7. **Breast Cancer**

Introduction

In Sweden like in other western countries, breast cancer is the most common malignancy among females with an estimated life time risk of 8–9 per cent. The number of new cases reported from the Swedish Cancer Registry in 2000 was 6 300 which corresponds to 29 per cent 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 ever since cancer registration was started in Sweden in the late 1950s. In part the increase is due to an ageing population, 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 post-menopausal hormone replacement therapy.

Survival has continuously improved 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 per cent and 75 per cent, 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 per cent 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 per cent.

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 convincingly demonstrated that some types of adjuvant systemic therapy can produce clinically significant improvements of both recurrence-free and overall survival. 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 as 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 which may interact with the radiation. This has raised questions as to how radiation is best integrated with systemic treatment. Also, it has 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, e.g. patients with spread to the axillary lymph nodes, leads to a significant increase in relapse-free survival. meta-analysis have shown that radiotherapy in theses subgroups of patients can reduce the risk for distant metastases and reduce the risk for cancer death. These analysis 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 successively improved, 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, i.e. a reduction in mortality by 20 per cent to 30 per cent, leading to an increased total survival after, e.g. ten years of 5 per cent to 10 per cent.

- 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 iscemic 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, e.g. 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, e.g. regarding different histopatholgic 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, e.g. pain, cancer lesions, fractures, neurologic 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. In fact, 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 focussing 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 or 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 focus should be given to more recent trials which have integrated radiation therapy with systemic treatment, and which 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	12/7 309	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	**57/346 717**	**33/37 273**	**7/3 644**	**97/387 634**

Assessment of new literature

Search methods and selection

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

Thus 42 articles were retrieved, which fulfilled these selection criterias. Reasons for exclusion of articles were:

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

Overview of new studies

Radiotherapy after mastectomy

Overview 1 and 2

Whether the addition of postoperative radiotherapy to mastectomy can reduce local recurrence rate, increased disease free and overall survival has been analysed in six randomized studies [19,33–36,43] and 5-meta-analysis [10–12,46,50]. The data from the randomized trials are included in the largest meta-analysis from the EDCTC-group in which the results are analysed on the basis of individual patient data [11]. In the meta-analysis, most of the patients were treated with either simple mastectomy or radical modified mastectomy but 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 [19]. The question of optimal radiation therapy technique was further elucidated in an exploratory meta-analysis [46]. Furthermore, the differential effect of radiation therapy on breast cancer specific and non-breast cancer specific mortality was thoroughly addressed in the two overviews from EBCTCG [11,12].
In the analysis of three randomized trials (the Uppsala-Örebro, Ontario, NSABP B-06) Levitt et al [26,27] 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 pulled the data of these three trials in a meta-analysis and demonstrated a 9.6 per cent relative reduction in the annual mortality in favour of the irradiated patients. (This meta-analysis is not shown in Overview 2).

The literature shows that:

- Postmastectomy radiation therapy gives a substantial reduction of 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, utilizing Bayesian statistics, also a reduction in overall mortality was demonstrated.
- There is an added value of radiotherapy in terms of decreased overall mortality in patients given adjuvant systemic therapy.
- Postmastectomy radiotherapy might give adverse cardiovascular effects. It is, however, likely that this adverse effect of radiotherapy regarding cardiovascular diseases is attributed to the radiation technique.
- There is insufficient knowledge on how different treatment volumes affects recurrence free and overall survival.

Radiotherapy in breast conservation surgery

Overview 3

Breast conserving surgery and radiotherapy have been evaluated against modified radical mastectomy in five randomized trials [1,13,22,25,47] and in one meta-analysis ([11] Overview 2). Breast conserving surgery + radiotherapy has been evaluated in six randomized trials [7,13,29,30, 38,48]. Whether the target volume for optimal radiotherapy should be wide or limited field has been the subject for one randomized study [32]. 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 conservation surgery results in a statistically and clinically significant reduction of ipsilateral breast recurrences and reduced need for salvage mastectomies.

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

Overview 4

The role of radiation boost after breast conservation surgery have been addressed in two randomized studies [2,39]. The impact of radiation therapy to IMC is investigated in a small randomized trial comparing breast conservation surgery plus radiotherapy + inclusion of IMC in the target volume [24].

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.

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

Overview 5

Breast conservation surgery + radiotherapy for DCIS has been investigated in two large randomized trials [15,23].

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 of 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

Overview 6

The addition of radiation therapy to breast conservation surgery after shorter or longer systemic therapy have been addressed in one randomized study [45]. In one study, radiotherapy was given concomitantly or after four courses of chemotherapy in patients with breast conservation therapy [37]. 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

Overview 7

Overview 7 is a compilation of eleven trials, four randomized trials [8,17,18,28] and seven retrospective studies [4,20,21,31,44,51,52]. The majority of the trials is relatively small or the trial designs are such that conclusions can not be drawn. Various aspects of cardiac morbidity are addressed in four trials [17,18,21,44].

The literature shows that:

- Cardiac events were more frequent among women irradiated because of left-sided tumours compared to right-sided tumours.
- Radiotherapy leads to increased proportion of patients with lung fibrosis and might lead to 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 statistical significant adverse effect on the cosmetic result.

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

	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**

*) In the figures within brackets all patients reported in the individual articles are counted. Many patients are reported in more than one article (2–4) and the figures without brackets 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. ([12]M1).
- There is strong evidence that postmastectomy radiation therapy increases the disease free survival rate. (*Pro:* [34]C1, [35]C1, [36]C2; *con*: [33]C2, [43]C3).
- There are conflicting data regarding the impact of postmastectomy radiotherapy upon overall survival. (*Pro:* [50]M1; *con:* [12]M1, [10]M2).
- There is strong evidence that breast cancer specific survival is improved by postmastectomy radiotherapy. ([12]M1).
- There is strong evidence for a decrease in non breast cancer specific survival after postmastectomy radiotherapy. ([12]M1, [10]M2).
- There is some evidence that overall survival is increased by optimal postmastectomy radiation therapy. ([46]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. ([50]M1).
- There is moderate evidence that the decrease in non breast cancer specific survival is attributed to cardiovascular disease in irradiated patients. ([11]M1, [10]M2, [17]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:* [13]C1, [22]C2, [25]C3, [1]C3, *con:* [47]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. ([13]C1, [47]C1).
- 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. ([13]C1, [47]C1, [22]C2, [1]C3, [25]C3, [48]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 ([27]M2) including three randomized studies [13,29,49] a survival advantage is demonstrated by Bayesian statistics. ([12]M1, [7]C1, [13]C1, [29]C1, [30]C1, [38]C1, [48]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. ([2]C1, [39]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 of both non-invasive and invasive ipsilateral breast recurrences. ([15]C1, [23]C1).
- There is insufficient evidence to define the optimal integration of systemic adjuvant therapy and postoperative radiotherapy. ([37]C2, [45]C2).
- There are limited data on radiotherapy related morbidity in breast cancer. No conclusions can be drawn. ([8]C2, [51]C2, [17]C3, [18]C3, [4]R2, [20]R2, [21]R3, [44]R3, [28]C1, [50]R2).

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Overview 1 *Breast cancer. Radiotherapy after modified radical mastectomy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Schmoor 2000 [43] GBCSG C	Benefit of postop RT **A:** RT 2 Gy/fr to 44–50 Gy/ 4.5–5 w + CHT **B:** CHT alone	1984–1989 Pre- and postmenopausal pts T1–4, N+ A 98 pts B 101 pts
Olson 1997 [33], ECOG C	Benefit of postop RT in LABC **A:** CHT + HT + RT 2 Gy/ fr to 46 Gy/4.5 w **B:** CHT + HT alone	1982–1987 T1–2 with fixation, T3 N1–2, T4 A 164 pts B 148 pts
Overgaard 1997 [34], DBCG C Update of DBCG trial 82 b	Benefit of postop RT **A:** RT 2 Gy/fr, 25 fr to 50 Gy/5 w + CHT **B:** CHT alone (At one center 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
Overgaard 1999 [35] C Update of DBCG trial 82 c	Benefit of postop RT **A:** RT as in ref [34] + TAM **B:** TAM alone	1982–1990 Postmenopausal high-risk pts [34] A 686 pts B 689 pts
Ragaz 1997 [36] C	Benefit of postop RT **A:** RT 2 Gy/fr to 35–37,5 Gy/ 3–4 w + CHT **B:** CHT alone	1979–1986 Premenopausal pts T1–4, N+ A 164 pts B 154 pts
Houghton 1994 [19], CRC C	Benefit of postop RT **A:** RT* **B:** No adjuvant therapy * Variation in RT technique, for details see refs [3,5]	1970–1975 St I–II (76% st I) < 70 y age A 1 376 pts B 1 425 pts

BCSS: breast cancer specific survival; CHT: chemotherapy; CI: confidence interval; CRC: Cancer Research Campaign; DBCG: Danish Breast Cancer Group; EBCTCG: Early Breast Cancer trialists Collaborative 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; w: week(s); y: year(s);
CHT ref [43]: CMF (Cyclophosphamide, methotrexate, 5-fluorouracil), modified, 6 m
CHT ref [33]: Cyclophosphamide + doxorubicin; HT = tamoxifen + fluoxymesterone
CHT ref [34]: CMF iv, modified (4 w interval), 7–8 m.
CHT ref [36]: CMF iv, 6–12 m

Results				Conclusion/Comments
Follow-up median 9 y				Small trial, inadequate power.
	LRR%	**EFS%**	**OS%**	**C 3**
A	6	47	46	
B	16	55	48	
	p=0.03	ns	ns	
Follow-up median 9 y				Small trial, inadequate power.
	EFS%	**OS%**		**C 2**
A	40	46		
B	44	47		
	ns	ns		
Follow-up median 9,5 y				Large trial. Possibly suboptimal systemic therapy and surgery. Multivariate analysis showed sign. improved OS and DFS irrespective of tumour size, number involved nodes, histopathology grade. **C 1**
	LRR%	**DFS%**	**OS%**	
A	9	48	54	
B	32	34	45	
	p<0.001	p<0.001	p<0.001	
Follow-up median 10 y				Large trial. Systemic therapy with TAM given for only 1 y. Surgery possibly suboptimal. **C 1**
	LRR%	**DFS%**	**OS%**	
A	8	36	46	
B	35	24	36	
	p<0.001	p<0.001	p<0.03	
Follow-up median 9 y				Small trial. **C2**
	LRR%	**DFS%**	**OS%**	
A	13	50	54	
B	33	33	46	
	p<0.003	p<0.007	ns	
A vs B	**RR**		**95% CI**	Large trial but outdated RT techniques (e.g. orthovoltage). Higher frequency of cardiac related deaths in left-sided breast cancer treated with orthovoltage. Increased inc. of secondary malignancy in group A. **C2**
Local relapse	0.44		0.39–0.51	
Survival	1.01		ns	
Death after 5 y				
all pts	1.5		1.01–2.29	
Left side ca	1.92		1.09–3.39	
Right side ca	1.19		ns	

Overview 2 *Breast cancer. Postoperative radiotherapy in early breastcancer, meta-analysis.*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Cuzick 1994 [10] M Update of ref [9]	Longterm cause specific mortality, after >10 y survival **A:** Simple mastectomy (SM) or radical mastectomy (RM) + RT **B:** Same surgery alone RT: mainly orthovoltage or Co^{60} Doses: 18–54 Gy/10–30 fr	1949–1979 8 trials Stage I–II The analysis includes only pts with >10 y survival: SM: 2 502 out of 4 579 pts RM: 1 807 out of 3 362 pts
EBCTCG 1995 [11] M	Role of postoperative RT, in early breast cancer 2 analysis 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
EBCTCG 2000 [12] M Update and extension of ref [11]	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

BCM: breast cancer mortality; BCS: breast conserving surgery; BCSS: breast cancer specific survival;
CI: 95% confidence interval; EBCTCG: Early Breast Cancer trialists Collaborative Group; fr: fraction;
LR: local recurrence; LRR: local relapse rate; MRM: modified radical mastectomy;
NBCSS: non breast cancer specific survival; ns: not significant; OR: odds ratio; pts: patient(s);
RM: radical mastectomy; RR: relative risk; RT: radiotherapy; SM: single mastectomy; y: year(s)

Results	Conclusion/Comments
Overall mortality at 10 y (after >10 y 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. **M 2**
Mortality% OR (A vs B) **at 10 y** **BCM** **non BCM** 1. A 40.3 0.94 1.24 B 41.4 (CI 0.88–1.00) (CI 1.09–1.42) 2. A 22.9 cause spec. mortality not reported B 22.9	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 1**
Mortality% **BCSS%** at 20 y **NBCSS%** at 20 y A 49.9 53.4 69.5 B 51.2 48.6 73.8 p=0.06 p=0.0001 p=0.0003 LRR at 10 y 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 particulary 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. **M 1**

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Overview 2 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
van de Steene 2000 [46] M Extended analysis of ref [11]	Role of RT in stage I–II breast cancer In-depth analysis of trials reported in ref [11]. Trial characteristics like small vs large, old vs recent etc. analysed.	36 trials on surgery + RT vs same surgery alone. 17 273 pts [11]
Whelan 2000 [50] M	Additional value of RT in pts given systemic therapy (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

Results	Conclusion/Comments
Factors sign. 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. **M 1**
Follow-up 7.7–14.5 y **OR (95% CI)** **Death** **LRR** A vs B 0.83 0.25 (0.74–0.94) (0.19–0.34) In multivariate analysis timing and RT technique identified as predictive factors for survival: benefit of radiation if started within 6 m, megavoltage better than ortovoltage.	Reduction of LRR translated into decreased mortality in pts given ST. **M 1**

Overview 3 *Breast cancer. Radiotherapy in breast conservation surgery (BCS).*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Arriagada 1996 [1] Update of refs [41,42] C	BCS + RT vs MRM **A:** BCS + RT 2.5 Gy/fr, 4 fr/w to 45 Gy + boost 15 Gy/5 fr/10 d **B:** MRM BCS = lumpectomy	1972–1979 Pre- and postmenopausal pts T ≤2 cm, N0–N+ A 88 pts B 91 pts
Jacobson 1995 [22] C	BCS + RT vs MRM **A:** BCS + RT 1.8 Gy/fr to 45–50.4 Gy + boost (Ir^{192} or EBRT) 15–20 Gy **B:** MRM BCS = lumpectomy N+ premenopaus pts got CHT, 6–12 m 1985–87: postmenopaus pts got TAM, 5 y	1979–1987 Pre- and postmenopausal pts T1–2, N0–N1 A 121 pts B 116 pts
Lee 1997 [25] 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) was given to a majority of pts in both groups.	1991–1994 T1–2, N0–N+ A 76 pts B 111 pts
van Dongen 2000 [47] C	BCS + RT vs MRM **A:** BCS + RT 2 Gy/fr to 50 Gy + Ir^{192} boost to 25 Gy **B:** MRM Systemic therapy was given in both groups: pts <55 y: CMF x 6 pts >55 y: HT at the discretion of each center. BCS = lumpectomy	1980–1986 Pre- and postmenopausal pts T1–2, N0–N+ A 448 pts B 420 pts

BCS: breast conservation surgery; CHT: chemotherapy; N0: clinically node negative; d: day(s); DFS: diseasefree survival; DM: distant metastases; DMFS: distant metastasesfree survival; EBRT: external beam radiotherapy; HT: hormonal therapy; LRR: local relapse rate; m: month(s); MRM: modified radical mastectomy; NR: not reported; ns: not significant; OS: overall survival; pts: patient(s); RT: radiotherapy; TAM: tamoxifen; w: week(s); y: year(s)
CHT ref [22]: doxorubicin, cyclophosphamide

Results	Conclusion/Comments
Follow-up 15 y **LRR% DM% OS%** A 13 27 73 B 18 34 65 ns ns ns	Small trial. No difference in LRR or OS. **C3**
Follow-up median 10 y **LRR% DFS% OS%** A 4 72 77 B 4 69 75 ns ns	Small trial. Low frequency of LRR. No difference between groups. **C2**
Follow-up median 38 m **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**
Follow-up median 13.5 y **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**

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Overview 3 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Fisher 1995 [13] Update of refs [14,16] C	Value of RT after BCS; BCS + RT vs MRM **A:** BCS **B:** BCS + RT 50–53 Gy/5w **C:** MRM BCS = lumpectomy	1976–1984 Pre- and postmenopausal pts T <4 cm, N0–N+ A 719 pts B 731 pts C 713 pts
Liljegren 1999 [30] C Update of ref [29]	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 y T <2 cm, N0 A 184 pts B 197 pts
Clark 1996 [7] C Update of ref [6,49]	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
Renton 1996 [38] C	Value of RT after BCS **A:** BCS + RT (details NR) **B:** BCS Systemic therapy was given to ER+ pts with TAM, 5 y; to ER- pts classic CMF x 6; BCS = wide local excision	1981–1990 Pre- postmenopausal T1–2, N0–1 A 208 B 210
Veronesi 2001 [48] 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: premenopaus CMF postmenopaus TAM	1987–1989 Pre- and postmenopausal T <2,5 cm, N0–N+ A 299 pts B 280 pts
Magee 1996 [32] C	Optimal RT target volume **A:** BCS + RT wide field, 40 Gy, 15 fr/3 w **B:** BCS + RT limited field, 40–42.5 Gy, 8 fr/2 w 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

Results	Conclusion/Comments
Follow-up >10 y **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 of breast recurrences with RT after BCS. **C1**
Follow-up median 7–8 y **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**
Follow-up median 7.6 y **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**
Minimum follow-up 5 **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**
Follow-up median 109 m **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**
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**

Overview 4 *Breast cancer. Effect of supplementary radiation (boost, internal mammary chain radiation, IMC).*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Bartelink 2001 [2] C	Role of RT boost after BCS **A:** BCS + RT 50 Gy/25 fr/5 w + boost 16 Gy/8 fr **B:** BCS + RT as A BCS = lumpectomy Systemic therapy: premenopaus N+ CHT postmenopaus 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
Romestaing 1997 [39] C	Role of RT boost after BCS **A:** BCS + RT 50 Gy/20 fr/4 w + boost 10 Gy/4 fr **B:** BCS + RT as A BCS = lumpectomy or quadrantectomy Premenopaus N+ CHT Postmenopaus N+ TAM	1986–1992 Pre- and postmenopausal pts T <3 cm, N0–N1 98% with free margins after BCS A 521 pts B 503 pts
Kaija 1995 [24] 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 gr A and 7% in group B.

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 lymphnodes; N-: negative lymphnodes; NR: not reported; ns: not significant; OS: overall survival; pts: patient(s); RT: radiotherapy; ST: systemic therapy; TAM: tamoxifen; w: week(s); y: year(s)

Results	Conclusion/Comments
Median follow-up 5.1 y **Act LRR% at 5 y** 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 of LRR, especially in pts <50 y. **C1**
Median follow-up 3.3 y **Act LRR% OS% at 5 y** A 3.6 92.9 B 4.5 90.4 p=0.044 ns	Large trial. Short follow-up. Sign. reduction of LRR. No difference in cosmetic outcome. **C1**
Median follow-up 2.7 y No serious acute or late side effects and no sign difference between groups. No sign difference in LRR.	Small trial. Short follow-up. No conclusion possible regarding effect or toxicity. **C3**

Overview 5 *Breast cancer. Radiotherapy in ductal carcinoma in situ (DCIS).*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Julien 2000 [23] C	Role of RT after BCS for DCIS **A:** BCS + RT 50 Gy/25fr/5 w **B:** BCS alone BCS = complete surgical excision (7 pts operated 3 times!)	1986–1996 DCIS <5 cm 1 002/1 010 pts analysed A 502 pts B 500 pts
Fisher 1998 [15] C	Role of RT after BCS for DCIS **A:** BCS + RT 50 Gy/25 fr/5 w (9% got a boost) **B:** BCS alone	1985–1990 Pre- and postmenopausal pts. All pts had tumour free margins after BCS. 814/818 pts included in analysis A 411 pts B 403 pts

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; w: week(s); y: year(s)

Results	Conclusion/Comments
Median follow-up 4.25 y **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 sign reduction of LR after RT. Sign reduction of invasive relapses. Sign increase of contralateral breast cancer in RT group. **C1**
Median follow-up 7.5 y **Act LRR% LRR% LRR% at 8 y** overall non-invasive ca 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 of LRR in irridiated groups. **C1**

Overview 6 *Breast cancer. Timing of radiotherapy (RT) and systemic therapy (ST).*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Wallgren 1996 [45] C	Role of RT after shorter or longer ST Studie 1. Premenopaus **A:** BCS + CMF x 6 + RT* (= RT started 7 m after BCS) **B:** BCS + CMF x 3 + RT* (= RT started 4 m after BCS) Studie 2. Postmenopaus **A:** BCS + TAM + RT* (= RT started 2 m after BCS) **B:** BCS + TAM + CMF x 3 + RT* (= RT started 4 m after BCS) *pts then randomized to ± CMF x 3, 1 course every 3rd month RT: 45–50 Gy/5 w	1986–1993 St II N+ Premenopaus: A 220 pts B 213 pts Postmenopaus: A 146 pts B 139 pts
Recht 1996 [37] C	Timing of radiotherapy and chemotherapy **A:** BCS + CHT x 4 (=12 w) + RT **B:** BCS + RT + CHT x 4 RT: 45 Gy/25 fr + boost 16–18 Gy CHT: CMF + doxorubicin + prednison /3 w interval	1984–1992 Premenopausal 75% St I, II; N0–N+ A 122 pts B 122 pts

BCS: breast conserving surgery; CHT: chemotherapy; CMF: cyclophosphamide, methotrexate, 5-fluorouracil; DMF: distant metastsis free; EBCTCG: Early Breast Cancer trialists Collaborative Group; fr: fraction(s); LFR: local failure free; LRR: local relapse rate; m: month(s); OS: overall survival; pts: patient(s); RT: radiotherapy; ST: systemic therapy; TAM: tamoxifen; w: week(s)

Results				Conclusion/Comments
Median follow-up 48 m				Subgroup analysis of pts treated with BCS + RT, included in 2 larger studies (EBCTSG VI, VII). Low power. No conclusion can be drown concerning timing of RT. **C2**
		LRF%	**OS%**	
Premenopaus:	A	9	84	
	B	8	90	
		ns	ns	
Postmenopaus:	A	3	89	
	B	6	89	
		ns	ns	
Median follow-up 58 m				Early CHT might reduce risk for distant recurrence. Small study. **C2**
Act	**LRR%**	**DMF%**	**OS%**	
A	14	75	81	
B	5	64	73	
	ns	p=0.05	ns	

Overview 7 *Breast cancer. Late morbidity in relation to radiation for breast cancer.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Höjris 2000 [20] R Extended analysis of ref [34,35] overview 1	Radiotherapy related morbidity **A:** MRM + RT **B:** MRM	Analysis of pts treated at a single center, participating in randomized trials (DBCG 82 b, c) ([34,35] overview 1) Pts in continuous CR high risk, age <70 y A 42 pts B 42 pts
Liljegren 1997 [28] C Extended analysis of ref [29,30] overview 3	Arm morbidity after radiotherapy **A:** BCS + RT **B:** BCS (for details see ref [29,30] overview 3)	Pts from ref [29,30] overview 3, analysed A 184 pts B 197 pts
Bentzen 1996 [4] R	Lung fibrosis in pts treated with tamoxifen and radiotherapy **A:** RT 1978–1980: 36.6 Gy/12 fr, 4 fr/w RT 1981–1982: 41 Gy/22 fr, 4 fr/w **B:** RT as A + TAM 30 mg/d, 1 y 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 lungdensity in apex of irridiated lung.

BCS: breast conserving surgery; BCQ: breast cancer chemotherapy questionnaire; CHT: chemotherapy; CMF: cyclophosphamide, methotrexate, 5-fluorouracil; d: day(s); DBCG: Danish breast cancer group; fr: fraction(s); HR: hazard ratio; m: month(s); MRM: modified radical mastectomy; OS: overall survival; pts: patient(s); QoL: quality of life; RT: radiotherapy; SPECT: single photos emission computerized tomography; TAM: tamoxifen; w: week(s); y: year(s)

Results	Conclusion/Comments
Median follow-up 9 y **Lymph-oedema %** / **Impaired shoulder mobility %** / **Lung-fibrosis %** A 14 / 50 / 60 B 3 / 15 / 8 p=0.01 / p<0.01 No difference in lung symtoms.	**R2**
Arm morbidity % **3–12 m** / **13–36 m** / **>36 m** A 36 / 25 / 23 B 42 / 23 / 16 ns Arm morbidity: pain, numbness, oedema, impaired mobility. Risk factors for arm morbidity: number of lymph nodes removed; age <65 y; employment.	The low arm morbidity might be attributed to low RT dose to the axilla. **C1**
Relative risk for lungfibrosis in group B 2.0. Sign correlation between RT dose and lungfibrosis.	Small study. **R2**

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Overview 7 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Curran 1998 [8] C Extended analysis of ref [47] overview 3	QoL and cosmesis after MRM or BCS + RT **A:** BSC + RT **B:** MRM (for details see ref [47] overview 3)	1980–1986 A 151 pts B 127 pts (see ref [47] overview 3) Only a fraction of centers participated in QoL evaluation.
Whelan 2000 [51] C Extended analysis of ref [7] overview 3	QoL and cosmesis after BCS + radiotherapy **A:** BCS + RT **B:** BCS (for detalis see ref [7] overview 3)	1984–1989 A 344 pts B 376 pts QoL data at 2 m available in 90% of pts. Data on fysical symtoms at 2 y a vailable in 75% of pts. QoL instrument: BCQ (higher score = better QoL)
Vrieling 1999 [52] R Extended analysis of ref [2] overview 4	RT boost and cosmesis **A:** BCS + RT + boost 16 Gy **B:** BCS + RT (for details see ref [2] overview 4)	1989–1996 Photografic scoring A 364 pts B 367 pts Digitized scoring A 1 621 pts B 1 580 pts
Liljegren 1997 [31] C Extended analysis of ref [29,30] overview 3	Cost and cost-effectiveness of postop. RT after BCS **A:** BCS + RT **B:** BCS For details see ref [29,30] overview 3	1981–1988 The analysis comprises 381 pts For details see ref [29,30] overview 3

Results	Conclusion/Comments
Parameter evaluated: Body image: gr B sign. better p=0.001 Fear of relapse: No difference gr A vs gr B Satisfaction with treatment: gr B sign. better p=0.001 Prognostic factors for worse cosmetic outcome: postmenopausal status and wide excision.	**C2**
At 2 m after treatment. BCQ score sign. higher in group B, p=0.0001. At 2 y no difference in skin irritation, breast pains or apperence of treated breast.	Longterm QoL: used method not validated. "Acute" QoL not surprisingly related to RT. **C2**
Follow-up 3 y Photografic 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 effect on the cosmetic result. **R2**
Cost of one avoided local relapse at 5 y in irridiated group: 338 000 SEK. Cost per gained quality adjusted life year (QUALY) was estimated to 0.2–3.9 million SEK!	The large range of calculated cost for one QUALY reflects the difficulty in performing health economical analysis. Cost and quality measure of treatments difficult to put into perspective. **C1**

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Overview 7 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Gyenes 1998 [17] C Extended analysis of ref [40]	Risk of cardiac morbidity and mortality **A:** MRM **B:** preop. RT (CO^{60}) + MRM **C:** MRM + postop. RT (electrons) RT dose 45 Gy/1.8 Gy/fr, 5 fr/w	1971–1976 Pre- and postmenopausal A 321 pts B 316 pts C 323 pts 3 dose volumes were estimated: Low dose volume = right side breast cancer, irradiated with CO^{60} or electrons Medium dose volume = left sided breast cancer irradiated with electrons High dose volume = left sided breast cancer, irradiated with CO^{60}
Hardenbergh 1999 [18] C Extended analysis of ref [37], overview 6	Cardiac toxicity of radiotherapy + doxorubicin **A:** BCS + CHT x 4 + RT **B:** BCS + RT + CHT x 4 For details see ref [37] overview 6	1984–1992 231 pts continuously followed with respect to cardiac events, defined as: mycardial infarction or clin. cardiac insufficiency.
Höjris 2000 [21] R Extended analysis of ref [34,35] overview 1	Myocardial perfusion imaging **A:** RT + systemic therapy (ST) **B:** ST alone for details see ref [34,35] overview 1 Myocardial perfusion investigated by SPECT	1982–1989 Pts with left sided breast cancer 17/47 pts evaluated A RT + ST: 10 pts (5 TAM, 5 CMF) B ST alone: 7 pts (1 TAM, 6 CMF)
Valagussa 1994 [44] R	Frequency and type of cardiac events Retrospective evaluation of pts from 3 randomized studies treated with: RT: 50 Gy/5 fr/w + boost 10 Gy (CO^{60} 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

Results	Conclusion/Comments
Median follow-up 20 y 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 regularily performed. **C3**
No cardiac events were observed in either treatment group.	Small study. **C3**
No difference between treatment groups was found.	Small study. No difference in scintigrafic findings. **R3**
Median follow-up 80 m **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**