PERGAMON

European Journal of Cancer 36 (2000) 1895–1908

European Journal of Cancer

www.ejconline.com

Current Controversies in Cancer

The impact of loco-regional radiotherapy on the survival of breast cancer patients

B. Cutuli T. Delozier L. Mauriac

Pro:

B. Cutuli *

Radiotherapy Department, Polyclinique de Courlancy, 38 rue de Courlancy, 51100 Reims, France

1. Introduction

Breast cancer includes a wide spectrum of lesions with various evolutionary potentials, ranging from *in situ* carcinoma to inflammatory tumours. In the first case, the evolution is initially local only, but in the second case, the potential metastatic spread is immediate and extremely frequent. Between these two extremes are the great majority of infiltrating carcinomas, which have a wide range of risk of loco-regional and metastatic relapse [1]. In this paper, we would like to argue in favour of the use of modern radiotherapy for infiltrating breast cancer. Firstly, we analyse the impact of radiotherapy after conservative breast surgery, and secondly, we assess the influence of radiotherapy on loco-regional control and survival after mastectomy.

2. Influence of radiotherapy on local control and survival after conservative breast surgery (CBS)

Until now, five randomised trials have compared conservative breast surgery alone and conservative breast surgery with breast irradiation of at least 50 Gy [2–6]. The results are detailed in Table 1. In all cases, radiotherapy resulted in a significant reduction in the local recurrence rates. In four out of five studies, a very small increase in long-term survival was apparent, but the follow-up remains too short to reveal a significant difference. However, in the Canadian trial [2], the arm with radiotherapy already shows a significant reduction in the subsequent metastases rate. Similarly, in the Scottish trial [4], the disease-free survival rates at 8 years were 73% and 53% with and without radiotherapy, respectively. A recent Bayesian analysis of these results confirms that the impact of radiotherapy should appear with a longer follow-up [7]. Moreover, whereas the local recurrence (LR) after CBS has long been considered as a lesser event, several recent papers confirm the unfavourable prognosis of LR, especially when it occurs within 3 years [8–16]. In two series, the relative risk (RR) of occurrence of metastases was three for women who developed LR compared with others without LR [6,15]. This point is illustrated in Table 2. Therefore, the analysis of risk factors for local recurrence becomes very important. With a combination of different parameters, namely clinical, pathological and therapeutic, it is henceforth possible to assess this risk, which varies from 3 to 40% after 10 years. Even in very selected cases, radiotherapy after breast conserving surgery remains essential. In a Boston series including 87 women (with a mean age of 67 years old) with pT_1N_o lesions (and excision margins exceeding 1 cm), 14 relapses (16%) were observed with only a 56-month follow-up [17]. Thus, until now, whole breast irradiation has been an essential component in the breast conservative approach. The exact role of the localised boost is still debated and a European Organization for Research and Treatment of Cancer (EORTC) large trial is still ongoing.

3. Influence of radiotherapy on loco-regional control and survival after mastectomy

3.1. Methodological considerations

The analysis of the impact of post-mastectomy radiotherapy is still under debate. Therefore, it is important

* Tel.: +33-3-26-84-02-84; fax: +33-3-26-84-70-20.
E-mail address: bruno.cutuli@bigfoot.com (B. Cutuli).

PII: S0959-8049(00)00279-3

Table 1
Comparative trials on conservative breast surgery without and with radiotherapy (XRT)

Author [Ref.]	Patients and inclusion criteria	Protocol	Follow-up (months)	LR (%)	OS (%)
Liljegren [5]	184	1) L + AD	120	24	90
	197	2) L + AD + XRT		8.5	91
	Stage I	(54 Gy/27 fr)		$P < 0.0001$	NS
Veronesi [6]	273	1) Q + AD	36[a]	9	UK
	294	2) Q + AD + XRT		0.3	UK
	T < 2.5 cm	(50 Gy/25 fr + 10 Gy/5 fr)		$P = 0.001$	NS
Clark [2]	421	1) L + AD	90[a]	35	76
	416	2) L + AD + XRT		11	79
	T = 4 cm, N0	(40 Gy/16 fr + 12.5/5 fr)		$P < 0.0001$	NS
Fisher [3]	589	1) MRM	144	UK	60
	628	2) L + AD		37	58
	634	3) L + AD + XRT		11	62
	T = 4 cm, N0-1	(50 Gy/25 fr)		$P = 0.001$	NS
Forrest [4]	294	1) L	68[a]	24.5	82
	291	2) L + XRT		5.8	83
	T = 4 cm, N0	(50 Gy: 20–25 fr + 15–30 Gy)			

AD, axillary dissection; LR, local recurrence; OS, overall survival; fr, fractions; L, lumpectomy; UK, unknown; XRT, radiotherapy; Q, quadrantectomy; NS, non significant; MRM, modified radical mastectomy.
[a] Median follow-up.

to note that until now, several data have been inconclusive and contradictory due to major methodological problems [18–21].

The real incidence of loco-regional recurrence (LRR) is difficult to assess. Indeed, there are many differences in patient selection (including several subgroups with various 'levels of risk'), in treatment modalities, such as the quality of axillary surgery (sampling or clearance versus full dissection), in radiotherapy techniques (on target volumes, total delivered dose and energy used) and finally in the use and modalities of adjuvant medical treatment (chemotherapy and tamoxifen). Moreover, the LRR rate can vary widely according to the definitions [19]. Indeed, on the one hand, some studies only included the 'isolated LRR' which generally refers to a first site of failure on the chest wall, or axillary, supraclavicular or internal mammary nodes, without the simultaneous presence of distant metastases. On the other hand, some studies included 'total LRR' with patients with simultaneous distant metastases (usually representing 15–25% of the total). Finally, the variations in the follow-up time can significantly affect the results.

3.2. *Impact of chest wall irradiation*

The chest wall is the most frequent site of relapse after mastectomy (50–60%). It may occur as a unique nodule (in the scar) or multiple nodules and/or zones of derm infiltration, together with inflammation. When patients with multiple loco-regional sites of recurrence are included, the chest wall may be involved in as many as 70–80% of patients. The prognosis of these relapses is very unfavourable with more than 50% experiencing subsequent metastases within 2 years [22–26].

Moreover, the psychological impact is disastrous and the treatment often ineffective, leading to a dramatic and painful loco-regional evolution. In the literature, chest wall irradiation significantly reduces the recurrence rates, especially in cases of nodal involvement and/or advanced lesions, with multiple foci or extensive lymphatic emboli [27–29]. The influence of chest wall irradiation on survival is difficult to assess because in the majority of cases, it is combined with regional nodal irradiation.

Table 2
Influence of local recurrence (LR) on subsequent metastatic risk and/or survival (these series include only isolated and operable LR, thus approximately 85% of cases)

Author [Ref.]	*n*	5-year survival (%)
Kurtz [12]	159	69 (57, 10 years)
Haffty [13]	87	55
Clark [2]	73	50[a]
		78[b]
Veronesi [6]	151	69[c]
Chaudary [15]	45	51[c]
Kemperman [14]	39	66[d]

[a] LR at 4 years.
[b] LR after 4 years.
[c] For patients with LR, the relative risk (RR) of metastasis was 3 compared with patients without LR.
[d] Survival after LR in 72% of patients treated with curative intent.

In a Swedish trial, 960 patients (stage I–III) were randomised into three arms: mastectomy alone (321), mastectomy and loco-regional irradiation (323) and preoperative irradiation and mastectomy (316). The chest wall and regional lymph nodes (axilla, internal mammary chain and supraclavicular fossa) were treated at 45 Gy in 25 fractions of 1.8 Gy [30]. With an 8-year follow-up, the loco-regional recurrence rate was 26% in the control arm versus 7% in both arms with radiotherapy ($P<0.001$). Following chest wall irradiation alone, the recurrence rates were 19% versus 5%, respectively. In a subsequent analysis with a 15-year follow-up, a survival benefit appeared in the irradiated patients of 4% and 9% in patients without and with axillary nodal involvement, respectively.

The impact of chest wall irradiation in patients with stage I–II tumours (T < 5 cm) and without or with a low nodal involvement (one or two axillary lymph nodes), but with a 'limited' excision (<5 mm), was analysed in a recent study with unfortunately only 34 cases [31]. Irradiation seemed to be potentially useful for patients under 50 years of age, since in its absence, the risk of RLP at 8 years was 28% whereas it was 0% for women older than 50 years of age. For T2 and T1 tumours, risks were 24% and 7%, respectively. If the excision margin was less than 2 mm, the risk of RLP was 24% whereas it was only 7% if the excision was wider.

3.3. Impact of the regional nodal irradiation

3.3.1. Radiotherapy of supraclavicular lymph nodes

The supraclavicular fossa is the second most common site of LRR, representing 15–35% of cases. Until now, we have known that irradiation significantly reduces the supraclavicular recurrences (which are the easiest to diagnose) in cases with risk factors such as histological axillary lymph node invasion and large tumours (Table 3) [32–34].

Table 3
Effectiveness of supraclavicular fossa irradiation

	Recurrence rates according to treatment (%)	
Author [Ref.]	Surgery	Surgery + XRT
Mastectomy		
Fletcher [28]	12%	1% (postop: 50 Gy) 2% (preop: 40 Gy)
Salles [32]	–	1.3%
Lumpectomy		
Recht [33]	–	0.6% (pN−) 0% (pN+)
Mazeron [34]	–	0.5% (N0) 2% (N1b)

N, Clinical axillary nodal status; pN, histological axillary nodal status; postop, postoperative; preop, preoperative; XRT, radiotherapy.

3.3.2. Radiotherapy of the internal mammary chain (IMC)

The efficiency of internal mammary chain irradiation is much harder to determine since only a computer tomography (CT) scan may detect a recurrence. Nevertheless, in studies on systematic internal mammary dissection, the invasion risk at this level varied from 7 to 44% in one study [35] and from 0 to 35% in another [24,36] and this risk is almost as important as this at the axillary level. Both these studies have convincingly shown the influence of this involvement on disease-free and global survival. The main risk factors of internal mammary chain involvement are: axillary histological involvement, histological size of the tumour above 2 cm, age under 40 years, whereas the influence of topography is still under debate, even if central and internal lesions are associated with slightly higher risks (Table 4).

The risk of IMC metastases is clearly correlated with the extent of axillary nodal involvement [37]. Veronesi and colleagues showed that internal mammary nodes (IMN) were positive in 17% of women with only one axillary positive node, in 25% with 2 or 3 and in 40% with 4 or more positive nodes [35]. Noguchi and coworkers found IMN metastases in 5% of node-negative women. In contrast, IMN metastases were found in 19% and 52% of women with one to three and more than three axillary-involved nodes, respectively [38].

A recent retrospective study analysed the outcome of 2396 patients treated by quadrantectomy, complete axillary dissection and mammary irradiation, with chemotherapy (classical cyclophosphamide, methotrexate, 5-fluorouracil (CMF)) for patients with axillary involvement [39]. There were 1619 tumours of outer topography and 777 sited in the centro-mammary area or in the inner quadrants. The axillary invasion rates

Table 4
Risk of internal mammary node involvement (IMN+) according to clinical and pathological characteristics[a]

	IMN+ (%)	*P* value
Tumour location		
Inner	19	
Central	22	NS
Outer	18	
T (cm)		
<2	16	
>2	24	0.007
Age (years)		
<40	28	
41–50	20	0.01
>50	16	
pN (Axilla)		
−	9	
+	29	0.00001

NS, non significant.
[a] Modified from Veronesi and colleagues [35].

were 38.1% and 26.3% in both groups, respectively. The metastasis risk and mortality rate have increased by 30% and 20% for central and inner tumours, respectively. These results let us suppose that the absence of irradiation of the internal mammary chain in this study could be the basis of a secondary spreading. This fact suggests that the internal mammary nodes may act as a 'sanctuary' site for metastases and, in the absence of clinically evident recurrence, they represent a source of distant dissemination, especially when adjuvant therapy was not used [19].

3.3.3. *Radiotherapy of axillary lymph nodes*

The risk of axillary recurrence, after a complete axillary dissection (including at least 10 lymph nodes belonging to the low and medium axillary groups), is weak, from 1 to 3% with or without histological axillary involvement, even in cases of extracapsular invasion or massive involvement [33]. In the case of axillary involvement, the adjunction of postoperative radiotherapy reduces the risk of axillary recurrence, but the benefit is weak; on the contrary, the risk of arm lymphoedema increases significantly in up to 25–30% of cases in some series [33,34].

Therefore, after a good axillary dissection, a systematic irradiation of the axilla in cases of nodal involvement has presently been given up by most teams, all the more so because an impact on survival has not been shown [24].

4. Impact of loco-regional irradiation on survival

4.1. *Former studies and meta-analysis*

Two studies [40,41] have also shown a benefit in loco-regional irradiation, but in the first one [40] the irradiation technique had been criticised because numerous patients had been irradiated by 200 kV photons, then by cobalt in full, especially on the internal mammary chain (IMC) with a total dose of 50 Gy in 20 fractions of 2.5 Gy, resulting in numerous long-term heart complications. Furthermore, in this study the chest wall had not been treated. Despite all these problems, there was a cumulative 10-year reduction of the metastasis rate from 54% to 31% in favour of the radiotherapy arm (for patients included in the second part of the trial who were no longer treated using orthovoltage photons). On the contrary, survival improved by only 6% (52% against 46%, P = NS) at 14 years because of an increase in heart-related mortality. A retrospective study by Villejuif [41] showed for the first time the influence of tumour location and the benefit for patients with axillary involvement in inner situations. Postoperative irradiation increased the survival rate from 24 to 44% at 16 years follow-up. The first meta-analysis [42] by the Early Breast Cancer Trialist Collaborative Group (EBTCG) showed a significant reduction of loco-regional isolated recurrences in patients who underwent radiotherapy (6.7% versus 19.6%). The size of this protective effect was not significantly affected by type of axillary surgery, nodal status or age. However, there was no significant difference in 10-year survival among the 17 273 women enrolled in such trials (mortality: 40.3% versus 41.4% with and without radiotherapy, respectively), but this study was open to much criticism. Indeed, it included an extremely heterogeneous series of patients with sometimes small lesions for which no benefit at all could obviously be shown. The other studies also often used insufficient irradiation doses (<45 Gy), or completely unsuitable techniques such as wide irradiation of the internal mammary chain, carried out only with cobalt photons, resulting in long-term heart complications or irradiation carried out with 200 or 250 kV photons. Consequently, these techniques induced an excess of cardiac deaths and other severe side-effects, such as large cutaneous fibrosis and/or lung damage. These facts translated into a reduced risk of death following radiotherapy due to breast cancer (odds ratio, 0.94, $P = 0.03$) but an increased risk of death following radiotherapy from other causes (odds ratio 1.24, $P = 0.002$).

In another meta-analysis taking into account more recent and better conducted trials (notably the Scandinavian trial), a very small benefit in survival in favour of loco-regional irradiation was found [43].

5. Results of recent randomised trials

Three recent randomised trials have clearly shown the impact of loco-regional irradiation not only in terms of local control, but also in terms of global survival, with a benefit of approximately 10% at 10 years [44–46]. The first Danish trial conducted between 1982 and 1989 (protocol 82-b) included 1708 premenopausal women with high risk factors (T > 5 cm and/or with axillary involvement, or histological invasion of the derm or pectoral) [44]. The second trial, carried out between 1982 and 1990 (protocol 82-c) included 1460 postmenopausal women with the same tumour characteristics [45].

All patients of protocol 82-b received nine cycles of chemotherapy (CMF) whereas patients of protocol 82-c received 30 mg of tamoxifen for 1 year. In both cases randomisation involved loco-regional irradiation, where 50 Gy in 25 fractions were given to the chest wall and to every nodal area, including the axilla in the radiotherapy group. The chest wall and internal mammary chain were exclusively treated by a direct electron beam in order to avoid lung and heart toxicity. Results are shown in Tables 5 and 6. The rates of loco-regional recurrences (isolated or with metastases) were 32% in

Table 5
10-year loco-regional recurrence (LRR) rates and disease-free (DFS) and overall survival (OS) rates according to different treatments and clinical/pathological parameters in the 82-b Danish trial (premenopausal women)

	XRT + CMF ($n=852$)			CMF ($n=856$)		
	LRR (%)	Survival (%)		LRR (%)	Survival (%)	
		DFS	OS		DFS	OS
Age (years)						
<40	11	44	55	44	26	38
40–49	8	54	59	29	36	48
50–59	10	40	45	30	34	45
pT (mm)						
<21	6	57	67	25	45	58
21–50	10	43	47	35	28	38
>50	12	37	40	42	22	33
pN						
0	3	74	82	17	62	70
1–3	7	54	62	30	39	54
>3	14	27	32	42	14	20
Grade						
I	6	63	71	29	47	62
II	7	46	52	31	29	40
III	18	35	39	46	20	27
Total	9[a]	48[a]	54[a]	32	34	45

Modified from Overgaard and colleagues [44]. CMF, cyclophosphamide, methotrexate, 5-fluorouracil; XRT, radiotherapy.
[a] All results in XRT arm are statistically different ($P<0.001$) in comparison with the arm without XRT.

Table 6
10-year loco-regional recurrence (LRR) rates and disease-free (DFS) and overall survival (OS) rates according to different treatments and clinical/pathological parameters in the 82-c Danish trial (postmenopausal women)

	XRT + tamoxifen ($n=686$)			Tamoxifen ($n=689$)		
	LRR (%)	Survival (%)		LRR (%)	Survival (%)	
		DFS	OS		DFS	OS
Age (years)						
<60	8	33	43	40	27	36
>60	1	37	46	33	23	37
pT (mm)						
<21	7	43	52	33	28	44
21–50	8	31	42	37	21	32
>50	10	29	30	34	22	29
pN						
0	6	43	56	23	40	55
1–3	6	44	55	31	31	44
>3	11	18	24	46	6	17
Grade						
I	6	44	55	27	29	43
II	9	34	44	39	21	32
III	10	25	26	42	18	29
Total	8[a]	36[a]	45[a]	35	24	36

Modified from Overgaard and colleagues [45]. XRT, radiotherapy.
[a] All results in arm with XRT are statistically different ($P<0.001$ for LRR and DFS and $P=0.03$ for OS) in comparison with the arm without XRT.

the CMF alone group, and 9% ($P<0.001$) in the CMF + radiotherapy group. In addition, survival rates at 10 years were 45% and 54% ($P=0.001$), respectively. These results were updated for postmenopausal patients [45] with a 35% rate of loco-regional recurrence in the tamoxifen alone group and an 8% rate in the tamoxifen + radiotherapy group ($P=0.001$). After a multivariate analysis, the authors confirm that for both trials (82-b and 82-c) additional irradiation increases survival whatever the tumour size, the number of involved lymph nodes and the histoprognostic grade may be. The survival rates are 45% in the tamoxifen + radiotherapy group against 36% ($P=0.003$) in the tamoxifen alone group. A similar result was seen in the two groups for women <60 years of age. The third trial by the Vancouver team was carried out from 1978 to 1986 in 318 premenopausal women with axillary involvement [46]. Every patient had undergone a modified radical mastectomy and firstly 12 then 6 (after 1981) cycles of CMF.

Randomisation would also involve loco-regional irradiation being given to the radiotherapy group which was delivered to the chest wall and inner mammary, supraclavicular and axillary nodes. Every area would be treated by cobalt photons, but the equivalent total doses administered would be less important than those in the Danish trial, approximately 40–45 Gy.

The main results are shown in Table 7. The follow-up of this study is important (150 months) and additional irradiation resulted in a 56% reduction of loco-regional recurrences and 34% of metastases. Breast cancer-related death decreased by 9% at 10 years. As in the Danish

Table 7
Results of the Vancouver trial

	CMF ($n=154$)	CMF + XRT ($n=164$)	
DFS			
10 years	41%	56%	$P=0.007$
15 years	33%	50%	
LRR			
10 years	25%	13%	$P=0.003$
15 years	33%	13%	
Disease-specific survival			
10 years	56%	65%	$P=0.005$
15 years	47%	57%	
Overall survival			
10 years	54%	64%	$P=0.07$
15 years	46%	54%	

Modified from Ragaz and colleagues [46]. DFS, disease-free survival; LRR, loco-regional recurrence rate; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; XRT, radiotherapy.

trial, the reduction in recurrences was observed in every subgroup (pN1-3 and pN > 3).

Both these studies give similar results, and show that a loco-regional irradiation carried out with modern techniques and adequate total doses, significantly reduces loco-regional recurrences but also increases survival, from 45% to 54% at 10 years for the Danish trial ($P < 0.001$) and from 56 to 65% for the Canadian trial ($P = 0.005$), respectively, whether women are menopausal or not.

5.1. Latest meta-analysis

A Belgian team [47] took the data from the EBCTCG meta-analysis in 1995 [42] dealing with the impact of radiotherapy in the treatment of breast cancer. As previously described, only a small benefit on survival at 10 years among approximately 17 000 patients treated was seen. However, after eliminating the 'small trials' (including those with less than 400 cases) and those started before 1970 (whose irradiation techniques and statistical methodology were almost always defective), the benefit on survival was obvious after irradiation of the 7840 remaining patients. One trial was negative, but the daily dose administered was insufficient. Similar results were recently presented by a Canadian team [48]. Eighteen randomised trials including 6367 patients treated from 1973 to 1984 were analysed in detail, with a precise report on the extent of the disease, the degree of axillary dissection, radiation technique and extent of radiation. Moreover, the dose and timing of radiation therapy were also reported. This study showed a reduction following radiotherapy both in local regional recurrence (odds ratio = 0.25, $P < 0.00001$) and mortality (odds ratio = 0.83, $P = 0.004$).

5.2. Long-term toxicity

The data on the long-term toxicity of radiotherapy must be interpreted very carefully. Once again, it is very important to differentiate the quality of modern irradiation techniques from those of former treatments carried out with old, if not dangerous, devices and modalities. The risk of contra-lateral breast cancer has been considered almost non-existent in the majority of studies, whether it be irradiation after mastectomy or after conservative surgery. The risk of developing a secondary oesophagus or lung cancer is also very low and in the few studies addressing this problem [49], it appears that tobacco plays a much more important role, similarly to that which has been observed in Hodgkin's disease. The risk of angiosarcoma after conservative treatment has also been assessed on a very large scale and is less than 1/1000 [50].

Moreover, these studies deal with a series of patients usually treated before the 1980s, thus almost always exclusively treated by cobalt photons. These studies are therefore not comparable with those using modern techniques with the wide use of the electrons of accelerators and regular quality controls. The same considerations apply to heart toxicity [51]. The exclusive use of cobalt photons in a volume which is often important (some patients had been treated on both mammary chains), sometimes with doses in fractions > 2.5 Gy caused coronary stenoses and a myocardial infarction-related high mortality which was shown in a meta-analysis published in 1994 [43]. This high mortality disappeared later with the use of other techniques which allowed underlying critical organs such as the left heart and lung to be spared. Indeed, the Danish group analysed both the 82-b and 82-c trials [52]: among 1545 women without radiotherapy and 1538 women who underwent loco-regional irradiation, the death rate by ischaemic heart disease was the same (0.8 versus 0.9%).

6. Conclusion and technical factors

Further to a mastectomy, an additional loco-regional irradiation carried out with modern techniques greatly improved the loco-regional control (even with the use of adjuvant medical treatments) and survival (by approximately 9%) in high-risk patients [44–47]. From now on, this treatment is indicated in cases with more than three involved axillary lymph nodes [19,44,45,53–56], as well as in those with one to three lymph nodes whatever the age of the patients may be.

In the absence of a lymph node invasion, for tumours under 5 cm, there are no randomised trials showing with certainty the benefit of loco-regional irradiation. Nevertheless, the latter might be useful for tumours of over 3 cm, including multi-focal and/or with multiple lymphatic or vascular emboli, with an inner or central location. Another EORTC trial is presently trying to answer this question.

Considering the increase in indications of adjuvant treatments, especially high doses of anthracyclines (type FEC 100: 5-fluorouracil, epirubicin, cyclophosphamide), the optimisation of techniques is essential in order to avoid potential cardiopulmonary toxicity [57]. The most important point concerns the internal mammary chain irradiation technique, which must include the first three or four intercostal spaces at approximately 2.5–3 cm deep and 3–5 cm laterally to the median line. This treatment should be carried out by a photon/electron-mixed direct beam which must represent at least 50% of the administered dose (in rule of 9–12 MeV after a CT scan or an ultrasound evaluation, in order to avoid the lung and heart, since the energy is not delivered more than 3 or 4 cm deep). The best technique is the use of alternating beams (photons and electrons), whether daily or weekly [58]. The total dose must not exceed 50 Gy with fractions of 2 Gy. The irradiation of the lower part of the axilla does not seem to be useful if a good dissection was carried out (with usually a sampling of 10 lymph nodes). Finally, use of loco-regional irradiation must be adapted to the chemotherapy treatment. Usually, the latter is postponed after mastectomy, but it can be carried out concomitantly during conservative treatments provided that there are certain precautions and a careful monitoring. As for other tumour locations, loco-regional control remains for breast cancer an essential factor in reducing the risk of distance diffusion and metastases [59–61].

References

1. Tubiana M. Postoperative radiotherapy and the pattern of distant spread in breast cancer. In Fletcher GH, Levitt SH, eds. *Non-disseminated Breast Cancer. Controversial Issues in Management*. Berlin, Springer-Verlag, 1993, 11–26.
2. Clark RM, Whelan T, Levine M, *et al*. Randomised clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst* 1996, **88**, 1659–1664.
3. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DKL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995, **333**, 1456–1461.
4. Forrest AP, Stewart HJ, Everington D, *et al*. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet* 1996, **348**, 708–713.
5. Liljegren G, Holmberg L, Bergh J, *et al*. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomised trial. *J Clin Oncol* 1999, **17**, 2326–2333.
6. Veronesi U, Luini A, Del Vecchio M, *et al*. Radiotherapy after breast-preserving surgery in women with localised cancer of the breast. *N Engl J Med* 1993, **328**, 1587–1591.
7. Levitt SH, Aeppli DM, Nierengarten ME. The impact of radiation on early breast carcinoma survival. A Bayesian analysis. *Cancer* 1996, **78**, 1035–1042.
8. Cutuli B, Velten M, Karst A, Jaeck D, Renaud R, Rodier JF. Dosimetric breast size: a new and useful parameter for the prediction of local recurrence after breast conservative treatment. *Eur J Cancer* 1997, **33**, 2432–2434.
9. Fortin A, Larochelle M, Laverdiere J, Lavertu S, Tremblay D. Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. *J Clin Oncol* 1999, **17**, 101–109.
10. Chauvet B, Simon JM, Reynaud-Bougnoux A, *et al*. Récidives mammaires après traitement conservateur des cancers du sein: facteurs prédictifs et signification pronostique. *Bull Cancer* 1990, **77**, 1193–1205.
11. Elkhuizen PH, Van ED, Vijver MJ, *et al*. Local recurrence after breast-conservating therapy for invasive breast cancer: high incidence in young patients and association with poor survival. *Int J Rad Oncol Biol Phys* 1998, **40**, 859–867.
12. Kurtz JM. Radiation therapy and breast preservation: past achievement, current results, and future prospects. *Semin Surg Oncol* 1992, **8**, 147–152.
13. Haffty BG, Reiss M, Beinfield M, Fisher D, Ward B, McKhann C. Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. *J Clin Oncol* 1996, **14**, 52–57.
14. Kemperman H, Borger J, Hart A, Perse H, Bartelink H, Van Dongen J. Prognostic factors for survival after breast conserving therapy for stage I and II breast cancer. The role of local recurrence. *Eur J Cancer* 1995, **31A**, 690–698.
15. Chaudary MA, Nagadowska M, Smith P, Gregory W, Fentiman IS. Local recurrence after breast conservation treatment: outcome following salvage mastectomy. *Breast* 1998, **7**, 33–38.
16. Veronesi U, Marubini E, Del Vecchio M, *et al*. Local recurrence and distant metastases after conservative breast cancer treatments: partly independent events. *J Natl Cancer Inst* 1995, **87**, 19–27.
17. Schnitt SJ, Hayman J, Gelman R, *et al*. A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. *Cancer* 1996, **77**, 1094–1100.
18. Rutqvist LE. Radiation therapy as an adjunct to primary surgery in early stage breast cancer: biological and clinical rationale. *Semin Radiat Oncol* 1999, **9**, 217–222.
19. Fowble B. Postmastectomy radiation in patients with one to three positive axillary nodes receiving adjuvant chemotherapy: an unresolved issue. *Semin Radiat Oncol* 1999, **9**, 230–240.
20. Arriagada R, Rutqvist LE, Le MG. Postmastectomy radiotherapy: randomized trials. *Semin Radiat Oncol* 1999, **9**, 275–286.
21. Overgaard M. Overview of randomized trials in high risk breast cancer patients treated with adjuvant systemic therapy with or without postmastectomy irradiation. *Semin Radiat Oncol* 1999, **9**, 292–299.
22. 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**, 33–39.
23. Recht A. The return (?) of postmastectomy radiotherapy. *J Clin Oncol* 1995, **13**, 2861–2864.
24. FNCLCC. *Standards, Options et Recommandations. Vol. 3 Cancers du Sein non Métastatiques*. Paris, Arnette Bleckwell, 1996.
25. Stefanik D, Goldberg R, Byrne P, *et al*. Local-regional failure in patients treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1985, **3**, 660–665.
26. Valagussa P, Bonadonna G, Veronesi U. Patterns of relapse and survival following radical mastectomy. Analysis of 716 consecutive patients. *Cancer* 1978, **41**, 1170–1178.
27. Auquier A, Rutqvist LE, Hoss H, Rotstein S, Arriagada R. Postmastectomy megavoltage radiotherapy: the Oslo and Stockholm Trials. *Eur J Cancer* 1992, **28A**, 433–437.
28. Fletcher GH, Neese MC, Oswald MJ. Long-range results for breast cancer patients treated by radical mastectomy and postoperative radiation without adjuvant chemotherapy: an update. *Int J Radiat Oncol Biol Phys* 1989, **17**, 11–14.
29. Edland RW. Presidential address: does adjuvant radiotherapy have a role in the postmastectomy management of patients with operable breast cancer, revisited? *Int J Radiat Oncol Biol Phys* 1988, **15**, 519–535.
30. Rutqvist LE, Petterson D, Johansson H. Adjuvant radiation therapy versus surgery alone in operable breast cancer: long-term follow-up of a randomized clinical trial. *Radiother Oncol* 1993, **26**, 104–110.
31. Freedman GM, Fowble BL, Hanlon AL, *et al*. A close or positive margin after mastectomy is not an indication for chest wall irradiation except in women aged fifty or younger. *Int J Radiat Oncol Biol Phys* 1998, **41**, 599–605.
32. Salles G, Romestaing P, Salerno N, Mahe M, Santena I, Gerard JP. La radiothérapie après mastectomie. Efficacité et tolérance à partir de l'étude de 557 observations. *Lyon Chir* 1990, **86**, 376–382.
33. Recht A, Houlihan MJ. Axillary lymph nodes and breast cancer. A review. *Cancer* 1995, **76**, 1491–1512.
34. Mazeron JJ, Otmezguine Y, Huart J, Pierquin B. Conservative treatment of breast cancer: results of management of axillary lymph node area in 3 353 patients. *Lancet* 1985, **1**, 1387–1395.

35. Veronesi U, Cascinelli N, Bufalino R, *et al*. Risk of internal mammary lymph nodes metastases and its relevance on prognosis of breast cancer patients. *Ann Surg* 1983, **198**, 681–684.
36. Bobin JY, Mayer M, Crozet B, Clavel M. Place du curage mammaire interne dans la stratégie thérapeutique moderne du cancer du sein. *Lyon Chir* 1984, **80**, 141–144.
37. Freedman GM, Fowble BL, Nicolau N, *et al*. Should internal mammary lymph nodes in breast cancer be a target for the radiation oncologist? *Int J Radiat Oncol Biol Phys* 2000, **46**, 805–814.
38. Noguchi M, Otha N, Koyanski N, *et al*. Reappraisal of internal mammary nodes metastases as a prognostic factor in patients with breast cancer. *Cancer* 1991, **68**, 1918–1925.
39. Zucali R, Mariani L, Marubini E, *et al*. Early breast cancer: evaluation of the prognostic role of the site of the primary tumor. *J Clin Oncol* 1998, **16**, 1363–1366.
40. Host H, Brennhovd ID, Loeb M. Post-operative radiotherapy in breast cancer. Long term results from OSLO Study. *Int J Radiat Oncol Biol Phys* 1986, **12**, 727–732.
41. Arriagada R, Le MG, Mouriesse H. Long-term effect of internal mammary chain treatment. Results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. *Radiother Oncol* 1988, **3**, 311–318.
42. Early Breast Cancer Trialist Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *N Engl J Med* 1995, **333**, 1444–1455.
43. Cuzick J, Stewart H, Rutqvist L, *et al*. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 1994, **12**, 447–453.
44. Overgaard M, Hansen PS, Overgaard J, *et al*. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 1997, **337**, 949–955.
45. Overgaard M, Jensen MB, Overgaard J, *et al*. Postoperative radiotherapy in high-risk post-menopausal breast cancer given adjuvant Tamoxifen; Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999, **353**, 1641–1648.
46. Ragaz J, Jackson SM, Le N, *et al*. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997, **337**, 956–962.
47. Van De Steene J, Soete G, Storme G. Adjuvant radiotherapy for breast cancer significantly improves survival: the missing link. *Radiother Oncol* 2000, **55**, 263–272.
48. Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer A meta-analysis? *J Clin Oncol* 2000, **18**, 1220–1229.
49. Inskip PD, Stovall M, Flannery JY. Lung cancer risk and radiation dose among women treated for breast cancer. *J Natl Cancer Inst* 1994, **86**, 983–988.
50. Marchal C, Weber B, De Lafontan B, *et al*. Nine breast angiosarcomas after conservative treatment for breast carcinoma: a survey from French Comprehensive Cancer Centers. *Int J Radiat Oncol Biol Phys* 1999, **44**, 113–119.
51. Kuske RR. Adjuvant chest wall and nodal irradiation: maximize cure, minimize late caridac toxicity. *J Clin Oncol* 1998, **16**, 2579–2588.
52. Højris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast cancer after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomized trials. *Lancet* 1999, **354**, 1425–1430.
53. Recht A, Bartelink H, Fourquet A, *et al*. Postmastectomy radiotherapy: questions for the twenty-first century. *J Clin Oncol* 1998, **16**, 2886–2889.
54. Korzeniowski S. "One to three" or "four or more"? Selecting patients for postmastectomy radiation therapy. *Cancer* 1997, **80**, 1357–1358.
55. Marks LB, Prosnitz KR. "One to three" or "four or more". Selecting patients for postmastectomy radiation therapy. *Cancer* 1997, **79**, 668–670.
56. Vicini FA, Horwitz EM, Lacerna MD, *et al*. The role of regional nodal irradiation in the management of patients with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys* 1997, **39**, 1069–1076.
57. Hijiyiannakis P, Yarnold JR. Mixing anthracyclines and radiotherapy in early breast cancer: how safe is it? *Eur J Cancer* 1996, **32A**, 1845–1848.
58. Cutuli B. Cancer du sein: intérêt de l'irradiation loco-régionale postopératoire après mastectomie. *Presse Med* 2000, **29**, 439–446.
59. Koscienly S, Tubiana M. The link between local recurrence and distant metastases in human breast cancer. *Int J Radiat Oncol Biol Phys* 1999, **43**, 11–24.
60. Gelman R, Harris JR. Editorial comment on "the link between local recurrence and distant metastases in human breast cancer" by Serge Koscienly and Maurice Tubiana. *Int J Radiat Oncol Biol Phys* 1999, **43**, 7–9.
61. Recht A, Gray R, Davidson NE, *et al*. Locoregional failure risk after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999, **17**, 1689–1700.

Contra:

T. Delozier *

Centre Francois-Baclesse, Service de Radiotherapie, B.P. 5026, F-14076, Caen Cedex 5, France

1. Introduction

Radical mastectomy was the first effective procedure in breast cancer. More extensive surgery does not improve long-term survival and less aggressive local treatment gives identical long-term survival to radical mastectomy. Modified radical mastectomy, and even more conservative procedures such as lumpectomy are now widely used.

Postoperative radiotherapy is another important local treatment. It is always performed after breast conservative surgery and frequently after mastectomy. The aim of postoperative radiotherapy is to reduce locoregional recurrences, therefore reducing mortality.

With technical progress, major postradiotherapy complications are less frequent, however its indications must be limited to patients for whom benefit is proved

* Tel.: +33-231-45-5050; fax: +33-231-45-5074.
E-mail address: t.delozier@baclesse.fr (T. Delozier).

PII: S0959-8049(00)00281-1