ACTA ONCOLOGICA

Vol. 30
No. 7

1991

TREATMENT OF EARLY BREAST CANCER WITH CONSERVATION OF THE BREAST

A review

P. E. LØNNING

Abstract

This paper reviews the current status of conservative treatment for early breast cancer. While the first patients were treated with such techniques more than 60 years ago, it is during the last decade that randomized trials have confirmed that such treatment is comparable to mastectomy in preventing breast cancer death. Radiotherapy to the breast after local tumour excision is important to prevent local breast relapse, but it is not clear whether it has any influence on the risk of distant metastases. Several questions remain to be answered. While most investigators agree that the breast should receive a radiation dose of about 50 Gy in 5 weeks, there is no general agreement about the need for a tumour bed booster dose. Considering patients with tumour infiltration at the surgical resection line for whom it is not possible for cosmetic reasons to perform re-resection, it is not clear whether an acceptable local control rate can be achieved through application of a high booster dose in the tumour bed. More trials are needed to show whether certain patients with small invasive carcinomas should be treated with wide local excision without radiotherapy. The need for radiotherapy after local excision for small intraductal (ductal carcinoma in situ) cancers is being addressed in ongoing trials.

Key words: Breast cancer, breast conserving therapy, local relapse risk, review.

The term 'breast-conserving treatment' includes techniques by which radical eradication of an early breast cancer (T1–2, N0–1, M0) is achieved without ablation of the mammary gland. Such treatment techniques have attracted widespread interest and recently become accepted alternatives to more radical and mutilating surgical procedures. The possibility of treating limited breast cancers without breast ablation was suggested more than 60 years ago. Hirsch (1) in Berlin and Keynes (2) in London published their first results in 1927 and 1929 respectively. Mustakallio (3) in Helsinki published his first series in 1945, and the Institute Curie group headed by Baclesse published their results in 1949 (4). The preliminary results achieved by these pioneers suggested that survival after breast-conserving treatment could be similar to that achieved after radical mastectomy. This view gained further support when a follow-up paper from St. Bartholomew's Hospital (5) in 1953 reported long-term survival to be similar among the patients treated conservatively by Keynes and breast cancer patients treated in the same hospital with mastectomy. During the 1960s more authors reported encouraging results with breast-conserving treatment (6–9), and during the last two decades multiple reports have been published:

1. The survival rate and risk of distant metastases following breast-conserving therapy and mastectomy have been compared in randomized trials.
2. Long-term (> 25 years) follow-up reports containing large numbers of patients have provided important information on long-term survival and risk of locoregional failure. These studies also give important information on long-term risks and possible treatment side-effects associated with breast-conserving therapy.
3. Possible risk-factors for locoregional failure have been studied meticulously in an attempt to exclude high-risk patients not suitable for conservative treatment modalities.

From the Department of Oncology and Radiophysics, Haukeland Sykehus, Bergen, Norway.

Submitted 26 September 1990.
Accepted for publication 21 December 1990.

Randomized trials comparing risk of distant metastases and the survival rate after breast-conserving therapy versus mastectomy

The question whether breast-conserving therapy is a safe alternative to mastectomy is part of a general discussion concerning the need for radical surgery to achieve optimal local control and prevent distant metastases in breast cancer patients. The aim of the classical radical mastectomy (Halstead) was to remove the tumour-containing breast with its ipsilateral axillary contents and pectoral muscles en bloc, thereby removing all the lymphatic channels connecting the breast and axillary nodes. However, a considerable proportion of patients with axillary node metastases also have subclinical metastases in the ipsilateral parasternal nodes, and this proportion is especially high (40–50%) in patients with medically or centrally located tumours (10, 11). Based on these findings, surgical techniques were invented which incorporated internal mammary node and/or supraclavicular fossa dissection (10, 12, 13). Several randomized trials have compared the possible benefit of such 'supra-radical' techniques with traditional mastectomy (11, 14, 15). Except for a possible small survival benefit related to internal mammary dissection for patients with centromedial tumours and axillary node metastases, treatment with such 'supra-radical' surgical techniques gave no survival benefit compared with the less mutilating therapy. Recent investigators, such as the NSABP-group, considered the extent of axillary lymphatic metastases as merely a marker of tumour dissemination in general, and suggested that local treatment of lymph node micro-metastases has little impact on the risk of a distant relapse (16). Several trials which compared radical mastectomy to simple mastectomy with or without primary radiotherapy revealed no difference in survival rate between the two treatment modalities (17–20). The view of the NSABP investigators gained further support by their findings that neither axillary dissection nor axillary irradiation for clinical N0 breast cancers gave any survival benefit (18), despite the fact that 25–30% of such patients are known to have microscopic tumour infiltration in one or more axillary nodes at the time of primary surgery (21–23). These findings stimulated interest in less mutilating surgical techniques including breast preservation.

The first randomized trial comparing breast-conserving treatment with mastectomy was initiated at Guy's Hospital in London in the 1960s (24). So far the results from 5 randomized trials have been published (24–28, Tables 1 and 2), and the results of another three trials are expected to be published in the near future (29–31). The results from 3 of the 5 published trials (26–28) and the preliminary results from the unpublished trials (29–31) confirm the theory that patients treated with breast-conservative treatment (limited surgery and radiation therapy) have a similar risk of distant metastases and a similar survival chance as patients treated with conventional mastectomy. Some important differences between these trials should be considered.

In 3 of the 5 trials (not the two from Guy's Hospital) the conservatively treated patients had limited axillary dissection. The Italian (26) and French (27) trials included only patients with T1 tumours. In the first of these trials (26) tumourectomy was conducted by 'quadrantectomy', a more extensive procedure than the 'lumpectomy' used in the other investigations. The NSABP-trial included tumours with a diameter of 4 cm or less, but patients with microscopic tumour involvement of the resection margins (10% of all patients initially treated with lumpectomy) went straight on to mastectomy (32).

The NSABP study (28) contained two breast-conserving arms, one with and one without breast radiotherapy. Thus, this investigation also provides some interesting information about the possible impact of local radiotherapy on the

Table 1

Patient and treatment characteristics in the randomized trials comparing breast-conserving therapy (lumpectomy or quadrantectomy) with or without radiotherapy (RT) with radical (RM) or modified total mastectomy (TM)

Ref. No.	Patients n	T/N	Therapy	Follow-up
24/25	188	T1–3 N0–1b	RM	20 y
	182		lump, RT breast/axilla	
25	130	T1–3a N0–1a	RM	10 y
	122		lump, RT, breast/axilla	
26	349	T1 N0	RM	10 y
	352		quadr, ax.diss, RT breast	
27	91	T1 N0–1b	TM	10 y
	88		lump, ax.diss, RT breast	
28	713	T1–2 N0–1b	TM	8 y
	719		lump, ax.diss, no RT	
	731		lump, ax.diss, RT breast	

Table 2

Results from the randomized trials comparing breast-conserving therapy (lumpectomy or quadrantectomy) with or without radiotherapy (RT) with radical (RM) or modified total mastectomy (TM)

Ref. No.	T/N	Distant-DFS	Survival
24,25	T1-3a N0-1b	No sign. difference	N_{1b} did sign. poorer with lump
25	T1-2 N0-1a	Sign. poorer with lump	Sign. poorer with lump
26	T1 N0	No sign. difference	No sign. difference
27	T1 N0-1b	No sign. difference	No sign. difference
28	T1-2 N0-1b	Lump-RT sign. poorer compared with TM	No sign. difference

risk of distant metastases. The study revealed a slightly, albeit significantly lower disease-free survival (DFS) and distant DFS for pN0 patients treated with limited surgery without radiotherapy compared with patients treated by mastectomy, but there is so far no significant difference in the total survival rate. Patients treated with limited surgery followed by breast radiotherapy had similar DFS and distant DFS as patients treated with mastectomy. This finding may be consistent with the recent results from a Swedish trial comparing sector resection with or without radiotherapy for T1 tumours (33). That trial revealed a non-signficant trend toward a better DFS among irradiated versus non-irradiated patients. Such a difference could possibly be due to a lead time bias. A high number of patients treated with breast-conserving surgery without radiotherapy will develop local breast relapses, and it may be anticipated that patients with local relapses are thoroughly staged for possible distant metastases.

The two trials from Guy's Hospital (24, 25) questioned the safety of breast-conserving therapy. As shown in Table 1, these trials included larger tumours than any of the other investigations. The first Guy's Hospital trial (24) reported a similar survival rate as well as a similar DFS rate for stage I patients treated with breast-conserving therapy compared with those with mastectomy. On the contrary, N1b patients treated with breast conservation had a poorer survival rate than those treated with mastectomy. No axillary surgery was performed, and the radiation dose in the axilla (25–27 Gy/12 days) was about half the dose needed to achieve optimal control of macroscopic disease (34). The risk of metastatic spread depends on the amount of tumour tissue present (35). Thus, while the NSABP trial could not document any survival benefit or effect on the risk of distant metastases from profylactic treatment of microscopic disease (18), it is possible that suboptimal treatment of palpable nodal metastases, leaving a substantial amount of viable tumour cells, may increase the risk of distant metastases. As to the second Guy's Hospital trial, only patients with clinically negative nodes were enrolled (25). In this trial, contrary to what was reported in the first trial, there was a survival difference in favour of mastectomy for node-negative patients. This result is more difficult to explain, except that it could have occurred by chance. Axillary surgery as well as radiotherapy has been found to have an impact neither on the survival rate nor on the DFS rate in node-negative patients (18), which suggests that the result of the second Guy's Hospital trial was not due to suboptimal treatment of axillary nodes. Nor is there evidence to suggest that it could be caused by suboptimal radiotherapy to the breast. In the two Guy's Hospital trials, all the conservatively treated patients received a breast radiation dose of about 38 Gy in 3 weeks, which gives a CRE value in the same range as that achieved by 50 Gy in 5 weeks.

In summary, these randomized trials provide strong evidence that many early breast cancers may be safely treated by limited surgery and radiotherapy, and it has come to be generally accepted that in many cases breast-conservative therapy may be the treatment of choice (36). Tumours < 4 cm in diameter N0/N1 may be treated conservatively with local excision as long as pathological examination shows the surgical resection line to be free from tumour tissue and the breast receives a radiation dose of about 50 Gy in 5 weeks. N1 patients should have proper axillary management. Notably, these trials do not provide sufficient information to address possible implications of tumour infiltration at the resection lines. Microscopic examination of the resection borders was not performed in these trials except for the NSABP and the French investigation. The French trial was small and included T1 tumours only. This trial could not document any detrimental effect of microscopic tumour infiltration at the resection line on long-term risk of local relapse. With the surgical technique employed in the Italian trial, most patients may be expected to achieve free resection lines. The results from the Guy's Hospital trials are somewhat contradictory and provide little information on the prognosis for stage I breast cancer patients treated with breast-conserving therapy.

Local relapse in the breast following breast-conserving therapy

Breast cancer is from a histopathological point of view often a multifocal disease. Dissection of ablative mammae specimens has confirmed multifocal breast cancer disease in between 13 and 75% of cases (37–42), depending on how meticulously sectioning is done. The ratio between in situ and invasive cancer components differs among the different studies. The clinical implications of non-invasive microfoci are uncertain, as such microfoci are found at autopsy among 15–20% of women with no clinical history of breast cancer (43). Contrarily, invasive foci are found in 1–2% of cases only (43). In women operated on for breast

cancer, microfoci of invasive cancer seem to occur mainly within a distance of 3–4 cm from the primary tumour (44).

The term 'local relapse' usually refers to all tumour relapses within the treated breast, while the term 'locoregional relapse' also includes the ipsilateral axilla, chest wall and (in some reports) supraclavicular fossa. There are some difficulties involved in comparing the results from different centres, as some studies report the total risk of a local failure independently of whether distant metastases occur, while others include local relapses as first sign of failure only. While most invasive breast tumour relapses appear as palpable tumours, regular mammographic examinations are required to detect in situ cancer relapses (45). A particular diagnostic problem relates to Paget's disease of the nipple occurring in a previously irradiated breast. In situ ductal carcinoma of the nipple is a frequent finding in mastectomy specimens (46), and such tumour cells may later develop into Paget's disease of the nipple. Paget's disease in patients previously treated with local excision and radiotherapy for breast carcinomas can occur (47, 48), and may easily be misinterpreted as postradiological alterations.

It is well known that a locoregional relapse following mastectomy carries a poor prognosis, as more than 90% of such patients will develop distant metastases and most of them die from their disease within the first decade after relapse (49–54). This is not the case with local breast relapses after breast-conservative treatment. If salvage surgery can be performed, 5- and 10-year actuarial survival after salvage has been reported to be 72–73% and 58% respectively (6, 55). About 90% of the patients with local relapse can be treated by mastectomy or local tumour excision (56, 57). Patients who develop extensive local relapse that cannot be controlled by surgery (58, 59) carry a poor prognosis with rapid development of systemic metastases (58). Second breast relapses in patients treated with salvage limited surgery can in most cases be saved by further surgery (60).

Several reports in the beginning of this decade suggested that breast relapse has little prognostic impact on the risk of distant metastases and breast cancer death (61–64). Later reports, partly by the same authors, reporting long-term follow-up results for a larger number of patients suggested that this may not necessarily be the case. There seems to be a difference between 'early' and 'late' breast relapses, as patients with local relapse within 3–5 years of primary therapy seem to have a higher risk of distant metastases and a poorer prognosis than patients with later relapse (55, 59, 65). The prognosis of patients with late relapse does not seem to be inferior to that for patients with similar primary tumour characteristics but without local breast relapse (55, 59, 66). An increasing number of local relapses are located 'elsewhere' in the breast as time from primary treatment increases (67), but the studies reported so far have not statistically confirmed a different prognosis for relapses occurring in the primary tumour area or elsewhere in the breast (59).

The prognosis for a local relapse treated by salvage surgery seems to depend on its size, with an excellent prognosis for small relapse (< 3 cm) but with a poorer prognosis for relapse with a diffuse infiltration or dermal involvement (68).

The finding that large and diffuse relapses as well as 'early' relapses carry a poor prognosis may not necessarily suggest any hazard related to breast-conserving therapy. It is well known that large and diffuse thoracic wall relapses following mastectomy carry a particularly poor prognosis (51, 52), and the possibility exists that local relapses in both instances are markers of a particularly aggressive tumour biology. In situ relapses bear an excellent prognosis (57).

The prognostic implications of a concomitant axillary relapse or an axillary failure as single first relapse is less clear. Patients treated at different centres may have received different primary treatment of their axillas, as axillary dissection in concert with breast-conservative therapy was not practised routinely in many centres during the early years of conservative treatment (25, 55, 56, 61, 69). The risk of an axillary relapse as first failure with or without a breast relapse has been reported in most series to be less than half the risk of a local breast relapse (57, 59, 70, 71); thus, it is more difficult to assess the prognostic impact of an axillary relapse statistically. While some authors claim that an axillary relapse with or without a breast relapse has no impact on survival as long as local control can be achieved (72), others have found an axillary relapse to have a negative impact on survival chance (59, 70, 71). Metastases in the thoracic wall, supraclavicular fossa or internal mammary nodes imply the same grave prognosis for patients treated with breast-conserving therapy as is seen following mastectomy (2, 57, 61).

Risk factors associated with local relapse: the influence of different treatment modalities

Factors predicting the occurrence of local breast failure have been studied meticulously. So far, however, most studies have been retrospective and it is difficult to assess the influence of each factor separately and especially how the importance of specific risk factors is influenced by the treatment modality. For example, both surgical technique and radiation dose might decide whether a certain histopathological parameter appears as a risk factor or not. Such an interaction could exist between tumour infiltration at the resection margin and tumour bed radiation dose. Surgical technique and radiation dose in the breast could also help to decide whether a large amount of intraductal carcinoma within an invasive tumour predicts an increased risk of local relapse, as this histopathological finding correlates to multifocality (73).

About 5–15% of local relapses occur in concert with distant metastases (55, 59, 68). During the first 5 years following primary treatment most local relapses occur in close relation to the primary tumour site with a yearly incidence of about 2%, declining after 5 years to a yearly actuarial risk of about 0.5% after eight years (67). Contrarily, the risk of developing a tumour 'elsewhere' in the breast increases slowly after primary treatment to reach an actuarial risk of about 1% yearly 5 years after primary therapy, remaining at this level thereafter (67).

Radiation therapy influences the breast relapse rate after lumpectomy. The NSABP-group reported 5-year actuarial local breast relapse rates of 7.7% and 27.9% for patients treated with lumpectomy with or without radiotherapy respectively (32). Non-randomized trials have revealed high local relapse rates in the 20–50% range during the first 3 years posttreatment for patients having limited surgery without radiotherapy for T1/T2 tumours (61, 74–78). This risk seems to be much lower for patients with T1 tumours treated with wide sector resection, for which local relapse rates of about 7% and 10% at 3 and 5 years respectively have been reported (33, 79). However, if radiotherapy is given to such patients they may have local relapse rates as low as 3 and 5% at 3 and 5 years (33, 80). Long-term follow-up reports for patients with T1 and T2 tumours treated with limited surgery with different radiotherapy regimens are given in Table 3. A considerable variation can be seen in the local failure rate. This is not only related to differences in radiation therapy, but could also be related to differences in surgical practice and patient inclusion criteria. Macroscopically inadequate excision of the tumour seems to be associated with an increased risk of a local relapse, even among patients receiving postsurgical radiotherapy. One study reported a 5-year actuarial risk of breast relapse of about 8% for patients treated with excisional biopsy with radiotherapy, but as high as 36% among patients treated with similar radiotherapy but having 'less than excisional biopsy' surgery (84). Similar results have been reported by others (65). In a randomized trial conducted at the Milan Cancer Institute (84) local failure rate was found to be higher among patients treated surgically with 'lumpectomy' compared with 'quadrantectomy'.

The impact of radiation dose on local relapse rate is difficult to assess. Except for the two studies comparing radiotherapy versus no radiotherapy (28, 33) no randomized studies have compared the efficacy of different radiation doses in preventing local relapses following breast-conserving therapy. Results related to the use of different radiotherapy regimens in different centres, cannot be directly compared as surgical technique as well as histopathological criteria for re-resection may also differ. Often the surgical technique is poorly defined (Table 4). It is well known that the response to radiotherapy depends critically on the tumour tissue burden (34, 86, 87), and the amount of microscopic tumour tissue left in the tumour bed may determine which radiation dose would be necessary to sterilize the area for tumour cells (86). The NSABP-group routinely performed mastectomy in all cases with microscopic tumour infiltration at the lumpectomy resection

Table 3

Radiotherapy and local relapse rate in the largest patient series [a]refers to local relapse as first failure without evidence of previous or concurrent distant metastasis, [b]refers to local relapses occurring before or simultaneously with distant metastasis, and [c]refers to all local failures whether they appeared before or after evidence of systemic disease

Ref. No.	Patients n	Radiotherapy			Local failure rate			
		Whole breast		Tumour bed	5 y	10 y	15 y	20 y
81	585	50 Gy	+	Ir-Implant	2%[a]			
80	1 232	50 Gy	+	10 Gy	4%[a,e]	10%[a,e]		
62	680	40 Gy[d]	±	5 Gy[d]	11%[a,e]	21%[a,e]	25%[a,e]	
67	597	60 Gy	+	Ir-Implant	10%[b]	16%[b]		
56	1 593	50/60 Gy	+	28/18 Gy	7%[b]	14%[b]	18%[b]	20%[b]
61	436	45 Gy[d]	+	15 Gy[d]	3%[b]	5%[b]		
55	518	57 Gy	+	7 Gy	7%[b]	11%[b]	18%[b]	
82	548	46/50 Gy	+	14/16 Gy	3%[a]			
82					6%[c]			
69	410	50 Gy	+	dose not stated	6–7%[c,e]			
33	566	50 Gy			8%[c]			
83	288	48 Gy[f]	+	dose not stated	15%[b,e]			
58	263	45 Gy[d]	+	15 Gy[d]	30%[c,e]			
65	235	40–85 Gy	(+ about 20 Gy)		12%[b,e]			

[d] Irradiation given in 2.5 Gy fractions (40 Gy gives a CRE about 1 460, 45 Gy gives a CRE about 1 580. For comparison, 50 Gy in 2 Gy fractions gives a CRE about 1 560).

[e] Actuarial relapse rate estimated from data or taken from curves.

[f] Fractions of 2.2 Gy.

Table 4

Tumour size criteria and surgical techniques used in the studies given in Table 3

Ref No.	Tumour size	Breast surgery
81	T1 and T2	'tumourectomy'; 1 cm normal tissue margin
80	T1	'quadrantectomy'
62	T1 and T2	variable
67	T1 and T2	'excisional biopsy' with 'small rim normal tissue'
56	T1 and T2	'tumourectomy'
61	< 25 mm	'excisional biopsy'
55	T1 and T2	'wide excision'
82	T1 and T2	'excisional biopsy', 45% additional re-resect.
69	T1 and T2	'simple lumpectomy' or 'segmental resection'
33	< 40 mm	'segmental mastectomy'
83	T1 and T2	'local excision'
58	T1 and T2	'macroscopic tumour-excision'
65	T1 and T2	'wide excision'

line, and 67% of such mastectomy specimens contained residual tumour tissue (88). Others (89) have found microscopic tumour infiltration at the primary resection line to correlate with residual tumour in 45 and 63% of T1 and T2 tumours respectively. Two different groups reported patients with tumour-free resection lines to have adequate local control following a radiation dose of 50 Gy/5 wks in the whole breast with no booster dose in tumour bed (32, 90). High radiation doses (60–70 Gy) in the whole breast give a poor cosmetic result (69). Contrarily, low radiation doses in the breast (with a CRE-value of about 1 300) may be associated with a high local relapse rate (91). Most centres now practise whole breast radiation to about 50 Gy/5 wks (CRE-value of about 1 560); the controversy is whether a booster dose in the tumour bed may be beneficial. The results referred to above (32, 90) suggest that this problem could be restricted to patients with tumour infiltration at the resection lines. In theory, local control could also be improved for patients with free resection lines, but with a local relapse rate of about 8% at 5 years (32) any possible benefit would be marginal. While the literature may give the impression of a controversy over the importance of free resection lines (62, 92), conflicting results could be due to different radiation doses. Many centres have not performed routine evaluation of resection lines until recently. Considering the studies in which microscopic examination of resection lines were performed, the Marseille group found local relapse rates of 6% and 22% at 5 years for patients with free versus tumour-infiltrated resection lines respectively (92), while others found microscopic infiltration to have no significant influence on the local relapse rate (58, 61, 81, 93). The Nottingham group (58) reported completeness of excision to be without importance for local relapse rate among patients treated with 60 Gy in the tumour bed, but they reported a remarkably high over all local relapse rate of 30% at 5 years. The Villejuif study recruited only patients with tumours less than 25 mm in diameter (61). They saw a tendency toward a higher relapse rate among patients receiving a tumour bed CRE of less than 1 840, but they did not assess a possible influence of tumour-free resection lines on the local relapse rate among patients receiving a CRE of less than 1 840. In the study from the Netherlands (81) the patients received a boost dose in the tumour bed by ^{192}Ir implantation (25 Gy, following total breast irradiation with 50 Gy in 5 weeks). This gives from a biological point of view a high radiation dose (CRE-value 2 200–2 300). The efficacy of such a high radiation dose is shown by its ability to induce complete tumour regression in more than 50% of T2 tumours treated without surgery (94). The technique used by the Marseille group (total breast received 50 Gy in 5 weeks followed by an electron beam boost of 20–25 Gy in the tumour bed) gives a lower CRE-value of about 2 000 in the tumour bed. The finding that a radiation dose of CRE 2 300 may provide a better local control than doses in the 1 700–2 000 range has been suggested by others (65). However, the Philadelphia group (93) found no association between tumour infiltration and risk of local relapse, despite a CRE-value in the breast of 1 750–1 800 (obtained by preoperative ^{192}Ir implantation + postoperative external beam irradiation). Others have reported a possible influence on local control of tumour bed radiation doses in the 50–70 Gy dose range (65, 95), but none of these investigators performed microscopic examination of the resection lines.

In conclusion, it seems possible that certain patients with tumour-infiltrated resection lines obtain adequate local control by high dose radiotherapy to the tumour bed (81, 96), but more studies are warranted to address this problem. The question has special implications for patients where free

resection lines cannot be achieved by re-excision, hence the only alternative to radiotherapy is total mastectomy (97).

There are no studies which answer the question whether the lymph node areas should be irradiated or not in breast-conserving therapy. Treatment policy varies among different centres considering both axillary and internal mammary node irradiation, and no randomized trials have been conducted. There is substantial evidence that radiotherapy (including irradiation of the lymph nodes) after mastectomy reduce the locoregional relapse rate but that it does not improve survival (18, 50, 98, 99). It is reasonable to assume that the same should also be valid for patients treated with breast-conservative therapy, but there is no direct proof for this hypothesis.

Recent studies suggest that adjuvant chemotherapy given with radiotherapy reduces local failure rate compared with radiotherapy alone (32, 100), similar to what has been found for mastectomy patients (101).

Risk factors associated with local relapse: clinical and histopathological factors

Histopathological factors predicting distant relapse are similar for patients treated with breast-conservative therapy and mastectomy (102).

Low age has been reported to be (65, 103, 104) or not to be (61, 105) associated with an increased risk of local breast relapse and locoregional relapse (72). This parameter is also related to the risk of a distant relapse and breast cancer death (106, 107).

Several histologic parameters, such as histology, extensive inflammatory infiltration, extensive necrosis, vascular invasion, intralymphatic extension and mononuclear cell reaction (58, 61, 88, 92, 108) have all been related to an increased local failure risk, but these findings are controversial (71, 103, 109). These parameters have variously been related to survival and DFS in patients treated with mastectomy (110–112). Thus, many of these parameters may be markers of an aggressive tumour biology associated with both local and distant relapse risk.

On the other hand, certain risk factors are associated with local breast failure after breast-conserving therapy without seeming to predict distant relapse. The importance of microscopically free margins has been discussed in the previous section, in conjunction with local radiotherapy. A large amount of in situ ductal carcinoma (DCIS) within an invasive carcinoma has been suggested to be a risk factor for local relapse in patients treated with breast-conserving therapy, but was found to have no influence on DFS in mastectomy patients (113). The term 'extensive intraductal carcinoma' (EIC) has been applied to invasive ductal carcinomas where $> 25\%$ of the tumour section is occupied by DCIS which infiltrates beyond the macroscopic tumour (114). EIC has been reported to be (81, 108, 114, 115) or not to be (61, 65, 69, 103) a risk factor for local relapse in patients treated with breast-conserving therapy. Possible reasons for this discrepancy have been discussed (116). As EIC seems to correlate with recurrences in the tumour bed (92), a possible influence of EIC on local relapse rate could depend on the extent of primary surgery but also on the radiation dose in the tumour bed (117). Results obtained by the Marseille group suggest that the increased risk of local relapses among young patients could be related to a high ratio of patients with EIC and/or high histologic grade (92), while the Harvard group (118) found age to be a prognostic factor in itself only partly related to the occurrence of EIC. Dissection of mastectomy specimens has revealed EIC to be correlated to multicentricity, particularly to DCIS-foci elsewhere in the breast tissue (73). In patients treated by re-excision following primary lumpectomy, the finding of residual tumour tissue was significantly correlated to the finding of EIC in the primary tumour (119).

Ductal and lobular breast carcinomas have different biological properties with different metastatic patterns (120, 121). Patients with infiltrating lobular carcinoma have been reported to have a 5-year actuarial risk of local failure of about 12–14%, (122, 123), which is in between the local relapse rate for patients with ductal carcinoma with (23%) or without (5%) EIC treated in the same centres (122). Only a small number of medullary and colloid breast cancers treated with breast-conservative treatment have been reported. So far no evidence suggests an increased local relapse rate for any of these tumour forms (108, 123). Paget's disease may be treated with limited surgery and radiotherapy or radiotherapy alone with an acceptable local control rate (124).

Concerning the influence of T- and N-category on local relapse rate, some authors found an influence of tumour size (T1 versus T2) on the risk of a local relapse (58, 65, 69, 88), while others found tumour size to be without influence (70, 81, 82, 103, 108, 125) or important only for patients treated with surgery without radiotherapy (91). A significant influence of node stage (pN0 versus pN1) has been reported by some investigators (58, 65, 70, 108, 125) but questioned by others (61, 82, 103). There is a high risk of local relapse following breast-conserving therapy if two or more separate carcinomas occur concomitantly in the same breast (126).

Cosmetic results after breast-conserving therapy

Most patients treated by breast-conserving therapy are satisfied with the cosmetic result (127, 128). They have been reported to have a somewhat better 'body image' than patients treated with mastectomy, but the difference is not large (129–131). Fear of relapse was found to be no higher among breast-conserving-treated patients than among mastectomized patients (130). When cosmetic results are evaluated, it is of importance to know that certain complications, such as telangiectasias and breast

retraction, develop slowly over the years (132, 133). Breast retraction has been reported to be the most disturbing cosmetic problem in the long run (134). The risk of a poor cosmetic result depends on the radiation dose delivered, and whole breast radiation doses of 60 Gy or more or skin doses above 50 Gy have both been related to a poor cosmetic result (132, 135). Interstitial irradiation with small implants has no negative impact on the cosmetic result, while larger implantation volumes have been found to impair it (133). Tumour size itself may be of minor importance, but the total amount of tissue excised seems to influence the cosmetic result (133, 136). Recently, surgical techniques of quadrantectomy versus lumpectomy were compared in a randomized trial, and the former technique was found to produce a significantly poorer cosmetic result (85). Radiation treatment of adjacent fields (axilla, supraclavicular fossa) (133) may also impair long-term cosmetic results, due to tissue retraction. Simultaneous radiotherapy and adjuvant chemotherapy seem to have a negative impact on the cosmetic result while sequential application of the same treatment modalities seems to have little influence (134).

Risk associated with radiation therapy after lumpectomy

Ionizing radiation is carcinogenic. Even low radiation doses used for benign breast conditions, especially when applied early in life, are known to increase the risk of breast cancer (137). The dose in the opposite breast during breast-conservative radiotherapy may be as high as 3–10% of the dose applied to the treated breast (138, 139). Evidence so far, however, suggests that radiotherapy in breast-conserving treatment (139) similar to radiotherapy after mastectomy (140, 141) does not significantly increase the risk of contralateral breast cancer. A few cases of angiosarcomas in irradiated breasts are described (142–144); this unusual complication has been related to radiotherapy as well as to postmastectomy lymphedema (145). The long-term risk of contralateral breast cancer has been found to be about 1% a year postmastectomy irrespective of whether radiation therapy was given or not (140). During the first 5 years after breast-conservative irradiation the chance of a new ipsilateral breast cancer is about half the risk of a contralateral one (59), after which the risk seems to be about 1% a year for each (143, 146). However, long-term follow-up studies are needed to assess whether this would also be the case with relatively young patients living for several decades following their treatment. So far there is no evidence of an increased risk of other malignancies after breast-conserving treatment with radiotherapy (139). However, more long-term studies are needed to address this question, bearing in mind that radiotherapy given to mastectomy patients in some services has been found to increase mortality more than 10 years posttreatment (147).

The most frequent benign complications after mastectomy are arm oedema and shoulder joint stiffness. These complications are related to the extent of axillary surgery and radiotherapy (148–150). Evidence so far suggests the same risk factors for these complications among patients treated conservatively (151).

Breast-conserving therapy for intraductal and intralobular carcinomas in situ

Intraductal carcinoma (DCIS) is the most frequent form of non-invasive breast cancer. It has been reported to account for 2–5% of all malignant breast tumours detected clinically as a lump in the breast (123, 152, 153), but 10–16% of malignant breast tumours diagnosed by mammographic screening (154, 155). The disease is often multicentric (156–158), and careful histopathological examination is required to exclude occult microinvasion (157, 158). There is no general agreement about treatment of this disease; mastectomy (157), as well as limited surgery with (159) or without (160) radiotherapy, has been used. After limited surgery without radiotherapy, a high local relapse rate (about 20–60%) has been reported (153, 160–165), about 50% of the relapses being invasive cancer (161, 162, 164). However, most series mainly contain clinical palpable tumours with a diameter of several cm, and the risk of occult invasion as well as multicentricity depends on tumour size (157). Contrarily, mammography can detect small, non-palpable intraductal carcinomas with micro-calcifications, and for such tumours local excision without radiotherapy may provide acceptable local control rates (146). The problem is currently being addressed in Danish (166) as well as Norwegian and Swedish multicentre studies. The survival rates for DCIS are excellent. The chance of lymph node metastases is negligible as long as no sign of microinvasion occurs (167), and the 5-year disease-free survival is between 95 and 100% (159, 168–170). While there is little doubt that the main hazard relates to an ipsilateral relapse, there is considerable variation among different reports concerning the risk of synchronous as well as metachronous contralateral non-invasive and invasive tumours (165, 171–175).

Intralobular cancer in situ does not as a rule produce palpable tumours itself, and is usually found coincidentally with benign lesions at biopsy (176). The disease is multicentric in about 50% of cases (156) and about 1/3 of the patients have contralateral synchronous non-invasive lesions (177). Long-term follow-up studies in patients treated with excisional biopsy suggest a risk of later ipsilateral invasive cancer of 5–15% at 10 years but possibly as high as 20–40% after 20 years (165, 176, 178–180). However, the risk of cancer in the contralateral breast is nearly as high as the risk of an ipsilateral tumour (176, 178). Thus, apart from local excision there is no sound rationale for aggressive surgery or radiation therapy in this disease.

Concluding remarks

Breast-conserving therapy seems to be a safe procedure for treatment of certain cases of early breast cancer, but more follow-up studies are needed to finally assess long-term results and possible hazards related to this therapy. Results from randomzied trials confirm that breast-conserving treatment by limited surgical excision followed by radiotherapy is as safe as mastectomy in preventing distant relapse and breast cancer death for unifocal T1 and T2 tumours up to a diameter of 4 cm. Limited surgery without irradiation is only warranted in trials evaluating the importance of radiotherapy for small tumours. Axillary surgery (node sampling or axillary dissection) should be done for proper staging, but there is no general agreement concerning the need for axillary or parasternal node irradiation. To address these questions is an important target for further studies in the field. More studies are needed to assess the possible influence of the tumour bed radiation dose on local control for patients with tumour infiltration at the surgical resection line.

ACKNOWLEDGEMENTS

This work was supported by grants from the Norwegian Cancer Society. The author wants to thank his colleagues, professor S. Kvinnsland at the Department of Oncology, University Hospital of Trondheim, and dr J. E. Varhaug, Department of Surgery, Haukeland University Hospital of Bergen for valuable criticism during the preparation of this manuscript. I want to thank Mr. R. Hafslund, senior physicist, Department of Radiophysic, Haukeland University Hospital for kindly calculating the cumulative radiation doses (CRE). The skillful secretarial assistance of Mrs. H. Hjortung during the preparation of this manuscript is highly appreciated.

Corresponding author: Dr Per Eystein Lønning, Department of Oncology and Radiophysics, Haukeland sykehus, N-5021 Bergen, Norway.

REFERENCES

1. Hirsch J. Radiumchirurgie des Brustkrebses. Dtsch Med Wochensch 1927; 34: 1419–21.
2. Keynes G. The treatment of primary carcinoma of breast with radium. Acta Radiol 1929; 10: 393–402.
3. Mustakallio S. Über die Möglichkeiten der Röntgentherapie bei der Behandlung des Brustkrebses. Acta Radiol 1945; 26: 503–22.
4. Baclesse F. Roentgen therapy as the sole method of treatment of cancer of the breast. AJR 1949; 62: 311–9.
5. Williams IG, Murley RS, Curwen MP. Carcinoma of the female breast: Conservative and radical surgery. Br Med J 1953; 2: 787–96.
6. Porritt A. Early carcinoma of the breast. Br J Surg 1964; 51: 214–6.
7. Peters MV. Wedge resection and irradiation. An effective treatment in early breast cancer. JAMA 1967; 200: 134–5.
8. Rissanen PM. A comparison of conservative and radical surgery combined with radiotherapy in the treatment of stage I carcinoma of the breast. Br J Radiol 1969; 42: 423–6.
9. Fleming J, Atkinson L. Carcinoma of the breast. Med J Aust 1961; 1: 281–7.
10. Urban JA, Marjani MA. Significance of internal mammary lymph node metastases in breast cancer. AJR 1971; 111: 130–6.
11. Lacour J, Bucalossi P, Cacers E, et al. Radical mastectomy versus radical mastectomy plus internal mammary dissection. Cancer 1976; 37: 206–14.
12. Andreassen M, Dahl-Iversen E, Sørensen B. Extended exeresis of regional lymph nodes at operation for carcinoma of breast and the result of a 5-year follow-up of the first 98 cases with removal of the axillary as well as the supraclavicular glands. Acta Chir Scand 1954; 107: 206–13.
13. Wangensteen OH. Another look at super-radical operation for breast cancer. Surgery 1957; 41: 857–61.
14. Meier P, Ferguson DJ, Karrison T. A controlled trial of extended radical versus radical mastectomy. Cancer 1989; 63: 188–95.
15. Kaae S, Johansen H. Five-year results: Two random series of simple mastectomy with postoperative irradiation versus extended radical mastectomy. AJR 1962; 87: 82–8.
16. Fisher B, Redmond C, Fisher ER, and participating NSABP investigators. The contribution of recent NSABP clinical trials of primary breast cancer therapy to an understanding of tumor biology—An overview of findings. Cancer 1980; 46: 1009–25.
17. Maddox WA, Carpenter JT, Laws HL, et al. A randomized prospective trial of radical (Halsted) mastectomy versus modified radical mastectomy in 311 breast cancer patients. Ann Surg 1983; 198: 207–12.
18. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. New Engl J Med 1985; 312: 674–81.
19. Brinkley D, Haybittle JL. Treatment of stage-II carcinoma of the female breast. Lancet 1966; 1: 291–5.
20. Turner L, Swindell R, Bell WGT, et al. Radical versus modified radical mastectomy for breast cancer. Ann R Coll Surg Engl 1981; 63: 239–43.
21. Rose CM, Botnick LE, Weinstein M, et al. Axillary sampling in the definitive treatment of breast cancer by radiation therapy and lumpectomy. Int J Radiat Oncol Biol Phys 1983; 9: 339–44.
22. Wallace IWJ, Champion HR. Axillary nodes in breast cancer. Lancet 1972; 1: 217–8.
23. Fisher B, Wolmark N, Bauer M, Redmond C, Gebhardt M. The accuracy of clincial nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. Surg Gynecol Obstet 1981; 152: 765–72.
24. Atkins H, Hayward JL, Klugman DJ, Wayte AB. Treatment of early breast cancer: A report after ten years of a clinical trial. Br Med J 1972; 2: 423–9.
25. Hayward JL. The Guy's Hospital trials on breast conservation. In: Harris JR, Hellman S, Silen W, eds. Conservative management of breast cancer. Philadelphia: Lippincott, 1983: 77–90.
26. Veronesi U, Banfi A, del Vecchio M, et al. Comparison of Halsted mastectomy with quadrantectomy, axillary dissection, and radiotherapy in early breast cancer: long-term results. Eur J Cancer Clin Oncol 1986; 22: 1085–9.
27. Sarrazin D, Lê MG, Arriagada R, et al. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. Radiother Oncol 1989; 14: 177–84.

28. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. New Engl J Med 1989; 320: 822–8.
29. Glatstein E, Straus K, Lichter A, et al. Results of the NCI early breast cancer trial. NIH consensus development conference on early stage breast cancer, 1990, June 18–21, NIH.
30. van Dongen JA. Randomized clinical trial to assess the value of breast conserving therapy in stage I and stage II breast cancer; EORTC trial 10801. NIH consensus development conference on early stage breast cancer, 1990, June 18–21, NIH.
31. Bilchert-Toft M. A Danish randomized trial comparing breast conservation with mastectomy in mammary carcinoma. NIH consensus development conference on early stage breast cancer, 1990, June 18–21, NIH.
32. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med 1985; 312: 665–73.
33. The Uppsala-Örebro Breast Cancer Study Group. Sector resection with or without postoperative radiotherapy for stage I breast cancer: A randomzied trial. J Natl Cancer Inst 1990; 82: 277–82.
34. Bataini JP, Picco C, Martin M, Calle R. Relation between time-dose and local control of operable breast cancer treated by tumorectomy and radiotherapy or by radical radiotherapy alone. Cancer 1978; 42: 2059–65.
35. Koscielny S, Tubiana M, Lê MG, et al. Breast cancer: Relationship between the size of the primary tumour and the probability of metastatic dissemination. Br J Cancer 1984; 49: 709–15.
36. National Institutes of Health. Consensus development conference statement: Treatment of early stage breast cancer. 1990, June 18–21.
37. Schwartz GF, Patchesfsky AS, Feig SA, Shaber GS, Schwartz AB. Multicentricity of non-palpable breast cancer. Cancer 1980; 45: 2913–6.
38. Fisher ER, Gregorio R, Redmond C, et al. Pathologic findings from the national surgical adjuvant breast project (Protocol No. 4). Cancer 1975; 35: 247–54.
39. Morgenstern L, Kaufman PA, Friedman NB. The case against tylectomy for caracinoma of the breast. Am J Surg 1975; 130: 251–8.
40. Qualheim RE, Gall EA. Breast carcinoma with multiple sites of origin. Cancer 1957; 10: 460–8.
41. Gallager HS, Martin JE. The study of mammary carcinoma by mammography and whole organ sectioning. Early observations. Cancer 1969; 23: 855–73.
42. Skjørten F, Amlie E, Larsen KA. On the occurrence of focal, occult in situ and invasive carcinoma in 150 mastectomy specimens. Eur J Surg Oncol 1986; 12: 117–21.
43. Nielsen M, Thomsen JL, Primdahl S, Dyreborg U, Andersen JA. Breast cancer and atypia among young and middle-aged women: A study of 110 medicolegal autopsies. Br J Cancer 1987; 56: 814–9.
44. Holland R, Veling SHJ, Mravunac M, Hendriks JHCL. Histologic multifocality of Tis, T1–2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer 1985; 56: 979–90.
45. Schnitt SJ, Connolly JL, Recht A, Silver B, Harris JR. Breast relapse following primary radiation therapy for early breast cancer. II. Detection, pathologic features and prognostic significance. Int J Radiat Oncol Biol Phys 1985; 11: 1277–84.
46. Menon RS, van Geel AN. Cancer of the breast with nipple involvement. Br J Cancer 1989; 59: 81–4.
47. Markopoulos C, Gazet JC. Paget's disease of the nipple occurring after conservative management of early breast cancer. Eur J Surg Oncol 1988; 14: 77–8.
48. Menzies D, Barr L, Ellis H. Paget's disease of the nipple occurring after wide local excision and radiotherapy for carcinoma of the breast. Eur J Surg Oncol 1989; 15: 271–3.
49. Donegan WL, Perez-Mesa CM, Watson FR. A biostatistical study of locally recurrent breast carcinoma. Surg Gynecol Obstet 1966; 122: 529–40.
50. Høst H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer—long-term results from the Oslo study. Int J Radiat Oncol Biol Phys 1986; 12: 727–32.
51. Bedwinek JM, Lee J, Fineberg B, Ocwieza M. Prognostic indicators in patients with isolated local-regional recurrence of breast cancer. Cancer 1981; 47: 2232–5.
52. Fentiman IS, Matthews PN, Davison OW, Millis RR, Hayward JL. Survival following local skin recurrence after mastectomy. Br J Surg 1985; 72: 14–6.
53. Gilliland MD, Barton RM, Copeland EM. The implications of local recurrence of breast cancer as the first site of therapeutic failure. Ann Surg 1983; 197: 284–7.
54. Toonkel LM, Fix I, Jacobson LH, Wallach CB. The significance of local recurrence of carcinoma of the breast. Int J Radiat Oncol Biol Phys 1983; 9: 33–9.
55. Fourquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: A 25-year follow-up. Int J Radiat Oncol Biol Phys 1989; 17: 719–25.
56. Kurtz JM, Amalric R, Brandone H, et al. Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. Cancer 1989; 63: 1912–7.
57. Recht A, Schnitt SJ, Connolly JL, et al. Prognosis following local or regional recurrence after conservative surgery and radiotherapy for early stage breast carcinoma. Int J Radiat Oncol Biol Phys 1989; 16: 3–9.
58. Locker AP, Ellis IO, Morgan DAL, Elston CW, Mitchell A, Blamey RW. Factors influencing local recurrence after excision and radiotherapy for primary breast cancer. Br J Surg 1989; 76: 890–4.
59. Kurtz JM, Spitalier J-M, Amalric R, et al. The prognostic significance of late local recurrence after breast-conserving therapy. Int J Radiat Oncol Biol Phys 1990; 18: 87–93.
60. Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier J-M. Results of wide excision for mammary recurrence after breast-conserving therapy. Cancer 1988; 61: 1969–72.
61. Clarke DH, Lê MG, Sarrazin D, et al. Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: Experience of the Institut Gustave-Roussy. Int J Radiat Oncol Biol Phys 1985; 11: 137–45.
62. Clark RM, Wilkinson RH, Mahoney LJ, Reid JG, MacDonald WD. Breast cancer: A 21-year experience with conservative surgery and radiation. Int J Radiat Oncol Biol Phys 1982; 8: 967–75.
63. Amalric R, Santamaria F, Robert F, et al. Radiation therapy with or without primary limited surgery for operable breast cancer: A 20-year experience at the Marseilles Cancer Institute. Cancer 1982; 49: 30–4.
64. Vilcoq JR, Calle R, Stacey P, Ghossein NA. The outcome of treatment by tumorectory and radiotherapy of patients with operable breast cancer. Int J Radiat Oncol Biol Phys 1981; 7: 1327–32.

65. van Limbergen E, van den Bogaert W, van der Schueren E, Rijnders A. Tumor excision and radiotherapy as primary treatment of breast cancer. Analysis of patient and treatment parameters and local control. Radiother Oncol 1987; 8: 1–9.
66. Ghossein NA, Vilcoq J, Stacey P, Asselain B. Is it necessary to irradiate the breast after conservative surgery for localized cancer? Arch Surg 1987; 122: 913–7.
67. Recht A, Silen W, Schnitt SJ, et al. Time-course of local recurrence following conservative surgery and radiotherapy for early stage breast cancer. Int J Radiat Oncol Biol Phys 1988; 15: 255–61.
68. Hafty BG, Goldberg NB, Fischer D, et al. Conservative surgery and radiation therapy in breast carcinoma: Local recurrence and prognostic implications. Int J Radiat Oncol Biol Phys 1989; 17: 727–32.
69. Delouche G, Bachelot F, Premont M, Kurtz JM. Conservation treatment of early breast cancer: Long-term results and complications. Int J Radiat Oncol Biol Phys 1987; 13: 29–34.
70. Spitalier JM, Gambarelli J, Brandone H, et al. Breast-conserving surgery with radiation therapy for operable mammary carcinoma: A 25-year experience. World J Surg 1986; 10: 1014–20.
71. Calle R, Vilcoq JB, Zafrani B, Vielh P, Fourquet A. Local control and survival of breast cancer treated by limited surgery followed by irradiation. Int J Radiat Oncol Biol Phys 1986; 12: 873–8.
72. Fowble B, Solin LJ, Schultz DJ, Goodman RL. Frequency, sites of relapse, and outcome of regional node failures following conservative surgery and radiation for early breast cancer. Int J Radiat Oncol Biol Phys 1989; 17: 703–10.
73. Holland R, Connolly JL, Gelman R, et al. The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. J Clin Oncol 1990; 8: 113–8.
74. Crile G, Cooperman A, Esselstyn CB Jr, Hermann RE. Results of partial mastectomy in 173 patients followed for from five to ten years. Surg Gynecol Obstet 1980; 150: 563–6.
75. Lagios MD, Richards VE, Rose MR, Yee E. Segmental mastectomy without radiotherapy. Short-term follow-up. Cancer 1983; 52: 2173–9.
76. Montgomery ACV, Greening WP, Levene AL. Clinical study of recurrence rate and survival time of patients with carcinoma of the breast treated by biopsy excision without any other therapy. J R Soc Med 1978; 71: 339–42.
77. Tagart REB. Partial mastectomy for breast cancer. Br Med J 1978; 2: 1268.
78. Kantorowitz DA, Poulter CA, Sischy B, et al. Treatment of breast cancer among elderly women with segmental mastectomy or segmental mastectomy plus postoperative radiotherapy. Int J Radiat Oncol Biol Phys 1988; 15: 263–70.
79. Greening WP, Montgomery ACV, Gordon AB, Gowing NFC. Quadrantic excision and axillary node dissection without radiation therapy: the long-term results of a selective policy in the treatment of stage I breast cancer. Eur J Surg Oncol 1988; 14: 221–5.
80. Veronesi U, Salvadori B, Luini A, et al. Conservative treatment of early breast cancer. Ann Surg 1990; 211: 250–9.
81. Bartelink H, Borger JH, van Dongen JA, Peterse JL. The impact of tumor size and histology on local control after breast-conserving therapy. Radiother Oncol 1988; 11: 297–303.
82. Solin LJ, Fowble B, Martz KL, Goodman RL. Definitive irradiation for early stage breast cancer: The university of Pennsylvania experience. Int J Radiat Oncol Biol Phys 1988; 14: 235–42.
83. Bulman AS, Zeitman A, Phillips RH, Ellis H. Interim results of treatment of breast cancer with breast conservation for all patients. Surgery 1987; 101: 395–9.
84. Schnitt SJ, Connolly JL, Harris JR, Hellman S, Cohen RB. Pathologic predictors of early local recurrence in stage I and II breast cancer treated by primary radiation therapy. Cancer 1984; 53: 1049–57.
85. Veronesi U, Volterrani F, Luini A, et al. Quandrantectomy versus lumpectomy for small size breast cancer. Eur J Cancer 1990; 26: 671–3.
86. Fletcher GH. Local results of irradiation in the primary management of localized breast cancer. Cancer 1972; 29: 545–51.
87. Hellman S. Improving the therapeutic index in breast cancer treatment: the Richard and Hinda Rosenthal Foundation Award Lecture. Cancer Res 1980; 40: 4335–42.
88. Fisher ER, Sass R, Fisher B, et al. Pathologic findings from the national surgical adjuvant breast project (Protocol 6). Cancer 1986; 57: 1717–24.
89. Solin LJ, Fowble B, Martz K, Pajak TF, Goodman RL. Results of re-excisional biopsy of the primary tumor in preparation for definitive irradiation of patients with early stage breast cancer. Int J Radiat Oncol Biol Phys 1986; 12: 721–5.
90. Pezner RD, Lipsett JA, Desai K, et al. To boost or not to boost: Decreasing radiation therapy in conservative breast cancer treatment when 'inked' tumor resection margins are pathologically free of cancer. Int J Radiat Oncol Biol Phys 1988; 14: 873–7.
91. Freeman CR, Belliveau NJ, Kim TH, Boivin J-F. Limited surgery with or without radiotherapy for early breast carcinoma. J Can Assoc Radiol 1981; 32: 125–8.
92. Kurtz JM, Amalric R, Ayme Y, Bressac C, Spitalier J-M. Risk factors for breast recurrence in premenopausal and postmenopausal patients with ductal cancers treated by conservation therapy. Cancer 1990; 65: 1867–78.
93. Mansfield CM. Intraoperative Ir-192 implantation for early breast cancer. Techniques and results. Cancer 1990; 66: 1–5.
94. Pierquin B, Owen R, Maylin C, et al. Radical radiation therapy of breast cancer. Int J Radiat Oncol Biol Phys 1980; 6: 17–24.
95. Recht A, Silver B, Schnitt S, Connolly J, Hellman S, Harris JR. Breast relapse following primary radiation therapy for early breast cancer. I Classification, frequency and salvage. Int J Radiat Oncol Biol Phys 1985; 11: 1271–6.
96. Krishnan EC, Krishnan L, Cytaki EP, et al. Radiobiological advantages of an immediate interstitial boost dose in conservative treatment of breast cancer. Int J Radiat Oncol Biol Phys 1990; 18: 419–24.
97. Aas T, Valen B, Varhaug JE, Mella O. Breast-conserving surgery of cancer mammae. Results from Haukeland sykehus 1983–1988. (In Norwegian.) Nord Med 1990; 105: 109–12.
98. Wallgren A, Arner O, Bergström J, et al. Radiation therapy in operable breast cancer: Results from the Stockholm trial on adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 1986; 12: 533–7.
99. Cuzick J, Stewart H, Peto R, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Cancer Treat Rep 1987; 71: 15–25.
100. Rose MA, Craig Henderson I, Gelman R, et al. Premenopausal breast cancer patients treated with conservative surgery, radiotherapy and adjuvant chemotherapy have a low risk of local failure. Int J Radiat Oncol Biol Phys 1989; 17: 711–7.

101. Buzdar AU, McNeese MD, Hortobagyi GN, et al. Is chemotherapy effective in reducing the local failure rate in patients with operable breast cancer? Cancer 1990; 65: 394–9.
102. Epstein AH, Connolly JL, Gelman R, et al. The predictors of distant relapse following conservative surgery and radiotherapy for early breast cnacer are similar to those following mastectomy. Int J Radiat Oncol Biol Phys 1989; 17: 755–60.
103. Calle R, Vilcoq JB, Zafrani B, Vielh P, Fourquet A. Local control and survival of breast cancer treated by limited surgery followed by irradiation. Int J Radiat Oncol Biol Phys 1986; 12: 873–8.
104. Kurtz JM, Spitalier J-M, Amalric R, et al. Mammary recurrences in women younger than forty. Int J Radiat Oncol Biol Phys 1988; 15: 271–6.
105. Solin LJ, Fowble B, Schultz DJ, Goodman RL. Age as a prognostic factor for patients treated with definitive irradiation for early stage breast cancer. Int J Radiat Oncol Biol Phys 1989; 16: 373–81.
106. Høst H, Lund E. Age as a prognostic factor in breast cancer. Cancer 1986; 57: 2217–21.
107. Adami H-O, Malker B, Meirik O, Persson I, Bergkvist L, Stone B. Age as a prognostic factor in breast cancer. Cancer 1985; 56: 898–902.
108. Lindley R, Bulman A, Parsons P, Philips R, Henry K, Ellis H. Histologic features predictive of an increased risk of early local recurrence after treatment of breast cancer by local tumor excision and radical radiotherapy. Surgery 1989; 105: 13–20.
109. Mate TP, Carter D, Fischer DB, et al. A clinical and histopathological analysis of the results of conservation surgery and radiation therapy in stage I and II breast carcinoma. Cancer 1986; 58: 1995–2002.
110. Davis BW, Gelber RD, Goldhirsch A, et al. Prognostic significance of tumor grade in clinical trials of adjuvant therapy for breast cancer with axillary lumph node metastasis. Caner 1986; 58: 2662–70.
111. Rosen PP, Saigo PE, Braun DW, Weathers E, De Palo A. Predictors of recurrence in stage I (T1 N0 M0) breast carcinoma. Ann Surg 1981; 193: 15–25.
112. Nealon TF, Nkongho A, Grossi C, Gillooley J. Pathologic identification of poor prognosis stage I (T1 N0 M0) cancer of the breast. Ann Surg 1979; 190: 129–32.
113. Rosen PP, Kinne DW, Lesser M, Hellman S. Are prognostic factors for local control of breast cancer treated by primary radiotherapy significant for patients treated by mastectomy? Cancer 1986; 57: 1415–20.
114. Osteen RT, Connolly JL, Recht A, Silver B, Schnitt SJ, Harris JR. Identification of patients at high risk for local recurrence after conservative surgery and radiation therapy for stage I or II breast cancer. Arch Surg 1987; 122: 1248–52.
115. Jacquemier J, Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier J-M. An assessment of extensive intraductal component as a risk factor for local recurrence after breast-conserving therapy. Br J Cancer 1990; 61: 873–6.
116. Fisher B, Wolmark N. Conservative surgery: The American experience. Semin Oncol 1986; 13: 425–33.
117. Recht A, Connolly JL, Schnitt SJ, et al. Conservative surgery and radiation therapy for early breast cancer: Results, controversies, and unsolved problems. Semin Oncol 1986; 13: 434–49.
118. Recht A, Connolly JL, Schnitt SJ, et al. The effect of young age on tumor recurrence in the treated breast after conservative surgery and radiotherapy. Int J Radiat Oncol Phys 1988; 14: 3–10.
119. Schnitt SJ, Connolly JL, Khettry U, et al. Pathologic findings on re-excision of the primary site in breast cancer patients considered for treatment by primary radiation therapy. Cancer 1987; 59: 675–81.
120. Martin MA, Welling RE, Strobel SL. Infiltrating lobular carcinoma of the breast treated with segmental and modified radical mastectomy. J Surg Oncol 1989; 41: 117–20.
121. Harris M, Howell A, Chrissohou M, Swindell RIC, Hudson M, Sellwood RA. A comparison of the metastatic pattern of infiltrating lobular carcinoma and infiltrating duct carcinoma of the breast. Br J Cancer 1984; 50: 23–30.
122. Schnitt SJ, Connolly JL, Recht A, Silver B, Harris JR. Influence of infiltrating lobular histology on local tumor control in breast cancer patients treated with conservative surgery and radiotherapy. Cancer 1980; 64: 448–54.
123. Kurtz JM, Jacquemier J, Torhorst J, et al. Conservation therapy for breast cancers other than infiltrating ductal carcinoma. Cancer 1989; 63: 1630–5.
124. Fourquet A, Campana F, Vielh P, Schlienger P, Jullien D, Vilcoq JR. Paget's disease of the nipple without detectable breast tumor. Conservative management with radiation therapy. Int J Radiat Oncol Biol Phys 1987; 13: 1463–5.
125. Osbourne MP, Ormiston N, Harmer CL, McKinna JA, Baker J, Greening WP. Breast conservation in the treatment of early breast cancer. A 20-year follow-up. Cancer 1984; 53: 349–55.
126. Leopold KA, Recht A, Schnitt SJ, et al. Results of conservative surgery and radiation therapy for multiple synchronous cancers of one breast. Int J Radiat Oncol Biol Phys 1989; 16: 11–6.
127. Holmberg L, Zarén E, Adami H-O, Bergström R, Burns T. The patient's appraisal of the cosmetic results of segmental mastectomy in benign and malignant breast disease. Ann Surg 1988; 207: 189–94.
128. McCormick B, Yahalom J, Cox L, Shank B, Massie MJ. The patient's perception of her breast following radiation and limited surgery. Int J Radiat Oncol Biol Phys 1989; 17: 1299–302.
129. Schain W, Edwards BK, Gorrell CR, et al. Psychosocial and physical outcomes of primary breast cancer therapy: mastectomy vs excisional biopsy and irradiation. Breast Cancer Res Treat 1983; 3: 377–82.
130. Bartelink H, van Dam F, van Dongen J. Psychological effects of breast conserving therapy in comparison with radical mastectomy. Int J Radiat Oncol Biol Phys 1985; 11: 381–5.
131. Holmberg L, Omne-Pontén M, Burns T, Adami HO, Bergström R. Psychosocial adjustment after mastectomy and breast-conserving treatment. Cancer 1989; 64: 969–74.
132. Habibollahi F, Mayles HMO, Mayles WPM, et al. Assessment of skin dose and its relation to cosmesis in the conservative treatment of early breast cancer. Int J Radiat Oncol Biol Phys 1988; 14: 291–6.
133. Olivotto IA, Rose MA, Osteen RT, et al. Late cosmetic outcome after conservative surgery and radiotherapy: Analysis of causes of cosmetic failure. Int J Radiat Oncol Biol Phys 1989; 17: 747–53.
134. Rose MA, Olivotto I, Cady B, et al. Conservative surgery and radiation therapy for early breast cancer. Long-term cosmetic results. Arch Surg 1989; 124: 153–7.
135. Harris JR, Levene MB, Svensson G, Hellman S. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. Int J Radiat Oncol Biol Phys 1979; 5: 257–61.
136. Pezner RD, Patterson MP, Hill LR, et al. Breast retraction assessment: An objective evaluation of cosmetic results of patients treated conservatively for breast cancer. Int J Radiat Oncol Biol Phys 1985; 11: 575–8.

137. Baral E, Larsson L-E, Mattsson B. Breast cancer following irradiation of the breast. Cancer 1977; 40: 2905–10.
138. Svensson GK, Kase KR, Chin LM, Harris JR. Dose to the opposite breast as a result of primary radiation therapy for carcinoma of the breast. Int J Radiat Oncol Biol Phys 1981; 7: 1209.
139. Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier J-M. Contralateral breast cancer and other second malignancies in patients treated by breast-conserving therapy with radiation. Int J Radiat Oncol Biol Phys 1988; 15: 277–84.
140. McCredie JA, Inch WR, Anderson M. Consecutive primary carcinomas of the breast. Cancer 1975; 35: 1372–7.
141. Schell SR, Montague ED, Spanos Jr., WJ, Tapley N duV, Fletcher GH, Oswald MJ. Bilateral breast cancer in patients with initial stage I and II disease. Cancer 1982; 50: 1191–4.
142. Givens SS, Ellerbroek NA, Butler JJ, Libshitz HI, Hortobagyi GN, McNeese MD. Angiosarcoma arising in an irradiated breast. A case report and review of the literature. Cancer 1989; 64: 2214–6.
143. Kurtz JM, Amalric R, Delouche G, Pierquin B, Roth J, Spitalier J-M. The second ten years: Long-term risks of breast conservation in early breast cancer. Int J Radiat Oncol Biol Phys 1987; 13: 1327–32.
144. Body G, Sauvanet E, Calais G, Fignon A, Fetissof F, Lansac J. Angiosarcome cutané du sein aprés adénocarcinome mammaire opéré et irradié. J Gynecol Obstet Biol Reprod 1987; 16: 479–83.
145. Ferguson DJ, Sutton HG, Dawson PJ. Late effects of adjuvant radiotherapy for breast cancer. Cancer 1984; 54: 2319–23.
146. Lagios MD, Margolin FR, Westdahl PR, Rose MR. Mammographically detected duct carcinoma in situ. Frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. Cancer 1989; 63: 618–24.
147. Cuzick J, Stewart H, Peto R, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Cancer Treat Rep 1987; 71: 15–29.
148. Swedborg I, Wallgren A. The effect of pre- and postmastectomy, radiotherapy on the degree of edema, shoulder-joint mobility, and gripping force. Cancer 1981; 47: 877–81.
149. Larson D, Weinstein M, Goldberg I, et al. Edema of the arm as a function of the extent of axillary surgery in patients with stage I-II carcinoma of the breast treated with primary radiotherapy. Int J Radiat Oncol Biol Phys 1986; 12: 1575–82.
150. Dewar JA, Sarrazin D, Benhamou E, et al. Management of the axilla in conservatively treated breast cancer: 592 patients treated at Institut Gustave-Roussy. Int J Radiat Oncol Biol Phys 1987; 13: 475–81.
151. Kissin MW, Querci della Rovere G, Easton D, Westbury G. Risk of lymphoedema following the treatment of breast cancer. Br J Surg 1986; 73: 580–4.
152. Bedwani R, Vana J, Rosner D, Schmitz RL, Murphy GP. Management and survival of female patients with 'minimal' breast cancer: as observed in the long-term and short-term surveys of the American College of Surgeons. Cancer 1981; 47: 2769–78.
153. Fisher ER, Sass R, Fisher B, et al. NSABP. Pathologic findings from the national surgical adjuvant breast project (Protocol 6) I. Intraductal carcinoma (DCIS). Cancer 1986; 57: 197–208.
154. Fagerberg G, Baldetorp L, Gröntoft O, Lundström B, Månson JC, Nordenskjöld B. Effects of repeated mammographic screening on breast cancer stage distribution. Results from a randomized study of 92934 women in a Swedish county. Acta Radiol Oncol 1985; 24: 465–73.
155. Andersson I. Radiographic screening for breast carcinoma. II. Prognostic consideration on the basis of a short-term follow-up. Acta Radiol Diagn 1981; 22: 227–33.
156. Rosen PP, Senie R, Schottenfeld D, Ashikari R. Noninvasive breast carcinoma. Frequency of unsuspected invasion and implications for treatment. Ann Surg 1979; 189: 377–82.
157. Lagios MD, Westdahl PR, Margolin FR, Rose MR. Duct carcinoma in situ. Relationship of extent of noninvasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. Cancer 1982; 50: 1309–14.
158. Ashikari R, Hajdu SI, Robbins GF. Intraductal carcinoma of the breast (1960–1969). Cancer 1971; 28: 1182–7.
159. Stotter AT, McNeese M, Oswald MJ, Ames FC, Romsdahl MM. The role of limited surgery with irradiation in primary treatment of ductal in situ breast cancer. Int J Radiat Oncol Biol Phys 1990; 18: 283–7.
160. Carpenter R, Boulter PS, Cooke T, Gibbs NM. Management of screen detected ductal carcinoma in situ of the female breast. Br J Surg 1989; 76: 564–7.
161. Page DL, Dupont WD, Rogers LW, Landenberger M. Intraductal carcinoma of the breast: Follow-up after biopsy only. Cancer 1982; 49: 751–8.
162. Betsill WL Jr, Rosen PP, Lieberman PH, Robbins GF. Intraductal carcinoma. Long-term follow-up after treatment by biopsy alone. JAMA 1978; 239: 1863–7.
163. Gallagher WJ, Koerner FC, Wood WC. Treatment of intraductal carcinoma with limited surgery: Long-term follow-up. J Clin Oncol 1989; 7: 376–80.
164. Price P, Sinnett HD, Gusterson B, Walsh G, A'Hern RP, McKinna JA. Duct carcinoma in situ: predictors of local recurrence and progression in patients treated by surgery alone. Br J Caner 1990; 61: 869–72.
165. Rosen PP, Braun DW, Kinne DE. The clinical significance of preinvasive breast carcinoma. Cancer 1980; 46: 919–25.
166. Andersen J, Blichert-Toft M, Dyreborg U. Carcinoma in situ mammae. Types, growing habits, diagnostics and treatment (In Danish.) Ugeskr Læger 1985; 147: 3306–9.
167. Silverstein MJ, Rosser RJ, Gierson ED, et al. Axillary lymph node dissection for intraductal breast carcinoma—is it indicated? Cancer 1987; 59: 1819–24.
168. Zafrani B, Fourquet A, Vilcoq JR, Legal M, Calle R. Conservative management of intraductal breast carcinoma with tumorectomy and radiation therapy. Cancer 1986; 57: 1299–301.
169. Kurtz JM, Jacquemier J, Torhorst J, et al. Conservation therapy for breast cancers other than infiltrating ductal carcinoma. Cancer 1989; 63: 1630–5.
170. Recht A, Danoff BS, Solin LJ, et al. Intraductal carcinoma of the breast: Results of treatment with excisional biopsy and irradiation. J Clin Oncol 1985; 3: 1339–43.
171. Farrow JH. The James Ewing Lecture. Current concepts in the detection and treatment of the earliest of the early breast cancers. Cancer 1971; 28: 1182–7.
172. Sunshine JA, Moseley HS, Fletcher WS, Krippaehne WW. Breast carcinoma in situ. A retrospective review of 112 cases with a minimum 10-year follow-up. Am J Surg 1985; 150: 44–9.
173. Carter D, Smith RRL. Carcinoma in situ of the breast. Cancer 1977; 40: 1189–93.
174. Fentiman IS, Fagg N, Millis RR, Hayward JL. In situ ductal carcinoma of the breast: implications of disease pattern and treatment. Eur J Surg Oncol 1986; 12: 261–6.
175. Temple WJ, Jenkins M, Alexander F, et al. Natural history of in situ breast cancer in a defined population. Ann Surg 1989; 210: 653–7.

176. Haagensen CD, Lane N, Lattes R, Bodian C. Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. Cancer 1978; 42: 737–69.
177. Rosen PP, Braun DW, Lyngholm B, Urban JA, Kinne DW. Lobular carcinoma in situ of the breast: Preliminary results of treatment by ipsilateral mastectomy and contralateral breast biopsy. Cancer 1981; 47: 813–9.
178. McDivitt RW, Hutter RVP, Foote FW Jr, Stewart FW. In situ lobular carcinoma. A prospective follow-up study indicating cumulative patient risks. JAMA 1967; 201: 96–100.
179. Andersen JA. Lobular carcinoma in situ. A long-term follow-up in 52 cases. Acta Pathol Microbiol Scand Sect. A 1974; 82: 519–33.
180. Curletti E, Giordano J. In situ lobular carcinoma of the breast. Arch Surg 1981; 116: 309–10.