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Evidence Review:

Radiotherapy after primary surgery for breast cancer

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Contents

1. Introduction

External beam radiotherapy (EBRT) is a component of standard practice in the treatment of breast cancer.

NICE issued pathway guidance in the treatment of 'early and locally advanced breast cancer: adjuvant therapy' in September 2013, recommending the use of EBRT at a total dose of 40 Gy in 15 fractions as standard practice for patients with breast cancer after primary surgery (including breast conserving surgery or mastectomy).

40 Gy in 15 fractions (excluding boost) is recommended for the majority of patients following primary surgery (breast conserving surgery or mastectomy) for breast cancer. Delivering the dose of radiation in no more than 15 fractions, rather than conventional schedules of up to 25 fractions, will prevent unnecessary travel, discomfort and inconvenience for many patients with no compromise to clinical effectiveness.

2. Summary of results

This evidence review looked at effectiveness and safety of use of 15 fractions as the core schedule (excluding boost) compared to other fractionation regimes in breast cancer.

Summary:
There is level 1 evidence that hypo-fractionated radiotherapy (HFRT), with 40 Gy delivered in 15 fractions over 3 weeks:
- has equivalent relapse rates as conventionally fractionated radiotherapy (CFRT), with 50 Gy over 25 fractions;
- have better distance relapse rates and survival rates than CFRT;
- reduces the risk of skin reactions and changes in breast appearance;
- in direct care delivery cost comparison, the cost of 15 fraction was less than that of 25 fractions.

None of the trials directly compare 15 fractions with other HFRT regimes. Hence, it is difficult to form an opinion about comparative efficacy of various hypofraction regimes.

Detailed summary:

Efficacy
Whole breast radiotherapy is used following either breast conserving therapy or a mastectomy with an intention to improve survival and reduce recurrences. The clinical efficacy of such treatments is measured in terms of the relapse rates, survival rates and toxicity rates. For the purpose of comparison, these rates are mapped to Cox proportional hazard regression model, which allows two fractional regimes to be compared with a hazard ratio (HR). With CFRT placed in the denominator, a HR less than 1 favours HFRT.
Majority of evidence base is from the following large randomised control trials comparing different HFRT regimes with CFRT:
• START pilot (comparing 39 Gy in 13 fractions and 42.9 Gy in 13 fractions over 5 weeks)
• START A (comparing 41.6 Gy in 13 fractions and 39 Gy in 13 fractions over 5 weeks)
• START B randomised control trial (comparing HFRT 40 Gy in 15 fractions over 3 weeks with CFRT 50 Gy in 25 fractions over 5 weeks)
• Whelan et al, 2002 (comparing 42.5 Gy in 16 fractions over 5 weeks)
• UK FAST (30 Gy and 28.5 Gy in 5 fractions over 5 weeks).
Haviland et al, 2013 publication on START B randomised control trial (RCT) with 10-years follow-up results provides most relevant evidence for 15 fractions. Data from four large RCTs and six smaller 6 smaller RCTs (< 500 participants), have been combined in two meta-analyses (James et al., 2010; Zhou et al, 2015).
All these trials are non-blinded, with the exception of the photo assessors used to determine any change in breast appearance. The study population was largely women with early stage, node negative, operable invasive breast cancer. Whelan et al, 2002 only included women treated with lumpectomy. Clinical equipoise was not maintained in most trials as patients could receive additional boost treatment, at the discretion of treating clinician. During the START B trial 43% of the patients received a 10 Gy boost over 5 fractions. This was evenly distributed over the control and trial arms.

Clinical effectiveness:
This was reported in terms of relapse rates and overall survival rates.
Relapse rates:
Relapse rates are reported as local (relapse in the breast or chest wall) and distance (relapse in non-irradiated organs). After 10 years, START B found no statistically significant difference for local relapse rates between HFRT and CFRT but found the distance relapse rates were lower with HFRT. This equivalence of local relapse rates was found in all RCTs and meta-analysis on the four large RCTs. The START A trial found that distance relapse rates were equivalent between HFRT and CFRT.

Survival rates:
The START B trial reported a significant improvement in the overall survival rate of HFRT (40 Gy in 15 fractions) with a HR 0.80 (p=0.042) after 10 years (Haviland et al., 2013). The other large RCTs (START Pilot, START A and Whelan et al, 2002) report similar survival rates compared to CFRT (50 Gy over 25 fractions). A meta-analysis of all four key RCTs comparing all hypofractionation schedules compared to CFRT found no statistically significant improvement in overall survival rates at 5 years, HR 0.89 (p=0.16), (James et al., 2010).

Safety outcomes:
Acute and late toxicities are measured by looking for change in breast appearance, skin reddening (telangiectasia) and oedema on the breast or arm. Late toxicities also include rates of rib fractures, lung fibrosis and ischaemic heart disease.

Changes in skin and breast appearance:
START B reported in both their 5 year and 10 year follow up that the risk of skin toxicities and change in breast appearance was lower in HFRT than in CFRT. In particular the hazard ratios for breast shrinkage, telangiectasia and breast oedema all favoured HFRT. Other toxicities demonstrated no differences between HFRT and CFRT. Other HFRT regimes also demonstrated reduced toxicity levels. For example, START A gave evidence for reduced rates of skin toxicities in the 39 Gy arm, but not the 41.6 Gy arm. A meta-analysis of 7 RCTs, comparing fractions of 2.5-3.0 Gy, found a HR for 0.50 (p=0.02) for grade 2/3 skin toxicity.

Other toxicities:
In both the START A and START B trials, there was no statistically significant difference in the rates of rib fracture, lung fibrosis and ischaemic heart disease after 10 years. However, experts have raised concerns about the long term risks, following HFRT. Appelt et al, 2012 mathematically modelled long term risk of mortality from radiation induced heart disease. 40 Gy /15 fractions, 39 Gy /13 fractions and 42.6 Gy / 16 fractions appear to have more favourable radiation doses to the heart, than 50 Gy /25 fractions.

Cost effectiveness:
Three studies reviewed in meta-analysis (Zhou et al., 2015) and Rajagopalan et al, 2015 have compared the total costs of 16 fractions HFRT to those of CFRT. They have all concluded that HFRT to be 10% to 30% lower cost than CFRT, depending on assumptions and specifics of the healthcare. None of the studies were based on the UK healthcare system.

3. Research questions

Is there evidence of equivalent or better clinical outcomes for the use of 15 fractions as the core schedule (excluding boost) compared to other fractionation regimes in breast cancer?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
1+	Systematic	12447	39 Gy, 13 fractions, 5 weeks 42.9 Gy, 13 fractions, 5 weeks 41.6 Gy, 13 fractions, 5 weeks 40 Gy, 15 fractions, 3 weeks 28.5 Gy, 5 fractions, 5 weeks 30 Gy, 5 fractions, 5 weeks	Clinical effectiveness of the intervention compared to existing interventions	Local recurrence rate	Local recurrence rate is similar between hypofractionated (HFRT) and conventionally fractionated RTs (CFRT), risk ratio (1.03 p=0.72) based on 9 studies.	Distance metastasis rate Overall Survival rate Disease free survival rate	Distinct metastasis rate also indicated no statistically significant difference, risk ratio = 0.88 (p=0.47) based on 4 studies in the 2.5-3 Gy fractions . Overall survival rates also indicated no statistically significant difference, risk ratio = 0.92 (p=0.21) based on 3 studies using 2.5-3 Gy fractions. Disease free survival indicated no statistically significant difference, risk ratio = 0.95 (p=0.53) based on 4 studies using 2.5-3 Gy fractions. Excellent/good cosmetic indicated no statistically significant difference, risk ratio = 0.94 (p=0.69) based on 5 studies using 2.5-3 Gy fractions. HFRT decreased risk in photographic changes in breast, risk ratio = 0.80 (p=0.0001) based on 4 studies including 2652 patients, using 2.5-3 Gy fractions.	Zhou, Zhi-Rui; Mei, Xin; Chen, Xing-Xing; Yang, Zhao-Zhi; Hou, Jing; Zhang, Li; Yu, Xiao-Li; Guo, Xiao-Mao. Systematic review and meta-analysis comparing hypofractionated with conventional fraction radiotherapy in treatment of early breast cancer. Surg Oncol 2015;24(3):200-211.	-	-	This Systematic review and meta-analysis updates previous reviews (James 10) with the addition an extra RCT, UK FAST in which the hypfractionated RT schedule is 28.5 Gy in 5 fractions over 5 weeks and 30 Gy in 5 fractions over 5 weeks. The review also used an additional 6 RCTs and 12 cohort studies. The principle outcome is that the local recurrence rate is still similar between hypofractionated (HFRT) and conventionally fractionated RTs (CFRT), risk ratio (1.03 p=0.72) based on 9 studies. Distinct metastasis rate also indicated no statistically significant difference, risk ratio = 0.88 (p=0.47) based on 4 studies in the 2.5-3 Gy fractions . Overall survival rates also indicated no statistically significant difference, risk ratio = 0.92 (p=0.21) based on 3 studies using 2.5-3 Gy fractions. Disease free survival indicated no statistically significant difference, risk ratio = 0.95 (p=0.53) based on 4 studies using 2.5-3 Gy fractions. Excellent/good cosmetic indicated no statistically significant difference, risk ratio = 0.94 (p=0.69) based on 5 studies using 2.5-3 Gy fractions. HFRT decreased risk in photographic changes in breast, risk ratio = 0.80 (p=0.0001) based on 4 studies including 2652 patients, using 2.5-3 Gy fractions. This effect was reversed when using higher dosage of fractions, 3-3.3 Gy had a risk ratio = 1.14 (p=0.07), based on 2 RCTs, while 5.7-6.0 Gy had a risk ratio = 1.42 (p=0.01). The risk of acute grade 2/3 skin reactions also reduced with HFRT, risk ratio = 0.5 (p=0.02), based on eight studies. There was no difference in risks of symptomatic radiation pneumonitis, cardiac related toxicity and symptomatic rib fracture. Two studies indicated that HFRT was 10% and 32% cheaper than CFRT.
1-	Systematic	>7000 patients	39 Gy, 13 fractions, 5 weeks 42.9 Gy, 13 fractions, 5 weeks 41.6 Gy, 13 fractions, 5 weeks 40 Gy, 15 fractions, 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Local tumour relapse (%) at 5 years.	START pilot: 12.1 (50Gy/25) vs 14.8 (39Gy/13) vs 9.6 (42.9 Gy/13) Whelan et al. 2002: 3.2 (50Gy/25) vs 2.8 (42.5Gy/16) START A: 3.2 (50Gy/25) vs 4.6 (39Gy/13) vs 3.2 (41.6Gy/13) START B: 3.3 (50 Gy/25) vs 2.0 (40Gy/15)	change in breast appearance at 5 years (%)	START pilot: 35.4 (50Gy/25) vs 27.4 (39Gy/13) vs 42.3 (42.9 Gy/13) START A: 42.9 (50Gy/25) vs 32.1 (39Gy/13) vs 43.6 (41.6Gy/13) START B: 42.2 (50 Gy/25) vs 36.5 (40Gy/15)	Yarnold, John; Haviland, Joanne. Hypofractionated adjuvant whole breast radiotherapy: progress and prospects. Acta Oncol 2010;49(8):1288-1292.	-	-	This systematic review compared 4 RCTs, without a meta-analysis, in particular START pilot, (Whelan et al. 02), START A 99-02 and START B 99-02. The results quotes have been combined in subsequent meta-analysis. Found no statistically significant difference in local relapse rates . See Koukourakis.
1+	Systematic	4472	Boost of typically 10 Gy over 5-6 fractions	Clinical effectiveness of the intervention compared to existing interventions	Local recurrence rate of patients who received boost vs those who didn't.	OR 0.91 (95% CL 0.77-1.08)	standard radiotherapy vs. hypofractionated. Boost vs no boost according to age.	standard radiotherapy vs. hypofractionated: OR 0.78 (95% CL 0.58-1.03)	Nilsson, Cecilia; Valachis, Antonis. The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: a meta-analysis of observational studies. Radiother Oncol 2015;114(1):50-55.	-	-	This systematic review and meta-analysis is focused on studies that just involve patients with ductal cancer in situ. The review found six studies, all either case-contol or cohort studies. They all used 16 fractions, with differing doses, for the hypofraction regime and compared with 50 Gy in 25 fractions. The only meta analysis of relevance found that the local recurrence rate OR 0.78 (p=0.08), i.e. no difference between hypofractionated and conventionally fractionated regimes.

1-	Systematic	7095 patients	(Whelan et al. 2002) - 42.5 Gy in 16 fractions over 22 days Start A - 41.6 or 39 Gy in 13 fractions over 5 weeks Start B - 40 Gy in 15 fractions over 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Local Relapse rate at 10 years (%) Local Relapse rate at 5 years (%) quoted in (Yarnold & Haviland, 2010).	(Whelan et al. 02) 6.7% local recurrence rate at 10 years in control and 6.2% in hypofraction. START Pilot 12.1% in control, 9.6% in hypofraction 1 and 14.8% in hypofraction 2.	Cosmetic outcome.	(Whelan et al. 02) Statistically similar cosmetic outcomes (excellent in 71.3% in control and 69.8% in hypofraction at 10 years. START pilot: Statistically similar cosmetic outcomes (excellent in 71% in control, 74% in hypofraction 1 and 58% in hypofraction 2 at 10 years.	Koukourakis, Georgios; Zacharias, Georgios; Petridis, Aristides. Evidence based whole breast hypo-fractionated radiation therapy in patients with early breast cancer. J BUON 2015;20(2):473-478.	-	-	This systematic review combines 4 RCTs without meta analysis. (Whelan et al. 02): 1234 patients, 612 given 50 Gy in 25 fractions over 35 days (control) and 622 given 42.5 Gy in 16 fractions over 22 days (hypofraction). 6.7% local recurrence rate at 10 years in control and 6.2% in hypofraction. Statistically similar cosmetic outcomes (excellent in 71.3% in control and 69.8% in hypofraction at 10 years. Also looked at START A and START B which has been summarised elsewhere. Also START Pilot: 470 patients received 50 Gy in 25 fractions over 5 weeks (control), 466 patients received 42.9 Gy in 13 fraction over 5 weeks (hypofraction 1) and 474 patients received 39 Gy in 13 fractions over 5 weeks (hypofraction 2). Local tumour relapse after 10 years 12.1% in control, 9.6% in hypofraction 1 and 14.8% in hypofraction 2. Statistically similar cosmetic outcomes (excellent in 71% in control, 74% in hypofraction 1 and 58% in hypofraction 2 at 10 years.
1++	Systematic	7095 patients	39 Gy, 13 fractions, 5 weeks 42.9 Gy, 13 fractions, 5 weeks 41.6 Gy, 13 fractions, 5 weeks 40 Gy, 15 fractions, 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Local recurrence in ipselateral breast.	Local recurrence at 5 years, risk ratio 0.93 (95% CL 0.73 - 1.19 p=0.55) based on 4 RCTs or with longer follow ups 0.97 (95% CL 0.76 - 1.22 p=0.78) Local recurrence at 10 years, risk ratio 0.99 (95% CL 0.77 - 1.29 p=0.96) based on 2 RCTs.	Appearance or cosmesis of treated breast. Overall survival rate Toxicity Cancer specific mortality Relapse free survival Mastectomy rate Quality of life Costs	o None of the four studies indicated a statistically significant difference in rates of breast cosmesis (appearance), but these were not combined in a meta analysis due to differences in scales being used. o Overall survival risk ratio 0.89 (95% CL 0.77 - 1.04 p=0.16) based on 4 RCTs o Acute radiation toxicity risk much lower in hypofraction RT, risk ratio 0.21 (95% CL 0.07 - 0.64 p=0.007) based on START A and START B. o Late radiation skin and subcutaneous toxicity at five years, risk ratio 0.99 (p=0.98) and 1.0 (p=0.99) based on Whelan et al. 2002 and START Pilot. o Ischaemic heart disease risk ratio 1.07 (p=0.91) based on START A and START B and rib fractures risk ratio 0.93 (p=0.92) based on Whelan et al. 2002, START A and START B	James, Melissa L.; Lehman, Margot; Hider, Phil N.; Jeffery, Mark; Hickey, Brigid E.; Francis, Daniel P.. Fraction size in radiation treatment for breast conservation in early breast cancer. Cochrane Database Syst Rev 2010;0(11):CD003860.	-	-	This systematic review combines 4 RCTs with meta analysis. Possible biases, of each study, are listed in the appendix. Principle points on each study are as follows: (Whelan et al. 2002) - 1234 patients with node negative invasive tumours, treated with lumpectomy and had negative pathological margins. - Excluded large breast (cup size separation >25cm), bilateral breast cancer, multicentric disease. 75% aged > 50 years. -622 received 42.5 Gy in 16 fractions (hypofraction) over 22 days and 612 received 50 Gy in 25 fractions over 35 days (control). -No women were treated with boosts START Pilot -1410 patients with invasive breast cancer, 81% had small or medium breasts - 474 patients received 39 Gy in 13 fractions over 5 weeks (hypofraction 1), 466 received 42.9 Gy in 13 fractions over 5 weeks (hypofraction 2) and 470 patients received 50 Gy in 25 fractions over 5 weeks (control). -Primary outcome was late change in breast appearance. - 75% of women received a boost of 14 Gy in 7 fractions, following clinical assessment START A - 2236 patients with invasive breast cancer, 85% had small or medium breasts. -750 patients had 41.6 Gy in 13 fractions over 5 weeks (hypofraction 1), 737 patients received 39 Gy in 13 fractions over 5 weeks (hypofraction 2), 749 patients received 50 Gy in 25 fractions over 5 weeks (control). -Primary outcome measures were local regional relapse, normal tissue effects and quality of life. -61% of women received a boost of 10 Gy in 5 fractions START B -2215 patients with invasive breast cancer , 83% had small or medium breasts. - 1110 patients received 40 Gy in 15 fractions over 3 weeks (hypofraction) and 1105 patients received 50 Gy in 25 fractions over 5 weeks (control). -Primary outcome measures were local regional relapse, normal tissue effects and quality of life. - Approximately 40% of women received a boost of 10 Gy in 5 fractions.
1++	Systematic	2644 patients	39 Gy, 13 fractions, 5 weeks 42.9 Gy, 13 fractions, 5 weeks	Clinical effectiveness of the intervention compared to existing interventions	Local recurrence in ipselateral breast.	Whelan et al. 02 local recurrence rates at 5 years 2.8% (HFRT) vs. 3.2% (CFRT). START pilot: Incidence ratio at 10 years 0.87 (p=0.50) (42.9Gy/13) and 1.35 (p=0.11) (39 Gy/13)	Appearance or cosmesis of treated breast. Overall survival rate Toxicity Cancer specific mortality Relapse free survival Mastectomy rate Quality of life Costs	(Whelan et al. 02) Good or excellent breast appearance: 76.8% (HFRT) vs 77.4% (CFRT) START Pilot: Good or excellent breast appearance: 41.8% (HFRT) vs. 39.1% (CFRT) Overall survival risk ratio: 0.97 (p=0.75) at 5 years from 2 studies. Skin toxicity: No differences between fractional regimes Cancer specific mortality, Relapse free survival, Mastectomy rate, Quality of life, Cost; no data.	James, Melissa L.; Lehman, Margot; Hider, Phil N.; Jeffery, Mark; Francis, Daniel P.; Hickey, Brigid E.. Fraction size in radiation treatment for breast conservation in early breast cancer. Cochrane Database Syst Rev 2008;0(3):CD003860.	-	-	This study is an earlier version of the (James 2010) systematic review based on just 2 RCTs. It's primary results are included in the summary of (James 2010).

3	Systematic	1807 patients	-	Other	Patients preference to breast radio therapy.	62% prefer hypofractionated whole breast irradiation, 28% prefer hypofractionated partial breast irradiation, 10 % prefer conventionally fractionated whole breast irradiation	-	-	Hoopes, David J.; Kaziska, David; Chapin, Patrick; Weed, Daniel; Smith, Benjamin D.; Hale, E. Ronald; Johnstone, Peter A.. Patient preferences and physician practice patterns regarding breast radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 2012;82(2):674-681.	-	-	This study is based on a questionnaire concerning patients preference for breast radio therapy. It was found 62% prefer hypofractionated whole breast irradiation, 28% prefer hypofractionated partial breast irradiation, 10 % prefer conventionally fractionated whole breast irradiation.
1++	Systematic	StartA-2236, StartB-2215	Start A - 41.6 or 39 Gy in 13 fractions over 5 weeks Start B - 40 Gy in 15 fractions over 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Relapse Rates	Hazard ratios at 10 years: Local relapse 0.90 (p=0.63) (41.6Gy/13) vs 1.20 (p=0.39) (39Gy/13) vs 0.70 (p=0.1) (40 Gy/15) Local-regional relapse 0.91 (p=0.65) (41.6Gy/13) vs 1.18 (p=0.41) (39Gy/13) vs 0.77 (p=0.21) (40 Gy/15) Distance relapse 1.08 (p=0.58) (41.6Gy/13) vs 1.24 (p=0.11) (39Gy/13) vs 0.74 (p=0.014) (40 Gy/15) Any breast cancer related event 0.94 (p=0.57) (41.6Gy/13) vs 1.08 (p=0.48) (39Gy/13) vs 0.79 (p=0.022) (40 Gy/15) All cause mortality 0.96 (p=0.74) (41.6Gy/13) vs 1.05 (p=0.69) (39Gy/13) vs 0.80 (p=0.042) (40 Gy/15)	Late adverse effects at 10 years, Tissue effects at 10 years,	Reported symptomatic rib fracture: START A: 0.7% (50 Gy) vs 1.1% (41.6 Gy) vs 1.2% (39 Gy); START B: 1.5% (50 Gy) vs 2.2% (40 Gy) Reported symptomatic lung fibrosis: START A: 0.8% (50 Gy) vs 1.2% (41.6 Gy) vs 1.1% (39 Gy); START B: 1.7% (50 Gy) vs 1.7% (40 Gy) Reported ischaemic heart disease: START A: 1.9% (50 Gy) vs 1.5% (41.6 Gy) vs 1.1% (39 Gy); START B: 2.1% (50 Gy) vs 1.5% (40 Gy) Hazard ratios for skin tissue effects that demonstates statistically significant differences with CFRT in at 10 years: START A - Breast Induration for 39 Gy 0.76 (p=0.034), Talangiectasia for 39 Gy 0.43 (p=0.003), Breast oedema for 39 Gy (p=0.001), Other toxicities for 39 Gy and 41.6 Gy demonstrated no statistically significant difference with 50Gy; START B - Breast shrinkage for 40 Gy 0.80 (p=0.015), Talangiectasia for 40 Gy 0.62 (p=0.032), Breast Oedema for 40 Gy 0.55 (p=0.001), Other skin toxicity for 40 Gy 0.65 (p=0.018), Other toxicities for 40 Gy demonstrated no statistically significant difference with 50Gy.	Haviland, Joanne S.; Owen, J. Roger; Dewar, John A.; Agrawal, Rajiv K.; Barrett, Jane; Barrett-Lee, Peter J.; Dobbs, H. Jane; Hopwood, Penelope; Lawton, Pat A.; Magee, Brian J.; Mills, Judith; Simmons, Sandra; Sydenham, Mark A.; Venables, Karen; Bliss, Judith M.; Yarnold, John R.; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14(11):1086-1094.	-	-	This study combines two RCTs (StartA and StartB) over a 10 year period, following the need for long term study highlighted in (James 10). StartA compares 50 Gy over 25 fractions with 39 Gy or 41.6 over 13 fractions. StartB compares 50 Gy over 25 fractions with 40 Gy over 15 fractions. Uses Cox proportional regression model to fit rates with respect to time, then calculate hazard ratio of rates. Hazard ratios for local-regional relapse rates between 50 Gy and 41.6 Gy were 0.91 (95 %CL 0.59-1.38) and between 50 Gy and 39 Gy were 1.18 (95 %CL 0.79-1.76). Concerns over increased risk of heart disease in higher dosage treatments were not supported in these trials. Disease-free survival, overall survival and distance relapse rates all statistically the same in StartA. In startB, fewer distance relapses in 40 Gy (HR 0.74 95 %CL 0.59-0.94) which contributed to lower overall survival rates (HR 0.8 95 %CL 0.65-0.99) and disease free survival rates (HR 0.79 95 %CL 0.65-0.97). With regards to tissue effects, most common was breast shrinkage, but statistically similar rates in both trials. Lower rates of breast oedemas and telangiectasia in both 39 Gy (HR 0.54 (0.37-0.78) and HR 0.43 (0.25-0.75)) and 40 Gy (HR 0.55 (0.39-0.79) and HR 0.62 (0.4-0.96)) than in 50 Gy, but based on low statistics (approx 5% of sample). Breast shrinkage also lower in 40 Gy (HR 0.8 (0.67-0.96).
4	Systematic	7095 patients	39 Gy, 13 fractions, 5 weeks 42.9 Gy, 13 fractions, 5 weeks 41.6 Gy, 13 fractions, 5 weeks 40 Gy, 15 fractions, 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Local recurrence in ipselateral breast. Appearance or cosmesis of treated breast.	No meta analysis made, rates quoted.	Overall survival rate Toxicity Cancer specific mortality Relapse free survival Mastectomy rate Quality of life Costs	No meta analysis made, rates quoted.	Caudrelier, J.-M.; Truong, P. T.. Role of hypofractionated radiotherapy in breast locoregional radiation. Cancer Radiother 2015;19(4):241-247.	-	-	This narrative review combines the results of 4 RCTs with additional commentary on lung effects.

1+	RCT	1234	42.5 Gy in 16 fractions over 22 days.	Clinical effectiveness of the intervention compared to existing interventions	Local recurrence rate	Lower recurrence local rate, HR (3.08 95% CL 1.22-7.76)	Mortality Toxicity	Mortality rate: 15.6% CFRT vs. 15.4% HFRT	Whelan, Timothy J.; Pignol, Jean-Philippe; Levine, Mark N.; Julian, Jim A.; MacKenzie, Robert; Parpia, Sameer; Shelley, Wendy; Grimard, Laval; Bowen, Julie; Lukka, Himu; Perera, Francisco; Fyles, Anthony; Schneider, Ken; Gulavita, Sunil; Freeman, Carolyn. Long-term results of hypofractionated radiation therapy for breast cancer. N. Engl. J. Med. 2010;362(6):513-520.	-	-	This paper presents the results of the long term (12 year) follow up of the (Whelan et al. 2002) RCT. The same exclusions have been applied again. In particular, the exclusion of large breasted women. Primary outcome is that there is no statistically significant difference between local recurrence rates (p=0.975). Although, an import point is that when the local recurrence rate is split by grade of tumour, it is found that the conventionally fractionated regime had a statistically significant lower recurrence local rate, HR (3.08 95% CL 1.22-7.76). The mortality rates were also found to be the same (p=0.56). Skin toxicity rates were marginally better in hypofractionated regimes, but this was not statistically significant.
1-	RCT	121	42 Gy in 15 fractions over 3 weeks	Other	Quality of life	See summary	-	-	Versmessen, Harijati; Vinh-Hung, Vincent; Van Parijs, Hilde; Miedema, Geertje; Voordeckers, Mia; Adriaenssens, Nele; Storme, Guy; De Ridder, Mark. Health-related quality of life in survivors of stage I-II breast cancer: randomized trial of post-operative conventional radiotherapy and hypofractionated tomotherapy. BMC Cancer 2012;12(0):495.	-	-	This RCT was focused on examining the quality of life of patients under going conventional radiotherapy verse hypofractional radiotherapy (HFRT). The study found that HFRT patients demonstrated faster improvement in role- and cognitive- functioning, as well as fatigue. However, there is concern of biases arising due to the sample size, in addition to the non blinding of the patients.
1-	RCT	70	42 Gy in 15 fractions over 3 weeks with Helical TomoTherapy plus additional boosts dependend on tumour and clinical discretion	Clinical effectiveness of the intervention compared to existing interventions	Occurrence of toxicity grade >1 change from baseline.	Skin at 2 years: 12/20 patients (60%) with CFRT vs 6/20 patients (30%) with HFRT. Lung toxicity at 2 years: 10/24 (42%) with CFRT vs 5/27 patients (22%) with HFRT.	-	-	Van Parijs, Hilde; Miedema, Geertje; Vinh-Hung, Vincent; Verbanck, Sylvia; Adriaenssens, Nele; Kerkhove, Dirk; Reynders, Truus; Schuermans, Daniel; Leysen, Katrien; Hanon, Shane; Van Camp, Guy; Vincken, Walter; Storme, Guy; Verellen, Dirk; De Ridder, Mark. Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial. Radiat Oncol 2012;7(0):80.	-	-	This RCT compares a new form of Helical TomoTherapy with 42Gy in 15 fractions over 3 weeks (HFRT) with the conventional radiotherapy of 50 Gy in 25 fractions over 5 weeks CFRT. The study finds that the HFRT have a lower rate of skin and lung toxicities after 2 years. However there are a number of concerns with the study. Firstly, the sample size is quite small and these results are typically based and betwee 20-30 patients in the respective arms. Secondly, there are a number of differences between the experimental and control arm, including fractional regime, type of radiotherapy and boost regime, hence it is difficult to distinguish the cause of any possible effects.

1+	RCT	2236	41.6 Gy in 13 fractions over 5 weeks. 39 Gy in 13 fractions over 5 weeks.	Clinical effectiveness of the intervention compared to existing interventions	Local recurrence in ipselateral breast. Appearance or cosmesis of treated breast.	Absolute differences in local relapse rates at 5 years were found to be 0.2% (95% CL -1.3% to 2.6 %) for 41.6 Gy, 0.9% (95% CL -0.8% to 3.7 %) for 39 Gy	Overall survival rate Toxicity Cancer specific mortality Relapse free survival Mastectomy rate Quality of life Costs	Breast swelling (hazard ratio 0.65 (95% CL 0.49% to 0.87%)) and change in breast appearance (hazard ratio 0.69 (95% CL 0.52% to 0.91%)) in the 39 Gy treatment	START Trialists' Group; Bentzen, S. M.; Agrawal, R. K.; Aird, E. G. A.; Barrett, J. M.; Barrett-Lee, P. J.; Bliss, J. M.; Brown, J.; Dewar, J. A.; Dobbs, H. J.; Haviland, J. S.; Hoskin, P. J.; Hopwood, P.; Lawton, P. A.; Magee, B. J.; Mills, J.; Morgan, D. a. L.; Owen, J. R.; Simmons, S.; Sumo, G.; Sydenham, M. A.; Venables, K.; Yarnold, J. R.. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008;9(4):331-341.	-	-	This is the study reporting the findings of the START A RCT. The principle results have already been summarised and combined in (James 2010). The absolute differences in local relapse rates at 5 years were found to be 0.2% (95% CL -1.3% to 2.6 %) for 41.6 Gy, 0.9% (95% CL -0.8% to 3.7 %) for 39 Gy, i.e. no statistically significant difference. There was a statistically significant difference in breast swelling (hazard ratio 0.65 (95% CL 0.49% to 0.87%)) and change in breast appearance (hazard ratio 0.69 (95% CL 0.52% to 0.91%)) in the 39 Gy treatment, relative to the 50 Gy treatment, observed based on blinded photographic assessment of 1055 patients. But this was not also see in 41.6 Gy trial.
1+	RCT	2215	40 Gy in 15 fractions over 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Local recurrence in ipselateral breast.	At 5 years hazard ratios for relapse rates: Local relapse: 0.72 (p=0.21) Local regional relapse: 0.79 (p=0.35) Distance relapse: 0.69 (p=0.01) Any breast cancer related event: 0.75 (p=0.02) All Cause Mortality: 0.76 (p=0.03)	Appearance or cosmesis of treated breast. Overall survival rate Toxicity	At 5 years hazard ratios for late time normal tissue effects with 95% confidence levels (CL) in brackets: Breast shrinkage 0.89 (0.7-1.12) Breast hardness 0.89 (0.73-1.09) Change in skin appearance 0.77 (0.61-0.98) Swelling in affected breast area 0.93 (0.65-1.33) Change in breast appearance 0.86 (0.70-1.05) Change in breast appearance (photographic) 0.83 (0.66-1.04)	START Trialists' Group; Bentzen, S. M.; Agrawal, R. K.; Aird, E. G. A.; Barrett, J. M.; Barrett-Lee, P. J.; Bentzen, S. M.; Bliss, J. M.; Brown, J.; Dewar, J. A.; Dobbs, H. J.; Haviland, J. S.; Hoskin, P. J.; Hopwood, P.; Lawton, P. A.; Magee, B. J.; Mills, J.; Morgan, D. a. L.; Owen, J. R.; Simmons, S.; Sumo, G.; Sydenham, M. A.; Venables, K.; Yarnold, J. R.. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008;371(9618):1098-1107.	-	-	This is the study reporting the findings of the START B RCT. The principle results have already been summarised and combined in (James 2010). Local relapses (defined as ipsilateral tumour in breasts or chest wall) events were 34/1105 for 50 Gy vs 25/1110 for 40 Gy giving a hazard ratio 0.72 (95% CL 0.43-1.21) p=0.21. I.e. There is a convoluted statistical analysis, in which a relative small sample is used to fit two regression models and the hazard ratio (HR) is related to ratio of gradients. This is the standard practice used in all RCTs, but it is unclear how robust this is against outliers. Other metrics (all evaluated at 5 years) include local-regional relapse (as with local relapse, but only including irradiated area) rate HR 0.79 (p=35), distant relapse rate 0.69 (p=0.01) (based on 87/1110 events for 40 Gy vs 122/1105 events for 50 Gy), any breast cancer related event HR 0.75(p=0.02) (based on 127/1110 events for 40 Gy vs 164/1105 events for 50 Gy), all cause mortality HR 0.76 (p=0.03) (based on 107/1110 events for 40 Gy vs 138/1105 events for 50 Gy). Change in breast appearance less likely in 40 Gy than 50 Gy, HR 0.83 (p=0.06). Change in skin appearance less likely in 40 Gy than 50 Gy, HR 0.77 (95% CL 0.61 - 0.98) These latter two results agree with START A.
1+	RCT	707 patients	40 Gy in 15 fractions over 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	local regional relapse	Local relapses (defined as ipsilateral tumour in breasts or chest wall) events were 34/1105 for 50 Gy vs 25/1110 for 40 Gy giving a hazard ratio 0.72 (95% CL 0.43-1.21) p=0.21	survival rates local regional tumour control	The relapse free survival rates at 2, 5, 10 and 15 years for 50 Gy were 86%, 73%, 59%, 44%, while for 40 Gy, 89%, 81%, 61%, 46%, HR 0.98. While for overall survival rates at 2,5, 10 and 15 years for 50 Gy were 92%, 81%, 67%, 52%, while for 50 Gy, 94%, 85%, 70%, 53% HR 1.02.	Spooner, D.; Stocken, D. D.; Jordan, S.; Bathers, S.; Dunn, J. A.; Jevons, C.; Dodson, L.; Morrison, J. M.; Oates, G. D.; Grieve, R. J.; West Midlands Oncology Breast Cancer Group. A randomised controlled trial to evaluate both the role and the optimal fractionation of radiotherapy in the conservative management of early breast cancer. Clin Oncol (R Coll Radiol) 2012;24(10):697-706.	-	-	This RCT began much earlier than the other studies and so has the advantage of longer follow up period. However, it suffers from having a smaller sample size. 707 patients were randomised to either receive radiotherapy (RT) (358) or not (349). Of those receiving RT 177 received 50 Gy in 25 fractions over 5 weeks, 181 received 40 Gy in 15 fraction over 3 weeks. There was statistically significant differences in most relapse rates between those receiving RT and those not receiving RT, but this is not of primary concern to the research questions. There was no statistically significant difference in the relapse rates of different fractional schedules. In particular, the relapse free survival rates at 2, 5, 10 and 15 years for 50 Gy were 86%, 73%, 59%, 44%, while for 40 Gy, 89%, 81%, 61%, 46%, HR 0.98. While for overall survival rates at 2,5, 10 and 15 years for 50 Gy were 92%, 81%, 67%, 52%, while for 50 Gy, 94%, 85%, 70%, 53% HR 1.02.

1+	RCT	1326	40 Gy in 15 fractions over 3 weeks. 50 Gy in 25 fractions over 5 weeks.	Clinical effectiveness of the intervention compared to existing interventions	Local relapse rates. Survival rates	Overall survival rates between treatments at 5 years HR 0.94 (p=0.34)	-	-	Kunkler, Ian H.; Williams, Linda J.; Jack, Wilma J. L.; Cameron, David A.; Dixon, J. Michael; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015;16(3):266-273.	-	-	This RCT is a repetition of the (Spooner 12) trial, but limiting the patients to ladies over the age of 65, suffering from low risk early breast cancer. Of 1326 patients, 658 received radiotherapy and were randomly given either 50 Gy in 25 fractions over 5 weeks or 40 Gy in 15 fractions over 3 weeks. Precise breakdown of number not stated. Unfortunately there is relatively little analysis comparing the two treatments, only a statement that there was no difference in overall survival rates between treatments at 5 years HR 0.94 (p=0.34).
1+	RCT	4451	41.6 Gy in 13 fractions over 5 weeks. 39 Gy in 13 fractions over 5 weeks. 42 Gy in 15 fractions over 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Breast symptoms Arm or Shoulder Symptoms	While there was some evidence of reduced numbers of adverse arm and shoulder effects in the hypofractionated regimes, these differences were not statistically significant. The only exceptions to this have already been mentioned, notably: The hazard ratio for change in skin appearance between 39 Gy and 50 Gy was 0.63 (p=0.0019) based on START A The hazard ratio for change in skin appearance between 40 Gy and 50 Gy was 0.76 (p=0.026) based on START B The hazard ratio for change in skin appearance between 41.6 Gy and 50 Gy was 0.83 (p=0.16) based on START A	-	-	Hopwood, Penelope; Haviland, Joanne S.; Sumo, Georges; Mills, Judith; Bliss, Judith M.; Yarnold, John R.; START Trial Management Group. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. Lancet Oncol. 2010;11(3):231-240.	-	-	This systematic review without meta-analysis is based on the RCTs START A and START B, but gives a more detailed analysis of the rates of breast conditions and arm or shoulder conditions. This includes a breakdown by fractional treatment and whether the patients received a boost or not. This has been based on quality of life questionnaires and blinded analysis of photos, both after 5 years. While there was some evidence of reduced numbers of adverse arm and shoulder effects in the hypofractionated regimes, these differences were not statistically significant. The only exceptions to this have already been mentioned, notably: - The hazard ratio for change in skin appearance between 39 Gy and 50 Gy was 0.63 (p=0.0019) based on START A - The hazard ratio for change in skin appearance between 40 Gy and 50 Gy was 0.76 (p=0.026) based on START B - The hazard ratio for change in skin appearance between 41.6 Gy and 50 Gy was 0.83 (p=0.16) based on START A
1-	RCT	279	30 Gy in 5 fractions over 5 weeks, 28.5 Gy in 5 fractions over 5 weeks	Clinical effectiveness of the intervention compared to existing interventions	Relation between breast volume and late adverse effects	See summary.	Relation between dosimetry and late adverse effects	See summary	Goldsmith, Christy; Haviland, Joanne; Tsang, Yat; Sydenham, Mark; Yarnold, John; FAST Trialists' Group. Large breast size as a risk factor for late adverse effects of breast radiotherapy: is residual dose inhomogeneity, despite 3D treatment planning and delivery, the main explanation?. Radiother Oncol 2011;100(2):236-240.	-	-	This RCT re-examines the UK FAST trial with the intention of testing the hypothesis that breast size a and dosimetry is associated with late adverse effects. If found that both breast size and dosimetry are correlated with late effects in univariate analysis, but only breast size is correlated with the risk of change in breast appearance. Primary concern is about the sample size. Regression model was fit with 279 patients of which 61 had mild change and 17 had marked change.

1+	RCT	915	30 Gy in 5 fractions over 5 weeks, 28.5 Gy in 5 fractions over 5 weeks	Clinical effectiveness of the intervention compared to existing interventions	Photographic breast appearance	After 2 years, there was a statistically significant difference in the photographic breast appearance between the 30 Gy regimen and the 50 Gy Regimen, with a risk ratio, for mild or marked change, being 1.7 (p<0.001). This difference was not seen between 28.5 Gy and 50 Gy (risk ratio 1.15 p=0.489).	Clinical assessments of radiation-induced changes	-	FAST Trialists group; Agrawal, Rajiv K.; Alhasso, Abdulla; Barrett-Lee, Peter J.; Bliss, Judith M.; Bliss, Peter; Bloomfield, David; Bowen, Joanna; Brunt, A. Murray; Donovan, Ellen; Emson, Marie; Goodman, Andrew; Harnett, Adrian; Haviland, Joanne S.; Kaggwa, Ronald; Morden, James P.; Robinson, Anne; Simmons, Sandra; Stewart, Alan; Sydenham, Mark A.; Syndikus, Isabel; Tremlett, Jean; Tsang, Yat; Wheatley, Duncan; Venables, Karen; Yarnold, John R.. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiother Oncol 2011;100(1):93-100.	-	-	This RCT presents the initial results of a 2 year follow op on the UK FAST trial began between 2004 and 2007. It's primary outcomes are breast appearance and clinical assessment of radiation induced changes in the breast. In the trial 915 women were randomly allocated to either the conventional radiotherapy, n=302 (50 Gy in 25 fractions over 5 weeks) or the hypofractionated treatments, n=308 (30 Gy in 5 fractions over 5 weeks) or n=305 (28.5 Gy in 5 fractions over 5 weeks). After 2 years, there was a statistically significant difference in the photographic breast appearance between the 30 Gy regimen and the 50 Gy Regimen, with a risk ratio, for mild or marked change, being 1.7 (p<0.001). This difference was not seen between 28.5 Gy and 50 Gy (risk ratio 1.15 p=0.489). There was also statistically significant differences in the distributions of acute skin reactions, with patients receiving 30 Gy displaying reduced reactions than those receiving 50 Gy.
`	RCT	124	40.5 Gy in 15 fractions over 3 weeks 45 Gy in 15 fractions over 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Rate of skin toxicity	See summary.	incidence of breast pain	See summary.	Chadha, Manjeet; Vongtama, Dan; Friedmann, Patricia; Parris, Celina; Boolbol, Susan K.; Woode, Rudolph; Harrison, Louis B.. Comparative acute toxicity from whole breast irradiation using 3-week accelerated schedule with concomitant boost and the 6.5-week conventional schedule with sequential boost for early-stage breast cancer. Clin. Breast Cancer 2012;12(1):57-62.	-	-	This RCT was focused on examining the acute toxicity of two hypofractionated regimes (40.5 Gy in 15 fractions over 3 weeks and 45 Gy in 15 fraction over 3 weeks) with the conventional regime (46.8 Gy in 25 fractions over 6.5 weeks). The study claims to find a lower incidence in skin toxicity in the hypofractionated regimes (p=0.0015) and lower rate of breast pain in the hypofractionated regime (p=0.045). However there are a number of concerns about the study. Firstly, the sample size is quite small 124 patients over three trials, the break down is not specified. Secondly, the analysis is done 8 weeks after treatment. Thirdly many of the details of the statistical analysis, such as the break down of events by regime, have not been stated and so it is difficult to assess the robustness of their conclusion. Therefore this study has not been used as evidence.
3	RCT	7095 patients	39 Gy, 13 fractions, 5 weeks 42.9 Gy, 13 fractions, 5 weeks 41.6 Gy, 13 fractions, 5 weeks 40 Gy, 15 fractions, 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Radiation dose to heart	See summary.	-	-	Appelt, A. L.; Vogelius, I. R.; Bentzen, S. M.. Modern hypofractionation schedules for tangential whole breast irradiation decrease the fraction size-corrected dose to the heart. Clin Oncol (R Coll Radiol) 2013;25(3):147-152.	-	-	This is a reanalysis of the data from START A, START B and (Whelan et al. 2002) with the intention of estimating the radiation dose to the heart during the respective fraction regimes. The motivation for this is concerns about long term toxicity of these RTs, particularly concerning mortality from radiation induced heart disease. It is found that 40 Gy in 15 fractions, 39 Gy in 13 fractions and 42.5 Gy in 16 fractions, but not 41.6 Gy in 13 fractions, all have more favourable doses to the heart than 50 Gy in 25 fractions.

4	Other	2800	APBI, 3 weeks hypofractionated, 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Not specified	-	-	-	Belkacemi, Yazid; Bourgier, Céline; Kramar, Andrew; Auzac, Guillaume; Dumas, Isabelle; Lacornerie, Thomas; Mége, Jean-Pierre; Mijonnet, Sylvie; Lemonnier, Jerôme; Lartigau, Eric. SHARE: a French multicenter phase III trial comparing accelerated partial irradiation versus standard or hypofractionated whole breast irradiation in breast cancer patients at low risk of local recurrence. Clin Adv Hematol Oncol 2013;11(2):76-83.	-	-	This review outlines the various trials being conducted on different fractional therapies and accelerated partial irradiation therapy.
4	Other	-	39 Gy, 13 fractions, 5 weeks 42.9 Gy, 13 fractions, 5 weeks 41.6 Gy, 13 fractions, 5 weeks 40 Gy, 15 fractions, 3 weeks	Clinical effectiveness of the intervention compared to existing interventions	Clinical guidelines	-	-	-	Belkacémi, Y.; Fourquet, A.; Cutuli, B.; Bourgier, C.; Hery, M.; Ganem, G.; Marsiglia, H.; Namer, M.; Gligorov, J.; Azria, D.; French Expert Review Board of Nice/Saint-Paul de Vence. Radiotherapy for invasive breast cancer: guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. Crit. Rev. Oncol. Hematol. 2011;79(2):91-102.	-	-	This systematic review of the literature has been conducted in order to clarify certain guidelines concerning post-breast surgery radiotherapy. The only studies it includes comparing hypofractionated regimes with conventionally fractionated regimes are the four discussed previously, START pilot, START A, START B and (Whelan et al. 2002). The study admits that relapse rates are the same between the two treatment regimes but does not go into any more details.
3	Case series	-	16 fraction with no boost	Cost effectiveness	-	-	-	-	Rajagopalan, Malolan S.; Flickinger, John C.; Heron, Dwight E.; Beriwal, Sushil. Changing practice patterns for breast cancer radiation therapy with clinical pathways: An analysis of hypofractionation in a large, integrated cancer center network. Pract Radiat Oncol 2015;5(2):63-69.	-	-	This study examines the factors that influence the use of hypofractional treatment over conventional treatments and hence is of little relevance to the research questions. However, it does make a useful cost comparison, based on US Medicare Physician fee schedule, 16 fraction with no boost would cost $6739.25 and 25 fractions would cost $8930.95. This is obviously very dependent on the fee schedule.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	Hypofractionation
Updated search terms - Population	breast OR DCIS OR ductal carcinoma in situ
Updated search terms - Intervention	Intervention part 1: hypofractionation OR hypofractionated OR fraction* Intervention part 2: fifteen OR 15
Updated search terms - Comparator	n/a
Updated search terms - Outcome	n/a

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	Clinical Trials Meta-Analysis and Review articles National guidelines and professional consensus guidance e.g. ASTRO NICE guidance
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist)
	Specific exclusion criteria
	n/a