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TOPIC PAPER

Treatment of the primary tumor in metastatic prostate cancer

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Abstract

The cornerstone of treatment for metastatic prostate cancer patients has been conventional androgen deprivation therapy, with additional systemic therapy initiated only after castration resistance, and local therapy reserved for palliation. Compelling results from modern trials challenge this paradigm, arguing for initiating escalated hormone therapy and/or chemotherapy during the castration-sensitive disease state for many patients. Furthermore, modern radiotherapy techniques allow for local control of disease with low risk of toxicity. Finally, new PET probes with enhanced sensitivity and accuracy are likely to become a part of routine staging and will lead to an increased incidence of patients with metastatic disease at presentation, with a shift toward identification of patients with limited metastatic disease. As such, the landscape is primed for investigations aimed to explore the role of primary tumor therapy for patients with metastatic prostate cancer. We review the existing data evaluating primary tumor therapy for patients with metastatic prostate cancer and describe ongoing clinical trials testing the hypothesis that primary tumor therapy may benefit patients with metastatic prostate cancer.

Keywords Prostate cancer · Oligometastatic · Radiotherapy · Hormone-sensitive metastatic

Introduction

The treatment intent for patients with metastatic prostate cancer is palliative [1]. The majority of metastatic prostate cancers will initially respond to treatments that interfere with the androgen receptor (AR) signaling axis [2]. Consequently, the principal component of the current standard of care for patients with metastatic prostate cancer is androgen deprivation therapy (ADT) [1]. ADT comprises systemic therapeutics that either reduce the synthesis of androgens [3] or competitively interfere with the binding of androgens to the AR. Prostate cancers that are responsive to ADT are considered castration (or hormone) sensitive. However, relapse on ADT is inevitable. Modern cohorts of patients treated with ADT alone have a median time to failure and overall survival of 11 and 42 months, respectively [4]. Patients are maintained on ADT continuously or, less frequently, intermittently, until death. The expected side effects of ADT include loss of sex drive, impotence, loss of bone mineral density, and exacerbation of underlying cardiovascular and metabolic disease [5]. Recently, there has been a shift in treatment strategies for men with metastatic prostate cancer with an increase in the use of enhanced hormonal or chemohormonal therapy supported by prospective Phase III trials [6, 7] as well as aggressive local therapy in the form of surgery or radiation.

The biological rationale for the local therapy of the primary tumor in patients with likely incurable metastatic disease is based on the concept that the primary tumor acts as both a source of metastatic cancer cells and proliferative factors, as well as a sanctuary site for the development of treatment-resistant clones. Historically, the primary tumor was believed to be the primary source of metastatic seeding and therefore removal of the primary tumor would prevent further dissemination of metastases. Recent studies have shown that the metastatic ecosystem is more complicated with multidirectional communication and flow between the primary tumor and metastatic sites, as well as seeding between metastatic sites [8, 9]. Even in this more complex metastatic ecosystem, treating the primary tumor may be beneficial as it remains a favorable environment for metastatic clones to "self-seed", leading to local progression

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and further metastatic potential [8]. Furthermore, there is also evidence that the primary tumor can produce tumor chemokines that promote the development of distant metastatic niches and dictate the patterns of metastatic spread [10]. Finally, the primary tumor in prostate cancer may facilitate resistance to ADT through local conversion of adrenal androgens as well as the selection and expansion of treatment-resistant prostate cancer subclones [11]. Another argument for offering aggressive local therapy in the setting of metastatic disease is an improvement in local control. Halting the local progression of disease can prevent the development of symptoms from primary tumor growth and invasion and decrease the need for palliative procedures and the associated procedural risks and complications [12–14].

The rationale for a treatment paradigm that includes aggressive treatment of the primary tumor in the context of metastatic disease has precedence in patients with ovarian, colorectal, and renal cell carcinomas for which local therapy in the metastatic setting is already a part of routine care. Two randomized trials found that radical nephrectomy and interferon immunotherapy were superior to interferon immunotherapy alone and improved survival in patients with metastatic renal cell cancer and a resectable primary [15, 16]. However, a recent Phase III trial, more reflective of current systemic therapy practice, randomized patients with intermediate to poor risk metastatic renal cancer to nephrectomy, followed by sunitinib versus sunitinib alone and found that sunitinib alone was not inferior [17]. It is too early to determine how this will impact current practice. Randomized prospective data on the role of surgical debulking in metastatic ovarian cancer is not available, but numerous retrospective studies convincingly support its role as primary treatment in the majority of stage III and IV patients [18–20]. A substantial minority of colorectal cancer patients with oligometastatic disease to the liver who undergo standard local therapy and complete resection of all metastases may be cured [21, 22]. Recently, molecular subtyping has identified a potentially curable oligometastatic state in colorectal liver metastases [23]. Although randomized prospective data on the impact of aggressive primary therapy in metastatic colon cancer patients is lacking, aggressive primary tumor therapy is a standard of care for appropriately selected patients with oligometastatic colon cancer [24]. In metastatic breast cancer, multiple retrospective studies have shown a benefit for definitive treatment of the primary tumor [25]. However, the results of a randomized trial at Tata Memorial Hospital showed no benefit with radical mastectomy or breast-conserving therapy in women with de novo metastatic breast cancer with complete or partial response to neoadjuvant chemotherapy or endocrine therapy [26]. In light of this evidence from other disease sites, it is still unknown at present if none, many, or a small subset of patients with metastatic prostate cancer may benefit from aggressive treatment to the primary tumor.

There is evidence that overall metastatic disease burden is an important prognostic factor for survival in patients with prostate cancer. It has been hypothesized that patients with low-volume metastatic disease, in particular, stand to benefit the most from aggressive local therapy. The incidence of patients presenting at diagnosis with metastatic prostate cancer has risen [27–29], potentially due to a reduction in the use of screening. A further increase is anticipated given the recent development of more sensitive diagnostic imaging [30], likely to enter routine care within the next few years. There is already substantial clinical evidence that definitive local therapy to the prostate when added to ADT can improve survival in patients with locally advanced [31, 32] and node-positive disease [33]. This review summarizes the current evidence and ongoing trials exploring the role of primary prostate cancer tumor therapy in patients with metastatic hormone-sensitive prostate cancer.

Retrospective evidence in favor of treating the primary tumor in patients with metastatic prostate cancer

Local therapy options for oligometastatic prostate cancer include radical prostatectomy, external beam radiotherapy, and brachytherapy. The impact of these local consolidative therapies on prostate cancer outcomes have been analyzed in several population-based retrospective studies (summarized in Table 1). Two reports from Culp et al. [34] and Antwi et al. [35] present Surveillance, Epidemiology, and End Results (SEER) database analyses of 8185 and 7858 patients, respectively. All patients who were included had M1a–M1c disease. Both studies compared the effects of no local treatment, radical prostatectomy, and brachytherapy on overall survival and prostate cancer-specific survival. Both studies excluded patients who underwent external beam radiotherapy due to the inability to distinguish between definitive or palliative external beam radiotherapy. Culp et al. analyzed 8185 patients with a median follow-up of 16 months and found that patients who underwent radical prostatectomy (RP: 245, or 2.9%) or brachytherapy (BT: 129, or 1.5%) had improved 5-year overall survival (67.4% RP, 52.6% BT vs. 22.5% NSR) versus those not receiving local therapy (NSR: 7811, or 95.4%). Antwi et al. analyzed an overlapping cohort of 7858 patients, 222 (2.8%) of whom received radical prostatectomy, 120 (1.5%) received brachytherapy, and 7516 (95.6%) received no further treatment. Using propensity score matching to control for the effects of baseline characteristics, they also found a significant percent decrease in risk for all-cause mortality (RP vs. no treatment: 73%; BT vs. no treatment: 57%) and prostate cancer-specific

Table 1 Nonrandomized studies of local therapy in metastatic prostate cancer

Study	Comparison groups	Number of metastases	Number of patients	Data source	Results
Culp et al. [34]	RP or BT vs. NLT	M1a–c	7811 (NLT) 245 (RP) 129 (BT)	SEER	5-year OS: 67.4% (RP), 52.6% (BT) vs. 22.5% (NLT) $p<0.001$ 5-year DSS: 75.8% (RP), 61.3% (BT), 48.7% (NLT) $p<0.001$
Antwi and Everson [35]	RP or BT vs. NLT	M1a–c	7516 (NLT) 222 (RP) 120 (BT)	SEER	Relative reduction in PrCaSM vs. NLT after PSM: 78% (RP), 60% (BT) $p<0.0001$
Satkunasivam et al. [36]	RP, IMRT, or CRT vs. NLT	M1a–c	3827 (NLT) 107 (CRT) 88 (IMRT) 47 (RP)	SEER-Medicare	Relative decrease in PrCaSM vs. NLT after PSM: 45% (RP) not significant, 53% (IMRT) $p=0.001$, 3% (CRT) not significant
Leyh-Bannurah et al. [39]	LT vs. NLT RP vs. RT	M1a–c	13,218 (NLT) 313 (RP) 161 (RT)	SEER	PSM CSM: HR 0.35, CI 0.26–0,46 (RP vs. NLT), $p<0.001$; HR 0.48, CI 0.35–0.66 (RT vs. NLT), $p<0.001$; HR 0.59, CI 0.35–0.99 (RP vs. RT), $p=0.048$
Loppenberg et al. [38]	LT vs. NLT	M1a–c	14,301 (NLT) 1470 (LT)	NCDB	PSM 3-year OMFS: 69% (LT), 54% (NLT) $p<0.001$
Gratzke et al. [43]	RP+ vs. RP−	M1	1464 (RP−) 74 (RP+)	Munich Cancer Registry	5-year OS: 55% (RP+), 21% (RP−) $p<0.01$
Heidenreich et al. [12]	ADT + RP vs. ADT	M1b and ≤ 3 mets	38 (ADT) 23 (RP)		OS: not significant PFS: 38.6 mo (ADT + RP) vs. 26.5 mo (ADT) $p=0.032$ Median time to CR: 40 mo (ADT + RP) vs. 29 mo (ADT) $p=0.04$ CSS: 95.6% (ADT + RP) vs. 84.2% (ADT) $p=0.043$
Cho et al. [41]	Prostate RT vs. no prostate RT	M1	63 (no RT) 39 (non-prostate RT) 38 (prostate RT)	Yonsei University	3-year OS: 69% (prostate RT) vs. 43% (no prostate RT) $p=0.004$ 3-year BCFFS: 52% (prostate RT) vs. 16% (no prostate RT) $p=0.002$
Parikh et al. [37]	LT (RP, IMRT, or CRT) vs. NLT	M1a–c	5224 (NLT) 622 (RP) 153 (CRT) 52 (IMRT)	NCDB	5-year OS: 45.7% (LT) vs. 17.1% (NLT) $p<0.01$
Steuber et al. [40]	RP vs. BST	M1b and < 3 mets	43 (RP) 40 (BST)	Martini-Klinik Prostate Cancer Center (RP) Copenhagen Prostate Cancer Center (BST)	No difference in OS ($p=0.25$) or CRFS ($p=0.92$)

Table 1 (continued)

Study	Comparison groups	Number of metastases	Number of patients	Data source	Results
Rusthoven et al. [42]	RT + ADT vs. ADT	M1	5844 (ADT) 538 (RT + ADT)	NCDB	PSM 5-year OS: 49% (RT + ADT) vs. 33% (ADT) $p < 0.001$ PSM MS: 55 mo (RT + ADT) vs. 37 mo (ADT) $p > 0.001$
Dall'Era et al. [27]	LT (RP or RT) vs. ADT	Locally advanced or M1	222 (ADT) 78 (RT) 14 (RP)	CDC POC-BP	9-year CSS: 24% (LT) vs. 27% (ADT) not significant 9-year OS: 14% (LT) vs. 17% (ADT) not significant

RP radical prostatectomy, *EBRT* external beam radiation, *IMRT* intensity-modulated radiation, *CRT* conformal radiotherapy, *BT* brachytherapy, *NLT* no local therapy, *LT* local therapy, *BST* best systemic therapy, *ACM* all-cause mortality, *BCFFS* biochemical failure-free survival, *CSM* cancer-specific mortality, *CSMFS* cancer-specific mortality-free survival, *CRFS* castration resistance-free survival, *CR* castration resistance, *DSS* disease specific survival, *OMFS* overall mortality-free survival, *PrCaSM* prostate cancer-specific mortality, *PSM* propensity score matching

mortality (RP vs. no treatment: 72%; BT vs. no treatment: 54%) with local therapy.

Another population-based study by Satkunasivam et al. [36] showed that radical prostatectomy and intensity-modulated radiotherapy were associated with a 52% and 62% decrease in prostate cancer-specific mortality after propensity score matching. Interestingly, 3D conformal radiation, which has now largely been supplanted by intensity-modulated radiotherapy was not associated with a survival benefit. Similarly, in an analysis of the National Cancer Database (NCDB), Parikh et al. found a significant decrease in risk of death for radical prostatectomy or intensity-modulated radiotherapy versus no local treatment that persisted after propensity score matching (HR 0.27 for RP and 0.41 for IMRT vs. no treatment, $p < 0.01$); no benefit was seen with conformal radiation [37]. The largest study to date was an analysis of 15,771 patients with metastatic prostate cancer in the NCDB by Loppenberg et al. [38]. The authors compared the outcomes of patients who received definitive local therapy with radical prostatectomy, external beam radiation, or brachytherapy (comprising a total of 1470 patients [9.5%]) versus patients who received nonlocal therapy (ADT, watchful waiting, non-prostate EBRT). After propensity score matching, they reported higher 3-year overall mortality-free survival with local therapy (69% vs. 54%).

Another large registry study of 13,692 patients in the SEER database by Leyh-Bannurah also found a significant decrease in risk for cancer-specific mortality with definitive local therapy (65% for RP and 52% for RT vs. no local treatment) [39]. The authors also compared the outcomes of patients who received radical prostatectomy versus patients who were treated with definitive brachytherapy with or without external beam radiotherapy and found a lower cancer-specific mortality favoring radical prostatectomy. In addition to these large registry based retrospective studies, two prospective case–control studies in Europe compared the outcomes of patients with metastatic prostate cancer who had radical prostatectomy versus matched control patients who received hormone therapy alone [12, 40]. Neither study found a difference in overall survival, but Heidenreich et al. [12] did find a statistically significant improvement in median progression-free survival (38.6 vs. 26.5 months), median time to castration resistance (40 vs. 29 months), and prostate cancer-specific survival (95.6% vs. 84.2%). However, the results of the Heidenreich study should be interpreted with the understanding that only patients who achieved a PSA nadir under 1.0 ng/mL were eligible to receive cytoreductive prostatectomy—perhaps, selecting for a more favorable subset of patients. Another prospective case–control study performed at Yonsei University in South Korea found that patients who received prostate radiotherapy had improved 3-year overall survival (69% vs. 43%) and biochemical failure-free survival (52% vs. 16%) compared to patients who received no local therapy or palliative radiotherapy that did not include the prostate [41]. The median radiation dose to the prostate was 60 Gy with a range of 30–72.6 Gy.

To more specifically examine the additive benefit of local therapy to ADT, Rusthoven et al. assessed the overall survival in the subcohort of 584 men in the NCDB who received definitive dose external beam radiotherapy to the prostate or to the prostate and pelvis with ADT, versus a larger cohort of 5844 patients receiving ADT alone. They reported a significant improvement in 5-year overall survival (49% vs. 33%) and median survival with the addition of radiation to ADT [42]. Patients received a median radiation dose of 75.6 Gy and patients who received radiation doses higher than 65 Gy had improved overall survival compared to those who received less than 65 Gy. A study by Gratzke and colleagues in patients from the Munich Cancer Registry

comparing patients who underwent radical prostatectomy to those who did not found a significant improvement in 5-year overall survival with radical prostatectomy (55% vs. 21%) [43]. Of the patients who did not receive radical prostatectomy, 389 received radiation; however the authors did not specify whether radiation was delivered with palliative or definitive intent.

A more recent study, however, found no survival benefit for aggressive local therapy when compared to ADT alone [27]. The authors analyzed 272 node-positive and 314 metastatic prostate cancer patients in the CDC Breast and Prostate Cancer Data Quality and Patterns of Care Study. While they found a significant improvement in 9-year overall survival in patients with node-positive disease following local therapy versus ADT alone (in accordance with randomized data), they did not identify a benefit among the patients with metastatic disease. Specifically, 9-year overall survival was 24% following conservative therapy versus 27% following either radical prostatectomy (14 patients, or 4.2%) or radiotherapy (78 patients, or 26.1%).

Cautious interpretation of these database and retrospective studies suggests the hypothesis that treatment of the primary tumor in the context of metastatic disease may impact survival in selected patients.

Prospective trials investigating the role of treatment of the primary tumor in patients with metastatic prostate cancer

The value of aggressive local therapy for metastatic prostate cancer patients needs to be addressed in prospective trials. Indeed, several trials for patients with de novo M1 hormone-sensitive prostate cancer are ongoing (summarized in Table 2) and two trials have recently published results.

The HORRAD trial randomized 432 patients with primary bone metastatic prostate cancer to either ADT alone or ADT plus 70 Gy conventionally fractionated radiotherapy to the prostate alone, excluding pelvic lymph nodes or metastatic sites [44]. Median survival in the ADT alone and ADT plus radiotherapy arms were 43 and 45 months, respectively. Notably, the median PSA was 145 ng/mL and the majority of patients had polymetastatic disease. The dose (70 Gy) and target volumes (prostate only) are not reflective of current practice. Subgroup analysis suggests a possible benefit to patients with oligometastatic disease (4 or fewer metastases), lower PSA, and Gleason score < 9, although this constituted a minority of the patients and statistical significance for the oligometastatic subgroup was not met. The authors concluded that future trials evaluating primary tumor therapy in M1 prostate cancer patients should focus on patients with oliogometastatic disease defined by modern imaging [44].

The much larger prospective, multi-arm randomized STAMPEDE trial very recently published the results of Arm H, which adds radiotherapy of the prostate to long-term ADT in patients with de novo M1 disease [45]. Two thousand and sixty-one patients were randomized to ADT alone versus lifelong ADT combined with radiotherapy to the prostate alone. Patients with any number of metastases as defined by planar bone scans and CT were included. Based on existing retrospective data, the STAMPEDE investigators specified a pre-planned subgroup analysis of patients with limited metastatic disease burden as opposed to high metastatic burden (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 other assessable patients were considered to have low metastatic burden) [46] to test the hypothesis that radiotherapy to the primary would be most effective in improving overall and failure-free survival in these patients. There was no overall survival benefit to the addition of prostate radiotherapy for the entire cohort, though failure-free survival was improved from 23 to 32% (HR 0.76, 0.68–0.84). However, the addition of prostate radiotherapy in the pre-specified subgroup with low-volume disease had an improvement in the 3-year overall survival from 73 to 81% (HR 0.68, 0.52–0.9), and an improvement in the 3-year failure-free survival from 33 to 50%. In contrast, there was no improvement in the 3-year overall survival in patients with high metastatic burden (54% vs. 53%, HR 1.07, 0.90–1.28); failure-free survival was also not improved in these patients (17% vs. 18%, HR 0.88, 0.77–1.01). The test for heterogeneity of treatment effect by metastatic burden on overall survival was significant (interaction $p = 0{\cdot}0098$). Notably, the allowed doses, 36 Gy delivered in 6 weekly fractions or 55 Gy in 20 fractions, were lower than the curative doses used for definitive prostate radiotherapy and was directed to the prostate alone. Neither the pelvic nodes (whether radiographically involved or not), seminal vesicles, nor visible metastases, were treated with radiotherapy.

The PEACE1 trial (NCT01957436) is a randomized four-arm trial in patients with de novo metastatic prostate cancer treated with ADT and docetaxel. Patients are randomized to additional treatment with abiraterone, prostate radiotherapy, and the combination of both. An advantage of this trial design is the incorporation of abiraterone, which was recently shown to improve survival when added to conventional ADT in patients with hormone-sensitive metastatic disease. Results, however, are not expected until 2030.

MD Anderson Cancer Center is conducting an ongoing multi-institutional randomized Phase II trial (NCT01751438) in men with de novo metastatic prostate cancer comparing best systemic therapy with definitive local therapy to the prostate against best systemic therapy alone. All patients receive 6 months of initial best systemic therapy. Patients who do not progress are then randomized 1:1 to local therapy (surgery or radiotherapy, investigators choice)

Table 2 Ongoing prospective trials incorporating primary tumor therapy for metastatic prostate cancer

Study	Local therapy	Number of metastases	Number of patients	Study arms	Primary endpoint	Study type
TRoMbone	RP	1-3 bone lesions	50	Standard of care RP + standard of care	Feasibility to randomize	RCT
Impact of Radical Prostatectomy as Primary Treatment in Patients With Prostate Cancer With Limited Bone Metastases (g-RAMPP, NCT02454543)	RP	1-5 bone lesions	452	Best systemic therapy RP + best systemic therapy	CSS	RCT
Local Treatment With RP for Newly-diagnosed mPCa (LoMP, NCT02138721)	RP		80	Routine care RP + routine care	PFS Time to Disease Event	Non-randomized
A Phase III of ADT + Docetaxel +/- Local RT +/- Abiraterone Acetate in Metastatic Hormone-naïve Prostate Cancer (PEACE1, NCT01957436)	Prostate EBRT 74 Gy in 37 fractions		1168	ADT + docetaxel ADT + docetaxel + abiraterone ADT + docetaxel + RT ADT + docetaxel + abiraterone + RT	OS PFS	RCT
Systemic and Tumor-Directed Therapy for Oligometastatic Prostate Cancer (NCT03298087)	RP ± adj RT, metastasis directed SBRT	1-5 metastases	28	Single arm	Undetectable PSA off ADT	Single arm Phase II
Best Systemic Therapy or Best Systemic Therapy Plus Definitive Treatment (NCT01751438)	RP or Prostate EBRT	M1	180	Best systemic therapy Best systemic therapy + RT/RP	PFS	RCT
Combining Ipilimumab, Degarelix, and Radical Prostatectomy in Men With Newly Diagnosed Metastatic Castration Sensitive Prostate Cancer or Ipilimumab and Degarelix in Men With Biochemically Recurrent Castration Sensitive Prostate Cancer After Radical Prostatectomy (NCT02020070)	RP	≤10 bone lesions	16	RP + Ipilimumab + Degarelix RP with Ipilimumab + Degarelix at recurrence	PSA response rate	Phase II
Radiotherapy for Oligometastatic Prostate Cancer (NCT01859221)	Prostate EBRT and metastasis directed SBRT/SHRT		48		PFS	Phase II
METACURE (NCT03436654)	RP ± adj RT, metastasis directed SBRT	Low volume M1	76	ADT + Apalutamide + RP ADT + Apalutamide + Abiraterone + Prednisone + RP	pCR	Phase II

Table 2 (continued)

Study	Local therapy	Number of metastases	Number of patients	Study arms	Primary endpoint	Study type
SWOG/NCTN S1802: Standard Systemic Therapy With or Without Definitive Treatment in Treating Participants With Metastatic Prostate Cancer (NCT03678025)	Standard systemic therapy ± surgery or radiation	M1	1273	ADT or ADT + Abiraterone + Prednisone ADT or ADT + Abiraterone + Prednisone + RT/RP	OS	RCT

RP radical prostatectomy, *EBRT* external beam radiation, *IMRT* intensity-modulated radiation, *SBRT* stereotactic ablative radiotherapy, *CSS* cancer-specific survival, *PFS* progression-free survival, *OS* overall survival

or best systemic therapy alone. The primary end point is progression-free survival with a planned interim analysis after 60 patients. Planned correlative studies include the development of a biomarker panel to predict benefit from local therapy and characterization of the prostate and associated stroma. This trial has completed accrual and initial results are anticipated in 2019. A larger SWOG/NCTN Phase III trial (NCT03678025) recently opened for enrollment and will randomize over 1200 patients to standard systemic therapy or standard systemic therapy with surgery or radiotherapy to the primary. Patients with polymetastatic and oligometastatic disease will be eligible and metastasis-directed therapy to up to four oligometastatic sites will be allowed. The primary endpoint of the trial will be overall survival with secondary end points of median overall survival, progression-free survival, and quality of life measures.

In general, the aforementioned trials test the hypothesis that local therapy may improve clinically meaningful outcomes for patients with hormone-sensitive M1 prostate cancer. However, all trials include indefinite ADT and do not explicitly explore the hypothesis that a curative intent therapy may be attempted for selected patients. A recent confluence of diagnostic and treatment advances now raise the question if a multimodal approach with aggressive, early treatment of newly diagnosed metastatic prostate cancer could be attempted with curative intent. These advances include the development of imaging with improved sensitivity of detection of metastatic prostate cancer [30], enhanced hormone therapies with proven survival benefit when used early during the hormone-sensitive disease state [6, 7], and metastasis-directed therapies, such as stereotactic body radiotherapy (SBRT), offering durable local control with low toxicity [47]. Memorial Sloan Kettering Cancer Center published a pilot study of 20 patients with de novo M1 prostate cancer who underwent ADT of 6–10 months, metastasis-directed SBRT, and radical prostatectomy [48]. Four of the 20 patients achieved an undetectable PSA after testosterone recovery, which was durable for at least 20 months after initiation of therapy. These data suggest that a combined modality approach directed toward all apparent sites of disease may benefit select patients.

Consequently, another set of ongoing trials explore the potential for multimodality therapy to eliminate all detectable disease and perhaps allow patients' durable disease control off therapy: a first step toward demonstration of a curative intent regimen for oligometastatic M1 prostate cancer.

A multi-institutional single arm Phase II trial sponsored by Veterans Affairs (NCT03298087) is testing the efficacy of combining radical prostatectomy, metastasis-directed SBRT, and 6 months of enhanced ADT with leuprolide, abiraterone, and apalutamide in patients with de novo hormone-sensitive M1a,b prostate cancer and one to five visible M1 metastases and allows staging by PSMA PET/CT.

The primary end point is the percent of patients with undetectable PSA 6 months after testosterone recovery. Several correlative analyses are planned utilizing high-throughput genomic analyses of prostate tissue to determine the primary metastasis-initiating lesion and pathways associated with the development of metastases.

Based on their pilot data, Memorial Sloan Kettering is initiating a randomized trial (Metacure) of multimodal therapy consisting of radical prostatectomy, ADT, apalutamide, and metastasis-directed SBRT versus the same plus abiraterone (NCT03436654). Patients with either localized very high-risk, low-volume de novo M1a,b, or recurrence after surgery with low-volume M1a,b prostate cancer are eligible.

Defining oligometastatic prostate cancer

A common theme in most of the ongoing trials incorporating treatment of the primary tumor in metastatic patients is selective enrollment of patients with limited metastatic disease, commonly referred to as oligometastatic disease. This is reflected in the range of number and sites of metastases allowable, commonly limited to three to five sites of distant metastases. This selection is based in part on the evolving concept that oligometastatic disease may represent a clinical state distinct from more extensive metastatic disease [49] that is more amenable to aggressive and curative intent therapy. Currently, there is no standardized definition of oligometastatic disease. Hellman and Weichselbaum initially described it as an early stage of progression in which metastases are limited in number and location [49]. Soloway found in 1988 that prostate cancer patients with less than six bone metastases on bone scans had 2-year survival rates of 94% [50]. Subsequently, Singh et al. retrospectively analyzed 369 prostate cancer patients who received definitive external beam radiation from 1970 to 1990 and found that among the patients who developed metastatic disease, those with fewer than five metastases had significantly better overall survival [51]. Subsequent reports have varied in their definition of the number of lesions that qualify as oligometastatic disease. The hypothesis that prostate cancer patients with oligometastatic disease may benefit most from aggressive therapy directed to the primary tumor is consistent with hypothesis generating (although under powered) subgroup analyses of the HORRAD trial [44], and subsequent confirmatory analyses of the much larger and adequately powered STAMPEDE trial [45] (described above).

The accurate identification of patients with oligometastatic disease remains a significant unmet need. Currently, about 5–10% of patients with prostate cancer present with M1 disease at diagnosis, although reduction in routine PSA screening may have increased this rate in recent years [27–29]. Conventional imaging for prostate cancer is insufficiently sensitive for accurate estimation of disease extent in many patients.

Conclusion

One published prospective randomized Phase III trial (STAMPEDE) demonstrated a survival benefit to radiotherapy directed to the primary tumor in patients with limited metastatic disease treated with ADT [45]. The results from multiple ongoing trials, largely focused on oligometastatic patients, will further establish the role for primary tumor and metastasis-directed therapy in patients with M1 disease. Improved imaging, in particular PSMA PET/CT, is expected to identify many patients presenting with advanced disease who otherwise would have been inaccurately staged by conventional imaging. Our treatment paradigms will continue to evolve as evidence mounts. Our prospective trials must keep up the pace.

Authors' contributions YY: data collection, data analysis, manuscript writing. AUK: data collection, data analysis, manuscript writing. NGN: data collection, data analysis, manuscript writing.

Compliance with ethical standards

Conflict of interest The authors have no potential conflicts of interest to disclose. As this is a review article, there was no research involving human participants or animals, nor informed consent needed.

References

1. Mohler JL, Lee RJ, Antonarakis ES et al (2018) National Comprehensive Cancer Network. Prostate Cancer (Version 4.2018). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 16 July 2018
2. Huggins C, Hodges CV (2002) Studies on prostatic cancer. J Urol 167:948–951. https://doi.org/10.1016/S0022-5347(02)80307-X
3. Schally AV, Arimura A, Kastin AJ et al (1971) Gonadotropin-releasing hormone: one polypeptide regulates secretion of luteinizing and follicle-stimulating hormones. Science 173:1036–1038
4. James ND, Spears MR, Clarke NW et al (2015) Survival with newly diagnosed metastatic prostate cancer in the "Docetaxel Era": data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). Eur Urol 67:1028–1038. https://doi.org/10.1016/j.eururo.2014.09.032
5. Nguyen PL, Alibhai SMH, Basaria S et al (2015) Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol 67:825–836. https://doi.org/10.1016/j.eururo.2014.07.010
6. Fizazi K, Tran N, Fein L et al (2017) Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 377:352–360. https://doi.org/10.1056/NEJMoa1704174
7. James ND, de Bono JS, Spears MR et al (2017) Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 377:338–351. https://doi.org/10.1056/NEJMoa1702900

8. Kim M-Y, Oskarsson T, Acharyya S et al (2009) Tumor self-seeding by circulating cancer cells. Cell 139:1315–1326. https://doi.org/10.1016/j.cell.2009.11.025
9. Gundem G, Van Loo P, Kremeyer B et al (2015) The evolutionary history of lethal metastatic prostate cancer. Nature 520:353–357. https://doi.org/10.1038/nature14347
10. Kaplan RN, Rafii S, Lyden D (2006) Preparing the "soil": the premetastatic niche. Cancer Res 66:11089–11093. https://doi.org/10.1158/0008-5472.CAN-06-2407
11. Cai C, Balk SP (2011) Intratumoral androgen biosynthesis in prostate cancer pathogenesis and response to therapy. Endocr Relat Cancer 18:R175–R182. https://doi.org/10.1530/ERC-10-0339
12. Heidenreich A, Pfister D, Porres D (2015) Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. J Urol 193:832–838. https://doi.org/10.1016/j.juro.2014.09.089
13. Won ACM, Gurney H, Marx G et al (2013) Primary treatment of the prostate improves local palliation in men who ultimately develop castrate-resistant prostate cancer. BJU Int 112:E250–E255. https://doi.org/10.1111/bju.12169
14. Steinberg GD, Epstein JI, Piantadosi S, Walsh PC (1990) Management of stage D1 adenocarcinoma of the prostate: the Johns Hopkins experience 1974 to 1987. J Urol 144:1425–1432
15. Flanigan RC, Salmon SE, Blumenstein BA et al (2001) Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 345:1655–1659. https://doi.org/10.1056/NEJMoa003013
16. Mickisch GH, Garin A, van Poppel H et al (2001) Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 358:966–970
17. Méjean A, Ravaud A, Thezenas S et al (2018) Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 379:417–427. https://doi.org/10.1056/NEJMoa1803675
18. Bristow RE, Tomacruz RS, Armstrong DK et al (2002) Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 20:1248–1259. https://doi.org/10.1200/JCO.2002.20.5.1248
19. Fader AN, Rose PG (2007) Role of surgery in ovarian carcinoma. J Clin Oncol 25:2873–2883. https://doi.org/10.1200/JCO.2007.11.0932
20. du Bois A, Reuss A, Pujade-Lauraine E et al (2009) Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 115:1234–1244. https://doi.org/10.1002/cncr.24149
21. Choti MA, Sitzmann JV, Tiburi MF et al (2002) Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 235:759–766
22. Pawlik TM, Scoggins CR, Zorzi D et al (2005) Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 241: 715–722:discussion 722–724
23. Pitroda SP, Khodarev NN, Huang L et al (2018) Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nat Commun. https://doi.org/10.1038/s41467-018-04278-6
24. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. PubMed NCBI. https://www.ncbi.nlm.nih.gov/pubmed/27380959. Accessed 2 Oct 2018
25. Harris E, Barry M, Kell MR (2013) Meta-analysis to determine if surgical resection of the primary tumour in the setting of stage IV breast cancer impacts on survival. Ann Surg Oncol 20:2828–2834. https://doi.org/10.1245/s10434-013-2998-2
26. Badwe R, Hawaldar R, Nair N et al (2015) Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol 16:1380–1388. https://doi.org/10.1016/S1470-2045(15)00135-7
27. DallEra MA, Lo MJ, Chen J et al (2018) Nine-year prostate cancer survival differences between aggressive versus conservative therapy in men with advanced and metastatic prostate cancer: local therapy in advanced prostate cancer. Cancer 124:1921–1928. https://doi.org/10.1002/cncr.31285
28. Kelly SP, Anderson WF, Rosenberg PS, Cook MB (2018) Past, current, and future incidence rates and burden of metastatic prostate cancer in the United States. Eur Urol Focus 4:121–127. https://doi.org/10.1016/j.euf.2017.10.014
29. Weiner AB, Matulewicz RS, Eggener SE, Schaeffer EM (2016) Increasing incidence of metastatic prostate cancer in the United States (2004–2013). Prostate Cancer Prostatic Dis 19:395–397. https://doi.org/10.1038/pcan.2016.30
30. Calais J, Cao M, Nickols NG (2018) The utility of PET/CT in the planning of external radiation therapy for prostate cancer. J Nucl Med 59:557–567. https://doi.org/10.2967/jnumed.117.196444
31. Widmark A, Klepp O, Solberg A et al (2009) Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 373:8
32. Warde P, Mason M, Ding K et al (2011) Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 378:2104–2111. https://doi.org/10.1016/S0140-6736(11)61095-7
33. James ND, Spears MR, Clarke NW et al (2014) Impact of node status and radiotherapy on failure-free survival in patients with newly-diagnosed non-metastatic prostate cancer: data from > 690 patients in the control arm of the STAMPEDE trial. Int J Radiat Oncol Biol Phys 90:S13. https://doi.org/10.1016/j.ijrobp.2014.05.095
34. Culp SH, Schellhammer PF, Williams MB (2014) Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol 65:1058–1066. https://doi.org/10.1016/j.eururo.2013.11.012
35. Antwi S, Everson TM (2014) Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis: a population-based, propensity score analysis. Cancer Epidemiol 38:435–441. https://doi.org/10.1016/j.canep.2014.04.002
36. Satkunasivam R, Kim AE, Desai M et al (2015) Radical prostatectomy or external beam radiation therapy vs no local therapy for survival benefit in metastatic prostate cancer: a SEER-medicare analysis. J Urol 194:378–385. https://doi.org/10.1016/j.juro.2015.02.084
37. Parikh RR, Byun J, Goyal S, Kim IY (2017) Local therapy improves overall survival in patients with newly diagnosed metastatic prostate cancer. Prostate 77:559–572. https://doi.org/10.1002/pros.23294
38. Löppenberg B, Dalela D, Karabon P et al (2017) The impact of local treatment on overall survival in patients with metastatic prostate cancer on diagnosis: a national cancer data base analysis. Eur Urol 72:14–19. https://doi.org/10.1016/j.eururo.2016.04.031
39. Leyh-Bannurah S-R, Gazdovich S, Budäus L et al (2017) Local therapy improves survival in metastatic prostate cancer. Eur Urol 72:118–124. https://doi.org/10.1016/j.eururo.2017.03.020
40. Steuber T, Berg KD, Røder MA et al (2017) 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. Eur Urol Focus 3:646–649. https://doi.org/10.1016/j.euf.2017.06.016

41. Cho Y, Chang JS, Rha KH et al (2016) Does radiotherapy for the primary tumor benefit prostate cancer patients with distant metastasis at initial diagnosis? PLoS One 11:e0147191. https://doi.org/10.1371/journal.pone.0147191
42. Rusthoven CG, Jones BL, Flaig TW et al (2016) Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. J Clin Oncol 34:2835–2842. https://doi.org/10.1200/JCO.2016.67.4788
43. Gratzke C, Engel J, Stief CG (2014) Role of radical prostatectomy in metastatic prostate cancer: data from the munich cancer registry. Eur Urol 66:602–603. https://doi.org/10.1016/j.eururo.2014.04.009
44. Boevé LMS, Hulshof MCCM, Vis AN et al (2018) 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. Eur Urol. https://doi.org/10.1016/j.eururo.2018.09.008
45. Parker CC, James ND, Brawley CD et al (2018) Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet. https://doi.org/10.1016/S0140-6736(18)32486-3
46. Sweeney CJ, Chen Y-H, Carducci M et al (2015) Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 373:737–746. https://doi.org/10.1056/NEJMoa1503747
47. Ost P, Reynders D, Decaestecker K et al (2018) Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 36:446–453. https://doi.org/10.1200/JCO.2017.75.4853
48. O'Shaughnessy MJ, McBride SM, Vargas HA et al (2017) A Pilot study of a multimodal treatment paradigm to accelerate drug evaluations in early-stage metastatic prostate cancer. Urology 102:164–172. https://doi.org/10.1016/j.urology.2016.10.044
49. Hellman S, Weichselbaum RR (1995) Oligometastases. J Clin Oncol 13:8–10. https://doi.org/10.1200/JCO.1995.13.1.8
50. Soloway MS, Hardeman SW, Hickey D et al (1988) Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer 61:195–202
51. Singh D, Yi WS, Brasacchio RA et al (2004) Is there a favorable subset of patients with prostate cancer who develop oligometastases? Int J Radiat Oncol Biol Phys 58:3–10. https://doi.org/10.1016/S0360-3016(03)01442-1