomised patients with a controlled primary malignancy and ≤5 oligometastatic lesions amenable to SBRT to either SOC versus SOC plus SBRT.[46] Of the 99 patients recruited, 16% were prostate cancers whereas the remainder were equally distributed between breast, colorectal, and lung cancers. With a median follow-up of 27 months, the median OS was 28 months for the SOC arm alone versus 41 months in SBRT arm (p=0.09). The median PFS was 6 months for the SOC arm compared to 12 months for the SBRT arm (p=0.001). Grade ≥2 toxicity was increased with SBRT at 30% compared to 9% in the SOC arm (p=0.022). The most common toxicity events with SBRT were fatigue (n=10), dyspnoea (n=9), or pain in the muscle/joint (n=7), bone (n=6) or non-specified pain (n=7). There were no differences seen in quality of life measures between the arms. Of note, three SBRT-related deaths (Grade 5) were reported. These were described as radiation pneumonitis (n=1), pulmonary abscess (n=1), and subdural haemorrhage after surgery to repair a SABR-related perforated gastric ulcer (n=1). These complications warrant further investigation in phase III trials.

Discussion

There is an emerging awareness that oligometastatic prostate cancer could be a viable and clinical relevant entity. There remains a lack of consensus for its identification and definition. Both these two aspects are intertwined and are needed to optimise selection of patients for the different clinical sub-types that may exist. Currently, simplistic number measures are used and based on conventional imaging criteria, but the field of imaging is changing rapidly with the introduction of molecular imaging such as PET/CT and functional MRI. PSMA PET/CT is now replacing choline PET/CT and is more readily available. New PET tracers are being investigated that may be more specific and/or sensitive for the detection and classification of oligometastatic prostate cancer and may subsequently replace PSMA PET/CT. Multimodality imaging could provide complementary information for different clinical subgroups. Clearly, the ability to accurately identify oligometastatic prostate cancer will also enable better disease definition and patient selection for treatment as well as permitting inter-study comparisons.

More importantly, a prognostic or predictive marker is needed. For clinical relevance, this disease needs to represent a phenotypically and biologically distinct entity that has a different prognosis to widespread metastatic disease, which is invariably fatal. There is much work to be done to identify an appropriate genetic signature for oligometastatic prostate cancer and also for each of its clinical subgroups, i.e., synchronous, metachronous, oligo-recurrent, and oligo-progressive to best define which men may benefit most.[50]

Currently, the published data on ablative therapy, particularly with SBRT, are most encouraging. Irrespective of the SBRT regime, higher local control rates have been reported when BED doses are >100 albeit with short follow-up. The STOMP trial[39] reported an ADT-free survival benefit, which is a new clinical endpoint that has still to be validated. The SABR-COMET trial[46] showed a strong beneficial signal for SBRT with a near doubling of the 5-year OS and PFS rates; however, the proportion of oligometastatic prostate cancer in SABR-COMET was less than a quarter of men recruited to the STOMP trial. The data from SABR-COMET have only been presented in abstract, thus it is uncertain about the impact of the three other different histologies entered or the distribution of the lesions across the different arms on outcomes. The toxicity reported within non-randomised but prospective studies have been minimal and acceptable even with re-treatments. This was reinforced by the STOMP trial, but the SABR-COMET trial had incurred three treatment-related deaths in the SBRT arm. This aspect is crucial given that the long-term beneficial outcomes of such aggressive local therapies have yet to be fully defined.

The data needed to enable best evaluation of this disease entity will have to come from well-designed adequately powered prospective randomised trials with appropriate comparator arms to enable full comparison of outcomes. Most ongoing clinical studies (Table 1) are limiting the number of detectable lesions to ≤5 with many investigators opting for ≤3 lesions with a size limit that is generally ≤5–6 cm in nodal and bone sites but may include up to 2–3 visceral sites. With encouraging results from the SABR-COMET phase 2 trial,[46] the SABR-COMET consortium has developed two follow-on phase 3 studies treating metachronous oligometastatic disease with a controlled primary in solid cancers. The SABR-COMET-3 study will aim to assess this approach in patients with ≤3 lesions and SABR-COMET-10 in patients with ≤10 lesions. The randomised phase II CORE study[24] has closed ahead of schedule in February 2019. Feasibility for the prostate cohort has been

Table 1
Studies listed in ClinicalTrials.org addressing oligometastatic disease in prostate cancer (excluding studies directed at primary prostate disease).

NCT ID	Title	RPN	Interventional model	Imaging for staging	No. OM	Clinical sites and other criteria	Primary outcome measure	Study group	Ref
NCT00544830	ADT and localized RT to metastases in patients with OM hormone-sensitive PC	29	SGA	BS, CT, MRI	≤5	Exclude CNS mets	Time to PSA relapse	City of Hope Medical Center	52
NCT01345539	Phase II study for curative intent treatment for patients with OM disease at initial presentation (UPCI #10−027)	44	SGA	FDG PET	≤5	≤3 organ systems, multiple histo types	Feasibility of SRS/SBRT	Uni Pittsburgh	53
NCT01345552	Phase II study of SRS for patients with oligo-recurrent disease (UPCI# 10−028)	44	SGA	FDG PET	≤5	NR, multiple histo types	Feasibility of SRS/SBRT	Uni Pittsburgh	54
NCT01558427	Salvage treatment or active clinical surveillance for OM PCr: a randomized phase II trial	54	RPA	NR	≤3	≤3	ADT free survival	Uni Hospital Ghent	55
NCT01777802	Observational study of immune responses in PC, lung, melanoma and breast cancer patients following SBRT, IMRT, or brachytherapy	130	Prosp Obs	NR	≤3	NR, multiple histo types	Change in immune biomarkers from baseline and after RT	Mayo Clinic	56
NCT01859221	Phase II SBRT and stereotactic hypofractionated RT for OM PC	48	NRPA	NR	NR	Exclude CNS disease	Improvement in median PFS over historic control rates in hormone receptive and CR subgroups	Uni Florida	57
NCT01957436	A phase III of ADT ± docetaxel ± local RT ± abiraterone acetate in metastatic hormone naïve prostate cancer	1168	RPA	BS, CT, MRI	NR	Excludes pelvic LN	OS and PFS	UNICANCER	58
NCT02170181	UTSW SBRT prospective clinical registry for OM disease, consolidation therapy, debulking prior to chemotherapy, or re-irradiation	5000	Prosp Obs	CT, PET	NR	≤ 7cm, all solid cancers	Patterns of care at 5 y	University of Texas Southwestern Medical Center	59
NCT02192788	Phase II study of SBRT as treatment for OM in PC	68		Choline PET, fMRI	<5	bone, LN, PSA DT>3m	Number of patients without disease progression of PC treated by SBRT	Hospital Provincial de Castellon	60
NCT02264379	Effectiveness and toxicity of a percutaneous high-dose PT in patients with OM of PC (Oli-P)	73	CC Obs	BS, CT, MRI, PET	≤5	NR	Toxicity at 24 m	Technische Universität Dresden	61
NCT02274779	Multicentric Phase II trial of salvage RT combined with hormonotherapy in OM pelvic node relapses of PC (OLIGOPELVIS/GETUG P07)	70	SGA	cPET	≤5	Pelvic LN only	biochemical or clinical relapse-free survival at 2 y	Institut Cancerologie de l'Ouest	62
NCT02489357	A pilot study of MK-3475 with cryotherapy for men with newly diagnosed OM PC	12	SGA	NR	≤4	Extrapelvic sites	Proportion of men with PSA < 0.6 ng/ml at 1 y	Johns Hopkins	63
NCT02563691	Comprehensive SBRT for OM PC: A Phase I/II study (CROP)	60	SGA	NR	≤5	Exclude prostate and pelvic LN, ≤3 in any given organ system	Incidence of late RT toxicities after SBRT to all sites of disease	Sunnybrook Health Sciences Centre	64
NCT02680587	Phase II randomized observation versus SBRT for OM PC (ORIOLE) trial	54	RPA	BS, CT, MRI, PET	≤3	PSA DT < 15m	Time to radiological progression	Johns Hopkins	65

(*continued on next page*)

Table 1 (*continued*)

NCT ID	Title	RPN	Interventional model	Imaging for staging	No. OM	Clinical sites and other criteria	Primary outcome measure	Study group	Ref
NCT02759783	A randomised trial of conventional care versus radioablation (SBRT) for extracranial OM (CORE)	206	RPA	BS, CT, MRI, fMRI, cPET, pPET	≤3	up to 2 organ systems only	PFS	Royal Marsden Hospital	24
NCT03160794	Phase II study: [^{18}F]DCFPyL PET/MRI for personalizing PC subclinical metastatic ablative MR-guided RT (MRgRT)	75	SGA	BS, CT, fMRI, PET	NR	NR	[18F]DCFPyL PET/MR identification of early OM with a rising PSA and negative staging (CS and BS) after SOC maximal local therapies	Uni Health Network Toronto	66
NCT03298087	Systemic and tumour-directed therapy for OM PC	28	SGA	CT, NaF PET, PSMA PET	≤5	Bone or LN only	PSA<0.05ng/mL at 6 m after testosterone recovery	VA Office	67
NCT03304418	A Phase II study of radium-223 and RT in hormone-naïve men with OM PC to bone	20	SGA	BS, CT, MRI	≤5	Bone only	Time to ADT use at 15 m	Uni Utah	68
NCT03361735	A Phase II trial of radium 223 dichloride in combination with ADT and SBRT for patients with OM castration sensitive PC	24	SGA	BS, CT, MRI, PET	≤4	Bone or LN mets <5 cm. Only 1 lung lesion < 2m. No liver mets	Time to treatment failure	City of Hope Medical Center	69
NCT03449719	A 2 arm, Phase II controlled randomized trial comparing efficacy and safety of abiraterone and abiraterone associated with of ablative RT in patients with OM CR PC (ARTO)	174	RPA	NR	≤3	Exclude visceral disease	rate of PSA response	Azienda Ospedaliero-Uni Careggi	70
NCT03503344	A randomized Phase II study of apalutamide ± SBRT in CR PC patients with OM disease on PSMA-PET imaging (PILLAR)	60	RPA	BC, CT, MRI, pPET	≤5	NR	Proportion of patients with serum PSA < 0.2 ng/mL	Uni California San Francisco	71
NCT03556904	Focal radiation for OM CR PC (FORCE): a Phase II randomized trial	72	RPA	BS, CT, MRI	≤5	NR	PFS at 18 m	Uni Michigan Cancer Center	72
NCT03630666	A study comparing intermittent ADT with or without salvage high-dose intensity modulation RT (IG-IMRT) to OM pelvic lymph nodes in biochemically-relapsing PC patients	256	RPA	cPET, pPET	≤5	NR	PFS	Institut Cancerologie de l'Ouest	73

ADT, Androgen deprivation therapy; Bone scintigraphy, 99mTc-MDP bone scintigraphy; CC, Case-control observational; CNS, Central nervous system; CT, Computed tomography; cPET, choline PET/CT; CR, castration-resistant; DT, Doubling time; Fmri, functional MRI; gPET, FDG PET/CT; Histo, histology; IM, Inventional model; IMRT, Intensity modulated radiotherapy; LN, Lymph nodes; m, months; MRI, magnetic resonance imaging; mets, Metastases; nPET, NaF PET/CT; NR, Not reported; NRPA, Non randomised parallel assignment; NTC ID, National Clinical Trials identifier; Obs, Observational; OM, oligometastases or oligometastatic; OS, Overall survival; PC, prostate cancer; PFS, Progression free survival; PET, positron emission tomography; pPET, PSMA PET/CT; PSA, Prostate specific antigen; RPA, Randomised parallel assignment; RPN, Recruitment Patient Number; RT, Radiotherapy; SBRT, Stereotactic body radiotherapy; SGA, Single Group Assignment; SOC, standard-of-care; SRS, Stereotactic radiosurgery; Uni, University of.

demonstrated with over 170 oligometastatic prostate men randomised. A prostate-specific phase III study (CORE-Prostate) evaluating up to three metachronous oligometastases in the setting of a controlled primary has been developed and is being assessed for funding. Other forthcoming trials include a new arm in the STAMPEDE multi-stage multi-arm trial to evaluate the benefit of treating the prostate primary and synchronous oligometastases at presentation. Translational studies are also underway in many of the trials listed in Table 1 including a larger worldwide collaborative study into oligometastatic prostate cancer guided by The Movember Foundation global action plan (GAP) 6 consortium.[51]

There are still many questions to be answered. What is the best imaging method or optimum combinations? Does early detection by imaging alone identify the appropriate clinical group? Is there an appropriate genetic signature for this disease? Does early ablative therapy of oligometastatic

disease translate into a survival benefit? Is postponement of systemic therapy clinically relevant? Are multimodality therapies in combination with ablative treatment better? Are there other clinically appropriate and relevant surrogate endpoints for this disease entity? Many of these questions remain, and hopefully, may be addressed in some of the current trials ongoing or being developed (see Table 1).

Summary

The oligometastatic concept in prostate cancer continues to be refined. There is emerging awareness that there may be several different clinical subgroups ranging from synchronous to metachronous presentations as well as oligo-recurrent and oligo-progressive settings. Each of these subgroups has different natural histories and their outcomes may differ with local ablative therapy. In a changing therapeutic landscape where combination systemic therapies are being utilised earlier for either advanced disease at diagnosis or on disease progression, the use of local ablative therapies with a good safety and toxicity ratio appears reasonable; however, rather than offering men suffering from oligometastatic prostate cancer these ablative therapies on the basis that it can provide good local control rates with minimal morbidity, it is incumbent on clinicians to define those men who would benefit. The emphasis should remain on recruiting such men into appropriate randomised clinical trials to best define suitable patient cohorts and the optimal treatment or its combination. It is also important to evaluate the cost-effectiveness of the proposed investigations and therapeutic interventions given that health costs are spiralling and resources are limited. The ultimate aim would be to clarify that oligometastatic prostate cancer is an identifiable prognostic subgroup and that local radical therapy can change the natural history for clinically relevant and beneficial patient outcomes.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The author acknowledges support from the Arcobaleno Cancer Trust and the Lord & Lady Marshall Charity Trust to the Urology Oncology Unit, Chelsea, for ongoing research in oligometastatic disease.

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