CPAG Summary Report for Clinical Panel – URN 1787 proton beam therapy for breast cancer

a) Proton beam therapy (PBT) vs photon radiotherapy

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Overall survival was measured as time from diagnosis to time of death or last follow-up (Chowdhary et al 2019). In Chowdhary et al 2019, five-year overall survival was 91.9% for PBT patients (n=871) and 88.9% for photon radiotherapy patients (n=723,621) (95% CI not reported). Overall survival was not associated with PBT in multivariate analysis (HR 0.85 (95%CI 0.68 to 1.07), p=0.168). This analysis adjusted for factors including age, race, insurance status, comorbidity, treatment facility type, income, residence location, education, tumour side, stage, receptor status, chemotherapy, endocrine therapy, type of surgery and year of diagnosis. There was also no significant association between overall survival and PBT 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. A high overall survival rate is important to clinicians, patients and their families. There was no difference for survival outcomes between different patient groups. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from a national database of patients treated in the US between 2004 and 2014. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The median follow-up of 62 months (range not reported) may not be long enough to assess the impact of treatment on overall survival.
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency	Not reported

	on care giver / supporting independence	
10.	Safety	Skin toxicity was assessed by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and Grade 5 = '*death related to adverse event*'[1]. Two specific skin toxicity adverse events were assessed by DeCesaris et al 2019: radiation dermatitis[2] and skin hyperpigmentation[3]. *Radiation dermatitis*: There were no Grade 4 or 5 cases. There was no significant difference in Grade 3 radiation dermatitis between PBT (n=39) and photon (n=47) radiotherapy (5.1% vs 4.3%, p=0.848). Acute radiation dermatitis ≥ Grade 2 was statistically significantly higher with PBT (69.2% vs 29.8%, p<0.01). The highest recorded grade of radiation dermatitis was also statistically significantly higher with PBT (p=0.002). *Skin hyperpigmentation*: There was no significant difference between PBT and photon radiation for skin hyperpigmentation ≥ Grade 2 (7.7% vs 12.8%, p=0.502). There was also no significant difference in the highest recorded grade of skin hyperpigmentation (p=0.413). At first clinical follow-up (within 8 weeks of treatment completion) there was no difference in sustained skin reactions between PBT (n=29) and photon radiotherapy (n=41) (Grade 1 radiation dermatitis 17.2% vs 19.5%, p=0.810; Grade 1 skin hyperpigmentation 65.5% vs 61.0%, p=0.698). Skin toxicity adverse events are important outcomes as they may affect function and quality of life. There was more Grade 2 (moderate) acute radiation dermatitis with PBT but there was no significant difference at clinical follow-up. There was no difference between the treatment groups in skin hyperpigmentation. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2015 and 2017. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. Only patients with weekly on-treatment visit documentation of acute treatment related toxicities were included. Data from first clinical follow-up were only available for 74% and 87% of PBT and photon patients respectively. Toxicities were primarily scored by the same physician for both treatments.
11.	Delivery of intervention	Not reported

CI - Confidence Interval; CTCAE - Criteria for Adverse Events; HR – Hazard Ratio; PBT – Proton Beam Therapy

[1] https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf

[2] Radiation dermatitis was scored as grade 1 = '*faint erythema or dry desquamation*'; grade 2 = '*moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema*'; grade 3 = '*moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion*'; grade 4 = '*life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated*'; grade 5 = '*death*'

[3] Skin hyperpigmentation was scored as grade 1 = '*hyperpigmentation covering <10% body service area; no psychological impact*'; grade 2 = '*hyperpigmentation covering >10% body service area; psychological impact*'. Grades 3 to 5 not applicable for this adverse event

No	Outcome measure	Summary from evidence review
1.	Patient-reported cosmetic result	Patient-reported cosmetic result was assessed by the Harvard Cosmesis Scale. This single-item question rates cosmetic result as 4 = '*excellent*', 3 = '*good*', 2 = '*fair*' or 1 = '*poor*'. Teichman et al 2018 reported a statistically significantly better mean (standard deviation (SD)) result for PBT (n=69) vs photon radiotherapy (n=56) (3.40 (0.75) vs 2.44 (0.96), p<0.001). Data were collected at a median of 6.5 years post-diagnosis. Cosmetic outcome is an important outcome as this may impact quality of life. Cosmetic result was judged more positively by patients who were treated with PBT. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2003 and 2012 who responded to a survey. The survey was sent to patients who were alive and disease-free 5 years or more after diagnosis. The response rate was 79%. The data may be subject to response bias as the people who responded to the survey may not reflect all patients treated. The proportion of non-responders who received PBT or photon radiotherapy was not specified. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. All but 2 of the 69 PBT patients received their treatment during a clinical trial. The photon radiotherapy patients received the conventional treatment at the time. This may have had a confounding effect on attitudes to the treatment received or perceptions of outcomes. The differences in treated volume (partial breast PBT vs whole breast photon radiotherapy) and delivery of radiotherapy (10 days vs 6 weeks) for the 2 groups may also have had a confounding effect.
2.	Patient-reported treatment outcome	Patient-reported treatment outcome was assessed by the Breast Cancer Treatment Outcome Scale. This 22-item questionnaire evaluates 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)*'. Teichman et al 2018 reported a statistically significantly better mean cosmetic score for PBT (n=72) vs photon radiotherapy (n=57) 1.45 vs 1.88, p<0.001). However the mean pain score was statistically significantly worse with PBT (1.42 vs 1.25, p<0.005). There was no significant difference in functionality (1.11 vs 1.17, p=0.311) or oedema (1.07 vs 1.12, p=0.526). The authors also created a weighted score based on the average of the 3 questions that patients thought were most important. This was statistically significantly better for PBT (1.84 vs 2.55, p<0.001). Standard deviation was not reported for this outcome. Data were collected at a median of 6.5 years post-diagnosis. Treatment outcome is an important outcome as it may impact quality of life. However, the clinical significance of this composite result is not clear as patients treated with PBT had statistically significant better cosmetic outcome but reported statistically significant worse pain. See above for limitations of Teichman et al 2018.
3.	Body image	Body image was assessed by the Body Image Scale. This 10-item self-reported questionnaire assesses feelings about appearance and changes

		which may have resulted from a disease or treatment during the prior week. Each item is 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*' and 4 = '*very much*'. Teichman et al 2018 reported a statistically significantly better mean (SD) result for PBT (n=72) vs photon radiotherapy (n=57) (12.04 (3.75) vs 13.91 (5.25), p<0.03). Data were collected at a median of 6.5 years post-diagnosis. Body image is an important outcome as this may impact quality of life. A statistical difference favouring PBT was reported. However the means reported suggest the difference may not be clinically significant. See above for limitations of Teichman et al 2018.
4.	General perspective	General perspective was 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*'. Teichman et al 2018 reported statistically significantly better mean scores for PBT (n=72) vs photon radiotherapy patients (n=57) for the following 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). The mean score was statistically significantly worse with PBT for the question: '*skin quality during treatment*' (1.50 vs 2.82, p<0.001). There was no significant difference for the following 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). Standard deviation was not reported for this outcome. Data were collected at a median of 6.5 years post-diagnosis. General perspective covers a range of areas that could impact quality of life. Some of the results favoured PBT. However, these did not translate to a difference between the groups for questions about change in daily life or upper arm/ mobility issues. See above for limitations of Teichman et al 2018.
5.	Fatigue	Fatigue was 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 (see below) was reported separately. Teichman et al 2018 reported a statistically significantly better mean (SD) result for PBT (n=72) vs photon radiotherapy patients (n=57) (15.3 (17.11) vs 27.25 (22.26), p<0.002). The authors also created a weighted score based on the average of the 3 questions that patients thought were most important. There was no significant difference between the groups (1.84 vs 2.55, p<0.001). Standard deviation was not reported for this outcome. 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. Data were collected at a median of 6.5 years post-diagnosis. Fatigue is an important outcome as this may impact quality of life. A statistical difference favouring PBT was reported. However there was no difference for the weighted mean, focusing on what patients thought was most important. The significance of the difference in recent tiredness is not clear.

		See above for limitations of Teichman et al 2018.
6.	Incremental cost effectiveness ratio (ICER)	ICER[4] was reported 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) (£40,102) or $100,000/ QALY (£80,205). In Mailhot Vega et al 2017, PBT was not cost effective for women without cardiac risk factors compared to photon radiotherapy at a threshold of $50,000/ QALY. 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 September 2019.

ICER - Incremental Cost Effectiveness Ratio; Gy – Gray; PBT – Proton Beam Therapy; QALY - Quality-Adjusted Life Year; SD – Standard Deviation

b) Proton beam therapy (PBT) (no comparator)

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Overall survival was measured from end of treatment to time of death or last follow-up. In Luo et al 2019 (n=42), overall survival was 97.2% (95%CI not reported) at a median follow-up of 35 months (range 1 to 55). The high overall survival rate of 97% will be of importance to clinicians, patients and their families. The results of this small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 US centre between 2013 and 2015. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 35 months may not be long enough to assess the impact of treatment on overall survival.

[4] 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

2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	In the two highest scoring studies (Luo et al 2019, Verma et al 2017), adverse events were assessed by the CTCAE Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and Grade 5 = '*death related to adverse event*'[1]. In Luo et al 2019 (n=42), there were no acute adverse events (<90 days after radiotherapy) of Grade 3 or higher. Grade 2 (moderate) acute adverse events included dermatitis (74%), skin pain (24%), oesophagitis (17%) and fatigue (2%). There was 1 (2%) Grade 3 (severe) chronic adverse event (pneumonitis) >90 days after radiotherapy. There were no Grade 2 chronic adverse events. The authors reported that no acute or chronic cardiac toxicities were reported. Median follow-up was 35 months (range 1 to 55). In Verma et al 2017 (n=91), there were no Grade 4 or 5 adverse events. Grade 3 (severe) adverse events included dermatitis (5%) and breast/ chest wall pain (1%). Grade 2 (moderate) adverse events included dermatitis (72%), breast/ chest wall pain (29%), oesophagitis (33%) and fatigue (15%). In addition, 8% developed a skin infection, 2% had uncomplicated rib fracture, and 3% had clinically evident lymphoedema. Adverse events were also separately reported for patients who received radiotherapy to the breast (n=27) and chest wall (n=66). The only Grade 3 adverse event for breast radiotherapy patients was dermatitis (7%). Grade 3 adverse events for chest wall radiotherapy patients included dermatitis (5%) and pain (2%). Grade 2 adverse events for breast radiotherapy patients included dermatitis (56%), pain (52%), oesophagitis (30%) and fatigue (7%). Grade 2 adverse events for chest wall radiotherapy patients included dermatitis (79%), pain (20%), oesophagitis (33%) and fatigue (5%). Median follow-up 15.5 months (range not reported). Adverse events are important outcomes as they may impact on quality of life. A small proportion of patients had Grade 3 (severe) adverse events in both studies. The proportion of patients experiencing Grade 2 (moderate) adverse events was higher, particularly for dermatitis.

		The results of these two small case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design of Verma et al 2017 introduces the possibility of selection bias in the completeness of the information reported. Both studies were conducted in the US, Luo et al between 2013 and 2015 and Verma et al between 2011 and 2015. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 35 and 15.5 months respectively may not be long enough to assess the impact of longer term toxicities.
11.	Delivery of intervention	Not reported

CI - Confidence Interval; CTCAE - Criteria for Adverse Events; PBT – Proton Beam Therapy

No	Outcome measure	Summary from evidence review
1.	Mortality	Mortality records the number of patients that had died at last follow-up. In Verma et al 2017 (n=91), 6 patients (7%) had died at a median follow-up of 15.5 months (range not reported). A low mortality rate of 7% will be of importance to clinicians, patients and their families. The results of this small retrospective case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The study was conducted at 1 US centre between 2011 and 2016. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 15.5 months may not be long enough to assess the impact of treatment on mortality.
2.	Disease free survival	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, regional or distant), measured from the end of treatment. In Bush et al 2014 (n=100), disease-free survival was 94% (95%CI not reported) with a median follow-up of 5 years (range not reported). Disease-free survival assesses the success of treatment and is important to clinicians, patients and their families. 94% of patients were disease free at 5 years follow-up. The results of this small prospective case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted in the US but the number of participating centres and year of treatment were not reported. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 5 years may not be long enough to assess the impact of treatment on disease free survival.
3.	Disease failure	Disease failure included loco-regional recurrence and distant disease. Loco-regional failure was defined as imaging evidence of tumour in the ipsilateral breast or chest wall and/ or ipsilateral lymphatics. Others failures were categorised as distant. In Verma et al 2017 (n=91), 12 patients (13%) had disease failure at a median follow-up of 15.5 months (range not reported). 10 patients (11%) had distant

		recurrence and 4 patients (4%) had loco-regional recurrence (2 patients had both distant and loco-regional recurrence). Median time to any disease failure was 8 months (range not reported). Disease failure assesses the success of treatment and is important to clinicians, patients and their families. Most of the disease failures observed were distant disease. See above for limitations of Verma et al 2017. The median follow-up of 15.5 months may not be long enough to assess disease failure.
4.	Loco-regional disease free survival	Loco-regional disease free survival was measured from end of treatment to time of loco-regional recurrence or last follow-up (Luo et al 2019). In Luo et al 2019 (n=42), loco-regional disease free survival was 96.3% (95%CI not reported) at a median follow-up of 35 months (range 1 to 55). Loco-regional disease free survival assesses the success of treatment and is important to clinicians, patients and their families. 96% of patients had not developed loco-regional recurrence at 35 months follow-up. See above for limitations of Luo et al 2019. The median follow-up of 35 months may not be long enough to assess the impact of treatment on loco-regional disease free survival.
5.	Loco-regional recurrence	Loco-regional recurrence was measured from end of treatment to time of loco-regional recurrence or last follow-up. In Chang et al 2013 (n=30), there were no cases of loco-regional recurrence at a median follow-up of 59 months (range 43 to 70). Loco-regional recurrence assesses the success of treatment and is important to clinicians, patients and their families. No patients had developed loco-regional recurrence at 59 months follow-up. The results of this very small prospective case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 centre in Korea between 2007 and 2009. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 59 months may not be long enough to assess the impact of treatment on loco-regional recurrence.
6.	Metastasis free survival	Metastasis free survival was measured from end of treatment to time of metastasis or last follow-up (Luo et al 2019). In Luo et al 2019 (n=42), metastasis free survival was 84.1% (95%CI not reported) at a median follow-up of 35 months (range 1 to 55). Metastatic disease indicates a progression of disease and is important to clinicians, patients and their families. 84% had not developed metastasis at 35 months follow-up. See above for limitations of Luo et al 2019. The median follow-up of 35 months may not be long enough to assess the impact of treatment on metastasis free survival.
7.	Distant metastasis	Distant metastasis was measured from end of treatment to time of distant metastasis or last follow-up. In Chang et al 2013 (n=30), there were no cases of distant metastasis at a

		median follow-up of 59 months (range 43 to 70). Distant metastasis indicated a progression of disease and is important to clinicians, patients and their families. No patients had developed distant metastasis at 59 months follow-up. See above for limitations of Chang et al 2013. The median follow-up of 59 months may not be long enough to assess the impact of treatment on distant metastasis.
8.	Physician-rated cosmetic outcome	Physician-rated cosmetic outcome assessed global cosmetic result, appearance of the surgical scar, breast size, breast shape, skin colour and location and shape of the areola and nipple. This was assessed on a 4-point scale where 0 = '*excellent result (no difference)*', 1 = '*good result (small difference)*', 2 = '*fair result (moderate difference)*', 3 = '*poor result (large difference)*'. Percentage of breast retraction was also assessed by comparing the lateral and vertical displacement of the nipple in the treated breast compared to the untreated breast. In Chang et al 2013, the proportion of outcomes rated '*excellent*' or '*good*' were: 84% at the end of radiotherapy (n=30), 80% at 2 months (n=80), 84% at 6 months (n=30), 77% at 1 year (n=30), 75% at 2 years (n=27) and 69% at 3 years (n=23). Mean percentage breast retraction increased statistically significantly over time from 10.5% at the end of treatment to 15.3% at 3 years (p=0.002). Cosmetic outcome is important as it may impact quality of life. Physician-rated cosmetic outcome was generally positive, but worsened over time. See above for limitations of Chang et al 2013. Cosmetic outcome was assessed by 1 radiation oncologist.
9.	Patient-reported cosmetic outcome	Patient-reported cosmetic result for the treated breast was assessed by the Harvard Cosmesis Scale. This single-item question rates cosmetic result as 4 = '*excellent*', 3 = '*good*', 2 = '*fair*' or 1 = '*poor*'. The proportion of patients who rated the cosmetic outcome as '*excellent*' or '*good*' was reported by Bush et al (2014). In Bush et al 2014 (n=100), the proportion of patients reporting an '*excellent*' or '*good*' result was between approximately 90% and 95% at baseline and at median 5 year follow-up (range not reported). The authors reported that no annual assessment was significantly different from baseline (figures not reported). Cosmetic outcome is an important outcome as this may impact on quality of life. Patient-rated cosmetic outcome was generally positive. See above for limitations of Bush et al 2014. Precise figures for this outcome were not available as the results were only presented graphically.
10.	Quality of life	Quality of life was 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). In Chang et al 2013 (n=30), there were no significant differences before treatment and after the last day of radiotherapy for any of the 6 functional subscales or 9 symptom subscales on the general quality of life questionnaire. There were also no significant differences for any of the 3 functional subscales or 3 symptom subscales on the breast cancer specific quality of life questionnaire. Impact of treatment on quality of life is important to clinicians, patients and their families. There was no difference in quality of life before and after treatment. See above for limitations of Chang et al 2013.
11.	Skin toxicity	Skin toxicity was assessed by the CTCAE Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and Grade 5 = '*death related to adverse event*'[1]. In Liang et al 2018 (n=23), 10 patients (43%) had Grade 3 radiation dermatitis. 23 patients (100%) had ≥ Grade 2 skin reactions including erythema or patchy moist desquamation confined to skin folds. Median follow-up was not reported. Skin toxicity adverse events are important outcomes as they may impact on quality of life. All patients had Grade 2 (moderate) toxicities and 43% had Grade 3 (severe) toxicities. The results of this very small retrospective case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The study was conducted at 1 US centre between 2012 and 2016. The applicability to current UK NHS clinical practice is unclear.
12.	Reconstruction complications	Reconstruction complications were reported for patients who received PBT after a mastectomy with immediate reconstruction. In Luo et al 2019 (n=42), 7 of 26 patients (27%) who underwent PBT after immediate reconstruction developed complications. This included 6 capsular contractures and 1 implant infection. Implants were removed in 5 patients. Reconstruction complications are important as they could lead to further surgery and impact quality of life. 27% of patients had complications and 19% had an implant removed. See above for limitations of Luo et al 2019.

CI – Confidence Interval; CTCAE - Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer 30 Quality of Life Questionnaire; EORTC QLQ-BR23- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer specific questionnaire; PBT – Proton Beam Therapy