OVERVIEW ARTICLE

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A Systematic Overview of Radiation Therapy Effects in Breast Cancer

Lars Erik Rutqvist, Carsten Rose and Eva Cavallin-Ståhl

From the Department of Oncology, Huddinge University Hospital, Stockholm (L.E. Rutqvist) and the Department of Oncology, University Hospital, Lund (C. Rose, E. Cavallin-Ståhl), Sweden

Correspondence to: Lars Erik Rutqvist, Department of Oncology, Huddinge University Hospital, SE-118 83 Stockholm, Sweden. E-mail: lars-erik.rutqvist@hs.se

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A systematic review of radiation therapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The procedures for evaluation of the scientific literature are described separately (Acta Oncol 2003; 42: 357–365). This synthesis of the literature on radiation therapy for breast cancer is based on data from 29 randomized trials, 6 meta-analyses and 5 retrospective studies. In total, 40 scientific articles are included, involving 41 204 patients. The results were compared with those of a similar overview from 1996 including 285 982 patients. The conclusions reached can be summarized as follows:

- There is strong evidence for a substantial reduction in locoregional recurrence rate following postmastectomy radiation therapy to the chest wall and the regional nodal areas.
- There is strong evidence that postmastectomy radiation therapy increases the disease-free survival rate.
- There are conflicting data regarding the impact of postmastectomy radiotherapy upon overall survival.
- There is strong evidence that breast cancer specific survival is improved by postmastectomy radiotherapy.
- There is strong evidence for a decrease in non-breast cancer specific survival after postmastectomy radiotherapy.
- There is some evidence that overall survival is increased by optimal postmastectomy radiation therapy.
- There is strong evidence that postmastectomy radiotherapy in addition to surgery and systemic therapy in mainly node-positive patients decreases local recurrence rate and improves survival.
- There is moderate evidence that the decrease in non-breast cancer specific survival is attributed to cardiovascular disease in irradiated patients.
- There are conflicting data whether breast conservation surgery plus radiotherapy is comparable to modified radical mastectomy alone in terms of local recurrence rate.
- There is strong evidence that breast conservation surgery plus radiotherapy is comparable to modified radical mastectomy alone in terms of disease-free survival and overall survival.
- There is strong evidence that postoperative radiotherapy to the breast following breast conservation surgery results in a statistically and clinically significant reduction of ipsilateral breast recurrences followed by diminished need for salvage mastectomies.
- There is strong evidence that the omission of postoperative radiotherapy to the breast following breast conservation surgery has no impact on overall survival. In one meta-analysis including three randomized studies a survival advantage is demonstrated by Bayesian statistics.
- There is strong evidence that the addition of a radiation boost after conventional radiotherapy to the tumour bed after breast conservation surgery significantly decreases the risk of ipsilateral breast recurrences but has no impact on overall survival after short follow-up.
- There is strong evidence for the use of postoperative radiotherapy to the breast following breast conservation surgery for DCIS (ductal breast cancer in situ). Radiotherapy leads to a clinically and statistically significant reduction of both non-invasive and invasive ipsilateral breast recurrences.
- There is insufficient evidence to define the optimal integration of systemic adjuvant therapy and postoperative radiotherapy.
- There are limited data on radiotherapy-related morbidity in breast cancer. No conclusions can be drawn.

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In Sweden, as in other Western countries, breast cancer is the most common malignancy among females, with an estimated lifetime risk of 8–9%. The number of new cases reported from the Swedish Cancer Registry in 2000 was 6 300, which corresponds to 29% of all new cancer cases among females. The median age of afflicted women is about 62 years.

The number of new cases has increased continuously since cancer registration was started in Sweden in the late 1950s. In part the increase is due to an ageing population,

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but there is also an increase in the age-adjusted incidence rate, which probably reflects an increasing population exposure to risk factors such as late age at first full-term pregnancy, late age at menopause, early menarche, obesity, and long-term use of postmenopausal hormone replacement therapy.

Survival has improved continuously over the past decades. Among cases diagnosed during the 1990s the relative survival rate, that is survival with adjustment for the expected mortality in an age-matched general population, at 5 and 10 years is about 85% and 75%, respectively. The most likely explanation for the upward survival trend is a combination of earlier diagnosis, in part due to the introduction of population-based screening during the 1980s and early 1990s, and, since the mid- to late 1980s, improved adjuvant systemic treatment. However, it cannot be ruled out that there is also an increased diagnosis of 'biologically benign' lesions that are impossible to distinguish, with conventional light microscopy, from breast cancers with malignant potential.

This report deals only with radiation therapy of invasive or non-invasive epithelial breast cancers.

Non-invasive breast cancer is often divided into ductal (DCIS) and lobular (LCIS) breast cancer in situ. LCIS is generally regarded as an indicator of an increased risk of invasive breast cancer anywhere in either breast. It is usually not considered to be a local therapeutic problem in its own right so radiation therapy plays no part in the clinical management of patients with LCIS. DCIS may progress into invasive breast cancer. The local recurrence rate after breast-conserving surgery alone for DCIS has been estimated at 25–30% after 5–10 years. About half of the recurrences are invasive. The risk of axillary spread or distant dissemination after local, radical therapy of DCIS is reported to be very low, about 1–2%.

The aim of radiation therapy and surgery is to achieve local control of the disease. The major cause of treatment failure, however, is distant metastases and not uncontrolled local disease. Whether uncontrolled local disease may be the cause of further systemic dissemination has remained controversial for several decades. Once distant disease has become clinically manifest, systemic treatment with a curative intent is not possible. These circumstances have been the impetus for several controlled trials of adjuvant systemic treatment with hormonal agents or cytotoxic chemotherapy. Several individual trials as well as the Oxford overviews of all available trials of systemic adjuvant therapy in early-stage breast cancer have demonstrated convincingly that some types of adjuvant systemic therapy can produce clinically significant improvements in both recurrence-free and overall survival. These studies were evaluated in SBU report 155/2, 2001 (1). Consequently, systemic adjuvant therapy has become the accepted standard for most breast cancer patients.

Surgery is the basic local therapy for nearly all patients with breast cancer although a small proportion of cases are diagnosed at an advanced stage, making radical surgery technically impossible. The effect of radiation therapy is greatest when the tumour burden is small. Higher doses of radiation are required to eradicate palpable breast tumours compared to the doses for subclinical disease. This circumstance is the basis for the common strategy to combine radiation therapy with surgical removal of the primary tumour. Such combined therapy has been basic for the development of breast-conserving surgical techniques, which are associated with high local recurrence rates unless radiation therapy is given to the remaining breast parenchyma.

It should be noted that because of the improvements in systemic adjuvant therapy of early breast cancer, postoperative radiation therapy is today frequently combined with different types of systemic treatment that may interact with the radiation. This has raised questions as to how radiation is best integrated with systemic treatment. It has also been argued that older trials, which did not include systemic treatment, may not be relevant to current medical practice.

The clinical settings where radiation therapy with a curative intent is commonly used in Sweden include postoperative treatment after mastectomy, and postoperative treatment after a breast-conserving procedure. These settings will be dealt with separately in this report. The role of radiation therapy in the management of patients with advanced disease is not included in the present report.

SUMMARY OF THE EARLIER REPORT, SBU 129/2

Conclusions

- Radiotherapy is the most effective method for preventing locoregional recurrence following primary surgery for invasive breast cancer, and radiotherapy is currently more effective than adjuvant chemotherapy after either mastectomy or breast-conserving surgery.
- Radiotherapy in patients at high risk for locoregional recurrence, for example patients with spread to the axillary lymph nodes, leads to a significant increase in relapse-free survival. Meta-analyses have shown that radiotherapy in theses subgroups of patients can reduce the risk for distant metastasis and reduce the risk for cancer death. These analyses have not statistically confirmed an improvement in total survival, probably because reduced mortality from breast cancer has been offset by increased mortality from cardiovascular disease. However, the results have improved successively, and survival gains are significantly greater in recent studies using modern treatment methods. It is probable that survival gains from radiotherapy do not exceed

those that can be achieved by other adjuvant treatment of breast cancer, such as chemotherapy or hormones; that is a reduction in mortality by 20–30%, leading to an increased total survival after, for example, 10 years of 5–10%.
- The heart is the most important organ at risk during radiotherapy for breast cancer. Minimizing radiation doses to the heart muscle and the coronary arteries is necessary for avoiding later effects of ischaemic cardiovascular disease. These side effects were particularly prominent in early treatment studies that used older radiotherapy methods.
- Radiotherapy in conjunction with breast-conserving surgery for invasive breast cancer significantly reduces the recurrence frequency in the breast. Clinical studies are under way that aim at further defining the role of radiotherapy as an element in a breast-conserving treatment strategy, for example determining the value of boost, and identifying prognostic/predictive factors for breast recurrence. Improved knowledge about such factors should eventually permit identification of patient groups at such low risk for breast recurrence that routine radiotherapy is unnecessary, or at such high risk—even with radiotherapy—that alternatives to breast-conserving surgery should be considered.
- Radiotherapy also reduces the risk for recurrence in the breast following breast-conserving surgery of DCIS. Controlled trials are under way that aim at more closely defining the roles of surgical methods and radiotherapy for various subgroups of patients, for example regarding different histopathological types of DCIS.
- Radiotherapy has a substantial palliative value to patients who cannot be cured. It can reduce, prevent or delay unpleasant symptoms from advanced disease; for example pain, cancer lesions, fractures, neurological symptoms, etc.

Discussion

The literature on radiation treatment of breast cancer is extensive. It is generally accepted that randomized trials provide the most reliable evidence of treatment effects. A considerable number of controlled clinical trials have been conducted over the years on radiation therapy for breast cancer. These trials date back to the late 1940s. Indeed, postmastectomy radiation therapy was the first local treatment for cancer to be tested in a randomized trial setting. The large number of randomized trials was the rationale for focusing the report on the results of such trials. The conclusions in the previous report were, in fact, based on evidence from large, unconfounded, randomized trials that are relevant to the clinical settings in which radiation therapy for breast cancer is commonly used in Sweden. Results based on retrospective evaluations of uncontrolled case series were generally not considered, particularly not on conclusions regarding treatment efficacy.

However, a drawback with the large number of trials was that many of them were conducted several decades ago and consequently used treatment techniques that are no longer relevant to medical practice. One can only speculate what the results of these trials would have been if more modern techniques had been available at the time. In addition, many of the trials were conducted prior to the era of adjuvant systemic therapy. It could be argued that more attention should be given to recent trials that have integrated radiation therapy with systemic treatment, and that have used more modern radiation therapy techniques.

Literature

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows (number of studies/number of patients)

	1 = High	2 = Moderate	3 = Low	Total
M	1/74 652	4/27 000	–	5/101 652
C	20/24 120	12/7 7309	6/2 183	38/33 612
P	–	–	–	–
R	17/247 945	9/2 964	1/1 461	27/252 370
L	16	5	–	21
O	3	3	–	6
Total	57/272 065	33/10 273	7/3 644	97/285 982

M = meta-analysis; C = controlled clinical trial; P = prospective trial; R = retrospective study; L = literature review; O = other studies.

ASSESSMENT OF NEW LITERATURE

Search methods and selection

A computerized literature search was conducted in Medline for papers published from 1994 to 2001 of controlled clinical trials or meta-analyses of trials of radiotherapy for breast cancer. The search yielded 175 articles. For evaluating treatment efficacy only randomized trials were further reviewed and included in this report. For the evaluation of side effects of treatment a few cohort studies with non-randomized controls were also used.

Thus 42 articles were retrieved that fulfilled these selection criteria. Reasons for exclusion of articles were

- not randomized trials
- not addressing effects or side effects of radiation of breast cancer
- data already included in the previous SBU report 129/2.

Overview 1

Breast cancer. Radiotherapy after modified radical mastectomy

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results				Conclusion/comments
Schmoor 2000 (7) GBCSG C	Benefit of postop. RT A: RT 2 Gy/fr to 44–50 Gy/ 4.5–5 weeks+CHT B: CHT alone	1984–1989 Pre- and postmenopausal pts T1–4, N+ A 98 pts B 101 pts	Follow-up median 9 years A B	LRR% 6 16 p = 0.03	EFS% 47 55 ns	OS% 46 48 ns	Small trial, inadequate power. C3
Olson 1997 (3), ECOG C	Benefit of postop. RT in LABC A: CHT+HT+RT 2 Gy/fr to 46 Gy/4.5 weeks B: CHT+HT alone	1982–1987 T1–2 with fixation, T3 N1–2, T4 A 164 pts B 148 pts	Follow-up median 9 years A B	EFS% 40 44 ns	OS% 46 47 ns		Small trial, inadequate power. C2
Overgaard 1997 (4), DBCG C Update of DBCG trial 82b	Benefit of postop. RT A: RT 2 Gy/fr, 25 fr to 50 Gy/5 weeks+CHT B: CHT alone (At one centre RT was given with 2.1 Gy/fr, 22 fr to 46 Gy)	1982–1989 Premenopausal high-risk pts T > 5 cm, N0; T1–4, N+ A 856 pts B 852 pts	Follow-up median 9.5 years A B	LRR% 9 32 p < 0.001	DFS% 48 34 p < 0.001	OS% 54 45 p < 0.001	Large trial. Possibly suboptimal systemic therapy and surgery. Multivariate analysis showed significantly improved OS and DFS irrespective of tumour size, number of involved nodes, histopathology grade. C1
Overgaard 1999 (5) C Update of DBCG trial 82c	Benefit of postop. RT A: RT as in Ref. (4)+TAM B: TAM alone	1982–1990 Postmenopausal high-risk pts (4) A 686 pts B 689 pts	Follow-up median 10 years A B	LRR% 8 35 p < 0.001	DFS% 36 24 p < 0.001	OS% 46 36 p < 0.003	Large trial. Systemic therapy with TAM given for only 1 year. Surgery possibly suboptimal. C1
Ragaz 1997 (6) C	Benefit of postop. RT A: RT 2 Gy/fr to 35–37.5 Gy/3–4 weeks+CHT B: CHT alone	1979–1986 Premenopausal pts T1–4, N+ A 164 pts B 154 pts	Follow-up median 9 years A B	LRR% 13 33 p < 0.003	DFS% 50 33 p < 0.007	OS% 54 46 ns	Small trial. C2
Houghton 1994 (2), CRC C	Benefit of postop. RT A: RT[1] B: No adjuvant therapy	1970–1975 st I–II (76% st I) < 70 years old A 1 376 pts B 1 425 pts	A vs. B Local relapse Survival Death after 5 years All pts Left-side cancer Right-side cancer	RR 0.44 1.01 1.5 1.92 1.19	95% CI 0.39–0.51 ns 1.01–2.29 1.09–3.39 ns	Large trial but outdated RT techniques (e.g. orthovoltage). Higher frequency of cardiac-related deaths in left-sided breast cancer treated with orthovoltage. Increased incidence of secondary malignancy in group A. C2	

Abbreviations: CHT = chemotherapy; CI = confidence interval; CRC = Cancer Research Campaign; DBCG = Danish Breast Cancer Group; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; fr = fraction; GBCSG = German Breast Cancer Study Group; HT = hormonal therapy; LABC = locally advanced breast cancer; LRR = local relapse rate; ns = not significant; OS = overall survival; pts = patient(s); RR = relative risk; RT = radiotherapy; TAM = tamoxifen.CHT Ref. (7): CMF (cyclophosphamide, methotrexate, 5-fluorouracil), modified, 6 months.
CHT Ref. (3): cyclophosphamide+doxorubicin; HT = tamoxifen+fluoxymesterone.
CHT Ref. (4): CMF i.v., modified (4-week interval), 7–8 months.
CHT Ref. (6): CMF i.v., 6–12 months.
[1]Variation in RT technique, for details see Refs (45, 46).

OVERVIEW OF NEW STUDIES

Radiotherapy after mastectomy

See Overviews 1 and 2 for a description of the trials, trial results and conclusions. Whether the addition of postoperative radiotherapy to mastectomy can reduce local recurrence rate and increase disease-free and overall survival has been analysed in six randomized studies (2–7) and five meta-analyses (8–12). The data from the randomized trials are included in the largest meta-analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (9) in which the results were analysed on the basis of individual patient data. In the meta-analyses, most of the patients were treated with either simple mastectomy or radical modified mastectomy and a minority with breast-conserving surgery. The radiation techniques used in the randomized trials were reported as being of reasonable technical quality except for one study where the radiotherapy was outdated (2). The question of optimal radiation therapy technique was further elucidated in an exploratory meta-analysis (11). Furthermore, the differential effect of radiation therapy on breast cancer specific and non-breast

Overview 2

Breast cancer. Postoperative radiotherapy in early breast cancer, meta-analyses

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Cuzick 1994 (8) M Update of Ref. (47)	Long-term cause specific mortality, after > 10 years survival A: SM or RM + RT B: Same surgery alone RT: Mainly orthovoltage or ^{60}Co Doses: 18–54 Gy/10–30 fr	1949–1979 8 trials Stage I–II The analysis includes only pts with > 10 years survival: SM: 2 502 out of 4 579 pts RM: 1 807 out of 3 362 pts	Overall mortality at 10 years (after > 10 years survival): 7% difference in favour of group B, ns Group A: RR for cardiac death: 1.62 (CI 1.25–2.1, p < 0.001) RR for breast cancer death: SM 0.77 (CI 0.61–0.97, p = 0.03) RM 1.08 ns	Results difficult to translate to current radiation techniques. M2
EBCTCG 1995 (9) M	Role of postoperative RT in early breast cancer 2 analyses performed: 1. A: Surgery + RT B: Same surgery alone 2. A: Mastectomy B: BCS + RT RT: 25–65 Gy/10–30 fr	1962–1984 Stage I–II 1. 36 trials 17 273 pts 2. 9 trials 4 891 pts	Mortality % at 10 y: 1. A 40.3 (BCM) 0.94 (non-BCM); B 41.4 (CI 0.88–1.00) (CI 1.09–1.42); 2. A 22.9; B 22.9. Cause specific mortality not reported	Comprehensive overview of all available trials. Decrease of breast cancer deaths and increase of intercurrent (mainly vascular) deaths. In analysis 1 LRR significantly decreased in irradiated pts. M
EBCTCG 2000 (10) M Update and extension of Ref. (9)	Role of RT in stage I–II breast cancer A: Surgery + RT B: Same surgery alone Surgery: MRM or BCS	Trials before 1990 40 trials Stage I–II 19 582 pts	Mortality%: A 49.9; B 51.2; p = 0.06. BCSS% at 20 years: A 53.4; B 48.6; p = 0.0001. NBCSS% at 20 years: A 69.5; B 73.8; p = 0.0003. LRR at 10 years was 8.8% in group A and 27.2% in group B (p < 0.00001)	Authors' conclusion: RT regimens able to produce the two-thirds reduction in LRR seen in these trials, but without long-term hazard, would be expected to produce an absolute increase in 20-year OS of about 2–4% (except for women at particularly low risk of LRR). The average hazard seen in these trials would, however, reduce this 20-year OS benefit in young women and reverse it in older women. M1
Van de Steene 2000 (11) M Extended analysis of Ref. (9)	Role of RT in stage I–II breast cancer In-depth analysis of trials reported in Ref. (9). Trial characteristics such as small vs. large, old vs. recent, etc. analysed.	36 trials on surgery + RT vs. same surgery alone 17 273 pts (9)	Factors significantly increasing the benefit of RT: – recent trial – large trial – use of standard fractionation – overall good prognosis pts included	Exploratory meta-analysis. In recent large trials with optimal RT technique, the survival is increased. M1
Whelan 2000 (12) M	Additional value of RT in pts given ST A: Surgery + ST + RT B: Same surgery and ST alone Surgery mainly MRM	1973–1984 18 trials Majority of pts N + 6 367 pts	Follow-up 7.7–14.5 years. OR (95% CI) A vs. B: Death 0.83 (0.74–0.94); LRR 0.25 (0.19–0.34). In multivariate analysis timing and RT technique identified as predictive factors for survival: benefit of radiation if started within 6 months, megavoltage better than orthovoltage	Reduction of LRR translated into decreased mortality in pts given ST. M1

cancer specific mortality was addressed thoroughly in the two overviews from the EBCTCG (9, 10). In an analysis of three randomized trials (the Uppsala–Örebro, Ontario, National Surgical Adjuvant Breast and Bowel Project B-06) (NSABP), Levitt et al. (13, 14) observed that most of the trials showed some overall survival benefit for patients allocated to radiation therapy, although this difference was not significant. In a further analysis using Bayesian statistics they pooled the data of these three trials in a meta-analysis and demonstrated a 9.6% relative reduction in the annual mortality in favour of the irradiated patients. (This meta-analysis is not shown in Overview 2.)

Overview 3

Breast cancer. Radiotherapy in breast conservation surgery

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Arriagada 1996 (15) Update of Refs (48, 49) C	BCS+RT vs. MRM A: BCS+RT 2.5 Gy/fr, 4 fr/week to 45 Gy+boost 15 Gy/5 fr/10 days B: MRM BCS = lumpectomy	1972–1979 Pre- and postmenopausal pts T ≤ 2 cm, N0–N+ A 88 pts B 91 pts	Follow-up 15 years LRR% DM% OS% A 13 27 73 B 18 34 65 ns ns ns	Small trial. No difference in LRR or OS. C3
Jacobson 1995 (17)C	BCS+RT vs. MRM A: BCS+RT 1.8 Gy/fr to 45–50.4 Gy+boost (^{192}Ir or EBRT) 15–20 Gy B: MRM BCS = lumpectomy N+ premenopausal pts received CHT, 6–12 months 1985–1987: postmenopausal pts received TAM, 5 years	1979–1987 Pre- and postmenopausal pts T1–2, N0–N1 A 121 pts B 116 pts	Follow-up median 10 years LRR% DFS% OS% A 4 72 77 B 4 69 75 ns ns	Small trial. Low frequency of LRR. No difference between groups. C2
Lee 1997 (18) C	BCS+RT vs. MRM A: BCS+RT 1.8–2.0 Gy/fr to 44–50 Gy+boost 10–20 Gy B: MRM BCS = lumpectomy Systemic therapy (CHT or TAM) given to a majority of pts in both groups	1991–1994 T1–2, N0–N+ A 76 pts B 111 pts	Follow-up median 38 months LRR% DFS% OS% A 3 94 94 B 2 89 94 ns ns	Small trial. Gross imbalance in number of pts, proportion of T-stages, nodal involvement in the two groups. C3
Van Dongen 2000 (19) C	BCS+RT vs. MRM A: BCS+RT 2 Gy/fr to 50 Gy+^{192}Ir boost to 25 Gy B: MRM Systemic therapy was given in both groups: pts < 55 years: CMF × 6 pts > 55 years: HT at the discretion of each centre BCS = lumpectomy	1980–1986 Pre- and postmenopausal pts T1–2, N0–N+ A 448 pts B 420 pts	Follow-up median 13.5 years LRR% DMFS% OS% A 20 61 65 B 12 66 66 p = 0.01 ns ns	Large trial. Significantly higher local recurrence rate in pts with BCS (group A). No survival impact. C1
Fisher 1995 (16) Update of Refs (50, 51) C	Value of RT after BCS; BCS+RT vs. MRM A: BCS B: BCS+RT 50–53 Gy/5 weeks C: MRM BCS = lumpectomy	1976–1984 Pre- and postmenopausal pts T < 4 cm, N0–N+ A 719 pts B 731 pts C 713 pts	Follow-up ≥ 10 years LRR% DFS% OS% A 35 NR 60 B 10 50 62 C NR NR 62 A vs. B p < 0.001 ns ns	Large trial. Significant decrease in breast recurrences with RT after BCS. C1
Liljegren 1999 (22) C Update of Ref. (21)	Value of RT after BCS A: BCS+RT 2 Gy/fr to 54 Gy B: BCS BCS = sector resection	1981–1988 Pre- and postmenopausal pts age < 80 years T < 2 cm, N0 A 184 pts B 197 pts	Follow-up median 7–8 years LRR% OS% A 8.5 77.5 B 24 78 p < 0.0001 ns	Pts with low-risk breast cancer. Increased LRR in not irradiated group but no impact on OS. C1
Clark 1996 (20) C Update of Refs (44, 52)	Value of RT after BCS A: BCS+RT 2.5 Gy/fr to 40 Gy+boost 12.5 Gy/5 fr B: BCS BCS = lumpectomy	1984–1989 Pre- and postmenopausal pts T < 4 cm, N0 A 416 pts B 421 pts	Follow-up median 7.6 years LRR% RFS% OS% A 11 51 79 B 35 70 76 p < 0.0001 NR ns	Large trial. Pts with relative low-risk breast cancer. The increased LRR in not irradiated group had no impact on OS. C1
Renton 1996 (23)C	Value of RT after BCS A: BCS+RT (details NR) B: BCS Systemic therapy was given to ER+pts with TAM, 5 years; to ER– pts classic CMF × 6; BCS = wide local excision	1981–1990 Pre- and postmenopausal pts T1–2, N0–1 A 208 pts B 210 pts	Minimum follow-up 5 years LRR% A 13 B 35 NR	For detail of RT the authors refer to a paper in press, which could not be identified. Figures on OS not reported. C1

Overview 3 (*Continued*)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Veronesi 2001 (24) Milan III C	Value of RT after BCS A: BCS+RT 2 Gy/fr to 50 Gy+ boost 10 Gy/5 fr B: BCS BCS = quadrantectomy Systemic treatment given to N+ pts: premenopausal CMF postmenopausal TAM	1987–1989 Pre- and postmenopausal pts T < 2.5 cm, N0–N+ A 299 pts B 280 pts	Follow-up median 109 months Act. LRR% OS% at 10 y A 5.8 82.4 B 23.5 76.9 p = 0.001 p = 0.33 No difference in frequency of contralateral breast cancer	Subgroup analysis of node-positive pts showed a significantly improved OS in irradiated group (p = 0.04). The benefit of radiation with respect to LRR diminished with increasing age. C1
Magee 1996 (25) C	Optimal RT target volume A: BCS+RT wide field, 40 Gy, 15 fr/3 weeks B: BCS+RT limited field, 40–42.5 Gy, 8 fr/2 weeks BCS = lumpectomy Wide field = breast+regional lymph nodes Limited fields = tumour bed	1982–1987 Pre- and postmenopausal pts T1–2, cN0 A 355 pts B 353 pts	Follow-up median 8 y Relapse rate,% OS% in breast in nodes A 13 12 72 B 25 24 73 p = 0.0001 p = 0.00005 ns	Large trial. No axillary exploration was performed. C1

Abbreviations: BCS = breast conservation surgery; CHT = chemotherapy; cN0 = clinically node negative; DFS = disease-free survival; DM = distant metastasis; DMFS = distant metastasis-free survival; EBRT = external beam radiotherapy; HT = hormonal therapy; LRR = local relapse rate; MRM = modified radical mastectomy; NR = not reported; ns = not significant; OS = overall survival; pts = patient(s); RT = radiotherapy; TAM = tamoxifen.
CHT Ref. (17): doxorubicin, cyclophosphamide.

The literature shows that:

- Postmastectomy radiation therapy provides a substantial reduction in the locoregional failure rate and improves disease-free survival.
- Postmastectomy radiation therapy reduces mortality due to breast cancer in subsets of patients. In one meta-analysis, however, using Bayesian statistics, a reduction in overall mortality was also demonstrated.
- There is an added value of radiotherapy in terms of decreased overall mortality in patients given adjuvant systemic therapy.
- Postmastectomy radiotherapy might cause adverse cardiovascular effects. However, these adverse effects might be attributed to the radiation technique.
- There is insufficient knowledge on how different treatment volumes affect recurrence-free and overall survival.

Radiotherapy in breast-conservation surgery

See Overview 3 for a description of the trials, trial research and conclusions. Breast-conserving surgery and radiotherapy have been evaluated against modified radical mastectomy in five randomized trials (15–19) and in one meta-analysis (9) (Overview 2). Breast-conserving surgery plus radiotherapy has been evaluated in five randomized trials (16, 20–24). Whether the target volume for optimal radiotherapy should be wide or limited field has been the subject for one randomized study (25). The majority of these trials are large and conclusive.

The literature shows that:

- Breast-conserving surgery plus radiation therapy is comparable to modified radical mastectomy alone in terms of local recurrence-free survival and overall survival.
- Postoperative radiation therapy to the breast following breast-conserving surgery results in a statistically and clinically significant reduction in ipsilateral breast recurrences and a reduced need for salvage mastectomies.

Effect of supplementary radiation (boost, internal mammary chain radiation (IMC))

See Overview 4 for a description of the trials, trial research and conclusions. The role of radiation boost after breast conservation surgery has been addressed in two randomized studies (26, 27). The impact of radiation therapy to IMC is investigated in a small randomized trial comparing breast conservation surgery plus radiotherapy plus inclusion of IMC in the target volume (28).

The literature shows that:

- The addition of radiation boost gives a small but significant reduction in local recurrence rate without any impact on survival after a relatively short follow-up period.
- The importance of inclusion of the internal mammary chain in the target volume has not been adequately evaluated.

Overview 4

Breast cancer. Effect of supplementary radiation (boost, internal mammary chain radiation, IMC)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Bartelink 2001 (26) C	Role of RT boost after BCS A: BCS+RT 50 Gy/25 fr/5 weeks+boost 16 Gy/8 fr B: BCS+RT as A BCS = lumpectomy Systemic therapy: Premenopausal N+ CHT Postmenopausal N+ TAM	1989–1996 Pre- and postmenopausal pts T1–3, N0–N2 5 318/5 569 analysed; 251 pts excluded due to non-radical surgery A 2 661 pts B 2 657 pts	Median follow-up 5.1 years Act LRR% at 5 years A 4.3 (3.8–4.7) B 7.3 (6.8–7.6) $p < 0.001$ OS similar in the two groups	Large trial. Reduction in LRR, especially in pts < 50 years. C1
Romestaing 1997 (27) C	Role of RT boost after BCS A: BCS+RT 50 Gy/20 fr/4 weeks+boost 10 Gy/4 fr B: BCS+RT as A BCS = lumpectomy or quadrantectomy Premenopausal N+CHT Postmenopausal N+TAM	1986–1992 Pre- and postmenopausal pts T < 93 cm, N0–N1 98% with free margins after BCS A 521 pts B 503 pts	Median follow-up 3.3 years Act LRR% OS% at 5 years A 3.6 92.9 B 4.5 90.4 $p = 0.044$ ns	Large trial. Short follow-up. Significant reduction in LRR. No difference in cosmetic outcome. C1
Kaija 1995 (28) C	Side effects of RT to IMC A: BCS+RT including IMC in the target volume B: BCS+RT BCS = segment resection RT: 3 different dose levels were used: 50 Gy+boost 10 Gy (71 pts), 54 Gy (44 pts) and 50 Gy (148 pts)	1989–1991 Pre- and postmenopausal pts St I–II 263/270 pts analysed A 131 pts B 132 pts Systemic therapy was given to 9% in group A and 7% in group B	Median follow-up 2.7 years No serious acute or late side effects and no significant difference between groups. No significant difference in LRR	Small trial. Short follow-up. No conclusion possible regarding effect or toxicity. C3

Abbreviations: BCS = breast-conserving surgery; CHT = chemotherapy; fr = fraction(s); HR = hazard ratio; IMC = internal mammary chain radiation; LR = local relapse; LRF = local relapse-free; LRR = local relapse rate; N+ = positive lymph nodes; ns = not significant; OS = overall survival; pts = patient(s); RT = radiotherapy; TAM = tamoxifen.

Radiation therapy and breast conservation surgery for ductal carcinoma in situ (DCIS)

See Overview 5 for a description of the trials, trial results and conclusions. Breast conservation surgery plus radiotherapy for DCIS has been investigated in two large randomized trials (29, 30).

The literature shows that:

- The use of postoperative radiotherapy to the breast following breast conservation surgery for DCIS results in a clinically and statistically significant reduction in both non-invasive and invasive ipsilateral breast recurrences.
- There is no difference in overall survival.
- There are conflicting data regarding contralateral breast cancer as a consequence of the addition of radiotherapy.

Timing of radiotherapy and systemic therapy

See Overview 6 for a description of the trials, trial results and conclusions. The addition of radiation therapy to breast conservation surgery after shorter or longer systemic therapy have been addressed in one randomized study (31). In one study, radiotherapy was given concomitantly or after four courses of chemotherapy in patients with breast conservation therapy (32). Both trials are small.

The literature shows that:

- No conclusion regarding timing of chemotherapy and radiotherapy can be drawn.

Late morbidity in relation to radiation for breast cancer

See Overview 7 for a description of the trials, trial results and conclusions. This is a compilation of 11 trials, 4 randomized trials (33–36) and 7 retrospective studies (37–43). The majority of the trials are relatively small or the trial designs are such that conclusions cannot be drawn. Various aspects of cardiac morbidity are addressed in four trials (34, 35, 38, 41).

The literature shows that:

- Cardiac events were more frequent among women irradiated because of left-sided tumours than right-sided tumours.

Overview 5

Breast cancer. Radiotherapy in ductal carcinoma in situ (DCIS)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Julien 2000 (30) C	Role of RT after BCS for DCIS A: BCS+RT 50 Gy/25 fr/5 weeks B: BCS alone BCS = complete surgical excision (7 pts operated on3 times!)	1986–1996 DCIS < 5 cm 1 002/1 010 pts analysed A 502 pts B 500 pts	Median follow-up 4.25 years Act LRF% HR OS% A 94 0.62 99 B 84 99 p = 0.005 Type of LR: DCIS% Invasive cancer% A 95 96 B 92 92 p = 0.06 p = 0.04	Overall significant reduction in LR after RT. Significant reduction in invasive relapses. Significant increase in contralateral breast cancer in RT group. C1
Fisher 1998 (29) C	Role of RT after BCS for DCIS A: BCS+RT 50 Gy/25 fr/5 weeks (9% received a boost) B: BCS alone	1985–990 Pre- and post-menopausal pts All pts had tumour-free margins after BCS 814/818 pts included in analysis A 411 pts B 403 pts	Median follow-up 7.5 years Act LRR% overall LRR% non-invasive ca LRR% at 8 y invasive ca A 12.1 8.2 3.9 B 26.8 13.4 13.4 p = 0.000005 p = 0.007 p = 0.000005 No difference in incidence of contralateral breast cancer between groups. No difference in OS	Large trial. Substantial reduction in LRR in irradiated groups. C1

BCS = breast-conserving surgery; DCIS = ductal carcinoma in situ; fr = fraction(s); HR = hazard ratio; LR = local relapse; LRF = local relapse-free; LRR = local relapse rate; OS = overall survival; pts = patient(s); RT = radiotherapy.

- Radiotherapy leads to an increased proportion of patients with lung fibrosis and might lead to an increased number of patients with lymphoedema.
- The results regarding cosmesis in patients treated with breast conservation surgery show little impact on cosmesis with additional radiotherapy.
- The addition of radiation boost to breast conservation surgery and radiotherapy has a clinically small but statistically significant adverse effect on the cosmetic result.

LITERATURE

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients)[1]

	1 = High	2 = Moderate	3 = Low	Total
M	4/27 240 (65 386)	2/2 442 (7 556)	–	6/29 682
C	15/9 455 (16 656)	8/529 (4 958)	6/629 (2 019)	29/10 613
R		3/909 (3 369)	2/– (842)	5/909
Total	19/36 695	13/3 880	8/629	40/41 204

[1]In the figures within parentheses all patients reported in the individual articles are counted. Many patients are reported in more than one article (2–4) and the figures without parentheses indicate number of patients only counted once.

CONCLUSIONS AND COMMENTS

- There is strong evidence for a substantial reduction in locoregional recurrence rate following postmastectomy radiation therapy to the chest wall and the regional nodal areas ((10) M1).
- There is strong evidence that postmastectomy radiation therapy increases the disease-free survival rate (pro (4) C1, (5) C1, (6) C2; con (3) C2, (7) C3).
- There are conflicting data regarding the impact of postmastectomy radiotherapy upon overall survival (pro (12) M1; con (10) M1, (8) M2).
- There is strong evidence that breast cancer specific survival is improved by postmastectomy radiotherapy ((10) M1).
- There is strong evidence for a decrease in non-breast cancer specific survival after postmastectomy radiotherapy ((10) M1, (8) M2).
- There is some evidence that overall survival is increased by optimal postmastectomy radiation therapy ((11) M1).
- There is strong evidence that postmastectomy radiotherapy in addition to surgery and systemic therapy in mainly node-positive patients decreases local recurrence rate and improves survival ((12) M1).

Overview 6

Breast cancer. Timing of radiotherapy and systemic therapy

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results				Conclusion/comments
Wallgren 1996 (31) C	Role of RT after shorter or longer ST Study 1. Premenopause A: BCS+CMF × 6+RT* (= RT started 7 months after BCS) B: BCS+CMF × 3+RT* (= RT started 4 months after BCS) Study 2. Postmenopause A: BCS+TAM+RT* (= RT started 2 months after BCS) B: BCS+TAM+CMF × 3+RT* (= RT started 4 months after BCS) *pts then randomized to ± CMF × 3, one course every third month RT: 45–50 Gy/5 weeks	1986–1993 St II N+ Premenopause: A 220 pts B 213 pts Postmenopause: A 146 pts B 139 pts	Median follow-up 48 months Premenopause: Postmenopause:		LRF% 9 8 ns 3 6 ns	OS% 84 90 ns 89 89 ns	Subgroup analysis of pts treated with BCS+RT included in two larger studies (IBCSG VI, VII). Low power. No conclusion can be drawn concerning timing of RT. C2
Recht 1996 (32) C	Timing of radiotherapy and chemotherapy A: BCS+CHT × 4 (= 12 weeks)+RT B: BCS+RT+CHT × 4 RT: 45 Gy/25 fr+boost 16–18 Gy CHT: CMF+doxorubicin+prednisone/3-week interval	1984–1992 Premenopausal 75% St I, II; N0–N+ A 122 pts B 122 pts	Median follow-up 58 months Act A B		LRR% 14 5 ns	DMF% 75 64 p = 0.05	OS% 81 73 ns	Early CHT might reduce risk for distant recurrence. Small study. C2

Abbreviations: BCS = breast-conserving surgery; CHT = chemotherapy; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; DMF = distant metastasis free; IBCSG = International Breast Cancer Study Group; fr = fraction(s); LFR = local failure free; LRR = local relapse rate; OS = overall survival; pts = patient(s); RT = radiotherapy; ST = systemic therapy; TAM = tamoxifen.

- There is moderate evidence that the decrease in non-breast cancer specific survival is attributed to cardiovascular disease in irradiated patients ((9) M1, (8) M2, (34) C3).
- There are conflicting data whether breast conservation surgery plus radiotherapy is comparable to modified radical mastectomy alone in terms of local recurrence rate. (pro (16) C1, (17) C2, (18) C3, (15) C3; con (19) C1).
- There is strong evidence that breast conservation surgery plus radiotherapy is comparable to modified radical mastectomy alone in terms of disease-free survival and overall survival ((16) C1, (19) C1).
- There is strong evidence that postoperative radiotherapy to the breast following breast conservation surgery results in a statistically and clinically significant reduction in ipsilateral breast recurrences followed by diminished need for salvage mastectomies ((16) C1, (19) C1, (17) C2, (15) C3, (18) C3, (24) C1).
- There is strong evidence that the omission of postoperative radiotherapy to the breast following breast conservation surgery has no impact on overall survival. In one meta-analysis ((13) M2) including three randomized studies ((21), (44), (16)) a survival advantage is demonstrated by Bayesian statistics ((10) M1, (20) C1, (16) C1, (21) C1, (22) C1, (23) C1, (24) C1).
- There is strong evidence that the addition of a radiation boost after conventional radiotherapy to the tumour bed after breast conservation surgery significantly decreases the risk of ipsilateral breast recurrences but has no impact on overall survival after short follow-up ((26) C1, (27) C1).
- There is strong evidence for the use of postoperative radiotherapy to the breast following breast conservation surgery for DCIS. Radiotherapy leads to a clinically and statistically significant reduction in both non-invasive and invasive ipsilateral breast recurrences ((29) C1, (30) C1).
- There is insufficient evidence to define the optimal integration of systemic adjuvant therapy and postoperative radiotherapy ((32) C2, (31) C2).
- There are limited data on radiotherapy-related morbidity in breast cancer. No conclusions can be drawn ((33)

Overview 7

Breast cancer. Late morbidity in relation to radiation for breast cancer

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Höjris 2000 (39) R Extended analysis of Refs (4, 5), Overview 1	Radiotherapy-related morbidity A: MRM+RT B: MRM	Analysis of pts treated at a single centre, participating in randomized trials (DBCG 82 b, c) ((4, 5), Overview 1) Pts in continuous CR high risk, age < 70 years A 42 pts B 42 pts	Median follow-up 9 years Lymph-oedema %: A 14, B 3 Impaired shoulder mobility %: A 50, B 15, p = 0.01 Lung fibrosis %: A 60, B 8, p < 0.01 No difference in lung symptoms	R2
Liljegren 1997 (36) C Extended analysis of Refs (21, 22), Overview 3	Arm morbidity after radiotherapy A: BCS+RT B: BCS For details see Refs (21, 22), Overview 3	Pts from refs (21, 22), Overview 3, analysed A 184 pts B 197 pts	Arm morbidity %: 3–12 months: A 36, B 42; 13–36 months: A 25, B 23, ns; > 36 months: A 23, B 16 Arm morbidity: pain, numbness, oedema, impaired mobility Risk factors for arm morbidity: number of lymph nodes removed; age < 65 years; employment	The low arm morbidity might be attributed to low RT dose to the axilla C1
Bentzen 1996 (37) R	Lung fibrosis in pts treated with TAM and RT A: RT 1978–1980: 36.6 Gy/12 fr, 4 fr/week RT 1981–1982: 41 Gy/22 fr, 4 fr/week B: RT as A+TAM 30 mg/day, 1 year RT: 8 MeV photons to supraclavicular fossa electrons to chestwall	1978–1982 Analysed pts included in DBCG 77c trial T ≥ 5 cm or N+ A 46 pts B 38 pts Standardized estimation of lung density in apex of irradiated lung	Relative risk for lung fibrosis in group B 2.0 Sign correlation between RT dose and lung fibrosis	Small study R2
Curran 1998 (33) C Extended analysis of Ref. (19), Overview 3	QoL and cosmesis after MRM or BCS+RT A: BSC+RT B: MRM For details see Ref. (19), Overview 3	1980–1986 A 151 pts B 127 pts (see Ref (19), Overview 3) Only a fraction of centres participated in QoL evaluation	Parameter evaluated: Body image: group B significantly better, p = 0.001 Fear of relapse: no difference group A vs. group B Satisfaction with treatment: group B significantly better, p = 0.001 Prognostic factors for worse cosmetic outcome: postmenopausal status and wide excision.	C2
Whelan 2000 (43) C Extended analysis of Ref. (20), Overview 3	QoL and cosmesis after BCS+RT A: BCS+RT B: BCS For details see Ref. (20), Overview 3	1984–1989 A 344 pts B 376 pts QoL data at 2 months available in 90% of pts Data on physical symptoms at 2 years available in 75% of pts QoL instrument: BCQ (higher score = better QoL)	At 2 months after treatment. BCQ score significantly higher in group B, p = 0.0001. At 2 years no difference in skin irritation, breast pains or appearance of treated breast.	Long-term QoL: method used not validated. 'Acute' QoL not surprisingly related to RT. C2
Vrieling 1999 (42) R Extended analysis of Ref. (26), Overview 4	RT boost and cosmesis A: BCS+RT+boost 16 Gy B: BCS+RT For details see ref. (26), Overview 4	1989–1996 Photographic scoring A 364 pts B 367 pts Digitized scoring A 1 621 pts B 1 580 pts	Follow-up 3 years Photographic scoring—global result: A 71% good to excellent result B 86% good to excellent result Digitized scoring: more breast retraction in boost group, p = 0.04	Boost of 16 Gy has adverse effects on the cosmetic result. R2

Overview 7 (*Continued*)

Author Year (Ref. no.) Design	Aim/study question	Patient population	Results	Conclusion/comments
Liljegren 1997 (40) C Extended analysis of Refs (21, 22), Overview 3	Cost and cost-effectiveness of postop. RT after BCS A: BCS+RT B: BCS For details see Refs (21, 22), Overview 3	1981–1988 The analysis comprises 381 pts For details see Refs (21, 22), Overview 3	Cost of one avoided local relapse at 5 years in irradiated group: 338 000 SEK. Cost per gained quality adjusted life year (QUALY) was estimated to be 0.2–3.9 million SEK!	The large range of calculated costs for one QUALY reflects the difficulty in performing health economic analyses. Cost and quality measure of treatments difficult to put into perspective. C1
Gyenes 1998 (34) C Extended analysis of Ref. (53)	Risk of cardiac morbidity and mortality A: MRM B: preop. RT (^{60}CO)+MRM C: MRM+postop. RT (electrons) RT dose 45 Gy/1.8 Gy/fr, 5 fr/week	1971–1976 Pre- and postmenopausal A 321 pts B 316 pts C 323 pts Three dose volumes were estimated: Low-dose volume = right-side breast cancer, irradiated with ^{60}CO or electrons Medium-dose volume = left-side breast cancer irradiated with electrons High-dose volume = left-side breast cancer, irradiated with ^{60}CO	Median follow-up 20 years HR of death due to cardiovascular disease Low-dose volume 1.0 Medium-dose volume 1.0 High-dose volume 2.0 (1.0–3.9) p = 0.04	Causes of deaths obtained from the Swedish death cause register. Postmortem examination was not performed regularly. C3
Hardenbergh 1999 (35) C Extended analysis of Ref. (32), Overview 6	Cardiac toxicity of radiotherapy+doxorubicin A: BCS+CHT × 4+RT B: BCS+RT+CHT × 4 For details see Ref. (32), Overview 6	1984–1992 231 pts continuously followed with respect to cardiac events, defined as: mycardial infarction or clinical cardiac insufficiency	No cardiac events were observed in either treatment group	Small study. C3
Höjris 2000 (38) R Extended analysis of Refs (4, 5), Overview 1	Myocardial perfusion imaging A: RT+ST B: ST alone For details see Refs (4, 5), Overview 1 Myocardial perfusion investigated by SPECT	1982–1989 Pts with left-side breast cancer 17/47 pts evaluated A RT+ST: 10 pts (5 TAM, 5 CMF) B ST alone: 7 pts (1 TAM, 6 CMF)	No difference between treatment groups was found	Small study. No difference in scintigraphic findings. R3
Valagussa 1994 (41) R	Frequency and type of cardiac events Retrospective evaluation of pts from 3 randomized studies treated with: RT: 50 Gy/5 fr/week+boost 10 Gy (^{60}CO or 6 MeV) CHT: doxorubicin based or CMF or doxorubicin+CMF	825 pts The risk for cardiac event related to side of breast cancer and type of treatment. Cardiac event = clinical cardiac insufficiency	Median follow-up 80 months Cardiac event % RT to left thorax 24 RT to right thorax 11 no RT 5.4 p = 0.0001 Cardiac event occurred in 0.8% of pts treated with doxorubicin-based CHT compared to 2.6% of pts not treated with doxorubicin, ns	R3

Abbreviations: BCS = breast-conserving surgery; BCQ = breast cancer chemotherapy questionnaire; CHT = chemotherapy; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; DBCG = Danish breast cancer group; fr = fraction(s); HR = hazard ratio; MRM = modified radical mastectomy; OS = overall survival; pts = patient(s); QoL = quality of life; RT = radiotherapy; SPECT = single photon emission computerized tomography; ST = systemic therapy; TAM = tamoxifen; CR = complete remission.

C2, (43) C2, (34) C3, (35) C3, (37) R2, (39) R2, (38) R3, (41) R3, (36) C1, (12) R2).

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