

## Exploiting the synergy of multimodal radiotherapy in prostate cancer

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### **Competing interests**

The authors declare no competing interests.

**Abstract** | Radiotherapy in combination with androgen deprivation therapy (ADT) is a standard treatment option for men with localized and locally advanced prostate cancer. However, emerging clinical evidence suggests that radiotherapy could be incorporated into multimodality therapy regimens beyond ADT, in combinations that include chemotherapy, radiosensitizing agents, immunotherapy, and surgery for localized and locally advanced prostate cancer, as well as in patients with oligometastatic disease where the low metastatic burden in particular may be treatable with these combinations. This multimodal approach is increasingly recognized to offer considerable clinical benefit, such as increased anti-tumour effects and survival benefits. Thus, radiotherapy is becoming a key component of multimodal therapy for many stages of prostate cancer, particularly for patients with oligometastatic disease.

### **Key points**

- Radiotherapy combined with androgen deprivation therapy (ADT) is a common treatment option for men with prostate cancer.

- In many patients, the use of radiotherapy is hindered by tumour resistance and a reduction in quality of life caused by toxic effects to normal tissue, which limits the radiation dose that can be delivered safely.
- Tumour control could be improved by using radiotherapy in combination with other treatments beyond ADT, including chemotherapy, radiosensitizing agents, immunotherapy, and surgery.
- This multi-modality approach could be beneficial in men with many stages of prostate cancer, including in the context of oligometastatic disease.
- A survival benefit from a multi-modality therapy approach appears to be achievable in the context of the low metastatic burden state of oligometastatic prostate cancer.

## **[H1]Introduction**

Prostate cancer is the most common male malignancy diagnosed in Europe, the USA and worldwide (1–3). Clinical decision making for men with prostate cancer is based on various classification systems, including the use of serum PSA level, clinical tumour stage, and Gleason grade group (4) (which are based on D’Amico’s description (5–8)) (**box 1**) as well as guidelines from the European Association of Urology (EAU) and joint guidelines from the American Urological Association (AUA), American Society for Radiation Oncology (ASTRO) and Society of Urologic Oncology guidelines (SUO) (7–11). Men with high-risk localized or locally advanced prostate cancer have a propensity for recurrence after loco-regional treatment (12). Patients with localized prostate cancer warranting radical treatment can be considered for radical radiotherapy (either external beam or brachytherapy) or radical prostatectomy based on their preferences, comorbidities, and physician recommendation (7,8). Men with locally advanced prostate cancer might receive radiotherapy with concomitant androgen deprivation therapy (ADT) or, increasingly, radical prostatectomy, with curative intent, again based on patient choice, physician recommendation, and competing comorbidity and operability.

Benefits of radiotherapy include the fact that it is non-invasive, and therefore may be used to treat prostate cancer in patients who are older or have greater co-morbidity than those who may receive surgery, and it requires no hospital in-patient stay. Whilst radiotherapy has recognized side effects, it can be used to treat prostate cancer whilst sparing men some of the side effects of surgery such as urinary incontinence. Despite technological advances in radiotherapy delivery such as the sparing of normal healthy tissues during treatment, patients with high-risk disease have a 32-70% 5-year biochemical recurrence rate (13) even when concomitant ADT is administered.

Radiotherapy combined with ADT was first shown to confer a survival benefit compared to radiotherapy alone for patients with locally advanced prostate cancer in 1997 (overall survival at five years’ follow-up 79%, 95% confidence interval 72-86%, in the combined-treatment group, versus 62%, 95% confidence interval 52-72%, in the radiotherapy alone group,  $p=0.001$ ) (14). Radiotherapy combined with ADT has also been investigated in the treatment of localized prostate cancer. For example, a phase 3 clinical trial from the Radiation Therapy Oncology Group (RTOG) investigated whether adding short-term ADT to radiotherapy could improve survival for patients with low- or intermediate-risk localized prostate cancer and serum PSA levels  $\leq 20\text{ng/mL}$  (15). In 2011 this study

reported that a significant decrease in 10-year prostate-cancer-specific mortality (hazard ratio for death with radiotherapy alone, 1.17;  $p=0.03$ ) and biochemical recurrence was observed in men receiving combined treatment compared with those who received radiotherapy alone. However, the 10-year biochemical recurrence rate was still 28% for men with intermediate-risk prostate cancer (15). ADT and radiotherapy have also been trialled in patients with high-risk prostate cancer. The 2008 RTOG 92-02 trial randomized patients with high-risk prostate cancer to receive radiotherapy plus short-term (4 months) or long-term (24 months) ADT, and demonstrated 10-year biochemical recurrence rates of 74% and 56% respectively (16). These data suggested that patients with high-risk prostate cancer harbour cells resistant to radiotherapy and ADT, and that this therapeutic approach could, therefore, be improved. Moreover, whilst the addition of concomitant ADT is a standard-of-care approach to the delivery of radiotherapy for localized and locally advanced prostate cancer, it may be possible to combine radiotherapy with an alternative adjunct, which has less toxicity and greater efficacy than ADT. This could result in several advantages for patients receiving radiotherapy, such as not causing the ADT-related side effects, and potentially increasing the cure rate of radiotherapy whilst reducing the radiotherapy dose (and associated side effects) needed to achieve that cure.

Although radiotherapy with concomitant ADT is now a standard-of-care option for patients with localized and locally advanced prostate cancer, it is only in the past 3 years that it has been used to treat the primary tumour in the context of oligometastatic disease based on evidence of a survival benefit (17). Whilst the presence of a low metastatic burden in some cancer patients has been recognized for a long time, oligometastatic prostate cancer is a relatively new concept that has gained interest in the last decade (18,19), and applies to patients with relatively few (typically 3–5, for example up to 3 in the STOMP trial (20), and up to 5 in the SABR-COMET trial (21)) small-volume (the number of lesions *per se* being more relevant than their size, though they are typically small) distant disease foci (19). Genomic data suggest that the biology of intermediate metastatic progression differs from widespread metastasis (22,23), and metastatic prostate cancer cells might re-seed to the primary lesion (24). Improvements in PET-CT imaging have facilitated precise quantification of metastases (25,26) and, therefore, increased diagnosis of oligometastatic prostate cancer (27). Patients with metastases were historically offered ADT and chemotherapy (9); however,

research is now focussing on improving clinical outcomes (28–30) with a newly established role for radiotherapy within a multimodality treatment approach (20,21,31).

Radiotherapy can reduce quality of life owing to acute and late adverse effects on sexual, urinary and bowel function (32–34) including dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis. In the EORTC 22991 trial (35) 50% of patients reported grade 1 acute genitourinary toxicity, 20% grade 2, and 2% grade 3, whilst 30% reported grade 1 acute gastro-intestinal toxicity, 10% grade 2, and 1% grade 3. Secondary malignancies of the bladder, colon, rectum and soft tissue, and urinary and gastrointestinal fistulae, are rarer late side effects of prostate cancer radiotherapy, occurring at low absolute rates post treatment, but nevertheless these are clinically significant sequelae of this treatment approach (34).

Further development of radiotherapy modalities is needed to increase tumoricidal effects whilst reducing unwanted adverse effects. Multimodality therapy could increase local tumour control by synergy from radiotherapy combined with other adjuncts, whilst potentially reducing the dose of radiotherapy needed for cure, thereby reducing the side effects of treatment.

In this Review we summarize current and emerging concepts in multimodal radiotherapy treatment strategies, particularly in the context of oligometastatic prostate cancer, and discuss the increasing clinical interest in exploiting potential additive and/or synergistic anti-tumour effects with immunotherapeutic strategies for all stages of prostate cancer.

## **[H1]Radiotherapy for prostate cancer**

Radiotherapy is one of two radical treatment options (the other being radical prostatectomy) delivered with curative intent to patients with intermediate-risk or high-risk non-metastatic prostate cancer (7–11). The 5Rs of radiation biology — repair, re-assortment, repopulation, reoxygenation, and radiosensitivity — underpin the mechanisms that are important in determining the response of a biological tissue or tumour to multiple doses of radiation (36).

## **[H2]Mechanisms of radiation damage**

Radiotherapy can cause tumour cell death through multiple mechanisms (**Fig. 1**), and it has been used to treat cancer based on the fact that malignant cells are more sensitive to ionizing radiation than normal cells (37). A major direct effect of radiotherapy on cancer cells is the generation of lethal

DNA double strand breaks resulting in apoptosis, whilst indirect effects can be mediated by free radicals produced from radiotherapy-induced ionization of cellular free water (38–40). Radiotherapy can also be toxic to tumours via inhibition of the proliferative capacity of malignant cells, induction of senescence, and precipitation of mitotic catastrophe during or after aberrant mitosis (41–43), and can also prompt immunogenic cell death through dispersion of radiotherapy-induced immune-stimulating tumour antigens released from dying tumour cells into the tumour microenvironment (44–49). Radiotherapy can also induce tumour microenvironment effects such as vascular endothelial damage which might activate hypoxia-mediated and cytokine-mediated anti-tumour immune responses (50), although the relative contribution of these tumour microenvironment effects to the anti-tumour response is unclear.

## [H2]Modalities of radiotherapy

Radiotherapy can be administered as external beam radiotherapy (EBRT), brachytherapy at high or low dose rates, combined EBRT and brachytherapy, or particle therapy (which includes proton beam therapy) (51), and any of these forms of ionizing radiation delivery can be combined with other therapies to produce additive or synergistic anti-tumour effects. The primary technological advances in radiotherapy delivery in the last decade have largely involved changes in dose fraction and increased safety of radiotherapy delivery. Novel uses of multimodality therapy, to include radiation plus adjunct treatment(s), could offer the best future approach to achieve increased efficacy of radiotherapy treatment, increased cure rates, and reduced treatment toxicity for patient benefit.

## [H3]External beam radiotherapy

External beam radiotherapy as a treatment for cancer was first brought to the attention of the medical community in 1922 in Paris, where evidence of the curative effect of ionizing radiation for advanced laryngeal cancer was presented to the international Congress of Oncology. Initially single irradiation fields were used with kilo-voltage energy, and in the late 1940s and early 1950s this was followed by mega-voltage energy radiation doses using cobalt source machines and early electric linear accelerators. The 1970s and 1980s saw the progression of therapy from 2-dimensional to 3-dimensional (3D) treatment plans as imaging progressed from plain X-ray images to computerized tomography (CT). Use of CT-based 3D radiotherapy improved tumour coverage, and reduced the

toxicity of treatment by allowing the target to be accurately visualized on CT scans, thereby sparing normal adjacent tissues. The development of CT planning software also facilitated the creation of more sophisticated and complex radiotherapy treatment plans (52). By the mid- to late-1990s the widespread application of intensity-modulated radiotherapy (IMRT) became possible due to the availability of appropriate hardware and software. New and improved treatment planning algorithms were required in order to deliver this treatment advance, using multiple smaller beams of ionizing radiation to produce a sculpted radiation dose distribution, effectively allowing the higher doses to be “bent” (or modulated) around nearby structures thereby sparing them from high dose radiation damage. Early IMRT required the linear accelerator gantry to be moved to each new position in a stepwise manner, creating a slow delivery process. However, in 2008 an algorithm was produced to generate an IMRT beam while the treatment gantry rotates in an arc around the patient (53). This allowed the treatment to be administered more rapidly, and also increased the ability to modulate the shape of the radiation beam. IMRT was further refined to volumetric modulated arc therapy (54–56), and IMRT enables target doses >70 Gray to be delivered whilst minimizing doses to non-malignant tissue (57,58).

Stereotactic body radiotherapy (SBRT) developed out of the historical use of highly focussed cobalt radiation for brain tumours, which was a discipline that developed in the 1960s and was termed stereotactic radiosurgery. The concept of stereotactic radiosurgery was that narrow radiation beams from several directions would focus on the target whilst sparing adjacent normal tissues with high accuracy. This technique would thereby allow delivery of high radiation doses to the target, leading to enhanced tumour control without significant treatment-related toxicity. The first commercial stereotactic radiosurgery system became available in 1967, and by the 1980s this had become a standard part of neurosurgical practice. SBRT took the same principle and applied it to extra-cranial tumours, and this was facilitated by advances in linear accelerator technology (both in terms of hardware and software), as well as improvements in treatment planning algorithms, and early reports of this new technique were published in the mid-1990s. SBRT became more widespread by around 2010, and awareness and popularity of this technique is increasing.

SBRT delivers EBRT with target localization using image guidance and 5–7 fractions of 6–10 Gray per fraction for treatment of the prostate gland. SBRT also enables treatment of metastatic sites using 3–7 fractions of 6–13 Gray (59–62).

Standard or conventional fractionated radiotherapy typically delivers a dose of 1.8-2 Gray to the tumour per fraction, typically administered daily for 5 days a week, for several weeks. This traditional fractionation regimen aims to maximize local tumour control while minimizing toxicity to adjacent healthy normal tissues based on radiobiology models. Hypofractionation describes a treatment regimen that delivers high doses of radiation using a shorter number of treatments as compared to conventional treatment regimens. There is no internationally recognized dose or number of treatments that constitute hypofractionation, however by definition the dose is greater than 2 Gray per fraction, and is typically 2.5-5 Gray per fraction. Profound fractionation, or ultrafractionation, accurately delivers a high irradiation dose in one or relatively few treatment fractions, typically between 1-8 fractions in number, again with no specific dose definition but typically with doses equal to or in excess of 6 Gray per fraction.

Studies to investigate outcomes after SBRT for prostate cancer are mostly non-randomized phase 2 trials (63). A pooled analysis of 1,100 patients from multi-institutional prospective phase 2 clinical trials with low- (58%), intermediate- (30%) or high-risk (11%) prostate cancer reported a 93% 5-year biochemical disease-free survival for all patients (95%, 84% and 81% for low-, intermediate- and high-risk patients respectively,  $p < 0.001$ ) (64).

Outcome data over a median follow-up of 3 years demonstrate that SBRT is well tolerated as a prostate cancer treatment and has minimal lasting effects on health-related quality of life (65). Data on SBRT for high-risk prostate cancer are more limited; the international Prostate Advanced in Comparative Evidence (PACE) phase III randomized clinical trial, which is due to report in 2021 (66), included no patients with high-risk disease. In parallel with the PACE study, a separate phase 3 clinical trial comparing SBRT with conventional radiotherapy or radical prostatectomy is currently underway to include individuals eligible for surgery (66); this trial will complete recruitment in late 2020. The Scandinavian HYPO-RTPC phase 3 clinical trial, which was the first phase 3 randomized controlled trial to investigate ultrahypofractionated versus conventionally fractionated radiotherapy, albeit using slightly different fraction sizes to the PACE study, demonstrated non-inferiority of ultrahypofractionated treatment compared to conventionally fractionated radiotherapy for intermediate- to high-risk prostate cancer in terms of failure-free survival (67). In this trial, early urinary toxicity was more pronounced with ultrahypofractionation than with conventional



fractionation, however late urinary and bowel toxicity was similar in both treatment groups. Taken together these results support the use of ultrahypofractionated radiotherapy for prostate cancer.

### [H3] Image-guided radiotherapy

The concept of image-guidance during radiotherapy refers to daily imaging during treatment in order to ensure accurate targeting of the tumour, and sparing of normal adjacent tissues. This is relevant to tumours such as prostate cancer where the position of the prostate gland might sometimes change between radiotherapy fractions according to bladder or rectal distension. Delivery of “dominant lesion boosts” during radiotherapy takes the use of image guidance a stage further, where a radiotherapy boost is given to the malignant lesion within the target organ, and this is an area of current investigation, although it is not yet part of conventional radiotherapy treatment. Approaches using the imaging capability of multifunctional MRI to guide the daily delivery of radiotherapy represents a pinnacle of image guided radiotherapy delivery, as this enables dose escalation to dominant intra-prostatic lesions (68), and this is currently being tested in the phase 3 PIVOTALBoost randomized clinical trial in the UK (69), which is currently open to recruitment.

### [H3]Brachytherapy

Brachytherapy comprises internalized radiotherapy using implanted Iodine-125, Palladium-103 or Caesium-131 radioisotope seeds (70). One advantage of brachytherapy over EBRT is that it permits extreme dose escalation that exceeds conventional EBRT and is delivered with high target conformity (71). Low dose-rate (for low- or intermediate-risk prostate cancer) permanent seed implantation, or high dose-rate temporary source implantation (for intermediate- or high-risk prostate cancer), may be used to treat localized disease (51,71). Both low-dose-rate and high-dose-rate brachytherapy can be used as a boost combined with ADT and EBRT for patients with intermediate-risk and high-risk prostate cancer and a good urinary flow rate, minimal lower urinary tract symptoms, and an optimal prostate gland size (51,72–74).

### [H3]Proton beam therapy

Proton beam therapy uses heavy particles such as protons and carbon ions to deposit the majority of the radiation dose directly within the tumour, and travel no further through the body, such that this

causes maximum radiation-induced DNA damage within malignant cells, whilst sparing adjacent normal tissues (75). Proton beam therapy delivers this potential dosimetric benefit by taking advantage of a concept known as the “Bragg peak” whereby the maximum dose delivery occurs immediately before particles come to rest, with a high dose being deposited at the target tumour, sparing surrounding healthy tissues (76). To date, the use of protons for prostate cancer radiotherapy is not preferable to conventional radiotherapy (77), as robust evidence for improved efficacy of proton beam therapy over standard photon-based radiotherapy or brachytherapy in this setting is absent. Studies have shown that daily changes in bowel and bladder filling, as well as variations in patient set up, may affect the range of protons in tissue. As a result of this patients are not treated with anterior-posterior beams but rather with opposed lateral beams with at least a proportion of the dose affecting the anterior rectal wall (78). A comparison of photon IMRT prostate plans with plans using two lateral opposed proton beams demonstrated that the conventional radiotherapy IMRT plans were more conformal, and therefore provided more radiotherapy dose to the volume of the target, than the proton beam plan (79). Studies have also demonstrated improved gastrointestinal toxicity in patients treated with IMRT for prostate cancer compared to proton therapy (80). In 2015 a case-matched study of 394 patients with prostate cancer treated with IMRT or proton therapy demonstrated no differences in acute or late gastrointestinal or genitourinary symptoms (81). There are no reported randomized controlled trials of proton beam therapy for prostate cancer (75), however a phase 3 clinical trial comparing proton therapy versus IMRT for low- or low-to-intermediate-risk prostate cancer is currently open to recruitment, and is due primary completion in late 2021 (82).

Interesting unanswered questions remain regarding the timing and sequence of delivery of radiotherapy to the primary prostate cancer and to draining pelvic lymph nodes. These questions are particularly pertinent when considering the use of multimodal therapy, to include radiotherapy, for prostate cancer in the context of optimizing synergy with other agents such as immunotherapy. There is no current information from clinical trials to inform clinicians regarding this, however one intriguing possibility is that radiotherapy might be delivered to the primary malignancy with the initial omission of the draining lymph nodes, in order to allow a therapeutic anti-cancer immune response to develop in these non-irradiated lymph nodes, and these lymph nodes may then be

irradiated at a later time-point in order to treat any micro-metastatic cancer cells. This question warrants investigation in future clinical trials.

### **[H1]Combining radiation and other modalities**

The success of radiotherapy in cancer treatment has led researchers and clinicians to combine it with other therapeutic modalities to further improve its effectiveness. Combining radiotherapy with other therapeutic approaches can generate additive or synergistic treatment effects, which might enable a reduction in the dose of radiotherapy, thereby reducing treatment-related toxicity and adverse effects. Rectal cancer (83) and oesophageal cancer (84) are examples of solid-organ malignancies where this approach has improved treatment.

### **[H2]Radiotherapy combined with surgery**

In the past, radical prostatectomy was offered cautiously for locally advanced prostate cancer, owing to risks of loco-regional disease recurrence (85); thus, radiotherapy and ADT were offered more commonly for this stage of disease (7), although contemporary data suggest encouraging cancer-specific survival and biochemical disease-free survival rates can be achieved with radical prostatectomy in this setting (86–88). Radiotherapy is offered after radical prostatectomy to improve outcomes in men with locally advanced prostate cancer with high-risk features such as extra-prostatic extension, seminal vesicle invasion, and/or positive surgical margins (7,9). It can be administered either as adjuvant radiotherapy, for example in men with high-risk disease features but undetectable post-operative PSA, or as salvage radiotherapy in patients with biochemical recurrence following radical prostatectomy (89).

Clinical practice differs across the world with respect to the timing of radiotherapy following radical prostatectomy. In the UK and Europe, the guidelines do not recommend immediate post-operative radiotherapy, even in the context of positive surgical margins; the EAU (90) and NICE (91) guidelines suggest that both immediate (adjuvant) and delayed (salvage) therapy are valid options. However, clinical practice in the USA differs slightly, where the AUA guidelines (11) recommend immediate radiotherapy for patients with high-risk features on histological examination of the radical prostatectomy specimen, based on different interpretation of the data.

The potential benefit of adjuvant radiotherapy versus salvage radiotherapy after radical prostatectomy has been examined in three randomized clinical trials (92–94). However, only one of these studies (94) included post-operative patients who had not developed biochemical relapse and, therefore, had a serum PSA level  $<0.2\text{ng/ml}$ . The EORTC 22911 (92) and SWOG 8794 (93) studies enrolled patients with a PSA  $>0.2\text{ng/ml}$  and  $>0.4\text{ng/ml}$  respectively; thus, these patients would be considered to have received salvage rather than adjuvant radiotherapy. A Cochrane review has concluded that offering adjuvant radiotherapy to men with prostate cancer with high-risk features such as extension beyond the prostate capsule into the seminal vesicles or positive surgical margins did not improve survival at 5-years follow-up, although survival was improved at 10-years follow-up (95). Whether immediate adjuvant radiotherapy is superior to early post-operative salvage radiotherapy is being evaluated in prospective randomized clinical trials including RADICALS (NCT00541047) (96) and RAVES (NCT00860652) (97). A 2019 update from RADICALS demonstrated no difference in disease recurrence at 5-years between men who routinely received radiotherapy following surgery compared with those who received radiotherapy at biochemical recurrence (98). This observation was confirmed in the 2019 ARTISTIC collaboration meta-analysis, which combined the results of RADICALS with those from RAVES and a similar trial termed GETUG-AFU17 (98,99), which was planned before the results of the trials were known. This meta-analysis was based on all 2,151 men in the 3 trials (1,074 men randomized to adjuvant radiotherapy, and 1,077 men randomized to early salvage radiotherapy, of whom 395 men have commenced salvage treatment), and this found no evidence that adjuvant radiotherapy improves event-free survival compared to early salvage radiotherapy (hazard ratio = 1.09;  $p=0.47$ ).

Initial data from the NRG Oncology/RTOG 0534 SPORRT trial (100) suggest that radiotherapy to treat the pelvic lymph nodes in addition to standard prostate bed provides a clinical benefit in patients with a rise in PSA after radical prostatectomy. A randomized clinical trial is underway in patients who have undergone surgery for intermediate-risk stage III or IV prostate cancer (101), which randomized patients to receive 6-months ADT together with adjuvant or salvage radiotherapy; the results of this trial are also awaited after primary completion of the study in 2022. These randomized clinical trials

are helping to inform the precise indications for post-prostatectomy radiotherapy, along with its optimal timing and potential need for ADT.

## [H2]Radiotherapy combined with ADT

Androgens promote prostate cancer cell proliferation (102,103); thus, ADT is a keystone of prostate cancer therapy. ADT is given concomitantly with radiotherapy, most commonly as neoadjuvant therapy, and then continuing during and beyond radiotherapy, although the timing and duration of ADT is uncertain given that the available evidence is based on trials using older radiation techniques (104,105). The combination of ADT and radiotherapy has improved treatment of prostate cancer, but there remains room for improvement in the biochemical control rate as demonstrated by clinical trials (101). Despite the uncertainty surrounding the optimal timing and necessary duration of ADT with newer radiotherapy techniques (105), patients with intermediate-risk localized prostate cancer typically receive neoadjuvant ADT for 3 months, and those with high-risk localized prostate cancer receive neoadjuvant ADT for 3-6 months (62). Data from the RTOG 9910 trial (106) suggest that prolonged neoadjuvant ADT for up to 28 weeks does not yield benefit, with extension of ADT duration from 8 weeks to 28 weeks before radiotherapy showing no improvement in outcomes at up to 10-years of follow-up (For the 8- and 28-week assignments, 10-year disease-specific survival rates for the 8- and 28-week neoadjuvant ADT assignments were 95% and 96% respectively; hazard ratio 0.81;  $p=0.45$ ). Men diagnosed with locally advanced disease continue to receive ADT for 2-3 years, although a 2018 study in men with high-risk localized prostate cancer suggests the length of adjuvant ADT following radiotherapy could be shortened from 36 to 18-months (107). Radiotherapy has been shown to be more effective with concomitant ADT (108–111), which has made this approach the standard of care for intermediate- and high-risk prostate cancer. The European Organisation for Research and Treatment of Cancer (EORTC) study 22863 was the first phase 3 study to show a significant overall survival benefit of radiotherapy combined with ADT in men with locally advanced prostate cancer (112). EORTC 22863 compared radiotherapy alone and in combination with ADT, and at 10-years follow-up overall survival remained significantly higher in the combination arm than in the radiotherapy-only arm (58.1% versus 39.8%,  $p=0.0004$ ) (112).

Historically, ADT was thought to confer a technical benefit for subsequent radiotherapy (and brachytherapy in particular) by reducing the prostate volume and, therefore, decreasing treatment-related morbidity (113,114). ADT might also improve the effectiveness of radiotherapy by inhibiting subsequent prostate cancer cell repopulation, and by improving reoxygenation and radiosensitization (115,116). However, preclinical studies using *in vitro* cell line and *in vivo* tumour xenografts have demonstrated that ADT inhibits mechanisms of the cellular DNA damage response, particularly non-homologous end-joining repair of radiation-induced DNA double-strand breaks, which increases the anti-tumour effects of radiotherapy (117–119). Preclinical studies using these models highlight therapeutic interactions whereby radiotherapy and ADT synergize to inhibit the DNA repair machinery and enhance apoptosis (112,120), and combined treatment improves tumour oxygenation and radiosensitizes prostate cancer (121). These observed synergistic mechanisms might explain the improved outcomes reported in a meta-analysis of fourteen clinical trials investigating combined radiotherapy and ADT, which indicated that combination therapy was associated with better or similar survival and disease-free outcomes than single-modality treatment with either ADT or radiotherapy alone, particularly in patients with high-risk disease (122). However, despite these benefits, even with combined radiotherapy and ADT, some patients with high-risk localized and locally advanced prostate cancer develop recurrent disease. For example, the landmark EORTC studies reporting the short- and long-term follow-up results of patients treated with combined radiotherapy and ADT reported a 5-year disease-free survival of only 74% in the combination arm (14,108). These data, considered alongside the adverse effects of ADT, has led to studies to investigate the combination of radiotherapy with systemic treatments such as chemotherapy and immunotherapy in men with high-risk prostate cancer.

#### [H2]Radiotherapy plus chemotherapy and ADT

The benefits of sequential addition of docetaxel to radiotherapy and ADT have been demonstrated in the RTOG 0521 (123) and STAMPEDE (124) trials. The RTOG 0521 trial suggested that overall survival is improved from 89% to 93% at 4-years ( $p=0.03$ ) by the addition of adjuvant chemotherapy to ADT and radiotherapy in men with localized, high-risk, hormone-sensitive prostate cancer (123). The STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial is a large clinical study assessing new treatment approaches for high-risk prostate

cancer (124). STAMPEDE included patients commencing long-term ADT for newly diagnosed locally advanced or metastatic prostate cancer, or who have relapsed after local therapy (including radiotherapy) with poor prognosis features. Addition of docetaxel to standard-of-care treatment in STAMPEDE was associated with a median 10-month improvement in overall survival, along with improvements in prostate-cancer-specific survival, failure-free survival, and skeletal-related events (124). The CHAARTED (Chemo-Hormonal Therapy versus Androgen Ablation Randomized Trial in Extensive Disease) trial (125) trial found that docetaxel chemotherapy improved survival in men with high-risk metastatic hormone-sensitive prostate cancer. At a median follow-up of 53.7 months, the median overall survival was 57.6 months for chemohormonal therapy versus 47.2 months for ADT alone ( $p=0.0018$ ). In light of these data, docetaxel is now offered earlier in the prostate cancer disease course than it was previously, in the adjuvant setting for metastatic hormone-sensitive prostate cancer, whereas in the past it had been confined to use in the hormone-resistant metastatic setting (126).

#### [H2]Radiotherapy plus chemotherapy alone

Concurrent chemotherapy can potentially radiosensitize some malignancies (127,128) such as cervical cancer (129,130). In terms of prostate cancer treatment, the fact that docetaxel has cytotoxicity mechanisms complementary with radiotherapy (131), including direct cytotoxic effects and disruption of cell division, suggests that this agent could be effectively combined with radiotherapy. *In vitro* and *in vivo* studies using human squamous cell, breast and cervical cancer cells demonstrate synergy combining docetaxel with irradiation (132,133). Although radiotherapy combined with chemotherapy alone is not currently considered standard-of-care in any prostate cancer disease setting, this treatment combination could potentially be useful for patients with intermediate-risk disease wishing to avoid the adverse effects of ADT. Concurrent chemoradiation for high-risk prostate cancer has been studied in phase I/II trials, providing preliminary safety and efficacy evidence including maximum tolerated doses of chemotherapy and radiation that can be safely delivered concurrently, and demonstrating feasibility of this approach (13,134–143). However, phase 3 randomized clinical trial evidence is necessary to determine any potential clinical benefit of chemoradiation versus combined ADT and radiotherapy for high-risk prostate cancer, and no such trial is currently in progress.

## [H2]Radiotherapy combined with immunotherapy

Cancer immunotherapy aims to overcome the weak immunogenicity of tumour-associated antigens, provoking an immune response to cancer cells while minimising autoimmunity (144). Radiotherapy has been regarded as being immunosuppressive (145), partly owing to its toxic effects on local lymphocytes and local recruitment of immunosuppressive cells such as tumour-associated macrophages and myeloid-derived suppressor cells (50); thus, it might be inappropriate to combine radiotherapy with immunomodulation (146). However, evidence now suggests that radiotherapy may be an immunostimulatory anti-prostate cancer therapy through several mechanisms such as neoantigen expression and altered inflammatory signals which can affect lymphocyte and dendritic cell activation (146). Thus, the relationship between ionizing radiation and immune reactivity is more complex than was previously thought. Mechanistic and *in vitro* and *in vivo* pre-clinical data regarding the use of radiotherapy and immunotherapy are accumulating, suggesting that opportunities exist to combine radiotherapy with immunotherapy. For example, radiotherapy-induced cell death, combined with upregulation of antigen availability and expression, increased tumour-associated antigen presentation, and inflammatory co-stimulatory cytokine signals, along with the overcoming of an immunosuppressive tumour microenvironment via a shift of the cytokine balance in favour of immunostimulation, can affect dendritic cell and CD8(+) T-cell activation, thereby promoting immune-mediated anti-tumour effects in various pre-clinical models (147,148).

Radiotherapy can be used as an adjunct to immunotherapy as it induces immunogenic cell death in susceptible cancer cells, which requires generation and release of tumour-associated antigens (145,149). These tumour-associated antigens are taken up by antigen-presenting cells such as dendritic cells and presented on type I MHC molecules to a T-cell receptor against a background of co-stimulatory signals between ligands and receptors on the antigen-presenting and T-cells, respectively (150). Release of tumour-associated antigens and recruitment of antigen-presenting cells at inflammatory sites is mediated by pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 following radiotherapy, activating the immune system and causing immunogenic cell death (151). Immunogenic cell death is characterized by particular hallmarks including calreticulin exposure and



release of ATP and HMGB1. A reciprocal relationship may exist whereby tumour irradiation stimulates the immune system, which in turn contributes to tumour cell death (44,152). Negative feedback mechanisms, including upregulation of the inhibitory signal CTLA-4, control immunogenic cell death by competitively inhibiting co-stimulatory signals expressed by antigen-presenting cells to T-cells (145,153); upregulation of CTLA-4 can reduce immune-mediated cell death via inhibition of T-cell function, and therefore inhibition of CTLA-4 function may provide a potential mechanism to promote radiotherapy-induced immunogenic cell death (145). Radiotherapy can prime immune responses against cancer cells, but its effects can also be constrained by immunosuppressive cells (145) such as myeloid-derived suppressor cells, regulatory T-cells, and tumour-associated macrophages (50,154). Radiotherapy can also lead to immunogenic modulation of tumour cells, such as molecular alterations in cancer cells that promote immune cell-mediated killing, including expression of genes important for immunological attack such as MHC-I which is responsible for presentation of endogenous antigens to cytotoxic T-cells (155). Immune cells can be directly affected by radiotherapy, which can upregulate expression of tumour-associated antigens (156), co-stimulatory molecules (157), death receptors (158), MHC moieties (156), cytokines and adhesion molecules (159,160), and downregulate regulatory T-cells, resulting in tumours becoming more susceptible to immune-mediated cytotoxicity (**figure 2**).

The immunostimulatory effects of radiotherapy combined with immunotherapies such as cancer vaccines and immune checkpoint inhibitors are of increasing interest. Several studies combining radiotherapy and immunotherapy have been conducted in patients with high-risk localized and metastatic castrate-resistant prostate cancer (**Table 1**). Therapeutic cancer vaccines such as sipuleucel-T (Provenge) enhance immune recognition of specific tumour-associated antigens, promoting immune-mediated cancer cell death (161). PROSTVAC is another vaccine which stimulates the immune system and enhances T-cell targeted destruction of PSA-expressing prostate cancer cells (162). Although cancer vaccines have not yet been combined with radiotherapy to treat prostate cancer as standard-of-care, evidence suggests that this tumour type can be converted from being immunologically 'cold' to 'hot' (163–165), and this change could be harnessed in combination with radiotherapy.

Another immunotherapeutic approach involves disruption of immune regulation using monoclonal antibodies to inhibit immune checkpoints to amplify and/or sustain cytotoxic T-cell activation (163). Ipilimumab blocks the inhibitory signal CTLA-4, thereby activating T-cells (166). Combined radiotherapy and anti-CTLA-4 in pre-clinical mouse models induces T-cell responses and enhances anti-tumour effects at the primary tumour site, and can also generate an abscopal effect, defined as a significant growth inhibition of the tumour outside of the treated field (167). A phase I/II study (168), and subsequent multi-institutional phase III trial (169,170), in men with metastatic castrate-resistant prostate cancer investigated anti-CTLA-4 with or without a concurrent 8 Gray single fraction of radiotherapy targeting a bony metastasis. The primary endpoint of improved overall survival was not achieved, although the  $p$ -value was close to statistical significance ( $p=0.0530$ ), and this suggests promise for future approaches.

PD-1 and PD-L1 inhibitors also block immune checkpoints (171). Targeting the PD-1 and/or PD-L1 axis might augment radiotherapy (172) as ionizing radiation can enhance the priming and effector phases of the anti-tumour T-cell response, and radiotherapy upregulates PD-L1 expression in cancer cells (172). Combined radiotherapy and PD-1 or PDL-1 inhibition could be a useful treatment approach in metastatic prostate cancer where the aim is to generate an effective anti-tumour immune response as a mechanism to treat metastatic disease, and proof-of-concept for this approach has been demonstrated in a pre-clinical mouse model (173). A clinical trial to investigate the potential of this combination in Gleason grade group 5 and/or oligometastatic prostate cancer patients is underway (174) and is testing the safety, tolerability, and effectiveness of an anti-PD-1 monoclonal antibody combined with high-dose radiotherapy.

#### [H1]Radiosensitizing agents

Improved understanding of the effects of radiotherapy on the systemic, vascular, stromal and immunological tumour microenvironment can facilitate the development of new molecularly targeted radiosensitizers to selectively target tumour-specific pathways important in radiation-induced cell death, ultimately improving anti-tumour effects of irradiation and minimizing toxic effects (**figure 3**). Several types of radiosensitizing agents including those that target the cellular stress response machinery or DNA damage repair mechanisms, and that might reduce intra-tumoral

hypoxia or have effects on the tumour microenvironment and/or immune response to radiotherapy, have been tested in combination experiments.

#### [H2]PARP inhibitors

Poly-(adenosine diphosphate-ribose)-polymerase (PARP) inhibitors are potential radiosensitizing agents (175). The central role of PARP enzymes in DNA repair makes them ideal targets for molecular inhibition in combination with DNA-damaging treatments such as ionizing radiation, especially for tumours with DNA repair defects, such as those with *BRCA* mutations (176), by increasing synthetic lethality. Tumours with *BRCA1* and *BRCA2* mutations have deficient homologous recombination repair pathways and, therefore, they depend on PARP-mediated base excision repair for survival (177,178). Thus, inhibition of PARP in these tumours is a promising strategy to selectively kill cancer cells by inactivating complementary DNA repair pathways (179). *PARP-1* and *PARP-2* are highly expressed in several cancer types, including prostate, breast and hepatocellular carcinoma (180–183), and causes resistance to cell-death ordinarily induced by DNA-damaging treatments such as radiotherapy (175). Numerous pre-clinical *in vitro* cell line and *in vivo* tumour xenograft model studies have demonstrated synergy from combined PARP inhibition and radiotherapy in a wide range of solid organ cancer types including prostate cancer (184–186). The PARP inhibitor olaparib is FDA approved to treat metastatic castrate-resistant prostate cancer, and might be especially efficacious in *BRCA*-mutated tumours given the potential for synthetic lethality in this setting (187). Clinical trials combining PARP inhibition and radiotherapy are currently underway (188,189).

#### [H2]mTOR inhibitors

The PI3K–AKT–mTOR pathway has been implicated in prostate cancer radioresistance (190). *PTEN* suppresses PI3K–AKT signalling pathways, and *PTEN* alterations, together with PI3K–AKT pathway activation, are common in prostate cancer (191). PI3K–AKT can be regulated by irradiation and promotes radioresistance by inhibiting apoptosis and promoting DNA damage repair (190). Inhibition of PI3K–AKT signalling using various chemical or small molecule inhibitors in pre-clinical *in vitro* cell line and *in vivo* xenograft prostate cancer models increases tumour cell sensitivity to radiotherapy (190,192–196). mTOR is a downstream kinase of AKT, and inhibiting mTOR might be clinically beneficial given the high prevalence of *PTEN* loss or inactivation in prostate cancer, and the

importance of PI3K–AKT signalling in radiotherapy response (190,197–199). The molecular inhibitor of mTOR everolimus as a radiosensitizing agent has been evaluated in a phase I open label clinical trial of 15 patients with high-risk locally advanced prostate cancer (200,201), and this study reported that the treatment was well-tolerated, with a recommended everolimus dose to take forward to future phase II studies.

## [H2] Tyrosine kinase inhibitors

Tyrosine kinase inhibitors are potential prostate cancer radiosensitizers (202,203). Sunitinib inhibits multiple tyrosine kinase receptors, and pre-clinical *in vitro* cell line and *in vivo* xenograft evidence in various cancer models from multiple organs demonstrates its activity against VEGFR2, PDGFR, C-kit and FLT3 (204–207). The potential radiosensitizing effects of sunitinib might be mediated via blockade of the MAPK–ERK pathway, resulting in both reduced tumour cell proliferation after irradiation and tumour vascular destruction through enhanced radiation-induced endothelial cytotoxicity in a Lewis carcinoma mouse model (203,208). Dasatinib is a tyrosine kinase inhibitor targeting the SRC family and PDGFR (209). *In vitro* and *in vivo* evidence suggests SRC is an important potential target for prostate cancer therapy (203), and pre-clinical studies in prostate cancer cell lines demonstrate that dasatinib inhibits key downstream pathways in metastasis, including AKT, FAK and STAT3, and that SRC inhibition by dasatinib may reduce the metastatic spread of prostate cancer cells (210). However, a phase I clinical trial investigating dasatinib combined with ADT and radiotherapy has closed due lack of patient recruitment (211). Thus, whether this type of multimodality approach can lead to clinical benefit in patients with prostate cancer remains undetermined.

## [H2] Ganetespib

Ganetespib targets the HSP90 component of a cell's stress response machinery (212). HSP90 aids cell survival after irradiation by inhibition of apoptotic signalling pathways (213) and inhibition of HSP90 function might, therefore, promote anti-tumour effects of radiotherapy. However, to date the combination of Ganetespib and radiotherapy has not been studied in early phase clinical trials.

## [H1]Radiotherapy for oligometastatic disease

Studies published since 2017 suggest that local therapy to the primary tumour, such as radiotherapy or radical prostatectomy, is feasible and safe in the oligometastatic setting (17,214,215).

## [H2]Clinical trials

The STAMPEDE trial (17), which reported an 11% survival advantage following delivery of radiotherapy to the prostate in the setting of low-volume low-burden oligometastatic prostate cancer, paved the way for multimodality studies in this clinical setting and resulted in changes to clinical practice. For example in the UK STAMPEDE has changed *de facto* clinical practice in the last year, albeit ahead of the periodically updated guidelines such as those issued by The National Institute for Health and Care Excellence. As such, radiotherapy to the primary tumour in addition to standard-of-care hormone therapy and chemotherapy, in the context of oligometastatic prostate cancer, has now become the accepted standard-of-care in light of the results of STAMPEDE. However, although a clinical benefit was observed following irradiation of the primary site in patients with low-volume low-burden metastatic prostate cancer in STAMPEDE (17), individuals with >3 metastases did not derive survival benefit. Men with newly diagnosed metastatic prostate cancer were randomized to receive either ADT with or without docetaxel or ADT with or without docetaxel plus prostate gland radiotherapy in a 1:1 ratio. Radiotherapy was administered in 2 different regimens (either a daily schedule of 55 Gray in 20 fractions over 4 weeks, or a weekly schedule of 36 Gray in 6 fractions over 6 weeks), and patients were stratified according to age, lymph node status, performance status, and docetaxel treatment. Patients receiving either radiotherapy regimen had an improved failure-free survival compared with standard of care (hazard ratio 0.07,  $p < 0.00005$ ), although no overall survival benefit was observed in unselected patients. Encouragingly, a subgroup analysis by disease burden revealed a hazard ratio of 0.68 in patients with low-burden disease, with a 3-year overall survival of 81% in patients receiving standard-of-care plus radiotherapy versus 73% in the standard of care arm. These results suggest that irradiation of the primary tumour in the setting of oligometastatic disease is beneficial.

The HORRAD trial (215) of radiotherapy for patients with any-burden metastatic prostate cancer found no significant difference in overall survival (hazard ratio: 0.90; 95% confidence interval: 0.70-1.14;  $p = 0.4$ ). A trend towards a clinical benefit of radiotherapy was observed, with a median time to PSA progression in the radiotherapy arm of 15 months versus 12 months in the control arm, along with a significant difference in Kaplan-Meier curves ( $p = 0.02$ ). However, the HORRAD was not

specifically performed in patients with solely oligometastatic disease. The results of additional trials are eagerly awaited, and include the phase III SWOG trial (NCT03678025) (216) investigating standard systemic therapy with or without definitive treatment (radical prostatectomy or radiation therapy) in men with metastatic prostate cancer, and the PEACE1 trial (NCT01957436) (217) in men with metastatic hormone-naïve prostate cancer, which is investigating ADT (+ docetaxel) +/- local irradiation to the prostate gland +/- abiraterone acetate and prednisone.

## [H2]The contribution of imaging

Improvements in imaging modalities such as PET–CT are resulting in increased detection of oligometastatic prostate cancer beyond that which was historically possible with conventional CT or <sup>99m</sup>Tc-methylenediphosphonate bone scans (218). This improved detection is driving informed decision-making in individual patients, leading to an increasingly aggressive approach to treating limited metastatic disease, to maximize clinical benefit beyond systemic ADT and chemotherapy. It is now being hypothesized that oligometastatic disease may be cured with local eradication therapies (219), and that a subset of patients might have durable responses to multimodality therapy incorporating local primary tumour therapy, metastasis-directed therapy, and systemic therapy (220). Decreasing the primary tumour burden improves survival in several metastatic solid organ malignancies (17,28), and data from studies in several types of cancer including colorectal (221,222), ovarian (223) and renal (224) malignancy suggest that patients with advanced low-burden metastatic disease undergoing local therapy to the primary tumour have improved cancer-specific and overall survival. These data from studies in other malignancies underpin the concept of localized radiotherapy plus metastasis-directed therapy and systemic therapy to improve oligometastatic prostate cancer outcomes.

## [H2]Metastasis-directed therapy

Metastasis-directed therapy uses local ablative therapy to specifically target metastases and avoid or delay the toxic effects of systemic therapy. Metastasis-directed therapy using SBRT has been investigated in oligometastatic prostate cancer (225–229). Although cancer-specific and overall survival outcomes are limited by short follow-up periods, promising early conclusions are identifiable. For example, the STOMP (20) trial was a multi-centre randomized phase II study evaluating the effect of SBRT in patients with asymptomatic metastatic prostate cancer. Patients were eligible if they had biochemical disease recurrence after primary treatment with curative intent, and

were found on imaging to have  $\leq 3$  extra-cranial lesions. STOMP enrolled 62 patients who were treated with either SBRT without ADT, or surveillance alone in the control arm. At a median follow-up duration of 3 years the ADT-free survival was 13 months for the surveillance group compared with 21 months for the SBRT group (20). The POPSTAR trial (230,231) was a non-randomized study investigating single treatment SBRT at 20 Gray for low-volume advanced prostate cancer in 33 patients. The approach was found to be safe and feasible, and at 2 years' follow-up the local and distant progression-free survival was 93% (95% confidence interval: 84-100%) and 39% (95% confidence interval: 25-60%) respectively, whilst the need for ADT had been avoided in almost half of all participants (20,231).

The results of the stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumours (SABR-COMET) phase II clinical trial suggest that treatment with SBRT improves overall survival in oligometastatic cancer, although this trial only included 16 patients (and 16% of participants) with prostate cancer in a trial of 99 individuals with various metastatic malignancies (21). At a median follow-up duration of 25 months in the control group versus 26 months in the SBRT group, median overall survival was 28 months (95% confidence interval: 19-33) in controls versus 41 months (26-not reached) in those who received SBRT (hazard ratio 0.57, 95% confidence interval: 0.3-1.1,  $p=0.09$ ). There are several other clinical trials in this area, such as CORE (conventional care versus SBRT for extra-cranial oligometastases) (232) which is due to report in 2024, and PCS IX (management of castration-resistant prostate cancer with oligometastases) (233) which is due to report in 2025.

Several further trials are ongoing in this area, such as STORM (salvage treatment of oligorecurrent nodal prostate cancer metastases) (234), which is investigating the potential benefit of metastasis-directed therapy (salvage lymph node dissection or SBRT) versus metastasis-directed therapy plus whole pelvis radiotherapy in patients with oligorecurrent nodal prostate cancer following failed primary treatment, and is due to report in 2023. The ORIOLE (stereotactic body radiation for prostate oligometastases) study is evaluating safety and efficacy of SBRT in patients with oligometastatic hormone-sensitive prostate cancer, and this study is due primary completion in 2020 (235,236). Further research in the context of oligometastatic prostate cancer investigating multimodality treatment combining radiotherapy with novel local, biological or systemic treatments is necessary. Overall, the available evidence suggests that SBRT to treat prostate cancer using local or metastasis-

directed radiotherapy is safe and improves outcomes in metastatic disease. Thus, this approach is gaining in popularity among oncologists and is becoming standard-of-care around the world (237). However, the implementation of SBRT in a radiotherapy department poses a number of challenges, such as the availability of the necessary clinical expertise and appropriate hardware and software modifications to linear accelerators (238,239); thus access to this treatment is not currently widely available. However, these challenges could be overcome by encouraging radiation oncology centres to set up SBRT multidisciplinary groups including clinicians, radiographers and physicists. These groups could work collaboratively with other centres already well practised in SBRT in order to develop the skills necessary to deliver this therapy.

### **[H1]Harnessing the tumour microenvironment**

In the past, research to improve prostate cancer outcomes has focused on enhancing local radiotherapy-induced cancer cell death, rather than maximizing potential effects of irradiation on the tumour microenvironment. Increased understanding of the changes induced in the vascular, stromal and immunological tumour microenvironment by irradiation, along with mechanisms of radioresistance and tumour recurrence, might guide the development of new treatments for high-risk prostate cancer via combinations of radiotherapy with other therapies.

### **[H2]Radiotherapy sensitivity gene signatures**

As the concept of personalized therapy becomes increasingly popular, patients' genetic variations and transcriptomic and proteomic tumour data are becoming more readily available, providing increased opportunities for novel target discovery (279) and the use of genomic techniques to guide radiation decisions (240). Several radiotherapy sensitivity-associated gene signatures have been reported for prostate cancer (241,242), although further clinical validation, along with benefit from clinical utility, is awaited. Nevertheless, it is an exciting possibility that pre-treatment analysis of patient samples might enable accurate prediction of radiotherapy response, thereby contributing to decision-making regarding selection of radiotherapy versus alternative treatments such as surgery.

### **[H2]Targeting tumour vasculature**



The tumour vasculature is one component of the tumour microenvironment that has been extensively studied with respect to radiotherapy. Ionizing radiation induces changes such as endothelial cell dysfunction, increased permeability, detachment from the basement membrane, and apoptosis (243,244), as well as dose-dependent destruction of the tumour microvasculature (245). Radiation can also lead to irregular subsequent proliferation of endothelial cells leading to irregular branching and diameter of the microvasculature (245). Radiotherapy-induced vascular damage can potentiate tumour hypoxia and promote radioresistance, and reduced oxygen delivery following irradiation leads to a reduction in the production of reactive oxygen species, thereby reducing cancer cell death (246). Hypoxia induces stabilization of HIF-1 $\alpha$ , which can promote radioresistance via induction of pro-angiogenic factors such as VEGF-A and VEGFR1, which leads to abnormal tumour blood vessel formation and further hypoxia (247). Strategies to restore pre-irradiation tumour oxygenation, and thereby improve the response to radiotherapy, have been attempted by combining radiation with additional agents. Such approaches have included combination of radiotherapy with red blood cell transfusion, erythropoietin administration, hyperbaric oxygen treatment, and drug-mediated inhibition of HIF-1 $\alpha$  (247,248). Whilst numerous clinical trials have demonstrated that hypoxic radiation resistance can be overcome, hypoxic modification has had no impact on clinical practice as none of these adjuncts have yet been incorporated into standard-of-care prostate cancer radiotherapy treatment, for reasons that are not entirely clear (248). Activation of HIF-1 $\alpha$  is associated with a variety of malignancies and oncogenic pathways (247,249). Thus, HIF-1 $\alpha$  is a key target for anti-cancer therapy, using molecular antagonists, gene therapy strategies, or blockade of HIF-1 $\alpha$ -interacting proteins. Pre-clinical and clinical trial results combining various agents and techniques (such as increased oxygen delivery using hyperbaric oxygen or erythropoietin or red blood cell transfusion, or drug-mediated targeting of hypoxic cells, or use of vascular targeting agents) with radiotherapy demonstrate that hypoxic radioresistance can indeed be overcome (248), however the heterogeneity of the tumour microenvironment and/or variation in the potential to increase the radiotherapy response from tumour to tumour may limit the practical utility of hypoxia reduction (50,248). Further research is necessary in this area in order to establish hypoxia reduction as a standard adjunct to radiotherapy treatment for prostate cancer.

### [H3]Vessel normalization

The tumour microvasculature is characterized by vessel immaturity (250). An approach known as “tumour vessel normalization” has been shown to increase the anti-tumour efficacy of radiotherapy, as well as other treatments such as chemotherapies and immunotherapies. Strategies to normalize tumour vasculature tip the balance between pro-angiogenic and anti-angiogenic signalling, inducing a more structurally and functionally normal vasculature (249). Improved structure and function of the vasculature increases tumour oxygenation (50,251) which may synergize with radiotherapy by reducing radioresistance. Vessel normalization can be achieved using vascular-targeted therapies (250,252–254). Anti-angiogenic agents such as VEGFR2 inhibitors in orthotopic human glioblastoma xenografts in murine brain, or angiostatin in a murine model of Lewis lung carcinoma, have been combined with radiotherapy in these pre-clinical studies along with *in vitro* cell line studies, and these have shown promise in terms of enhanced tumour control, oxygenation, and vascular normalization (255–258). However, the use of anti-angiogenic agents alongside radiotherapy is not currently a standard treatment option as the efficacy of this combination is variable, and how best to combine these therapeutic modalities to achieve maximum response and minimal toxic effects in patients remains unclear (259).

### [H2]Modulation of immune recognition

Prostate cancer can evolve to evade immune recognition (260,261), which is a hallmark of cancer (262). Combining immunomodulation and radiotherapy might overcome suppression of the adaptive immune response induced by cancer cells and the tumour microenvironment (50,263,264). A multimodality treatment approach including radiotherapy might cause abscopal effects and systemic anti-tumour activity (265). Irradiation can trigger immunostimulatory responses (**figure 2**), which can promote immunogenic cell death, for example through the emission of signals from dying neoplastic cells that elicit tumour-specific cytotoxic T-cell responses (45,266,267). Moreover, these signals released from dying cancer cells following their exposure to ionizing radiation can stimulate antigen-presenting cells to cross-prime antigen-specific adaptive immune responses (45,266,267). However, tumours can develop mechanisms to counter effective T-cell responses capable of inducing immunogenic cell death; such mechanisms include tumour-mediated promotion of immunosuppression, generation of central and peripheral tolerance mechanisms that restrict

tumour-specific T-cell responses, and induction of anergy or exhaustion in previously activated T-cells (268–270). Developing therapies to overcome these obstacles and harness a post-radiotherapy anti-tumour immune response is an exciting area of research. Such approaches might include combining radiotherapy with immune checkpoint inhibitors, molecular inhibitors of the influx of immunosuppressive cells such as macrophages and myeloid-derived suppressor cells into the irradiated tumour microenvironment, and/or combination with anti-tumour vaccines (269,270). Many of these combinations are being tested in pre-clinical models, and it is likely that some of these multimodality therapy options could be taken forward to early phase clinical trials in prostate cancer patients in the next 5 years.

## [H2]The value of pre-clinical models

Radiotherapy treatment for high-risk and metastatic prostate cancer aims to tip the balance of the tumour microenvironment response towards anti-cancer effects. Research using clinically relevant pre-clinical models of the tumour microenvironment is necessary to elucidate the optimal radiotherapy dose and delivery, and timing and sequence of multi-modality therapies, for immune priming. Many of these pre-clinical models include immunocompetent mouse models of prostate cancer. To date the available evidence from pre-clinical models suggests that the optimal timing of delivery of the adjunct treatment with radiotherapy is specific to the tumour type and immunotherapy used (153,271,272). As an example of this principle, experiments in a murine breast cancer tumour model treated with 20 Gray radiation delivered with either anti-CTLA4 antibody or anti-OX40 agonist antibody highlighted the fact that the optimal timing of these therapies varied. Anti-CTLA4 was most effective when given prior to radiation therapy due to regulatory T-cell depletion, whereas anti-OX40 agonist antibody was optimal when delivered one day post-irradiation during a window of increased antigen presentation (271). Furthermore, pre-clinical evidence suggests that the dose and fractionation of radiotherapy is important to harness the benefit of these treatment combinations (273–275). For example, a single 15 Gray fraction was more effective than 3x5 Gray in terms of generating anti-tumour immune responses in mice with melanoma tumours (274), whereas in a mouse model of breast cancer an enhanced anti-tumour effect at the primary tumour site, or an abscopal effect, was only seen when and anti-CTLA-4 antibody was combined with fractionated radiotherapy (3x8 Gray or 5x6 Gray), and not when combined with a single 20 Gray

fraction (273). Future research is required focussing on how the tumour microenvironment can be modulated by clinically relevant radiotherapy doses and fractionation schedules to augment anti-tumour activity.

## **[H1]Future directions**

Improved radiotherapy delivery has increased the efficacy of this treatment modality for prostate cancer. Outcomes of therapy using conventional fractionation plateau once patients are treated with >78 Gray (276), and so the strategy has now moved towards delivery of hypofractionated radiotherapy (277). SBRT to the prostate gland in the localized disease setting is the culmination of hypofractionation, and single-fraction doses of SBRT to the prostate gland are now being investigated (278). Single fraction doses of irradiation to the prostate have been attempted in the past using high dose-rate brachytherapy, which was associated with high biochemical control rates, particularly in patients with low-risk and intermediate-risk prostate cancer, and low complication rates (279–281). The outcomes using SBRT are unlikely to be substantially different from those observed using brachytherapy, but we must await the data from this single-fraction SBRT study (expected primary completion date late-2020) before conclusions can be drawn.

Strategies to target dysregulated cancer molecular pathways might increase the anti-tumour effects of radiotherapy and reduce toxic effects by specifically targeting malignant cells with relative sparing of normal cells (128). Such strategies are currently a focus of research.

## **[H1]Conclusions**

Technical advances in the delivery of radiotherapy to treat prostate cancer have led to improved outcomes, but radiation does not provide a cure in all patients, and it could be further refined in order to reduce treatment-related toxic effects. Such advances could potentially be achieved by multimodality therapy approaches combining radiotherapy with other treatment agents, which have the potential to further improve outcomes of radiotherapy in both the localized and locally advanced prostate cancer disease settings. Moreover, a large clinical trial (17) has reported that local

radiotherapy treatment of the primary tumour combined with existing standard-of-care treatment in patients with low-burden oligometastatic prostate cancer improves disease-specific survival. These advances and new opportunities suggest that incorporating radiotherapy within a true multimodality approach to treat clinically significant prostate cancer could improve outcomes for patients in the future.

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## **Glossary:**

### **Abscopal effect**

A systemic anti-tumour immune response induced by local irradiation, with regression of non-irradiated metastatic lesions at a distance from the primary site of irradiation.

### **Biochemical recurrence following surgery**

Defined as a confirmed post-operative PSA value  $\geq 0.2$  ng/mL and rising, without evidence of distant metastases (8,90,282,283).

### **Bragg peak**

The peak on the Bragg curve, which plots the energy loss of ionizing radiation (protons,  $\alpha$ -rays, and other ion rays) as they travel through matter. The peak occurs immediately before the particles come to rest.

### **Brachytherapy**

Internalized radiotherapy using implanted iodine-125, palladium-103 or caesium-131 radioisotope seeds

### **Calreticulin**

An endoplasmic reticulum-associated chaperone protein, which is exposed in the outer leaflet of the plasma membrane of stressed or dying cells, where it functions as a potent “eat-me” (i.e. phagocytosis) signal.

### **CTLA-4**

Cytotoxic T-lymphocyte associated protein 4, a protein receptor that functions as an immune checkpoint and down-regulates immune responses.

### **External beam radiotherapy**

External delivery of irradiation using several types of energy (for example photons, electrons, or heavy particles).

### **FAK**

Focal adhesion kinase, a protein involved in cell-cell adhesion and migration, and which can promote malignant cellular invasion and metastasis.

### **HIF-1 $\alpha$**

Hypoxia-inducible factor 1-alpha, a subunit of the hetero-dimeric hypoxia-inducible factor 1 (HIF-1) transcription factor encoded by the *HIF1A* gene.

### **HSP90**

Heat shock protein 90, a chaperone protein that promotes protein folding and stabilization against heat stress, thereby potentially promoting tumour growth.

### **HMGB1**

High mobility group box 1 protein, encoded by the *HMGB1* gene, which functions to organize DNA and regulate transcription.

### **Immunogenic cell death**

Immune-mediated cell killing secondary to radiation-induced generation of mutated tumour antigens, which subsequently stimulate the immune system

### **Immunomodulation**

Regulation of the immune system, whereby the immune responses are induced, amplified, reduced, or prevented according to the therapeutic goal.

### **Mitotic catastrophe**

A mechanism of delayed mitosis-linked cell death. It describes a sequence of events resulting from premature or inappropriate entry of cells into mitosis, caused by chemical or physical stresses.

### **Oligometastatic prostate cancer**

Prostate cancer with relatively few (up to 3–5) small-volume distant disease foci.

### **PD-1**

Programmed cell death protein 1, a cell surface protein that down-regulates the immune system's response by suppressing T cell inflammatory activity.

### **PD-L1**

Programmed death-ligand 1, a trans-membrane protein that suppresses the adaptive immune system.

### **5Rs of radiation biology**

Repair, reassortment, repopulation, reoxygenation and radiosensitivity. Each of these terms describes a cellular mechanism by which to understand the success or failure of localized radiotherapy.

### **Salvage radiotherapy**



Delivery of radiotherapy with curative intent to patients with biochemical recurrence (defined as a postoperative serum PSA  $\geq 0.2$  ng/mL, without evidence of distant metastases)

### **Stereotactic body radiotherapy**

Delivery of external beam radiotherapy for treatment of prostate cancer, with target localization using image guidance and 5-7 fractions of 6-10 Gray per fraction to the prostate gland.

### **Therapeutic ratio**

Index between the cytotoxic effects of radiotherapy and complications in normal tissues, per unit dose of ionizing radiation.

### **Tumour-associated antigen**

An antigenic peptide produced in tumour cells, which can trigger an immune response. It could potentially be used as a tumour marker and/or a therapeutic target.

### **Tumour vessel normalisation**

A spectrum of biological changes to the tumour vasculature including increased pericyte coverage, improved perfusion, reduced vascular permeability, and reduced hypoxia.

### **VEGF-A**

Vascular endothelial growth factor A is a peptide encoded by the *VEGFA* gene and which acts on endothelial cells to increase vascular permeability, and induce angiogenesis, vasculogenesis and endothelial cell growth, and promote cellular migration and inhibit apoptosis.

### **VEGFR1/2**

Vascular endothelial growth factor receptor 1 or 2, which are proteins with tyrosine protein kinase activity that regulate cellular proliferation and differentiation.

**Box 1** | EAU risk groups for biochemical recurrence of localized and locally advanced prostate cancer.

<b>Low-risk localized:</b>	PSA < 10ng/mL, Gleason grade group 1, and cT1–2a
<b>Intermediate-risk localized:</b>	PSA 10-20ng/mL or Gleason grade group 1–3 or cT2b
<b>High-risk, localized:</b>	PSA > 20ng/mL or Gleason grade group >3 or cT2c
<b>High-risk, locally advanced:</b>	Any PSA, any Gleason grade group, cT3–T4 or N+ disease

**Table 1 |** Clinical trials of combined immunotherapy and radiotherapy for prostate cancer.

Study	Design	<i>n</i>	Treatment	Measurements	Outcomes
Serial assessment of lymphocytes and apoptosis in the prostate during coordinated intra-prostatic dendritic cell injection and radiotherapy (165).	Non-randomized, open label pilot study in 5 men with high-risk localized prostate cancer	5	28 months of ADT + 45 Gray EBRT in 25 fractions over 5 weeks + DC injections after fractions 5, 15 and 25	Interval biopsies and blood tests to assess immune reaction	Some response seen to suggest priming of CD8+ T-cells to test peptides
Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multi-center phase I/II study (168).	Non-randomized, open-label phase I/II trial in men with mCRPC with disease progression after discontinuation of ADT who had received $\leq 1$ previous course of chemotherapy	50	Comparison of ipilimumab 10mg/kg monotherapy ( $n=16$ ) or ipilimumab in combination with ERBT ( $n=24$ ).	PSA decline and tumour response	8 patients had PSA declines of >50%; 1 patient had a complete PSA response 6 patients had stable disease
Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial (169).	Multi-centre, randomized double blind phase III trial in men with mCRPC who had progressed after docetaxel	799	Patients were randomized to receive bone-directed radiotherapy (8 Gray in 1 fraction) followed by either ipilimumab 10mg/kg or placebo every 3 weeks for up to 4 doses	OS	Median 11.2 months with ipilimumab and 10.0 months with placebo (HR 0.85; 95% CI 0.72-1.00; $p=0.053$ )

Combination of Nivolumab immunotherapy with radiation therapy and androgen deprivation therapy, NCT03543189 (in progress) (174).	Open-label, single group assignment	34	Post ADT, participants will receive nivolumab, high dose rate brachytherapy and external beam radiation therapy, followed by a 2 year follow-up period	Safety, and relapse-free survival rate	Trial in progress, estimated completion 2021
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Abbreviations: ADT – androgen deprivation therapy; CI – confidence interval; DC – dendritic cell; EBRT – external beam radiotherapy; HR – hazard ratio; IFN- $\gamma$  – interferon gamma; mCRPC – metastatic castrate-resistant prostate cancer; OS – overall survival; PSA – prostate specific antigen; RT - radiotherapy

### **Figure legends:**

**Figure 1 | Direct and indirect effects of ionizing radiation on DNA.** Ionizing radiation causes direct effects on DNA by inducing ionization of cellular molecules, which damage DNA by causing single or double strand breaks. Indirect damage to DNA can be caused via the production of free radicals derived from the ionization or excitation of the intracellular water component. These DNA damage effects can result in cellular senescence or cell death via apoptosis, mitotic catastrophe, autophagy, necrosis, or immunogenic cell death mechanisms. In addition to DNA damage in tumour cells, radiotherapy also has multiple effects on the wider tumour microenvironment, including the induction of inflammation, increased cytokine signalling endothelial cell damage in blood vessels, hypoxia and stromal remodelling.

**Figure 2 | Immunogenic cell death and immunogenic modulation of tumour cells by radiotherapy.**

Radiotherapy induces several cellular events that may activate the immune system, including expression of tumour-associated antigens (TAAs), increased expression of MHC Class I molecules, increased expression of co-stimulatory molecules and reduced expression of immunosuppressive molecules, and increased expression of death receptors, adhesion molecules, stress ligands and cytokines and chemokines. In the presence of radiation- induced endogenous danger signals (DAMPs), dendritic cells that have taken up potential TAAs become activated and mature. Upon reaching lymphoid tissue, these mature activated dendritic cells migrate and cross-present TAAs to T-cells, resulting in cross-priming of an effector anti-tumour immune response capable of immunogenic cell death. Radiotherapy causes double strand DNA breaks resulting in a signalling cascade that ultimately upregulates NF- $\kappa$ B. Expression of NF- $\kappa$ B target genes in tumour cells is an important mechanism by which radiotherapy causes immunogenic modulation of tumour cells.

**Figure 3 | Molecularly targeted agents as potential radiosensitizers.** 1. Regulation of cell death pathways by heat shock proteins (HSP90) following irradiation-induced cellular stress. HSP90 inhibits caspase-dependent apoptotic cell death providing protection from apoptosis-inducing treatments such as radiotherapy. 2. DNA damage response (DDR) pathways. Agents acting in different repair processes, including base excision repair (BER), single strand break (SSB), non-homologous end-

joining (NHEJ), and homologous recombination (HR) are important targets for radiosensitization. 3. Proliferation of prostate cancer cells is under the control of the PI3K–AKT–mTOR signalling pathway. As major growth factor receptors (such as EGFR and VEGFR) require this downstream kinase pathway, this is a promising target for radiosensitization.

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