THEMATIC REVIEW

Management of early-stage metastatic prostate cancer: appraisal of locoregional treatments and radiation therapy, with or without immunomodulation

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Abstract

The current standard for the management of locally advanced and early stage metastatic prostate cancer relies on a backbone of androgen deprivation therapy (ADT) combined with radiotherapy (RT), a regimen that at a glance appears relatively straightforward. The emergence of newer diagnostic, genomic and imaging modalities have allowed for better disease risk-stratification and opened avenues for the development of more patient-centered treatment strategies. This review aims to highlight the central role of RT as part of a multi-modal approach and discuss established and emerging data for the management of locally advanced disease, biochemical recurrence, and oligometastatic disease, as well as the use of immunotherapies and radio-isotopes. This review will also briefly discuss ongoing clinical trials that provide new insights into the paradigm shift in the management of locally advanced prostate cancer.

Key Words

- ▶ prostate cancer
- ▶ endocrine therapy
- ▶ radiotherapy
- ▶ locally advanced

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Introduction

With an estimated 190,000 new cases in the US in 2020, prostate cancer is the second most common cancer diagnosis in men following cutaneous cancer (<https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html>). The year 2021 will mark the 80th year since the use of castration or androgen deprivation therapy (ADT) for prostate cancer which remains a cornerstone of treatment (Perlmutter & Lepor 2007). Despite decades of advances, prostate cancer remains the second most common cause of cancer-related death in men, necessitating the development of new treatments.

Throughout the advances in the last several decades, RT has remained a pillar of treatment. The combination

of RT with newer technologies, such as advanced assays, genomic risk stratification, and systemic therapies, which have allowed for more effective disease detection, risk stratification and treatment delivery. With the development of these tools, physicians are becoming better equipped to tailor treatments to individual patients and improve patient outcomes.

This review seeks to discuss some emerging roles and developments in RT-based modalities for the treatment of prostate cancer. Specifically, we will discuss emerging and established data for the use of RT in combination with hormonal therapy or immunotherapy, and therapeutic radioisotopes for locally advanced prostate cancer defined

as locally advanced disease, biochemically recurrent disease, and oligometastatic disease.

Locally advanced prostate cancer

Per the Eighth Edition of the American Joint Committee on Cancer (AJCC) criteria, locally advanced prostate cancer is defined as T3 to T4 disease that has spread to involve one or several of the following: prostate capsule, seminal vesicles, regional pelvic lymph nodes, or adjacent organs such as the bladder, rectum, or pelvic wall. The Advanced Prostate Cancer Consensus Conference (APCCC) defines the locally advanced disease as node-positive nonmetastatic prostate cancer and distinguishes between clinical node-positive (cN+) disease and pathologic node-positive (pN+) as distinct entities (Gillessen *et al.* 2020).

For patients with cN+ disease, the Radiation Therapy Oncology Group (RTOG) 8531 study defined the standard of care by showing that the addition of long-term ADT to adjuvant RT resulted in a significant improvement in progression-free survival (PFS) (Pilepich *et al.* 2005). However, the long-term use of ADT has come into question because of cardiovascular side effects (Gillessen *et al.* 2020). Some study results have supported long-term ADT use (Bolla *et al.* 2009,2010); however, RTOG 9408 showed that RT and short-term use (4 months) were associated with decreased disease-specific mortality compared to RT alone (Jones *et al.* 2011). *Post-hoc* analysis of RTOG 9408 showed that the benefit of ADT was seen primarily among men with intermediate-risk disease, and short-term ADT was likely insufficient for men with high-risk disease. Consequently, given the mixed evidence regarding the duration of ADT, the consensus from APCCC for cN1 disease involves the radical locoregional treatment, whether in the form of surgery or RT plus ADT, without consensus for duration.

For patients undergoing prostatectomy, the detection of lymph node metastases is a poor prognostic sign for which adjuvant recommendations have not been clearly defined. In a large retrospective analysis of over 1300 post-prostatectomy patients who were either placed under observation or given ADT $\pm$ adjuvant RT, a significant increase in overall survival (OS) was found with ADT plus RT (Touijer *et al.* 2018).

With the known morbidity of RT or ADT, patient selection is an important consideration. Another series highlighted this importance by showing that the benefit of adjuvant RT in combination with ADT was limited to two groups: (1) patients with 1 or 2 positive nodes, pathological Gleason score between 7 and 10, and pT3b/4 disease or

positive surgical margins and (2) patients with 3 or 4 positive nodes, regardless of other tumor characteristics (Abdollah *et al.* 2018). Therefore, patients with one or two involved nodes require further risk stratification before adding RT to their treatment regimen.

Given that the cornerstone treatment of locally advanced prostate cancer relies on a backbone of ADT and RT, there are several ongoing clinical trials that will continue to address the question of duration of therapy (NCT01122121 and NCT02799706) (Table 1). With the development of more sophisticated imaging modalities, the incidence of newly diagnosed locally advanced prostate cancer is likely to increase because of stage migration. This will continue to emphasize the importance of high-level evidence to guide the treatment of patients with locally advanced prostate cancer.

Biochemical recurrence after locoregional treatment

Biochemical recurrence (BCR) can occur as PSA recurrence after definitive local treatment or as PSA persistence after definitive treatment. Per the National Comprehensive Cancer Network (NCCN) definition, persistence is the failure of PSA to become undetectable after surgery, whereas the European Association of Urology (EUA) definition is PSA > 1.0 ng/mL within 4 to 8 weeks after surgery (Roach *et al.* 2006, Heidenreich *et al.* 2014, Pisansky *et al.* 2019, Van den Broeck *et al.* 2020) and has consistently been associated with poor oncological outcomes (Preisser *et al.* 2019). Risk factors for PSA persistence include higher pre-operative PSA levels, advanced pathological T stage and International Society of Urological Pathology (ISUP) grade, positive surgical margins, and pathologic node-positive status (Preisser *et al.* 2019). Therefore, it is essential to use effective imaging for staging workup in order to help identify these patients. Currently, there is a prospective study that aims to assess whether PSMA PET/CT should replace conventional imaging for the initial staging of patients with high-risk features (Gleason grade group ≥ 3 , PSA ≥ 20 ng/mL, or clinical stage $\geq$ T3) (Hofman *et al.* 2018).

Another population with actively evolving clinical treatment strategies is patients who experience BCR after locoregional treatment. The definition of BCR varies based on prior treatment received and distinguishes between surgical or non-surgical approaches. After definitive RT, the definition of BCR is a > 2 ng/mL increase in the nadir prostate-specific antigen (PSA) level after RT or ADT (Shipley *et al.* 2017). After prostatectomy, BCR is

Table 1 Summary of selective clinical trials evaluating the treatment of locally advanced and oligometastatic prostate cancer as well as combination radiation and immunotherapy modalities.

Identifier and trial name	Patient group	Estimated patient enrollment	Standard arm	Experimental arm	Primary end point	Estimated completion date
Locally advanced Pca						
Leuporelin associated with radiotherapy vs leuporelin alone in T3–T4 or pT3 (on Biopsy) N0, M0 prostate cancer NCT01122121	Locally advanced Pca, T3–4, N0 and M0	273	Hormone alone (leuporelin) q3 months for 3 years	Leuporelin q3 months for 3 years and RT	Progression-free survival	June 29, 2009, completed
Trial comparing irradiation plus long-term adjuvant androgen deprivation with GnRH antagonist vs GnRH agonist plus flare protection in patients with very high risk localized or locally advanced prostate cancer (PEGASUS) NCT02799706	Locally advanced Pca, PSA $\geq$ 10–20 ng/mL, GS $\geq$ 8, cT3–4, cN+ or pN1	885	Concomitant RT with long-term GnRH agonist, non-steroidal anti-androgen (min 18 months)	Concomitant RT with long-term GnRH antagonist (degarelix)	Progression-free survival	June 2024, recruiting
Oligometastatic Pca						
Cytoreductive prostatectomy vs cytoreductive prostate irradiation as a local treatment option for metastatic prostate cancer: a multicentric feasibility trial (LoMP II) NCT03655886	Histologically proven Pca with newly diagnosed metastatic disease (radiographic)	86	Radical prostatectomy	Radiotherapy	Feasibility of randomization between both arms	August 2022, recruiting
Clinical registry for oligometastatic disease, consolidation therapy, debulking prior to chemotherapy, or re-irradiation NCT02170181	Histologically confirmed malignancy that is locally advanced or metastatic. Oligometastatic disease up to six sites of extracranial disease amenable to SBRT	5000	Observational study with four arms treating with SBRT: (1) oligometastatic, (2) consolidation (residual), (3) Norton-Simon (debulking), (4) re-irradiation	-	Patterns of care	December 2026, recruiting
RT and immunotherapy						
Phase 3 study of ProstateAtak® immunotherapy with standard radiation therapy for localized prostate cancer (PrTK03) NCT01436968	Intermediate-risk Pca defined by: PSA 10–20 ng/mL, GS = 7, T2b–2c w single high-risk feature (PSA > 20 ng/mL, GS 8–10 or T3a)	711	RT $\pm$ short term ADT with placebo + valacyclovir	RT $\pm$ short term ADT with ProstateAtak® + valacyclovir	Disease-free survival	June 2023, recruiting

(Continued)

Table 1 Continued.

Identifier and trial name	Patient group	Estimated patient enrollment	Standard arm	Experimental arm	Primary end point	Estimated completion date
Combination of nivolumab immunotherapy with radiation therapy and androgen deprivation therapy NCT03543189	High-risk Pca defined by: GS 9–10 with >30% cores involved. Any PSA or T-stage. Oligometastatic disease defined as ≤ three sites of metastatic disease	34	Long term ADT + nivolumab + brachytherapy + EBRT	-	Phase I: dose-limiting toxicity, phase II: relapse-free survival rate	December 2021, recruiting
Prostate cancer with oligometastatic relapse: combining stereotactic ablative radiotherapy and durvalumab (MED14736) (POSTCARD) NCT03795207	Rising PSA after definitive treatment with maximum of five bone or lymph node metastases	96	SBRT	Durvalumab with SBRT	2-year progression-free survival	September 2024, recruiting
Apalutamide with or without stereotactic body radiation therapy in treating participants with castration-resistant prostate cancer (PILLAR) NCT03503344	Castration resistant disease, five lesions on CT scan, >1 but ≤5 lesions on PSMA PET and amenable to SBRT	60	Apalutamide alone until disease progression or unacceptable toxicity	Apalutamide with SBRT	Undetectable PSA at 6 months after therapy	December 2024, recruiting
Immune responses in prostate, lung, melanoma and breast cancer patients following stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT) or brachytherapy (SBRT). NCT01777802	Oligometastatic prostate, lung, breast and melanoma patients	130	Observational study looking at changes in immune markers after delivery of SBRT, IMRT or brachytherapy in patients with oligometastatic disease	-	Change in immune circulating tumor markers	January 2021, recruiting

Source ClinicalTrials.gov

ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; GnRH, gonadotropin-releasing hormone; GS, Gleason score; IMRT, intensity-modulated radiation therapy; Pca, prostate cancer; PSA, prostate specific antigen; PSMA, prostate specific membrane antigen; SBRT, stereotactic body radiation; RT, radiotherapy.

defined as > 0.2 ng/mL as defined per the EUA, American Society for Radiation Oncology (ASTRO), and American Urological Association (AUA) (Heidenreich *et al.* 2014, Pisansky *et al.* 2019). It is important to note that BCR after primary treatment does not necessarily lead to clinically progressive disease. Therefore, the EAU developed a prognostication system based on disease extent and PSA characteristics that stratifies patients into a low-risk or high-risk group (Perera *et al.* 2020, Van den Broeck *et al.* 2020). This prognostication system was subsequently validated by Tilki *et al.* (Tilki *et al.* 2019). Low-risk BCR among patients after prostatectomy is defined as PSA doubling time > 12 months and pathological ISUP grade < 4 , whereas, low-risk BCR after definitive RT is defined as PSA doubling time > 18 months from RT or last luteinizing hormone-releasing hormone (LHRH) treatment and biopsy ISUP grade < 4 .

After confirming BCR, imaging is used to assess for the presence of local or distant disease. However, conventional imaging modalities are limited by low sensitivity. For instance, both scintigraphy and 18-F sodium fluoride (NaF) PET imaging visualize osteoblastic activity and thus do not indicate the full extent of disease activity or volume. Given these limitations, other tracers have been developed to more accurately characterize BCR.

The most common PET tracer used in oncology is 18F-fluorodeoxyglucose (FDG), which visualizes glucose metabolism. However, this has several limitations for prostate cancer, such as the bladder having intense uptake and thereby obscuring visualization of nearby disease and low glucose metabolic pathway use in prostate cancer (Liu *et al.* 2010). Another tracer is 11C-choline/18F-choline, which visualizes membrane turnover and has shown increased sensitivity; however, it is very PSA-dependent (Giovacchini *et al.* 2010) and hence limits its utility in the postsurgical setting. Another novel tracer, which received FDA approval in 2016, is 18F-fluciclovine (Axumin). This tracer is an amino acid analog, and though it is also PSA-dependent, it has been shown to have a negative predictive value of 100% with PSA values of more than 1.05 ng/mL (Schuster *et al.* 2014). This has made Axumin a valuable tool for informing treatment; for instance, it can widen RT fields because more local disease is visualized or it can help identify distant metastases.

Currently, there is evidence suggesting that prostate-specific membrane antigen (PSMA) PET/CT imaging has the highest sensitivity for detecting recurrent prostate cancer. Briefly, PSMA is a type-II transmembrane glycoprotein that is specifically upregulated among patients with prostate cancer and hence makes it a potential diagnostic

and therapeutic target (Chang 2004). PSMA PET has thus become the recommended imaging modality in the setting of rising PSA (Gillesen *et al.* 2020) to identify sites of failure. For instance, in a retrospective study by Schiller *et al.* (Schiller *et al.* 2021) using ^{68}Ga -PSMA-PET/CT, the study team generated a heat map to represent the most common sites of failure. These sites included nodal regions not covered in the current RTOG pelvic nodal atlas, such as the para-aortal, pararectal, paravesical, preacetabular, presacral, and inguinal regions. Their results suggest that the guidelines may warrant revision for patients with high-risk prostate cancer patients who are undergoing salvage therapy.

The EAU guidelines include recommendations for the treatment of patients with rising PSA levels; specifically, treatment suggestions are given for patients whose PSA levels rise from undetectable range and have pathology showing high-risk features. Evidence supports the use of a multi-modal approach; however, no consensus exists regarding the duration of ADT treatment or timing of RT. Long-term ADT use was supported in RTOG 9601, in which patients with PSA persistence or PSA recurrence who received 2 years of bicalutamide (150 mg daily) with RT were found to have statistically significant improvement in OS compared to those who received RT alone (Shipley *et al.* 2017). The use of short-term ADT among patients with rising PSA was assessed in the GETUG-16 study, in which the 6-month use of gonadotropin-releasing hormone (GnRH) along with RT was associated with improvement in PFS, and *post-hoc* analysis showed improvement in metastasis-free survival (MFS) (Carrie *et al.* 2016, 2019). More recently, the results from the SPPORT trial (RTOG 0534) also demonstrated the benefit of a short course (4–6 months) of ADT coupled with RT for patients with rising PSA levels (Pollack *et al.* 2018). However, to date, these data are only available in abstract form. Among patients with rising PSA levels after prostatectomy, the treatment recommendations proposed by the APCC in 2019 are a combination of RT and ADT; despite the lack of consensus, short course ADT is often favored (Gillesen *et al.* 2020).

The most recently published EUA guidelines propose that the management of BCR after curative intent should be discussed in a multidisciplinary setting and evaluated for a multi-modality approach. In the setting of BCR after RP treatment includes early salvage radiotherapy in men who have experienced two consecutive PSA rises, despite a negative PET/CT (strong recommendation). Similarly, in the setting of BCR following RT multi-modality approaches should be evaluated for highly selected patients (strong recommendation) (Mottet *et al.* 2021).

Radiation for oligometastatic prostate cancer

As progress continues to be made with advanced imaging techniques, more patients with metastatic disease will continue to be identified, and many of these patients may have an oligometastatic disease. The concept of oligometastasis originally developed in the 1990s to describe a distinct stage of disease with limited metastatic tumor burden, allowing for a therapeutic window for treatment with curative rather than palliative intent (Hellman & Weichselbaum 1995). In 1995, Hellman and Weichselbaum hypothesized that eradicating low-volume disease with ablative therapy might improve survival (Hellman & Weichselbaum 1995). Subsequent studies (Ost *et al.* 2015, 2018) have demonstrated that the ablative treatment of patients with ≤ 3 lesions led to better prognoses than that of patients with higher volume disease (De Bruycker *et al.* 2017). To date, there is no consensus on the definition of oligometastatic prostate cancer, as many factors can be considered, such as the location and number of metastases, synchronous vs metachronous metastases, and whether tumors are hormone-sensitive or castration-resistant. In a recent systematic review of literature for oligometastatic prostate cancer found that, while the definition varied with regards to the number of lesions, the most commonly used definition included patients with ≤ 3 bone metastases (Miura *et al.* 2020).

Currently, there is a breadth of literature examining the management of oligometastatic disease in prostate cancer, and this research can be classified into two categories: management of *de novo* metastatic disease or development of metastatic disease after definitive therapy.

Historically, for patients with newly diagnosed metastatic prostate cancer (mPCA), the standard of care has been a systemic therapy with a backbone of androgen deprivation. However, growing evidence is emerging favoring the addition of local therapy such as RT to androgen deprivation for oligometastatic disease (Parker *et al.* 2018, Boevé *et al.* 2019, Burdett *et al.* 2019). One of the first prospective randomized controlled trials to evaluate the management of patients with oligometastatic disease was the HORRAD trial (Boevé *et al.* 2019). In this study, patients with newly diagnosed mPCA without any prior treatment were randomized to either ADT alone or RT with ADT; the results showed no difference in OS between the two groups (Boevé *et al.* 2019).

In the STAMPEDE trial, patients with newly diagnosed mPCA were randomized to standard of care (lifelong ADT with or without upfront docetaxel) or standard of care plus RT, with patients stratified based on the metastatic

burden. High metastatic burden was considered ≥ 4 bone metastases with ≥ 1 metastasis located outside the vertebral body or pelvis, visceral metastasis, or both; all other patients were considered to have the low metastatic burden (Kyriakopoulos *et al.* 2018). As with the HORRAD study, there was no OS benefit for unselected patients. However, subset analysis showed improved 3-year OS of 81% vs 73% for patients with a low metastatic burden who were treated with radiotherapy (HR 0.68 (95% CI 0.52–0.90); $P=0.007$) (Parker *et al.* 2018). A large meta-analysis on pooled data from the HORRAD, STAMPEDE, and the PEACE trials showed that men with <4 bone metastases had a 7% improvement in 3-year survival when treated with RT and that prostate radiotherapy improved 3-year biochemical progression and failure-free survival by about 10%, but the size of the effect varied by metastatic burden (Burdett *et al.* 2019). Based on the current evidence, the APCCC recommended that, for patients with a low metastatic burden, RT to the prostate can be offered in conjunction with systemic therapy (Gillesen *et al.* 2020).

The STOMP trial studied patients who had developed oligometastatic disease, defined as a PSA relapse with up to three extracranial metastases (N1 or M1), after definitive treatment. Patients were randomized to surveillance or metastasis-directed therapy (MDT) in the form of either metastasectomy or stereotactic body radiotherapy (SBRT). At a follow-up of 3 years, ADT-free survival was longer (21 months vs 13 months) for the metastasis-directed therapy group, with similar quality of life between the two arms (Ost *et al.* 2018). Similarly, in the ORIOLE trial, patients with one to three asymptomatic metastases were randomized to SBRT or observation, and the study showed that SBRT significantly improved PFS ($P=0.002$) (Phillips *et al.* 2020). In this trial, investigators also assessed for T-cell receptor expression and observed that SBRT generated a systemic immune response. Similarly, in a recent study by Siva *et al.*, the authors evaluated the use of stereotactic ablative body radiotherapy (SABR) in a single fraction to metastatic sites and showed that over one-third of patients did not experience progression, were free from ADT at 2 years, had low morbidity, and experienced low impact on quality of life (Siva *et al.* 2018). Currently, the NCT03655886 trial aims to examine the role of surgery vs RT in the treatment of oligometastatic prostate cancer (Table 1).

As our understanding of oligometastatic disease in prostate cancer continues to evolve, several factors will need further consideration. First, the number and location of lesions as well as chronicity and castration status are all important aspects of the definition of oligometastatic prostate cancer as each of these factors may be prognostic

for RT benefit. Secondly, there is evidence that metastatic disease involving only the lymph nodes may be a separate entity from a metastatic disease involving other sites (Gillesen *et al.* 2020). Finally, several clinical trials have demonstrated that disease burden is a key component not only in prognosis but also in treatment options and goals of care (Kyriakopoulos *et al.* 2018, Ost *et al.* 2018, Parker *et al.* 2018, Boevé *et al.* 2019). An observational study aims to assess the patterns of care in patients with oligometastatic disease by sorting them into four categories: oligometastatic patients treated with SBRT to discrete lesions, consolidation group where SBRT is used on residual disease, Norton-Simon arm where SBRT is used for debulking and finally the re-irradiation group (NCT02170181), which is still in the recruitment stage with expected completion in December 2026 (Table 1).

As we continue to gather more evidence regarding oligometastatic prostate cancer, we will continue to see a shift in the treatment paradigm. Current studies highlight the importance of patient selection and discussion of multi-modality approaches. In fact, the EAU now recommends that ADT as monotherapy should not be utilized in patients newly diagnosed with M1 disease as long as they do not have contraindications for combination therapy and have sufficient life expectancy, provided they are willing to accept the increased risk of side effects (Mottet *et al.* 2021).

The potential acute and late effects of RT should be discussed with patients when considering local therapy in addition to ADT. Acute bowel and bladder toxicity are possible; for reference, patients in the STAMPEDE-RT trial who underwent local RT reported acute bladder toxicity of RTOG grade 3 or 4, 5% of the time and grade 3 or 4 acute bowel toxic effect 1% of the time—no grade 5 toxic effects were reported (Parker *et al.* 2018). In the same study, late toxicity of grade 3 or 4 was slightly higher for patients receiving RT compared to ADT alone at 4% vs 1%; however, this study also showed that patients reporting at least grade 3 or worse adverse events were similar at 6 months, 1 year, and 2 years (Parker *et al.* 2018).

Radiation and immunotherapy for prostate cancer

Another area of rapid development in prostate cancer research is the use of immunotherapy, which in the form of checkpoint inhibitors, has revolutionized the treatment paradigm of several advanced malignancies over the past 5 years (Garon *et al.* 2015, Bellmunt *et al.* 2017, Wolchok *et al.* 2017, Motzer *et al.* 2018).

Unfortunately, the response of prostate cancer to immunotherapy has been less robust than many other solid malignancies (Madan & Gulley 2019, Zhao *et al.* 2019). This is believed to be due to several prostate cancer characteristics, including reduced T-cell infiltration, downregulated major histocompatibility complex (MHC) expression, and lower expression of programmed death-ligand (PD-L1) (Patel *et al.* 2020). A success story in immunotherapy in prostate cancer involves the development of Sipuleucel-T, an autologous dendritic cell vaccine, for mPCa (Kantoff *et al.* 2010), and more recently and Pembrolizumab (anti-PD1) (Graff *et al.* 2016). Pembrolizumab gained FDA approval as the only checkpoint inhibitor approved for patients with tumors showing microsatellite instability (MSI) (Le *et al.* 2017).

The role of immunotherapy alone on mPCa has been evaluated in many trials, here we offer a brief summary. Large phase III clinical trials have failed to show improvement in OS with ipilimumab (a CTLA-4 inhibitor) (Kwon *et al.* 2014, Beer *et al.* 2017). However, these trials did demonstrate an acceptable toxicity profile, improved PFS with ipilimumab, and PSA response. Because of the limited benefit of monotherapy, ongoing trials are investigating combination immunotherapy. For instance, the CheckMate 650 trial is evaluating ipilimumab and nivolumab for patients with metastatic castration-resistant prostate cancer (mCRPC) and is comparing cohorts of patients whose diseases have progressed after second-generation hormone therapy and have not received chemotherapy to those whose diseases have progressed after taxane-based chemotherapy. Initial results have shown a response rate of 26% in the chemotherapy-naïve cohort and 10% in the group who failed taxane-based therapy (Sharma *et al.* 2020).

Combined therapy with tyrosine kinase inhibitors and checkpoint inhibitors is also being investigated. A recent phase I study (COSMIC-021) evaluated the objective response rate of patients with mCRPC who were treated with cabozantinib (tyrosine kinase inhibitor) with atezolizumab (anti PD-L1 antibody). The results showed an objective response rate of 32%, with 4.5% of patients had a complete response and 27% had a partial response (NCT03170960). Other ongoing trials are investigating other combination immunotherapies and evaluating responses in subpopulations with diseases that are thought to be more immunogenic, such as patients with CDK12 mutations (NCT03204812, NCT03570619).

Another emerging promising therapy is chimeric antigen receptor (CAR) T lymphocytes. These cells are engineered to use selected receptors for targeting specific

cancer antigens. Several phase I trials are ongoing, including those investigating PSMA (NCT04249947).

RT may have the potential to augment immunotherapy. Several reports have demonstrated that RT induces a proinflammatory microenvironment that is thought to increase the likelihood of response to immunotherapies (Di Maggio *et al.* 2015, Asna *et al.* 2018, Dallos & Drake 2018). Growing evidence shows that RT can modulate a tumor to become an immuno-stimulatory milieu by up-regulating surface molecules involved in immune recognition and translocating antigens to the tumor-cell surface, rendering them more sensitive to cytotoxic T lymphocyte- (CTL) mediated lysis (Chakraborty *et al.* 2004, Gameiro *et al.* 2014, 2016). Preclinical studies have suggested ablative-dose RT between 5 and 20 Gy may have stronger immunostimulatory effects (Patel *et al.* 2018, Walle *et al.* 2018). Ablative-dose RT transforms the immunosuppressive tumor microenvironment by increasing CD8+ T-cell infiltration and reducing myeloid-derived suppressor cell levels (Filatenkov *et al.* 2015). Importantly, this was observed only with ablative-dose RT and not with conventional RT. Stereotactic ablative radiotherapy (SABR), with the advantage of delivering ablative doses of RT over a very short period to achieve localized and high-dose distribution, could potentially enhance the immunostimulatory effects of RT in the prostate while minimizing the off-target immune-suppressive effects on peripheral immune cells that occur with conventional daily RT (Filatenkov *et al.* 2015).

Nivolumab is another anti-PDL-1 MAB that is widely used in several malignancies. In one of the first studies evaluating nivolumab for castration-resistant PCa, none of the 17 patients enrolled demonstrated a significant treatment response (Topalian *et al.* 2012). However, subsequent studies have shown that there may be dramatic responses to immune checkpoint inhibitors in select populations, in combination with androgen receptor-targeted agents (Carosella *et al.* 2015, Mahoney *et al.* 2015, Graff *et al.* 2016). In a small phase I/II study by Yuan *et al.*, the investigators evaluated the role of nivolumab in combination with ADT and high-dose brachytherapy (HDR) followed by external beam RT and saw that the combination was not only well-tolerated but, on rebiopsy after HDR, 50% of the patients had no residual tumor in four out of six biopsy cores, and there was increased CD8+ and CD4+ T cell infiltration in tumor samples of early responders (Yuan *et al.* 2021). Several clinical trials further investigating the combination of RT and immunotherapy are currently recruiting

patients (NCT01436968, NCT01436968, NCT03543189, NCT03795207, NCT01777802) (Table 1).

Radioisotope treatment for prostate cancer

One of the most common causes of morbidity and mortality among patients who progress to mPCA is the development of bone metastases. Though EBRT has long been used for palliation of symptomatic bone lesions, it lacks tumor specificity and often results in increased irradiation to normal surrounding tissues and organs at risk.

Radium-223 is an alpha emitter that has been shown to target bone metastases by selectively binding to areas of high cell turnover (Bruland *et al.* 2006, Gómez-Veiga *et al.* 2018). The advantage of alpha emitters is that, because of high linear energy transfer, they are able to deposit more energy at shorter ranges (<100 µm) (Bruland *et al.* 2006). The proposed mechanism of action involves forming complexes with hydroxyapatite in areas of high cell turnover (e.g. bone metastases) using high-energy RT, leading to irreparable DNA damage (Henriksen *et al.* 2002). The ALSYMPCA trial, in which patients with mCRPC and symptomatic bone lesions were randomized to receive either placebo or radium-223, showed that radium-223 prolonged time to symptomatic bone events, reduced the risk of suffering an event by 34%, and decreased use of EBRT for bone management of bone metastases (Hoskin *et al.* 2014).

Another class of radioisotope that has been extensively studied for prostate cancer is targeted toward the cell surface protein PSMA. In a large systematic review that summarized the use of the beta emitter lutetium-177, the authors reported an average PSA decline in 75% of patients, which was supported by radiographic evidence of objective responses and stable disease (Yadav *et al.* 2019). The VISION trial, which completed accrual in 2018, aims to evaluate the efficacy of ¹⁷⁷-Lu-PSMA-617 among patients with mCRPC with PSMA-expressing tumors as determined by PSMA PET imaging (Sartor *et al.* 2020).

Another agent presently under study is actinium-225 (²²⁵-Ac-PSMA-617). This alpha emitter has been shown in a small case series to cause PSA decline and has a good toxicity profile (Kratochwil *et al.* 2016). Another therapeutic radioisotope is ¹⁷⁷-Lu-J591, which is a radiolabeled humanized MAB. Early phase trials have shown PSA response rates limited by reversible myelosuppression (Tagawa *et al.* 2010); however, more information is needed with regards to efficacy and safety.

Considerable progress has been made in the development of new targeted therapeutics beyond radium-223. However, data is still lacking on their efficacy, toxicity, and combination with standard treatment techniques. At present, there are promising data suggesting that these radioisotopes may be beneficial for carefully selected patients.

Conclusion

The year 2021 marks the 80th anniversary of ADT for prostate cancer. Though much progress has been made since the incorporation of ADT in the treatment algorithm, prostate cancer remains a significant cause of cancer-related death. While RT, surgery, and ADT remain the backbone of prostate cancer treatment, several recent developments are taking us beyond these therapies. Improvements in prostate cancer-specific imaging modalities are improving staging and evaluation, allowing for better informed treatment planning. Some of these newer technologies are allowing physicians to diagnose patients with oligometastatic disease and through the use of ablative therapies treat these patients with curative rather than palliative intent. Combination immunotherapies augmented by RT show promise to improve clinical outcomes. Finally, radioisotopes have been shown to effectively target and treat prostate cancer with high tumor specificity and remain a potent therapeutic option for select patients.

Declaration of interest

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