NHS England

Evidence review: Proton beam therapy for breast cancer

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Contents

1 Introduction

Introduction

- Breast cancer is the most common cancer in the UK. (NHS England 2018).
- Breast cancer most commonly starts in the cells that line the ducts of the breast (CRUK 2018a).
- The most common symptoms of breast cancer include a breast lump, a change in the appearance or feel of a breast, pain, changes to the texture of the skin or the position of the nipple or fluid leakage from the nipple (CRUK 2018a).
- Treatment options include surgery to remove the tumour, radiotherapy, chemotherapy, targeted therapies and hormone therapy (NHS Choices 2016).

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

- NICE have not published any guidance on the use of proton beam therapy in breast cancer.

The indication and epidemiology

- In 2014 there were 54,800 new cases of female breast cancer and 390 new cases of male breast cancer (NHS England 2018).
- Annual incidence rates for breast cancer in the UK are projected to rise by 2% between 2014 and 2035 to 210 cases per 100,000 females (NHS England 2018).
- About one in eight women will get breast cancer at some point (NHS England 2018). Almost half of breast cancer cases diagnosed in the UK each year are in people aged 65 and over (NHS England 2018).
- The prognosis for breast cancer has improved in recent decades in the UK with a five year survival of 87% and a ten year survival of 78% (CRUK 2018b).

Standard treatment and pathway of care

- Photon radiotherapy is standard care in the NHS in England.

The intervention (and licensed indication)

- Proton beam therapy (PBT) is an alternative to conventional photon radiotherapy.
- Photons deliver a continuous energy beam which can cause damage to surrounding healthy tissue (CADTH 2017). Protons deliver most of their energy deposition at a near-fixed point or target (the Bragg peak), after which essentially no dose is deposited (Verma et al 2016). Protons deposit minimal energy before and after the tumour, thereby sparing healthy tissue (CADTH 2017).

Rationale for use

- The improvement in long-term survival amongst breast cancer patients has increased concerns about the longer-term side effects of radiotherapy for breast cancer (NHS England 2018).
- There is interest in methods of reducing the treatment volume by only treating the area of the breast where the cancer is located, or reducing radiotherapy dose to the normal tissue (NHS England 2018).

2 Summary of results

- In total, three studies were included in this evidence review (Galland-Girodet et al 2014; Bush et al 2014 and Mailhot Vega et al 2017).
- This evidence review identified one non-randomised comparative study reporting clinical outcomes for PBT compared to photon radiotherapy with 98 patients and a median follow-up of 82.5 months (Galland-Girodet et al 2014). One prospective uncontrolled study with clinical and toxicity outcomes for 100 patients receiving PBT and a median five year follow-up was also included (Bush et al 2014). The gender of the patients was not reported in either study. Other uncontrolled studies (e.g. retrospective studies and smaller prospective studies) were not included as these represent lower quality evidence than the included studies according to established hierarchy of evidence criteria[1]. Physics planning papers such as dosimetric planning studies were not eligible for inclusion in the review.
- Local failure rate. There was no significant difference in the seven year local failure rate for PBT (11%) compared to photon radiotherapy (4%) (p=0.22) (Galland-Girodet et al 2014).
- Physician-rated cosmetic outcome[2]. At one year follow-up the proportion of physicians rating overall cosmetic outcome as good or excellent was similar for PBT (100%) and photon radiotherapy (97%) (p value not reported). At seven years follow-up, a higher proportion of physicians rated overall cosmetic outcome as good or excellent for photon radiotherapy patients (94%) compared to PBT patients (62%) (p=0.03). There were no incidences of poor cosmetic outcome in either group at any time point (Galland-Girodet et al 2014). In the uncontrolled study (Bush et al 2014) the proportion of physicians reporting an excellent or good cosmetic outcome for PBT patients was in the region of 95%[3] from baseline to a median five year follow-up.
- Patient-rated cosmetic outcome[2]. The proportion of patients rating overall cosmetic outcome as good or excellent was similar at one year follow-up at 100% for PBT and 93% for photon radiotherapy (p value not reported). At seven years there was no significant difference in this outcome with 92% for PBT and 96% for photon radiotherapy (p=0.95). There were no incidences of poor cosmetic outcome in either group at any time point (Galland-Girodet et al 2014). In the uncontrolled study (Bush et al 2014) the proportion of patients reporting an excellent or good cosmetic outcome for PBT patients was in the region of 90% to 95%[4] from baseline to a median follow-up of five years.
- Patient satisfaction. This assessed patient's satisfaction with the fact that they had received partial breast irradiation (as PBT or photon radiotherapy) rather than whole breast irradiation. No comparative analysis was reported, but the proportion of patients who were totally satisfied with partial breast irradiation was high. At one year follow-up this was 94% for PBT and 98% for photon radiotherapy. At seven years follow-up this was 85% for PBT and 96% for photon radiotherapy (Galland-Girodet et al 2014).
- A prospective uncontrolled study (Bush et al 2014) provided survival outcomes for PBT patients but no comparative evidence was available for this outcome. At a median of five

[1] https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
[2] The Harvard 4-point cosmetic scoring system was used to assess cosmetic outcomes. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted) (https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566)
[3] These data were presented graphically in the study and precise figures were not reported
[4] These data were presented graphically in the study and precise figures were not reported

years follow-up, overall survival was 95% (95%CI not reported); disease-free survival was 94% (95%CI not reported) and recurrence-free survival was 97% (95%CI 93 to 100).

- **Safety.** The comparative study by Galland-Girodet et al (2014) reported safety outcomes up to seven years follow-up. There were no significant differences for PBT compared to photon radiotherapy in physician assessed skin toxicities (erythema or dry or moist desquamation) at five years follow-up[5]. There were no significant differences between the groups in incidence of breast pain, oedema, fibrosis, fat necrosis, rib pain or fracture at five or seven years follow-up. There were significant differences at five years in favour of photon radiotherapy:
    - A greater number of cases with PBT (44%) compared to photon radiotherapy (2%) had moderate skin colour change (p≤0.0001).
    - There was significantly more patchy atrophy in the irradiation portal with PBT (50%) compared to photon radiotherapy (5%) (p≤0.0001).
    - Skin colour change (p=0.02) and late skin toxicity (p=0.029) were also reported to be significantly worse for PBT compared to photon radiotherapy at five years but no figures were reported.

  At seven years follow-up there was significantly more telangiectasia[6] >4cm^2 with PBT (38.5%) compared to photon radiotherapy (4%) (p=0.0013) (Galland-Girodet et al 2014)[7].
- In the prospective uncontrolled study of patients who all received PBT (Bush et al 2014) there were no adverse effects of grade three (severe or medically significant but not immediately life-threatening) or higher during PBT or up to three months after treatment[8]. Mild to moderate (grade 1 or 2) radiation dermatitis was experienced by 62% of patients. All patients completed their treatment without interruption. There were few late side effects reported (7% grade 1 telangiectasia and 1% fat necrosis requiring drainage) and no late cases of rib fracture, clinical pneumonitis or cardiac events.
- **Cost-effectiveness.** One study compared the cost-effectiveness of PBT and photon radiotherapy for breast cancer, modelling patient selection factors and scenarios for which PBT may be cost-effective due to differences in mean heart dose with a lifetime horizon (Mailhot Vega et al 2017). At a threshold of $50,000/ quality-adjusted life year (QALY) (£37,663[9]), PBT was not cost-effective for women without cardiac risk factors compared to photon radiotherapy. There were some scenarios (e.g. women aged 50 years receiving a mean heart dose of 9Gy and women aged 60 years receiving a mean heart dose of 10Gy) where PBT was cost-effective compared to photon radiotherapy for women with one or more cardiac risk factors. At a threshold of $100,000/ QALY (£75,347) there were scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost-effective compared to photon radiotherapy for both women with and without cardiac risk factors. The model used a societal perspective (rather than direct costs) and a lifetime horizon ending at patient death or age 100 years. This, in addition to the fact that the willingness to pay thresholds used are higher than the threshold that is commonly used

[5] Not reported at seven years
[6] Dilation of the capillaries causing red or purple clusters on the skin or other organs, often spidery in appearance (https://en.oxforddictionaries.com/definition/telangiectasia)
[7] Not reported at five years
[8] The grading system used to assess adverse events was not specified. However the language used (e.g. the description of grade 1 or 2 adverse effects as mild to moderate) is consistent with the National Cancer Institute Common Terminology Criteria for Adverse Events (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)
[9] Conversions from US dollars to UK pounds were calculated in June 2018

by NICE in the UK (£20,000 to £30,000), suggest that the findings have limited applicability to the NHS in England.

- The best quality clinical evidence about the effectiveness of PBT compared to photon radiotherapy for breast cancer comes from one non-randomised comparative study (Galland-Girodet et al 2014) and should be treated with caution. Where significant differences were observed between the groups these favoured photon radiotherapy. These significant differences primarily concerned cosmetic outcomes from the physician's perspective.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: Medline, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1st January 2008 and 1st May 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. The higher quality papers which matched the PICO were selected for inclusion in this review using established hierarchy of evidence criteria[10].
- Physics planning papers such as dosimetric planning studies were not eligible for inclusion in the review as specified by the PICO criteria.
- Although systematic reviews were identified in the search (e.g. Verma et al 2016) these were descriptive reviews without meta-analysis and they included both studies that did and did not meet the PICO. Therefore individual studies were included in this review in preference to the published systematic reviews.
- The studies matching the PICO after review of the full text were discussed with NHS England before the final study selection[11]. As a comparative study with clinical outcomes was available (Galland-Girodet et al 2014), this was agreed as the main source of evidence supplemented by a prospective uncontrolled study with clinical and toxicity outcomes and five year follow-up (Bush et al 2014, n=100). An additional uncontrolled study of a similar size (Verma et al 2017, n=91) was considered but ultimately not included in the review due to being a lower quality study with a shorter follow-up period (median 15.5 months) in comparison to the seven and five year follow up periods in the included studies.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7).

[10] https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
[11] Teleconference with NHS England, 13th June 2018

- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8).

4 Results

This evidence review identified one non-randomised comparative study reporting clinical outcomes for PBT compared to photon radiotherapy (Galland-Girodet et al 2014). This study included 98 patients (gender not specified) and had a median follow-up of 82.5 months. Due to the limited availability of comparator studies which met the PICO criteria, this comparative study was supplemented by a prospective uncontrolled study with clinical and toxicity outcomes and median follow-up of five years (Bush et al 2014; n=100, gender not specified). A cost-effectiveness study was also identified (Mailhot Vega et al 2017). Full details of the study designs and outcomes are summarised in the evidence tables in section 7.

1. **Is there evidence that proton beam therapy (PBT) is equivalent in efficacy for survival and progression free survival to photon radiotherapy?**

No studies reported survival or progression free survival for PBT compared to photon radiotherapy.

The non-randomised comparative study (Galland-Girodot et al 2014) reported local failure rate, physician- and patient-rated cosmetic outcome and patient satisfaction. The prospective, uncontrolled study (Bush et al 2014) reported overall survival, disease-free survival and recurrence-free survival for patients receiving PBT. This uncontrolled study also reported physician- and patient-rated cosmetic outcome.

Survival
There are no comparative studies for PBT versus photon radiotherapy which report survival or progression free survival.

Survival outcomes for patients receiving PBT were reported in one uncontrolled study (Bush et al 2014, n=100). At a median of five years follow-up, overall survival was 95% (95%CI not reported); disease-free survival was 94% (95%CI not reported) and recurrence-free survival was 97% (95%CI 93 to 100).

Local failure rate[12]
There was no significant difference in the seven year local failure rate between the PBT (11%) and photon radiotherapy groups (4%) (p=0.22) (Galland-Girodot et al 2014, n=98).

Cosmetic outcome and patient satisfaction were also reported in the two studies, although they are not directly relevant to this question about survival or progression-free survival.

Physician-rated cosmetic outcome
Physician-rated cosmetic outcome[13] was reported in both the non-randomised comparative study (Galland-Girodot et al 2014, n=98) and the uncontrolled study (Bush et al 2014, n=100). The results of the comparative study showed that:

[12] Local failure generally means recurrence of disease at the treatment site or surrounding area.
[13] The Harvard 4-point cosmetic scoring system was used to assess cosmetic outcomes. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted) (https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566)

- At one year follow-up, similar proportions of physicians rated overall cosmetic outcome as good or excellent for PBT (100%) and photon radiotherapy (97%) (p value not reported). At seven years follow-up, the proportion of physicians rating overall cosmetic outcome as good or excellent was significantly lower for PBT (62%) than photon radiotherapy (p=0.03).
- There were no incidences of poor cosmetic outcome in either group at any time point.

In the uncontrolled study (Bush et al 2014) the proportion of physicians reporting an excellent or good cosmetic outcome for PBT patients was in the region of 95%[14] from baseline to a median five year follow-up.

Patient-rated cosmetic outcome

Both studies reported patient-rated cosmetic outcome[15] (Galland-Girodot et al 2014, n=98; Bush et al 2014, n=100). The results of the comparative study showed that:

- At one year follow-up, similar proportions of patients rated their overall cosmetic outcome as good or excellent for PBT (100%) and photon radiotherapy (93%) but no p value was reported.
- At seven years follow-up, there was no significant difference in the proportion of patients rating overall cosmetic outcome as good or excellent for PBT (92%) and photon radiotherapy (96%) (p=0.95).
- There were no incidences of poor cosmetic outcome in either group at any time point.

In the uncontrolled study (Bush et al 2014) the proportion of patients reporting an excellent or good cosmetic outcome for PBT patients was in the region of 90 to 95%[16] from baseline to a median follow-up of five years.

Patient satisfaction

Patient satisfaction was reported in the non-randomised comparative study (Galland-Girodot et al 2014), which assessed patient's satisfaction with partial breast irradiation (PBI) using either PBT or photon radiotherapy rather than whole breast irradiation (WBI).

- At one year follow-up, the proportion of patients who were 'totally satisfied' with PBI was 94% for PBT and 98% for photon radiotherapy.
- At seven year follow-up, this was 85% for PBT and 96% for photon radiotherapy. No comparative analysis was reported for these time points.

2. Are there patient characteristics that increase the risk of toxicity in breast radiotherapy with photons?

No studies assessed if there are patient characteristics that increase the risk of toxicity in breast radiotherapy with photons. Although Galland-Girodot et al (2014) included a group of patients who received photon radiotherapy the study did not include any analysis on whether any patient characteristics increase the risk of toxicity in breast radiotherapy with photons.

[14] These data were presented graphically in the study and precise figures were not reported

[15] The Harvard 4-point cosmetic scoring system was used to assess cosmetic outcomes. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted) (https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566)

[16] These data were presented graphically in the study and precise figures were not reported

3. Does delivery of radiation by protons compared with photons reduce the risks of toxicity to key organs when treating breast cancer with radiotherapy? The organs at risk are: heart and lung.

3a. By how much does the delivery of radiation by protons reduce the risks of toxicity to the key organs?

No studies assessed if delivery of radiation by protons compared with photons reduces the risks of toxicity to key organs such as the heart and lungs when treating breast cancer with radiotherapy.

Other safety outcomes following radiotherapy were reported by one non-randomised comparative study (Galland-Girodot et al 2014, n=98) where patients received either PBT or photon radiotherapy and one uncontrolled study (Bush et al 2014, n=100) where all patients received PBT.

The comparative study (Galland-Girodot et al 2014) reported physician evaluation of safety outcomes at five and seven years follow-up:

- There were no significant differences between PBT and photon radiotherapy in skin toxicities (erythema or dry or moist desquamation) at five years[17] or incidence of breast pain, oedema, fibrosis, fat necrosis, rib pain or fracture at five or seven years follow-up[18].
- There were significant differences at five years in moderate skin colour change with a greater number of cases with PBT (44%) compared to photon radiotherapy (2%) ($p \leq 0.0001$). There was also significantly more patchy atrophy in the irradiation portal with PBT (50%) compared to photon radiotherapy (5%) ($p \leq 0.0001$).
- Skin colour change ($p=0.02$) and late skin toxicity ($p=0.029$) were also reported to be significantly worse for PBT compared to photon radiotherapy at five years but no figures were reported.
- At seven years follow-up there was significantly more telangiectasia >4cm^2 with PBT (38.5%) compared to photon radiotherapy (4%) ($p=0.0013$)[19].

In the uncontrolled study (Bush et al 2014) there were no adverse effects of grade three (severe or medically significant but not immediately life-threatening) or higher during PBT or up to three months after treatment[20]. Mild to moderate (grade 1 or 2) radiation dermatitis was experienced by 62% of patients. All patients completed their treatment without interruption. There were few late[21] side effects reported (7% grade 1 telangiectasia and 1% fat necrosis requiring drainage) and no late cases of rib fracture, clinical pneumonitis or cardiac events.

4. Are there any particular characteristics of the tumour that increase the risk of late toxicity?

No studies assessed whether different tumour characteristics increase the risk of late toxicity. Although Galland-Girodot et al (2014) and Bush et al (2014) included discussion of late toxicities (median follow-up periods of 82.5 months and five years) neither included any subgroup analysis.

[17] Not reported at seven years
[18] Additional information on safety outcomes was only presented graphically
[19] Not reported at five years
[20] The grading system used to assess adverse events was not specified. However the language used (e.g. the description of grade 1 or 2 adverse effects as mild to moderate) is consistent with the National Cancer Institute Common Terminology Criteria for Adverse Events (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)
[21] No definition of late side effects was provided

5. **Are there any particular characteristics of the radiation delivery strategy that increase the risk of late toxicity?**

No studies assessed whether there are any particular characteristics of the radiation delivery strategy that increase the risk of late toxicity. In Galland-Girodot et al (2014), toxicity outcomes were reported separately for the PBT and photon radiotherapy groups as discussed in question 3. There were some differences in late skin changes and toxicities favouring the photon radiotherapy group. There was no additional analysis on different characteristics of the radiation delivery strategy.

6. **What is the evidence of cost-effectiveness of protons compared with photons for people with breast cancer?**

6a. Is there evidence of cost-effectiveness in any subgroups?

One study (Mailhot Vega et al 2017) considered the cost-effectiveness of PBT compared to photon radiotherapy for breast cancer. This study modelled scenarios for which PBT would potentially be cost-effective compared to photon therapy using a societal perspective across a lifetime horizon (up to 100 years).

- At a threshold of $50,000/ QALY (£37,663[22]), PBT was not cost-effective for women without cardiac risk factors compared to photon radiotherapy. This remained the case following sensitivity analysis.
- For a subset of the women who had one or more cardiac risk factors, the model indicates that at a threshold of $50,000/ QALY (£37,663), PBT was cost-effective compared to photon radiotherapy. The criteria for these subsets were based on age and the mean radiotherapy heart dose (e.g. women aged 50 years receiving a mean heart dose of 9Gy and women aged 60 years receiving a mean heart dose of 10Gy).
- At a threshold of $100,000/ QALY (£75,347) there were scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost-effective compared to photon radiotherapy for both women with and without cardiac risk factors.

7. **What key factors might need to be included in a study looking at the clinical effectiveness of proton beam therapy compared to photon radiotherapy?**

One non-randomised comparative study (Galland-Girodot et al 2014) has compared clinical and safety outcomes for PBT and photon radiotherapy. The existing evidence base would be strengthened by a randomised controlled trial of PBT compared to photon radiotherapy.

Although we have not systematically searched the clinical trails.gov website, we are aware of one RCT in progress[23]. This illustrates that RCT design for comparing PBT to photon radiotherapy in breast cancer patients is possible. Reviewing existing trials underway will help to inform current gaps in research and inform future research commissioned in the UK.

[22] Conversions from US dollars to UK pounds were calculated in June 2018

[23] RADCOMP (NCT02603341). A second phase III RCT (BREAST P1) was referred to in the PWG feedback but we have not been able to identify the NCT reference

5 Discussion

One non-randomised comparative study has assessed clinical and safety outcomes for PBT compared to photon radiotherapy for breast cancer. There was no difference in local failure rate between the two groups at seven year follow-up. There was a significant difference in longer term physician-rated cosmetic outcomes favouring photon radiotherapy but no difference in patient-rated cosmetic outcomes over the seven year follow-up period. Both physicians and patients used the Harvard 4-point cosmetic scoring system to assess cosmetic outcomes. This is a subjective scale based on comparing the appearance of the treated breast to the untreated breast. No statement on blinding or inter-rater reliability was made. There is no indication that physician assessors were blinded to treatment group when assessing cosmetic outcomes which increases the risk of bias in the assessment of cosmetic outcomes. The number of patients for whom data were available varied over the follow-up period. By 7 years follow-up data on cosmetic outcomes were available for13 PBT patients and 50 photon radiotherapy patients. A variety of skin toxicity and other safety outcomes were reported for PBT compared to photon therapy. These either showed no difference between the groups or showed worse outcomes with PBT compared to photon radiotherapy. Where figures for the outcomes were reported, the proportion of patients affected was between one third and half of PBT patients compared to 5% or less of photon radiotherapy patients. The use of PBT was determined by proton beam availability. There were no significant differences between the photon and PBT groups at baseline.

One prospective uncontrolled study included 100 patients followed-up for a median of five years. This reported high overall, disease-free and recurrence-free survival rates with PBT, although the lack of comparator for these outcomes limits the conclusions that can be drawn. Cosmetic outcomes were assessed using the subjective Harvard 4-point cosmetic scoring system. In this study, there were no acute (during PBT to three months after treatment) or late adverse effects of grade 3 or higher. Approximately two thirds of patients experienced mild to moderate acute skin toxicities with PBT. No patients interrupted their treatment due to adverse effects.

Neither study included subgroup analysis for different patient characteristics. Patient gender was not reported. In one study patients were treated in the US between 2003 and 2006. In the other study year of treatment was not specified. The applicability of the results to current UK practice is unclear.

One cost-effectiveness study modelled patient selection factors and scenarios for which PBT may be cost-effective compared to photon therapy due to differences in age and mean heart dose. This considered cost effectiveness at two willingness to pay thresholds ($50,000/ QALY (£37,663) and $100,000/ QALY (£75,347). These were higher than the threshold commonly used by NICE in the UK (£20,000 to £30,000) which limits the study's applicability to a UK context. The model used a lifetime horizon ending at patient death or age 100 years, which may make intervention appear more cost-effective than if a lower, more realistic, life-expectancy had been applied. The model also used a societal perspective rather than direct costs which are more typically used to assess cost-effectiveness in the UK. At the lower $50,000/ QALY threshold, PBT was not cost-effective compared to photon radiotherapy for any women who did not have cardiac risk factors[24]. There were some scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost-effective compared to photon radiotherapy for women with one or more cardiac risk factors (e.g. women aged 50 years receiving a mean heart dose of 9Gy and women aged 60 years receiving a mean heart dose of 10Gy). The study did not model outcomes for male patients with breast cancer.

[24] Cardiac risk factors was not defined by the study authors

The results of this cost-effectiveness study should be treated with caution. The 100 year life expectancy, the inclusion of societal costs and the high willingness to pay thresholds mean that the results are not generalisable to the NHS in England.

6 Conclusion

Currently, the best quality clinical evidence about the effectiveness of PBT compared to photon radiotherapy for breast cancer comes from a single, non-randomised, comparative study and therefore should be treated with caution. There was no difference in local failure rate between the two groups at seven year follow-up. Where significant differences were observed between the groups these favoured photon radiotherapy, although these differences primarily concerned subjective cosmetic outcomes from the physician's perspective which may be at risk of bias. There is some modelling evidence that PBT might be cost-effective compared to photon radiotherapy in some scenarios but the applicability of this finding to a UK context is questionable due to the modelling approach, the assumptions used and the application of a higher cost-effectiveness threshold than is used by the NHS in England.

7 Evidence Summary Table

For abbreviations see list after each table

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Gallan d-Girodet et al (2014)	P1 – non-randomised phase 1 trial 3 US sites, October 2003 to April 2006 This study was designed as a prospective phase 1 clinical-dose escalation trial of accelerated partial-breast	Patients ≥18 years with pT1[25] invasive breast cancer with no cancer in nearby lymph nodes (N0) and no metastasis (M0) Mean age 61 years (range not reported) Patient gender not reported Tumour side Left: 59% Right: 41% No significant differences	N=98 Photon-based 3D-APBI (photon) radiotherapy: 79 PBT (3D conformal or double scattered proton radiation[26]): 19 All patients received partial breast irradiation of 32Gy in 8 fractions given twice daily over 4 consecutive days Median follow-up 82.5	Primary Clinical effectiveness	Local failure rate	7-year cumulative incidence of local failure rate • PBT: 11% (2/19) • Photon: 4% (3/79) No significant difference between the photon and PBT groups (p=0.22) All recurrences occurred outside the original site	6	Direct	This paper reported outcomes for a subgroup of patients who received 32Gy of either PBT or photon-based 3D-APBI The use of PBT was determined by proton beam availability. There were no significant differences between the photon and PBT groups at baseline Patient gender was not reported. Gender was not cited as an inclusion or exclusion criteria. No subgroup analysis based on patient characteristics was performed The Harvard 4-point cosmetic scoring system was used to assess cosmetic outcomes. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted)[27] No statement on blinding was made. There is no indication that physician assessors were blinded to treatment group when assessing cosmetic outcomes which introduces the risk of bias
				Primary Clinical effectiveness	Physician-rated cosmetic outcome	Using the Harvard 4-point cosmetic scoring system **At 1-year follow-up** PBT: • Excellent 67% (12/18) • Good 33% (6/18) • Fair 0 • Poor 0 Photon: • Excellent 79% (58/73) • Good 18% (13/73) • Fair 3% (2/73) • Poor 0 **At 5-years follow-up** PBT: • Excellent 25% (4/16) • Good 31% (5/16)			

[25] 'T' refers to the size and extent of the primary tumour (with higher numbers indicating larger tumours) (https://www.cancer.gov/about-cancer/diagnosis-staging/staging)
[26] PBT beam arrangements were at the discretion of the treating physician
[27] https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	irradiation (APBI) for patients with early stage breast cancer. Multiple treatment techniques were allowed, including mixed photons and electrons, photons only and PBT	between the groups at baseline	months (range 1.6 to 103.8)			• Fair 44% (7/16) • Poor 0 Photon: • Excellent 58% (34/59) • Good 32% (19/59) • Fair 10% (6/59) • Poor 0 **At 7-years follow-up:** PBT: • Excellent 31% (4/13) • Good 31% (4/13) • Fair 38% (5/13) • Poor 0 Photon: • Excellent 64% (32/50) • Good 30% (15/50) • Fair 6% (3/50) • Poor 0 The proportion of physicians rating overall cosmetic outcome as good or excellent over time was displayed graphically. The authors reported that there was no significant difference between the groups at 1 or 2 year follow-up, but that a significant difference, favouring photons, was found after 3 years follow-up. However, figures for this significant comparison were only reported for 7 year follow-up (p=0.03): PBT rated excellent/good at 7 years: 62% Photon rated excellent/good at 7 years: 94%			The number of patients for whom data were available varied over the follow-up period. By 7 years follow-up data on cosmetic outcomes were available for13 PBT patients and 50 photon radiotherapy patients This was a small non-randomised comparative study conducted at 3 centres over 3 years with 7 year follow-up. Patients were treated in the US between 2003 and 2006 which may limit the applicability to current UK practice
				Primary Clinical effectiveness	Patient-rated cosmetic outcome	Using the Harvard 4-point cosmetic scoring system **At 1-year follow-up** PBT:			

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Excellent 56% (10/18) • Good 44% (8/18) • Fair 0 • Poor 0 Photon: • Excellent 60% (33/55) • Good 33% (18/55) • Fair 7% (4/55) • Poor 0 **At 5-years follow-up** PBT: • Excellent 44% (7/16) • Good 44% (7/16) • Fair 12% (2/16) • Poor 0 Photon: • Excellent 60% (36/60) • Good 33% (20/60) • Fair 7% (4/60) • Poor 0 **At 7-years follow-up:** PBT: • Excellent 61% (8/13) • Good 31% (4/13) • Fair 8% (1/13) • Poor 0 Photon: • Excellent 59% (27/46) • Good 37% (17/46) • Fair 4% (2/46) • Poor 0 The proportion of patients rating overall cosmetic outcome as good or excellent over time was displayed graphically. The authors reported that there was no significant difference between the groups at any time point from 1 to 7			

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						years follow-up. However, figures for these non-significant comparisons between groups were only reported for 5 (p=0.69) and 7 (p=0.95) years follow-up. PBT rated excellent/good at 5 years: 88% Photon rated excellent/good at 5 years: 93% PBT rated excellent/good at 7 years: 92% Photon rated excellent/good at 7 years: 96%			
				Primary Clinical effectiveness	Patient satisfaction	Patient satisfaction to partial breast irradiation (PBI) was assessed using 3 response categories **At 1-year follow-up** PBT: • Totally satisfied 94% (17/18) • Not totally satisfied but would choose PBI again 0 • Not totally satisfied and would choose whole breast irradiation (WBI) 6% (1/18) Photon: • Totally satisfied 98% (53/54) • Not totally satisfied but would choose PBI again 2% (1/54) • Not totally satisfied and would choose WBI 0 **At 5-years follow-up** PBT: • Totally satisfied 88% (14/16) • Not totally satisfied but would choose PBI again 6% (1/16) • Not totally satisfied and would choose WBI 6% (1/16)			

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Photon: • Totally satisfied 93% (56/60) • Not totally satisfied but would choose PBI again 3.5% (2/60) • Not totally satisfied and would choose WBI 3.5% (2/60) **At 7-years follow-up** PBT: • Totally satisfied 85% (11/13) • Not totally satisfied but would choose PBI again 0 • Not totally satisfied and would choose WBI 15% (2/13) Photon: • Totally satisfied 96% (43/45) • Not totally satisfied but would choose PBI again 2% (1/45) • Not totally satisfied and would choose WBI 2% (1/45) No statistical comparison at these time-points was reported. There was reported to be no significant difference between the groups at 3 year follow up (p=0.96) (category proportions not reported)			
				Safety	Safety	Skin toxicities were graded on a 4-point scale: none; mild; moderate and severe **Physician evaluation at 5 years:** Significantly more moderate skin colour change with PBT (44%) compared to photon (2%) (p≤0.0001) Significantly more development of patchy atrophy in the irradiation portal with PBT (50%) compared to photon (5%) (p≤0.0001)			

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						No significant differences between PBT and photon for rates of erythema or dry or moist desquamation **Physician evaluation at 7 years:** Skin colour change (p=0.02) and late skin toxicity (p=0.029) significantly worse with PBT compared to photon (figures not specified) Telangiectasia was assessed using 4 categories: none; 1-2cm^2; 2-4 cm^2; >4 cm^2 Significantly more telangiectasia >4cm^2 with PBT (38.5%) compared to photon (4%) (p=0.0013) No significant differences between PBT and photon in incidence of breast pain, oedema, fibrosis, fat necrosis, rib pain or fracture at 5 or 7 years follow-up Additional information on safety outcomes was only presented graphically			
Mailhot Vega et al (2017)	S2 – cost-effectiveness model This cost-effectiveness study modelled patient selection factors	Patients with breast cancer Model entrants could be healthy; alive with coronary heart disease (CHD) or dead	Photon radiotherapy (mean heart dose range 1Gy to 10Gy) PBT (where the average PBT plan yielded a mean heart dose of 0.5Gy)	Cost-effectiveness	Incremental cost-effectiveness ratio (ICER)	**At a threshold of $50,000/QALY (£37,663):** PBT was not cost-effective for women without cardiac risk factors PBT was cost-effective in 2 scenarios for women with ≥1 cardiac risk factors: • 50 years old receiving a mean heart dose of 9 Gy • 60 years old receiving a mean heart dose of 10 Gy ***Sensitivity analysis***	5	Direct	Cardiac risk factors were not defined The model assumed no difference in tumour control with PBT and photon radiotherapy. A five year survival rate of 94% was assumed The model assumed that differences in mean heart dose would result in different rates of major cardiac events Costs included treatment costs (incorporating capital cost of construction, overhead, salary, land, personnel and facilities) and assuming a facility lifespan of 30 years; diagnosis and

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	and scenarios for which PBT would potentially be cost-effective compared to photon therapy due to differences in mean heart dose Data to populate the model were taken from published studies, US guidance and average Medicare reimbursements		The model considered women aged 40, 50 or 60 years The model included women with or without cardiac risk factors			PBT was not cost-effective for any scenarios for women with no cardiac risk factors PBT was cost-effective in 3 scenarios for women with ≥1 cardiac risk factors: • 40 years old receiving a mean heart dose of 9Gy • 50 years old receiving a mean heart dose of 7Gy • 60 years old receiving a mean heart dose of 8Gy **At a threshold of $100,000/QALY (£75,347):** PBT was cost-effective in 2 scenarios for women with no cardiac risk factors: • 40 years old receiving a mean heart dose of 10Gy • 50 years old receiving a mean heart dose of 9Gy PBT was cost-effective in 3 scenarios for women with ≥1 cardiac risk factors: • 40 years old receiving a mean heart dose of 6Gy • 50 years old receiving a mean heart dose of 5Gy • 60 years old receiving a mean heart dose of 6Gy ***Sensitivity analysis*** PBT was cost-effective in 3 scenarios for women with no cardiac risk factors: • 40 years old receiving a mean heart dose of 9Gy • 50 years old receiving a mean heart dose of 7Gy • 60 years old receiving a mean heart dose of 9Gy			medical management of CHD; annual electrocardiogram Costs and QALYS were discounted at an annual rate of 3% Sensitivity analysis included percutaneous coronary intervention (PCI), chance of PCI occurring in an inpatient or outpatient setting and elevated risk of death from CHD Conversions from US dollar to UK sterling were calculated in June 2018 Model cycles were equivalent to 1 year with simulations using a lifetime horizon ending at patient death or age 100 years. This time horizon is implausible and may make the treatment appear more cost-effective than if a lower, more realistic life expectancy had been applied The analysis used a societal perspective for 2012 US dollars. Modelling using direct costs is more typically used in the UK and would be more applicable to a UK NHS context and the thresholds commonly used by NICE to assess cost-effectiveness The results are not generalisable to a UK NHS setting due to the inclusion of indirect costs, US costs, unrealistic life expectancy and a high willingness to pay threshold

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						PBT was cost-effective in 3 scenarios for women with ≥1 cardiac risk factors: • 40 years old receiving a mean heart dose of 5Gy • 50 years old receiving a mean heart dose of 4Gy • 60 years old receiving a mean heart dose of 5Gy			

3D-APBI – Three Dimensional Accelerated Partial-Breast Irradiation; CHD – Coronary Heart Disease; Gy – Gray; ICER - Incremental Cost-Effectiveness Ratio; PBT – Proton Beam Therapy; PCI - Percutaneous Coronary Intervention; QALY - Quality-Adjusted Life Year

Use of proton beam therapy to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Bush et al (2014)	P1 – prospective cohort study This study was an uncontrolled prospective phase 2 trial to assess the efficacy and toxicity of PBT	Patients with invasive nonlobular breast cancer with a maximal dimension of 3cm and no cancer in nearby lymph nodes All patients were T1 or T2 Patients were excluded if	N=100 Partial breast irradiation using PBT Patients underwent partial mastectomy followed by PBT to the surgical bed Patients received 40 Gy in 10 fractions daily for 2 weeks	Primary Clinical effectiveness	Overall survival	95% (median follow-up 5 years) 95%CI not reported	5	Direct	This study used a skin-sparing technique to reduce skin toxicity. This was an immobilization system designed to provide a reproducible position that rigidly immobilises the skin surface of the breast Patient gender was not reported. Gender was not cited as an inclusion or exclusion criteria. No subgroup analysis based on patient characteristics was performed The authors provided limited details for the outcomes reported. The grading system used to assess adverse events was not specified. However the language used (e.g. the description of grade 1 or 2 adverse effects as mild to moderate) is consistent with the
				Primary Clinical effectiveness	Disease-free survival	94% (median follow-up 5 years) 95%CI not reported			
				Primary Clinical effectiveness	Recurrence-free survival rate	97% (95%CI 93 to 100) (median follow-up 5 years) No local failures with recurrence at the original tumour site			
				Primary Clinical effectiveness	Physician-rated cosmetic outcome	Assessed as excellent, good, fair or poor using the Harvard 4-point cosmetic scoring system The proportion reporting an excellent or good result was presented graphically.			

Use of proton beam therapy to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	for partial breast irradiation Treatment years not stated Number of centres not stated	they had extensive ductal carcinoma in situ Mean age 63 years (range 41 to 83) Patient gender was not reported Tumour side Left: 52% Right: 48%	17% received chemotherapy 78% received hormone therapy Median follow-up 60 months			This was in the region of 95% from baseline to five year follow-up. The authors report that no annual assessment was significantly different from baseline but did not report p values			National Cancer Institute Common Terminology Criteria for Adverse Events[28]. The Harvard 4-point cosmetic scoring system was used to assess cosmetic outcomes. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted)[29] The study had a median follow-up of 60 months (5 years) The prospective design of the study reduces the possibility of selection bias in the study population. The number of participating centres and year of treatment were not reported. The risk of bias due to different practices in different centres or over time is unknown. The applicability to current UK practice is not clear
				Primary Clinical effectiveness	Patient-rated cosmetic outcome	Assessed as excellent, good, fair or poor using the Harvard 4-point cosmetic scoring system The proportion reporting an excellent or good result was presented graphically. This was in the region of 90 to 95% from baseline to five year follow-up. The authors report that no annual assessment was significantly different from baseline but did not report p values			
				Safety	Safety	**Acute adverse effects** (from PBT initiation to 3 months after completion): No cases of ≥grade 3 acute skin reactions Grade 1-2 radiation dermatitis: 62% No other acute toxicities reported All patients completed their treatment without interruption **Late adverse effects[30]:** Grade 1 telangiectasia: 7% Fat necrosis requiring drainage: 1% No cases of rib fracture, clinical pneumonitis or cardiac events			

[28] https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
[29] https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566
[30] No definition of late side effects was provided

Gy – Gray; PBT – Proton Beam Therapy

8 Grade of Evidence Table

For abbreviations see list after each table

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Local failure rate	Galland-Girodet et al (2014)	6	Direct	C	Local failure generally means recurrence of disease at the treatment site or surrounding area. In Galland-Girodet et al (2014), all recurrences occurred outside the treatment original site. There was no significant difference in the 7-year local failure rate between the PBT (11%) and photon groups (4%) (p=0.22). The significance of local failure rate outside of the original treatment site is not clear. However, the results indicate that patients treated with PBT were no more or less likely to experience this outcome. These results should be treated with caution as they are based on a small, non-randomised trial which included 79 patients who received photon radiotherapy and 19 patients who received PBT and had a median follow-up of 82.5 months. The study was conducted at 3 US centres over a 3 year period from 2003 to 2006 which may limit the applicability to current UK practice. The use of PBT was determined by proton-beam availability rather than randomised patient selection. There were no significant differences between the treatment groups at baseline.
Physician-rated cosmetic outcome	Galland-Girodet et al (2014)	6	Direct	C	The proportion of physicians who rated the cosmetic outcome after partial breast irradiation as good or excellent was reported annually between 1 and 7 years follow-up using the Harvard 4-point cosmetic scoring system. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted)[31]. At 1 year follow-up the proportion of physicians rating overall cosmetic outcome as good or excellent was similar for PBT (100%) and photon radiotherapy (97%).The study authors reported this as a non-significant result but did not provide a p-value. At 7 years, the proportion of physicians rating overall cosmetic outcome as good or excellent was significantly higher for photon radiotherapy (94%) than PBT (62%) (p=0.03). Relative to clinical outcomes, it is not clear what the importance of cosmetic outcome following partial breast irradiation is to physicians. These results should be treated with caution. There is no indication that physician assessors were blinded to treatment group when assessing cosmetic outcomes which introduces the risk of bias. The study authors did

[31] https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					not provide precise figures or p values for all of the time points assessed. These results are based on a small, non-randomised trial which included 79 patients who received photon radiotherapy and 19 patients who received PBT and had a median follow-up of 82.5 months. The study was conducted at 3 US centres over a 3 year period from 2003 to 2006 which may limit the applicability to current UK practice. The use of PBT was determined by proton-beam availability rather than randomised patient selection. There were no significant differences between the treatment groups at baseline.
Patient-rated cosmetic outcome	Galland-Girodet et al (2014)	6	Direct	C	The proportion of patients rating cosmetic outcome after partial breast irradiation as good or excellent was reported annually between 1 and 7 years follow-up using the Harvard 4-point cosmetic scoring system. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted)[32]. At 1 year follow-up the proportion of patients rating overall cosmetic outcome as good or excellent was similar for PBT (100%) and photon radiotherapy (93%).The study authors reported this as a non-significant result but did not provide a p-value. At 7 years, there was no significant difference in this outcome between PBT (92%) and photon radiotherapy (96%) (p=0.95). Relative to clinical outcomes, it is not clear what the importance of cosmetic outcome following partial breast irradiation is to patients. These results should be treated with caution. The study authors did not provide precise figures or p values for all of the time points assessed. These results are based on a small, non-randomised trial which included 79 patients who received photon radiotherapy and 19 patients who received PBT and had a median follow-up of 82.5 months. The study was conducted at 3 US centres over a 3 year period from 2003 to 2006 which may limit the applicability to current UK practice. The use of PBT was determined by proton-beam availability rather than randomised patient selection. There were no significant differences between the treatment groups at baseline.
Patient satisfaction with partial breast irradiation	Galland-Girodet et al (2014)	6	Direct	C	This outcome assessed patient's satisfaction with the partial breast irradiation (PBI) (as PBT or photon radiotherapy) that they had been treated with rather than whole breast irradiation (WBI). The response categories were 'totally satisfied'; 'not totally satisfied but would choose PBI again'; 'not totally satisfied and would choose WBI'. The proportion of patients who were 'totally satisfied' was 94% for PBT and 98% for photon radiotherapy at 1 year follow-up. At 7 years this was 85% for PBT and 96% for photon radiotherapy. No comparative analysis was reported for these time points.

[32] https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Patient satisfaction with PBI (as opposed to WBI) was high for both treatment groups. The importance of this outcome to patients is not clear. These results should be treated with caution. The study authors did not provide precise figures or p values for all of the time points assessed. These results are based on a small, non-randomised trial which included 79 patients who received photon radiotherapy and 19 patients who received PBT and had a median follow-up of 82.5 months. The study was conducted at 3 US centres over a 3 year period from 2003 to 2006 which may limit the applicability to current UK practice. The use of PBT was determined by proton-beam availability rather than randomised patient selection. There were no significant differences between the treatment groups at baseline.
Safety	Galland-Girodet et al (2014)	6	Direct	C	A range of safety and adverse events were reported at 5 and 7 years follow-up including breast pain, oedema, fibrosis, fat necrosis, rib pain or fracture as well as physician-assessed skin toxicities which were graded on a 4-point scale (none; mild; moderate; severe). No further definition of the grading categories was provided. In addition, telangiectasia[33] was assessed on a 4-point scale (none; 1-2cm^2; 2-4cm^2; >4cm^2). There was no significant difference between the groups for rates of erythema or dry or moist desquamation (skin toxicities). There was also no significant difference between the groups in incidence of breast pain, oedema, fibrosis, fat necrosis, rib pain or fracture (figures not provided). Where significant differences existed these favoured photon radiotherapy. For example: • At 5 years there was significantly more moderate skin colour change with PBT (44%) compared to photon radiotherapy (2%) (p≤0.0001) and significantly more development of patchy atrophy in the irradiation portal with PBT (50%) compared to photon radiotherapy (5%) (p≤0.0001). • Skin colour change (p=0.02) and late skin toxicity (p=0.029) were also reported to be significantly worse for PBT compared to photon radiotherapy at five years but no figures were reported. • At 7 years there was significantly worse skin colour change (p=0.02) and late skin toxicity (p=0.029) with PBT (figures not provided). There was also significantly more telangiectasia >4cm^2 with PBT (38.5%) compared to photon radiotherapy (4%) (p=0.0013). A variety of skin toxicity and other safety outcomes were reported. These either showed no difference between the groups or showed worse outcomes with PBT compared to photon radiotherapy. Where figures for the outcomes were reported, the proportion of patients affected was between one third and half of PBT patients compared to 5% or less of photon radiotherapy patients.

[33] Dilation of the capillaries causing red or purple clusters on the skin or other organs, often spidery in appearance (https://en.oxforddictionaries.com/definition/telangiectasia)

Use of proton beam therapy (PBT) Vs. photon-based radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					These results should be treated with caution. There is no indication that physician assessors were blinded to treatment group when assessing cosmetic outcomes which introduces the risk of bias These results are based on a small, non-randomised trial which included 79 patients who received photon radiotherapy and 19 patients who received PBT and had a median follow-up of 82.5 months. The study was conducted at 3 US centres over a 3 year period from 2003 to 2006 which may limit the applicability to current UK practice. The use of PBT was determined by proton-beam availability rather than randomised patient selection. There were no significant differences between the treatment groups at baseline.
Incremental cost-effectiveness ratio (ICER)	Mailhot Vega et al (2017)	5	Direct	C	This outcome reported the ICER[34] for a range of different scenarios based on the woman's age and mean radiotherapy heart dose. A treatment strategy was assessed for cost-effectiveness against a willingness to pay threshold of either $50,000/ quality-adjusted life year (QALY) (£37,663) or $100,000/ QALY (£75,347). At a threshold of $50,000/ QALY, PBT was not cost-effective for women without cardiac risk factors compared to photon radiotherapy. This remained the case following sensitivity analysis. • At a threshold of $50,000/QALY PBT was cost-effective compared to photon radiotherapy for women with 1 or more cardiac risk factors for 50 year old women receiving a mean heart dose of 9Gy and 60 year old women receiving a mean heart dose of 10Gy. • At a threshold of $100,000/ QALY there were scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost-effective compared to photon radiotherapy for both women with and without cardiac risk factors. This study indicates that for some women with 1 or more cardiac risk factors, there may be patient selection factors (based on age and mean heart dose) for which PBT would potentially be more cost-effective than photon radiotherapy at a willingness to pay threshold of $50,000. These results are not generalisable to a UK NHS context because the willingness to pay thresholds used were higher than the threshold that is commonly used by NICE (£20,000 to £30,000). Additional concerns include the use of a societal perspective for 2012 US dollars. This overestimates the duration of the effect and underestimates the ICER value. The study also used of a lifetime horizon ending at patient death or age 100 years which may make the intervention appear more cost-effective than if a lower, more realistic, age cut-off had been used. Conversions from US dollars to UK pounds were calculated in June 2018.

[34] Mailhot Vega et al (2017) described the ICER as the ratio of the difference in costs between PBT and photon radiotherapy and the difference in effectiveness between PBT and photon radiotherapy

3D-APBI – Three Dimensional Accelerated Partial-Breast Irradiation; CHD – Coronary Heart Disease; Gy – Gray; ICER - Incremental Cost-Effectiveness Ratio; PBT – Proton Beam Therapy; PCI - Percutaneous Coronary Intervention; QALY - Quality-Adjusted Life Year

Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival	Bush et al (2014)	5	Direct	C	Overall survival was not defined by Bush et al (2014) but is generally measured from the end of treatment to the date of death. Overall survival was 95% (95%CI not reported) with a median follow-up of five years. Overall survival was high. A high overall survival rate is important to clinicians, patients and their families. These results do not indicate if overall survival following PBT is different to photon radiotherapy, as the study was an uncontrolled prospective study including 100 patients with a median follow-up of 60 months (5 years). The number of participating centres and year of treatment were not reported. The lack of comparator limits the strength of the conclusions that can be drawn.
Disease-free survival	Bush et al (2014)	5	Direct	C	Disease-free survival was not defined by Bush et al (2014) but is generally the time period without any signs or symptoms of disease (local or distant), measured from the end of treatment. Disease-free survival was 94% (95%CI not reported) with a median follow-up of five years. Disease-free survival was high. Disease-free survival is an important primary outcome for patients and their families as well as clinicians. These results do not indicate if disease-free survival following PBT is different to photon radiotherapy, as the study was an uncontrolled prospective study including 100 patients with a median follow-up of 60 months (5 years). The number of participating centres and year of treatment were not reported. The lack of comparator limits the strength of the conclusions that can be drawn.
Recurrence-free survival rate	Bush et al (2014)	5	Direct	C	Recurrence-free survival was not defined by Bush et al (2014) but is generally measured from the end of treatment to first recurrence at the treatment site or surrounding area. Recurrence-free survival was 97% (95%CI 93 to 100) with a median follow-up of five years. There were no local failures with recurrence at the original tumour site. Recurrence-free survival was high. Recurrence-free survival is an important primary outcome for patients and their families as well as clinicians.

Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					These results do not indicate if recurrence-free survival following PBT is different to photon radiotherapy, as the study was an uncontrolled prospective study including 100 patients with a median follow-up of 60 months (5 years). The number of participating centres and year of treatment were not reported. The lack of comparator limits the strength of the conclusions that can be drawn.
Physician-rated cosmetic outcomes	Bush et al (2014)	5	Direct	C	The Harvard 4-point cosmetic scoring system was used to assess the proportion of physicians who rated the cosmetic outcome as good or excellent. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted)[35]. The proportion of physicians reporting an excellent or good cosmetic result was approximately 95% from baseline to a median 5 year follow-up. The authors report that no annual assessment was significantly different from baseline (figures not reported). It is not clear what the importance of cosmetic outcome is to physicians, relative to clinical outcomes. Precise figures were not available as the results were only presented graphically. These results do not indicate if physician-rated cosmetic outcomes following PBT are different to photon radiotherapy, as the study was an uncontrolled prospective study including 100 patients with a median follow-up of 60 months (5 years). The number of participating centres and year of treatment were not reported. The lack of comparator limits the strength of the conclusions that can be drawn.
Patient-rated cosmetic outcomes	Bush et al (2014)	5	Direct	C	The Harvard 4-point cosmetic scoring system was used to assess the proportion of patients who rated the cosmetic outcome as good or excellent. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted)[36]. The proportion of patients reporting an excellent or good result was between 90 to 95% from baseline to a median 5 year follow-up. The authors report that no annual assessment was significantly different from baseline (figures not reported).

[35] https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566
[36] https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566

Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					It is not clear what the importance of cosmetic outcome is to patients, relative to clinical outcomes. Precise figures were not available as the results were only presented graphically. These results do not indicate if patient-rated cosmetic outcomes following PBT are different to photon radiotherapy, as the study was an uncontrolled prospective study including 100 patients with a median follow-up of 60 months (5 years). The number of participating centres and year of treatment were not reported. The lack of comparator limits the strength of the conclusions that can be drawn.
Safety	Bush et al (2014)	5	Direct	C	Bush et al (2014) did not specify the grading system used to assess adverse events. However the language used (e.g. the description of grade 1 or 2 adverse effects as mild to moderate) is consistent with the National Cancer Institute Common Terminology Criteria for Adverse Events[37]. This has 5 grades: grade 1 'mild'; grade 2 'moderate', grade 3 'severe or medically significant but not immediately life-threatening; grade 4 'life-threatening consequences'; grade 5 'death'. Bush et al (2014) reported acute adverse effects (from PBT initiation to 3 months after completion) and late adverse effects. No definition of late adverse effects was provided. There were no acute adverse effects of grade 3 or higher. Grade 1-2 radiation dermatitis was experienced by 62% of patients. All patients completed their treatment without interruption. Late adverse effects included grade 1 telangiectasia (7%) and fat necrosis requiring drainage (1%). No late cases of rib fracture, clinical pneumonitis or cardiac events were observed. Serious adverse events are of high importance to patients and clinicians. Lower grade adverse events, particularly those which can be treated may be of lower importance compared to primary clinical outcomes such as overall survival or progression free survival. In this study, no patients interrupted their treatment due to adverse effects. These results do not indicate if safety outcomes following PBT are different to photon radiotherapy, as the study was an uncontrolled prospective study including 100 patients with a median follow-up of 60 months (5 years). The number of participating centres and year of treatment were not reported. The lack of comparator limits the strength of the conclusions that can be drawn.

Gy – Gray; PBT – Proton Beam Therapy

[37] https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

9 Literature Search Terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients of any age with or without pectus excavatum with breast cancer with or without metastatic disease where primary radiotherapy is indicated in the care pathway.
I – Intervention Which intervention, treatment or approach should be used?	Proton beam therapy Radiotherapy with protons Protons Particle therapy
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	(Photon) radiotherapy *Subgroups* Partial breast radiation Deep inspiration breath hold radiotherapy Volumetric arc radiotherapy IMRT (intensity modulated radiotherapy) Stereotactic ablative body radiotherapy
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Acute toxicity Morbidity Survival Toxicity Late radiation effects Radiation toxicity Late side effects Cardiac toxicity Lung radiation toxicity Other evaluations of quality of life Cost-effectiveness
Assumptions / limits applied to search • English language • Peer reviewed publications • Clinical outcome research • Exclude physics planning papers such as dosimetric planning • Exclude conference abstracts Publications from 2008	

10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers published in English from 1st January 2008 to 1st May 2018. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 1st May 2018
Embase search:

1 exp breast cancer/
2 (breast adj2 (cancer? or neoplas* or malignan* or tumour? or tumor? or carcinoma? or metasta*)).ti,ab.
3 1 or 2
4 Proton Therapy/

5	((proton* or particle) adj3 (therap* or radiotherap* or treatment)).ti,ab.
6	4 or 5
7	3 and 6
8	limit 7 to (english language and yr="2008 -Current")
9	conference*.pt.
10	8 not 9

11 Evidence Selection

- Total number of publications reviewed: 42
- Total number of publications considered potentially relevant: 17
- Total number of publications selected for inclusion in this briefing: 3

12 References

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