Clinical Commissioning Policy:
Proton beam therapy for breast cancer (all ages) [210402P] (URN: 1787)

Publication date: June 2021 **version number:** V1.0

Commissioning position

Summary

Proton beam therapy (PBT) is not recommended to be available as a treatment option for breast cancer.

Executive summary

Equality statement

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

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

Plain language summary

About breast cancer

Breast cancer is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). It is the most common cancer in the United Kingdom (UK) with 55,000 people diagnosed with the disease in 2016. Breast cancer mainly affects women and occurs rarely in men.

When it has not spread to other parts of the body, breast cancer is usually treated with surgery followed by radiotherapy. Other treatments such as hormone therapy, chemotherapy and targeted therapies are often given before and/ or after surgery to reduce risk of the disease returning (referred to as disease recurrence) and improve chance of long-term survival.

About current treatments

Radiotherapy is a treatment where radiation is used to kill cancer cells. There are many different ways you can have radiotherapy. For the treatment of breast cancer, radiotherapy is typically delivered using high energy x-rays (or photons) given by a machine. This is sometimes referred to as conventional radiotherapy.

Conventional photon radiotherapy is often given to patients following breast conserving surgery or removal of the breast (mastectomy) to reduce the risk of local recurrence in patients where the breast cancer has not spread to other parts of the body. When this treatment is delivered using the most modern techniques, the risk of serious side-effects is low.

About proton beam therapy

Proton beam therapy (PBT) provides radiation by delivering a beam of proton particles rather than x-rays. The physical properties of proton beam therapy result in reduced dose being deposited in the normal tissue beyond the tumour, tumour bed or lymph nodes (target tissues). This is in contrast to x-rays where there is dose extension beyond the target tissues.

What we have decided

NHS England has carefully reviewed the evidence to treat breast cancer with proton beam therapy. We have concluded that there is not enough evidence to make the treatment available at this time.

Links and updates to other policies

Not applicable.

Committee discussion

The Clinical Panel considered that there was not sufficient evidence to support a routine commissioning position.

See the committee papers (link) for full details of the evidence.

The condition

Breast cancer is a common cancer in women and occurs rarely in men. When it has not spread to other parts of the body, it is usually treated with surgery followed by radiotherapy. Other treatments such as hormone therapy, chemotherapy and targeted therapies are often given before and/ or after surgery to reduce risk of recurrence and improve chance of long-term survival.

Current treatments

Conventional photon radiotherapy is often given to patients following breast conserving surgery or removal of the breast (mastectomy) to reduce the risk of local recurrence in patients where the breast cancer has not spread to other parts of the body. When this treatment is delivered using the most modern techniques, the risk of serious side-effects is low.

Given the dramatic improvements in long- term survival of breast cancer patients in recent decades, there is now more emphasis on tailoring breast radiotherapy based on risk of relapse to maximise likelihood of cure and minimise long-term side effects. For example, patients with low risk of relapse may be treated with partial breast radiotherapy to the part of the breast where the cancer was located (tumour bed) as this has been shown to be as effective as whole breast radiotherapy but with fewer side effects to normal breast tissue. Patients with a moderate risk of relapse usually receive radiotherapy to the whole breast and those with a higher risk may be offered a “boost dose” to the tumour bed and/or radiotherapy to the lymph gland (nodal) regions. Patients may also benefit from heart-sparing radiotherapy, especially if they have a left-sided cancer, and particularly if lymph nodes behind the breast bone (called internal mammary nodes (IMN)) need treating. Heart-sparing techniques should be available for all who may benefit (NICE guidelines 2018).

Heart-sparing radiotherapy

There are a number of radiotherapy techniques capable of reducing heart doses, including deep- inspiration breath-hold (DIBH) and types of radiotherapy that shape dose away from the heart (volumetric intensity modulated radiotherapy – IMRT):

- ***Deep-inspiration breath-hold (DIBH):*** DIBH techniques have been shown to reduce mean heart dose by at least half for most patients. The UK HeartSpare study (Bartlett et al, 2013) demonstrated that use of a natural breath-hold technique in which a patient simply takes a breath in and holds it during their radiotherapy treatment is as effective as machine-assisted breath-hold in moving the heart out of the radiotherapy fields. The use of deep-inspiration breath-hold techniques is now a standard of care across the UK (RCR Breast Radiotherapy Consensus Guidelines, 2016 and NICE guidelines, 2018).

- ***Volumetric intensity modulated radiotherapy – IMRT:*** A commonly used volumetric IMRT technique is volumetric-modulated arc therapy (VMAT), which can be combined with DIBH. This technique has been shown in planning studies to reduce doses to heart and lung tissues, particularly in women requiring treatment of the lymph nodes behind the breastbone (the internal mammary chain) (Osman et al, 2014, Ranger et al, 2018). There remains however a small population of women requiring internal mammary chain radiotherapy whose anatomy (usually pectus excavatum) makes it difficult to irradiate the target volume without delivering high doses to heart, lung and/or contralateral breast tissues. In this highly specific circumstance, PBT is postulated to offer an advantage over photons in individual patients.

Proposed treatments

PBT provides radiation by delivering a beam of proton particles rather than X-rays. The physical properties of PBT result in reduced dose being deposited in the normal tissue beyond the tumour, tumour bed or lymph nodes (target tissues). This is in contrast to X-rays where there is dose extension beyond the target tissues. Given these properties, PBT may be helpful in the small population of women requiring internal mammary chain radiotherapy and/or with unusual chest wall shapes in more fully covering the tissue that needs to be treated (breast/ chest wall or nodes) and reducing unwanted radiation doses to healthy tissues including heart, lungs and unaffected breast. In this context, an evidence review was undertaken.

Epidemiology and needs assessment

Breast cancer is the most common cancer in women in the UK affecting 1 in 8 women and made makes up 31% of all female cancer diagnoses in the UK in 2016. It also occurs more rarely in men. Around 54,500 cases of female breast cancer were diagnosed in the UK in 2016, together with 360 male cases. Almost half of breast cancer cases diagnosed in the UK each year are in people aged 65 and over. Incidence rates are projected to rise by 2% between 2014 and 2035 to 210 cases per 100,000 females in 2035. Breast cancer is more common in white females than in Asian or black females (CRUK, 2019).

There were around 11,400 breast cancer deaths in the UK in 2017. Mortality rates for breast cancer are projected to fall by 26% in the UK between 2014 and 2035, to 31 deaths per 100,000 females by 2035. Overall, 78% of women survive their breast cancer by 10 years or more, and 65% by 20 years or more in England and Wales (CRUK, 2018b). An estimated 491,300 women who had previously been diagnosed with breast cancer were alive in the UK at the end of 2010. (CRUK 2019)

Given the improvement in long-term survival amongst breast cancer patients, there is increasing concern about the longer-term side-effects of radiotherapy for breast cancer. Therefore, recent

studies have focussed on either reducing the treatment volume (by treating only the part of the breast where the cancer was located) or reducing the dose to the normal tissues (for example, heart-sparing radiotherapy).

Evidence summary

NHS England has concluded that there is not sufficient evidence to support a policy for the routine commissioning of PBT for the treatment of breast cancer.

Two evidence reviews were conducted to explore the role of protons in breast cancer radiotherapy and to identify subgroups of patients that might gain additional benefit from protons.

Summary of evidence: The use of protons in breast radiotherapy

- Fourteen studies were included in this evidence review. These were three retrospective comparisons of PBT and photon radiotherapy, ten case series on PBT and one cost effectiveness study. No controlled studies comparing the clinical effectiveness or safety of PBT and photon radiotherapy were identified.
- One of the three retrospective comparisons included 724,492 patients consisting of 871 PBT patients and 723,621 photon radiotherapy patients (Chowdhary et al 2019). The other two retrospective comparisons had 86 (39 PBT and 47 photon radiotherapy) and 129 (72 PBT and 57 photon radiotherapy) patients respectively (DeCesaris et al 2019, Teichman et al 2018). Sample sizes in the ten case series ranged from ten to 100. Six of these were prospective case series (Luo et al 2019, Smith et al 2019, Bradley et al 2016, Bush et al 2014, Chang et al 2013, MacDonald et al 2013). Four were retrospective case series (Liang et al 2018, Ovalle et al 2018, Verma et al 2017, Cuaron et al 2015).

Clinical effectiveness[1]

- **Overall survival/ mortality** (one retrospective comparison (n=724,492) and four case series (total n= 263 (range 30 to 100)): In the retrospective comparison five year overall survival was 91.9% for PBT patients (n=871) and 88.9% for photon radiotherapy patients (n=723,621). PBT was not associated with overall survival in multivariate analysis (hazard ratio 0.85 (95%CI 0.68 to 1.07), p=0.168). In three case series overall survival ranged from 95% to 100% for median follow-up ranging from 35 months to five years. One case series reported mortality at 7% with a median follow-up of 15.5 months.
- **Disease progression**[2] (five case series, total n=293 (range 30 to 100)): Disease free survival[3] was 94% at a median follow-up of five years in one case series and disease failure[4] was 13% at a median follow-up of 15.5 months in another case series. Loco-regional disease free survival was 96% and 97% (95%CI 93% to 100%) in two case series with median follow-up of 35 months and five years respectively. In another case series there were no cases of loco-regional recurrence at a median follow-up of 59 months. Metastasis free survival was 84% at a median follow-up of 35 months in one case series. In two other case series 3% and 0% of patients developed distant metastasis with median follow-up of 9.3 months and 59 months respectively.
- **Physician-rated cosmetic outcome**[5] (two case series, total n=130 (range 30 to 100)): In one case series the proportion of physicians reporting an '*excellent*' or '*good*' cosmetic

1 95% confidence intervals and standard deviations are provided where reported
2 A range of outcomes relating to local, regional or distant disease progression were reported in the case series
3 Not further defined
4 Including loco-regional recurrence and distant disease
5 One study used an author-developed scale and one study the Harvard Cosmesis Scale. In both cases outcomes were rated as '*excellent*', '*good*', '*fair*' or '*poor*'. One study also reported percentage of breast retraction assessed by comparing the lateral and vertical displacement of the nipple in the treated breast compared to the untreated breast

outcome was approximately 95%[6] from baseline to a median follow-up of five years. In the second case series the proportion of outcomes rated '*excellent*' or '*good*' was 84% at the end of radiotherapy (n=30) and 69% at three years follow-up (n=23). In this study mean percentage breast retraction increased significantly over time from 10.5% at the end of treatment to 15.3% at three years (p=0.002).

- **Patient-reported cosmetic outcome[7]/ body image[8]** (one retrospective comparison (n=129) and one case series (n=100)): In the retrospective comparison mean (standard deviation (SD)) cosmetic outcome was statistically significantly better for PBT patients (n=69) vs photon radiotherapy patients (n=56) (3.40 (0.75) vs 2.44 (0.96), p<0.001) at a median of 6.5 years post-diagnosis. Body image was also statistically significantly better for PBT patients (n=72) vs photon radiotherapy patients (n=57) (12.04 (3.75) vs 13.91 (5.25), p<0.03). In the case series, the proportion of PBT patients reporting an '*excellent*' or '*good*' cosmetic outcome was between approximately 90% and 95%6 from baseline to a median follow-up of five years.
- **Patient-reported treatment outcome[9]/ general perspective[10]** (one retrospective comparison) (n=129)): For treatment outcomes at a median of 6.5 years post-diagnosis, PBT (n=72) was statistically significantly better than photon radiotherapy (n=57) for the mean cosmetic subdomain (1.45 vs 1.88, p<0.001). However, the mean pain subdomain was statistically significantly worse with PBT (1.42 vs 1.25, p<0.005) and there was no significant difference in the functionality (1.11 vs 1.17, p=0.311) or oedema (1.07 vs 1.12, p=0.526) subdomains. For general perspective, mean scores were statistically significantly better for PBT patients for five (of nine) questions: '*happy with treatment choice*' (4.92 vs 4.20, p<0.001), '*skin "felt different" since treatment*' (1.22 vs 1.95, p<0.001), '*changed attitude about sex*' (1.41 vs 1.94, p=0.012), '*breast cancer changed views of "myself and body*"' (1.57 vs 2.16, p=0.008) and '*worry about "disease coming back*"' (2.31 vs 3.27, p<0.001). However, mean score was statistically significantly worse with PBT for one question: '*skin quality during treatment*' (1.50 vs 2.82, p<0.001). There was no significant difference for three questions: '*changed how I live my daily life*' (2.00 vs 2.30, p=0.197), '*role of spirituality/ religion*' (4.35 vs 4.00, p=0.116) and '*upper arms/ mobility issues*' (1.19 vs 1.30, p=0.348).
- **Quality of life[11]** (one case series (n=30)): There were no significant differences in quality of life before treatment and after the last day of PBT for any of the 21 subscales assessed on a general or breast cancer specific quality of life questionnaire.

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6 These data were presented graphically in the study and precise figures were not reported

7 Assessed by the Harvard Cosmesis Scale which rates cosmetic result as 4 ='*excellent*', 3 ='*good*', 2 ='*fair*' or 1 ='*poor*'

8 Assessed by the Body Image Scale. A 10-item self-reported questionnaire assessing feelings about appearance and changes which may have resulted from a disease or treatment during the prior week. Scored from 1 to 4 with higher scores indicating more dissatisfaction/ negative feelings, where 1 ='*not at all*', 2 ='*a little*', 3 ='*quite a bit*', 4 ='*very much*'

9 Assessed by the Breast Cancer Treatment Outcome Scale. A 22-item questionnaire evaluating functional and cosmetic outcome, reported as 4 subdomains: cosmetic, breast specific pain, functionality and oedema. Items are scored from 1 to 4 based on any difference between the treated and untreated breast where 1 = '*none*', 2 = '*slight*', 3 = '*moderate*' and 4 = '*large (major)*'

10 Assessed by 9 questions generated by the study authors which were scored on a 5-point scale from 1 = '*not at all*' to 5 = '*very much*'

11 Assessed by the European Organization for Research and Treatment of Cancer 30 Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC breast cancer specific questionnaire (EORTC QLQ-BR23). These are scored out of 100 with higher functional scores and lower symptoms scores indicating better quality of life. The EORTC QLQ-C30 includes 6 functional subscales (global health status, physical, role, emotional cognitive and social functioning) and 9 symptom subscales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The EORTC QLQ-BR23 includes 3 functional subscales (body image, sexual function and future perspective) and 3 symptom subscales (systemic therapy side effects, breast symptoms and arm symptoms)

Safety

- **Adverse events** (two retrospective comparisons (n=86 and n=129) and ten case series (total n=432 (range 10 to 100)): Some studies reported a range of adverse events. Others reported specific safety outcomes such as skin toxicity, fatigue or complications for PBT patients who had received immediate reconstruction following mastectomy.
- No Grade 5 (death) or Grade 4 (life threatening) adverse events were reported.
- In one retrospective comparison, there was no significant difference in Grade 3 (severe) acute[12] radiation dermatitis between PBT (n=39) and photon radiotherapy (n=47) (5.1% vs 4.3%, p=0.848). Grade 3 adverse events reported in seven case series included radiation dermatitis (between two and ten cases in four studies) and single cases of pneumonitis, breast/ chest wall pain, wet desquamation and fatigue.
- In one retrospective comparison, acute radiation dermatitis ≥ Grade 2 (moderate) was statistically significantly higher with PBT vs photon radiotherapy (69.2% vs 29.8%, p<0.001). There was no significant difference in ≥ Grade 2 acute skin hyperpigmentation (7.7% vs 12.8%, p=0.502). Grade 2 adverse events reported in nine case series included radiation dermatitis (between 33% and 100% in six studies); oesophagitis (between 2% and 33% in four studies); pain (between 24% and 29% in three studies); fatigue (between 2% and 42% in four studies); skin hyperpigmentation (between 30% and 75% in two studies); erythema/ moist/ wet desquamation (between 7% and 100% in three studies); induration (7% in one study); infection (10% in one study) and oedema (3% in one study). In addition, one study reported 5% of patients with skin hyperpigmentation that was described as moderate/ severe and two cases of moderate or severe retraction or significant asymmetry between breasts.
- In one retrospective comparison mean (SD) fatigue[13] was statistically significantly better for PBT patients (n=72) vs photon radiotherapy patients (n=57) (15.3 (17.11) vs 27.25 (22.26), p<0.002) at a median of 6.5 years post-diagnosis. The proportion of patients responding '*yes*' to the question '*have you felt unusually tired or fatigued in the last week*' was 25% for PBT (n=71) and 63% (n=51) for photon radiotherapy. No significance test was reported.
- Reconstruction complications, reported in two case series, were experienced by 27% and 39% of patients respectively. These patients received PBT after a mastectomy with immediate reconstruction. In one study five of 26 patients (19%) had implants removed. In the other study eight of 51 patients (16%) had implants removed.
- Other ungraded adverse events reported included small numbers of cases of skin infection, rib fracture and clinically evident lymphoedema.
- Two studies specified that patients completed their treatment without interruption. One study reported that two patients did not complete the prescribed treatment. Other studies did not include specific statements regarding treatment interruption or discontinuation.

Subgroups

- No evidence suggesting that subgroups of patients may benefit from PBT more than the wider population was identified. In one retrospective comparison that included 871 PBT patients there was no significant association between PBT and overall survival for subgroups of patients based on tumour side, quadrant location, type of surgery (mastectomy vs breast conserving), node positivity, N2-N3 positivity or the inclusion of lymph node irradiation. In one case series adverse events were reported separately for patients who received PBT to the breast (n=27) or chest wall (n=66). However, no significance tests comparing breast and chest wall radiotherapy were reported.

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12 Not further defined

13 Assessed by the Brief Fatigue Inventory. This 9-item self-reported questionnaire is scored on a scale of 0 '*no fatigue*' to 10 '*as bad as you can imagine*'. An average total score was calculated for 8 of the 9 items. The 9th item was reported separately

Cost effectiveness

- One US study compared the cost effectiveness of PBT and photon radiotherapy.
- At a threshold of $50,000/ quality-adjusted life year (QALY) (£40,102[14]), 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 at this threshold compared to photon radiotherapy for women with one or more cardiac risk factors.
- At a threshold of $100,000/ QALY (£80,205) there were scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost effective compared to photon radiotherapy for women with and without cardiac risk factors.

Conclusion

- Three retrospective comparative studies were identified which assessed clinical or safety outcomes for PBT compared to photon radiotherapy for breast cancer. However, these studies reviewed outcomes for patients who had received PBT or radiotherapy treatments rather than prospectively randomising patients to a treatment. In all three studies there were significant differences between the groups at baseline which may have had a confounding effect on the outcomes reported. Other limitations include very small numbers of patients and follow-up durations that may be insufficient to assess the effectiveness of some outcomes. The ten small case series do not provide any information on the effectiveness and safety of PBT compared to photon radiotherapy.
- None of the studies identified were conducted in the UK. It is not clear how generalisable the findings are to current UK NHS clinical practice.
- The cost effectiveness 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 by NICE in the UK (£20,000 to £30,000), suggest that the findings have limited applicability to the NHS in England.

Summary of evidence: The use of protons in partial breast radiotherapy

- 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).
- The best quality clinical evidence about the effectiveness of protons compared to photon radiotherapy for partial breast radiotherapy comes from a 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).
- The Galland-Girodet study reported, at 7 years, the physician rating of overall cosmetic outcome was good or excellent for 62% of PBT patients, compared with 94% for photon patients (P=.03). Skin toxicities were more common for the PBT group: telangiectasia, 69% and 16% (P=.0013); pigmentation changes, 54% and 22% (P=.02); and other late skin toxicities, 62% and 18% (P=.029) for PBT and photons, respectively. There were no significant differences between the groups in the incidences of breast pain, oedema, fibrosis, fat necrosis, skin desquamation, and rib pain or fracture. The study further reports patient-reported cosmetic outcomes at 7 years were good or excellent for 92% and 96% of PBT and photon patients, respectively (P=.95). Overall patient satisfaction was 93% for the entire cohort. The 7-year local failure rate for all patients was 6%, with 3 local recurrences in the PBT group (7-year rate, 11%) and 2 in photon-treated patients (4%) (P=.22).

14 Conversions from US dollars to UK pounds were calculated in September 2019

- Overall, where significant differences were observed between the groups these favoured photon radiotherapy. However, the evidence is low quality and does not provide conclusive evidence for the treatment of patients requiring partial breast irradiation.

Overall, from both evidence reviews, protons have not been shown to provide an advantage over photons radiotherapy for patients with breast cancer or specific subgroups of breast cancer patients.

Prospective, comparative, randomised controlled studies with long follow-up are required to provide more robust evidence on the effectiveness and safety of PBT compared to photon radiotherapy in patients with breast cancer.

Policy review date

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

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

Definitions

Breast Cancer	The most common cancer in women and occurs more rarely in men.
Photon Radiotherapy	Provides radiation by delivering a beam of photons (X-rays). The vast majority of radiotherapy is presently delivered via this method (also known as conventional radiotherapy).
Intensity Modulated Radiotherapy (IMRT)	IMRT is an advanced form of conventional radiotherapy using multiple static fields to shape the dose of radiation to match the tumour and is very precise. By doing this it allows a reduction of radiation dose to healthy surrounding tissues and so reduces late side effects of treatment.
Deep Inspiratory Breath Hold (DIBH)	When a patient is undergoing breast radiotherapy and is asked to take a deep breath, the heart moves back and the radiation dose to the heart is dramatically reduced, particularly for left sided breast cancers. The use of deep-inspiration breath-hold techniques is now a standard of care across the UK (RCR Breast Radiotherapy Consensus Guidelines, 2016).
Volumetric-modulated arc therapy (VMAT)	VMAT is an advanced radiotherapy technique using arcs of radiation, rather than individual beams (as used in IMRT). It has been shown in planning studies to reduce doses to heart and lung tissues, particularly in women requiring treatment of the lymph nodes behind the breastbone (the internal mammary chain).

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