Title: Prostate radiotherapy in newly diagnosed metastatic prostate cancer

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Abstract (200 words)

Purpose of review: To review the role of prostate radiotherapy in the multimodal management of newly diagnosed metastatic hormone naïve prostate cancer.

Recent findings: Two randomized controlled trials have evaluated the role of prostate radiotherapy with systemic therapy (ADT +/- Docetaxel) in newly diagnosed metastatic hormone sensitive prostate cancer. In a combined cohort of over 2000 patients, prostate radiotherapy with systemic therapy improved survival over systemic therapy alone in patients with low metastatic burden but not in high burden patients. Prostate radiotherapy with systemic therapy is now a recommended first line option for newly diagnosed men with low metastatic burden prostate cancer. The current recommended definition for low metastatic burden is based on conventional imaging (^{99m}Tc bone scans and CT/MRI). Cross-correlative studies are required to pick an appropriate threshold for sensitive imaging modalities such as PSMA PET or whole body MRI. Ongoing trials are evaluating prostate RT in this setting combined with Abiraterone/Docetaxel and metastasis directed therapy.

Summary: Prostate radiotherapy with systemic therapy improves survival in patients with newly diagnosed, low metastatic burden prostate cancer and is a recommended first line treatment option. Ongoing trials are evaluating combination with metastasis directed therapy and other systemic treatments.

Keywords: de-novo, hormone naïve, newly diagnosed, metastatic, prostate cancer, radiotherapy

Key points:

(3-5 key points/sentences that summarize your article)

- Two phase III randomized controlled trials, the HORRAD and the STAMPEDE trial's "M1|RT comparison" have now reported on the role of prostate radiotherapy with systemic therapy (ADT +/-Docetaxel) in mHNPC.
- Successful treatment outcome is predicated on metastatic burden based on conventional imaging (^{99m}Tc bone scans and CT/MRI).
- Prostate RT with systemic therapy improves overall and failure-free survival in patients with low metastatic burden but not in patients with high metastatic burden.
- Prostate RT with systemic therapy is now recommended as a first line option for newly diagnosed men with a low metastatic burden prostate cancer.
- Ongoing trials are evaluating the combination of prostate RT with ADT (+/-Docetaxel/Abiraterone) and metastasis directed therapy.

1 Introduction

In newly diagnosed high risk localized prostate cancer, a multimodal approach is recommended whereby prostate radiotherapy (RT) with androgen deprivation therapy (ADT) results in improved survival compared to RT or ADT alone (1-3). However, in the absence of evidence for benefit in metastatic prostate cancer, an international *modus operandi* was adopted wherein prostate RT was not recommended and systemic treatments alone were standard of care. Nevertheless, based on preclinical data and theories of an intermediate metastatic stage, the role of prostate RT in metastatic prostate cancer has now been evaluated in two phase III trials. In a combined cohort of over 2000 patients, the HORRAD and the STAMPEDE "M1|RT comparison" trials have evaluated the therapeutic advantage associated with adopting a multi modal approach in men with newly diagnosed metastatic hormone naïve prostate cancer (mHNPC) (4, 5). In this review, we summarize the data from these trials to guide and expand the use of multimodal treatment in metastatic prostate cancer.

2 Evidence from randomized controlled trials

The HORRAD and the STAMPEDE "M1|RT comparison" trials have evaluated the role of prostate RT in de novo mHNPC **(Table 1)**. HORRAD enrolled men with newly diagnosed mHNPC with bone metastasis on bone scintigraphy between 2004 and 2014. Overall, 432 patients were randomized in a 1:1 ratio to receive prostate RT + ADT or ADT alone (5). At a median follow-up of 47 months, there was no evidence of improvement in overall survival (OS) associated with the radiotherapy intervention (hazard ratio [HR] = 0.90, 95% confidence interval [CI] 0.70 – 1.14). However, in a subgroup of 160 patients with < 5 bone metastases, prostate RT + ADT showed some evidence of OS benefit over ADT alone (HR=0.68, 95% CI 0.42 – 1.10), although statistical significance was not reached. A similar trend was not seen in patients with ≥5 bone metastases (HR=1.06, 95% CI 0.80 – 1.39). However, both subgroups were inadequately powered to reach definitive conclusions. Furthermore, the presence of concomitant non-regional lymph node or visceral metastasis was not known, therefore a contemporary metastatic burden definition could not be considered.

The STAMPEDE trial's M1|RT comparison (Arm H) also assessed the role of prostate RT with ADT (+/- docetaxel) in newly diagnosed mHNPC (4). Between, 2013 and 2016, 2061 patients underwent stratified 1:1 randomization to receive ADT (+/- Docetaxel) or prostate RT + ADT (+/- Docetaxel). At a median follow-up of 37 months, prostate RT improved failure-free survival (HR=0.76, 95% CI 0.68 – 0.84; p-value<0.001) but not OS (HR= 0.92, 95% CI 0.80–1.06; p-value=0.266). However, in a pre-specified, directionally hypothesised, subgroup analysis by metastatic burden based on the CHAARTED definition (6), a significant heterogeneity was noted between the low and high burden subgroups for OS (interaction p-value = 0.0098) and FFS (interaction p-value = 0.002). As hypothesized in the M1|RT comparison's pre-specified statistical analysis plan, OS (HR=0.68, 95% CI 0.52–0.90; p-value=0.007) and FFS (HR=0.59, 95% CI 0.49–0.72; p-value<0.0001) were significantly improved in the low metastatic burden subgroup (n=819) with prostate RT + ADT (+/-Docetaxel) over ADT (+/-Docetaxel) alone. No such benefit was noted in the high metastatic burden subgroup (n=1120) for OS (HR=1.07, 95% CI 0.90– 1.28; p-value=0.420) or FFS (HR=0.88, 95% CI 0.77–1.01; p-value=0.059). An interaction was also noted for prostate cancer specific survival (interaction p-value=0·007) with a statistically significant benefit associated with prostate RT + ADT (+/-Docetaxel) in the low metastatic burden subgroup (HR=0.65, 95% CI 0.47–0.90) but not in the high volume subgroup (HR=1.10, 95% CI 0.92–1.32). Based on the results of these trials, the 2019 NCCN, EAU and ESMO guidelines recommend prostate RT + ADT as a first line option for newly diagnosed patients with low metastatic burden disease (2, 3, 7).

2.1 Prostate radiotherapy schedules

In both trials, the clinical target volume incorporated the prostate gland alone (+/- seminal vesicles if involved). Pelvic lymph nodes were not included in target volumes. In the HORRAD trial, treatment arm patients received a conventionally fractionated dose of 70 Gy in 2 Gy fractions over 7 weeks. During the study, a schedule of 57.76 Gy in 19 fractions of 3.04 Gy, three times a week for 6 weeks was also added, but outcomes by RT schedule was not evaluated. In the STAMPEDE trial's M1|RT

comparison, the treatment arm patients were nominated for one of two schedules. A weekly schedule of 36 Gy in 6 consecutive weekly fractions of 6 Gy was designated for 48% (n=497) and a daily schedule of 55 Gy in 20 daily fractions of 2.75 Gy over 4 weeks was chosen for 52% (n=535) of the patients. No heterogeneity of effect on OS was noted between the weekly and daily schedules (interaction p-value=0.27).

The RT schedules used in these trials differ from the ones currently used in localized prostate cancer. In 2012, when the STAMPEDE M1|RT comparison was designed, the standard RT schedule (74 Gy in 37 fractions over 7.5 weeks) used at the time for localized disease was felt to be too burdensome for patients with metastatic disease. Based on an investigator survey, the two more convenient schedules were chosen. Now, with evidence of benefit from prostate RT in low metastatic burden patients, the contemporary hypofractionation schedule of 60 Gy in 20 fractions, as used for high risk localised prostate cancer, might be preferred (8). Further studies will be required to explore the role of dose escalation and optimisation.

2.2 Safety and adverse events

There have been concerns that hypo-fractionation may increase the risk of late treatment-related toxicity (9, 10). In the STAMPEDE trial, grade 3 or 4 adverse events on the RTOG scale were modest in the prostate RT arm (5 %); 5% patients reported their worst acute bladder toxic effect as grade 3 or 4, and 1% reported their worst acute bowel toxic effect as grade 3 or 4; grade 5 toxic effects were not observed. Furthermore, a low incidence of grade 3 and 4 late effects was reported by patients in both control and prostate RT arms (1% control vs 4% prostate RT). No difference was seen in CTCAE grade 3 or worse in between the control group (38%) and the prostate RT group (39%); with no evidence of a difference in time to first grade 3 or worse event (HR=1.01, 95% CI 0.87–1.16; p-value=0.941). Adverse events and toxicity outcomes were not reported in the HORRAD trial.

The M1|RT comparison also evaluated symptomatic local events (SLE). This was defined as a composite endpoint evaluating urinary tract infection, new urinary catheterisation, acute kidney injury, transurethral resection of the prostate, urinary tract obstruction, ureteric stent, nephrostomy, colostomy or surgery for bowel obstruction. There was no difference in the frequency of SLE between the control and prostate RT arms and no evidence of a difference in time to first SLE by treatment allocation (HR=1.07, 95% CI 0.93–1.22; p-value=0.349). However, at current follow up it is too early to rule out a beneficial effect of prostate RT for preventing SLE as these tend to occur late during disease progression (4, 11).

2.3 Sequencing of systemic therapies with prostate RT

In both the trials, patients started lifelong ADT prior to RT. In the HORRAD trial, patients were started on ADT within 2 weeks of randomization and received RT within 12 weeks of starting ADT. This trial enrolled between 2004 - 2014, well before the introduction of therapies such as Abiraterone, Enzalutamide and Radium-223. A breakdown of subsequent life prolonging treatments received in the trial's deceased population showed no significant difference between the arms. In the prostate RT arm, the majority of patients received Docetaxel (46%), while other life-prolonging therapies such as Abiraterone (18%), Cabazitaxel (9%), Enzalutamide (8%) and Radium-223 (3%) were used less frequently.

In the STAMPEDE Arm H, patients started ADT within 12 weeks of randomization and commenced RT as soon as possible thereafter. Docetaxel was also permitted following its approval in the UK in December 2015: 18% of the patients received ADT + Docetaxel in both arms. It was administered as six 3 weekly cycles of 75 mg/m², with or without prednisolone 10 mg daily. In the prostate RT arm, patients received Docetaxel first followed by prostate RT within 4 weeks of the last Docetaxel cycle. No significant heterogeneity in outcomes was noted based on Docetaxel use (interaction p-value =0.63). Furthermore, there was no difference in the use of subsequent life prolonging therapies between the two arms. In the prostate RT arm, the majority of the patients received Docetaxel

(33%), Enzalutamide (36%) or Abiraterone (20%) at progression. Optimal sequencing of systemic therapies after failure of first line therapy remains an ongoing area of research.

Currently, an incongruity exists between the NCCN, EAU and ESMO guidelines regarding the use of early docetaxel with prostate RT. The NCCN and EAU recommend prostate RT + ADT as a first line option, while ESMO has made no such distinction, recommending prostate RT + systemic therapy (ADT + Docetaxel) (2, 3, 7). In the STAMPEDE M1|RT comparison, 18% of the patients received prostate RT + ADT + docetaxel and no evidence of heterogeneity was found based on docetaxel use (4). However, patients receiving docetaxel were enrolled at a later stage of the trial (post Dec-2015) and therefore had a shorter follow-up. Emerging data from phase 3 trials evaluating prostate RT + ADT + docetaxel in high risk localized prostate cancer suggests that the triple combination improves relapse free survival, but the results for overall survival are immature (12-15). The GETUG-12 and the STAMPEDE trials have demonstrated statistically significantly improved relapse free survival but no improvement in overall survival. By contrast, the RTOG-05201 trial has reported that prostate RT + ADT + Docetaxel improved both overall (HR=0.69, 90% CI 0.49 - 0.97) and disease free survival (HR= 0.76, 95% CI 0.58 - 0.99) over prostate RT + ADT alone (13). Therefore, a combination of prostate RT with ADT and early Docetaxel can be the preferred first line option in low metastatic burden if patients are fit enough for it.

3 Role of imaging in defining metastatic burden

Based on the results from the M1|RT comparison of STAMPEDE Arm H, the recommended criteria to select newly diagnosed low metastatic burden mHNPC patients for prostate RT is based on ^{99m}Tc bone scan and CT/MRI (2, 3, 7). The pre-specified metastatic burden subgroup analysis in the STAMPEDE trial used a previously described criteria (CHAARTED) to classify patients (4, 6). Based on the CHAARTED criteria, patients with any visceral metastasis or ≥4 bone metastasis with ≥1 outside the vertebral column/pelvis were considered as high burden with all other patients classified as low burden (6). A criticism of this criterion is that a patient could have ≥ 4 bone metastases within the

pelvis/spine and still be classified as low burden. Additionally, this definition is based on prognostic factors from the systemic therapy era (6, 16). To guide it's use as a predictor of benefit from prostate RT, an exploratory analysis of the STAMPEDE trial M1|RT comparison based on based on metastatic site, location and number has refined this criterion (ESMO 2019 abstract number 1199).

The imaging modality used to evaluate M stage in both HORRAD and STAMPEDE was standard CT/MRI and ^{99m}Tc Bone scan. The STAMPEDE results show that the bone metastasis number on bone scan was *predictive* of treatment outcome regarding RT to the prostate using CHAARTED based criteria. This raises the question of which imaging modality should be used for staging in the modern era. Use of other imaging modalities, such as ^{68}Ga-PSMA PET or whole body MRI, to evaluate metastatic burden has become widespread in some countries but it has not been validated in large scale randomised studies and it is not currently recommended outside a clinical trial (2, 17, 18). As these modalities have a higher sensitivity, they are likely to detect more metastases than those detected by conventional imaging (19-21). Therefore, the threshold for low metastatic burden might differ substantially depending on the imaging modality used. Further study of the clinical utility of modern imaging and its influence on the natural history of disease and treatment outcome will require validation in properly conducted studies if this uncertainty is to be overcome. Additionally, future trials could and should evaluate quantitative measures of metastatic burden. Methods currently available include the automated bone scan index or maximum standardized uptake values (SUV_{max}) as predictive biomarkers to select patients for multi-modal treatment. These are currently under-utilised despite their proven utility (22-24). In future, the metastatic burden criteria are likely to require further optimization as our understanding of disease burden and metastatic distribution in relation to treatment benefit improves.

4 Biological rationale for impact of metastatic burden on efficacy of prostate RT

This section discusses plausible biological rationale by which metastatic progression could be reduced by using multimodal strategies in patients with low metastatic burden (25-27).

4.1 Disruption of metastatic dissemination

The metastatic cascade involves a number of steps, wherein cancer cells within the prostate acquire characteristics enabling invasion and migration to distant sites through haematogenous or lymphatic routes (26-28). In the metastatic process, cancer cells within the primary and the metastatic sites undergo spatio-temporal evolution dictated by the tumour microenvironment and systemic treatment pressures. A number of studies have used whole genome or exome sequencing to infer metastatic phylogeny in prostate cancer (29-33). Although all clones can be traced to the primary, complex modes of progression have been demonstrated in advanced disease with primary to metastasis, metastasis to metastasis and metastasis to primary all being possible (29, 30). Furthermore, metastatic dissemination can occur in temporally separated waves during disease progression (30). In patients with low metastatic burden, the prostate could be the predominant source of metastatic clones, whereas in high burden, metastasis to metastasis progression may be the dominant mode of spread. In this circumstance, treating the primary would have a limited effect on metastatic progression. Therefore, treatment of the primary in mHNPC could disrupt metastatic progression in low burden patients but not in high burden patients. This hypothesis is supported by the observed heterogeneity in metastasis progression free survival in the STAMPEDE trial. In the low burden subgroup, metastatic progression was delayed in patients treated with prostate RT + systemic therapy compared to systemic therapy alone (HR=0.80, 95%CI 0.63 – 1.01; restricted means survival time [RMST] difference=3.1 months, 95%CI 0.2 – 6 months). No such effect was observed in the high burden subgroup (HR=1.10, 95%CI 0.95 – 1.28). Similar heterogeneity in progression free survival between low and high metastatic burden subgroups was also observed in the HORRAD trial (34).

4.2 Primary derived molecular components

A number of other primary derived components such as exosomes, cytokines and other molecules have been shown to have a tropic action “preparing” distant metastatic niches (35-38). It may be

hypothesised that prostate RT disrupts release of primary derived molecular components which have been shown to work in this way. In low metastatic burden patients it is possible that the predominant source of such cytokines may be the prostate, while in high metastatic burden patients, distant metastases may become the major source as disease load increases beyond a biological threshold. In such circumstances, treating the primary might lower the circulating levels of such molecules significantly in low burden patients but not in high burden. This notion can be further interrogated using FFS, which was largely driven by PSA failure. In the low metastatic burden subgroup, a statistically significant improvement in FFS was noted (HR=0.59, 95% CI 0.49–0.72; RMST difference = 8.6 months). This suggests that the major source of PSA was the primary tumour. However, in the high metastatic burden subgroup, no significant difference was noted (HR=0.88, 95% CI 0.77–1.01; RMST difference = 1.5 months), suggesting that the main source of PSA was the metastatic sites and not the primary tumour. Similar heterogeneity in FFS between low and high metastatic burden subgroups was also seen in the HORRAD trial (34). PSA through its serine protease activity been shown to promote cell invasion and induce an osteoblastic phenotype in-vitro and in-vivo (39-41). It might therefore be speculated that reducing absolute PSA levels might limit the development of new bone metastases.

4.3 Immune mediated mechanisms

Radiotherapy induces cell death and secondary release of pro-inflammatory cytokines, tumour associated antigens (TAA), damage associated molecular patterns (DAMP) and other chemokines (42, 43). RT also upregulates MHC-I on cancer cells, leading to the recognition of TAAs by cytotoxic T cells, enabling them to mount an anti-tumour response (44, 45). Therefore, prostate RT can potentially initiate a systemic, or “abscopal” immune response, resulting in anti-tumorigenic responses in distant metastases. Whilst this is possible, there might also be a threshold beyond which the immune system is unable to cope with a high burden of disease. This might explain the “threshold effect” seen with metastasis number on bone scan and response to primary radiotherapy (4).

Future trials evaluating prostate RT with checkpoint blockade may demonstrate augmented immune mediated anti-tumour effects (46). Again, this might be "burden" related: a phase III trial in metastatic castration resistant prostate cancer (mCRPC) evaluating metastasis directed RT (8 Gy for at least one or up to five bone fields) followed by Ipilimumab suggested that the combination was only beneficial in a subgroup of patients with lower disease burden (HR=0.74, 95% CI 0.61–0.89) (47, 48). Another phase III trial evaluating Ipilimumab monotherapy without RT did not demonstrate any such effect (49). This suggests that RT might be required to unmask the beneficial effect of immunotherapy. Two additional case reports of mCRPC patients from these trials reported long term complete remission of disease in patients who received combined RT and Ipilimumab (50). However, identification of specific patients of this type remains investigational. Currently, a phase II study is evaluating ADT in combination with SBRT and Pembrolizumab with or without a TLR9 agonist in newly diagnosed oligometastatic HNPC (NCT03007732) (51).

4.4 Prevention of systemic treatment induced lineage plasticity in the primary

A number of genomic studies based on prostatectomy specimens have demonstrated multi-focality and intra-tumour heterogeneity in prostate cancer (52-55). This heterogeneity provides an environment where specifically directed systemic therapies such as ADT/Docetaxel/Abiraterone can act to invoke a "lineage crisis", wherein cancer cells undergo trans-differentiation or de-differentiation to a lethal phenotype which then develops as the dominant and progressive cell-type (56). Prostate RT could prevent such crisis from occurring in the primary, thereby preventing spatio-temporally separated waves of lethal clones emerging from the primary to propagate new metastatic sites.

4.5 Genomic and transcriptomic differences based on metastatic burden

A recent study conducted single cell transcriptomic profiling of metastatic cells obtained from low and high metastatic burden breast cancer xenografts has shown that metastatic cells from low burden tissues were different from those arising from high burden tissues and that they had increased

expression of stem cell, epithelial-to-mesenchymal transition, pro-survival, and dormancy-associated genes (57). On the other hand, high metastatic burden was found to be associated with increased proliferation and MYC expression. Further in-vivo evaluation showed that progression to high burden could be attenuated by treatment with dinaciclib, a cyclin-dependent kinase (CDK) inhibitor. These findings support a hierarchical model for metastasis, in which burden directed systemic treatment could delay progression. Currently, genomic analysis of primary prostate cancer samples allied to systemic genomic sampling, linked to accurate and quantified image analysis is ongoing within the STAMPEDE trial. It is hoped that this will also inform whether the metastatic burden criteria can be better understood with the use of genomic markers (58).

5 Future directions

Ongoing phase III trials are evaluating prostate RT linked to additional systemic treatments (Docetaxel/Abiraterone) and/or metastasis-directed therapy in newly diagnosed mHNPC **(Table 2).** The PEACE-1 trial (NCT01957436) has completed its enrolment and the primary analysis is expected to be conducted in 2019 (59). It has randomized de novo mHNPC patients in a 1:1:1:1 ratio to arm A (ADT + Docetaxel), arm B (ADT + Docetaxel + Abiraterone), arm C (ADT + docetaxel + prostate RT) or arm D (ADT + Docetaxel + Abiraterone + prostate RT). This trial will provide new data regarding the benefit of adding Abiraterone+/-Docetaxel to prostate RT + ADT. Another trial, the SWOG 1802 (NCT03678025) is evaluating the efficacy of local treatment in de-novo mHNPC (60). It is a two stage trial; in the first step, patients who are eligible to undergo radical prostatectomy (RP) are registered to receive best systemic therapy (BST) for at least 28 weeks. In the second step, patients who do not progress on BST for at least 28 weeks undergo a stratified randomization in a 1:1 ratio to BST or BST + RP/RT. Data from the phase 2 suggests that this approach enriches patients with low metastatic burden (78% low burden)(61). However, one could reason that patients who do not respond to systemic therapy alone would be the ones who would require treatment of the primary as well.

Therefore, excluding patients with low burden disease from treatment of the primary based on response to systemic therapy is investigational.

The planned arm M comparison within the STAMPEDE multi arm multi stage trial will also evaluate the added value of metastasis-directed therapy + prostate RT in low burden metastatic patients. This study has a recruitment target of approximately 2200 patients and it will combine standard treatment including radiotherapy to the prostate, with a randomisation to receive SABR for men with metastases in extra-pelvic lymph nodes and/or bone metastases up to a maximum of 5 lesions. It is expected that the arm M comparison of the STAMPEDE trial will commence in early 2020.

6 Conclusions

Prostate radiotherapy with ADT improves survival and is a recommended first line option for men presenting with low metastatic burden prostate cancer. Currently, the recommended criteria to characterize metastatic burden is based on conventional imaging (^{99m}Tc bone scans and CT/MRI) and low burden can be defined as patients with only non-regional lymph nodes or <4 bone metastasis based (+/-LN) and no visceral metastasis on conventional imaging. Defining metastatic burden based on newer imaging modalities such as PSMA PET or WB-MRI is currently investigational. Emerging data suggests that heterogeneity in metastatic disease and progression demands a multi-modal approach which integrates local, systemic and possibly metastasis directed therapy to achieve effective oncological control. On-going trials evaluating prostate RT with metastasis directed therapy ± other systemic agents will provide further data in the future which will establish the utility of this approach.

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** Studies of outstanding interest

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Table legend

Table 1: Summary of the HORRAD trial and the STAMPEDE trial's "M1RT comparison" trial characteristics and results.

Table 2: Ongoing and planned phase 3 clinical trials evaluating prostate radiotherapy in newly diagnosed metastatic hormone naïve prostate cancer.

Table 1: Summary of the HORRAD trial and the STAMPEDE trial's "M1RT comparison" trial characteristics and results.

	HORRAD		**STAMPEDE M1|RT comparison**	
	ADT (n=216)	**ADT + RT (n=216)**	**SOC (n=1029)**	**SOC + RT (n=1032)**
Eligibility	Newly diagnosed previously untreated, histologically confirmed prostate cancer patients with bone metastasis on bone scintigraphy. Age <80 and PSA ≥ 20ng/ml		Newly diagnosed M1a-c prostate cancer patients with no previous radical treatment.	
Enrolment period	November 2004 - September 2014		January 22nd, 2013 - September 2nd, 2016	
Age in years, median	67	67	68	68
PSA ng/mL, median	125	149	98	97
Low burden n(%)	89 (41%)	71 (33%)	409 (42%)	410 (43%)
Androgen deprivation therapy	Androgen receptor inhibitor (eg, bicalutamide, 50 mg once daily) for 4 wk as flare reduction and concurrent treatment with a luteinising hormone-releasing-hormone (LHRH) agonist. All patients started with an LHRH agonist 1–2 wk after randomisation		All patients were intended for long term androgen deprivation therapy and started treatment no earlier than 12 weeks before randomisation.	
Docetaxel use	NA		Docetaxel was permitted in addition to hormone therapy after its approval in the UK on Dec 17, 2015. Docetaxel, when used, was given as six 3 weekly cycles of 75 mg/m², with or without prednisolone 10 mg daily before RT	
Radiotherapy schedule	NA	RT commenced within 3 months of starting ADT. 70 Gy in 35 fractions of 2 Gy within an overall treatment time of 7 wks. Optional schedule - 57.76 Gy in 19 fractions of 3.04 Gy, three times a week for 6 wks.	NA	RT was commenced as soon as practicable after randomisation and within 3-4 weeks after last docetaxel dose. Either 36 Gy in six consecutive weekly fractions of 6 Gy, or 55 Gy in 20 daily fractions of 2.75 Gy over 4 weeks.
Follow up, median (IQR)	47 months (IQR 36- 68)		37 months (IQR 24–48)	
OS in all patients	HR: 0.90, 95 %CI (0.70 - 1.14)		HR: 0.92, 95%CI (0.80 - 1.06), p=0.266	
OS in low burden	HR: 0.68, 95%CI (0.42 - 1.10)		HR: 0.68, 95%CI (0.52 - 0.90), p =0.007	
OS in high burden	HR: 1.06 95%CI (0.80 - 1.39)		HR: 1.07, 95%CI (0.90 - 1.28), p=0.420	
Subsequent life prolonging treatments received‡	Docetaxel 42%, Cabazitaxel 7%, Enzalutamide 13 %, Abiraterone 17%, Radium 223 3%	Docetaxel 46%, Cabazitaxel 9%, Enzalutamide 8 %, Abiraterone 18%, Radium 223 3%	Docetaxel 33%, Cabazitaxel 6%, Enzalutamide 32%, Abiraterone 21%, Radium 223 9%	Docetaxel 33%, Cabazitaxel 6%, Enzalutamide 36%, Abiraterone 20%, Radium 223 8%

***HORRAD: High burden defined as ≥ 5 bone metastasis, low burden <5 bone metastasis. STAMPEDE: High burden defined as patients with any visceral metastasis or ≥4 bone metastasis with ≥1 outside the vertebral column/pelvis. All other patients not meeting the high burden criteria were classified as low burden.**

‡HORRAD reported subsequent life prolonging treatments for patients who died, STAMPEDE trial reported subsequent life prolonging treatments for patients who progressed.

Abbreviations: ADT – androgen deprivation therapy, SOC – standard of care, IQR – interquartile range, OS – overall survival, HR – hazard ratio, CI – confidence interval

Table 2: Ongoing and planned phase 3 clinical trials evaluating prostate radiotherapy in newly diagnosed metastatic hormone naïve prostate cancer.

Identifier	Title	Patient population	Arms	Primary endpoints	Estimated enrolment
NCT01957436	A Phase III Study for Patients With Metastatic Hormone-naïve Prostate Cancer (PEACE1)	De-novo M1 patients are randomized in 1:1:1:1 ratio.	Arm A : ADT + Docetaxel vs Arm B : ADT + Docetaxel + Abiraterone vs Arm C : ADT + Docetaxel + RT vs Arm D : ADT + Docetaxel + Abiraterone + RT	Overall and progression free survival	1173
NCT03678025	Phase III Randomized Trial of Standard Systemic Therapy (SST) Versus Standard Systemic Therapy Plus Definitive Treatment (Surgery or Radiation) of the Primary Tumour in Metastatic Prostate Cancer	Step 1: Newly diagnosed M1 patients with no prior local therapy for prostate cancer and who have received systemic therapy for <28 weeks and have not progressed and have surgically resectable disease are eligible for registration. Step 2: Registered patients with no evidence of disease progression during the 28 weeks of systemic therapy by PSA measure, bone scan and CT or MRI or symptomatic deterioration (as defined by physician discretion) are randomized in 1:1 ratio	Best systemic therapy vs Best systemic therapy + Local treatment (RT/RP)	Overall survival	1273

Abbreviations: ADT – androgen deprivation therapy, RT-radiotherapy, RP- radical prostatectomy