MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
28 & 29 July 2020

Agenda Item No	6.1
National Programme	Cancer
Clinical Reference Group	Radiotherapy
URN	1901

Title
External beam radiotherapy of the prostate for newly diagnosed patients with hormone sensitive prostate cancer presenting with low volume metastatic disease.

Actions Requested	1. Support the adoption of the policy proposition.
	2. Recommend its relative prioritisation.

Proposition
The policy proposition recommends that external beam radiotherapy be added to the current standard of care for people with newly diagnosed, hormone sensitive, low volume, metastatic prostate cancer. Development of the policy proposition is supported by a review of the latest available clinical evidence in line with standard processes.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Cancer Programme confirms the proposition is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality & Health Inequalities Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.

3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment Report

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	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) (NHS England Clinical Commissioning Policy Statement, 2016, NHS England Reference: B15/PS/a), but patients who received docetaxel were excluded from this SRMA. The effectiveness of prostate radiotherapy in the group of patients who are also treated with these newer 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, 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 these studies.
2.	Progression free survival	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 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, 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.
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	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[1] 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. Within the treatment window, the most common symptomatic treatment events, affecting more than 10 patients in a group, were

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

		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.
11.	Delivery of intervention	Not reported

No	Outcome measure	Summary from evidence review
1.	Deaths from any cause	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 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. See above for limitations of Burdett et al (2019).
2.	Number of patients with symptomatic clinical or radiological progression or death (progression events)	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 proportion 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.
3.	Number of patients with biochemical, clinical or radiological progression or death (failure events)	Failure events were defined by Burdett et al (2019) as biochemical (a rise in PSA by a predefined amount), 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 proportion 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 group of patients with low volume metastatic disease, and this limits the usefulness of this outcome measure to this RER.
4.	Failure free survival	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), 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. See above for limitations of Parker et al (2018).
5.	Prostate cancer specific survival	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. See above for limitations of Parker et al (2018).
6.	Metastatic progression free survival	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. 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. See above for limitations of Parker et al (2018).

7.	Symptomatic local event free survival	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 (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. See above for limitations of Parker et al (2018).

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Cancer Programme of Care on 24th April 2020.