Oligometastatic Disease in Prostate Cancer. Evolving paradigm: current knowledge, diagnostic techniques and treatment strategies

Keywords
cancer, treatment, prostate, oligometastatic

Abstract
Although the oligometastatic type of prostate cancer (PCa) is the subject of much research, it still has no clear biological and clinical specification. It is a condition between localized and extensive PCa, in which early diagnosis and treatment are favorable prognostic factors. Not so long ago, just the presence of metastases was considered a poor prognosis with limited therapeutic options. Such patients were treated as if they had advanced cancer and received hormonal treatment. However, clinical trials have shown that Androgen Deprivation Therapy (ADT) can be delayed in patients with an oligometastatic PCa (OMPCa). New therapeutic methods are being developed thanks to the advanced research and various concepts to understand the underlying biology of this type of cancer. In this review, the intention is to bring together the latest information in this domain.

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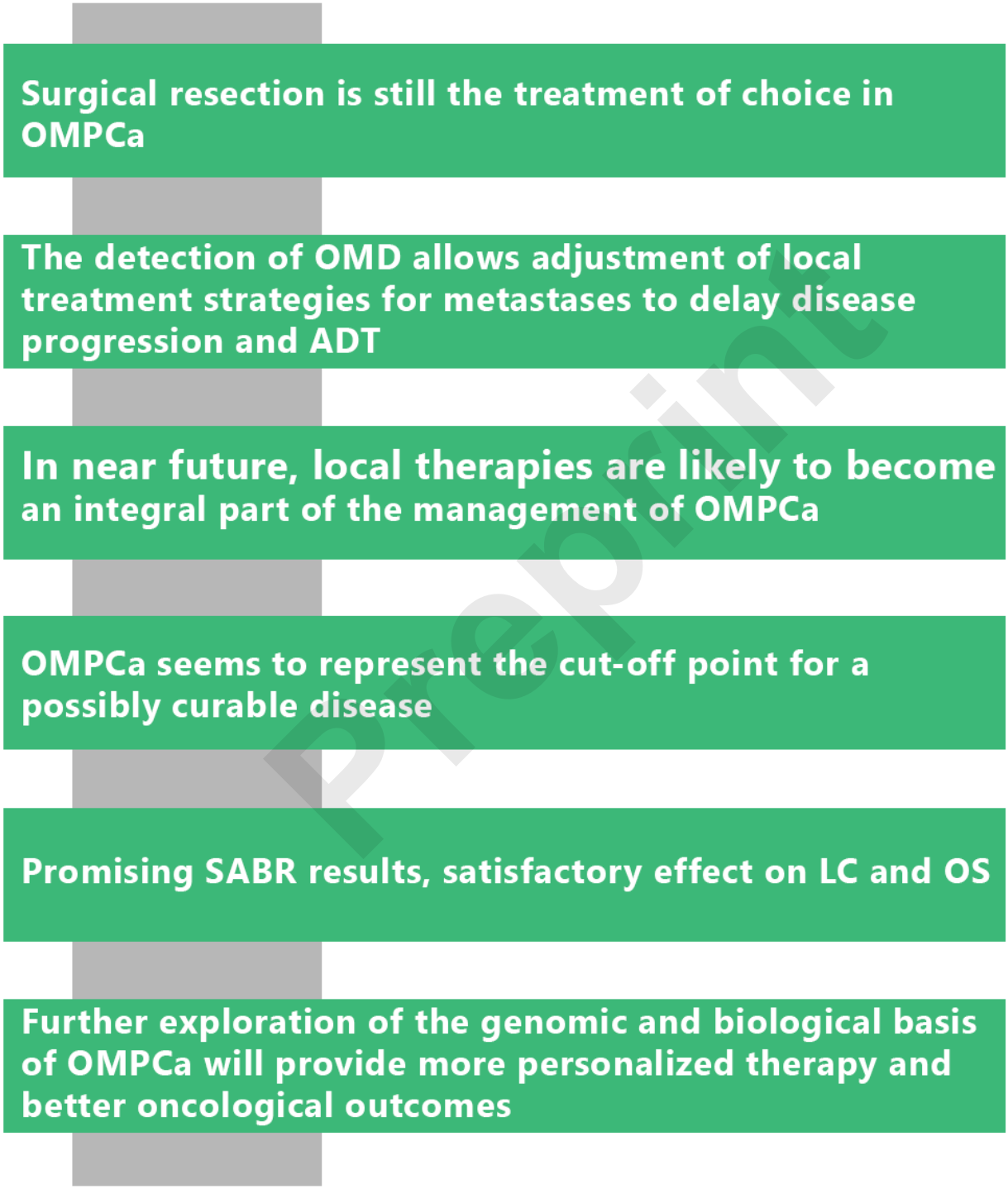
Graphical abstract



Abstract: Although the oligometastatic type of prostate cancer (PCa) is the subject of much research, it still has no clear biological and clinical specification. It is a condition between localized and extensive PCa, in

which early diagnosis and treatment are favorable prognostic factors. Not so long ago, just the presence of metastases was considered a poor prognosis with limited therapeutic options. Such patients were treated as if they had advanced cancer and received hormonal treatment. However, clinical trials have shown that Androgen Deprivation Therapy (ADT) can be delayed in patients with an oligometastatic PCa (OMPCa). New therapeutic methods are being developed thanks to advanced research and various concepts to understand the underlying biology of this type of cancer. In this review, the intention is to bring together the latest information in this domain.

Introduction

PCa is one of the most commonly diagnosed cancers and cause of death among men worldwide. In 2020, the number of new cancer cases was 1,414,259 (7.3%) and the number of deaths was 375,304 (3.8%) [1]. These numbers are expected to increase in the coming years due to the COVID-19 pandemic and an ageing population. Also due to improvements in diagnostic capabilities, the number of diagnoses continues to rise, with the authors [2] predicting an increase of 15097 new diagnoses by 2025.

Between the two distinct clinical stages of PCa (a benign, locally limited form and a widely spread malignancy) is oligometastatic carcinoma [3].

The clinical definition of OMPCa depends on the number of lesions (a limitation of $\leqslant 5$ is used in most publications), mainly because of the simplicity of patient classification and the correlation between clinical findings and the number of lesions. This type was described more than 25 years ago and has not yet been characterised morphologically, immunohistochemically or genomically, but it has been shown to be represented by slower growth and a less aggressive phenotype and susceptibility to metastasis-directed therapy (MDT) [4]. To date, no therapeutic recommendations have been made for this group of patients. The definition and management, as well as the role of AS [5] and local therapies [6] as treatment modalities in this type of cancer are controversial.

Publications [7], [8] have shown good clinical response and better prognosis after MDT in patients with <5 metastases. In OMPCa patients, surgical metastasectomy and/or stereotactic radiotherapy (SABR) as a form of MDT has been shown to be associated with improved survival or delayed systemic treatment [9], while RT of the primary tumour improves overall survival (OS) [10] (Table 1).

Table 1. presenting the results of the STAMPEDE trial.

First author (year)	Study design	Oligometastatic definition	Intervention (numer of patients)	Outcomes
Parker et al. (2018)	A randomised controlled phase 3 trial.	Low metastatic burden (LMB) defined as< 4 bone metastases or any number of exclusively vertebrae or pelvis osseous site (42%) High metastatic burden (HMB) (58%)	SOC (lifelong ADT+ docetaxel) (n=1029) vs SOC +RT (n=1032)	LMB 3 -yr OS=73% (SOC) 81% (SOC+RT) HMB 3 -yr OS= 54% (SOC) 53% (SOC+RT) LMB 3 -yr FFS=33% (SOC) 50% (SOC+RT) HMB 3 -yr FFS= 17% (SOC) 18% (SOC+RT) LMB 3 -yr PFS=58% (SOC) 63% (SOC+RT) HMB 3 -yr PFS= 35% (SOC) 30% (SOC+RT) LMB 3 -yr CSS=79% (SOC) 86% (SOC+RT) HMB 3 -yr CSS= 58% (SOC) 56% (SOC+RT)

ADT- androgen deprivation therapy; CSS- cancer specific survival; FFS- failure free survival; HMB- high metastatic burden; LMB-low metastatic burden; OS- overall survival; PFS- progression free survival; RT- radiotherapy; SOC- standard of care.

This review aims to bring together the latest information on the effectiveness of therapies targeting metastatic and localised lesions in patients with OMPCa.

2. Methods

We conducted this review by browsing MEDLINE (by PubMed) and Cumulative Index to Nursing and the Cochrane Central Register of Controlled Trials (CENTRAL) (by Cochrane Library) for study reports.

Publications other than original research reports (e.g., editorials, commentaries and letters) were also included. We included only articles published in English, without restrictions on publication status or year.

The following keywords were used: (“prostate cancer" OR "prostate neoplasm" OR "prostate tumor") AND ("oligometastatic prostate" OR "prostate oligometastases" OR "OMD") AND ("surgery" OR "prostatectomy" OR "radical prostatectomy" OR "local treatment") AND ("radiotherapy" OR "radiosurgery" OR "metastasis directed theraphy" OR "prostate metastasis directed therapy' OR “'SBRT' OR 'radical cytoreductive prostatectomy').

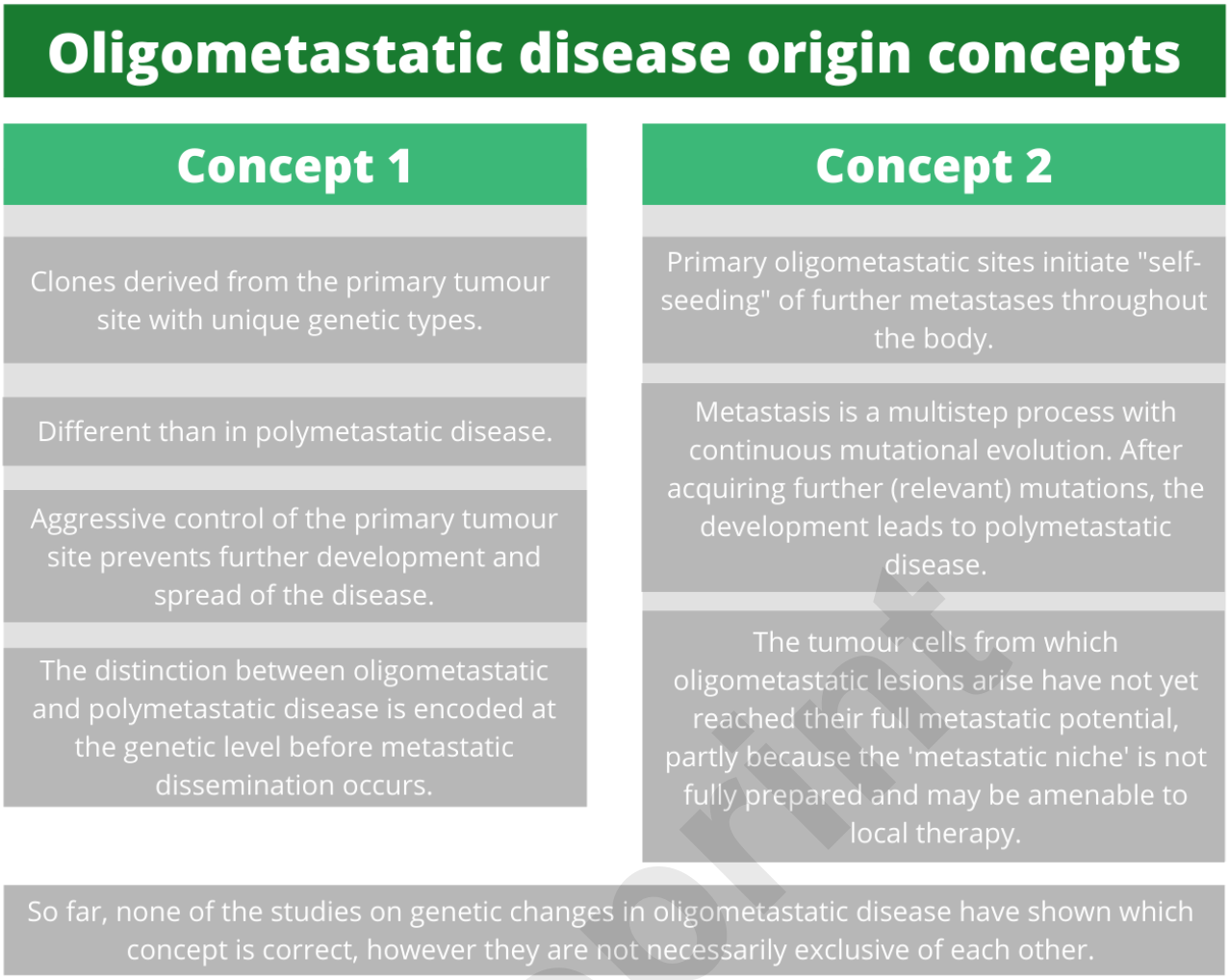
This study aimed to analyse the efficacy of therapies targeting metastatic and local lesions in OMPCa patients. Search strategies included free-text terms and controlled vocabulary specifying eligible participants, interventions and outcomes, and study design search filters (except Cochrane Library). Authors also sought study reports from other sources, including bibliographies of relevant systematic reviews, backward and forward citation searches of included study reports using Web of Science. Then we carried out data extraction, further screening for relevant articles based on a full-text review.

2.1. Oligometastasis disease (OMD)

As mentioned above, in 1995, Hellman et al. [3] proposed a definition of a new form of cancer occurring between locally limited and systemically metastatic disease. Since then, the number of scientific articles has steadily increased in the following years, and OMD has remained at the center of researchers' attention.

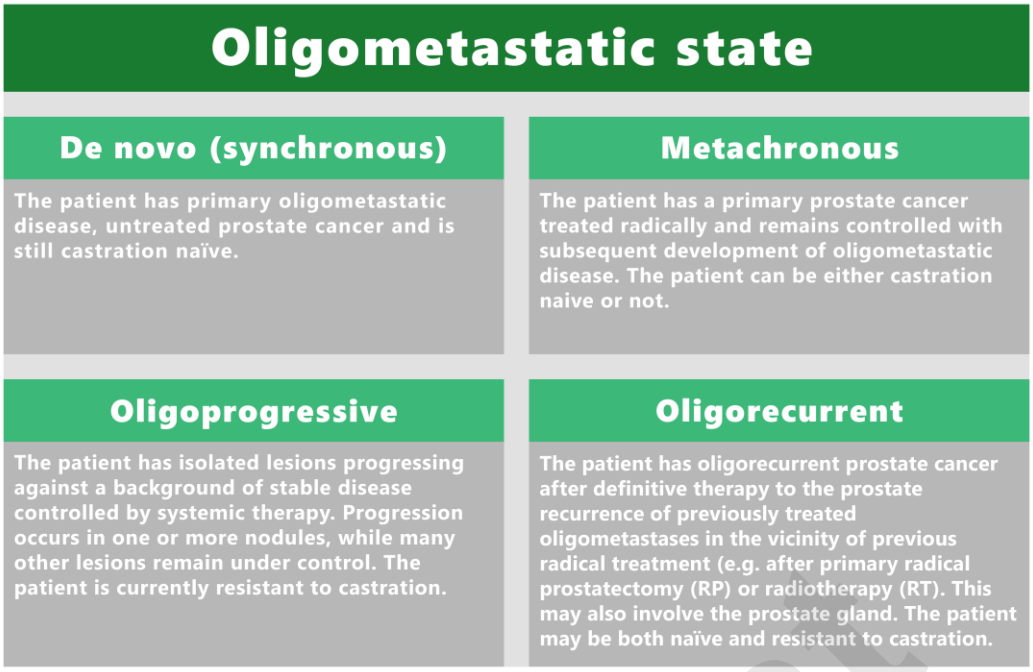
The term "oligometastatic prostate cancer" refers to a wide range of diseases (Figure 1) currently distinguished solely based on clinical features.

Figure 1. Graphic showing oligometastatic disease origin concepts.



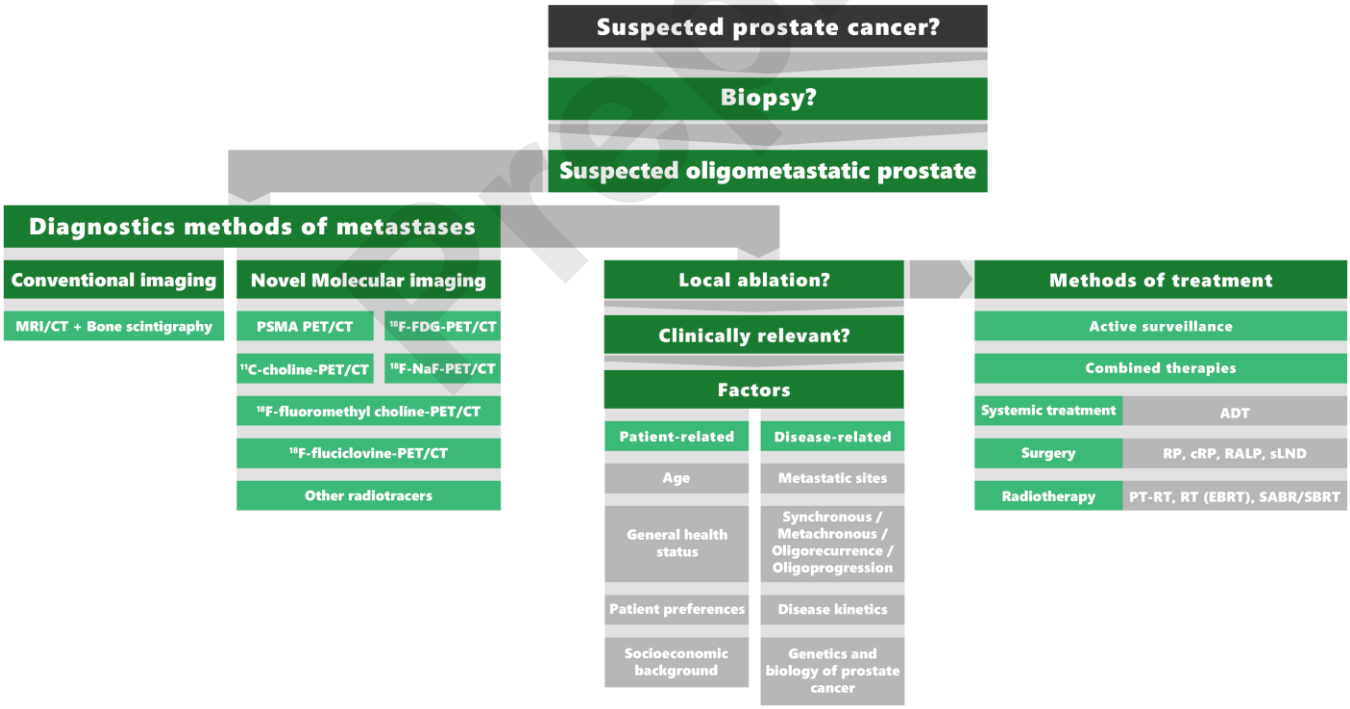
However, we still do not have a universally accepted one [11]. The consensus of the ESTRO-ASTRO group of radiation oncologists [12] dealing with this problem was to consider OMD a form that meets the following conditions: the number of metastases ≤5, and the use of MDT should enable safe removal of the lesions. At the same time, control of the primary tumour is optional. However, some situations should be considered individually - sometimes, even multiple lesions grouped in one organ/region can be safely treated. In this case, the management should depend on the individual patient's characteristics. There are different [13]concepts to explain the biology of oligometastases (Figure 2).

Figure 2. Graphic showing the division of the oligometastatic state.



In the future, the presence of factors (Figure 3.) may help us distinguish OMD from the still invisible but aggressive form of the disease and consider MDT's advisability.

Figure 3. A scheme for multistage decision-making in patients with OMPCa.



Theoretically, it is possible to monitor the progression of the disease with follow-up imaging studies. Their performance within 2-3 months usually gives us clear indications on the direction of treatment that should be undertaken. However, it should be remembered that such management delays the treatment. Monitoring is therefore risky due to the dangers of progression, which may narrow therapeutic options. It is also essential to determine whether the metastases occurred in the primary stage or during the disease.

On this basis, we distinguish two main subcategories: synchronous (diagnosed at the time of diagnosis) and metachronous (which appeared after treatment of the primary tumour) [14]. Metachronous metastases include oligorecurrent and oligoprogressive metastases (Figure 1).

In the oligoprogressive type, progression occurs in one or more lesions while many remain under control. According to the definition, these metastases appear ≥ 3 months after the primary diagnosis [15]. For this reason, we usually know the dynamics of disease progression, e.g. we have a series of previous imaging studies. Hence, retrospective assessment of tumour size and other features facilitates the decision on appropriate treatment. The term de novo oligometastases refers to newly diagnosed cases (synchronous with the primary tumour) (Figure 1). Due to the lack of information regarding tumour kinetics in synchronous metastases, patients usually start treatment with systemic therapy. Clinicians opt for local treatment after reasonable control is achieved (figure 3).

2.2 What is the role and effectiveness of MDT and/or prostate-targeted therapy (PTT) in OMPCa?

2.2.1. The role and effectiveness of PTT- local treatments in OMPCa

External beam radiotherapy (EBRT) and radical prostatectomy (RP) were conventionally proposed for the treatment of locally advanced PCa only. Over time, the use of these methods has evolved. The concept that oligometastases are curable is becoming more readily accepted, and technological advances in PCa are leading to better therapeutic outcomes [16].

2.2.1.1.The role of EBRT in local control (LC)

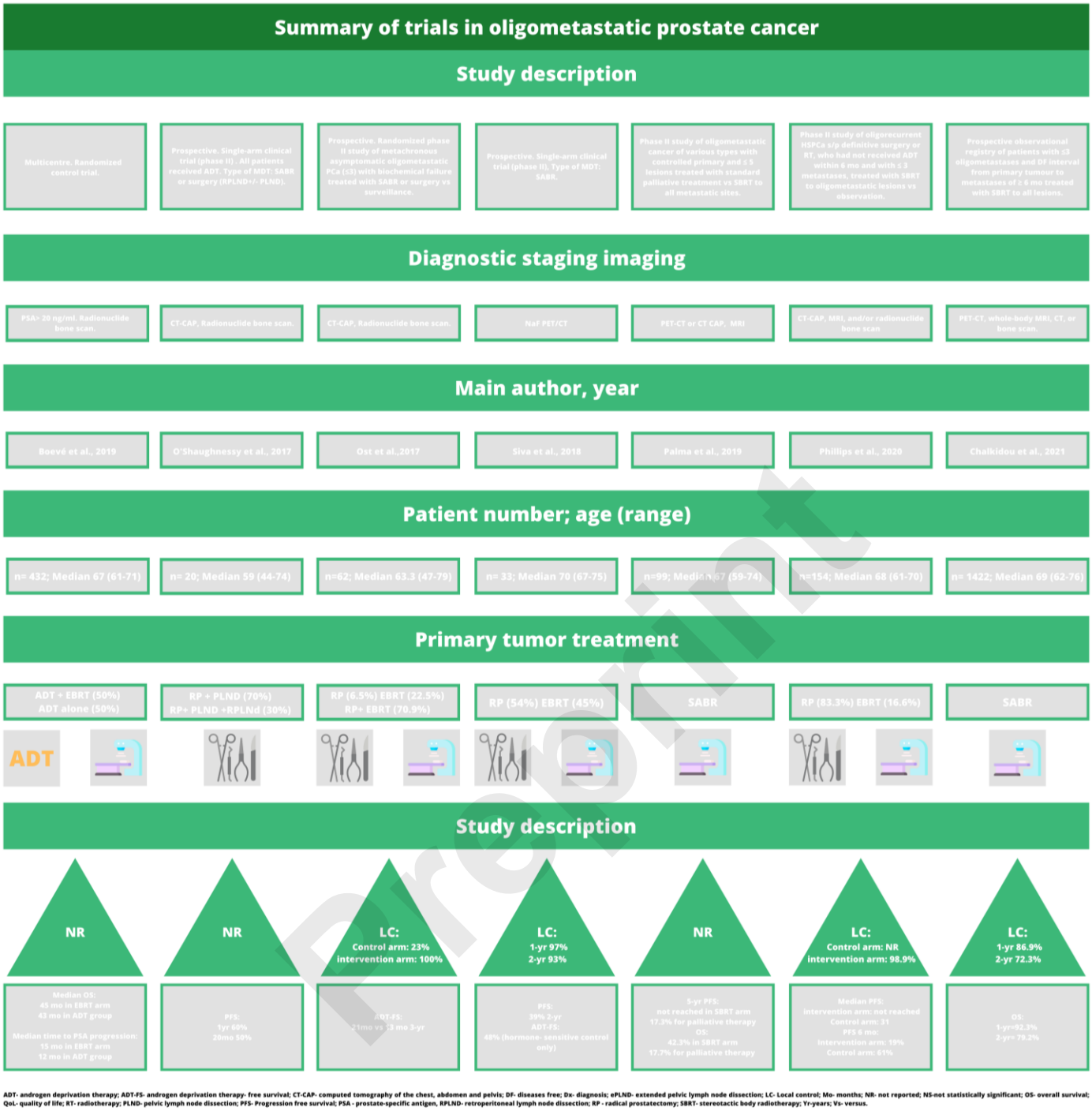
The results of radiotherapy modality studies for MDT in OMPCa have been reported in publications [14], [17]. SBRT achieved 5-year LC of up to 92% and OS of 88%.

2.2.1.2 Role of RT targeting the prostate gland

Two prospective, randomised studies have been published [10], [18] comparing the prognosis of patients receiving RT + ADT or ADT alone.

In the first multicentre, controlled HORRAD trial [18], 432 patients with de novo mPCa were divided into standard ADT or EBRT + ADT groups. OS was assessed and did not differ significantly between groups (figure 4). Nevertheless, RT significantly improved the median time to PSA progression. Limitations of this study were the low dose of irradiation (only 70 Gy) and the lack of information on visceral metastases.

Figure 4. Summary of trials in OMPCa



ADT- androgen deprivation therapy; ADT-FS- androgen deprivation therapy- free survival; CT-CAP- computed tomography of the chest, abdomen and pelvis; DF- diseases free; Dx- diagnosis; ePLND- extended pelvic lymph node dissection; LC- Local control; Mo- months; NR- not reported; NS-not statistically significant; OS- overall survival; QoL- quality of life; RT- radiotherapy; PLND- pelvic lymph node dissection; PFS- Progression free survival; PSA - prostate-specific antigen, RPLND- retroperitoneal lymph node dissection; RP - radical prostatectomy; SBRT- stereotactic body radiotherapy; Yr-years; Vs- versus.

Furthermore, a study [19] showed that for PCa bone oligometastases, RT proves to be an effective method for long-term pain relief (Table 4).

The second prospective study [10] STAMPEDE included more patients (n=2061). The results suggested no improvement in OS (Figure 4) when RT was added to ADT in newly diagnosed mPCa patients. However, similar to the HORRAD study, OS was better in the low metastatic burden (LMB) subgroup (3-year OS 73% with ADT vs 81% with ADT+RT). Likewise, 3-year prostate CCS was better in the LMB subgroup (79% in ADT vs 86% in ADT+RT).

Similar results were reported in a recently published systematic review [20], including publications [10], [18]. In unselected patients, RT + ADT did not improve survival. However, a significant difference was observed in the effect of a metastatic burden on survival (with a 7% improvement in 3-year OS) in the LMB group. An improvement in ADT-free survival (ADT-FS) was also observed in the LMB arm.

We are awaiting additional results from an ongoing study on CRP in HSPC with de novo metastases [21]. Based on the results, prostate-targeted radiotherapy (PTT-RT) may be proposed as a standard treatment option in men with LMB. However, clinicians should interpret the data with caution due to reports that argue against implementing new treatments in the absence of convincing results from phase 2 and 3 trials [22].

SBRT, due to its excellent LC and limited side effects, is a promising therapeutic modality in OMPCa. The most extensive prospective study to date (n=1422) [23]verifying the utility of SBRT showed that its use was associated with improved OS and high efficacy (Figure 4). These results support the benefits of SBRT, and the NHS recommended SBRT as a treatment option for OMD in March 2020.

2.2.1.3. The role of cytoreductive radical prostatectomy (CRP)

The advantages of cytoreductive radical prostatectomy (cRP) in mPCa have been demonstrated in retrospective studies [24]–[26].

Jang et al. [27] analysed the history of 79 patients with mPCa treated with RALP (robot-assisted laparoscopic prostatectomy) or ADT. They showed that RALP for OMPCa improved oncological outcomes, disease progression-free survival (PFS) and cancer-specific survival (CSS) (table 3). A study [28]evaluated the results of radical prostatectomy (RP) in 11 patients with OMPCa with a follow-up period of at least five years. It was shown that RP could be a safe procedure with acceptable oncological outcomes at long-term follow-up in selected patients (Table 3). These results have also been confirmed in other studies [29], [30].

Table 3. Table of outcomes in local therapy in OMPCa.

First author (year)	Study design	Oligometastatic definition	Intervention (number of patients)	Outcomes
Jang et al. (2018)	Retrospective	on bone scan up to 5 metastases	Robot-assisted RP (n=38)	Median PFS= 75 mo; median CSS= not reached
Gandaglia et al. (2017)	Retrospective	≤5 oligometastases on bone scan with/ without pelvic or retroperitoneal LN involvement	RP and extended pelvic LN dissection (n = 11), with adjuvant ADT (n=10)	7- yr clinical PFS= 45%; 7-yr CSS= 82%
Heidenreich et al. (2015)	Prospective	≤3 metastases on bone scan	cRP (n = 23)	Median time to development of CR= 40 mo; PFS= 38.6 mo; CSS= 95.6%

ADT = androgen-deprivation therapy; CSS = cancer-specific survival; CR= castration resistance; cRP- cytoreductive prostatectomy; FFS- failure-free survival; LN = lymph node; mo-months; OS-overall survival; PFS = progression-free survival; RP= Radical prostatectomy; PSA = prostate-specific antigen.

However, the risk of selection bias in these retrospective studies should be considered. The subsequent prospective study [31] had a lower risk of selection bias.

In the study [31], no significant effect of CRP on survival was observed, but the rate of locoregional complications was lower. Similarly, a publication [32] showed that CRP does not improve tumour-specific survival in PCa patients with skeletal metastases but provides better LC and better biochemical recurrence-free survival.

Heidenreich et al. [32] investigated whether performing CRP in PCa patients with three or fewer bone metastases provides any benefit. The control and experimental arm consisted of 23 patients with similar clinical, biological and oncological characteristics. Comparing the experimental group with the control group showed a longer median time to development of castration resistance and better clinical PFS and CSS (Table 4) [33].

Table 4. Table of retrospective studies of MDT in OMPCa.

First author (year)	Oligometastatic definition	Intervention (numer of patients)	Outcomes	Toxicity
Ost et al. (2016)	Majority with ≤3 oligometastases.	SBRT (n=119)	3-yr distant PFS=31%; 3-yr OS= 95%	17 (14%) patients had grade 1, and 3 (3%) patients had toxicity grade 2. No grade ≥3 toxicity occurred.
Ost et al. (2018)	N1 and M1a/b disease on imaging, with ≤3 synchronous oligometastases.	Surgery/SBRT vs surveillance (n=62)	3-yr follow-up: Median ADT-FS: 21 vs 13 mo. Median PSA PFS: 10 vs 6 mo.	6 patients (17%) had grade 1. No grade ≥2 toxicity occurred.
Ponti et al. (2015)	NA	SBRT (n=16) and concomitant ADT (n = 10)	LC and a decrease in serum PSA in 94% of patients. Mean time to ADT delay-23.7 mo. OS at 19 mo: 94% 2-yr bPFS= 44%; (median follow-up of 29.4 mo.) LC= 94%	1 patient had G2 acute gastrointestinal Toxicity and 1 had G3 late gastrointestinal toxicity.
Decaestecker et al. (2014)	Majority with ≤3 synchronous oligometastases.	Repeated SBRT until ≥3 metastases detected (n=50)	Median PFS=19 mo Median ADT-FS=25 mo 2- and 5-yr CSS= 96% and 90%, respectively.	7 (14%) patients had grade I and 3 (6%) had grade II (according to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] v3.0).
Tabata et al. (2012)	Bone metastases of EOD I are defined as < 6 bone metastases on bone scan, with each site being <50% the size of a vertebral body.	RT (n=35)	3-yr OS= 77%; 1 mo after RT 88% of patients who had pain were improved. Median duration of pain relief: 12 mo.	Pathological fracture and SCC were not seen at treated sites but developed at non-irradiated sites in 3 patients (8.6%) and 1 patient (2.8%), respectively.
Ahmed et al. (2013)	≤5 oligometastases.	SBRT + ADT (n=15) SBRT (n=17)	LC =100% at a median follow-up of 6 mo; 12-mo CSS= 100%; 40% PSA nadir undetectable in 9 (53%) patients, 12-mo	No acute grade >3 No late toxicity (According to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] v3.0).

			distant progression free.	
Berkovic et al. (2013)	≤3 synchronous metastases in bone and/or lymph node on PET.	SBRT repeated until >3 metastases developed (n = 24)	Median ADT-FS= 38 mo; 2-yr LC= 100%; 2-yr clinical PFS= 42%	8% of patients had acute grade 2 genitourinary; 6% had acute grade 2 gastrointestina. No grade ≥3 toxicity occurred.
Cysouw et al. (2018)	≤4 Metachronous metastases on [18F]-fluoromethylcholine PET/CT scan	SBRT (n=40)	Median PFS= 11.5 mo	NA
Guler et al. (2018)	on 68Ga-PSMA PET/CT scan up to 3 metastases	RT (n=23)	1- yr LC= 100%; 1-yr PFS=51%; 1-yr OS=100%	1 (4.3%) patient had acute grade 2 gastrointestina. No grade ≥3 toxicity occurred.
Wu et al. (2016)	on bone scans + F-18 choline PET/CT up to 3 metastases	ADT + RT (n=30)	3-yr PFS= 23% 3- yr OS= 69% Long-course RT was associated with superior 3-yr OS vs short-course RT (76% vs 44%)	3 (10%) patients had acute toxicity: 2 grade 1 and 1 grade 2.

ADT- Androgen deprivation therapy; ADT-FS- ADT-free survival; bPFS- biochemical; CSS- cancer-specific survival; EBRT- External beam radiation therapy; G = grade; LC- local control; mo- months; NA- Not applicable; OS- Overall survival; PFS- Progression-Free Survival; PSA = prostate-specific antigen; RT- Radiation therapy/ radiotherapy; SCC- spinal cord compression.

Grade III or higher Clavien-Dindo adverse events occurred in 29 of 193 patients [26]–[28], [32], [33]. The incidence of grade I-III adverse events was the same or even better than in the control group. No grade IV or V complications, according to Clavien-Dindo, were observed in the RP group [32].

A meta-analysis and retrospective cohort study [34] compared survival outcomes in the RP+ ADT vs ADT-only group of patients with OMPCa. The results suggest that the addition of surgery does not increase CRPC-free survival. However, this meta-analysis showed that patients with OMPCa may benefit from RP + ADT in OS. Although, it should be noted that there is a risk of potential bias due to the limited number of studies, which may have contributed to this result. Therefore, further prospective studies and randomised controlled clinical trials should be conducted to test whether surgery is a beneficial intervention in OMPCa.

In conclusion, retrospective studies have shown many positive results, and prospective studies have not demonstrated an effect on OS. Retrospective studies are subject to selection bias. Adverse events were within acceptable limits and contributed to reducing local symptoms, and LC was effective. However, to draw reliable conclusions, we must await the results of future prospective studies, including the TRoMbone study [ISRCTN15704862], studies on RP in OMPCa with bone oligometastases [35], [36], [NCT02454543], [NCT02742675] which are currently ongoing. These will undoubtedly provide valuable information on men with OMPCa and hopefully demonstrate the efficacy of targeted therapies in these conditions.

2.2.2. The role of MDT in OMPCa.

As with other cancers, there is growing evidence to support the use of MDT in OMPCa, due to the delayed onset of castration resistance and improved PFS [14], [17]. Most publications on MDT are retrospective, single-center studies [19], [37]–[47]. Many of these [42]–[47] and other retrospective studies [39], [48]–[53] suggest that MDT for OMPCa improves PFS.

In the past, the role of local treatment was limited to palliative treatment. However, in recent years, this method has become increasingly important, with the main hope being to improve OS.

Studies on MDT in OMPC have mainly focused on the most common metastases, i.e., bone or lymph nodes.

Visceral metastases are less frequent and herald a worse prognosis [54]. Whether MDT (e.g., SABR) or surgical intervention is beneficial in this situation or whether prompt systemic treatment is preferred is still unclear. In men with distant metastases after primary treatment, all treatment modalities have early benefits in inhibiting disease progression [8]. Although the location of metastases is an important prognostic factor (Figure 3), it is unclear whether the benefits of MDT are different. Rogowski et al. [55] showed that MDT provides good LC and is safe in OMPCa. At two-year follow-up, progression was not observed in more than 40% of participants.

However, in the STOMP study, there was no difference in the effects of MDT between bone and nodal metastases, indicating that both groups benefited [8]. Grade II-V toxicity was not observed in any group, and MDT was not associated with impaired quality of life (QoL).

A systematic review [56], including four controlled trials (two randomised [8], [57] and two non-randomised [38], [58]) involving 169 patients with bone, node and visceral metastases showed that two investigated options for MDT: RT and surgery - are promising therapies for oligometastatic hormone-sensitive (omHSPCa). However, this still requires confirmation in extensive cohort studies.

Whether subsequent MDTs can benefit patients or result in systemic treatment not being administered in time arises. Given the relatively promising results of MDT and the slow progression of PCa, this method should be used primarily in young men and older patients in good condition without comorbidities.

2.2.2.1. The role of SABR in the treatment of metastasis in OMPCa.

In oligoreccurent patients, SABR has gained popularity because of its durable and safe lesion control and ability to delay ADT. A flagship example of this approach is the prospective multicenter phase II STOMP study [8], which randomized LMB patients with biochemical recurrence (BCR). After primary treatment between surveillance (AS) and MDT (81% SABR or 19% surgical resection). In this study, an additional round of MDT was allowed for patients with relapse and <3 metastases. The indication for initiating ADT was a progression of treated lesions or finding >3 metastases.
Patients in both the observation and MDT arms were more likely to avoid ADT (Table 4). At a median follow-up of 3 years, 19% of patients with oligorecurrence in the surveillance arm and 39% in the MDT arm did not indicate to start ADT. This study demonstrates that flip-targeted therapy in men with oligorecurrence PCa can be safely and effectively delayed, thus protecting patients from adverse effects such as hot flashes, fatigue or sexual dysfunction.

However, it should not only be the preferred treatment option in this group of patients- a study [59] showed that (SBRT) is the optimal treatment for elderly patients, allowing reasonable tumour control and limiting side effects, as it is associated with minimal toxicity. Furthermore, phase II studies suggest that SBRT combined with palliative treatment can improve OS and delay initiating systemic therapy in OMD patients.
In studies [39], [41], the authors demonstrated a long median ADT-FS after SBRT treatment (Table 4), confirming that patients can avoid aggressive treatment. This is important because, in some patients, systemic therapy leads to a state of androgen resistance and treatment-induced linear crisis [60].

The optimistic results of studies to date can significantly affect healthcare costs [61]. This treatment should be appreciated for its low toxicity and cost-effectiveness [62]–[66]. Kumar et al. [66] showed that delaying

tumour progression by SABR makes this treatment cost-effective and achieves an increase in QALYs from 2.96 (with standard therapy) to 4.84 (with SABR).

In the single-arm, prospective POPSTAR study [38], SABR was used to treat metastases (single fraction dose was 20 Gy). Thirty-three men with ≤3 metastases (oligorecurrent: 22/33 mCSPC and 11/33 mCRPC) were included in the study (figure 4). One patient (3%) developed grade ≥III toxicity, and no patient died during the study. Male patients who relapsed had M1b disease at study inclusion.

In another prospective, single-arm TRANSFORM trial [40], oligoreccurent OMPCa was treated with MDT. The study results showed that 58.1% of patients did not require treatment intensification. The primary end-point was the proportion of patients who did not need treatment intensification after two years.
However, most of the papers on SBRT are retrospective studies. Of these, Nicosia et al. [67] retrospectively evaluated the efficacy of SBRT in the treatment of lymph node (LN) metastases in a population of 109 men. They obtained 1-, 2- and 3-year LC rates of 93.1%, 86.6% and 86%, respectively. The 1.3-year nodal PFS was 59%, 29%, with a median nodal PFS of 15 months. Survival times after 1.3 years were 100% and 95%. No acute or late grade ≥ II toxicities were observed. SBRT is, therefore, a tolerable and effective treatment for LN metastases in PCa.

These studies have shown that SABR reduces the risk of progression of new metastases and has an acceptable safety profile with no treatment-related deaths.

The SABR-COMET trial [68] is a prospective phase II study, but it should be noted that only 99 men participated. Men with oligoprogressive disease and ≤ 5 metastases were randomized to standard systemic therapy (SST) + palliative treatment or SST + SABR.

Therefore, even patients with poor performance status and frailness can be considered for SABR. Nevertheless, a single fraction of 20 Gy applied in the POPSTAR trial was associated with a 15% higher rate of grade II complications than 30 Gy in three fractions in the STOMP trial [8], [38]. Toxicity after SABR is generally mild, even if treatment is administered daily. However, therapy every other day is often used to reduce the risk of toxicity, as it is associated with less toxicity [69].

A benefit in OS and PFS after SABR has been demonstrated (figure 4). The results of this study have prompted other phase III trials to confirm these results [70], [71].

2.2.3.Stereotactic body radiation therapy (SBRT) and elective nodal radiotherapy (ENRT)

De Bleser et al. [72] compared outcomes and toxicity between SBRT (minimum dose of 5 Gy per fraction per shift in up to 10 fractions) and ENRT (minimum amount of 45 Gy in up to 25 fractions). 3-year metastasis-free survival = 68% with SBRT and 77% with ENRT. Local progression was observed in 50 patients after SBRT and 9 patients after ENRT. Early and late toxicities after ENRT were significantly higher than after SBRT, but most were limited to grade 2. Because nodal recurrence was less frequent after ENRT than after SBRT, the authors concluded that ENRT should be the preferred treatment option. This publication also demonstrated that prophylactic node irradiation could reduce the risk of recurrence.

3. Discussion

Despite the still undetermined biological basis of OMPCa, studies suggest that interventions such as RP, local and metastasis-targeted RT can be performed with minimal risk of side effects. In addition, publications show oncological benefits in men undergoing MDT treatment of primary cancer within the gland, both in LC and distant progression, demonstrating whether ablative treatments such as SABR

improve survival requires RCTs with OS as the primary endpoint. It is worth bearing in mind that the widely used disease PFS is not an appropriate surrogate endpoint, as radical treatment or removal of visible metastases will inevitably improve disease PFS without necessarily affecting OS.

ADT-FS has emerged as a new primary endpoint that tends to be potentially beneficial in terms of quality of life and less toxicity for patients [8], [38], [61]. ADT-FS, however, may be of limited use in synchronous and de novo OMPCa types, where ADT + intensive systemic treatment has a clear survival benefit [73].

Nevertheless, the results described are optimistic. MDT should also be considered to prevent the emergence of a castration-resistant state via delaying ADT.

The good results obtained with MDT may be explained by the fact that it causes changes in the microenvironment of the tumour tissue, following cytotoxicity caused by irradiation or surgical resection. It treats primary metastases but can also cause an "abscopal effect" [74], [75]. An extrinsic effect (abscopal) is a process in which local tumour treatment leads to the antitumour impacts observed outside the radiation field at a considerable distance from it [76]. Based on the existing literature, abscopal effects are observed in patients treated with RT [77], oncothermia [78] or a combination of them. Local irradiation of a tumour at one site induces the entry of tumour antigens or inflammatory response factors into the circulatory system, which may cause an increased defence response directed against non-irradiated tumour lesions displaying similar tumour antigens [79].This is supported by the potential benefits of immunotherapy and the evidence of the activity of immune checkpoint inhibitors in mCRPC [80], [81].

Intensive research is underway to uncover the biological and biochemical (immunology) basis [82], [83] of its mechanisms of action as well as the possibility of exploiting its impact in regular oncology practice.

It is still unclear which treatment is most beneficial. Is the optimal treatment for de novo oligometastases: 1. ablative only at the primary site 2. at the primary site and regional foci of disease or 3. at all distant sites and the initial site.

Supporting evidence in favour of maximal tumour removal includes 1. the Norton-Simon hypothesis [84] that removal of the tumour results in increased sensitivity to systemic treatment and 2. reduction of the possibility of metastatic spread from the metastatic site ± initial sites [85]. However, "better than expected" results after ablative treatment [27], [28], [86]suggest that incomplete ablation will be the treatment option of choice, at a minimum for a subset of patients. The ablation effect mentioned above may be related to this [76], [77].

In addition, the [57] ORIOLE study in men undergoing SABR identified T cell receptor expansion, which is promising. At the beginning of the study, four (8.2%) lesions showed a complete radiological response, although they did not receive direct irradiation. Response to the in situ vaccine is in favour of that.

It is unclear whether OMPCa de novo and CS oligorecurrent status are molecularly distinct, albeit the clinical relevance is essential to answer it. The findings may also reveal other important questions about optimal therapy. For example, even well-tolerated treatments may not be appropriate in older patients with severe comorbidities and "molecularly favourable" OMD.

4. Conclusions

Most published data show that surgical resection is still the treatment of choice in OMPCa. The detection of OMD allows adjustment of local treatment strategies for metastases to delay disease progression and ADT. In near future, local therapies are likely to become an integral part of the management of OMPCa.

SABR is promising. Numerous retrospective and prospective studies have demonstrated its effect on LC and OS. However, further randomised comparative studies are needed to establish MDT's role and optimal timing. According to their individual preferences, they are already being prioritised in specific situations and are a viable option for some patients. It is a well-tolerated type of MDT with demonstrated palliative advantages and evidence supporting further research on its potential to achieve sustained control of disease,

either standalone or when used with systemic treatments in PCa. Currently, relieving pain in symptomatic lesions is the most common indication for using it. Local ablation of limited metastases can result in prolonged cancer control. In addition, it plays a vital role as an addition to or substitutes for systemic therapy in the palliative condition, and its minor side effects amount enhances this.

OMPCa seems to represent the cut-off point for a possibly curable disease. Precise genetic characterisation of this condition is the aim of The Movember group [87]. This identification will provide us with a more specific definition and allow us to develop more personalised therapies.

It seems that in the future, in addition to clinical criteria, OMPCa will be defined on the basis of biological and genomic characteristics, thus allowing therapeutic decisions to be made with greater precision and selecting those patients who will benefit most from MDT. The ideal therapy for OMPCa should be based on rapid, non-invasive and accurate diagnosis and individualized treatment. Scientists and clinicians worldwide should join forces in pursuit of a better future.

References

[1] J. Ferlay *et al.*, "Cancer statistics for the year 2020: An overview," *International Journal of Cancer*, vol. 149, no. 4, pp. 778–789, Aug. 2021, doi: 10.1002/ijc.33588.

[2] F. D. Gaylis *et al.*, "Change in prostate cancer presentation coinciding with USPSTF screening recommendations at a community-based urology practice," *Urologic Oncology: Seminars and Original Investigations*, vol. 35, no. 11, pp. 663.e1-663.e7, Nov. 2017, doi: 10.1016/j.urolonc.2017.06.059.

[3] S. Hellman and R. R. Weichselbaum, "Oligometastases.," *Journal of Clinical Oncology*, vol. 13, no. 1, pp. 8–10, Jan. 1995, doi: 10.1200/JCO.1995.13.1.8.

[4] B. Bernard, B. Gershman, R. J. Karnes, C. J. Sweeney, and N. Vapiwala, "Approach to Oligometastatic Prostate Cancer," *American Society of Clinical Oncology Educational Book*, no. 36, pp. 119–129, May 2016, doi: 10.1200/EDBK_159241.

[5] S. Luzzago *et al.*, "A novel nomogram to identify candidates for active surveillance amongst patients with International Society of Urological Pathology (ISUP) Grade Group (GG) 1 or ISUP GG2 prostate cancer, according to multiparametric magnetic resonance imaging findings," *BJU International*, vol. 126, no. 1, pp. 104–113, Jul. 2020, doi: 10.1111/bju.15048.

[6] A. Kluytmans, J. J. Fütterer, M. Emberton, M. Sedelaar, and J. Grutters, "Exploring the risk-reward balance in focal therapy for prostate cancer—a contribution to the debate," *Prostate Cancer and Prostatic Diseases*, vol. 22, no. 3, pp. 382–384, Sep. 2019, doi: 10.1038/s41391-018-0125-y.

[7] M. J. Connor, V. Khoo, V. Watson, and H. U. Ahmed, "Radical Treatment Without Cure: Decision-making in Oligometastatic Prostate Cancer," *European Urology*, vol. 79, no. 4, pp. 558–560, Apr. 2021, doi: 10.1016/j.eururo.2021.01.029.

[8] P. Ost *et al.*, "Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial," *Journal of Clinical Oncology*, vol. 36, no. 5, pp. 446–453, Feb. 2018, doi: 10.1200/JCO.2017.75.4853.

[9] M. J. Connor, T. T. Shah, G. Horan, C. L. Bevan, M. Winkler, and H. U. Ahmed, "Cytoreductive treatment strategies for de novo metastatic prostate cancer," *Nature Reviews Clinical Oncology*, vol. 17, no. 3, pp. 168–182, Mar. 2020, doi: 10.1038/s41571-019-0284-3.

[10] C. C. Parker *et al.*, "Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial," *The Lancet*, vol. 392, no. 10162, pp. 2353–2366, Dec. 2018, doi: 10.1016/S0140-6736(18)32486-3.

[11] V. Khoo, "New concepts in prostate cancer management: the conundrum of managing oligometastatic disease in prostate cancer—through the looking glass darkly," *Clinical Radiology*, vol. 74, no. 11, pp. 865–875, Nov. 2019, doi: 10.1016/j.crad.2019.05.003.

[12] Y. Lievens *et al.*, "Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document," *Radiotherapy and Oncology*, vol. 148, pp. 157–166, Jul. 2020, doi: 10.1016/j.radonc.2020.04.003.
[13] V. Khoo, "Is There Another Bite of the Cherry? The Case for Radical Local Therapy for Oligometastatic Disease in Prostate Cancer," *European Urology*, vol. 69, no. 1, pp. 13–14, Jan. 2016, doi: 10.1016/j.eururo.2015.07.073.
[14] J. J. Tosoian, M. A. Gorin, A. E. Ross, K. J. Pienta, P. T. Tran, and E. M. Schaeffer, "Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations," *Nature Reviews Urology*, vol. 14, no. 1, pp. 15–25, Jan. 2017, doi: 10.1038/nrurol.2016.175.
[15] P. Szturz, D. Nevens, and J. B. Vermorken, "Oligometastatic Disease Management: Finding the Sweet Spot," *Frontiers in Oncology*, vol. 10, Dec. 2020, doi: 10.3389/fonc.2020.617793.
[16] H. H. Yao, M. K. Hong, N. M. Corcoran, S. Siva, and F. Foroudi, "Advances in local and ablative treatment of oligometastasis in prostate cancer," *Asia-Pacific Journal of Clinical Oncology*, vol. 10, no. 4, pp. 308–321, Dec. 2014, doi: 10.1111/ajco.12256.
[17] K. C. Koo and P. Dasgupta, "Treatment of Oligometastatic Hormone-Sensitive Prostate Cancer: A Comprehensive Review," *Yonsei Medical Journal*, vol. 59, no. 5, p. 567, 2018, doi: 10.3349/ymj.2018.59.5.567.
[18] L. M. S. Boevé *et al.*, "Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial," *European Urology*, vol. 75, no. 3, pp. 410–418, Mar. 2019, doi: 10.1016/j.eururo.2018.09.008.
[19] K. Tabata *et al.*, "Radiotherapy for Oligometastases and Oligo-Recurrence of Bone in Prostate Cancer," *Pulmonary Medicine*, vol. 2012, pp. 1–6, 2012, doi: 10.1155/2012/541656.
[20] S. Burdett *et al.*, "Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis," *European Urology*, vol. 76, no. 1, pp. 115–124, Jul. 2019, doi: 10.1016/j.eururo.2019.02.003.
[21] W. Ranasinghe, B. F. Chapin, I. Y. Kim, P. Sooriakumaran, and N. Lawrentschuk, "The cytoreductive prostatectomy in metastatic prostate cancer: what the individual trials are hoping to answer," *BJU International*, vol. 125, no. 6, pp. 792–800, Jun. 2020, doi: 10.1111/bju.15055.
[22] D. A. Palma *et al.*, "The oligometastatic state—separating truth from wishful thinking," *Nature Reviews Clinical Oncology*, vol. 11, no. 9, pp. 549–557, Sep. 2014, doi: 10.1038/nrclinonc.2014.96.
[23] A. Chalkidou *et al.*, "Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study," *The Lancet Oncology*, vol. 22, no. 1, pp. 98–106, Jan. 2021, doi: 10.1016/S1470-2045(20)30537-4.
[24] B. Löppenberg *et al.*, "The Impact of Local Treatment on Overall Survival in Patients with Metastatic Prostate Cancer on Diagnosis: A National Cancer Data Base Analysis," *European Urology*, vol. 72, no. 1, pp. 14–19, Jul. 2017, doi: 10.1016/j.eururo.2016.04.031.
[25] R. Satkunasivam *et al.*, "Radical Prostatectomy or External Beam Radiation Therapy vs No Local Therapy for Survival Benefit in Metastatic Prostate Cancer: A SEER-Medicare Analysis," *Journal of Urology*, vol. 194, no. 2, pp. 378–385, Aug. 2015, doi: 10.1016/j.juro.2015.02.084.
[26] S. Knipper *et al.*, "Outcome of patients with newly diagnosed prostate cancer with low metastatic burden treated with radical prostatectomy: a comparison to STAMPEDE arm H," *World Journal of Urology*, vol. 38, no. 6, pp. 1459–1464, Jun. 2020, doi: 10.1007/s00345-019-02950-0.
[27] W. S. Jang *et al.*, "Does robot-assisted radical prostatectomy benefit patients with prostate cancer and bone oligometastases?," *BJU International*, vol. 121, no. 2, pp. 225–231, Feb. 2018, doi: 10.1111/bju.13992.
[28] G. Gandaglia *et al.*, "Radical Prostatectomy in Men with Oligometastatic Prostate Cancer: Results of a Single-institution Series with Long-term Follow-up," *European Urology*, vol. 72, no. 2, pp. 289–292, Aug. 2017, doi: 10.1016/j.eururo.2016.08.040.

[29] Y. Guo *et al.*, "The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score is a Novel Significant Prognostic Factor for Patients with Metastatic Prostate Cancer Undergoing Cytoreductive Radical Prostatectomy," *J Cancer*, vol. 10, no. 1, pp. 81–91, 2019, doi: 10.7150/jca.27210.
[30] T. Lan, Y. Chen, Q. Su, and J. Ye, "Oncological Outcome of Cytoreductive Radical Prostatectomy in Prostate Cancer Patients With Bone Oligometastases," *Urology*, vol. 131, pp. 166–175, Sep. 2019, doi: 10.1016/j.urology.2019.03.040.
[31] T. Steuber *et al.*, "Does Cytoreductive Prostatectomy Really Have an Impact on Prognosis in Prostate Cancer Patients with Low-volume Bone Metastasis? Results from a Prospective Case-Control Study," *European Urology Focus*, vol. 3, no. 6, pp. 646–649, Dec. 2017, doi: 10.1016/j.euf.2017.06.016.
[32] A. Heidenreich, D. Pfister, and D. Porres, "Cytoreductive Radical Prostatectomy in Patients with Prostate Cancer and Low Volume Skeletal Metastases: Results of a Feasibility and Case-Control Study," *Journal of Urology*, vol. 193, no. 3, pp. 832–838, Mar. 2015, doi: 10.1016/j.juro.2014.09.089.
[33] F. Poelaert *et al.*, "Cytoreductive Prostatectomy for Metastatic Prostate Cancer: First Lessons Learned From the Multicentric Prospective Local Treatment of Metastatic Prostate Cancer (LoMP) Trial," *Urology*, vol. 106, pp. 146–152, Aug. 2017, doi: 10.1016/j.urology.2017.02.051.
[34] S. Si, B. Zheng, Z. Wang, and Z. Niu, "Does surgery benefit patients with oligometastatic or metastatic prostate cancer? – A retrospective cohort study and meta-analysis," *Prostate*, vol. 81, no. 11, pp. 736–744, Aug. 2021, doi: 10.1002/pros.24170.
[35] P. Sooriakumaran, "Testing radical prostatectomy in men with prostate cancer and oligometastases to the bone: a randomized controlled feasibility trial," *BJU International*, vol. 120, no. 5B, pp. E8–E20, Nov. 2017, doi: 10.1111/bju.13925.
[36] S. Buelens *et al.*, "Multicentre, prospective study on local treatment of metastatic prostate cancer (LoMP study)," *BJU International*, p. bju.15553, Aug. 2021, doi: 10.1111/bju.15553.
[37] F. Pasqualetti *et al.*, "[18F]Fluorocholine PET/CT-guided stereotactic body radiotherapy in patients with recurrent oligometastatic prostate cancer," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 47, no. 1, pp. 185–191, Jan. 2020, doi: 10.1007/s00259-019-04482-6.
[38] S. Siva *et al.*, "Stereotactic Abative Body Radiotherapy (SABR) for Oligometastatic Prostate Cancer: A Prospective Clinical Trial," *European Urology*, vol. 74, no. 4, pp. 455–462, Oct. 2018, doi: 10.1016/j.eururo.2018.06.004.
[39] K. Decaestecker *et al.*, "Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence," *Radiation Oncology*, vol. 9, no. 1, p. 135, Dec. 2014, doi: 10.1186/1748-717X-9-135.
[40] P. Bowden *et al.*, "Fractionated stereotactic body radiotherapy for up to five prostate cancer oligometastases: Interim outcomes of a prospective clinical trial," *International Journal of Cancer*, vol. 146, no. 1, pp. 161–168, Jan. 2020, doi: 10.1002/ijc.32509.
[41] P. Berkovic *et al.*, "Salvage Stereotactic Body Radiotherapy for Patients With Limited Prostate Cancer Metastases: Deferring Androgen Deprivation Therapy," *Clinical Genitourinary Cancer*, vol. 11, no. 1, pp. 27–32, Mar. 2013, doi: 10.1016/j.clgc.2012.08.003.
[42] S. G. C. Kroeze *et al.*, "Prostate-specific Membrane Antigen Positron Emission Tomography–detected Oligorecurrent Prostate Cancer Treated with Metastases-directed Radiotherapy: Role of Addition and Duration of Androgen Deprivation," *European Urology Focus*, vol. 7, no. 2, pp. 309–316, Mar. 2021, doi: 10.1016/j.euf.2019.08.012.
[43] M. Cysouw *et al.*, "Prognostic Value of [18 F]-Fluoromethylcholine Positron Emission Tomography/Computed Tomography Before Stereotactic Body Radiation Therapy for Oligometastatic Prostate Cancer," *International Journal of Radiation Oncology*Biology*Physics*, vol. 101, no. 2, pp. 406–410, Jun. 2018, doi: 10.1016/j.ijrobp.2018.02.005.
[44] C. L. Moyer *et al.*, "Stereotactic ablative radiation therapy for oligometastatic prostate cancer delays time-to-next systemic treatment," *World Journal of Urology*, vol. 37, no. 12, pp. 2623–2629, Dec. 2019, doi: 10.1007/s00345-018-2477-2.
[45] P. Ost *et al.*, "Progression-free Survival Following Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Treatment-naive Recurrence: A Multi-institutional Analysis," *European Urology*, vol. 69, no. 1, pp. 9–12, Jan. 2016, doi: 10.1016/j.eururo.2015.07.004.

[46] O. C. Guler *et al.*, "The feasibility of prostate-specific membrane antigen positron emission tomography(PSMA PET/CT)-guided radiotherapy in oligometastatic prostate cancer patients," *Clinical and Translational Oncology*, vol. 20, no. 4, pp. 484–490, Apr. 2018, doi: 10.1007/s12094-017-1736-9.

[47] A. Soldatov *et al.*, "Patterns of Progression After 68Ga-PSMA-Ligand PET/CT-Guided Radiation Therapy for Recurrent Prostate Cancer," *International Journal of Radiation Oncology*Biology*Physics*, vol. 103, no. 1, pp. 95–104, Jan. 2019, doi: 10.1016/j.ijrobp.2018.08.066.

[48] K. A. Ahmed, B. M. Barney, B. J. Davis, S. S. Park, E. D. Kwon, and K. R. Olivier, "Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer," *Frontiers in Oncology*, vol. 2, 2013, doi: 10.3389/fonc.2012.00215.

[49] B. A. Jereczek-Fossa *et al.*, "Robotic Image-Guided Stereotactic Radiotherapy, for Isolated Recurrent Primary, Lymph Node or Metastatic Prostate Cancer," *International Journal of Radiation Oncology*Biology*Physics*, vol. 82, no. 2, pp. 889–897, Feb. 2012, doi: 10.1016/j.ijrobp.2010.11.031.

[50] A. Muacevic, M. Kufeld, C. Rist, B. Wowra, C. Stief, and M. Staehler, "Safety and feasibility of image-guided robotic radiosurgery for patients with limited bone metastases of prostate cancer," *Urologic Oncology: Seminars and Original Investigations*, vol. 31, no. 4, pp. 455–460, May 2013, doi: 10.1016/j.urolonc.2011.02.023.

[51] K. Aitken *et al.*, "Initial UK Experience of Stereotactic Body Radiotherapy for Extracranial Oligometastases: Can We Change the Therapeutic Paradigm?," *Clinical Oncology*, vol. 27, no. 7, pp. 411–419, Jul. 2015, doi: 10.1016/j.clon.2015.03.006.

[52] E. Ponti *et al.*, "Salvage Stereotactic Body Radiotherapy for Patients With Prostate Cancer With Isolated Lymph Node Metastasis: A Single-Center Experience," *Clinical Genitourinary Cancer*, vol. 13, no. 4, pp. e279–e284, Aug. 2015, doi: 10.1016/j.clgc.2014.12.014.

[53] E. De Bleser, P. T. Tran, and P. Ost, "Radiotherapy as metastasis-directed therapy for oligometastatic prostate cancer," *Current Opinion in Urology*, vol. 27, no. 6, pp. 587–595, Nov. 2017, doi: 10.1097/MOU.0000000000000441.

[54] C. G. Drake, "Visceral metastases and prostate cancer treatment: 'die hard,' 'tough neighborhoods,' or 'evil humors'?," *Oncology (Williston Park)*, vol. 28, no. 11, pp. 974–80, Nov. 2014.

[55] P. Rogowski *et al.*, "Outcomes of metastasis-directed therapy of bone oligometastatic prostate cancer," *Radiation Oncology*, vol. 16, no. 1, p. 125, Dec. 2021, doi: 10.1186/s13014-021-01849-8.

[56] M. J. Connor *et al.*, "Targeting Oligometastasis with Stereotactic Ablative Radiation Therapy or Surgery in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review of Prospective Clinical Trials," *European Urology Oncology*, vol. 3, no. 5, pp. 582–593, Oct. 2020, doi: 10.1016/j.euo.2020.07.004.

[57] R. Phillips *et al.*, "Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer," *JAMA Oncology*, vol. 6, no. 5, p. 650, May 2020, doi: 10.1001/jamaoncol.2020.0147.

[58] M. J. O'Shaughnessy *et al.*, "A Pilot Study of a Multimodal Treatment Paradigm to Accelerate Drug Evaluations in Early-stage Metastatic Prostate Cancer," *Urology*, vol. 102, pp. 164–172, Apr. 2017, doi: 10.1016/j.urology.2016.10.044.

[59] I. W. Winter, T. D. Smile, and G. M. M. Videtic, "Approach to Oligometastatic Cancer in the Elderly Patient," *Current Oncology Reports*, vol. 23, no. 11, p. 122, Nov. 2021, doi: 10.1007/s11912-021-01123-w.

[60] G. Roubaud, B. C. Liaw, W. K. Oh, and D. J. Mulholland, "Strategies to avoid treatment-induced lineage crisis in advanced prostate cancer," *Nature Reviews Clinical Oncology*, vol. 14, no. 5, pp. 269–283, May 2017, doi: 10.1038/nrclinonc.2016.181.

[61] E. De Bleser *et al.*, "A Trial-Based Cost-Utility Analysis of Metastasis-Directed Therapy for Oligorecurrent Prostate Cancer," *Cancers (Basel)*, vol. 12, no. 1, p. 132, Jan. 2020, doi: 10.3390/cancers12010132.

[62] M. J. Zelefsky *et al.*, "Phase 3 Multi-Center, Prospective, Randomized Trial Comparing Single-Dose 24 Gy Radiation Therapy to a 3-Fraction SBRT Regimen in the Treatment of Oligometastatic Cancer," *International Journal of Radiation Oncology*Biology*Physics*, vol. 110, no. 3, pp. 672–679, Jul. 2021, doi: 10.1016/j.ijrobp.2021.01.004.

[63] M. T. Winkelmann, S. Clasen, P. L. Pereira, and R. Hoffmann, "Local treatment of oligometastatic disease: current role," *The British Journal of Radiology*, vol. 92, no. 1100, p. 20180835, Aug. 2019, doi: 10.1259/bjr.20180835.

[64] X. M. Qu *et al.*, "Is SABR Cost-Effective in Oligometastatic Cancer? An Economic Analysis of the SABR-COMET Randomized Trial," *International Journal of Radiation Oncology*Biology*Physics*, vol. 109, no. 5, pp. 1176–1184, Apr. 2021, doi: 10.1016/j.ijrobp.2020.12.001.

[65] F. Macbeth and T. Treasure, "Local treatment of 'Oligometastases': Wishful thinking is not supported by available evidence," *Clinical Oncology*, vol. 32, no. 6, p. 409, Jun. 2020, doi: 10.1016/j.clon.2020.02.032.

[66] A. Kumar, C. Straka, P. T. Courtney, L. Vitzthum, P. Riviere, and J. D. Murphy, "Cost-Effectiveness Analysis of Stereotactic Ablative Radiation Therapy in Patients With Oligometastatic Cancer," *International Journal of Radiation Oncology*Biology*Physics*, vol. 109, no. 5, pp. 1185–1194, Apr. 2021, doi: 10.1016/j.ijrobp.2020.09.045.

[67] L. Nicosia *et al.*, "Recurrence pattern of stereotactic body radiotherapy in oligometastatic prostate cancer: a multi-institutional analysis," *Strahlentherapie und Onkologie*, vol. 196, no. 3, pp. 213–221, Mar. 2020, doi: 10.1007/s00066-019-01523-9.

[68] D. A. Palma *et al.*, "Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial," *The Lancet*, vol. 393, no. 10185, pp. 2051–2058, May 2019, doi: 10.1016/S0140-6736(18)32487-5.

[69] C. R. King, J. D. Brooks, H. Gill, and J. C. Presti, "Long-Term Outcomes From a Prospective Trial of Stereotactic Body Radiotherapy for Low-Risk Prostate Cancer," *International Journal of Radiation Oncology*Biology*Physics*, vol. 82, no. 2, pp. 877–882, Feb. 2012, doi: 10.1016/j.ijrobp.2010.11.054.

[70] R. Olson *et al.*, "Stereotactic ablative radiotherapy for the comprehensive treatment of 1–3 Oligometastatic tumors (SABR-COMET-3): study protocol for a randomized phase III trial," *BMC Cancer*, vol. 20, no. 1, p. 380, Dec. 2020, doi: 10.1186/s12885-020-06876-4.

[71] D. A. Palma *et al.*, "Stereotactic ablative radiotherapy for the comprehensive treatment of 4–10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial," *BMC Cancer*, vol. 19, no. 1, p. 816, Dec. 2019, doi: 10.1186/s12885-019-5977-6.

[72] E. De Bleser *et al.*, "Metastasis-directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy," *European Urology*, vol. 76, no. 6, pp. 732–739, Dec. 2019, doi: 10.1016/j.eururo.2019.07.009.

[73] I. D. Davis *et al.*, "Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer," *New England Journal of Medicine*, vol. 381, no. 2, pp. 121–131, Jul. 2019, doi: 10.1056/NEJMoa1903835.

[74] E. B. Golden *et al.*, "Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial," *The Lancet Oncology*, vol. 16, no. 7, pp. 795–803, Jul. 2015, doi: 10.1016/S1470-2045(15)00054-6.

[75] F. Guisier, S. Cousse, M. Jeanvoine, L. Thiberville, and M. Salaun, "A rationale for surgical debulking to improve anti-PD1 therapy outcome in non small cell lung cancer," *Scientific Reports*, vol. 9, no. 1, p. 16902, Dec. 2019, doi: 10.1038/s41598-019-52913-z.

[76] J. Welsh, J. J. Bevelacqua, L. Dobrzyński, S. A. R. Mortazavi, S. Farjadian, and S. M. J. Mortazavi, "Abscopal Effect Following Radiation Therapy in Cancer Patients: A New Look from the Immunological Point of View," *Journal of Biomedical Physics and Engineering*, Feb. 2019, doi: 10.31661/jbpe.v0i0.1066.

[77] N. Dagoglu, S. Karaman, H. B. Caglar, and E. N. Oral, "Abscopal Effect of Radiotherapy in the Immunotherapy Era: Systematic Review of Reported Cases," *Cureus*, Feb. 2019, doi: 10.7759/cureus.4103.
[78] H. F. Alshaibi, B. Al-shehri, B. Hassan, R. Al-zahrani, and T. Assiss, "Modulated Electrohyperthermia: A New Hope for Cancer Patients," *BioMed Research International*, vol. 2020, pp. 1–13, Nov. 2020, doi: 10.1155/2020/8814878.
[79] B. Link, A. Torres Crigna, M. Hölzel, F. A. Giordano, and O. Golubnitschaja, "Abscopal Effects in Metastatic Cancer: Is a Predictive Approach Possible to Improve Individual Outcomes?," *Journal of Clinical Medicine*, vol. 10, no. 21, p. 5124, Oct. 2021, doi: 10.3390/jcm10215124.
[80] S. I. Gutiontov, S. P. Pitroda, and R. R. Weichselbaum, "Oligometastasis: Past, Present, Future," *International Journal of Radiation Oncology*Biology*Physics*, vol. 108, no. 3, pp. 530–538, Nov. 2020, doi: 10.1016/j.ijrobp.2020.02.019.
[81] W. Ngwa, O. C. Irabor, J. D. Schoenfeld, J. Hesser, S. Demaria, and S. C. Formenti, "Using immunotherapy to boost the abscopal effect," *Nature Reviews Cancer*, vol. 18, no. 5, pp. 313–322, May 2018, doi: 10.1038/nrc.2018.6.
[82] I. B. Mihaylov, T. M. Totiger, T. M. Giret, D. Wang, B. Spieler, and S. Welford, "Toward prediction of abscopal effect in radioimmunotherapy: Pre-clinical investigation," *PLOS ONE*, vol. 16, no. 8, p. e0255923, Aug. 2021, doi: 10.1371/journal.pone.0255923.
[83] D. Wang *et al.*, " Research Progress and Existing Problems for Abscopal Effect ," *Cancer Management and Research*, vol. Volume 12, pp. 6695–6706, Aug. 2020, doi: 10.2147/CMAR.S245426.
[84] L. Norton and R. Simon, "The Norton-Simon hypothesis revisited.," *Cancer Treat Rep*, vol. 70, no. 1, pp. 163–9, Jan. 1986.
[85] G. Gundem *et al.*, "The evolutionary history of lethal metastatic prostate cancer," *Nature*, vol. 520, no. 7547, pp. 353–357, Apr. 2015, doi: 10.1038/nature14347.
[86] U. Bashir *et al.*, "Impact of Ga-68-PSMA PET/CT on management in prostate cancer patients with very early biochemical recurrence after radical prostatectomy," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 46, no. 4, pp. 901–907, Apr. 2019, doi: 10.1007/s00259-018-4249-z.
[87] S. M. Bruinsma *et al.*, "The Movember Foundation's GAP3 cohort: a profile of the largest global prostate cancer active surveillance database to date," *BJU International*, vol. 121, no. 5, pp. 737–744, May 2018, doi: 10.1111/bju.14106.