

**Clinical  
Commissioning  
Policy Proposition:  
Hypofractionated  
external beam  
radiotherapy in the  
treatment of localised  
prostate cancer**



First published: TBC

**Prepared by NHS England Specialised Services Clinical Reference Group for Radiotherapy**

Published by NHS England, in electronic format only.

Draft for Public Consultation

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# 1 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 and it usually 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', this provides an indication of how large the cancer is and how far it has spread and helps to identify the best treatment for patients. Where prostate cancer is diagnosed at an early stage, which means that it is completely contained (or 'localised') within the prostate and has not spread anywhere else in the body, the chances of survival are generally good, with almost all men surviving 5 years or more after diagnosis. Since the introduction of prostate-specific antigen (PSA) testing, most prostate cancer cases are now diagnosed at an early stage (Cancer Research UK, 2017).

## **About current treatments**

Treatment options for prostate cancer include different types of radiotherapy ( external-beam radiotherapy and brachytherapy), surgery (called 'radical prostatectomy'), active surveillance and watchful waiting. Treatment choice is determined by individual patient preference, stage of cancer and overall health status. As well as being staged, localised prostate cancer is also risk assessed into three groups, high, intermediate and low. These risk categories also play a role in determining the best treatments and overall management plan for patients.

All prostate cancer treatments are associated with side-effects. Prostate cancer, and its treatment, are the leading cause of cancer years lived with disability. This is because prostate cancer is a common cancer and because men with localised disease usually have a long life expectancy. Management plans and treatment choices are often influenced by the potential treatment-related toxicities and side-effects.

## **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'). It is not a new treatment for prostate cancer. Hypofractionated radiotherapy is a new way of delivering external beam radiotherapy treatments and involves the safe delivery of higher doses of radiation in a smaller number of daily treatments, as compared to usual ( or 'conventional') external beam radiotherapy treatment.

## **What we have decided**

NHS England has carefully reviewed the evidence to treat localised prostate cancer with hypofractionated external beam radiotherapy and have concluded that there is sufficient evidence to consider making the treatment available, alongside other treatment options for localised prostate cancer.

## 2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission hypofractionated external beam radiotherapy for the treatment of localised prostate cancer.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether hypofractionated external beam radiotherapy for the treatment of localised prostate cancer will be routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

## 3 Proposed Intervention and Clinical Indication

### Proposed Intervention

Radiotherapy is the safe use of ionising radiation to kill cancer cells with the aim of cure or effective palliation. The aim of radiotherapy is to deliver as high a dose of radiation as possible to the cancerous tumour/s, whilst sparing the surrounding normal tissues. Radiotherapy is often used on its own or as part of a treatment plan including surgery or chemotherapy, or both.

External beam radiotherapy is generally delivered by a megavoltage machine, usually a Linear Accelerator, which is a generic term for all megavoltage radiotherapy equipment. Hypofractionation describes a treatment regimen that delivers high doses of radiation using a shorter number of treatments as compared to conventional treatment regimens.

Hypofractionated external beam radiotherapy for the treatment of localised prostate cancer uses larger than conventional fraction sizes (more than 2Gy) usually delivered over a shorter overall treatment time, for example, 60Gy in 20 daily fractions of 3Gy over 4 weeks. Conventionally fractionated radiotherapy is defined as 2Gy per day up to a usual dose of at least 74Gy in 37 daily fractions over 7 ½ weeks.

#### Clinical indication

Prostate cancer is the most common cancer in men in the UK, with 41,736 new cases in 2011 (Cancer Research UK, 2017). Since the introduction of prostate-specific antigen (PSA) testing, most men diagnosed have localised disease.

Management options include external beam radiotherapy, brachytherapy, radical prostatectomy, active surveillance (for men with low-risk disease) and watchful waiting (for those unsuitable for radical curative treatment). External-beam radiotherapy is most appropriate for men with intermediate or high risk disease (National Comprehensive Cancer Network, 2011).

All prostate cancer treatments are associated with side-effects. Prostate cancer and its treatment are the leading cause of cancer years lived with disability (Soerjomataram et al., 2012) because prostate cancer is both common, and men with localised disease have a long life expectancy. Management plans and treatment choices are often influenced by potential treatment-related toxicities.

## **4 Definitions**

The prostate - is a small gland in the pelvis found only in men. About the size of a walnut, it's located between the penis and the bladder and surrounds the urethra. 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.

Localised Prostate Cancer - is defined as disease which is confined to the prostate

gland and immediate surrounding area including the seminal vesicles.

Risk – localised prostate cancer is grouped into low, intermediate and high risk categories. The risk category influences how the prostate cancer is managed. This assessment is based on tumour extent (“T” stage), histological architecture (Gleason score) and Prostate Specific Antigen level.

Low risk localised prostate cancer – is unlikely to grow or spread for many years and generally is diagnosed where all of the following factors are present:

- PSA level less than 10 ng per ml;
- Gleason score no higher than 6;
- T stage of between T1 and T2a (National Comprehensive Cancer Network 2016)

Intermediate risk localised prostate cancer – is unlikely to grow or spread for a few years and generally is diagnosed where one or more of the following factors is present:

- PSA level between 10 and 20 ng/ml
- Gleason score of 7;
- T stage of T2b and T2c (National Comprehensive Cancer Network 2016)

High risk localised prostate cancer – may grow or spread within a few years and generally is diagnosed where any one of the following factors is present:

- PSA level higher than 20 ng/ml;
- Gleason score between 8 and 10; and
- T stage of equal to or greater than T3 (National Comprehensive Cancer Network 2016)

Radiotherapy - is the safe use of ionising radiation to kill cancer cells with the aim of cure or effective palliation.

External beam radiotherapy - is delivered by a linear accelerator, which focuses high-energy radiation beams onto the area requiring treatment.



Fraction – is the term describing how the full dose of radiation is divided into a number of smaller doses called fractions. The fractions are given to discrete and well-delineated tumours as a series of treatment sessions which make up a radiotherapy course.

Hypofractionation - describes a treatment regimen that delivers high doses of radiation using a shorter number of treatments as compared to conventional treatment regimens.

A/B Ratio – the curvature for a cell survival curve for a particular tissue type which usefully predicts which pattern of radiotherapy fractionation should be used to maximise tumour sensitivity whilst sparing normal tissue.

Image Guided Radiotherapy (IGRT) - Imaging at pre-treatment and delivery, the result of which is acted upon, that improves or verifies the accuracy of radiotherapy. IGRT encompasses the whole range of imaging, from simple to more complex imaging, that allows direct visualisation of the tumour and surrounding tissue.

Gray (Gy) is 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

Conventionally fractionated radiotherapy - is defined as 2Gy per day up to a usual dose of at least 74Gy in 37 daily fractions over 7 ½ weeks.

Hypofractionated external beam radiotherapy – describes a treatment regimen that uses larger than conventional fraction sizes (more than 2Gy) usually delivered over a shorter overall treatment time e.g. 60Gy in 20 daily fractions of 3Gy over 4 weeks.

Intensity modulated radiotherapy (IMRT) - is a type of conformal radiotherapy (a type of external beam radiotherapy). Conformal radiotherapy shapes the radiation beams to fit the area of the cancer; IMRT sculpts this shape even more precisely.

## 5 Aims and Objectives

This policy proposition considered: Hypofractionated external beam radiotherapy, as part of the treatment pathway for adult patients with localised prostate cancer.

The objectives were to establish via an evidence review the following:

Efficacy, safety and toxicity profile of hypofractionated radiotherapy compared with conventional radiotherapy in the treatment of localised prostate cancer.

## 6 Epidemiology and Needs Assessment

### Epidemiology

Prostate cancer is the most common cancer in men in the UK, with 41,736 new cases in 2011 (Cancer Research UK, 2017).

### Needs Assessment

The national Radiotherapy Dataset (RTDS) records radiotherapy activity; data contained within RTDS identifies that approximately 9,000 patients receive radical prostate external beam radiotherapy every year in England (RTDS, 2015). Of those patients currently receiving radical prostate external beam radiotherapy, it is estimated that approximately 70% of patients are suitable for hypofractionated external beam radiotherapy, in accordance with the clinical eligibility criteria.

The needs assessment is based on expert clinical consensus because not all patients receiving radical prostate external beam radiotherapy, as reported within the RTDS, would be eligible for hypofractionated radiotherapy. The ineligible groups are: (i) patients requiring treatment to the prostate and pelvic nodes (i.e., not localised); and (ii) patients that require both brachytherapy and external beam radiotherapy. RTDS does not currently routinely report this level of clinical detail and, as a result, the policy recommends that a reporting benchmark of 70% is used to assess policy compliance.

## 7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

An evidence review was undertaken to assess the evidence for the use of hypofractionated external beam radiotherapy in the treatment of prostate cancer. Four large randomised trials have been reported in the last 12 months. All reported efficacy outcomes as well as toxicity profiles:

- The CHHiP trial (Dearnaley et al., 2016; Wilkins et al., 2015; Dearnaley et al., 2012) randomised 3,216 men, with low, intermediate and high risk disease, to receive either conventional fractionated radiotherapy (CFRT) delivering 74Gy in 37 fractions over 7.4 weeks compared with hypofractionated radiotherapy (HFRT) 60Gy/20 fractions over 4 weeks or 57Gy/19 fractions over 3.8 weeks. It tested the hypothesis that HFRT is non-inferior for efficacy compared with CFRT.
- The PROFIT trial (Catton et al., 2017) randomised 1206 men with intermediate risk disease. They received CFRT of 78Gy delivered in 39 fractions over 8 weeks or HFRT 60Gy delivered in 20 fractions over 4 weeks. This tested the hypothesis that HFRT is non-inferior for efficacy compared with CFRT.
- The RTOG 0415 trial (Lee et al., 2016) randomised 1092 men with low risk disease comparing daily schedules of 73.8Gy delivered in 41 fractions with 70Gy delivered in 28 fractions. This tested the hypothesis that HFRT is non-inferior for efficacy compared with CFRT in men.
- The HYPRO trial (Inrocci et al., 2016; Aluwini et al., 2016; Aluwini et al., 2015) randomised 804 men with intermediate and high risk prostate cancer to receive either CFRT of 78Gy delivered over 39 fractions in 8 weeks or HFRT with 64Gy delivered over 19 fractions in 6.5 weeks. This tested the hypotheses that dose-escalated HFRT was superior to CFRT but without increasing side-effects.

### Survival outcomes

The CHHiP trial (Dearnaley et al., 2016) reported that after a median follow-up of 62 months the proportion of patients who were biochemical/clinical failure free at 5 years was:

- 74 Gy 88.3% (95% confidence interval 86.0-90.2);
- 60 Gy 90.6% (88.5-92.3);
- 57 Gy 85.9% (83.4-88.0).

60Gy was shown to be non-inferior to 74Gy (hazard ratio 0.84) but non-inferiority could not be claimed for 57Gy (hazard ratio 1.20). There was no heterogeneity of effect for different risk groups. Overall survival was similar between CFRT and HFRT groups; of 252 deaths reported, only 16% were prostate cancer related.

The PROFIT (Catton et al., 2017) trial primary end point was biochemical-clinical failure: the critical hazard ratio for non-inferiority was 1.32. The median follow-up was 6.0 years. The 5 year biochemical-clinical failure event rate was 21% in both groups (hazard ratio 0.96).

The estimated 5 year disease-free survival in RTOG 0415 (Lee et al., 2016) was 85% for CFRT and 86% for HFRT (hazard ratio 0.85). The cumulative incidence of biochemical recurrence at 5 years was 8% and 6% in the CFRT and HFRT groups, respectively (hazard ratio 0.77). Both end points met the protocol-specified non-inferiority criterion (hazard ratio < 1.52,  $P < 0.001$ ). Overall 5 year estimated survival was similar at 93%. Deaths were most commonly due to cardiovascular disease and second cancers. The HFRT schedule was non-inferior to CFRT.

In the HYPRO trial the proportion of patients free of biochemical/clinical failure at 5 years was 81%/ 77% (hazard ratio 0.86;  $P=0.36$ ) for HFRT/CFRT groups, respectively (Inrocci et al, 2016).

### Genitourinary and Gastrointestinal toxicity outcomes

In the CHHiP study (Dearnaley et al., 2016; Dearnaley et al., 2012), acute Radiation Therapy Oncology Group bowel and bladder symptoms peaked sooner with HFRT

schedules (4 - 5 weeks) than CFRT (7 - 8 weeks). There was a higher proportion of grade 2 peak gastrointestinal toxicity in both HFRT groups (CFRT 25%: HFRT 38%;  $P < 0.0001$ ). By 18 weeks both bowel and bladder toxicity was similar for CFRT/HFRT. There were no differences in long-term side-effects between CFRT and HFRT groups in either the proportion or cumulative incidence of patients reporting grade 2 gastrointestinal/genitourinary toxicity at 5 years (cumulative incidence: 74Gy: 13.7%/9.1%; 60Gy: 11.9%/11.7%; 57Gy: 11.3%/6.6%). There was a slightly higher rate of grade 2 gastrointestinal/genitourinary side-effects in the 60Gy group compared with 57Gy at 2 and 5 years. Patient reported outcomes suggest an overall low incidence of gastrointestinal and genitourinary symptoms in all treatment groups (Wilkins et al., 2015).

The PROFIT trial (Catton et al., 2017) reported acute genitourinary/gastrointestinal toxicity as similar in both arms of trial, based on the abstract review. However, late gastrointestinal toxicity favoured the 60Gy arm (grade 2 CFRT 14%: HFRT 9%;  $P=0.006$ ).

In the RTOG 0415 trial (Lee et al., 2016) the reported results for toxicity show acute gastrointestinal/genitourinary side-effects were similar in the randomised groups. Late grade 2 gastrointestinal/ genitourinary adverse events were increased with hypofractionation (HFRT 22%/30%: CFRT 14%/23%).

In the HYPRO trial (Aluwini et al., 2015) grade 2 acute bowel toxicity was higher with hypofractionation (CFRT 31%; HFRT 42%;  $P=0.0015$ ) although the difference disappeared three months after radiotherapy and there was no difference in bladder toxicity. The cumulative grade 3 late genitourinary toxicity (Aluwini et al., 2016) was higher with hypofractionation (HFRT 19%, CFRT 13%;  $P=0.02$ ) but the incidence of grade 2 bowel toxicity at 3 years was similar (CFRT 18%, HFRT 22%). The study did not demonstrate that HFRT was non-inferior for either acute or late genitourinary/gastrointestinal toxicity compared with CFRT.

#### Radiobiological interpretation

The CHHiP trial suggests that 60Gy in 20 fractions is equivalent to about 76Gy/38

fractions - very like the 78Gy/39 fractions in PROFIT. The identical outcomes in the two arms of the PROFIT study are ideal for calculating the  $a/b$  ratio for prostate cancer. Using the outcomes at 5 years the  $a/b$  ratio is estimated as 1.3Gy, which is slightly lower than the estimate from the CHHiP trial of 1.8Gy which used ADT in most patients (Dearnaley et al., 2017).

The HYPRO study had a hypofractionated schedule designed to be equivalent to 90.4Gy in 2Gy/fraction (assuming  $a/b$  of 1.5Gy) compared with 78Gy/39 fractions for CFRT, yet the increase in outcome at 5 years was only 3.4%. The schedule was protracted by delivering three fractions per week and it may be that the effect of overall treatment time contributed, with the course taking 6.5 weeks as shown in table 1. Similarly the hypofractionated arm of the RTOG 0415 trial might also have been expected to result in less biochemical failures than the standard arm (assuming a low  $a/b$  ratio), yet there is only a 2% increase in prostate-specific antigen control at 5 years (Dearnaley et al., 2016b).

#### Clinical predictors for adverse events and/or relapse

The HYPRO trial results show that a strong independent predictor of relapse was high risk (>25%) of seminal vesicle involvement. Conversely the authors also report lower failure rates for the HFRT group in patients with a Gleason score <6. The authors have also published a single abstract (Wortel et al., 2016) noting that sexual function outcomes, including erectile deterioration and orgasmic function, were similar between both arms of the study and that no statistically significant differences between the HFRT and CFRT groups were observed.

For genitourinary and gastrointestinal toxicity a number of the studies reported statistically significant results following treatment for those patients reporting toxicity at baseline. In particular, the study by (Pollack et al., 2013) concluded that the hypofractionation regimen used is most appropriate for men without "substantial baseline urinary dysfunction". The RTOG 0415 trial also noted that patients with large prostates may be at higher risk of adverse events (Lee et al., 2016).

A major caveat is that none of the studies was specifically designed to address some of these specific clinical sub-grouping questions. Further refinement of study

designs and sub-group analyses are needed to address these questions more robustly.

### Summary

- The largest and most generalizable study to NHS practice is the CHHiP trial which randomised 3,216 patients to receive either conventional fractionated radiotherapy (CFRT) at 74Gy delivered in 37 fractions over 7.4 weeks, hypofractionated radiotherapy (HFRT) 60Gy/20 fractions over 4 weeks or 57Gy/19 fractions over 3.8 weeks.
- The CHHiP study confirms that the 60Gy/20 fractions schedule is safe and effective when compared to the CFRT with 90.6% of patients biochemical/clinical failure free at 5 years compared to 88.3% in the CFRT group. 60Gy was shown to be non-inferior, hazard ratio 0.84 compared to the CFRT group at 5 years.
- There was no difference in long term genitourinary and gastrointestinal side effects at 5-years, although data showed acute, short-lasting side effects peaked sooner in the HFRT group at 4-5 weeks.
- Evidence from the CHHiP trial shows that treatment of the prostate with seminal vesicles is safe and effective at 60Gy/20. The PROFIT trial has used the same HFRT schedule as CHHiP and results further demonstrate non-inferiority compared to CFRT.
- All patient subgroups (NCCN low, intermediate and high risk) can be considered for HFRT. The evidence is most robust for the intermediate risk group, but no heterogeneity of effect has been shown between risk groups.
- Presently the safety data related to high dose HFRT for the treatment of pelvic lymph nodes is limited and the recommendation for hypofractionation relates to radiotherapy for prostate +/- seminal vesicles alone (the most usual indication). It is presently uncertain whether it is possible to identify some patients with troublesome urinary/bowel symptoms pre-radiotherapy who may be unsuited to HFRT.

### Conclusion

Hypofractionated radiotherapy has been shown to be both safe and effective when

delivered at 60Gy / 20 fraction schedule over a four week period when compared to conventional radiotherapy.

Intensity modulated radiotherapy techniques with strict normal tissue dose constraints should be used and image guidance techniques recommended to reduce side effects.

Long term follow-up of phase 3 studies is recommended to determine if differences between radiotherapy schedules become apparent after 10 years or more.

Evaluation of clinical and biological parameters to predict outcome (efficacy and side effects) on an individual patient basis is encouraged.

## 8 Proposed Criteria for Commissioning

All patients with prostate cancer should have their care managed by a variety 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.

The tumour specific MDT is responsible for radiotherapy case selection and should take into consideration patient comorbidities, potential adverse events and likely outcomes of treatment.

### Eligibility Criteria

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

1. Low risk localised prostate cancer which is suitable for treatment with external beam radiotherapy rather than active surveillance, brachytherapy or radical prostatectomy.
2. Intermediate risk localised prostate cancer which is suitable for treatment with external beam radiotherapy rather than radical prostatectomy or brachytherapy.
3. High risk localised prostate cancer where the target volume is limited to the



prostate and seminal vesicles.

#### Exclusion criteria

Hypofractionated treatment should not be routinely advised where the target volume also includes the pelvic lymph nodes, involved seminal vesicles (T3b) or in post-prostatectomy patients.

#### Dose and fractionation

The recommended dose and fractionation schedule for the majority of patients will be 60Gy in 20 fractions over a period of four weeks. The treatment should include four weekends. For patients who are more elderly and frail or with clinically significant bowel or bladder disorder a lower dose schedule using 57Gy in 19 fractions can be used. This schedule is slightly less effective but is associated with a slightly lower incidence of both bowel and bladder side effects. Additional scientific inquiry is needed to determine if the presence of troublesome pre-radiotherapy bladder or bowel symptoms should be used to modify fractionation recommendations for particular patient groups.

#### Treatment techniques

Intensity modulated radiotherapy techniques should be used (forward or inverse planned). In addition, a high level of treatment accuracy using image guidance (IGRT) at appropriate points during the course of treatment is required and dose constraints must be rigorously applied.

## **9 Proposed Patient Pathway**

The service specification for radiotherapy (B01/S/a) 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.

## 10 Proposed Governance Arrangements

The service specification for radiotherapy (B01/S/a) describes the governance arrangements for this service. In particular, 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 and Providers should produce annual Clinical Governance reports as part of NHS Clinical Governance reporting system.

## 11 Proposed Mechanism for Funding

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

## 12 Proposed Audit Requirements

Radiotherapy providers must submit their activity to the national Radiotherapy Dataset (RTDS) on a monthly basis. For reporting purposes, it is expected that 70% of prostate cancer patients requiring radical external beam radiotherapy should receive hypofractionated radiotherapy (i.e., 20 fractions of treatment).

Where the reporting benchmark is not met (i.e., 70%), reasons must be recorded by the Trust and be shown to be appropriate for the treated case-mix. Providers should be aware that NHS England will audit variation in the rates of treatment courses exceeding 20 fractions using RTDS data.

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.

### 13 Documents That Have Informed This Policy Proposition

- Radiotherapy service specification for radiotherapy (B01/S/a).
- NICE Urology Improving Outcomes Guidance.

### 14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

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