Proton beam therapy for prostate cancer

QUESTION(S) TO BE ADDRESSED

1. What is the clinical effectiveness of proton beam therapy in the treatment of prostate cancer?

2. What is the cost effectiveness of proton beam therapy in the treatment of prostate cancer?

These questions were agreed with NHS England and the chair of the Clinical Reference Group.

SUMMARY

Background

- Proton beam therapy is a form of radiotherapy. It is intended to treat malignancies effectively with less risk of collateral damage to neighbouring tissues than conventional radiotherapy.
- One possible indication for proton beam therapy is prostate cancer, the commonest cancer in British men.

Clinical effectiveness

- We found a systematic review which covered a variety of potential indications for proton beam therapy. It included three randomised controlled trials of proton beam therapy for prostate cancer:
    - The first trial randomised participants between proton beam therapy and photon treatment. There were no significant differences in overall survival, disease-specific survival, total recurrence-free survival or local control between the two arms.
    - The second trial randomised participants between two doses of proton beam therapy. Overall survival was similar for the two groups, but rates of biochemical failure were higher for the low dose group, and more of these patients subsequently required androgen deprivation for recurrence.
    - The third trial compared five different proton beam therapy fractionation and dose regimes. Rates of biochemical failure were similar in the five arms.

- The review also included three non-randomised studies:

  - The first study reported quality-of-life data from men who had received either proton beam therapy or intensity-modulated photon radiotherapy. There were no differences for most measures, but the men who received proton beam therapy had more rectal urgency and frequent bowel movements.
  - The second study compared men who had received intensity-modulated radiotherapy, proton beam therapy and three-dimensional conformal photon radiotherapy. Each treatment had a different pattern of adverse effects, with none emerging as safer.
  - The third study reported no significant differences in further cancer treatment, urinary incontinence, erectile dysfunction or hip fracture in men who had received intensity-modulated photon radiotherapy and proton beam therapy. Those who had proton beam therapy were more likely to experience gastrointestinal morbidity.

- We found one further controlled study which reported no differences in gastrointestinal or genitourinary toxicity between men treated with proton beam therapy and intensity-modulated photon radiotherapy.

Cost effectiveness

- We found a systematic review of the cost effectiveness of radiotherapy for prostate cancer. It included two analyses:

  - The first reported a comparison of proton beam therapy and intensity-modulated photon radiotherapy. The authors estimated that the incremental cost per quality-adjusted life year was US$63,578 (£42,400) for a man of 70 years and US$55,726 (£37,200) for a man of 60 years. These costs are above thresholds for NHS treatment.
  - The second study compared the cost effectiveness of proton beam therapy, stereotactic body radiotherapy and intensity-modulated photon radiotherapy. Proton beam therapy was dominated by stereotactic body radiotherapy, being more expensive and producing lower quality of life. Compared with intensity-modulated photon radiotherapy, proton beam therapy had a cost per quality-adjusted life year of US$36,344,000 (£24,230,000).

Activity and cost

- No cost or activity data were available.

Equity

- We identified no specific equity issues.

1 Context

1.1 Introduction

Proton beam therapy is a form of radiotherapy. It is intended to treat malignancies effectively while reducing the risk of collateral damage to neighbouring tissues which may follow standard, photon-based radiotherapy. However, there is uncertainty about the indications for which it is clinically and cost-effective.

1.2 Existing national policies and guidance

We found no existing national policies or guidance.

2 Epidemiology

Prostate cancer is the commonest cancer among British men. It affects about one in twelve men, giving rise each year to around 30,000 new cases and 10,000 deaths. Its causes remain uncertain, though heredity plays a part and diet may well influence risk.

Symptoms include urinary difficulties and, if the cancer has spread, bone pain from secondary tumours. Prostate cancer is particularly common among older men; two-thirds of those who die from prostate cancer are over the age of 75 years. Prostate cancer may be diagnosed when men are investigated for benign prostate disease, also a common condition in elderly men.

Treatments for localised prostate cancer, where the cancer is believed to be confined to the prostate at diagnosis, include active monitoring, radical prostatectomy, external beam radiotherapy and brachytherapy. External beam radiotherapy is usually with photons, but some oncologists advocate the use of proton beam therapy for this indication.

3 The intervention

Radiotherapy uses radiation to destroy malignant tissue while minimising damage to adjacent normal tissue. Proton beam therapy uses a high-energy beam of protons as treatment, rather than high-energy X-rays used in standard radiotherapy for patients with cancer. It is intended to deliver highly targeted radiation to the tumour with less collateral damage.

The only NHS proton beam therapy centre is at the Clatterbridge Cancer Centre NHS Foundation Trust. It delivers a low-energy proton therapy specifically for patients with eye tumours. Patients who require proton therapy for other tumours may be referred overseas via the NHS Proton Overseas Programme.

The Department of Health intends to establish high energy proton beam therapy services in the UK. Two facilities are being planned in Manchester and London, and are expected to start in 2018. There are as yet no policies on which tumours will be treated at these centres.

4 Findings

In November 2014, we searched for evidence about the clinical and cost effectiveness of proton beam therapy for the treatment of prostate cancer. With the agreement of NHS England and the chair of the Clinical Reference Group, we included only studies which compared clinical outcomes in real patients, not those of simulations or modelling. We excluded uncontrolled studies.

We obtained the full text of studies with abstracts reporting results from proton beam therapy and other treatments, whether or not they were separately reported in the abstract; in these cases, we included results for proton beam therapy for prostate cancer when they were separately reported in the full text of the paper.

The search strategy is in the appendix.

4.1 Evidence of effectiveness

We found a systematic review which covered a variety of potential indications for proton beam therapy.[1] It included studies reporting clinical outcomes of proton beam therapy published between 1990 and May 2014. The review included three randomised controlled trials of proton beam therapy for prostate cancer:

- Shipley et al reported results in 202 men with advanced prostate cancer.[2] After all the participants had received a standard dose of conventional photon beam radiotherapy, they were randomised between proton beam therapy or additional photon treatment. Those in the first arm received more radiation. There were no significant differences in overall survival, disease-specific survival, total recurrence-free survival or local control between the two arms. The proton beam therapy participants had more rectal bleeding.

- In Zeitman et al's trial, all 394 randomised men also received conventional photon radiotherapy.[3] Half then had a lower dose of proton beam therapy, while the rest received a dose about 50% higher. Overall survival was similar for the two groups, but rates of biochemical failure were higher for the low dose group, and more of these patients subsequently required androgen deprivation for recurrence.

- Kim et al compared five different proton beam therapy fractionation and dose regimes in 82 men with prostate cancer.[4] Rates of biochemical failure were similar in the five arms.

Patel also included three non-randomised studies:

- Hoppe et al reported quality-of-life data from men who had received either proton beam therapy or intensity-modulated photon radiotherapy for prostate cancer.[5] There were no differences between the groups in the frequency of bowel symptoms, urinary incontinence, urinary irritative or obstructive symptoms or sexual problems, but the men who received proton beam therapy had more rectal urgency and frequent bowel movements. Underlying differences between the two groups make it difficult confidently to attribute these outcomes to the effects of treatment.

- Gray et al compared men from the same cohort as Hoppe et al who had received intensity-modulated radiotherapy with a different proton beam therapy cohort and with a third group who had received three-dimensional conformal photon radiotherapy.[6] In the first two months after treatment, patients in the two photon groups reported adverse changes in their rectal/bowel quality of life, and those who had received intensity-modulated radiotherapy also reported adverse changes in urinary symptoms. At one and two years, all three groups reported a deterioration in bowel quality of life. At one year, the proton beam therapy cohort had more frequent urinary symptoms, but by two years, all three groups had returned to pre-treatment levels of urinary quality of life. This study was also affected by confounding which the authors did not attempt to correct.

- Sheets et al reported an analysis of a large United States database linked to Medicare.[7] They analysed results from men who had received radiation as primary treatment of prostate cancer within a year of diagnosis, and reported that men who had received intensity-modulated photon radiotherapy were less likely to experience gastrointestinal morbidity than those who had received proton beam therapy. There were no significant differences in further cancer treatment, urinary incontinence, erectile dysfunction or hip fracture.

Table 1: Controlled studies of proton beam therapy in prostate cancer

Study	Patients	Intervention	Comparator	Outcomes	Comments
Shipley et al [2] Randomised trial Boston, Massachusetts	202 men with locally advanced prostate cancer (T3 or T4, Nx, N0-2, M0), who all received 50.4 Gy by four-field photons.	An additional 25.2 cobalt gray equivalent (CGE) by conformal protons (the high dose arm, 103 patients, total dose 75.6 CGE)	An additional 16.8 Gy by photons (the conventional dose arm, 99 patients, total dose 67.2 Gy).	Median follow-up of 61 months, range 3 to 139 months. Results for participants completing randomised treatment (93 in the high dose arm and 96 in the conventional dose arm): Local control, overall survival, disease-specific survival, total recurrence-free survival and local control: no significant differences. Grade 1 and 2 rectal bleeding: high-dose arm 32%, conventional dose arm 12%, P = 0.002.	The design of the trial conflates a comparison of modes of radiotherapy with a comparison of doses. The higher, proton-mediated dose did not appear to improve outcomes, but increased the risk of adverse reactions to treatment.
Zeitman et al [3] Randomised trial Loma Linda, California, and Boston,	393 men with early prostate cancer (T1b to T2b prostate cancer and prostate-specific antigen ≤ 15	A higher additional proton radiation dose of 28.8 CGE	A lower additional proton radiation dose of 19.8 CGE	Median follow-up 8.9 years, range 0.8 to 12.5 years. Local failure: higher dose versus lower dose hazard ratio of 0.57, P < 0.0001, 95% confidence interval (CI) 0.43 to 0.74), after	Since participants in both arms of the trial received proton beam therapy, the results cannot

Massachusetts	ng/mL), who all received conformal photon therapy to a fixed dose of 50.4 Gy.			adjustment for other covariates. Biochemical failure[1]: conventional dose arm 32.3% (95% CI, 25.7% to 39.0%), high dose arm 16.7% (95% CI, 10.8% to 22.7%), P = 0.0001. Overall survival: conventional dose 78.4%, higher dose 83.4%, P = 0.41.	assist in reducing uncertainty about the relative value of photon and proton treatment.
Kim et al [4] Randomised trial Seoul, Korea	82 men with androgen-deprivation therapy-naive prostate adenocarcinoma (stage T1 to 3 N0 M0).	A five arm trial, with all radiation as proton beam therapy: Arm 1, 60 CGE /20 fractions/5 weeks Arm 2, 54 CGE/15 fractions/5 weeks Arm 3, 47 CGE/10 fractions/5 weeks Arm 4, 35 CGE/5 fractions/2.5 weeks Arm 5, 35 CGE/5 fractions/5 weeks.		Median follow-up 42 months, range 11 to 52 months. There was no statistically significant difference in biochemical failure free survival among the five arms (P-value not reported).	This study was probably underpowered, but would in any case not have reduced uncertainty about the relative value of photon and proton treatment.
Hoppe et al [5] Comparison of two cohorts, one from Jacksonville Florida, the other from 9 university	1243 men with localised prostate cancer who received proton beam therapy.	Proton beam therapy, total dose 78 to 82 Gy	Intensity-modulated photon radiotherapy (IMRT), total dose 75.6 to 79.2 Gy	Only significant differences: bowel urgency IMRT 15%, PBT 7%, P = 0.02; bowel frequency IMRT 10%, PBT 4%, P = 0.05.	IMRT participants were older (69 vs 66 years, P < 0.001), had larger prostates (49.5g vs 41.5

[1] Defined as the first of three successive increases in PSA level, with the failure backdated to a point halfway between the first increase and the last non-increasing value or initiation of salvage therapy

hospitals in the United States	204 men from a separate cohort study treated with intensity-modulated photon radiotherapy.				g, P = 0.0014), were less likely to be white (81% versus 91% white, P < 0.001), were more likely to receive androgen deprivation therapy (24% vs 15%, P < 0.001) and received lower minimum dose (median 70.9 Gy vs 74.1 Gy, P < 0.001) and maximum dose (81.5 Gy vs 83.2 Gy, P < 0.001). Results were Bonferroni-corrected for multiple comparisons.
Gray et al [6] Comparison of three cohorts, one from 9 university	371 men with localised prostate cancer who received radiotherapy but	PBT 74 to 82 Gy	IMRT 75.6 to 79.2 Gy, 3DCRT 75.6 to 79.2 Gy.	2 to 3 months after treatment: IMRT and 3DCRT participants reported adverse changes in their rectal/bowel quality of life[2] (-16.0 and -7.2 respectively, P <	Participants receiving PBT were younger than the IMRT and 3DCRT

[2] All scales 0 to 100, lower scores worse

hospitals in the United States who had IMRT (as in Hoppe et al) and two from Boston, Massachusetts who received PBT or three-dimensional conformal photon radiotherapy (3DCRT).	no androgen deprivation therapy: PBT 95, IMRT 153, 3DCRT 123			0.001 for both). All participants reported adverse changes in urinary irritation and obstruction, though only in the case of IMRT did this exceed the threshold of at least 0.5 standard deviations for clinical significance. IMRT participants reported adverse changes in urinary continence (-7.9, P < 0.001). At one and two years, all three groups reported a deterioration in bowel quality of life. At one year, the proton beam therapy cohort had more frequent urinary symptoms, but by two years, all three groups had returned to pre-treatment levels of urinary quality of life.	cohorts (median ages 64, 69 and 70 years respectively, P < 0.001), had lower prostate specific antigen levels (median 5.2, 5.8 and 7.5 ng/ml respectively, P < 0.001). IMRT participants were less likely to be Black (6%, 18% and 2% respectively, P < 0.001). The 3DCRT cohort had fewer men with T1 tumours (80%, 80% and 40% respectively, P < 0.001).
Sheets et al [7] Comparison of cohorts from 16 US cancer registries, with linked Medicare data on healthcare utilisation	12,976 men who had localised prostate cancer and at least a year of claims data and who had received radiotherapy as primary	PBT, dose not reported	IMRT and CRT, doses not reported	Median follow-up: PBT 50 months, IMRT 46 months, CRT 64 months. Only the IMRT cohort were compared with PBT, after propensity adjustment. Increased rate of gastrointestinal diagnoses with	PBT patients were younger (36% less than 70 years, compared with 20% for IMRT, P < 0.001), more likely to be white (93% vs 85%, P

	treatment within a year of diagnosis. Number of participants: IMRT 6666, CRT 6310, 684 PBT.			PBT (rate ratio IMRT vs PBT 0.66, 95% CI 0.49 to 0.88) and of gastrointestinal procedures (0.60, 95% CI 0.46 to 0.78). No significant differences in further cancer treatment, urinary incontinence, erectile dysfunction or hip fracture.	< 0.001) and more likely to be married (77% vs 71%, P < 0.001). No adjustment for multiple comparisons.
Fang et al [8] Controlled study Philadelphia, USA	394 patients with localised prostate cancer. 79.2 Gray (Gy) either by PBT (181 men) or IMRT (213 patients).	PBT 79.2 Gy	IMRT 79.2 Gy	Median follow-up: IMRT 47 months (range, 5-65 months), PBT 29 months (range, 5-50 months). Bladder and rectum dosimetry variables were significantly lower for PBT versus IMRT (P ≤ .01). Multivariable analysis: grade ≥2 acute gastrointestinal (GI) toxicity odds ratio (OR), 0.27, 95% confidence interval (CI) 0.06 to 1.24, P = 0.09; grade ≥2 acute genitourinary (GU) toxicity OR 0.69, 95% CI, 0.32 to 1.51, P = 0.36; grade ≥2 late GU toxicity hazard ratio (HR) 0.56, 95% CI 0.22 to 1.41, P = 0.22; grade ≥2 late GI toxicity HR 1.24, 95% CI 0.53 to 2.94, P = 0.62.	Patients were case- matched on risk group, age, and prior GI and GU disorders, resulting in 94 matched pairs. Residual confounding was adjusted for by using multivariable regression.

Patel et al concluded that "[Proton beam therapy] appears to hold no clear benefit over [intensity-modulated photon radiotherapy] for the management of patients with prostate cancer".

We found one controlled studies not included in Patel et al's review. Fang et al reported a study in which men with prostate cancer received radiation of equivalent relative biological effectiveness delivered with either proton beam therapy or intensity-modulated photon radiotherapy.[8] Patients were case-matched on risk group, age, and prior gastrointestinal and genitourinary disorders. Bladder and rectum dose was lower with proton beam therapy, but there were no significant differences between the two modes of radiotherapy in the risk of more severe gastrointestinal or genitourinary toxicity.

4.2 Trials in progress

We searched clinicaltrials.gov and found two controlled trials in progress comparing proton beam therapy for prostate cancer with conventional radiotherapy. NCT00969111 is a non-randomised comparison of proton beam therapy and intensity-modulated photon radiotherapy after radical prostatectomy. NCT01617161 is a randomised trial of proton beam therapy versus intensity-modulated photon radiotherapy for low or intermediate risk prostate cancer.

4.3 Evidence of cost-effectiveness

We found a systematic review of the cost effectiveness of radiotherapy for prostate cancer.[9] The authors, Amin et al, searched for studies published from 2003 to December 2013. They found one study comparing proton beam therapy with intensity-modulated photon radiotherapy, and one comparing both techniques with stereotactic body radiotherapy.

- Konski et al reported a comparison of proton beam therapy and intensity-modulated photon radiotherapy.[10] The authors assumed that proton beam therapy would allow a 10 Gy increase in radiation without increased toxicity; as Amin et al point out, this is unproven. The analysis is based on US health care costs and therefore of limited relevance to the UK.

  Using Markov modelling over 15 years, Konski et al estimated that the incremental cost per quality-adjusted life year of proton beam therapy at US$63,578 (£42,400) for a man of 70 years and US$55,726 (£37,200) for a man of 60 years. The authors did not report their sensitivity analysis thoroughly enough to allow an assessment of whether plausible estimates would have led to different conclusions. Even with their unproven assumption of benefit, proton beam therapy is not cost-effective enough for routine use. Konski et al concluded "proton beam therapy is not cost effective for most patients with prostate cancer."

- Pathan et al used a similar technique to compare the cost effectiveness of proton beam therapy, stereotactic body radiotherapy and intensity-modulated photon radiotherapy.[11] However, they more conservatively assumed that all three treatments had the same effectiveness, but differed in side-effects. Based on

published studies, proton beam therapy was assumed to carry lower risks of genito-urinary side effects than the alternatives, along with similar risks of gastro-intestinal and sexual adverse effects to intensity-modulated photon radiotherapy.

Based on US health care costs, the lifetime costs of each treatment were proton beam therapy US$69,412 (£46,300), stereotactic body radiotherapy US$24,873 (£16,600) and intensity-modulated photon radiotherapy US$33,068 (£22,000). Stereotactic body radiotherapy also yielded more quality-adjusted life years, making it the most cost effective treatment. Proton beam therapy was therefore dominated by stereotactic body radiotherapy, being more expensive and producing lower quality of life.

Different assumptions in the sensitivity analysis did not alter these conclusions. With the toxicity of proton beam therapy and stereotactic body radiotherapy set as equal, the cost per quality-adjusted life year of proton beam therapy was US$13,755,207 (£9,170,000). Under this assumption. proton beam therapy yielded 0.01 more quality-adjusted life years than intensity-modulated photon radiotherapy at an incremental cost of US$36,344, a cost per quality-adjusted life year of US$36,344,000 (£24,230,000).

Taken together, these studies explore the cost effectiveness of using proton beam therapy in two distinct ways – to use similar doses to achieve the same therapeutic effect at lower risk of side effects, and to use higher doses to irradiate the tumour more thoroughly. Neither appears cost effective.

We found no controlled studies not included in Amin et al's review.

4.4 Safety

Data on side effects are provided above.

4.5 Summary of section 4

Despite the high prevalence of the diagnosis, the evidence about the effectiveness of proton beam therapy for prostate cancer is far from conclusive:

- Shipley et al's trial compares a higher radiation dose delivered with protons with a lower dose delivered with photons.[2] It indicates that more proton radiation does not improve outcomes but gives rise to more adverse effects.
- Zeitman et al's trial is a comparison on two doses of proton beam therapy and therefore does not address the central uncertainty about the technique's effectiveness relative to other forms of radiotherapy. It suggests higher doses are more effective.[3]
- Kim et al's trial was too small to reach useful conclusions, and in any case was also a comparison of different proton beam therapy regimes.[4]
- Hoppe et al reported slightly lower rates of side effects with proton beam therapy than intensity-modulated photon radiotherapy.[5] However, this study was an

unrandomised comparison of two cohorts not assembled with this hypothesis in mind, and was confounded by differences between the men in each cohort.

- Gray et al's study had the same drawbacks as Hoppe et al's.[6] It reported different patterns of adverse effects from different forms of radiotherapy, with no technique emerging as least toxic.
- Sheets et al indicated no significant differences in toxicity, apart from a higher risk of gastrointestinal adverse effects after proton beam therapy than after intensity-modulated photon radiotherapy.[7]
- Fang et al's study indicates no advantages from proton beam therapy.[8]

The analyses of cost effectiveness are based on this insecure and inconclusive evidence of the relative effectiveness and safety of proton beam therapy. They do not indicate that the treatment is cost effective.

5 Cost and activity

No cost or activity data were available.

6 Equity issues

We identified no specific equity issues.

7 Discussion and conclusions

1. What is the clinical effectiveness of proton beam therapy in the treatment of prostate cancer?

   We found only one study comparing the therapeutic effects of proton beam therapy with those of alternative forms of radiotherapy for prostate cancer. It indicated that proton beam therapy was more toxic but no more effective, but this may be because of the higher amount of radiation delivered by proton beam therapy in this trial. We found no evidence to support the use of proton beam therapy for prostate cancer.

2. What is the cost effectiveness of proton beam therapy in the treatment of prostate cancer?

   The analyses that we found report that proton beam therapy is less cost effective than other forms of radiotherapy.

8 References

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9 Search Strategy (search date November 2014)

1 Proton Therapy/

2 Protons/tu [Therapeutic Use]

3 (proton* adj3 beam*).ti,ab.

4 (proton* adj5 (therap* or treat* or radiat* or radiotherap* or irradiat*)).ti,ab.

5 pbrt.ti,ab.

6 pbt.ti,ab.

7 proton*.ti.

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 limit 8 to english language

10 2014*.dp,ed,yr.

11 9 and 10

12 limit 11 to "reviews (maximizes specificity)"

13 exp Prostatic Neoplasms/

14 (prostat* adj3 (cancer? or carcinoma? or neoplas* or tumo?r? or malignan*)).ti,ab.

15 13 or 14

16 11 and 15

17 Chordoma/

18 chordoma?.ti,ab.

19 skull base*.ti,ab.

20 chondroid.ti,ab.

21 17 or 18 or 19 or 20

22 11 and 21

23 Craniopharyngioma/

24 (craniopharyngioma? or cranio-pharyngioma?).ti,ab.

25 rathke cleft*.ti,ab.

26 23 or 24 or 25

27 11 and 26