Chapter 10
Radiotherapy for Advanced Prostate Cancer

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Introduction

All cancers in the human body are assigned using various methods to prognostic groups. Classically this is performed using TNM staging and/or histologic grading systems [1]. Prostate cancer is no exception, and accurate risk stratification is paramount to appropriately guide therapy for men with prostate cancer. Traditionally, the treatment of localized or non-metastatic malignancies includes radical local therapy with either radiotherapy or surgery [2]. In contrast, the role of local therapy with patients with metastatic disease was limited – mainly intended for palliation of advanced symptoms, such as pain, bleeding, or addressing spinal cord compression. In absence of optimal systemic therapy, it was challenging to demonstrate isolated benefit of local therapy to primary or metastatic sites [3, 4]. However, with advancement of systemic treatment, there has been rekindled interest in the role of local therapy in patients with metastatic malignancies. As demonstrated in breast cancer, the benefit of local therapy is more pronounced in presence of effective systemic therapies [5]. Similar advancements have been noticed in prostate cancer. From the approval of docetaxel in the early 2000s, to the surge of newer anti-androgen and chemotherapeutic options in the last few years, there now is an unprecedented arsenal of highly effective life-prolonging systemic therapies for men with advanced prostate cancer [6–15]. This begs the question to what the current role of local therapy in men with advanced prostate cancer is.

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K. L. Stratton, A. K. Morgans (eds.), *Urologic Oncology*,
https://doi.org/10.1007/978-3-030-89891-5_10

In this chapter, we review the historical role of both external beam and systemic radionuclide forms of radiotherapy for men with advanced prostate cancer. Additionally, guideline-concordant indications for radiotherapy are reviewed. Finally, emerging roles of external beam and novel systemic radionuclide forms of radiotherapy for advanced prostate cancer are discussed.

Palliative Radiotherapy for Advanced Prostate Cancer

Radiotherapy can be given for solely palliative intent and/or to improve oncologic outcomes (i.e., progression-free survival or overall survival). In this section we will review the uses of radiotherapy in advanced prostate cancer in settings in which the primary or sole intent is to provide palliation and improve quality of life.

External Beam Radiotherapy

Radiotherapy is commonly used as a highly effective form of palliation for patients with metastatic cancer. Common indications include palliation of biologic pain, bleeding, obstruction, brain metastases, and epidural spinal cord compression (Table 10.1) [16]. In prostate cancer, given the most common site of metastases is the bone, palliative radiotherapy is commonly used for palliation of skeletal pain in this patient population. In fact, a common mode by which patients in clinical trials of advanced prostate cancer experience a "progression" event is by experiencing clinical progression in a way that necessitates treatment with palliative external beam radiotherapy.

Table 10.1 Indications of palliative radiotherapy by symptoms in advanced prostate cancers

Symptoms/Indications	Etiology
Pain	Skeletal metastasis Visceral metastasis Spinal cord compression Nerve impingement
Obstructive symptoms such as hesitancy in urination, poor or intermittent urinary stream, prolonged micturition, anuria	Bladder infiltration or bladder outlet obstruction
Bleeding such as hematuria or blood in the stool	Hematuria from bladder infiltration Rectal wall infiltration leading to rectal bleeding
Neurologic symptoms such as headache, seizure, neurologic dysfunction	Brain or dural-based metastasis Spinal cord compression
Post-surgical fixation or instrumentation	Stabilization of pathologic fracture

The optimal control of pain in cancer patients relies on understanding the underlying pathophysiology and molecular mechanisms of the pain experience and is best achieved through multidisciplinary management [17]. Palliative external beam radiotherapy is most effective for biologic or oncologic sources of pain. The hallmarks of biologic pain are pain at rest, especially during nighttime or early morning that can occur even without movements. Such pain is associated with a diurnal variation in systemic corticosteroid levels and is directly related to the local inflammation caused by remodeling of the bones by active tumors [18]. A recent meta-analysis demonstrated that palliative external beam radiotherapy results in overall response rate in terms of pain control of more than 60%, independent of number of fractions. Additionally, complete response in pain control in which patients no longer require systemic treatment for pain is noted in approximately 1/4th of patients [19].

Another common cause of pain in cancer patients is mechanical. Such pain usually originates from a pathologic or non-pathologic fracture. Palliative radiotherapy is unlikely to improve this pain, but rather mechanical stabilization is likely to improve symptoms. Mechanical pain is most commonly exacerbated by movement and is relieved by rest. Although there is often a mixed component of biologic and mechanical pain, radiotherapy is not effective in alleviating the mechanical component of the pain, whereas surgical fixation or procedures such as vertebroplasty or kyphoplasty have been proven to be beneficial [20].

Another common indication for palliative radiotherapy is malignant epidural spinal cord compression. This is an alarming sequela of spine metastases that have been left untreated and therefore have progressed to the point of cortical destruction and compression of the thecal sac. This can either be an acute or chronic process. Early detection is the key to reverse the potential neurological consequences of malignant spinal cord compression with treatment. Depending on the level of the spinal cord or cauda equina that is being compressed, patients may complain of pain, focal weakness or paraplegia, sensory loss, or loss of bowel or bladder function. Having neurologic symptoms for more than 72 hours before initiating treatment significantly reduces the chances of restoring complete neurological function in a patient [21].

Prostate cancer represents a moderately radiosensitive tumor; therefore, external beam radiotherapy provides a durable local control and optimal decompression for spinal cord compression originating from prostate cancer. The acuity and severity of the compression helps guide the decision of whether to proceed with immediate surgical decompression followed by a re-exploration combined with postoperative radiotherapy or proceed with radiotherapy alone. If the latter is chosen, more advanced radiotherapy techniques such as stereotactic body radiotherapy (SBRT) are not used in the presence of significant epidural or intramedullary disease. In such cases standard conventional radiotherapy, commonly in 10 fractions, 3 Gy per fraction to a total of 30 Gy, is used [21].

Fortunately, prostate cancer rarely causes brain metastases. When they occur, brain metastases usually originate from the more aggressive subtypes of prostate cancer such as small cell variant or neuroendocrine prostate cancer. Thus, new onset of headaches, blurry vision, or other neurologic deficits in these patients that cannot

readily be explained should prompt imaging of the brain, preferably with an MRI with and without contrast. When present these are treated most commonly with stereotactic radiosurgery alone or in combination with resection or whole brain radiotherapy depending on the size and number of lesions [22].

In advanced prostate cancer, especially before 2018, it was uncommon for patients who presented with de novo metastatic disease to receive treatment to their prostate. However, an untreated prostate cancer can continue to progress locally despite several lines of systemic therapy and result in significant deterioration in quality of life. This is most often related to local obstruction of the urinary tract from either direct compression or extension into the urethra or invasion or compression into the bladder and ureteral orifices. This leads to the requirement for either temporary intermittent self-catheterization, permanent Foley or suprapubic catheterization, or often repeated transurethral resections of the prostate. Similarly, although less common, a locally advanced primary can cause compression or infiltration into the rectum leading to obstruction, fistula, or bleeding. Palliative local radiotherapy can ameliorate these symptoms. Early institution of palliative local radiotherapy when the tumor is small allows for safe delivery of optimum dose to address these symptoms and to avoid any undue radiation-induced morbidity. Therefore, multidisciplinary care including input from urology is important to have prior to proceeding with palliative local radiotherapy. Various dose fractionation schedules can be used, but typically something less than a definitive dose of radiotherapy is used to minimize the risk of side effects.

Bleeding is a common manifestation from local invasion of prostate cancer, and radiotherapy is an effective method to reduce bleeding if the source of the bleed can be identified [23, 24]. Various schedules have been studied. This ranges from an abbreviated course, termed “quad-shot”, of two treatments given in the same day 6–8 hours apart, 2 days in a row to other common palliative schedules of 4 Gy x 5 fractions or 3 Gy x 10 fractions.

Radionuclides

Various radionuclides have been and are currently used for the primary purpose of palliation of symptoms in oncology. Strontium-89 and samarium-153 were the two most commonly used and studied in advanced prostate cancer for palliation.

Strontium-89 has a physical half-life of 50.6 days and emits beta radiation. Strontium emits a small fraction of gamma photons and thus poses minimal radiation exposure risk to those in contact with the patient. This radioisotope is preferentially taken up by the bone with metastatic prostate cancer at a ratio of 10:1 compared to healthy normal bone and can remain in these metastatic lesions for up to 100 days. Strontium undergoes urinary excretion. Strontium-89 is most commonly administered with an activity of 1.48–2.22 MBq (40–60 μCi per kilogram of body weight, approximately 4 mCi [148 MBq] for standard weight) given by intravenous infusion over several minutes.

There is evidence to support the use of strontium, including a phase III placebo-controlled randomized controlled trial that evaluated conventional palliative

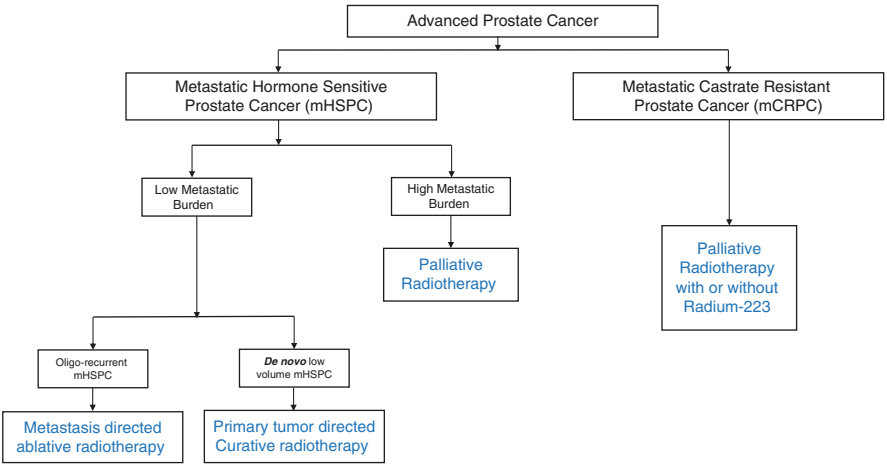
radiotherapy ± strontium-89. This trial used a single injection of 10.8 mCi of strontium or placebo in 126 patients with metastatic castration-resistant prostate cancer (mCRPC). There was an improvement in complete pain relief at 3 months with strontium-89 compared to placebo (40% vs. 23%) and a significant reduction in the need for subsequent and continued analgesic use ($P < 0.05$). A significantly smaller proportion of patients treated with strontium experienced new sites of pain compared with placebo ($P < 0.002$). Finally, treatment with strontium resulted in a longer disease-free interval and longer interval before subsequent retreatment with radiotherapy (35 weeks vs. 20 weeks) [25]. Another 2x2 factorial randomized clinical trial investigated the clinical efficacy and cost-effectiveness of strontium-89 with or without docetaxel and/or zoledronic acid in metastatic castrate-resistant prostate cancer. Cox regression analysis adjusted for all stratification variables showed benefit of strontium-89 on clinical progression-free survival (HR 0.85; 95%CI, 0.73–0.99; $P = 0.03$). However, there was no additional advantage of strontium-89 with respect to overall survival [26].

Samarium-153 has a short physical half-life of 46.3 hours and emits both beta and gamma radiation. The gamma radiation can be used for a low-resolution bone scan. Samarium is bound to ethylenediamine tetramethylene phosphonic acid (EDTMP) which confers bone-seeking properties. Samarium-153 lexidronam is most commonly administrated with an activity of 37.0 MBq (1.0 mCi) per kilogram of body weight and given intravenously over several minutes.

The use of samarium-153 was evaluated in a phase III randomized controlled trial of 152 patients with mCRPC and randomized patients to samarium-153 at 1 mCi/kg vs. nonradioactive samarium-152. This study demonstrated that use of samarium-153 led to a significant improvement in pain scale scores by week 1 and pain intensity visual analogue scale scores by week 2 compared to the nonradioactive samarium-152. There was also a significant reduction in opioid consumption by week 3 with samarium-153 use [27]. There are two major sources of toxicity from samarium-153 treatment: targeting of sites other than the bone and due to the presence of unchelated samarium. Sm3+ metal has been found to distribute to the liver, lungs, and spleen. Thus, it is paramount that the amount of unchelated Sm3+ is as low as possible to avoid uptake by the liver and hepatotoxicity [28]. Additionally, bone marrow toxicity is often observed during samarium-153 therapy. Furthermore, significant radiation from 153Sm is often delivered to the bladder wall and kidneys [28]. Samarium-153 and strontium-89 emit high-energy beta particles and result in bone marrow toxicity [29]. This is why radium-223, an alpha emitter, has gained popularity in recent times. We have reviewed radium-223 later in this chapter.

Radiotherapy with Oncologic Intent for Advanced Prostate Cancer

Traditionally radiotherapy has been used with palliative intent in advanced prostate cancer as described in the previous section. However, several seminal randomized studies over the past decade have demonstrated substantial improvement in oncological outcome with use of radiotherapy with definitive intent in advanced prostate



A simple algorithm for radiotherapeutic management of advanced prostate cancer

cancer. These include primary tumor-directed radiotherapy in metastatic hormone-sensitive prostate cancer (mHSPC) with low metastatic volume, ablative radiotherapy to metastatic sites in oligometastatic HSPC or oligorecurrent HSPC, and finally systemic radionuclide therapy with radium-223 in metastatic castrate-resistant prostate cancer (Table 10.2).

Treatment of the Primary

Combination of androgen deprivation therapy with local radiotherapy has been a well-established modality to treat high-risk localized, locally advanced, or clinically node-positive prostate cancer [2, 30–34]. However, because of no specified requirement of baseline imaging as a part of trial protocol and poor sensitivity and specificity of conventional imaging when these trials were conducted, a notable proportion of the enrolled patients presumably harbored metastatic disease and benefitted from this combined modality treatment. This hypothesis was tested in multiple retrospective studies. A large non-randomized registry-based study demonstrated that treatment to the primary with radiotherapy in mHSPC patients significantly improvement overall survival on multivariable and propensity score matched analysis (HR 0.62, 95% CI, 0.55–71, $p < 0.001$) [35].

Subsequently a number of randomized studies investigated this hypothesis. The first reported phase III randomized trial was the HORRAD trial. This was a relatively small randomized trial in men with mHSPC (n = 432). Patients were randomly allocated to either ADT alone or ADT in conjunction with prostate-directed radiotherapy. Radiotherapy was delivered to the prostate and base of the seminal vesicles with a 1 cm margin to a total dose of 70 Gy in 35 fractions using conventional fractionation or 57.76 Gy in 19 fractions using moderate hypofractionation. At a median follow-up of almost 4 years, the primary endpoint of overall survival

Table 10.2 Selected randomized evidence supporting definitive role of radiotherapy and systemic radionuclide therapy in advanced prostate cancer

Trial	Patient population	Treatment arms	Endpoint	Findings	Toxicity
Metastatic hormone-sensitive prostate cancer					
STAMPEDE Arm H (Phase III)	Newly diagnosed metastatic castrate-sensitive prostate cancer (pre-planned stratification into low volume vs. high volume metastatic burden based on CHAARTED definition)	Standard of care systemic therapy (ADT±Docetaxel) Vs. Systemic therapy + primary tumor directed radiotherapy (55 Gy in 20 fractions over 4 weeks or 36 Gy in 6 fractions over 6 weeks) 1:1 Randomization	Primary: OS Secondary: FFS Toxicity	For the entire study cohort: Control vs. radiotherapy: Improvement in FFS (median: 13 months vs. 17 months; HR: 0.76, 95% CI: 0.68–0.84) No improvement in OS (Median: 46 months vs. 48 months; HR: 0.92, 95% CI: 0.80–1.06) Low metastatic burden: Improvement in OS with radiotherapy (3-year OS: 73% vs. 81% HR: 0.68, 95% CI: 0.52–0.90) High metastatic burden: No Improvement in OS with radiotherapy (HR: 1.07, 95% CI: 0.90–1.28)	Late grade ≥3 adverse events: At 6 months (control vs. radiotherapy): 21% vs. 22% At 12 months (control vs. radiotherapy): 12% vs. 13% At 24 months (control vs. radiotherapy): 15% vs. 13%

(continued)

Table 10.2 (continued)

Trial	Patient population	Treatment arms	Endpoint	Findings	Toxicity
ORIOLE	Oligo-recurrent hormone-sensitive prostate cancer ≤3 metastases detectable by conventional imaging who had not received ADT within 6 months of enrollment or 3 or more years total	SABR vs. observation 2:1 randomization	Primary: Progression at 6 months Progression included biochemical, symptomatic, clinical, or radiographic progression, or death or initiation of ADT, or withdrawal after randomization	Proportion of disease progression at 6 months (control vs. SABR): 61% (95% CI: 38.5-79.6) vs. 19% (95% CI: 9.6-35.4) ($P = 0.005$) Median PFS (control vs. SABR): 5.8 months vs. NR (HR: 0.30, 95% CI: 0.11-0.81, $P = 0.002$)	No grade 3 or higher adverse events were identified New Grade 2 adverse events at 90 days (control vs. SABR): 0% vs. 9% New Grade 2 adverse events at 180 days (control vs. SABR): 0% vs. 6%
STOMP	Oligorecurrent prostate cancer with up to 3 metastases as detected by choline PET-CT and controlled primary	MDT of all detected lesions (with metastasectomy or SBRT) vs. surveillance 1:1 randomization	Primary: ADT-free survival, defined as the time between random assignment and the start of palliative ADT or death because of any cause. The indication to start ADT was symptomatic progression, progression to more than three metastases, or local progression of metastases	MDT vs. surveillance arm: 5-year ADT-free survival: 34% vs. 8%, HR: 0.57, 80% CI: 0.38–0.84, $P = 0.06$ (tests were performed two-sided; $P < 0.20$ was deemed significant)	Six patients developed grade 1 toxicity in the MDT arm. No grade 2 or higher toxicity was observed. Patient-reported QoL findings were similar between the two arms

SABR COMET (Phase II)	Patients with controlled primary tumor and one to five metastatic lesions (multiple tumor types enrolled; included patients with prostate cancer)	Palliative standard of care Vs. Metastasis-directed stereotactic ablative radiotherapy (30–60 Gy in three to eight fractions) Single fractions of 16–24 Gy were permitted for targets in the brain and vertebrae 2:1 randomization	Primary: OS Secondary: PFS Toxicity QoL	Control vs. ablative radiotherapy: 5-year OS: 17.7% (95% CI: 6% to 34%) vs. 42.3% (95% CI: 28% to 56%); (HR: 0.47, 95% CI: 0.27–0.81, stratified log-rank $P = 0.006$) Median PFS: 5.4 months (95% CI: 3.2–6.8) vs. 11.6 months (95% CI: 6.1–23.4); (HR: 0.48, 95% CI: 0.31–0.76, stratified log-rank test $P = 0.001$)	Grade ≥2 adverse events: Control vs. ablative radiotherapy: 9% vs. 29% 3 (4.5%) treatment-related deaths in the ablative radiotherapy group No differences in patient-reported QoL between treatment groups
Metastatic castrate-resistant prostate cancer					
ALSYMPCA	Treatment-resistant castration-resistant metastatic prostate cancer with ≥2 bone metastases detected on skeletal scintigraphy and no visceral metastases and had received docetaxel, were not fit for, or declined docetaxel, or it was not available	Six injections of radium-223 (at a dose of 50 kBq per kilogram of body weight IV) or matching placebo 2:1 Randomization	Primary: OS Secondary: Time to the first symptomatic skeletal event and various biochemical end points	Radium-223 vs. placebo: Median OS: 14.9 months vs. 11.3 months (HR: 0.70, 95% CI: 0.58–0.83) Median time to the first symptomatic skeletal event: 15.6 months vs. 9.8 months (HR: 0.66, 95% CI: 0.52–0.83)	No difference in the grade ≥3 hematologic (25% vs. 18%) or non-hematologic side effects between the Radium-223 vs. placebo group

was not statistically significantly different between arms (HR, 0.90, 95% CI, 0.70–1.14). On an unplanned subgroup analysis based on the metastatic burden or volume of disease, patients with ≤5 metastases had a greater relative benefit compared to patients with >5 metastases. This potential treatment-volume interaction suggested that patients with low-volume disease would preferentially benefit from definitive treatment of the primary tumor [36].

Shortly after the HORRAD trial was published, the large Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) trial, arm H, reported its results. This trial enrolled men with mHSPC and investigated the use of standard systemic therapy with or without treatment of the primary tumor with definitive radiotherapy. Standard systemic therapy consisted of ADT or combination of ADT and docetaxel. The study enrolled nearly 2000 patients and had a primary endpoint of overall survival. Radiotherapy was delivered to the prostate gland with a margin of 10 mm (8 mm posteriorly). Two fractionation schedules were permitted, including a moderate hypofractionation schedule of 55 Gy in 20 fractions or an ultra-hypofractionation schedule of 36 Gy in 6 weekly fractions. Considering the treatment-volume interaction seen in the HORRAD trial, the investigators integrated a detailed prespecified subgroup analysis plan to assess the primary and secondary endpoints based on volume of disease. This was done prior to unblinding. Approximately 40% of men had low-volume disease (per the CHAARTED definition) and the proportion was near identical in the two treatment arms.

There was no significant difference in overall survival in the overall cohort (HR 0.92, 95% CI, 0.80–1.06; $p = 0.266$). Failure-free survival was significantly improved by the addition of radiotherapy to the primary (HR 0.76, 95% CI, 0.68–0.84). In the prespecified subgroup analysis, patients with low-volume disease had an improvement in both failure-free survival and overall survival (HR 0.68, 95% CI, 0.52–0.90; $p = 0.007$) with primary tumor-directed radiotherapy. However, there was no overall survival benefit of prostate-directed radiotherapy in the high-volume subgroup (HR 1·07, 95% CI, 0·90–1·28). Notably, there was no evidence that use of docetaxel had an impact on the magnitude of benefit with prostate-directed radiotherapy. Furthermore, there was no significant increase in time to toxicity or long-term rates of grade 3+ toxicity with radiotherapy to the primary [37].

Treatment of Metastatic Lesions

In the last decade or so, there has been a significant interest in using radiotherapy to consolidate metastatic sites. The goal of metastasis-directed radiotherapy (MDT) is to delay the need for systemic therapy, improve progression-free survival, and potentially improve overall survival. Although we are still in the incipient phase of demonstrating benefit of MDT with respect to oncologically robust endpoints such as overall survival, improvement in endpoints such as progression-free survival has been noticed with MDT in a number of randomized clinical studies.

Stereotactic body radiotherapy (SBRT) and stereotactic ablative body radiotherapy (SABR) are terms that describe a method of external beam radiotherapy that accurately delivers a high irradiation dose to an extracranial target in 5 or few treatment fractions. SBRT has been commonly adopted as a preferred method of MDT over conventionally fractionated (longer-course) radiotherapy or other ablative or surgical techniques. This is in part due to the convenience and noninvasive nature, but also due to the radiobiologic rationale that prostate cancer has a low α/β ratio. This means that for an equal risk of normal tissue damage one can have greater tumor cell kill with high dose per fraction. Moreover, such ablative dose of radiotherapy also portends microvascular damage which has a substantial effect on the tumor cell kill. Based on different systematic reviews and meta-analyses, SBRT maximizes the therapeutic ratio as it confers excellent local control (80–90%) and portends low rates of moderate to severe toxicity (<10% and < 5%, respectively) [21, 38, 39].

There is emerging and growing data to support the role of MDT in both prostate cancer and other cancer types. Non-small cell lung cancer has appreciated the largest oncologic benefits from MDT. To date, two trials have shown overall survival benefits with metastasis-directed radiotherapy, despite their small sample size and phase II nature. Gomez et al. randomized patients with ≤3 metastases to maintenance systemic therapy with or without total consolidation of local tumor and MDT. The trial stopped early after enrolling 49 patients due to the early overall survival benefit seen from radiotherapy on interim analysis [40]. SABR-COMET was another phase II randomized trial investigating the benefit of metastasis-directed ablative radiotherapy in oligometastatic malignancies regardless of the primary site, and approximately 15% of patients enrolled had prostate cancer. This trial randomized patients to standard systemic therapy with or without MDT for patients with oligometastatic cancer (≤5 metastases). In their initial report, SBRT-based MDT led to significant prolongation of progression-free survival (6 months in control group vs. 12 months in the SBRT group (HR 0.47, 95% CI, 0.30–0.76; stratified log-rank $p = 0.0012$)) [41]. After a median follow-up of 51 months, the 5-year OS rate was 17.7% in the control group (95% CI, 6–34%) versus 42.3% in SBRT group (95%CI, 28–56%; stratified log-rank $P = 0.006$). However, MDT was also associated with increased risk of grade 2 or higher adverse events (9% in the control group vs. 29% in MDT group, $P = 0.03$). There were three deaths (4.5%) in the SABR arm that were possibly, probably, or definitely related to treatment [42].

Two small phase II randomized trials have evaluated the role of MDT in metastatic prostate cancer. There is a wealth of retrospective data and single-arm trials, but this will not be discussed. STOMP was a randomized phase II trial, which randomized 62 patients to observation +/− MDT with a primary endpoint of ADT-free survival. Importantly, this trial had prespecified indications for initiation of ADT. Patients enrolled had oligorecurrent prostate cancer based on PET choline imaging with ≤3 metastases, and thus these patients were more akin to biochemically recurrent disease than de novo M1 disease by conventional imaging. MDT was given as SBRT in most patients (25 of 31), and at a median 3-year follow-up, the use of MDT improved median ADT-free survival from 13 to 21 months and median

time to PSA-progression from 6 to 10 months [43]. There was no clinically or statistically meaningful between-arm difference in the mean change in score from baseline to 3 months and 1 year. For example, mean (95% CI) difference between the arms for change in global health status score from baseline to 3 months was 0 (−7 to 6). The same for baseline to 1 year was 2 (−9 to 6) [43]. The second phase II trial was the Observation verus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE), which enrolled 54 men with oligorecurrent prostate cancer, but unlike STOMP which was a 1:1 randomization, ORIOLE was a 2:1 randomization of observation +/− MDT with SBRT. The primary endpoint was progression by 6 months, which was a composite endpoint including ADT initiation, PSA progression, symptomatic progression, or death. The primary endpoint was improved with SBRT (19% vs. 61%; HR 0.30, 95% CI, 0.11–0.81; $P = 0.002$). There was no grade 3 or higher adverse events from MDT [44].

Radionuclide Therapy

Radium-223 dichloride is currently the most common form of systemic radionuclide therapy for the treatment of prostate cancer. Radium is a bone-seeking calcium analogue that has a half-life of 11.4 days and emits high-energy alpha particles. Unlike samarium and strontium, the alpha particles from radium-223 have a high biologic effectiveness and linear energy transfer. However, alpha particles have a short path length of <10 cell lengths. This short length of trajectory helps in minimizing bone marrow toxicity with alpha particle-based treatment. However, this is one of the reasons for which Ra-223 is unable to reach tumor extension beyond the bone. Radium-223 is primarily cleared through the intestine [45]. Radium-223 is most commonly given as a monthly (q4 week) injection (50 kBq/kg intravenous) for a total of six cycles.

Radium-223 has FDA approval for the treatment of symptomatic bone metastases from mCRPC. However, unlike samarium-153 and strontium-89, radium-223 has been shown to improve both pain and overall survival. This finding was from the multinational phase III, double-blind, randomized controlled trial of 922 men with symptomatic mCRPC. Patients were randomized to six injections of radium-223 (50 kBq/kg) versus placebo. The trial was stopped early at a planned interim analysis after an overall survival benefit was reached (median overall survival with radium-223 treatment was 14.0 vs. 11.2 months; $P = 0.0019$; HR 0.695, 95% CI, 0.552–0.875). Additionally, radium-223 resulted in a lower incidence of skeletal-related events ($P = 0.016$). Radium-223 was generally well tolerated (grade 3–4 neutropenia of 1.8% vs. 0.8%, and thrombocytopenia 4% vs. 2%, respectively) [15].

An important discussion point that is often overlooked is that when radium-223 was tested in the landmark phase III trial, other novel androgen signaling inhibitors (ARSIs) had not gained FDA approval yet. Thus, radium-223 was generally used early in the treatment course of mCRPC. In contrast, since the approval of enzalutamide, abiraterone, and other agents, radium-223 is commonly a 3rd- or fourth-line

therapy. Such delay in the use of this radioisotope has been found to portend poor compliance, and this in turn brings down the expected benefit from this radioisotope therapy. Furthermore, it becomes increasingly less likely that these patients harbor isolated osseous disease without any extension to periosseous soft tissue or epidural extension, potentially limiting the efficacy of radium-223 [46].

Future Indications of Radiotherapy for Advanced Prostate Cancer

Radiotherapy is a critically important tool to be used in men with advanced prostate cancer to prolong life and improve quality of life. However, there are even further areas that radiotherapy has the potential to improve outcomes for men in this patient population. The use of SBRT as MDT has its primary evidence in oligorecurrent prostate cancer. Ongoing trials are evaluating the role of radiotherapy to sites of metastases in both de novo mHSPC in the next arm of the STAMPEDE trial (arm M) and in mCRPC (e.g., FORCE trial, NCT03556904). These trials will help to establish additional contexts where MDT with radiotherapy may become part of the routine standard of care. There is also interest in understanding if treatment of the primary with radiotherapy may have benefit in high-volume metastatic disease when used concurrently with treatment of the metastases, in essence to functionally render these patients more akin to low-volume disease.

Additionally, other radionuclides are being studied. The most exciting are based on targeting prostate-specific membrane antigen (PSMA). The molecules are linked commonly to the beta-emitter, lutetium-177, which has shown promise. 177Lu-PSMA-617 delivers beta-particle radiation selectively to PSMA-positive cells and the surrounding microenvironment. Several new alpha-particle emitting agents such as actinium-225, bismuth-212, terbium-149, astatin-211 are being actively evaluated for PSMA-based targeted alpha particle therapy [47]. Moreover, in the recently presented phase III randomized VISION trial, addition of lutetium-177-PSAM-617(LuPSMA) to standard of care in men with PSMA-avid metastatic castrate-resistant prostate cancer was associated with a 38% reduction in the risk of death (HR 0.62, 95%CI, 0.52–0.74) and a 4-month improvement in overall survival. Furthermore, LuPSMA combined with standard of care treatment significantly improved radiographic progression-free survival (rPFS) by a median of 5.3 months (median rPFS, 8.7 vs. 3.4 months; HR 0.40, 99.2% CI, 0.29–0.57; $p < 0.001$, one-sided). There was a higher rate of high-grade (grade 3–5) treatment-related adverse events with LuPSMA (28.4% vs. 3.9%). Additionally, there were five deaths attributable to the experimental treatment. In terms of specific adverse events, treatment with LuPSMA was associated with increased rates of bone marrow suppression, xerostomia, and nausea and vomiting [48, 49]. Note should be made of the fact that only about 1/2 of the patients in both arms received one or two taxane-based regimens before being given trial regimen. Hence there remains a doubt on the actual efficacy of the LuPSMA therapy in patients heavily pre-treated with taxane-based regimens.

Conclusion

Radiotherapy is now used in the vast majority of patients with advanced prostate cancer. This ranges from palliation (e.g., bone pain, urinary or rectal obstruction or bleeding, or epidural spinal cord compression) to treatment of the primary or metastases for oncologic benefit. Palliation can be accomplished with both external beam radiotherapy or radionuclides, such as strontium or samarium. These radionuclides have largely been replaced by radium-223, which not only provides palliation of pain but also prolongs survival. External beam radiotherapy directed to primary tumor has been shown to confer survival advantage in low-volume mHSPC. PSMA ligand-based radionuclide therapy has also demonstrated survival advantage in metastatic castrate-resistant prostate cancer. Furthermore, MDT using SBRT has been shown to delay progression and forestall use of ADT in men with oligorecurrent mHSPC. Trials are ongoing or maturing to further establish the oncologic benefit of MDT in de novo mHSPC, use of MDT in patients with >5 metastases. Given the critical role radiotherapy has in the multidisciplinary management of advanced prostate cancer, incorporation of radiation oncology and nuclear medicine into the care team is paramount for optimizing overall outcome in this patient population.

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