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ORIGINAL ARTICLE

A systematic review of contemporary management of oligometastatic prostate cancer: fighting a challenge or tilting at windmills?

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Abstract

Purpose Amongst the unanswered questions regarding prostate cancer (PCa), the optimal management of oligometastatic disease remains one of the major concerns of the scientific community. The very existence of this category is still subject to controversy. Aim of this systematic review is to summarize current available data on the most appropriate management of oligometastatic PCa.

Evidence acquisition All relevant studies published in English up to November the 1st were identified through systematic searches in PubMed, EMBASE, Cochrane Library, CINAHL, Google Scholar and Ovid database. A search was performed including the combination of following words: (prostate cancer) and (metastatic) and [(oligo) or (PSMA) or (cytoreductive) or (stereotaxic radiotherapy) or (prostatectomy)]. 3335 articles were reviewed. After title screening and abstract reading, 118 papers were considered for full reading, leaving a total of 36 articles for the systematic review.

Evidence synthesis There is still no consensus on the definition of oligometastatic disease, nor on the imaging modalities used for its detection. While retrospective studies suggest an added benefit with the treatment the primitive tumor by cytoreductive prostatectomy (55% survival rate vs 21%, $p < 0.001$), prospective studies do not validate the same outcome. Nonetheless, most studies have reported a reduction in local complications after cytoreductive prostatectomy (< 10%) compared to the best systemic treatment (25–30%). Concerning radiotherapy, an overall survival benefit for patients with a low metastatic burden was found in STAMPEDE (HR 0.68, 95% CI 0.52–0.90; $p = 0.007$) and suggested in subgroup analysis of the HORRAD trial. Regarding the impact of metastases-directed therapy (MDT), the STOMP and ORIOLE trials suggested that metastatic disease control might improve androgen deprivation therapy-free survival (in STOMP: 21 vs 13 months for MDT vs standard of care). Nonetheless, the impact of MDT on long-term oncologic results remains unclear. Finally, oligometastatic disease appears to be a biologically different entity compared to high-burden metastatic disease. New findings on exosomes appear to make them intriguing biomarkers in the early phases of oligometastatic PCa.

Conclusion Oligometastatic PCa is today a poorly understood disease. The implementation of new imaging techniques as whole-body MRI and PSMA PET/CT has increased exponentially the number of oligometastatic patients detected. Data of available trials suggest a benefit from cytoreductive prostatectomy to reduce local complication, though its impact on survival remains unknown. Radiotherapy may be beneficial for patients with low-burden metastatic PCa, while MDT may delay the need for androgen deprivation therapy. Results from ongoing trials data are eagerly awaited to draw reliable recommendations.

Keywords Prostate · Cancer · Oligometastatic · Cytoreductive surgery · Radiotherapy · Metastasis-directed therapies

Abreviations

ADT	Androgen deprivation therapy
CT	Computed tomography
EBRT	External beam radiation therapy
HR	Hazard ratio
ICECaP	Intermediate clinical criteria in prostate cancer
MDT	Metastasis-directed therapy
MRI	Magnetic resonance imaging
M0	Nonmetastatic
PCa	Prostate cancer
PICOS	Population, intervention, comparator, outcome and study design

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PRISMA	Preferred reporting items for systematic reviews and meta analyses
RP	Radical prostatectomy
SBRT	Stereotactic body radiotherapy
99mTc-MDP	99mTechnetium-methylene diphosphonate

Introduction

Amongst the unanswered questions regarding prostate cancer (PCa), the optimal management of oligometastatic disease remains one of the major concerns of the scientific community today. Indeed, following the recommendations of the United States preventive services Task Force in 2012 not to screen for PCa [1], there has been an increase in the incidence of metastatic PCa; moreover, in 2017 in the United Kingdom, PCa mortality was higher than for breast cancer [2].

The increasing clinical utility and utilization of nuclear imaging based on tracers such as ^{68}Ga-labeled prostate-specific membrane antigen (PSMA) ligands, as well as whole-body magnetic resonance imaging (MRI), is improving the detection of low-volume metastatic disease, with the development of a new clinical entity-defined oligometastatic PCa [3]. We are faced more often with oligometastic patients who have been previously classified as having either localized disease or m0 disease [4]. Debates over the lack of disease-specific information have animated the scientific community.

Until recently, Docetaxel and Abiraterone were reserved for metastatic castration-resistant prostate cancer. CHARTEED, STAMPEDE and LATITUDE trials revealed that they were associated with a survival benefit even for hormone-sensitive prostate cancer. Subgroup analyzes have shown that, unlike docetaxel, which is only effective for high volumes, Abiraterone acetate is effective for high and low volumes [5]. The same research strategy could be adopted for the implications of surgery and radiotherapy for patients with oligometastatic prostate cancer and is currently under investigation with some trials reporting intriguing findings.

Is aggressive treatment of the primary tumor and metastatic lesions the new paradigm? Does this clinical strategy improve oncologic outcomes? Aim of this systematic review is to summarize the current available data on the most appropriate management of oligometastatic PCa.

Evidence acquisition

This systematic review was conducted in line with the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines [6]. All relevant studies published in English up to November the 1st 2018 were identified through systematic searches in PubMed, EMBASE, Cochrane Library, CINAHL, Google Scholar and Ovid database. A search was performed including the combination of following words: (prostate cancer) and (metastatic) and [(oligo) or (PSMA) or (cytoreductive) or (stereotaxic radiotherapy) OR (prostatectomy)]. Although recent articles were prioritized, manuscripts with relevant historical findings were referenced if necessary. Only publications in English language were considered. According to the PRISMA guidelines, we used the Population, Intervention, Comparator, Outcome, and Study design (PICOS) approach to define study eligibility.

- Population: patients with oligometastatic prostate cancer.
- Intervention: local and metastasis-directed therapies in patients with oligometastatic prostate cancer.
- Comparator: standard of care (i.e., androgen deprivation therapy with taxane chemotherapy or abiraterone).
- Outcomes: improvement of oncologic outcomes (metastatic-free survival, cancer specific survival, overall survival). Progression of local symptoms, need for surgery due to local symptoms.
- Studies: translational science studies, cohort studies, case–control studies, prospective studies. Case reports, editorials, and letters were excluded during the systematic review process. We searched also the abstracts of ASCO and EAU conferences in urology in 2017–2018. Finally, if two or more studies reported results of overlapping surgical series, we selected the one with the largest sample size.

The initial list of selected papers was enriched by individual suggestions of the authors of the present review. After duplicates were removed, two authors (AS and SA) completed an independent review of 3335 articles. After title screening and abstract reading, 118 papers were considered for full reading, leaving a total of 36 articles for the systematic review. Any discrepancies in study inclusion were resolved by a senior author (FA), who was in charge of supervising the systematic review process. The PRISMA flow chart depicting the process for the systematic literature search and selection of the studies is shown in Fig. 1.

Evidence synthesis

Definition of oligometastatic disease

The term oligometastatic disease was described for the first time in 1995 by Hellman and Weichselbaum. It was defined as a limited number of clinically detectable metastases, and its prognostic and therapeutic value was considered to be in-between localized and metastatic disease [7]. However, a number of researchers still question the very

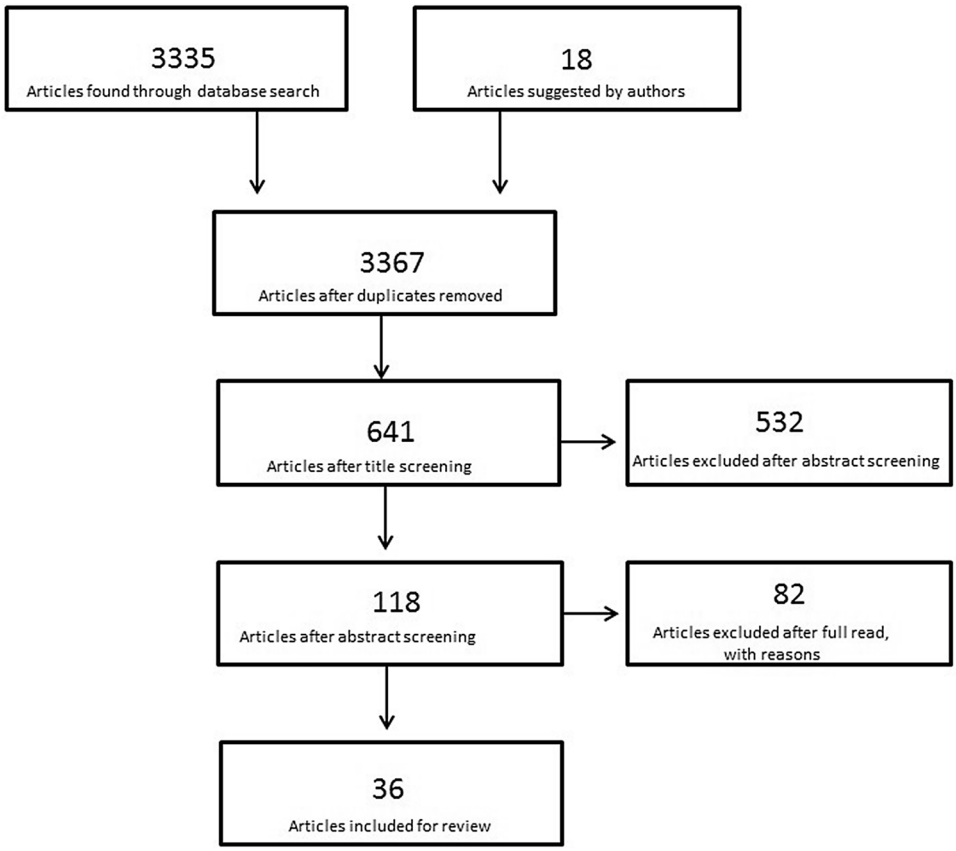

Fig. 1 The PRISMA flow chart

existence of this entity, believing that the oligometastatic state is rather a micrometastatic situation, in which, given the limitation of imaging techniques, only a limited number of solid lesions are detected. However, the kinetics in of development of metastasis would be different. For micrometastatic lesions, metastases would develop over a short interval; for a true oligometastatic, the lesions would have a slow kinetics and would be responsible for the persistence of the oligometastatic phenotype for months or years. Nonetheless, currently, no test is available to differentiate such two distinct clinical scenarios.

There is no consensus on the definition of oligometastatic disease [4]. Some definitions incorporate the site and number of metastases to define the oligometastatic state [8]. In fact, literature suggests reporting five variables in the description of oligometastatic disease: the distinction between synchronous and metachronous metastases, the number and site of lesions, castrate-resistant status, and lastly the imaging modality used to define oligometastatic disease. With the progress of molecular imaging techniques, more and more metastases are being detected. Therefore, many patients considered to be nonmetastatic (M0) on conventional imaging might have oligometastatic disease, particularly nowadays as imaging is performed at lower PSA thresholds compared to the past [9].

To date, three categories of oligometastatic PCa have been defined: de novo oligometastases (synchronous oligometastases), recurrent (metachronous oligometastases), and progressive (induced oligometastases).

Imaging modality

Currently metastatic workup for PCa patients includes imaging with 99mTechnetium-methylene diphosphonate (99mTc-MDP) bone scan, as well as computed tomography (CT). The European Association of Urology recommends the use of these conventional imaging modalities [10]. However, it is clear that an oligometastatic state may be merely a reflection of imaging capability [11]. Sterzing et al. [12] investigated the value of PSMA PET/CT in the initial staging of 15 men harboring high-risk clinically localized PCa: interestingly, 9 of the 15 patients in the study did present synchronous metastatic lesions.

The emergence and widespread use of whole-body MRI or PSMA PET/CT have led to an increased detection of metastatic PCa, particularly at low levels of PSA [13]. This is leading inevitably to a modification in the management of PCa: Albisinni et al. and Roach et al. using a prospective study showed that PSMA PET/CT changed disease management in, respectively, 76% and 62% of patients compared

to conventional staging [14, 15]. It is important to note that bone scans have a sensitivity of 65%, which indicates that a significant portion of metastatic disease is not being detected. Finally, it seems that there is a correlation between the increase of publications of PSMA PET/CT and the growing number of publications regarding oligometastatic PCa [16].

Rationale behind local and metastasis directed therapy

Debulking surgery is part of the therapeutic arsenal of many cancerous diseases. It seems that tumor reduction could improve survival, increase the response to systemic therapies and reduce loco-regional complications. Thus, according to some investigators, by eradicating the primary tumor site, we may observe a suppression of growth factors, immunosuppressive cytokines and consequently a secondary wave of metastases [17].

The prostate is considered by many authors as an elusive organ. Despite taxane chemotherapy and/or aggressive hormonal treatment, fatal clones persists and are thought to be involved in metastatic disease progression, resistance to castration and ultimately death [18, 19]. In a cohort of 58 patients with high-risk localized prostate cancer, Taplin et al. revealed that more than half of patients had aggressive residual disease on prostatectomy samples after hormonal therapy using a combination of LHRH agonist with abiraterone acetate [20]. Ross et al. obtained comparable results in patients treated with docetaxel/bevacizumab [21]. Moreover, in support of the beneficial role of cytoreductive surgery, we can highlight the study by Tzelepi et al. which demonstrated, at a molecular level, that "lethal prostate cancer" persists in the primary site despite systemic therapy [22, 23].

Described for the first time in 1953, the abscopal effect corresponds to the phenomenon of metastasis regression subsequent to therapeutic irradiation aimed at the primary tumor site [22]. Several theories tried to explain this phenomenon; the most plausible one being the induction of natural immunity following irradiation. In fact, the inflammation caused at the irradiated site, while destroying the tumor cells, could promote antigen presentation and the subsequent anticancerous immune reaction.

With the advent of immunotherapy, the abscopal effect remains a source of enthusiasm, giving hope for a possible improvement in the means of treating cancer [23, 24].

Nowadays, the consensus is that most metastatic PCa are not amenable to a definitive cure; especially while taking into consideration that the pathophysiology of metastases remains unclear. Nevertheless new concepts emerge and they could help developing novel treatment strategies. Thus, both the hypothesis of "seed and soil" and the theory of simple cell migration from primary organs to target organs became outdated. According to Comen et al. [25], "self-seeding" would be the multidirectional ability of cancer cells not only to seed to distant organs, but also to self-seed another primary tumor. For Pienta et al., it is rather a concept of diaspora metastases [26]. Finally, within his review about "intra-temporal heterogeneity of the patient", Haffner et al. explains that the lethal clone is always born out of a relatively undeveloped cancer in the primary tumor, and not arousing from a higher primitive cancer or a lymph node metastasis resected during a prostatectomy [27].

An increase in circulating tumor cells has been shown to be associated with tumor progression and a diminished survival. Hence, according to Resel-Folkersma et al., a reduction in the number of circulating PCa tumor cells leads to an improved survival [28]. Those paradigms taken together would, therefore, push the scientific community in directing treatment at both the primitive and the metastatic disease sites.

However, some controversy still exists, as some authors argue that the suppression of the primary tumor could promote angiogenesis and increase its metastatic potential. After targeting the primary tumor, growth factors influence both the metastatic behavior and the outcome of the host for the tumor known as Fisher effect [29]. Consequently, the recurrence of metastatic cancer years or even decades after treatment would be explained by the concept of tumor dormancy [30]. Interventional procedures would be responsible for the acceleration of the metastatic process by the increase of circulating tumor cells and their vascular supply known as Folkman effect [30]. As the abscopal effect in addition to both Fisher and Folkman effects are all well documented, the scientific debate remains open and no definite conclusions can be drawn yet.

Role of cytoreductive prostatectomy

Cytoreductice prostatectomy is feasible. It has been the subject of multiple retrospective studies that reveal a maximum benefit of cytoreductive treatment in patients with metastatic PCa. Indeed, Gratzke et al. analyzed data from the Munich Cancer Registry between 1998 and 2010 [31]. Of the 1538 newly diagnosed patients with metastatic PCa in the Munich region (4.6 million inhabitants), 74 patients (5%) had radical prostatectomy (RP+). When evaluating survival in RP+ vs RP− groups, patients in the RP+ group showed a 55% survival rate at 5 years versus 21% in the RP− group ($p < 0.01$). Similar results have been reported by several authors [32–37]. Nonetheless, a close analysis of these retrospective studies reveals a major selection bias. In fact, only the best-performing patients and those who had responded well to hormonotherapy had cytoreductive surgery.

Steuber et al. proceeded with a prospective study to diminish selection bias [38]. A group of 43 patients

undergoing cytoreductive prostatectomy were matched to a control group consisting of 40 patients receiving best systemic therapy. The inclusion criteria used were newly diagnosed prostate cancer with 1–3 bone metastases. Of note, PET/CT was not used. The patients had to be asymptomatic without visceral metastasis with a locally resectable tumor ≤ cT3 and a PSA less than or equal to 150 mg/mL at the time of diagnosis. In addition, the selected patients should not have benefited from previous treatment for metastases such as radiotherapy. Men undergoing surgery were younger, had lower initial PSA ($p = 0.02$) and lower cT stage ($p < 0.01$). While many retrospective studies acknowledged the importance of cytoreductive surgery on overall survival, this prospective study revealed the lack of positive impact of cytoreductive prostatectomy on castration resistance-free survival and overall survival in a limited sample of patients. One of the main limitations of this study is that OS might have been influenced by the shorter follow-up period in the CRP group and that the two groups were not randomized but matched.

Regarding the safety and feasibility aspects, Preisser et al. compared the perioperative results between radical cytoreductive prostatectomy and radical prostatectomy for non-metastatic PCa [39]. They reported that the former has more complications, longer hospital stays, and thus a higher hospital cost [39]. However, it appears throughout most studies that cytoreductive prostatectomy reduces long-term local symptoms, as bleeding, bladder outlet obstruction and ureteral obstruction [38, 40]. The late local complication rate after radical cytoreductive prostatectomy was reported at 20% compared to 46.7% for patients who received radiotherapy and 54.3% for best systemic therapy [40]. In a recent systematic review, Albisinni et al. concluded that some men could truly benefit from CRP but the optimal patient selection method is still unknown. As such, to date, this experimental approach should be performed only within clinical trials [41].

Role of radiation for the control of the primary disease

Prostatic definitive radiotherapy could find a place in the setting of metastatic PCa. In fact, both of Löppenberg et al. and Rusthoven et al. retrospectively found an improvement in overall survival for patients who underwent radiation therapy targeting the prostate in comparison to those who received only hormonal treatment [37, 42, 43]. The major limitations of these studies are their retrospective nature and therefore, a selection bias might be affecting the actual results. The HORRAD study attempts to overhaul this limitation [43]. Indeed, it is a multi-centric prospective study, randomized controlled trial recruiting 432 patients with PSA > 20 ng/mL and primary bone metastatic PCa on bone scan between 2004 and 2014. The objective was to compare irradiation of primary prostatic tumor with external beam radiation therapy (EBRT) with androgen deprivation therapy (ADT) versus ADT only. The trial revealed no significant difference in overall survival. However, subgroup analysis suggests that radiotherapy to the prostate actually improves overall survival in patients with a low metastatic burden (< 5 bone lesions). The criticism that could be made concerning this study is that the irradiation dose used for the prostate was only 70 Gy adding to the fact that the prostate fossa was the only irradiated area. STAMPEDE is a phase 3 randomized controlled trial using a multiarm, multistage platform design. In a recent analysis, its investigators compared 1032 men receiving ADT with Docetaxel and radiotherapy, while another 1029 treated by ADT and Docetaxel. The definition of metastatic burden was similar to the one used in the CHAARTED trial: high metastatic burden was defined as four or more bone metastases with one or more outside the vertebral bodies, or pelvis or visceral metastases or both; all others were considered to have a low metastatic burden. The primary objective of the study was overall survival. Radiation therapy was well tolerated, as there were only 5% adverse effects during radiotherapy and 4% at a later stage. The authors found similar proportion of patients reporting at least one serious adverse event between the two study groups. The trial suggests that the addition of radiation therapy to standard therapy improves survival without failure [hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.68–0.84; < 0.0001], but does not improve overall survival (HR 0.92, 95% CI 0.80–1.06, $p = 0.2266$). Similarly to the HORRAD trial, subgroup analysis showed that for patients with a low metastatic burden, overall survival was improved (HR 0.68, 95% CI 0.52–0.90; $p = 0.007$; 3-year survival 73% in control vs 81% with radiotherapy). Radiotherapy gave a three-year survival of 81% in these men, compared to 73% in the standard treatment group. According to the authors, radiotherapy to the prostate should become a standard treatment option for men with newly diagnosed disease with a low metastatic burden [44].

Role of metastasis-directed therapy

Metastasis-directed therapy (MDT) is a direct consequence of the emergence of new imaging modalities. It either consists of surgical resection or stereotactic radiation therapy to low-volume oligometastatic lesions in selected PCa patients [45]. MDT supposed benefits are: cancer control, slowing down of further metastases and avoiding or delaying ADT-related toxicity. Stereotactic body radiotherapy (SBRT) allows treating metastases with minimal side effects. The ultimate question remains the same, what are we actually gaining in terms of overall survival of patients. Data from retrospective studies, treating over 1000 patients in total,

suggest that cancer specific and overall survival is improved with MDT compared to the standard of care. MDT treatment regimens vary with different radiotherapy techniques, doses, and volumes [46]. Prospective studies digging further into MDT effects are in progress. Among those studies, STOMP and ORIOLE trials are worth mentioning [47, 48]. The primary end point of both trials was ADT-free survival. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) is a prospective, randomized, multicentric Phase II trial. Between August 2012 and August 2015, 62 patients were randomly assigned (1:1) to either surveillance or MDT of all detected lesions (surgery or SBRT). At a median follow-up time of 3 years, the median ADT-free survival was 21 months for the MDT group and 13 months for the surveillance group [hazard ratio 0.60 (80% CI 0.40–0.90); log-rank $p = 0.11$] [47]. Regarding the ORIOLE trial (observation versus stereotactic ablative radiation for oligometastatic prostate cancer), this is a phase II randomized, non-blinded interventional study (NCT02680587). Preliminary results reported during ASCO GU in February 2018 suggested that 67% of patients in the surveillance group progressed at 6 months, while only 29% in the SABR group [48]. Despite encouraging data, some authors remain skeptical that MDT will delay the use of ADT. Moreover, this argument is a weak endpoint compared to progression-free survival or overall survival especially given that timing for using hormonotherapy remains controversial. For Murphy et al., the approach to metastatic PCa "catching 'em all", or "pokemet", must be considered experimental [17]. Moreover, according to Montorsi et al., only two thirds of the patients with positive images on PET choline and PSMA had an actual relapsing disease at lymph node level on pathological examination [49]. It is important to remember that new imaging modalities can inform us about the status of the disease at a specific moment in time. Thus, we have no further evidence on the kinetics behind disease progression. It seems logical that patients with slow cancer growth must be treated differently compared to those with rapidly progressive disease. New biomarkers are mandatory to help determining the natural history of the disease and to select the patients who could actually benefit from MDT. Finally, successful disease management is relative. Should we rely on symptomatology, biology, radiologic progression, overall survival, or recurrence-free survival? Some authors advocate the use of more relevant parameters, such as those described in the project intermediate clinical criteria in prostate cancer (ICECaP) [50].

Ongoing trials and emerging molecular techniques for detection of oligometastases

In the light of the results obtained through this review of the literature, it seems that we lack quality evidence justifying the use of local therapy or MDT in oligometastatic PCa patients. Fortunately, the scientific community has become aware of the problem and a number of randomized controlled trials are underway. Tables 1 and 2 summarize the currently published and ongoing trials. These prospective trials are analyzing the role of cytoreductive prostatectomy, as in the TroMbone trial, as well as definitive prostate radiotherapy in metastatic PCa and MDT. Furthermore, the biology of oligometastatic disease is currently being explored. Is oligometastasis disease a biologically different entity compared to high-burden metastasis disease? Or are we just temporally anticipating? The discovery of micro-RNA (miRNA) seems to give a start of answers to many questions that arise. These short noncoding RNA molecules (19–22 nucleotides) are involved in the downregulation of the target mRNA and in the metastatic cascade [51]. According to Formosa et al., a series of miRNAs called oligomers would be typical of oligometastatic diseases, and thus have a role in the development of the oligometastatic state and the transition from an oligometastatic state to a polymetastatic disease [52]. An in vitro model revealed the existence of significant downregulation of ten different miRNAs encoded at the 14q32,31 locus with apoptosis, PCa cell-cycle progression, also cell migration and/or invasion, and tumor suppression. More recently, Lussier et al. analyzed the function of miR-654: a significant decline in its expression would be correlated with a higher incidence of metastatic events, a lymph node invasion and higher PSA levels [53].

Exosomes are nanoscale extracellular vesicles that allow tumor cells to exchange genetic material. Through the creation of a pro-tumor microenvironment and the modification of the local stroma, exosomes are at the origin of premetastatic niches promoting the growth of tumor cells, their invasion and their immune suppression [54]. By analyzing the exosome proteins derived from PCa cells, the researchers found a high level of molecules stimulating tumor cell migration and metastasis: the b4 and avb6 integrins, vinculin and the Trop-2 transmembrane glycoprotein [55, 56]. These new findings on exosomes appear to make them ideal biomarkers in the early phases of oligometastatic tumors, prompting the discussion on future biomarkers to segregate which patients should undergo cytoreductive surgery + MDT compared to ADT + chemotherapy/second-line hormones.

Conclusion

Recent breakthroughs on exosomes and the increasing clinical utility of nuclear imaging based on tracers such as PSMA ligands are improving the understanding of oligometastatic PCa. To date, survival benefit from cytoreductive prostatectomy is not supported by current evidence and remains experimental, though probably improving

Table 1 Role of local therapy: randomized trials and their characteristics

Study name	Country primary investigator	Inclusion	Phase	Design	Estimated participant	Primary endpoint	Start	Close to recruitment in	NCT/NRT number	Results
STAMPEDE	UK; N James; University Hospital; Birmingham	M1	Phase II and Phase III	SOC (ADT) and prostate RT, (two possible RT schedules)	1032	OS	January 2013 (Arm H)	September 2016 (Arm H)	NCT 00268476	Radiotherapy improved Failure-free survival (HR 0.76, 95% CI 0.68–0.84; $p < 0.0001$) but not OS (HR 0.92, 95% CI 0.80–1.06; $p = 0.266$)
HORRAD	Netherlands; G van Andel; Onze lieve; Amsterdam	M1b	Phase II	ADT with EBRT vs ADT alone	432	OS	June 2004	August 2014	NCT 271	Median OS 45 months (95% CI 40.4–49.6) in the ADT + EBRT group vs 43 months (95% CI 32.6–53.4) in the ADT group ($p = 0.4$)
PEACE 1	Europe; K Fizazi; Gustave Roussy; Paris	M1	Phase III	SOC (ADT ± Docetaxel) ± abiraterone acetate with or without Prostate RT	1168	OS, PFS	October 2013	May 2017	NCT01957436	
SWOG 1802	USA, B F Chapin; M.D. Anderson, Houston	M1	Phase II I	RP or EBRT + SoC vs SoC	1165	OS	December 2015	March 2018	NCT01751438	
g-RAMPP	Germany; Markus Graefen; Martini-Klinik; Hamburg	M1b (≤ 5 met)	Phase III	SOC with RP-eLND vs SOC alone	452	CSS	May 2015	April 2025	NCT02454543	
TRoMbone	UK; Freddie Hamdy; Oxford University; London	M1b (≤ 3 met)	Feasibility	RP-eLND + SoC vs SoC	50	Feasibility	February 2017	November 2018	ISRCTN 15704862	

ADT androgen deprivation therapy, *CI* confidence interval, *CSS* cancer-specific survival, *EBRT* external beam radiation therapy, *OS* overall survival, *PFS* progression-free survival, *RP* radical prostatectomy, *RT* radiotherapy, *SOC* standard of care, *STAMPEDE* systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy, *TroMbone* testing radical prostatectomy in men with prostate cancer and oligometastases to the bone

Table 2 Role of MDT: randomized trials and their characteristics

Trial	Estimated enrollment	Inclusion criteria	Arms	Primary outcome	Results
STOMP	62 patients	N1 + M1 ≤ 3 lesions by choline PET	Arm A: active surveillance Arm B: SBRT or surgery for metastases. ADT at progression	ADT-free survival	Median ADT-free survival Arm A: 13 mo (80% CI 12–17 months) versus Arm B: 21 months (80% CI 14–29 months) (HR 0.60; $p = 0.11$)
ORIOLE	54 participants	≤ 3 bone mets	Observation vs SBRT ± DCFPyL-PET/MR, no ADT	PFS	Interim results Progression at 6 months 71% (5/7) on observation arm versus 33% (4/12) for the SBRT arm.
Sunnybrooke	60 participants	M1a-b ≤ 5	Prostate 35 Gy/5fx, Nodes 25-35 Gy/5fx, Mets 30-40 Gy/5fx, ADT at least 1 year	Toxicity	
OLIGOPEL-VIS-GETUG-P07	70 participants	≤ 5 pelvic LNs by choline PET	Pelvic LN 45 Gy, LN + boost 66 Gy, and ADT 6 mo	BF	
Univ Florida	48 participants	M1 excluding CNS	SBRT or stereotactic hypofractionated RT ADT for all	PFS	
NRG	12 breast cancer; 11 non-small cell lung cancer 13 prostate cancer	≤ 4 mets, NSCLC, breast, or prostate	SBRT, ADT allowed	Recommended SBRT dose	
CORE	206 participants	≤ 3 mets NSCLC, breast, or prostate	SBRT vs SOC	PFS	
GICOR	68 participants	N1 + m1 ≤ 5 by choline PET	SBRT, ADT allowed	PFS	

ADT androgen deprivation therapy, *BF* biochemical failure, *CI* confidence interval, *Fx* fractions, *Gy* grays, *LN* lymph node, *MDT* metastasis-directed therapy, *Mets* metastasis, *NSCLC* non-small cell lung cancer, *PET* positron emission tomography, *PFS* progression-free survival, *RT* radiotherapy, *SBRT* stereotactic body radiotherapy, *SOC* standard of care

local symptoms of PCa. Prospective studies suggest that radiotherapy may be beneficial in patients with low-burden metastatic disease, and data from recent trials support MDT, with an improvement of at least androgen deprivation-free survival. Ongoing trials are eagerly awaited to draw reliable recommendations.

Author contributions AS: project development, data collection, data analysis, manuscript writing. SA: project development, data collection, data analysis, manuscript writing. FA: project development, data analysis, manuscript writing. GA: project development, data analysis. WAHO: data collection. RD: data analysis, manuscript writing. SR: data collection. AT: data collection. AB: data collection. AM: project development. TK: project development, data analysis, manuscript writing. AA: project development, data analysis, manuscript writing. KE: project development, data analysis, manuscript writing. AK: project development, data analysis, manuscript writing. AI: project development, data analysis, manuscript writing. TR: project development, data analysis, manuscript writing. AP: project development, data analysis, manuscript writing.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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