Clinical Commissioning Policy: External beam radiotherapy for patients presenting with hormone sensitive, low volume metastatic prostate cancer at the time of diagnosis [URN: 1901]

Commissioning Position

Summary

A final decision as to whether external beam radiotherapy to the prostate with newly diagnosed low volume metastatic, hormone sensitive, prostate cancer will be routinely commissioned will made by NHS England following a recommendation from the Clinical Priorities Advisory Group. The proposal is: External beam radiotherapy (EBRT) to the prostate is recommended to be available as a treatment option through routine commissioning for patients presenting with hormone-sensitive, low volume metastatic prostate cancer at the time of diagnosis within the criteria set out in this document.

Executive Summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain language summary

About prostate cancer

The prostate is a small gland located at the base of the bladder. Prostate cancer only affects people with a prostate; this means that this policy applies to any person with a prostate. The condition often develops very slowly meaning that there may be no signs of the cancer for many years. It is the most common cancer affecting men in the UK, with 41,736 new cases in 2011 (Cancer Research UK, 2017).

When prostate cancer is diagnosed it is "staged", providing an indication of the size of the cancer and whether it has spread to other parts of the body. Metastatic prostate cancer means that it has spread (metastased) beyond the prostate gland, most commonly to the bones and lymph nodes. At the point of diagnosis, approximately 18% of cases are metastatic. Metastatic prostate cancer can be further classified into either low or high volume (/burden) disease, based on the number of metastases found in the body.

About the current treatment

It is not possible to cure metastatic prostate cancer but treatments, such as initial hormone therapy (i.e. androgen deprivation therapy [ADT]) and chemotherapy, can keep it under control, sometimes for several years. These treatments are aimed at extending life expectancy and maintaining a good quality of life.

About the new treatment

Radiotherapy is the safe use of ionising radiation to kill cancer cells with the aim of cure or effective symptom relief (called 'palliation'). Radiotherapy has been historically used as a treatment for symptom control in the treatment of metastatic prostate cancer.

This policy considers whether external beam radiotherapy (EBRT), a method of delivering radiotherapy, should be offered as an additional treatment for people with low volume, metastatic prostate cancer. It is thought that the addition of EBRT in this group of patients, where the number of metastases is low and not too widespread in the body, extends overall survival and slows down progression of the disease.

Treatment with EBRT would be directed at the prostate gland and would be given either within three months of starting hormone therapy or within 6-12 weeks of completing chemotherapy treatment.

What we have decided

NHS England has carefully reviewed the evidence to treat hormone-sensitive, low volume metastatic prostate cancer with EBRT. We have concluded that there is enough evidence to make the treatment available at this time.

Committee discussion

The Clinical Priorities Advisory Group are asked to consider the evidence and the policy proposition. See the committee papers (link) for full details of the evidence.

The condition

Prostate cancer is the most common cancer in men in the UK. It usually develops slowly, so there may be no signs of the disease for many years.

Most cases of prostate cancer are diagnosed with localised disease since the introduction of prostate-specific antigen (PSA) testing. Where metastatic disease is diagnosed, it is incurable, however, patients can survive for many years with a good quality of life with various systemic treatment options.

Approximately 18% of newly diagnosed cases are metastatic at the point of diagnosis (Cancer Research UK, 2019). Metastatic prostate cancer can be further subclassified according to the number of metastases throughout the body. In a large randomised trial (Parker *et al.* 2018) about 40% of people had had low-volume metastasis (i.e. a smaller number of metastases); the remainder had high-volume metastasis indicating a larger number of metastases.

This policy has been developed for any person with a prostate who has hormone sensitive, low volume metastatic prostate cancer at the time of diagnosis. The term low metastatic volume is defined in this policy as:

- Four or fewer bone metastasis; AND
- No visceral metastases confirmed on bone scintigraphy and standard axial imaging (using either Computed Tomography [CT] or Magnetic Resonance Imaging [MRI]).

Current treatments

The initial treatment approach for metastatic prostate cancer is ADT (achieved either surgically with bilateral orchidectomy or drug treatment) with upfront docetaxel chemotherapy for six cycles (NHS England Clinical Commissioning Policy Statement, 2016, NHS England Reference: B15/PS/a) as an option if the patient is fit enough. Sometimes chemotherapy, when offered, is declined due to patient preference, and some patients are not fit enough to be offered chemotherapy due to comorbidities and performance status.

About the new treatment

Administration of EBRT to the prostate, should be offered to any person with hormone sensitive, low volume metastatic prostate cancer (as defined in this policy) at the time of the diagnosis and within three months of starting hormone therapy or within 6-12 weeks after completing Docetaxel if given. It is thought that the addition of EBRT in the treatment of low volume metastatic prostate cancer extends overall survival.

To maximise benefit and reduce the side effects due to damage of nearby tissues, the radiotherapy is given as a number of sessions over a period of weeks in an outpatient setting. A radiotherapy fractionation schedule of 36Gray (Gy) in six weekly fractions is recommended.

What we have decided

NHS England has carefully reviewed the evidence to treat the prostate in people newly diagnosed with hormone sensitive, low volume metastatic prostate cancer with EBRT. We have concluded that there is enough evidence to make the treatment available at this time in line with the clinical criteria as set out in this document.

Epidemiology and Needs Assessment

Prostate cancer is the most common cancer affecting men in England, with 40,331 new cases of prostate cancer in 2015 (Cancer Research UK, 2019). Approximately, 18% of prostate cancer cases are metastatic at the point of diagnosis (Cancer Research UK, 2019), equivalent to 7,260 new cases per year. For people with metastatic prostate cancer, one-year net survival is 85% whilst five-year net survival rate is 30% (Cancer Research UK, 2019).

It is estimated that overall approximately 40% of patients with metastatic prostate cancer have a low volume disease at diagnosis; of this patient cohort, it is estimated that 80% will be eligible to receive and choose radiotherapy, equivalent to approximately 2,300 new cases per year in England.

Evidence summary

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[1] 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).
- 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)

[1] 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: 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, p=0.033); 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[2] (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[3] (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[4] 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.

[2] This outcome was not further defined.
[3] This outcome was not further defined.
[4] 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).

- 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[5] 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. 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 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.

[5] 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).

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.

Implementation

Criteria

All patients with prostate cancer should have their care managed by a range of different specialists working together as part of a tumour specific cancer multi-disciplinary team (MDT). This includes urologists, clinical and medical oncologists, specialist nurses, therapeutic radiographers, radiologists and pathologists.

Approval for use of prostate radiotherapy in patients with low volume metastases will be evaluated through the MDT process which includes a clinical oncologist.

Case selection should take into consideration patient comorbidities, potential adverse events and likely outcomes of treatment.

Inclusion criteria:

Patients meeting the following criteria should be considered for prostate radiotherapy:

- Newly diagnosed hormone-sensitive prostate carcinoma with low volume metastatic disease (defined as: four or fewer bone metastasis AND no visceral metastases) confirmed on bone scintigraphy and standard axial imaging[6] (using either CT or MRI); AND
- No previous radical treatment; AND
- Within three months of starting hormone therapy or within 6-12 weeks after completing Docetaxel if given.

Exclusion criteria:

- High volume metastatic disease having: “five 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).
- Life expectancy of less than 2 years.
- Contraindications to prostate radiotherapy.

Dose and fractionation:

Patient convenience is a key consideration and particularly important for patients with metastatic disease. Radiobiological modelling predicts that there is equivalence in clinical effect between the different schedules. However, the radiotherapy fractionation schedule of 36Gray (Gy) in six consecutive weekly fractions of 6 Gy is recommended. This schedule is supported by the results of a recently reported RCT using a small number of fractions for the radical treatment of localised disease (Widmark *et al.* 2019).

Intensity modulated radiotherapy techniques (including volumetric modulated arc therapy, VMAT) should be used and will require a high level of treatment accuracy using image-guided radiotherapy (IGRT).

Patient Pathway

[6] Current definitions of low volume metastatic disease is based on conventional imaging using standard axial imaging (either CT or MRI) and bone scintigraphy. Caution will be required in extrapolating these results to patients imaged with more sensitive techniques (for example: PSMA PET). For example, patients with low volume disease on conventional imaging should not be denied prostate radiotherapy because they have additional lesions identified on a PET scan.

The Service Specification for External Beam Radiotherapy Services (NHS England Reference: 170091S) describes the detail of the care pathways for this service. Radiotherapy is part of an overall cancer management and treatment pathway. Decisions on the overall treatment plan should relate back to an MDT discussion and decision. Patients requiring radiotherapy are referred to a clinical oncologist for assessment, treatment planning and delivery of radiation fractions. Each fraction of radiation is delivered on one visit, usually on an outpatient basis. Patients with hormone sensitive, low volume metastatic prostate cancer at the time of diagnosis should be considered for prostate radiotherapy within three months of starting hormone therapy or within 6-12 weeks after completing docetaxel if given.

The increasing usage of upfront docetaxel is unlikely to influence the positive impact of EBRT to the prostate on patient survival. Radiotherapy remains the most effective non-surgical treatment for the primary tumour thereby conceptually reducing the release of growth promoting compounds, blocking further metastatic spread as well as reducing the viability of existing low volume metastatic disease. By sequencing radiotherapy to follow chemotherapy, it is anticipated that normal tissue radiation effects will not be enhanced.

Governance Arrangements

The Service Specification for External Beam Radiotherapy Services (NHS England Reference: 170091S) describes the governance arrangements for this service. It is imperative that the radiotherapy service is compliant with the Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) 2000.

Clinical governance systems and policies should be in place and integrated into organisational governance with clear lines of accountability and responsibility for all clinical governance functions. Providers should produce annual clinical governance reports as part of NHS clinical governance reporting system.

Mechanism for funding

Radiotherapy planning and delivery is reimbursed though national prices included within the National Tariff Payment System.

Audit requirements

Radiotherapy providers must submit their activity to the national Radiotherapy Dataset (RTDS) monthly. Radiotherapy services are subject to regular self-assessment by the national Specialised Commissioning Quality Surveillance Team. The quality system and its treatment protocols will be subject to regular clinical and management audit.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base, then a new Preliminary Policy Proposition needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Bone scintigraphy	A type of nuclear medicine procedure that uses small amounts of radioactive material to

	diagnose and assess the severity of a variety of bone diseases and conditions, including fractures, infection, and cancer.
Computed Tomography (CT)	A type of scan which uses X-rays and a computer to create detailed images of the inside of the body.
External beam radiotherapy (EBRT)	A form of radiotherapy delivered by a linear accelerator, which focuses high-energy radiation beams directed onto the target area from outside of the body.
Fractionation	A term describing how the full dose of radiation is divided into a number of smaller doses called fractions. The fractions are given as a series of treatment sessions which make up a radiotherapy course.
Gray (Gy)	The international system (SI) unit of radiation dose. One Gray is the absorption of one joule of energy, in the form of ionizing radiation, per kilogram of matter.
Hormone sensitive	The disease can be treated with and responds to hormone therapy.
Metastatic / Metastasis	In metastasis, cancer cells break away from the original (primary) tumour, travel through the blood or lymph system, and form a new tumour in other organs or tissues of the body. The new, metastatic tumour is the same type of cancer as the primary tumour.
Magnetic resonance imaging (MRI)	A type of scan that uses strong magnetic fields and radio waves to produce detailed images of the inside of the body
Prostate gland	A small gland in the pelvis which is about the size of a walnut and located between the penis and the bladder and which surrounds the urethra. Prostate cancer can only develop in people that have a prostate. This means that this policy applies to males that have a prostate, transgender women and intersex individuals. The main function of the prostate is to help in the production of semen. It produces a thick white fluid that is mixed with the sperm produced by the testicles, to create semen.
Radiotherapy	The safe use of ionising radiation to kill cancer cells with the aim of cure or effective palliation.
Visceral	Refers to the internal organs of the body, specifically those within the chest (e.g. heart or lungs) or abdomen (e.g. liver, pancreas or intestines).

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