Table 15: studies included in the evidence review for breast radiotherapy after breast-conserving surgery

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Blamey, R, Bates, T, Chetty, U, Duffy, S, Ellis, I, George, D, Mallon, E, Mitchell, M, Monypenny, I, Morgan, D, Macmillan, R, Patnick, J, Pinder, S, Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial, European journal of cancer (Oxford, England : 1990), 49, 2294-302, 2013 **Ref Id** 552391 **Country/ies where the study was carried out** UK **Study type**	**Sample size** 1135 patients randomised - not interested in 20 patients that were only randomised based on Tamoxifen **Characteristics** Gender: 100% women Age: Mean 57; range 33-69 Ethnicity: NR **Inclusion criteria** Eligibility included women under 70 years of	**Interventions** **Intervention arm:** wide local excision (WLE) ± tamoxifen **Control arm:** WLE + whole breast radiotherapy ± tamoxifen	**Details** **Intervention arm (RT-):** WLE was defined in the trial protocol as surgical removal of the tumour mass with minimum width of 0.5–1.0 cm of surrounding uninvolved tissue confirmed by histological examination (if necessary, after a re-excision). Tamoxifen 20 mg daily for 5 years was prescribed to women randomised to tamoxifen and to those receiving tamoxifen by the elective choice of the Unit. **Control arm (RT+):** WLE was defined in the trial protocol as surgical removal of the tumour mass with minimum width of 0.5–1.0 cm of surrounding uninvolved tissue confirmed by histological examination (if necessary, after a re-excision). Tamoxifen 20 mg daily for 5 years was prescribed to women randomised to tamoxifen and to those receiving tamoxifen by the elective choice of the Unit. Whole breast irradiation was given with fractionation in the range between 40 Gy in 15 fractions and 50 Gy in 25 fractions. A boost to the tumour bed was recommended, but not obligatory.	**Results** **Local recurrence (Median follow-up 121 months):** O-E: 14.72; V: 14.82	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias**

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RCT **Aim of the study** To identify a group in which the absolute risk of LR is low enough to omit treatment with RT, and to compare the effects on LR of adjuvant tamoxifen with RT **Study dates** Recruitment February 1992 - October 2000 **Source of funding** NHS Breast Screening Programme and Cancer Research UK	age with primary operable unilateral invasive breast cancer with no evidence of metastases. T he invasive carcinomas had to be of histological grade 1 or specific good prognosis special types (tubular, cribriform, tubular/cribrifor m, papillary or mucinous). Tumours had to be of maximum diameter 20 mm or less and have no evidence of lympho-vascular invasion (LVI). Histological examination of lymph nodes, excised by sampling or				Low **Selective reporting** Low **Indirectness** None **Limitations** No additional limitations **Other information** BASO II trial

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	dissection, had to be negative. **Exclusion criteria** Ineligible were patients with DCIS and microinvasive carcinoma alone, those with Paget's disease of the nipple, patients with synchronous bilateral breast cancer, those with a previous diagnosis of any cancer other than adequately treated basal cell carcinoma of the skin, and pregnant or lactating women. Also excluded were those women with evidence of distant metastases and those with				

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	other diseases that might preclude adequate surgery, adjuvant therapy or follow-up. Similarly those with planned receipt of any adjuvant therapy other than those within the trial were ineligible for trial entry. **Reported subgroups** All patients: T stage (1), N stage (0), Margins (negative)				
Full citation Holli, K, Hietanen, P, Saaristo, R, Huhtala, H, Hakama, M, Joensuu, H, Radiotherapy after segmental resection of breast cancer with	**Sample size** 264 randomised (1 subsequently refused RT)	**Interventions** **Intervention arm:** segmental breast resection (lumpectomy) and dissection of the ipsilateral axilla	**Details** **Intervention arm (RT-):** Surgery consisted of segmental breast resection (lumpectomy) and dissection of the ipsilateral axilla - the mammary gland was dissected free in the plane of Scapas fascia down to the pectoral muscle. The pectoral fascia was included in the specimen. Nonpalpable tumours were localized with wire-	**Results** **Local recurrence (Median follow-up 12.1 years):** O-E: 11.00; 11.08	**Selection bias: random sequence generation** Computer program–generated

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favorable prognostic features: 12-year follow-up results of a randomized trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 27, 927-32, 2009 **Ref Id** 551555 **Country/ies where the study was carried out** Finland **Study type** RCT **Aim of the study** To compare breast-conserving surgery versus similar surgery followed by postoperative breast irradiation among women diagnosed with small size invasive breast cancer.	**Characteristics** Gender: 100% women Age: Median RT+ 56.3; Median RT- 55.6; range 37.4-85.2 Ethnicity: NR **Inclusion criteria** Age at random assignment had to be older than 40 years; the greatest tumour diameter measured microscopically had to be 20mm or less; histologic grade had to be either 1 (well differentiated) or 2 (moderately differentiated);	**Control arm:** segmental breast resection (lumpectomy) and dissection of the ipsilateral axilla + whole breast radiotherapy	hook marking. Levels I and II lymph node dissection were performed through a separate axillary incision. **Control arm (RT+):** Surgery consisted of segmental breast resection (lumpectomy) and dissection of the ipsilateral axilla - the mammary gland was dissected free in the plane of Scapas fascia down to the pectoral muscle. The pectoral fascia was included in the specimen. Nonpalpable tumours were localized with wire-hook marking. Levels I and II lymph node dissection were performed through a separate axillary incision. Postoperative radiation therapy was given by using a linear accelerator from two opposed tangential breast fields that provides approximately 5 MeV photon energy. A cumulative radiation dose of 50 Gy was administered within 5 weeks by using 2Gy daily fractions and wedge compensators to achieve a uniform dose. The planned target volume encompassed the entire ipsilateral breast and the lower ipsilateral axillary contents (levels I and II). No booster dose was given at the surgical bed. The ipsilateral supraclavicular lymph nodes were not included in the target volume.	**OS (Median follow-up 12.1 years):** O-E: 41.53; V: 89.55	random digits: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Low **Selective reporting** Low **Indirectness** None

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Study dates Surgery occurred between May 1990 and September 1999 **Source of funding** Pirkanmaa Hospital District, Tampere University Hospital, the Finnish Breast Cancer Group, Cancer Society of Finland, the Academy of Finland, and Sigrid Juselius Foundation.	progesterone receptor (PR) status had to be positive (ie,10%of tumour cell nuclei stained positively in immunohistochemistry); the cell proliferation rate had to be low (i.e., either S phase fraction determined by DNA flow cytometry 7% or 10% of cancer cell nuclei stained for Ki-67 in immunohistochemistry); and the tumour had to be unifocal in a preoperative mammogram. The surgical resection margins had to be free of cancer with at least 1 cm of healthy breast				**Limitations** Rates of recurrence similar to previous trials where less emphasis was placed on entering patients with cancer with low biologic aggressiveness, which would suggest that the methods used to identify cancers with low biologic aggressiveness may not have worked as intended. **Other information**

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	tissue between the cancer and resection margin, as assessed by microscopy. If the tumour size was too small to allow sampling for DNA flow cytometry and hormone receptor analysis (i.e., patient cases with a primary tumour 5mm in diameter), histologic grade 1 or 2 together with small size were considered sufficient evidence of low biologic aggressivenes s. **Exclusion criteria** Patient cases with tumours				

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	that had an extensive intraductal component, axillary nodal metastases (pN), or distant metastases were excluded from the study. **Reported subgroups** All patients: T stage (1), N stage (0), Margins (negative)				
Full citation Hughes, K, Schnaper, L, Bellon, J, Cirrincione, C, Berry, D, McCormick, B, Muss, H, Smith, B, Hudis, C, Winer, E, Wood, W, Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of	**Sample size** 647 enrolled, 636 randomised **Characteristics** Gender: 100% women Age: ≥70 years (Mean/range NR)	**Intervention arm:** lumpectomy + tamoxifen **Control arm:** lumpectomy + tamoxifen + whole breast radiotherapy	**Details** **Intervention arm (RT-):** lumpectomy with a clear margin (absence of tumour at the inked margin). Axillary node dissection was allowed but not encouraged. 20mg tamoxifen per day for 5 years initiated during or after irradiation. Adjuvant hormonal treatment beyond 5 years was discretionary **Control arm: (RT+):** lumpectomy with a clear margin (absence of tumour at the inked margin). Axillary node dissection was allowed but not encouraged. 20mg tamoxifen per day for 5 years initiated during or after irradiation. Adjuvant hormonal treatment beyond 5 years	**Results** **Locoregional recurrence (10 year follow-up):** O-E: 8.15; V: 4.78 **OS (10 year follow-up):** O-E: 4.15; V: 85.12	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear

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CALGB 9343, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31, 2382-7, 2013 **Ref Id** 552485 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To compare the efficacy of tamoxifen alone with tamoxifen plus radiotherapy in older women with ER-positive, clinical stage I breast cancer **Study dates** Recruited July 1994 - February 1999	Ethnicity: 90% Caucasian, 7% Black, 2% Hispanic <1% Asian **Inclusion criteria** Women age 70 years with clinical stage I, ER-positive breast cancer and no history of cancer other than in situ cervical or nonmelanoma skin cancer within 5 years were eligible. Initial eligibility criteria included breast cancers up to 4 cm regardless of oestrogen receptor status, but this was reduced in August 1996 to 2 cm (T1) with ER-		was discretionary. RT included tangential fields to the entire breast followed by an electron boost to the lumpectomy site.		**Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** No additional limitations

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Source of funding Not reported	positive or indeterminate receptor status. Patients were required to have clinically negative axillae. **Exclusion criteria** No additional criteria reported **Reported subgroups** All participants: N stage (0), Age (65+), Margins (negative)				**Other information** CALGB 9343 trial
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Selection bias: random sequence generation**
Kunkler, I, Williams, L, Jack, W, Cameron, D, Dixon, J, Breast-conserving surgery with or without irradiation in women	1326 randomised - 44 (5 in RT- and 39 in RT+) did not receive allocated	**Intervention arm:** BCS + no radiotherapy	**Intervention arm (RT-):** No details for breast conserving surgery procedures provided. Tamoxifen (20 mg daily for 5 years) as the standard adjuvant endocrine treatment, but we allowed other forms of adjuvant and neoadjuvant endocrine treatment.	**Local recurrence (median follow-up 5 years):** O-E: 6.89; V: 4.19	Permuted blocks: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial, The Lancet. Oncology, 16, 266-73, 2015 **Ref Id** 553117 **Country/ies where the study was carried out** UK, Greece, Australia, Serbia **Study type** RCT **Aim of the study** To assess the effect of omission of whole-breast irradiation after breast-conserving surgery on local control. **Study dates** Recruited April 2003 - December 2009	treatment; 3 patients in RT- arm declined hormone treatment and 1 in each arm did not meet inclusion criteria. **Characteristics** Gender: 100% women Age: RT+ Median 70, IQR 67-74; RT- Median 69, IQR 67-73 Ethnicity: NR **Inclusion criteria** Women aged ≥65 years with breast cancer who had undergone breast-	**Control arm:** BCS + whole breast radiotherapy	**Control arm (RT+):** No details for breast conserving surgery procedures provided. Radiotherapy administered according to local practice in every centre. However, guideline was 40-50Gy (2.66-2.00Gy per fraction in 15-25 fractions) over 3-5 weeks at megavoltage irradiation to the breast. Breast boosts with electrons of 10–15 Gy at appropriate energy or an iridium implant (e.g., 20 Gy to 85% reference isodose) were permitted. Guidelines on radiotherapy included some form of immobilisation, a planned target volume of the whole breast (margin of 1 cm), and all patients being simulated to establish the volume of lung irradiated (maximum lung thickness no greater than 3 cm). We specified that the peripheral lymphatic system was not to be irradiated. Tamoxifen (20 mg daily for 5 years) as the standard adjuvant endocrine treatment, but we allowed other forms of adjuvant and neoadjuvant endocrine treatment.		**Selection bias: allocation concealment** Used independent randomisation service: Low **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Similar rates of loss to follow-up in both arms: Low **Selective reporting** Low **Indirectness**

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Source of funding Chief Scientist Office of the Scottish Government and the Breast Cancer Institute at the Western General Hospital, Edinburgh	conserving surgery and pathological axillary staging. Cancer must be: T1-T2, N0, M0 hormone (ER/PR/both) receptor positive, excised with clear (≥1mm) margins, and receiving neoadjuvant hormonal treatment. **Exclusion criteria** Excluded patients if younger than 65 years or if they had a history of previous in-situ or invasive breast cancer of either breast. Also excluded women with current or				Population: not stated that it is limited to invasive breast cancer: serious **Limitations** Absence of detailed information on comorbidities and on adherence to endocrine treatment. Few patients were included with grade 3 tumours, therefore limited applicability in this groups. **Other information** PRIME II trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	previous malignant disease within the past year, other than non-melanomatous skin cancer or carcinoma in situ of the cervix. **Reported subgroups** All patients: N stage (0), Age (65+), Margins (negative)				
Full citation Wickberg, A, Holmberg, L, Adami, H, Magnuson, A, Villman, K, Liljegren, G, Sector resection with or without postoperative radiotherapy for stage I breast cancer: 20-year results of a randomized trial, Journal of clinical oncology : official journal of the American	**Sample size** 381 randomised **Characteristics** Gender: 100% women Age: Mean 60; SD 11.2 Ethnicity: NR	**Interventions** **Intervention arm:** sector resection and axilla dissected to levels I and II **Control arm:** sector resection and axilla dissected to levels I and II +	**Details** **Intervention arm (RT-):** sector resection and axilla dissected to levels I and II **Control arm (RT+):** sector resection and axilla dissected to levels I and II. Radiotherapy total dose of 54Gy in 27 fractions delivered to target volume, defined as breast parenchyma plus 1cm.	**Results** **OS (20 year follow-up):** O-E: 5.66; V: 59.99	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Unclear

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Society of Clinical Oncology, 32, 791-7, 2014 **Ref Id** 552969 **Country/ies where the study was carried out** Sweden **Study type** RCT **Aim of the study** To investigate how radiotherapy adds to tumour control using a standardised surgical technique with meticulous control of surgical margins. **Study dates** Recruited 1981 - 1988 **Source of funding**	**Inclusion criteria** Women ≤80 years old with a unifocal invasive breast cancer of histopathologic stage I **Exclusion criteria** No additional criteria reported **Reported subgroups** All patients: Adjuvant systemic therapy (none)	whole breast radiotherapy			**Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** Low statistical power

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Swedish Cancer Society; the Local Research Committee; University Hospital, Orebro; and the Regional Research Foundation, Uppsala/Orebro, Sweden.					**Other information** Uppsala/Orebro trial
Full citation Williams, L, Kunkler, I, King, C, Jack, W, Pol, M, A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial, Health technology assessment (Winchester, England), 15, i-xi, 1-57, 2011 **Ref Id** 552070 **Country/ies where the study was carried out**	**Sample size** 255 randomised **Characteristics** Gender: 100% women Age: Mean 72.6; SD 5.1 Ethnicity: NR **Inclusion criteria** Age of ≥ 65 years, receiving	**Interventions** **Intervention arm:** breast-conserving surgery only **Control arm:** breast conserving surgery + post-operative radiotherapy	**Details** No further detail reported.	**Results** **OS (5 year follow-up):** O-E: 1.28; V: 7.71 **Treatment-related morbidity - fractures (5 year follow-up):** RT-10/86; RT+ 9/85 **Treatment-related morbidity - congestive cardiac failure (5 year follow-up):** RT-3/86; RT+ 3/85	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
UK **Study type** RCT **Aim of the study** To assess whether omission of post-operative radiotherapy in women with 'low-risk' early breast cancer treated by breast conserving surgery and adjuvant endocrine therapy improves quality of life and is more cost-effective **Study dates** Recruited 1999 - 2004 **Source of funding** Health Technology Assessment programme of the National Institute for Health Research	adjuvant endocrine therapy. Medically suitable to attend for all treatments and follow-up. Histologically confirmed unilateral breast cancer of TNM stages T0–2, N0 and M0. No axillary node involvement on histological assessment. Had breast-conserving surgery with complete excision on histological assessment. Able and willing to give informed consent. **Exclusion criteria** Past history of pure in situ			**Treatment-related morbidity - myocardial infarction (5 year follow-up):** RT- 5/86; RT+ 6/85 **Treatment-related morbidity - secondary cancer (5 year follow-up):** RT- 6/86; RT+ 0/85 **Treatment-related morbidity - score ≥10 on HADS anxiety sale (5 year follow-up):** RT- 12/101; 9/105 **Treatment-related morbidity - score ≥10 on HADS depression sale (5 year follow-up):** RT- 3/101; RT+ 1/105 **HRQoL - EQ5D score (5 year**	significant impact: Low **Detection bias** Low for recurrence and survival, High for all other outcomes **Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** Number of outcomes reported in insufficient detail. Relatively short follow-up period. **Other information** PRIME trial

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	carcinoma of either breast or previous or concurrent malignancy within the past 5 years other than non-melanomatous skin cancer or carcinoma in situ of cervix. Grade III cancer with lymphovascular invasion (LVI) (because of a higher risk of local recurrence). **Reported subgroups** All patients: N stage (0), Age (65+), Margins (negative)			**follow-up):** RT-N=83, M=0.77, SD=0.25; RT+ N=85, M=0.79, SD=0.28	

BASO, British Association of Surgical Oncologists; BCS, Breast conservation surgery; CALGB, Cancer and Leukemia Group B; DCIS, ductal carcinoma in situ; DNA, deoxyribonucleic acid; ER, oestrogen receptor; EQ5D, EuroQol Research Foundation measure of general health status; Gy, gray; HADS: Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; IQR, interquartile range; LR, local recurrence; LVI, lymphovascular invasion; NHS, National Health Service; NR, not reported; PR, progesterone receptor; PRIME, Postoperative Radiotherapy in Minimum-Risk Elderly; RCT, randomised controlled trial; RT, radiotherapy; SD, standard deviation; WLE, wide local excision