NHS England

Evidence review: Prostate external beam radiotherapy for newly diagnosed patients with prostate cancer who have low volume metastatic disease

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1 Introduction

Introduction

- Prostate cancer is the most common form of cancer in men. Early prostate cancer is usually asymptomatic, and a significant proportion of patients present with metastatic disease. It most commonly spreads to bones, and more than four in five men with advanced prostate cancer have bone metastases. It also commonly spreads to lymph nodes, particularly those in the pelvic area near the prostate (Prostate Cancer UK 2016). A significant proportion of patients with prostate cancer present with bone pain. Many others present with urinary symptoms due to more local effects of the cancer. To date, standard treatment of patients with metastatic prostate cancer has not included localised treatment of the prostatic disease (Boevé et al 2019). The aim of this rapid evidence review (RER) is to review the evidence for external beam radiotherapy to the prostate for patients with newly diagnosed prostate cancer who have low volume metastatic disease at diagnosis.

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- Current NICE guidance on the diagnosis and management of prostate cancer (NICE 2019) does not include radiotherapy to the prostate for patients with metastatic disease. For this group of patients the recommendations are around information and support, including palliative care, and treatments aimed at reducing the effects of androgens on tumour growth, for example orchidectomy and anti-androgen therapy (ADT), with no mention of prostate radiotherapy. The NICE guidance also recommends:

> *"Offer docetaxel chemotherapy to people with newly diagnosed metastatic prostate cancer who do not have significant comorbidities"* (NICE 2019)

The indication and epidemiology

- In England from 2012 to 2016 (five years), nearly 200,000 men were diagnosed with prostate cancer, of whom about 36,500 had metastatic disease (stage 4) at diagnosis (Office of National Statistics (ONS) 2019).
- This review relates to the subset of these patients who have low volume metastatic disease at diagnosis. There is no agreed definition of low volume metastatic disease, and different studies have used different, and sometimes more than one, definition (see below). The proportion of patients who have metastatic prostate cancer at diagnosis who have a low metastatic volume (the group relevant to this review) is not published by the ONS and varied in two randomised controlled trials (Boevé et al 2019 and Parker et al 2018) from 17% to 50% depending on the trial and the definition used. This may reflect selection bias, and the true proportion may be different.
- On follow-up until 2017, overall five year survival from prostate cancer of all stages at diagnosis was 87.1% whereas for those diagnosed at stage 4 (with metastatic disease), the five year survival was 47.7% (ONS 2019). The five year survival rate for patients with low volume metastatic disease, the group relevant to this review, is not clear from ONS reports. However, the study by Parker et al (2018) that is included in this RER reports three year survival rates for the 1029 patients in the control group of 73% for those with a

low metastatic burden[1] and 54% for those with a high metastatic burden (62% for the whole cohort).

- Metastatic prostate cancer is incurable and to date treatment has focussed on reducing androgen activity and on information, support and palliative care.
- Earlier studies suggested that there may be benefit from radiotherapy to the prostate soon after diagnosis, even in patients whose disease is metastatic at diagnosis, and particularly for those with low volume metastatic disease. Randomised controlled trials were then carried out and results have recently been published.

Standard treatment and pathway of care

- Patients diagnosed with metastatic prostate cancer are offered information, support and treatment to reduce androgen activity, such as bilateral orchidectomy and anti-androgen treatments (NICE 2019). NICE guidance does not include mention of prostate radiotherapy for this group of patients.
- Recently, chemotherapeutic agents such as docetaxel (six cycles) have been introduced as part of standard care for patients who are fit enough to tolerate it (NICE 2019). Abiraterone is another such drug which is increasingly becoming part of standard care (Boevé et al 2019), and is currently being considered by NICE[2] (NICE 2019).
- External beam radiotherapy is used for palliation for symptomatic disease/metastases and is usually given later in the pathway (NICE 2019).

The intervention

- The intervention of interest in this review is external beam radiotherapy to the prostate. This is radiotherapy given by using ionising radiation (for example, high energy X-rays) produced in a machine and directed at the prostate from outside the patient, with the aim of destroying cancer cells. For maximum benefit and to reduce side effects due to damage to nearby tissues, it is usually given over a number of sessions over several weeks in an outpatient setting. The exact schedules (number of sessions, dose per session and interval between sessions) vary and are described below for each of the included studies. Both the total dose and the dose in each individual session may be important in terms of effectiveness and side effects.

Rationale for use

- Preliminary non-randomised studies noted a correlation between improved overall survival and use of radiotherapy to the prostate in patients with newly diagnosed prostate cancer with metastases, and randomized trials of this have now been published suggesting that this is beneficial in low volume metastatic disease.
- One possible explanation for this is that in animal models of cancer, primary tumours are thought to metastasise both by disseminating tumour cells into the circulation and also by "priming the premetastatic niche". It is thought that proliferation of tumour cells at distant sites to form overt metastases is dependent on compounds secreted by the primary tumour into the circulation. This would mean that local treatment of the primary tumour

[1] High and low metastatic burden were defined by Parker et al (2018) according to whether or not patients had "four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both".
[2] The NICE single technology appraisal for abiraterone for treating newly diagnosed metastatic hormone-naive prostate cancer was suspended in April 2019 while NICE is in discussion with the company about price (NICE 2019).

might inhibit not just the initiation of distant disease, but also the progression of existing metastases (Parker et al 2018).

2 Summary of results

- This review is based on one systematic review and meta-analysis (SRMA) (Burdett et al 2019) that included two randomised controlled trials (RCTs) (Parker et al 2018 (STAMPEDE); Boevé et al 2019 (HORRAD)) of prostate external beam radiotherapy (EBRT) for patients with newly diagnosed metastatic hormone-sensitive prostate cancer. The RCT by Parker et al (2018) is also included separately as it provides some additional information.
- The two included studies reported a range of clinical effectiveness outcomes for patients with low metastatic burden, and in addition Parker et al (2018) reported a number of safety outcomes, although these were not reported separately for patients with low metastatic burden. No studies were identified which reported cost-effectiveness. Patients in both control and EBRT groups received long-term androgen deprivation therapy.
- Three different definitions of low volume metastatic disease were used for the analyses reported in this review. The patients included in these three definitions overlapped and were not separate populations. The three definitions were:
  Definition 1: fewer than five bone metastases (one study, n=963) (Burdett et al 2019)
  Definition 2: Gleason sum score[3] less than 9, fewer than five metastases and prostate specific antigen (PSA) less than 142 ng/ml (one study, n=846) (Burdett et al 2019)
  Definition 3: not having: "four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both" (one study, n=819) (Parker et al 2018)

Clinical effectiveness

Outcomes are reported by the above definitions of low volume metastatic disease.

Overall survival

- Definition 1: (n=963). There was a statistically significant seven percentage point improvement in survival at three years (95% confidence interval (CI) 2 to 11) from 70% to 77% in the EBRT group compared to controls (hazard ratio (HR) 0.73, 95% CI 0.58 to 0.92, p=0.0071).
- Definition 3: (n=819). Three year survival was 81% in the EBRT group compared to 73% for controls (HR 0.68, 95% CI 0.52 to 0.90, p=0.007); and mean survival in the EBRT group was for 49.1 months compared to 45.4 months for controls, a difference of 3.6 months (95% CI 1.0 to 6.2).

Deaths from any cause

- Definition 1: There were 140 deaths in the EBRT group (n=488) (28.7%) and 164 in the control group (n=475) (34.5%) (p value not reported).
- Definition 2: There were 113 deaths in the EBRT group (n=426) (26.5%) and 135 in the control group (n=420) (32.1%) (p value not reported).

[3] Gleason sum score is a score between 2 and 10 based on microscopic appearance of cancer cells, with a higher score indicating a more aggressive cancer and worse prognosis

- Definition 3: There were 90 deaths in the EBRT group (n=410) (22.0%) and 116 in the control group (n=409) (28.4%) (p value not reported).

Number of patients with symptomatic clinical or radiological progression or death (progression)

- Definition 1: There were 222 patients with progression events in the EBRT group (n=488) (45.5%) and 235 in the control group (n=475) (49.5%) (p value not reported).
- Definition 2: There were 192 patients with progression events in the EBRT group (n=426) (45.1%) and 204 in the control group (n=420) (48.6%) (p value not reported).

Progression free survival (PFS)

- Definition 3: Three year PFS was 63% in the EBRT group (n=410) compared to 58% for controls (n=409) (HR 0.78, 95% CI 0.63 to 0.98, p=0.033); and mean PFS was 42.9 months compared to 39.4 months, a difference of 3.5 months (95% CI 0.4 to 6.7).

Number of patients with biochemical, clinical or radiological progression or death (failure)

- Definition 1: There were 296 patients with failure events in the EBRT group (n=488) (60.7%) and 349 in the control group (n=475) (73.5%) (p value not reported).
- Definition 2: There were 253 patients with failure events in the EBRT group (n=426) (59.4%) and 306 in the control group (n=420) (72.9%) (p value not reported).
- Definition 3: There were 204 patients with failure events in the EBRT group (n=410) (49.8%) and 261 with failure events in the control group (n=409) (63.8%).

Failure free survival (FFS)

- Definition 3: Three year FFS was 50% in the EBRT group (n=410) compared to 33% for controls (n=409) (HR 0.59, 95% CI 0.49 to 0.72, p<0.0001); and mean FFS was 36.1 months compared to 27.4 months, a difference of 8.6 months (95% CI 5.6 to 11.7).

Prostate cancer specific survival (PCSS):

- Definition 3: Three year PCSS was 86% in the EBRT group (n=410) compared to 79% for controls (n=409) (HR 0.65, 95% CI 0.47 to 0.90, p=0.010); and mean PCSS was 51.8 months compared to 48.6 months, a difference of 3.3 months (95% CI 1.0 to 5.5).

Metastatic progression free survival (MPFS):

- Definition 3: Three year MPFS was 67% in the EBRT group (n=410) compared to 62% for controls (n=409) (HR 0.80, 95% CI 0.63 to 1.01, p value not reported); and the mean MPFS was 44.2 months compared to 41.1 months, a difference of 3.1 months (95% CI 0.2 to 6.0).

Symptomatic local event free survival (SLEFS):

- Definition 3: Three year SLEFS was 72% in the EBRT group (n=410) compared to 65% for controls (n=409) (HR 0.82, 95% CI 0.64 to 1.05); and the mean SLEFS was 44.0 months compared to 41.6 months, a difference of 2.4 months (95% CI -0.7 to 5.4).

Safety

Adverse events were reported by Parker et al (2018) for the entire cohorts of patients who were randomised to receive EBRT or no EBRT, and not separately for those with low volume metastatic disease.

Most common symptomatic local events (one study, EBRT n=1032, control n=1029)

- During and after the treatment window, urinary tract infection was reported more frequently in patients treated with prostate radiotherapy than in the control group (3% vs

1% during the treatment window and 7% vs 5% after the treatment window). However, no p values or confidence intervals were reported.

- The next most common symptomatic local event during the treatment window was a urinary catheter[4] (2% and 1% in EBRT and control groups respectively, p value not reported).
- The other more common symptomatic local events after the treatment window were a urinary catheter (3% and 3% in EBRT and control groups respectively), acute kidney injury (3% and 3%), urinary tract obstruction (2% and 2%) and ureteric stent[5] (1% and 2%).

Acute bladder or bowel adverse effects of radiotherapy (one study, EBRT patients who started EBRT and completed at least one acute toxicity form, n=920)

- No deaths relating to acute RTOG[6] scale (grade 5) toxic effects of radiotherapy were reported
- Five percent (48 patients) had acute RTOG scale grade 3 or 4 acute adverse events (5% (43 patients) for bladder and 1% (8 patients) for bowel-related events)

Late bladder or bowel adverse effects of radiotherapy (one study, EBRT patients who started EBRT and had at least one follow-up assessment, n=988)

- No deaths relating to late RTOG scale (grade 5) toxic effects of radiotherapy were reported
- Four percent had late RTOG scale grade 3 or 4 events, most commonly diarrhoea, proctitis, cystitis and haematuria

Adverse effects of cancer therapy drugs (one study, patients with at least one follow-up assessment, EBRT n=985, control n=1050)

- Grade 3 or worse adverse events on the CTCAE scale[7] were of similar frequency in patients who received prostate radiotherapy (39%) and controls (38%) (p value not reported), as was the time to first CTCAE grade 3 or worse adverse event (HR 1.01, p=0.941), and these were dominated by side effects of long term androgen deprivation therapy.

Cost-effectiveness

- No studies assessing the cost-effectiveness of prostate radiotherapy for people with prostate cancer with low volume metastatic disease were identified.

Radiotherapy schedules used

- Four different prostate EBRT schedules were used. In Parker et al (2018) patients received either the first or second of the radiotherapy schedules listed below, and in Boevé et al (2019) patients received either the third or the fourth of the schedules below.

[4] This outcome was not further defined
[5] This outcome was not further defined
[6] Radiation Therapy Oncology Group (RTOG) toxicity grading scale grades acute and late radiation toxicity from 0 (no symptoms) to 5 (death directly related to radiation effects), with separate descriptions for each organ/organ system (Cox et al 1995).
[7] CTCAE, the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, is a set of criteria for the standard classification of adverse effects of drugs used for cancer therapy from 1 (mild) to 5 (death).

Neither the individual studies nor the SRMA described how it was decided which schedule patients would receive.

Used in Parker et al (2018):

- 36 Gy in six consecutive weekly fractions of 6 Gy
- 55 Gy in 20 daily fractions of 2.75 Gy over four weeks

Used in Boevé et al (2019):

- 70 Gy in 35 fractions of 2.0 Gy over seven weeks
- 57.76 Gy in 19 fractions of 3.04 Gy over six weeks

Limitations

- The evidence presented in this review is from the SRMA (Burdett et al 2019) and one of the RCTs (Parker et al 2018). Outcomes are reported for between 410 and 488 patients with low volume metastatic disease who were treated with EBRT, and between 409 and 475 controls. The number of patients depends on the definition of low volume metastatic disease used in the studies. While both included studies were generally of good quality, the SRMA only reported the statistical significance of findings graphically for some of the outcome measures (HR values not reported), limiting the interpretation of those findings.
- The exact definition of low volume metastatic disease was different in the different studies and no sensitivity analysis was reported regarding the optimal definition. Generalisability of the results also needs to take account of the imaging methods used in the studies, which although remaining the current "standard of care", were not the highest resolution methods available today, and the fact that the majority of patients did not also receive chemotherapeutic drugs such as docetaxel, which are increasingly being used today. Radiotherapy schedules used were lower than standard radical prostate radiotherapy doses.
- No relevant studies of cost-effectiveness were identified.

Conclusions

- The evidence suggests a benefit from the addition of EBRT to standard care in terms of overall survival of seven to eight percentage points at three years, as well as improvements in other survival-related outcome measures. Severe adverse events (RTOG scale grade 3 or 4) related to the radiotherapy were relatively infrequent (around 5% of patients acutely and 4% late), with no radiotherapy-related deaths reported.
- While the evidence suggests that the addition of prostate radiotherapy may be beneficial for this group of patients, the interpretation of these results in the context of current approaches to treatment is not straightforward.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).

- The PICO was used to search for relevant publications in EMBASE, MEDLINE and Cochrane (see section 10 for search strategy).
- The search dates for publications were between the 1st of January 2009 and the 2nd of April 2019.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Because randomised controlled trial (RCT) results were available, lower quality evidence (for example non-randomised cohort studies) was not included.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

This evidence review identified one systematic review and meta-analysis (SRMA) (Burdett et al 2019), which included two randomised controlled trials (RCTs) of patients with recently diagnosed metastatic hormone-sensitive prostate cancer treated with prostate external beam radiotherapy (EBRT). The SRMA analysed two groups of patients from the trials identified by two different definitions of low metastatic burden. The first group, who had fewer than five bone metastases, included 803 patients from the STAMPEDE trial (Parker et al 2018) and 160 patients from the HORRAD trial (Boevé et al 2019), of whom 488 were treated with EBRT. The second group had a Gleason sum score[8] less than nine, fewer than five bone metastases and prostate specific antigen (PSA) less than 142 ng/ml. Using this definition, the SRMA included 772 patients from the STAMPEDE trial and 74 patients from the HORRAD trial, of whom 426 were treated with EBRT. All patients received long-term androgen deprivation therapy (ADT) as part of standard care, and control patients received standard care without prostate radiotherapy.

The results from the HORRAD trial (Boevé et al 2019) that pertain to patients with newly diagnosed prostate cancer who have low volume metastatic disease were well covered by the SRMA by Burdett et al (2019) and hence that paper was not also included separately in this RER. However, the SRMA by Burdett et al (2019) provided little detail regarding the adverse effects of radiotherapy that were reported by Parker et al (2018) and also excluded 129 patients with a low metastatic burden whose planned standard care included docetaxel. For this reason, results of the STAMPEDE trial (Parker et al 2018) are also included separately in this RER. The STAMPEDE trial defined low metastatic burden differently from Burdett et al (2019). High metastatic burden was defined as four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both, and the remaining patients for whom data on metastases were available were reported as having a low metastatic burden: 819 had low metastatic burden, of whom 410 received prostate radiotherapy (for 122 (5.9%) patients metastatic burden could not be classified) (Parker et al 2018). Patients were followed up for a mean of 41.9 months in STAMPEDE and 47 months in HORRAD (Burdett et al 2019).

[8] Gleason sum score : a score between 2 and 10 based on microscopic appearance of cancer cells, with a higher score indicating a more aggressive cancer and worse prognosis

1. **In patients with newly diagnosed prostate cancer who have low volume metastatic disease, what is the clinical effectiveness of the addition of external beam radiotherapy to the prostate to standard care compared with standard care alone?**

The clinical effectiveness outcomes reported in the SRMA were overall survival, deaths, progression events (the number with symptomatic clinical or radiological progression or death), and failure events (the number with clinical, radiological or biochemical progression or death). The STAMPEDE trial (Parker et al 2018) also reported progression free survival, failure free survival, prostate cancer specific survival, metastatic progression free survival and symptomatic local event free survival.

Overall survival

For overall survival, among patients with fewer than five bone metastases, Burdett et al's (2019) SRMA reported a seven percentage point improvement in survival (95% CI 2 to 11) at three years from 70% to 77%. They reported a hazard ratio (HR) for survival of 0.73 (95% confidence interval (CI) 0.58 to 0.92, p=0.0071).

Using their definition of a low metastatic burden (see above), Parker et al (2018) reported a three year survival of 81% in the EBRT group compared to 73% for controls (p value not reported). They reported a HR for survival of 0.68 (95% CI 0.52 to 0.90, p=0.007). Mean survival was 49.1 months in the EBRT group compared to 45.4 months for controls, a difference of 3.6 months (95% CI 1.0 to 6.2). (Survival probabilities and mean survival time estimates were restricted to patients' first 59 months on the trial.)

Deaths from any cause

Among patients with fewer than five bone metastases, Burdett et al's (2019) SRMA reported 140 deaths from any cause among 488 patients treated with EBRT in addition to standard care (28.7%) and 164 deaths among 475 controls (34.5%) (p value not reported). Among patients with a low metastatic burden, defined as Gleason sum score less than 9, fewer than five metastases and PSA less than 142 ng/ml, Burdett et al (2019) reported 113 deaths from any cause among 426 patients treated with EBRT in addition to standard care (26.5%) and 135 deaths among 420 controls (32.1%) (p value not reported).

Using their definition of a low metastatic burden (see above), Parker et al (2018) reported 90 deaths from any cause among 410 patients treated with EBRT (22.0%) compared to 116 deaths among 409 controls (28.4%) (p value not reported).

Number with symptomatic clinical or radiological progression or death (progression events)

The number of patients with fewer than five bone metastases who had symptomatic clinical or radiological progression or death (excluding biochemical progression) was reported by Burdett et al (2019) as 222 patients among 488 patients treated with EBRT (45.5%) compared to 235 patients among 475 controls (49.5%) (p value not reported). Among patients with a low metastatic burden, defined as Gleason sum score less than 9, fewer than five metastases and PSA less than 142 ng/ml, there were 192 patients with progression events among 426 patients treated with EBRT (45.1%) compared to 204 patients among 420 controls (48.6%) (p value not reported) (Burdett et al 2019).

Progression free survival (PFS)

Using their definition of a low metastatic burden (see above), Parker et al (2018) reported that three year PFS was 63% among 410 patients treated with EBRT and 58% among 409 controls (p value not reported). They reported a HR for PFS of 0.78 (95% CI 0.63 to 0.98, p=0.033). Mean

PFS was 42.9 months in the EBRT group compared to 39.4 months for controls, a difference of 3.5 months (95% CI 0.4 to 6.7). (Survival probabilities and mean survival time estimates were restricted to patients' first 59 months on the trial.)

Number with biochemical, clinical or radiological progression or death (failure events)
The number of patients with fewer than five bone metastases who had biochemical[9], clinical or radiological progression or death (failure events) was reported by Burdett et al (2019) as 296 patients among 488 patients treated with EBRT (60.7%) compared to 349 patients among 475 controls (73.5%) (p value not reported). Among patients with a low metastatic burden, defined as Gleason sum score less than 9, fewer than five metastases and PSA less than 142 ng/ml, there were 253 patients with failure events among 426 patients treated with EBRT (59.4%) compared to 306 patients among 420 controls (72.9%) (p value not reported) (Burdett et al 2019).

Using their definition of a low metastatic burden (see above), Parker et al (2018) reported 204 patients with failure events in the EBRT group (n=410) (49.8%) and 261 with failure events in the control group (n=409) (63.8%).

Failure free survival (FFS)
Using their definition of a low metastatic burden (see above), Parker et al (2018) reported that three year FFS was 50% in the EBRT group compared to 33% for controls (p value not reported). They reported a HR for FFS of 0.59 (95% CI 0.49 to 0.72, p<0.0001). Mean FFS was 36.1 months in the EBRT group compared to 27.4 months for controls, a difference of 8.6 months (95% CI 5.6 to 11.7). (Survival probabilities and mean survival time estimates were restricted to patients' first 59 months on the trial.)

Prostate cancer specific survival
Among patients with a low metastatic burden (defined above), Parker et al (2018) reported that three year prostate cancer specific survival was 86% among 410 patients treated with EBRT compared to 79% among 409 controls (p value not reported). They reported a HR for prostate cancer specific survival of 0.65 (95% CI 0.47 to 0.90, p=0.010). Mean prostate cancer specific survival was 51.8 months in the EBRT group compared to 48.6 months for controls, a difference of 3.3 months (95% CI 1.0 to 5.5). (Survival probabilities and mean survival time estimates were restricted to patients' first 59 months on the trial.)

Metastatic progression free survival
Among patients with a low metastatic burden (defined above), Parker et al (2018) reported that three year metastatic progression free survival was 67% among 410 patients treated with EBRT compared to 62% among 409 controls (p value not reported). They reported a HR for metastatic progression free survival of 0.80 (95% CI 0.63 to 1.01, p value not reported). Mean metastatic progression free survival was 44.2 months in the EBRT group compared to 41.1 months for controls, a difference of 3.1 months (95% CI 0.2 to 6.0). (Survival probabilities and mean survival time estimates were restricted to patients' first 59 months on the trial.)

Symptomatic local event free survival
Among patients with a low metastatic burden (defined above), Parker et al (2018) reported that three year symptomatic local event free survival was 72% among 410 patients treated with EBRT compared to 65% among 409 controls (p value not reported). They reported a HR for symptomatic local event free survival of 0.82 (95% CI 0.64 to 1.05). Mean symptomatic local event free survival was 44.0 months in the EBRT group compared to 41.6 months for controls, a

[9] Biochemical progression was defined in the HORRAD trial as a PSA increase after the initiation of ADT of >50% of the lowest PSA value after the start of treatment (with a minimum of 1 ng/ml), and in the STAMPEDE trial as a rise above the lowest PSA within 24 weeks of enrolment of 50% to at least 4 ng/ml (Burdett et al (2019)

difference of 2.4 months (95% CI -0.7 to 5.4). (Survival probabilities and mean survival time estimates were restricted to patients' first 59 months on the trial.)

2. In patients with newly diagnosed prostate cancer who have low volume metastatic disease, what is the safety of the addition of external beam radiotherapy to the prostate to standard care compared with standard care alone?

Parker et al (2018) reported adverse events for the entire cohorts of patients who were randomised to receive EBRT (n=1032) or no EBRT (n=1029), and not separately for those with low volume metastatic disease. Adverse event outcomes reported were symptomatic treatment events, acute and late urinary and bowel adverse effects of radiotherapy and adverse effects of cancer therapy drugs.

Most common symptomatic local events

Within the treatment window the most common symptomatic local events, affecting more than 10 patients in a group, were urinary tract infection (31 patients, 3%, in the EBRT group and 14 patients, 1%, of controls) and urinary catheter[10] (18 patients, 2%, in the EBRT group and 14 patients, 1%, of controls) (p values were not reported).

After the treatment window the most common symptomatic treatment events, affecting more than 10 patients in a group, were urinary tract infection (75 patients, 7%, in the EBRT group and 49 patients, 5%, of controls), urinary catheter (36 patients, 3%, in EBRT group and 35 patients, 3%, of controls), acute kidney injury (35 patients, 3%, in the EBRT group and 31 patients, 3%, of controls), urinary tract obstruction (17 patients, 2%, in the EBRT group and 24 patients, 2%, of controls), and ureteric stent[11] (7 patients, 1%, in the EBRT group and 16 patients, 2%, of controls (p values were not reported).

Acute bladder and bowel adverse effect of radiotherapy

Parker et al (2018) reported acute adverse effects of radiotherapy on the RTOG scale[12] as grade 3 or 4 in 48 (5%) of 920 patients allocated to EBRT who started radiotherapy and who completed at least one acute toxicity form. For 43 patients (5%), their worst acute bladder toxic effect was grade 3 or 4. For 8 patients (1%), their worst acute bowel toxic effect was grade 3 or 4. No acute grade 5 radiotherapy related toxic effects (deaths) were reported.

The incidence of acute bladder and bowel effects of radiotherapy (RTOG grade 1-4) in those who nominated the weekly radiotherapy schedule were: 282 patients (65%) with acute bladder effects and 206 (47%) with acute bowel effects. For those who nominated the daily radiotherapy schedule these rates were 341 (71%) with acute bladder effects and 297 (62%) with acute bowel effects. p values were not reported.

Late bladder and bowel adverse effects of radiotherapy

Late grade 3 and 4 RTOG effects of radiotherapy were reported in 37 (4%) of 988 patients in the group who received EBRT and had at least one follow-up assessment: diarrhoea in 12 patients, proctitis in 11, cystitis in seven, haematuria in six, urethral stricture in four and bowel obstruction in one. Among control patients who received some radiotherapy at some point (n=187), 1 patient (1%) had diarrhoea. No late grade 5 radiotherapy related toxic effects (deaths) were reported. p values were not reported.

[10] This outcome was not further defined.
[11] This outcome was not further defined
[12] Radiation Therapy Oncology Group (RTOG) toxicity grading scale grades acute and late radiation toxicity from 0 (no symptoms) to 5 (death directly related to radiation effects), with separate descriptions for each organ/organ system.

Adverse effects of cancer therapy drugs (CTCAE) scale[13]
The proportion of patients reporting at least one grade 3 or worse event was 39% (380 of 985 patients) in the EBRT group and 38% (398 of 1050) in the control group (of patients who had at least one follow-up assessment). The time to the first grade 3 or worse event was similar in both groups (time not reported), HR 1.01 (95% CI 0.87 to 1.16, p=0.941), and these events were dominated by side effects of long term ADT (Parker et al 2018).

Parker et al (2018) also reported the proportion of patients reporting grade 3 or worse adverse events at six months as 22% (212 of 981) in the EBRT group and 21% (225 of 1047) among controls. At one year the corresponding proportions were 13% (78 of 594) in the EBRT group and 12% (78 of 594) among controls and at two years these proportions were 13% (37 of 293) in the EBRT group and 15% (37 of 240) among controls. (p values not reported). (Note that data were available for fewer patients at the later time intervals.)

3. **In patients with newly diagnosed prostate cancer who have low volume metastatic disease, what is the cost effectiveness of the addition of external beam radiotherapy to the prostate to standard care compared with standard care alone?**

No studies assessing the cost-effectiveness of the addition of prostate EBRT in newly diagnosed patients with prostate cancer who have low volume metastatic disease were identified.

4. **From the evidence selected, what are the schedules of radiotherapy used by the research studies?**

In the STAMPEDE trial (Parker et al 2018), the intervention was external beam radiotherapy to the prostate with an 8mm margin posteriorly and 10mm margin elsewhere, commencing as soon as practicable after randomisation and within three to four weeks after the last docetaxel dose. One of two schedules was nominated prior to randomisation: either 36 Gy in six consecutive weekly fractions of 6 Gy (168 patients in the EBRT group and 190 controls) or 55 Gy in 20 daily fractions of 2.75 Gy over four weeks (242 patients in the EBRT group and 219 controls). The methodology for nominating patients to the different radiotherapy schedules was not described. Parker et al (2018) report that both radiotherapy dose schedules were lower than standard radical radiotherapy doses and were chosen for patient convenience based on a survey of investigators' opinions.

In the HORRAD trial (Boevé et al 2019), the external beam radiotherapy intervention to the prostate was either 70 Gy in 35 fractions over seven weeks or 57.76 Gy in 19 fractions over six weeks, commenced within three months of starting ADT. The authors did not describe how it was decided which schedule patients would receive. The number of patients with low volume metastatic disease receiving each of these radiotherapy schedules was not reported.

5 Discussion

The evidence identified regarding the clinical effectiveness of prostate radiotherapy for patients with newly diagnosed prostate cancer with low volume metastatic disease consists of one SMRA

[13] CTCAE, the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, are a set of criteria for the standard classification of adverse effects of drugs used for cancer therapy from 1 (mild), 2 (moderate), 3 (severe but not immediately life-threatening), 4 (life-threatening) to 5 (death).

(Burdett et al 2019), which included two RCTs (Boevé et al 2019 and Parker et al 2018), one of which (Parker et al 2018) also provided some additional data relating to patients who received docetaxel as standard care and to adverse events. All patients had newly diagnosed metastatic hormone-sensitive prostate cancer.

The results suggest that for patients with fewer than five bone metastases, compared with those receiving standard care, patients who also received prostate EBRT had a statistically significant improvement in overall survival (Burdett et al 2019). Three year survival was improved by seven percentage points (95% CI 2 to 11) from 70% to 77% (HR for survival 0.73, 95% CI 0.58 to 0.92, p=0.0071) (Burdett et al 2019). Among those with a low metastatic burden defined as not having "four or more bone metastases with one or more outside the vertebral bodies or pelvis or visceral metastases or both", there was an improvement in three-year survival from 73% to 81%, suggesting a statistically significant mean survival improvement of around 3.6 months (95% CI 1.0 to 6.2) (Parker et al 2018). The RCT reported by Parker et al (2018) using this definition of low metastatic burden also reported statistically significant improvements in progression free survival, failure free survival and prostate cancer specific survival. The SRMA (Burdett et al 2019) did not report measures of statistical significance for these outcome measures in patients meeting other definitions of low metastatic burden, although some were reported graphically.

The RCTs were generally of good quality, with clearly pre-defined aims, and intention to treat analyses. Although patients, clinicians and investigators were not blinded to the treatments received, most of the outcome measures (including the primary outcome measure of overall survival) were sufficiently objective for this not to be an important concern. However, it may have introduced some bias into reporting of some of the more subjective symptoms, cause of death and adverse events.

These findings suggest that radiotherapy to the prostate is of benefit to patients with newly diagnosed prostate cancer who have low volume metastatic disease. However, the definition of low volume metastatic disease was chosen in these studies based on the data that were available and previous definitions. Although benefit was seen with more than one definition of low metastatic volume, no sensitivity analyses were carried out to elicit the optimal definition that would provide the best threshold for effectiveness of this treatment, and the best definition to use is not clear. Results for subgroups such as age, tumour stage and concomitant treatments were also not provided for the group of patients with low volume metastatic disease.

All the patients in the trial by Boevé et al (2019) and the majority in the trial by Parker et al (2018) did not receive docetaxel as standard care. Patients who received docetaxel were excluded from the SRMA by Burdett et al (2019), but were included in Parker et al's (2018) own analysis. Docetaxel is now increasingly used as standard care in this group of patients, as is abiraterone (Boevé et al 2019) (although the latter is not approved by NICE for use in the NHS for this indication (NICE 2019)). It is possible that the effectiveness of radiotherapy to the prostate is different to that observed in these studies if it is used in conjunction with these drugs.

Additionally, these trials open up the question of whether there may be further benefit from additional radiotherapy to the metastases themselves (Parker et al 2018) (radiotherapy to metastases is currently used later for symptomatic control where needed). If early metastasis-directed radiotherapy becomes standard practice for this group of patients, this may have an impact on the overall effectiveness of prostate radiotherapy.

When interpreting these results in the context of up to date treatment for patients with newly diagnosed metastatic prostate cancer, it is also important to note that the studies used the current "standard of care" imaging techniques to identify metastases and to define metastatic burden.

Parker et al (2018) used whole body scintigraphy and CT or MRI staging scans and Boevé et al (2019) used bone scintigraphy, whereas newer imaging techniques[14], as and if they become available on the NHS, are likely to identify larger numbers of metastases. Definitions of low volume metastatic disease identified using newer imaging techniques may therefore be different from those used in these studies.

Although different radiotherapy schedules were used, a comparison of their effectiveness and safety in patients with low metastatic volume was not reported.

Adverse events relating to radiotherapy were reported in detail by Parker et al (2018) but only for the whole cohort of 1032 patients randomised to receive prostate radiotherapy and 1029 controls, not specifically for the group of patients with low volume metastatic disease. During and after the treatment window, urinary tract infection was reported more frequently in patients treated with prostate radiotherapy than in the control group (3% vs 1% during and 7% vs 5% after the treatment window). However, no p values or confidence intervals were reported and so it is not clear whether the differences are statistically significant. Among the group receiving radiotherapy, no deaths relating to acute or late RTOG scale[15] (grade 5) toxic effects of radiotherapy were reported. Five percent of patients had acute RTOG scale grade 3 or 4 adverse events (5% for bladder and 1% for bowel-related events), and 4% had late RTOG scale grade 3 or 4 events, most commonly diarrhoea, proctitis, cystitis and haematuria. (The timescales relating to "acute" and "late" events were not reported). Grade 3 (severe but not immediately life-threatening) or worse adverse events on the CTCAE scale for adverse effects of drugs used for cancer therapy were of similar frequency in patients who received prostate radiotherapy and controls (39% and 38 % respectively), as was the time to the first CTCAE grade 3 or worse adverse event.

No evidence was identified relating to the cost-effectiveness of prostate radiotherapy in this patient group.

Future research where standard care includes more recently adopted treatments, such as docetaxel, as well as newer imaging techniques, would be useful, as would sensitivity analyses regarding the optimal definition of low volume metastatic disease that provides the greatest benefit from prostate radiotherapy in terms of both clinical effectiveness and cost-effectiveness. The addition of early metastasis-directed radiotherapy may also merit research.

6 Conclusion

The evidence regarding the clinical effectiveness of prostate external beam radiotherapy for newly diagnosed patients with prostate cancer who have low volume metastatic disease comes from two RCTs of patients with hormone-sensitive prostate cancer and a SRMA of their results. Outcomes are reported for between 410 and 488 patients with low volume metastatic disease who were treated with EBRT, and between 409 and 475 controls. The number of patients depends on the definition of low volume metastatic disease used in the studies. The evidence suggests a benefit from the addition of EBRT to standard care in terms of overall survival of seven to eight percentage points at three years, as well as improvements in other survival-related

[14] Examples of newer imaging techniques are multiparametric MRI scans and positron emission tomography (PET) scans such as prostate-specific membrane antigen PET scans, not all of which are currently available on the NHS.
[15] Radiation Therapy Oncology Group (RTOG) toxicity grading scale grades acute and late radiation toxicity from 0 (no symptoms) to 5 (death directly related to radiation effects), with separate descriptions for each organ/organ system. For example grade 3 and 4 late haematuria radiation toxicity are defined respectively as frequent haematuria and severe haemorrhagic cystitis (RTOG Foundation 2019).

outcome measures. Severe adverse events related to the radiotherapy were relatively infrequent (around 5% of patients acutely and 4% late), with no radiotherapy-related deaths reported.

While both included studies were generally of good quality, the SRMA only reported the statistical significance of findings graphically for some of the outcome measures (HR values not reported), limiting the interpretation of those findings. The exact definition of low volume metastatic disease was different in the different studies and no sensitivity analysis was reported regarding the optimal definition. In addition, the definition used would need to be reconsidered if higher resolution imaging techniques are used, as these are likely to identify larger numbers of metastases than the imaging techniques used in these studies. Generalisability of the results also needs to take account of the fact that the majority of patients did not also receive chemotherapeutic drugs such as docetaxel, which are increasingly being used today. Radiotherapy schedules used were lower than standard radical prostate radiotherapy doses. No relevant studies of cost-effectiveness were identified.

Patients with newly diagnosed metastatic prostate cancer and their clinicians need to be able to make decisions about their best course of treatment. While the evidence suggests that the addition of prostate radiotherapy may be beneficial for this group of patients, the interpretation of these results in the context of current approaches to treatment is not straightforward.

7 Evidence Summary Table

For abbreviations see list after table

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Burdett et al 2019	S2 – Adaptive meta-analysis Includes two published RCTs. STAMPEDE trial (Parker et al 2018) conducted in 117 hospitals in Switzerland and the UK; HORRAD trial (Boevé et al 2019) conducted in 28 centres	n=2126 Men with newly diagnosed metastatic hormone-sensitive prostate cancer starting or responding to first-line hormone therapy (ADT). Of the 2126 patients, 963 had fewer than 5 bone metastases. Two groups with low volume metastatic disease were defined:	STAMPEDE trial: Intervention: EBRT 36 Gy in 6 fractions over 6 weeks or 55Gy in 20 fractions over 4 weeks plus ADT; Control: ADT (LHRH agonist or antagonist or orchidectomy). HORRAD trial: Intervention: EBRT 70 Gy in 35 fractions over 7 weeks or 57.76 Gy in 19 fractions over 6 weeks plus ADT; Control: ADT (LHRH agonist or orchidectomy). Patients followed up for	Primary Clinical effectiveness	Survival (to death from any cause)	**Patients with <5 bone metastases (n=963)** 3-year survival EBRT: 77% Control: 70% Difference in survival: 7% (95% CI 2% to 11%) HR (for entire follow-up period) 0.73, 95% CI 0.58 to 0.92, p=0.0071	8	Direct	In line with the PICO, only results for patients with low volume metastatic disease are included here. Results were also provided for the interaction ratios between treatment of patients with low vs high metastatic burden, but these are not reported here as they are not within the scope of the PICO for this RER. Some of the results for patients with low volume metastatic disease were presented graphically, with numbers of events reported, but values for the hazard ratios (HRs) not reported. HRs were only reported for survival (in relation to patients with low volume metastatic disease). Low volume metastatic disease was defined in two ways: 1. Fewer than five bone metastases 2. Gleason sum score <9, fewer than 5 bone metastases and prostate specific antigen (PSA) ≤142 (HORRAD median) Study methods and analyses were published before the trial results were known, although subgroups for metastatic burden were adjusted to match those reported in the studies. The only analyses that were not pre-planned were those relating outcome to disease volume and the analysis of FFS by <5 vs ≥5 metastases. The latter are described as "exploratory" analyses. Making decisions regarding analysis prior to knowledge of results reduces the risk of bias in choice of analysis.
				Primary Clinical effectiveness	Deaths from any cause / total treated; % (numbers in brackets are the numbers from STAMPEDE and HORRAD respectively)	**Patients with <5 bone metastases (n=963)** EBRT: 140 (105+35) / 488 (399+89) ; 28.7% Control:164 (130+34) / 475 (404+71); 34.5% p value not reported **Patients with low volume disease defined as Gleason sum score[17] <9, <5 bone metastases and PSA ≤142) (n=846)** EBRT: 113 (101+12) / 426 (387+39) ; 26.5% Control: 135 (120+15) / 420 (385+35); 32.1% p value not reported			

[17] Gleason Sum score: a score between 2 and 10 based on microscopic appearance of cancer cells, with a higher score indicating a more aggressive cancer and worse prognosis.

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	in The Netherlands. Patients were randomised between 2013 and 2016 (STAMPEDE trial) and between 2004 and 2014 (HORRAD trial)	1. (n=963) with<5 bone metastases, of whom 488 received EBRT + ADT (399 from STAMPEDE and 89 from HORRAD) and 475 received ADT (404 from STAMPEDE and 71 from HORRAD) 2. (n=846) with Gleason sum score <9, <5 bone lesions and PSA<142 ng/ml, of whom 426 received EBRT +ADT (387 from STAMPEDE and 39 from	median 41.9 months in STAMPEDE trial and 47 months in HORRAD trial.	Secondary Clinical effectiveness	Number of patients with symptomatic clinical or radiological progression or death, excluding biochemical progression (progression) (numbers in brackets are the numbers from STAMPEDE and HORRAD respectively)	**Patients with <5 bone metastases (n=963)** Patients with progression/total treated: EBRT: 222 (184+38) / 488 (399+89); 45.5% Control: 235 (200+35) / 475 (404+71); 49.5% p value not reported **Patients with low volume disease defined as Gleason sum score <9, <5 bone metastases and PSA ≤142) (n=846)** Patients with progression/total treated: EBRT: 192 (179+13) / 426; 45.1% Control: 204 (188+16) / 420; 48.6% p value not reported			The authors obtained some data that were unpublished or prepublication from the RCT authors, which allowed them to harmonise outcome and subgroup definitions across trials. There is no single agreed definition of low volume metastatic disease and the definitions of low vs high volume metastatic disease used in this study were dictated by the data collected in the two trials (the HORRAD trial collected the number of bone metastases in three prespecified categories (<5, 5–15, and >15) and the STAMPEDE trial collected the absolute number of metastases up to 9 and then >9). This means that the cut-off of 5 bone metastases as a definition of the metastatic burden was dictated by the studies and no analysis was done to consider whether a different cut-off may be more appropriate. For example it is not known whether patients with 5 or 6 metastases may also benefit from prostate radiotherapy. For "low volume disease", the HORRAD trial used a definition based on PSA, Gleason sum score and number of metastases for which there were sufficient data from the STAMPEDE trial to adopt the same definition for both trials and for the meta-analysis. Again this definition was pre-defined by the HORRAD study and does not necessarily represent the best threshold of effectiveness of prostate radiotherapy. No sensitivity analysis was performed to determine the best cut-off values for low volume disease in relation to the effectiveness of prostate radiotherapy. The STAMPEDE trial itself used a different definition of low volume metastatic disease (see Parker et al 2018 below). The STAMPEDE trial was much larger than the HORRAD trial (n=1694 vs n=432) and heavily influenced the results.
				Secondary Clinical effectiveness	Number of patients with biochemical, clinical or radiological progression (failure) (numbers in brackets are the numbers from STAMPEDE and HORRAD respectively)	**Patients with <5 bone metastases (n=963)** Patients with failure/total treated: EBRT: 296 (238+58) / 488; 60.7% Control: 349 (297+52) / 475; 73.5% p value not reported **Patients with low volume disease defined as Gleason sum score[18] <9, <5 bone metastases and PSA ≤142) (n=846)** Patients with failure/total treated: EBRT: 253 (230+23) /426; 59.4% Control: 306 (284+22) / 420; 72.9% p value not reported			
				Secondary	Adverse events (AEs)	Adverse events were not reported separately for those with low volume			

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		HORRAD) and 420 received ADT (385 from STAMPEDE and 35 from HORRAD) For the complete cohort of 2126 men (not provided separately for patients with low volume metastatic disease): 89% in STAMPEDE had bone metastases, 5% also had visceral metastases. All in HORRAD had bone metastases.		Safety		metastatic disease. The following are for patients with high and low volume metastatic disease combined. STAMPEDE trial (n=849): Of those who received prostate EBRT: 4% had severe acute bladder toxicity; 1% had severe acute bowel toxicity (RTOG scale[19]); 4% had severe late effects. See Parker et al (2018) below for further details. HORRAD trial: not reported.			A further 367 patients in the STAMPEDE trial received docetaxel in addition to ADT as standard care and their results were not included in the meta-analysis. Results for the subset of this group that had low volume metastatic disease are not published separately. As docetaxel treatment is now being used more routinely for this group of patients, the results for those patients are likely to be more relevant to current practice, and the effectiveness of radiotherapy may be different when used in conjunction with this drug. Imaging techniques have improved over recent years and the definitions used for number of metastases are based on the techniques available at the time of the two RCTs. Higher resolution imaging may find a greater number of metastases in the same patients and the results of this study need to be interpreted in conjunction with knowledge of the imaging techniques that were used in those studies. The STAMPEDE trial used whole body scintigraphy and CT or MRI staging scans (Parker et al 2018) and in the HORRAD trial, bone scintigraphy was used (Boevé et al 2019). Neither used, for example, prostate-specific membrane antigen positron emission tomography, which is likely to identify larger numbers of metastases. Patients, clinicians and investigators were not blinded to the treatments received (Parker et al 2018; Boevé et al 2019). This could potentially introduce bias if a particular result was anticipated. However, outcome measures included in this meta-analysis were sufficiently objective for this not to be an important concern.

[19] Radiation Therapy Oncology Group (RTOG) toxicity grading scale grades acute and late radiation toxicity from 0 (no symptoms) to 5 (death directly related to radiation effects), with separate descriptions for each organ/organ system (Cox et al 1995)

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Median age: 68 years in STAMPEDE; 67 years in HORRAD. WHO/ECOG performance status[16] 0: 71% of STAMPEDE; 84% of HORRAD patients. Gleason sum score ≥8: 79% of STAMPEDE; 66% of HORRAD patients. Trials were ineligible if they included men who had stopped responding to first-line ADT, had castrate-refractory							

[16] WHO/ECOG performance status: a measure of how the disease affects daily living abilities: 0 (fully active), 1 (restricted in physically strenuous activity), 2 (ambulatory and capable of all self-care but not work), 3 (limited self-care and confined to bed or chair for >50% of waking hours), 4 (completely disabled/confined to bed or chair), 5 (dead).

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		prostate cancer or in whom radiotherapy was administered to metastases.							
Parker et al 2018	P1 - Randomised controlled trial (STAMPEDE) 117 hospitals in Switzerland and the UK Randomisation between 2013 and 2016	n=2061 Men with newly diagnosed prostate cancer with metastatic disease confirmed by bone scintigraphy and soft-tissue imaging done within 12 weeks of starting ADT, with no previous radical treatment, and all intended for long term ADT. Docetaxel (+/- prednisolone) permitted	Intervention: EBRT to prostate with 8mm margin posteriorly and 10 mm margin elsewhere, in addition to standard ADT (GnRH agonist or antagonist or orchidectomy) Radiotherapy commenced as soon as practicable after randomisation and within 3-4 weeks after last docetaxel dose Patient nominated one of 2 schedules prior to randomisation: 36 Gy in 6 consecutive weekly	Primary Clinical effectiveness	Survival (to death from any cause) (survival probabilities and mean survival time estimates restricted to first 59 months on the trial)	**Patients with low metastatic burden (see right hand column for definition)** EBRT n=410 Control n=409 3 year survival EBRT: 81% Control: 73% p value and numbers not reported Mean survival EBRT: 49.1 months Control: 45.4 months Difference 3.6 (95% CI 1.0 to 6.2) months Deaths (entire follow-up period): EBRT: 90 deaths Control: 116 deaths HR 0.68, 95% CI 0.52 to 0.90 p=0.007	8	Direct	This RCT was incorporated within a multi-arm multistage protocol. In line with the PICO, only results for patients with low volume metastatic disease (40% of the study population) are included here, apart from results for AEs. Parker et al (2018) only reported AEs for the whole cohort (with both high and low volume metastatic disease), and their results for the more common and more severe AEs have been included in this table (for the whole cohort). Metastatic burden was assessed through whole-body scintigraphy and CT or MRI staging scans, with high metastatic burden defined as 4 or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both. Other patients for whom data on metastases were available were reported as having a low metastatic burden. For 5.9% of patients (122) there was insufficient information for their metastatic burden to be classified. This definition of low metastatic burden was the same as that used in a previous trial (CHAARTED, Sweeney et al 2015) and includes patients with any number of metastases provided they are confined to lymph nodes and the axial skeleton. Sensitivity analyses were not reported to help determine whether a different definition/cut-off may provide a better demarcation between those more and less likely to benefit from prostate radiotherapy.
				Primary Clinical effectiveness	Failure free survival (FFS) (to first evidence of at least one of biochemical failure, progression locally or in	**Patients with low metastatic burden (see right hand column for definition)** EBRT n=410 Control n=409 3 year FFS EBRT: 50% Control: 33% p value and numbers not reported			

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		from December 2015. EBRT 1032; Controls 1029 Of these, 819 had a low metastatic burden: EBRT 410; Controls 409. In the low metastatic burden cohort: Planned to receive early docetaxel: EBRT group 62; Controls 67 Median PSA: EBRT group 55 ng/ml (interquartile range (IQR) 23-138);	fractions of 6 Gy (168 patients in EBRT group; 190 controls) or 55 Gy in 20 daily fractions of 2.75 Gy over 4 weeks (242 patients in EBRT group; 219 controls) Follow-up: every 6 weeks for 6 months, then 12 weekly to 2 years then 6 monthly to 5 years post randomisation, then annually Median follow-up 37 months (IQR 24 to 48) (for all 2061 patients)		lymph nodes or in distant metastases, or death from prostate cancer) (survival probabilities and mean survival time estimates restricted to first 59 months on the trial)	Mean FFS EBRT: 36.1 months Control: 27.4 months Difference 8.6 (95% CI 5.6 to 11.7) months Failure events (entire follow-up period) EBRT: 204 events Control: 261 events HR 0.59, 95% CI 0.49 to 0.72 p<0.0001			Randomisation was stratified for hospital, age (<70 vs ≥70 years), nodal involvement (positive, negative, unknown), WHO performance status (0 vs 1 or 2), planned ADT, and regular aspirin or non-steroidal anti-inflammatory drug (yes or no). From December 2015, planned docetaxel use was added as a stratification factor. Analysis was on an intention to treat basis and the survival analysis for patients with a low metastatic burden was specified a priori. Survival probabilities and mean survival time estimates are based on restriction to the first 59 months on the trial. Of 1032 patients randomised to receive EBRT, 968 started within one year and 906 received the planned schedule. For those who did not receive EBRT, this was mainly due to patient choice Results by subgroups such as age, tumour stage and docetaxel treatment are not provided separately for the group of patients with a low metastatic burden. It is possible that the effectiveness of radiotherapy to the prostate is different when used together with docetaxel or other chemotherapeutic agents (eg abiraterone), which are increasingly being used as part of standard care. A relatively small proportion of patients received docetaxel in this study (roughly one sixth). Two different radiotherapy dose schedules were trialled but a comparison of their relative effectiveness in patients with a low metastatic burden was not reported. The schedules were both lower than standard radical prostate radiotherapy doses and were chosen for patient convenience, based on a survey of investigators' opinions.
				Secondary Clinical effectiveness	Prostate cancer-specific survival (PCSS) (Pre-defined criteria were used to indicate whether prostate cancer was the likely cause of death) (survival probabilities and mean survival time estimates restricted to first 59 months on the trial)	**Patients with low metastatic burden (see right hand column for definition)** EBRT n=410 Control n=409 3 year PCSS EBRT: 86% Control: 79% p value and numbers not reported Mean PCSS EBRT: 51.8 months Control: 48.6 months Difference 3.3 (95% CI 1.0 to 5.5) months PCSS HR 0.65, 95% CI 0.47 to 0.90 p=0.010			

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Controls 48 IQR 19-120) 76% had bone metastases 77% had Gleason score 8-10 (unknown for 29) 75% had WHO performance status of 0 Median age 68 years (IQR 63-73)		Secondary Clinical effectiveness	Progression free survival (PFS) (defined as FFS excluding biochemical events) (survival probabilities and mean survival time estimates restricted to first 59 months on the trial)	**Patients with low metastatic burden (see right hand column for definition)** EBRT n=410 Control n=409 3 year PFS EBRT: 63% Control: 58% p value and numbers not reported Mean PFS EBRT: 42.9 months Control: 39.4 months Difference 3.5 (95% CI 0.4 to 6.7) months PFS HR 0.78, 95% CI 0.63 to 0.98 p=0.033			Patients, clinicians and study staff were not blinded to the treatments received. This could potentially introduce bias if a particular result was anticipated. However, outcome measures were sufficiently objective for this not to be an important concern, except potentially for the reporting of cause of death (which was classified by the site investigator) and some of the more subjective symptoms and adverse events. Median follow-up (37 months) was shorter than median survival (46 months) which could be relevant particularly to counts of symptomatic local events, which can occur late. Biochemical failure (increase in PSA) was specified as a primary outcome measure but results for this were not reported in the paper. However, the difference between PFS and FFS, both of which were reported, is that biochemical failure is included in the latter. Burdett et al (2019) report that in the HORRAD trial, biochemical progression was defined as the time between diagnosis and a PSA increase after the initiation of ADT of >50% of the lowest PSA value after the start of treatment (with a minimum of 1 ng/ml), and in the STAMPEDE trial as a rise above the lowest PSA within 24 weeks of enrolment of 50% to at least 4 ng/ml. Imaging techniques have improved over recent years and the definitions used for number of metastases are based on the techniques available at the time of the RCT. Newer higher resolution imaging may find a greater number of metastases in the same patients and the results of this study need to be interpreted in conjunction with knowledge of the imaging techniques that were used in the study (whole body scintigraphy and CT or MRI staging scans).
				Secondary Clinical effectiveness	Metastatic progression free survival (MPFS) (to new metastases or progression of existing metastases or death) (survival probabilities and mean survival time estimates restricted to first 59 months on the trial)	**Patients with low metastatic burden (see right hand column for definition)** 3 year MPFS EBRT (n=410): 67% Control (n=409): 62% p value and numbers not reported Mean MPFS EBRT: 44.2 months Control: 41.1 months Difference 3.1 (95% CI 0.2 to 6.0) months MPFS HR 0.80, 95% CI 0.63 to 1.01 p value not reported			

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Secondary Safety	Symptomatic local event free survival (SLEFS) (definition not reported) (survival probabilities and mean survival time estimates restricted to first 59 months on the trial)	**Patients with low metastatic burden (see right hand column for definition)** EBRT n=410 Control n=409 3 year SLEFS EBRT: 72% Control: 65% p value and numbers not reported Mean SLEFS EBRT: 44.0 months Control: 41.6 months Difference 2.4 (95% CI -0.7 to 5.4) months SLEFS HR 0.82 (95% CI 0.64 to 1.05)			
				Secondary Safety	Adverse events (AEs) Only reported for all patients that received prostate radiotherapy (n=1032) and for all controls (n=1029), and not separately for the group with low volume metastatic disease.	**Symptomatic local events** Most common symptomatic local events within the treatment window (where >10 patients in a group affected): Urinary tract infection EBRT (n=1032): 3% (31 patients) Control (n=1029): 1% (14 patients) Urinary catheter EBRT (n=1032): 2% (18 patients) Control (n=1029): 1% (14 patients). p values not reported Most common symptomatic treatment events after the treatment window (where >10 patients in a group affected): Urinary tract infection EBRT (n=1032): 7% (75 patients)			

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Control (n=1029); 5% (49 patients) Urinary catheter EBRT (n=1032): 3% (36 patients) Controls (n=1029): 3% (35 patients) Acute kidney injury EBRT (n=1032): 3% (35 patients) Control (n=1029): 3% (31 patients) Urinary tract obstruction EBRT (n=2032): 2% (17 patients) Control (n=1029): 2% (24 patients) Ureteric stent EBRT (n=1032): 1% (7 patients) Control (n=1029): 2% (16 patients) p values not reported **Acute bladder or bowel adverse effects (timescale not reported)** Grade 3 or 4 (RTOG scale[20]) acute adverse effects EBRT (n=920[21]): 5% (48 patients) Worst acute bladder toxic effect grade 3 or 4: EBRT: 5% (42 patients). Worst acute bowel toxic effect grade 3 or 4: EBRT: 1% (8 patients). No acute grade 5 toxic effects reported. Grade 1-4 (RTOG scale) acute bladder effects			

[12] Radiation Therapy Oncology Group (RTOG) toxicity grading scale grades acute and late radiation toxicity from 0 (no symptoms) to 5 (death directly related to radiation effects), with separate descriptions for each organ/organ system and for acute and late toxicity. For example grade 3 and 4 late haematuria radiation toxicity are defined respectively as frequent haematuria and severe haemorrhagic cystitis (RTOG Foundation 2019).
[21] Patients allocated to EBRT who started radiotherapy and who completed at least one acute toxicity form

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						EBRT weekly schedule (n=437): 65% (282 patients)) EBRT daily schedule (n=483): 71% (341 patients) Grade 1-4 (RTOG scale) acute bowel effects EBRT weekly schedule (n=437): 47% (206 patients) EBRT daily schedule (n=483): 62% (297 patients) p values not reported **Late bladder or bowel adverse effects (timescale not reported)** Grade 3 and 4 (RTOG scale) late adverse effects[22]: EBRT (n=988) : 4% (37 patients) Diarrhoea n=12, proctitis n=11, cystitis n=7, haematuria n=6, urethral stricture n=4, bowel obstruction n=1. Controls who received some radiotherapy at some point (n=187): 1% (1 patient) Diarrhoea n=1 No late grade 5 toxic effects reported. p value not reported **Adverse effects of cancer therapy drugs (CTCAE[23] scale)[24]** At least one grade 3 or worse event: EBRT (n=985): 39% (380 patients) Control (n=1050): 38% (398 patients)			

[22] Patients who started radiotherapy and had at least one follow-up assessment
[23] CTCAE, the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, are a set of criteria for the standard classification of adverse effects of drugs used for cancer therapy: 1 (mild), 2 (moderate), 3 (severe but not immediately life-threatening), 4 (life-threatening) and 5 (death) (US Department of Health and Human Services 2010).
[24] Patients with at least one follow-up assessment analysed according to the treatment approach started

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Dominated in both groups by side effects of long term ADT (no detail or examples provided). Time to first grade 3 or worse event similar in both groups, HR 1.01, 95% CI 0.87 to 1.16, p=0.941. At 6 months, proportion reporting grade 3 or worse AE: EBRT (n=981): 22% (212 patients) Controls (n=1047): 21% (225 patients) At 1 year, proportion reporting grade 3 or worse AE: EBRT group: 78 (13%) of 594 Controls: 63 (12%) of 531 At 2 years, proportion reporting grade 3 or worse AE: EBRT group: 37 (13%) of 293 Controls: 37 (15%) of 240 (data not available for all patients)			

Abbreviations: ADT – androgen deprivation therapy; AE – adverse events; CTCAE – common terminology criteria for adverse events; EBRT – external beam radiotherapy; FFS – failure free survival; HR – hazard ratio; IQR – interquartile range; MPFS – metastatic progression free survival; PCSS – prostate cancer specific survival; PFS – progression free survival; PICO – population, intervention, comparator, outcomes; PSA – prostate specific antigen; RCT – randomised controlled trial; RER – rapid evidence review; RTOG – Radiation Therapy Oncology Group; SLEFS – symptomatic local event free survival.

8 Grade of Evidence Table

For abbreviations see list after table

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival	Burdett et al 2019	8	Direct	A	Overall survival was defined by Burdett et al (2019) as the time from randomisation to death from any cause. In their systematic review and meta-analysis (SRMA) of two randomised controlled trials (RCTs), Burdett et al (2019) reported survival for patients with low volume metastatic disease defined as fewer than five bone metastases. Among 963 patients with fewer than five bone metastases, there was a statistically significantly improved survival among patients who were treated with external beam radiotherapy (EBRT) compared to standard care alone. This translated to a seven percentage point improvement in survival (95% CI 2 to 11) at three years from 70% to 77%. (Hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.58 to 0.92; p=0.0071). The results suggest that prostate radiotherapy provides a statistically significant overall survival benefit of seven percentage points at three years in patients with newly diagnosed prostate cancer who have low volume metastatic disease. This increase of approximately a further seven in every 100 patients being alive three years after randomisation to receive prostate radiotherapy is likely to be important to patients. This is an important outcome measure because it takes into account any increased survival that results from the treatment as well as any mortality related to the treatment. The SRMA included two RCTs of prostate EBRT in patients with newly diagnosed metastatic hormone-sensitive prostate cancer and suggests a benefit to patients with low volume metastatic disease over the median follow-up period in the two RCTs of 41.9 months (Parker et al 2018, n=804) and 47 months (Boevé et al 2019, n=160) respectively. The SRMA is generally of good quality. However, thresholds chosen to define low volume metastatic disease were based on the data available and not on a sensitivity analysis. This means that the threshold of metastatic volume below which prostate radiotherapy is likely to be beneficial is not clear. Treatment with chemotherapeutic agents such as docetaxel is increasingly becoming part of standard care (Boevé et al 2019), but patients who received docetaxel were excluded from this study. The effectiveness of prostate radiotherapy in the group of patients who are also treated with these drugs may be different from that observed in this study. Additionally, newer imaging techniques, with higher resolution than were used in these studies, are increasingly being used to identify metastases (although not current “standard of care”), and adoption of the definitions of low volume metastatic disease used here will need to take account of the imaging techniques used in practice and those used in these studies.
	Parker et al 2018	8	Direct		

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Deaths from any cause	Burdett et al 2019	8	Direct	A	The number of deaths from any cause includes deaths due to prostate cancer, deaths due to side effects of treatment and deaths from other causes. Burdett et al (2019) reported the number of deaths from any cause during the follow-up period of the included studies for patients with low volume metastatic disease defined in two different ways. Patients were followed up for a median of 41.9 months (Parker et al 2018, n=804) and 47 months (Boevé et al 2019, n=160) in the two RCTs respectively. Among patients with fewer than five bone metastases, Burdett et al (2019) reported 140 deaths from any cause among 488 patients who were treated with EBRT (28.7%) in addition to standard care and 164 deaths among 475 controls who received standard care alone (34.5%). Among patients with a low metastatic burden defined as Gleason sum score[25] less than 9, fewer than five metastases and prostate specific antigen (PSA) less than 142 ng/ml, Burdett et al (2019) reported 113 deaths from any cause among 426 patients treated with EBRT in addition to standard care (26.5%) and 135 deaths among 420 controls (32.1%) (p values not reported). Because statistical analyses of these results were not presented, it is not clear whether they represent a significant reduction in death rates. However, the increased survival reported (see above) suggests that all-cause mortality is reduced by prostate radiotherapy in patients with fewer than five metastases and there may be five or six fewer deaths per 100 patients in the 3.5 to four years after prostate radiotherapy. The results suggest a reduction in deaths from any cause and this is an important outcome measure because it takes account of any increase in deaths due to side effects of treatment as well as any reduction in deaths due to the treatment effect. The SRMA included two RCTs of prostate EBRT in patients with newly diagnosed metastatic hormone-sensitive prostate cancer and suggests a benefit to patients with low volume metastatic disease over the median follow-up period in the two RCTs of 41.9 months (Parker et al 2018) and 47 months (Boevé et al 2019) respectively. The SRMA is generally of good quality. However, thresholds chosen to define low volume metastatic disease were based on the data available and not on a sensitivity analysis. This means that the threshold of metastatic volume below which prostate radiotherapy is likely to be beneficial is not clear. Treatment with chemotherapeutic agents such as docetaxel is increasingly becoming part of standard care (Boevé et al 2019), but patients who received docetaxel were excluded from this study. The effectiveness of prostate radiotherapy in the group of patients who are also treated with these drugs may be different from that observed in this study. Additionally, newer imaging techniques, with higher resolution than were used in these studies, are increasingly being used to identify metastases (although not current "standard of care"), and adoption of the definitions of low volume metastatic disease used here will need to take account of the imaging techniques used in practice and those used in these studies.
	Parker et al 2018	8	Direct		

[25] Gleason sum score: a score between 2 and 10 based on microscopic appearance of cancer cells, with a higher score indicating a more aggressive cancer and worse prognosis

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Number of patients with symptomatic clinical or radiological progression or death (progression events)	Burdett et al 2019	8	Direct	B	Progression events were defined by Burdett et al (2019) as clinical or radiological progression or death, and do not include biochemical evidence of progression, such as a rise in PSA. In the SRMA by Burdett et al (2019), patients were followed up for a median of 41.9 months (Parker et al 2018, n=804) and 47 months (Boevé et al 2019, n=160) in the two RCTs respectively. Burdett et al (2019) defined low volume metastatic disease in two different ways. For patients with fewer than five bone metastases, there were 222 patients with progression events in the EBRT group (n=488) (45.5%) and 235 in the control group (n=475) (49.5%) (p value not reported). Among patients with a low metastatic burden defined as Gleason sum score less than 9, fewer than five metastases and PSA less than 142 ng/ml, there were 192 patients with progression events in the EBRT group (n=426) (45.1%) and 204 in the control group (n=420) (48.6%) (p value not reported). Although the percent of patients experiencing progression events was lower in the group treated with EBRT compared to controls, there was no statistical analysis of this difference and without this, these results do not provide evidence that prostate radiotherapy reduces or delays progression events in patients with newly diagnosed prostate cancer with low volume metastatic disease because the difference observed could have been due to chance. Prevention of progression is an important outcome for patients. Although the SRMA is generally of good quality, it did not provide any statistical analysis of the difference in progression events separately for the group of patients with low volume metastatic disease, and this limits the usefulness of this outcome measure to this RER.
Progression free survival	Parker et al 2018	8	Direct	B	Progression free survival (PFS) was defined by Parker et al (2018) as the time from randomisation to the first evidence of at least one of progression locally or in lymph nodes or in distant metastases, or death from prostate cancer. The definition does not include biochemical evidence of progression, such as a rise in PSA. In the RCT of EBRT in patients with newly-diagnosed metastatic prostate cancer who were also intended for long term androgen deprivation treatment (Parker et al 2018), patients were followed up for a median of 37 months. Among patients with a low metastatic burden (n=819), three year PFS was reported as 63% among 410 patients treated with EBRT compared to 58% among 409 controls (p value not reported). The authors reported a HR for PFS of 0.78, 95% CI 0.63 to 0.98, p=0.033; and the mean PFS was 42.9 months in the EBRT group compared to 39.4 months for controls, a difference of 3.5 (95% CI 0.4 to 6.7) months. Low metastatic burden was defined as not having: “four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both”. These results suggest that prostate radiotherapy provides a statistically significant improvement in PFS in patients with low volume metastatic disease, with approximately five fewer patients in 100 experiencing progression of the cancer (excluding biochemical progression) or prostate cancer related death in the first three years after prostate radiotherapy, and people on average surviving for 3.5 months longer before progression or

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					prostate cancer related death. Although this is likely to be important to patients, improvement in overall survival is arguably more important. This RCT is generally of good quality. However, although predefined criteria were used to determine whether the cause of death listed by the site investigator was a prostate cancer specific cause of death, there could have been some bias related to the identification of the cause of death by the site investigator, as cause of death is not always clear-cut. Also, the threshold chosen to define low volume metastatic disease was based on that used in a previous study (a study of chemohormonal therapy rather than radiotherapy (Sweeney et al 2015)), and was not based on a sensitivity analysis to determine the optimal threshold. A relatively small proportion of patients (129 of 819 with low metastatic burden) had docetaxel included in their planned standard care in this study. These were the patients who were randomised more recently. Treatment with chemotherapeutic agents such as docetaxel is increasingly becoming part of standard care, and the effectiveness of prostate radiotherapy in the group of patients who were also treated with docetaxel was not analysed separately and may be different from the overall effectiveness of prostate radiotherapy observed in this study. Additionally, newer imaging techniques, with higher resolution than were used in this study, are increasingly being used to identify metastases (although not current "standard of care"), and adoption of the definition of low volume metastatic disease used here will need to take account of the imaging techniques used in practice and those used in this study.
Number of patients with biochemical, clinical or radiological progression or death (failure events)	Burdett et al 2019	8	Direct	A	Failure events were defined by Burdett et al (2019) as biochemical (a rise in PSA by a predefined amount[26]), clinical or radiological progression or death. In the study by Burdett et al (2019), patients were followed up for a median of 41.9 months (Parker et al 2018, n=804) and 47 months (Boevé et al 2019, n=160) in the two RCTs respectively. Burdett et al (2019) defined low volume metastatic disease in two different ways. Among patients with fewer than five bone metastases, there were 296 patients with failure events in the EBRT group (n=488) (60.7%) and 349 in the control group (n=475) (73.5%) (p value not reported). Among patients with a low metastatic burden defined as Gleason sum score less than 9, fewer than five metastases and prostate specific antigen (PSA) less than 142 ng/ml, there were 253 patients with failure events in the EBRT group (n=426) (59.4%) and 306 in the control group (n=420) (72.9%) (p value not reported). Although the percent of patients experiencing failure events was lower in the group treated with EBRT compared to controls, there was no statistical analysis of this difference and without this, these results do not provide evidence that prostate radiotherapy reduces or delays failure events in patients with newly diagnosed prostate cancer with low volume metastatic disease, because the difference observed could have been due to chance. Prevention of biochemical, clinical and radiological progression or death (failure) is an important outcome for patients. Although the SRMA is generally of good quality, it did not provide any statistical analysis of the difference in progression events separately for the
	Parker et al 2018	8	Direct		

[26] Biochemical progression was defined in the HORRAD trial as a PSA increase after the initiation of ADT of >50% of the lowest PSA value after the start of treatment (with a minimum of 1 ng/ml), and in the STAMPEDE trial as a rise above the lowest PSA within 24 weeks of enrolment of 50% to at least 4 ng/ml

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					group of patients with low volume metastatic disease, and this limits the usefulness of this outcome measure to this RER.

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Failure free survival	Parker et al 2018	8	Direct	B	Failure free survival (FFS) was defined by Parker et al (2018) as the time from randomisation to at least one of biochemical failure (rise in PSA[27]), progression locally or in lymph nodes or in distant metastases, or death from prostate cancer. In the RCT of EBRT in patients with newly-diagnosed metastatic prostate cancer who were also intended for long term androgen deprivation treatment (Parker et al 2018), patients were followed up for a median of 37 months. Among patients with a low metastatic burden (n=819), three year FFS was reported as 50% among 410 patients treated with EBRT compared to 33% among 409 controls (p value not reported). The authors reported a HR for FFS of 0.59, 95% CI 0.49 to 0.72, p<0.0001; and the mean FFS was 36.1 months in the EBRT group compared to 27.4 months for controls, a difference of 8.6 (95% CI 5.6 to 11.7) months. Low metastatic burden was defined as not having: "four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both". These results suggest that prostate radiotherapy provides a statistically significant improvement in FFS in patients with low volume metastatic disease, with approximately 17 fewer patients in 100 experiencing failure (progression of the cancer biochemically or locally or in lymph nodes or in distant metastases or prostate cancer related death) in the first three years after prostate radiotherapy, and people on average surviving for 8.6 months longer before failure. Although this is likely to be important to patients, improvement in overall survival is arguably more important. This RCT is generally of good quality. However, although predefined criteria were used to determine whether the cause of death listed by the site investigator was a prostate cancer specific cause of death, there could have been some bias related to the identification of the cause of death by the site investigator, as cause of death is not always clear-cut. Also, the threshold chosen to define low volume metastatic disease was based on that used in a previous study (a study of chemohormonal therapy rather than radiotherapy (Sweeney et al 2015)), and was not based on a sensitivity analysis to determine the optimal threshold. A relatively small proportion of patients (129 of 819 with low metastatic burden) had docetaxel included in their planned standard care in this study. These were the patients who were randomised more recently. Treatment with chemotherapeutic agents such as docetaxel is increasingly becoming part of standard care, and the effectiveness of prostate radiotherapy in the group of patients who were also treated with docetaxel was not analysed separately and may be different from the overall effectiveness of prostate radiotherapy observed in this study. Additionally, newer imaging techniques, with higher resolution than were used in this study, are increasingly being used to identify metastases (although not current "standard of care"), and adoption of the definition of low volume metastatic disease used here will need to take account of the imaging techniques used in practice and those used in this study.

[27] Biochemical progression was defined by Parker et al (2018) as a rise above the lowest PSA within 24 weeks of enrolment of 50% to at least 4 ng/ml

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Prostate cancer specific survival	Parker et al 2018	8	Direct	B	Prostate cancer specific survival only takes into account deaths that were likely to have been due to prostate cancer. In the RCT by Parker et al (2018), prostate cancer specific survival included all patients who had not died of a cause thought likely to have been related to prostate cancer during the trial follow-up period and within their first 59 months in the trial. Three year survival and mean survival were also reported. In the RCT of EBRT in patients with newly-diagnosed metastatic prostate cancer who were also intended for long term androgen deprivation treatment (Parker et al 2018), patients were followed up for a median of 37 months. Among patients with a low metastatic burden (n=819), three year prostate cancer specific survival was reported as 86% among 410 patients treated with EBRT compared to 79% among 409 controls (p value not reported). The HR for prostate cancer specific survival was 0.65, 95% CI 0.47 to 0.90, p=0.010; and the mean prostate cancer specific survival was 51.8 months in the EBRT group compared to 48.6 months for controls, a difference of 3.3 (95% CI 1.0 to 5.5) months. Low metastatic burden was defined as not having: “four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both”. These results suggest that prostate radiotherapy provides a statistically significant improvement in prostate cancer specific survival in patients with low volume metastatic disease, with approximately seven fewer patients in 100 dying of prostate cancer in the first three years after prostate radiotherapy, and people on average surviving for 3.3 months longer before succumbing to prostate cancer. Although this is likely to be important to patients, improvement in overall survival is arguably more important. This RCT is generally of good quality. However, although predefined criteria were used to determine whether the cause of death listed by the site investigator was a prostate cancer specific cause of death, there could have been some bias related to the identification of the cause of death by the site investigator, as cause of death is not always clear-cut. Also, the threshold chosen to define low volume metastatic disease was based on that used in a previous study (a study of chemohormonal therapy rather than radiotherapy (Sweeney et al 2015)), and was not based on a sensitivity analysis to determine the optimal threshold. A relatively small proportion of patients (129 of 819 with low metastatic burden) had docetaxel included in their planned standard care in this study. These were the patients who were randomised more recently. Treatment with chemotherapeutic agents such as docetaxel is increasingly becoming part of standard care, and the effectiveness of prostate radiotherapy in the group of patients who were also treated with docetaxel was not analysed separately and may be different from the overall effectiveness of prostate radiotherapy observed in this study. Additionally, newer imaging techniques, with higher resolution than were used in this study, are increasingly being used to identify metastases (although not current “standard of care”), and adoption of the definition of low volume metastatic disease used here will need to take account of the imaging techniques used in practice and those used in this study.
Metastatic progression free survival	Parker et al 2018	8	Direct	B	Metastatic progression free survival (MPFS) was defined by Parker et al (2018) as the time from randomisation to new metastases or progression of existing metastases or death.

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Survival therefore included all patients who were alive and did not have new metastases or progression of existing metastases during the trial follow-up period. In the RCT of EBRT in patients with newly-diagnosed metastatic prostate cancer who were also intended for long term androgen deprivation treatment, patients were followed up for a median of 37 months. Among patients with a low metastatic burden (n=819), Parker et al (2018) reported three year MPFS as 67% in the EBRT group (n=410) compared to 62% for controls (n=409) (p value not reported). The HR for MPFS was 0.80, 95% CI 0.63 to 1.01, p value not reported; and the mean MPFS was 44.2 months in the EBRT group compared to 41.1 months for controls, a difference of 3.1 (95% CI 0.2 to 6.0) months. Low metastatic burden was defined as not having: “four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both”. These results suggest that prostate radiotherapy provides a statistically significant increase in survival without new metastases or progression of existing metastases of an average of about 3.1 months in patients with newly diagnosed prostate cancer who have low volume metastatic disease. There may be about five more patients per 100 treated with prostate radiotherapy who are alive and do not have new metastases or progression of existing metastases three years after prostate radiotherapy, but the p value was not reported for this, and so the level of certainty around this figure is less clear. This RCT is generally of good quality. However, the threshold chosen to define low volume metastatic disease was based on that used in a previous study (a study of chemohormonal therapy rather than radiotherapy), and was not based on a sensitivity analysis to determine the optimal threshold. A relatively small proportion of patients (129 of 819 with low metastatic burden) had docetaxel included in their planned standard care in this study. These were the patients who were randomised more recently. Treatment with chemotherapeutic agents such as docetaxel is increasingly becoming part of standard care, and the effectiveness of prostate radiotherapy in the group of patients who were also treated with docetaxel was not analysed separately and may be different from the overall effectiveness of prostate radiotherapy observed in this study. Additionally, newer imaging techniques, with higher resolution than were used in this study, are increasingly being used to identify metastases (although not current “standard of care”), and adoption of the definition of low volume metastatic disease used here will need to take account of the imaging techniques used in practice and those used in this study.
Symptomatic local event free survival	Parker et al 2018	8	Direct	B	Symptomatic local event free survival was reported in the RCT by Parker et al (2018), but was not clearly defined. It appears to relate to the time from randomisation to either death or symptomatic local events such as urinary tract infection, need for a urinary catheter or acute kidney injury, which may have occurred either during or after the treatment window but within the follow up period of the study and not more than 59 months after entry to the trial (see adverse events below for further details). In the RCT of EBRT in patients with newly-diagnosed metastatic prostate cancer who were also intended for long term androgen deprivation treatment, patients were followed up for a median of 37 months. Among patients with a low metastatic burden (n=819), Parker et al

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					(2018) reported three year symptomatic local event free survival as 72% in the EBRT group (n=410) compared to 65% for controls (n=409) (p value not reported). The HR for symptomatic local event free survival was 0.82(95% CI 0.64 to 1.05); and the mean symptomatic local event free survival was 44.0 months in the EBRT group compared to 41.6 months for controls, a difference of 2.4 (95% CI -0.7 to 5.4) months. Low metastatic burden was defined as not having: "four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both". These results suggest that in patients with newly diagnosed prostate cancer who have low volume metastatic disease there is no statistically significant difference between prostate radiotherapy and control treatment in symptomatic local event free survival, and that three years after prostate radiotherapy approximately seven more patients in a 100 are alive and have not had symptomatic local events. However, no p value was provided for the number of extra months of symptomatic local event free survival gained and the 95% CI for the increase crossed zero, making the level of certainty around this gain less clear. This RCT is generally of good quality. However, the threshold chosen to define low volume metastatic disease was based on that used in a previous study (a study of chemohormonal therapy rather than radiotherapy), and was not based on a sensitivity analysis to determine the optimal threshold. A relatively small proportion of patients (129 of 819 with low metastatic burden) had docetaxel included in their planned standard care in this study. These were the patients who were randomised more recently. Treatment with chemotherapeutic agents such as docetaxel is increasingly becoming part of standard care, and the effectiveness of prostate radiotherapy in the group of patients who were also treated with docetaxel was not analysed separately and may be different from the overall effectiveness of prostate radiotherapy observed in this study. Additionally, newer imaging techniques, with higher resolution than were used in this study, are increasingly being used to identify metastases (although not current "standard of care"), and adoption of the definition of low volume metastatic disease used here will need to take account of the imaging techniques used in practice and those used in this study.
Adverse events	Parker et al 2018	8	Direct	B	Adverse events are potentially harmful unwanted health effects which have occurred as a side-effect of treatment. Adverse events reported included symptoms relating to the bowel and bladder, which may be radiotherapy-related. These were recorded using the Radiation Therapy Oncology Group (RTOG) toxicity grading scale which grades acute and late[28] radiation toxicity from 0 (no symptoms) to 5 (death directly related to radiation effects), with separate descriptions for each organ/organ system. Adverse effects of drugs used for cancer therapy were recorded using the CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0) classification: 1 (mild), 2 (moderate), 3 (severe but not immediately life-threatening), 4 (life-threatening) and 5 (death). Adverse events were reported for patients randomised to either the prostate radiotherapy (n=1032) or control (n=1029) groups, but the groups were not split into high or low volume metastatic disease.

[28] The timescales for acute and late radiation toxicity were not reported.

Prostate external beam radiotherapy compared to standard care for newly diagnosed patients with prostate cancer who have low volume metastatic disease					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Within the treatment window, the most common symptomatic treatment events, affecting more than 10 patients in a group, were urinary tract infection (31 patients, 3%, in the EBRT group and 14 patients, 1%, of controls) and urinary catheter (18 patients, 2%, in the EBRT group and 14 patients, 1%, of controls). p values were not reported. After the treatment window, the most common symptomatic treatment events, affecting more than 10 patients in a group, were urinary tract infection (75 patients; 7%, in the EBRT group and 49 patients, 5%, of controls), urinary catheter (36 patients, 3%, in EBRT group and 35 patients, 3%, of controls), acute kidney injury (35 patients, 3%, in the EBRT group and 31 patients, 3%, of controls), and urinary tract obstruction (17 patients, 2%, in the EBRT group and 24 patients, 2%, of controls). Seven patients treated with EBRT (1%) and 16 (2%) of the controls needed a ureteric stent. p values were not reported. In the EBRT group, 5% had acute RTOG scale grade 3 or 4 adverse events (5% for bladder and 1% for bowel related events), and 4% had late RTOG scale grade 3 or 4 events, most commonly diarrhoea, proctitis, cystitis and haematuria. No deaths relating to acute or late RTOG scale (grade 5) toxic effects of radiotherapy were reported. The time to the first CTCAE grade 3 or worse adverse event was similar in both groups (HR 1.01, 95% CI 0.87 to 1.16, p=0.941), and they were dominated by side effects of long term androgen deprivation therapy. Overall rates of CTCAE grade 3 or worse events were 39% in the EBRT group and 38% in the control group, with corresponding rates at six months, one year and two years being 22%, 13% and 13% in the EBRT group and 21%, 12% and 15% in the control group respectively. Adverse events are important to patients because if serious and/or common they may outweigh the benefits associated with prostate radiotherapy. These results suggest that the radiotherapy schedules used in these studies were relatively well tolerated with around 5% of patients having acute and 4% having late RTOG scale grade 3 or 4 side effects of radiotherapy, and no radiotherapy-related deaths among over 1000 patients. Patients were followed up for a median of 37 months (interquartile range 24 to 48 months). The data on adverse effects of radiotherapy, although based on relatively large numbers of patients, include patients who had high volume metastatic disease as well as those with low volume metastatic disease, the latter making up about 40% of the total. It is possible that the frequency of side effects of radiotherapy is different in people with low volume metastatic disease compared to the total cohort. However, as they are likely to have a lower cancer burden, it is likely that, if there is any difference, it would be in the direction of fewer adverse effects. The frequency of side effects may also be affected by other treatments that patients receive. Relatively few patients (under 20%) in the study cohort received docetaxel. However, treatment with chemotherapeutic agents such as docetaxel is increasingly becoming part of standard care, and the incidence of adverse effects of prostate radiotherapy in the group of patients who were also treated with docetaxel was not analysed separately and may be different from the overall incidence of adverse effects of prostate radiotherapy observed in this study. Also, patients, clinicians and study staff were not blinded to the treatments received, and this could have introduced bias in the reporting of some of the more subjective adverse effects, although most of those reported could be considered to be relatively objective.

Abbreviations: AE – adverse events; CTCAE – common terminology criteria for adverse events; EBRT – external beam radiotherapy; FFS – failure free survival; HR – hazard ratio; IQR – interquartile range; MPFS – metastatic progression free survival; PCSS – prostate cancer specific survival; PFS – progression free survival; PICO – population, intervention, comparator, outcomes; PSA – prostate specific antigen; RCT – randomised controlled trial; RER – rapid evidence review; RTOG – Radiation Therapy Oncology Group.

9 Literature Search Terms

P –Population and Indication Describe the relevant population and indication provided previously including if necessary disease severity or duration, previous treatment, new or recurrent symptoms, any specific co-morbidities and other population factors (for example, age range). Add details of any subgroups or stratifications for which separate evidence may be required.	Patients of all ages who have newly diagnosed prostate cancer who have low volume metastatic disease [As there are multiple definitions, include patients with low volume disease, however defined in the study. For example, in the CHAARTED trial high volume metastatic disease was defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis; all other patients had 'low volume disease', including those with lymph node metastases.]
I – Intervention Describe the intervention details provided previously including if necessary details of treatment, mode of delivery, size/frequency/duration of dose, position of intervention in treatment pathway (e.g. first/second line/salvage) and any background / concomitant medication	External beam radiotherapy to the prostate plus standard care (see below) [Include all schedules of radiotherapy used in studies]
C – Comparators What is/are the main alternative/s to compare with the intervention being considered? Describe the comparator details provided previously including if necessary details of treatment, mode of delivery, size/frequency/duration of dose, position of intervention in treatment pathway (e.g. first/second line/salvage) and any background / concomitant medication	Standard care for newly diagnosed metastatic prostate cancer: Androgen deprivation therapy +/- upfront chemotherapy (Docetaxel x 6 cycles), +/- palliative radiotherapy for symptomatic metastases [For information: androgen deprivation therapy consists of either orchidectomy or drug treatments including but not limited to gonadotrophin releasing hormone analogue For information: upfront chemotherapy is offered to patients who are fit enough dependent on comorbidties but may also be declined due to patient preference]
O – Outcomes Outcomes should be patient focussed and relate to those detailed in the PPP and the Research Questions covering clinical effectiveness, safety and cost effectiveness as required. Examples will be topic specific but might include intermediate or short-term outcomes; mortality; morbidity; quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*<u>Critical to decision-making:</u>* *Overall survival* *Prostate cancer specific survival* *Progression free survival (including biochemical failure)* *Biochemical failure [For information: Examples include ASTRO or Phoenix definitions]* *Side effect profile (e.g. acute and late urinary toxicity (catheter, urinary retention, incontinence, nocturia); acute and late bowel toxicity, erectile dysfunction)* *Quality of life* *Adverse events* *<u>Important to decision-making:</u>* *Cost effectiveness*
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies.

Language	English only
Patients	Human studies only
Age	All ages
Date limits	2009-2019
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials
Study design	Case reports, case series, resource utilisation studies

10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers published in English from the 1st January 2009 to the 2nd April 2019. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 2nd April 2019
Medline search:

# ▲	Searches
1	exp Prostatic Neoplasms/
2	Neoplasm Metastasis/
3	1 and 2
4	(prostat* adj5 metasta*).ti,ab.
5	(prostat* and metasta*).ti.
6	3 or 4 or 5
7	exp Prostatic Neoplasms/rt [Radiotherapy]
8	Radiotherapy/
9	(radiotherap* or radiation or irradiat*).ti.
10	(external beam radiotherap* or external beam radiation or ebrt).ti,ab.
11	((radiotherap* or radiation or irradiat*) adj10 (concurrent* or addition* or (standard adj3 care) or added)).ti,ab.
12	7 or 8 or 9 or 10 or 11
13	6 and 12
14	exp animals/ not humans.sh.
15	13 not 14
16	(comment or editorial or letter or news or "review").pt. or case report.ti,ab.
17	15 not 16
18	limit 15 to "reviews (maximizes specificity)"
19	17 or 18
20	limit 19 to (english language and yr="2009 -Current")

11 Evidence Selection

- Total number of publications reviewed: 64
- Total number of publications considered potentially relevant: 18
- Total number of publications selected for inclusion in this briefing: 2

References from the PWG supplied in the PPP		Paper selection decision and rationale if excluded
1	Parker C.C., James N.D., Brawley C.D., Clarke N.W., Hoyle A.P., Ali A. et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet Oct 2018; 392: 2353–66	Included
2	Boeve L.M.S., Hulshof M.C.C.M., Vis A.N., Zwinderman A.H., Twisk J.W.R., Witjes W.P.J. et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. European Urology March 2019; 75(3):410-418	Excluded because the subsequent systematic review and meta-analysis by Burdett et al (2019) includes this randomised controlled trial and covers it well.
3	Rusthoven C.G., Jones B.L., Flaig T.W., Crawford D., Koshy M., Sher D.J. et al. Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer. Journal of Clinical Oncology 2016 Aug 20;34(24):2835-42	Excluded because this is a retrospective study and not a randomised controlled trial and there were randomised controlled trials and a systematic review and meta-analysis available, which means that non-randomised studies add very little.

12 References

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