Adjuvant Radiotherapy in Breast Cancer

The Treatment of Lymph Node Areas

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Acta Oncologica Vol. 39, No. 3, pp. 295–305, 2000

Adjuvant radiotherapy decreases the risk of locoregional recurrences threefold, according to the results of many randomized trials and overviews. In patients treated with total mastectomy, the risk of local recurrence is mainly related to the number of involved axillary nodes, i.e. about 25%, 35% and 55% at 10 years when 1–3, 4–9 and 10 or more nodes are involved, respectively. In contrast, at 10 years, less than 15% of patients with negative axillary nodes relapse locally. The effect of adjuvant radiotherapy on distant metastases and overall survival is a controversial issue. On the one hand, recent results are compatible with the existence of a mechanism of secondary dissemination generated from locoregional tumor nests. The beneficial effect of radiotherapy can be observed whether with or without adjuvant systemic treatment. On the other hand, a deleterious late toxic effect, mainly cardiac, has also been shown. The importance of improvements in radiation techniques and quality assurance to obtain a positive balance in terms of overall survival is emphasized.

Received 22 June 1999
Accepted 18 October 1999

Patients with resected early breast cancer without adjuvant radiotherapy have a high risk of locoregional recurrence (1–3). This risk is related to some prognostic factors, the most important being axillary node involvement in patients treated with total mastectomy (4–6), while in those treated with breast-conserving surgery the most important factors are tumor related, such as tumor size and histologic grade, and host factors, such as age (7). Locoregional radiotherapy decreases the risk of local recurrence threefold, and this effect is quantitatively similar for both patients treated with mastectomy or breast-conserving surgery (3, 8). The use of radiotherapy with this particular aim is largely accepted, except for patients who have a low risk of locoregional recurrence, i.e. equal or less than 10% at 10 years. The most controversial issues are the irradiation of lymph node areas and the possible effect of adjuvant radiotherapy on overall survival. The systemic hypothesis (9, 10) does not recognize that the latter effect exists, by arguing that distant metastases are already generated by the primary tumor at the time of local treatment.

Locoregional recurrences are generated from tumor cells left at the time of surgery in the tumor bed defined widely, i.e. breast, chest wall, axillary and internal mammary chain lymph nodes. Local recurrence may develop after a variable free interval that probably depends on the tumor duplication time, the presence of hormonal receptors in the tumor and patient factors, such as age.

The existence of the secondary dissemination phenomenon, i.e. possibility of metastasis generated from locoregional tumor nests, is a matter of controversy (11–28). However, this hypothesis may be evaluated through the effect of locoregional treatments on distant metastasis rates or on overall survival. These latter effects would benefit patients at high risk of local recurrence and without microscopic distant metastases at the time of primary treatment. However, more recently, the interest in locoregional, postoperative radiotherapy may be extended to patients with microscopic distant metastases who benefit from adjuvant hormonal treatment and/or chemotherapy. Therefore, adjuvant radiotherapy including regional lymph node areas may have a current interest in the management of early breast cancer, as it has been recently reported in three randomized trials (29–31). We analyze this role as it has been evaluated in the medical literature, with special emphasis on the results of randomized trials.

NATURAL HISTORY

William Halsted (32) defined the basis of oncologic surgery, including unresectability criteria and the basis of en-bloc surgery. This approach was based on the concept that cancer was limited, first, to the breast and then to the regional nodes. Tumor extension was supposed to follow a step-by-step process and distant dissemination was sec-

 ISSN 0284-186X

ondary to locoregional extension. We know that this process of tumor progression is not a rule in all cases and that direct hematogenous dissemination is a common mechanism, but in effect the concept predicted that locoregional treatment could cure selected patients with breast cancer. In radical mastectomy clinical series, it has been shown that long-term survival is possible in patients who do not receive adjuvant systemic treatment. For instance, it has been reported that among 1 458 patients, 43% were free of cancer at 30-years' follow-up (33). At the Institut Gustave-Roussy (IGR), among 1 425 patients with positive axillary nodes, 30% of patients were alive at 25 years' follow-up without adjuvant chemotherapy (4).

Results of breast-conserving surgery series have been considered by many authors as an argument against the Halstedian hypothesis. However, this is related to confusion between the concept and the Halsted operation itself. Indeed, breast-conserving surgery (and postoperative radiotherapy) is as a complete local treatment as the radical or extended mastectomy (3). This statement is corroborated by the results of the first randomized trial on breast-conserving surgery, coordinated at Guys' Hospital in London (34). The results showed that patients with positive axillary nodes had a higher survival rate if treated by radical mastectomy as compared to breast-conserving surgery. However, patients treated in the latter group did not have a complete axillary dissection and received a very low total radiation dose to the breast and lymph node areas (between 25 and 36 Gy). These patients developed a high rate of locoregional recurrence and eventually a lower survival rate. In summary, the Guys' trial showed that non-radical local treatment might have an impact on overall survival.

PARAMETERS OF RADIATION TREATMENTS

To analyze the randomized trials on lymph-node irradiation, it would be useful to consider some basic aspects on parameters of radiotherapy, such as energy, total dose, dose per fraction, target volumes and critic organs.

1) *Energy*: This parameter is related to the dose distribution and percentage of depth dose. Before the 1950s and the use of Co60 photons, radiation oncologists used kilovoltage x-rays that gave 100% of the dose to the skin, whereas megavoltage radiotherapy (Co60 photons have an energy of 1.25 Mega-electron Volt or MV) allows the sparing of the first millimeters of skin with a better dose distribution in depth. At the present time, Co60 photons or 4–6 MV photons produced by a linear accelerator is the standard therapy for the treatment of breast cancer patients. Linear accelerators also allow the direct use of electrons, the main characteristic of electrons being that, as particles, they are absorbed in the first centimeters of depth with a complete spare of deep tissues.

2) *Total dose*: The importance of total dose in terms of locoregional control and complications has been clearly established for all tumors, including breast cancer (8, 35–38). In summary, a total dose equivalent to 45 Gy in conventional fractionation gives a threefold decrease in the relative risk of local recurrence, for instance from 30% to 10% at 10 years. Increasing the dose beyond 45 Gy would give a twofold decrease in the risk of recurrence with each increase of 15 Gy, for instance from 10% to 5% at 10 years, justifying the use of boost-dose in patients treated with breast-conserving surgery (8). The latter hypothesis has been evaluated in two randomized trials, one already published included 1 024 patients (39) and the other included more than 5 000 patients (40) whose results are awaited. These considerations stress the importance of total dose as a critical parameter in terms of local control.

3) *Dose per fraction*: Conventional fractionation is defined as 5 fractions of 2 Gy per week; below this value the radiobiological effect is decreased (lost in local control) and above this value the effect is increased mainly in normal tissues, with an increment of complications or treatment sequelae (36, 41).

4) *Target volumes*: The total radiation treatment after mastectomy includes the chest wall, the axillary, supraclavicular and the internal mammary chain (IMC) lymph nodes. The regional treatment varies from one center to another and from one trial to another. It has been shown that axillary irradiation is not needed after complete axillary dissection and that the postoperative treatment only increases the arm complication rate (42, 43). Thus, lymph node irradiation is currently limited to the apex of the axilla, supraclavicular and IMC, except for cases in which a massive involvement of the axillary fat tissue is found (44, 45). Irradiation of the breast or chest wall is generally performed, as this is the major site of failure. The irradiation of the IMC is based on the high risk of lymph node involvement when axillary nodes are involved; tumor site is not a strong predictive factor of IMC involvement as shown in an IMC dissection trial (46). In a total of 631 patients with node-negative axillae, the histologic IMC involvement was about 10%, whereas in 795 patients with node-positive axillae, the IMC involvement was 22% for external tumors and 37% for internal or central tumors. The supraclavicular nodes are currently irradiated if the IMC is treated, as was done in the Oslo II trial (47), but supraclavicular irradiation has not been specifically evaluated in a randomized trial.

5) *Organs at risk*: The most important organs at risk in the adjuvant setting are the lungs and heart. Their irradiation at full dose, even if partially, may induce significant late complications. As the treatment of the axillary and supraclavicular area can increase the risk of lymph edema, the treated volume should be restricted and overlapping of fields avoided; with a good technique, plexopathy should not be observed at the usual delivered doses (41).

RANDOMIZED TRIALS: MATERIAL AND METHODS

The major randomized trials that each included more than 500 patients, evaluating postoperative radiotherapy and conducted on patients primarily treated with mastectomy with or without axillary dissection, are summarized in Table 1.

The Manchester trial (48, 49)

This trial was performed between 1949 and 1955, and included a total of 1 461 patients who were treated with radical mastectomy. The trial was carried out in two periods. Between 1949 and 1952 patients in the radiotherapy arm were treated with the 'quadrate' technique, including chest wall and the apex of the axilla. From 1952 to 1955, the 'peripheral' technique was used, including the apex of the axilla, the supraclavicular and IMC nodes, but excluding the chest wall. All patients were treated with kilovoltage.

The NSABP-02 trial (50)

This trial was conducted from 1961 to 1968 and included 1 882 patients. Postoperative radiotherapy was given with kilo- or megavoltage. The control group also included patients receiving adjuvant Thio-TEPA. This trial, not included in Table 2, has been criticized because only 1 103 patients (59%) were considered eligible for analysis.

The CRC trial (51–55)

This large trial included, from 1970 to 1975, 2 800 patients treated with mastectomy without axillary dissection. All volumes were treated with mega or kilovoltage at a variable total dose from 28.5 to 46 Gy.

The NSABP-04 trial (56–59)

The trial included 1 765 patients and was conducted from 1971 to 1974. Patients were treated with or without axillary dissection, and with the megavoltage technique in the RT arm. Only 717 patients treated with total mastectomy without axillary dissection are included in Tables 1 and 2, as the other groups were confounded by the type of surgery.

The Oslo trials

The first Oslo trial (47, 60), conducted from 1964 to 1967, included 546 patients treated with the kilovoltage technique in the radiotherapy arm. The second Oslo trial (47, 61), from 1968 to 1972, included 542 patients and used Co60 to treat the supraclavicular and IMC nodes (excluding the chest wall) by an anterior direct field. All patients included in the trial received ovarian irradiation.

The Stockholm trial (62, 63)

This trial was conducted from 1971 to 1976 and included 960 patients in three arms: control, preoperative and post-

Table 1

Large unconfounded randomized trials (at least including 500 patients) evaluating post-mastectomy radiotherapy

Trial[1] (reference)	Axillary Dissection	Adjuvant systemic treatment	No. of patients	Energy[2] (voltage)	Total dose	Fraction size	Target volume[3]
Manchester Q[4] (48, 49)	Yes	No	720	KV	3 500–4 000 Röentgen	233–266 Röentgen	Chest wall, axilla
Manchester P[5] (48, 49)	Yes	No	741	KV	3 250–4 250 Röentgen	217–283 Röentgen	Chest wall excluded
CRC (51–55)	No	No	2 800	KV/MV	28.5–46 Gy	Variable	Standard
NSABP 04[6] (56–59)	No	No	717	MV	45 Gy	1.8 Gy	Standard
Oslo I (60)	Yes	Ovarian ablation	546	KV	25–41 Gy	Variable	Standard
Oslo II (47, 61)	Yes	Ovarian ablation	542	MV	50 Gy	2.5 Gy	Chest wall excluded
Stockholm (62–64)	Yes	No	960	MV	45 Gy	2.0 Gy	Standard
DBCG (29) Premenopausal	Yes	CMF	1 708	MV	48–50 Gy	2.0–2.18 Gy	Standard
DBCG (30) Postmenopausal	Yes	Tamoxifen	1 375	MV	48–50 Gy	2.0–2.18 Gy	Standard

[1] Each trial included at least 500 patients, totaling 10 109 patients.
[2] KV = kilovoltage; MV = megavoltage.
[3] Standard target volume: includes chest wall, axilla, supraclavicular and IMC nodes.
[4,5] Quadrate and peripheral technique: see text.
[6] Includes only clinical node-negative patients.

Table 2

Main results of large, unconfounded, randomized trials (at least 500 patients) evaluating post-mastectomy radiotherapy

Trial (reference)	No. of patients RT/control	Loco-regional recurrence rate (%)	Metastasis-free rate (%)	Overall survival rate (%)	Comments
Manchester Q (48)	327/393	29/48	–	55/57	Crude rates
Manchester P(48)	382/359	28/45	–	57/61	Crude rates
CRC (51)	1376/1424[1]	11/30	67/65	73/70	5-year rates
NSABP 04 (59)	352/365	5/12	69/71	59/54	10-year rates
Oslo I (60, 61)					
Stage I	173/172	5/8	86/87	75/75	10-year rates
Stage II	109/92	11/35	58/57	49/43	
Oslo II (47)					
Stage I	170/186	2/5	53/44	73/80	10-year rates
Stage II	95/91	10/22	67/51	58/50	
Stockholm (63)	316 preop	11			
	323 postop	9			15-year rates
	321 control	33			
Postop, Stage I	204/197	5/23	74/75	67/62	
Postop, Stage II	118/120	15/48	48/31	39/30	
DBCG (29)	852/856	9/32*	66/74*	54/45**	*Crude rates
Premenopausal					**10-year rates
DBCG (30)	686/689	8/35*	39/25**	45/36***	*Crude rates
					**Crude rates of metastases
Postmenopausal					***10-year rates

RT = adjuvant radiotherapy; Preop = preoperative radiotherapy; Postop = postoperative radiotherapy.
[1] Results are given for 2 243 evaluable patients.

operative radiation therapy. All volumes were treated with two megavoltage techniques along two periods of the trial (64).

The Danish trials (29, 30)

These trials were conducted from 1982 to 1989 and included 1 708 premenopausal patients receiving adjuvant CMF chemotherapy and in 1 375 postmenopausal patients receiving treatment with tamoxifen. All volumes were treated with megavoltage techniques.

RESULTS OF RANDOMIZED TRIALS

The main results of the largest trials, as reported by the trialists, are presented in Table 2. All of these trials show a significant decrease in locoregional recurrence when adjuvant radiotherapy is given, but without any significant effect of post-mastectomy radiotherapy on overall survival, except in the Danish trials.

In the 1990s, a joint study was conducted on the two largest randomized trials without adjuvant chemotherapy—Oslo and Stockholm—using the megavoltage technique (65). Results were divided according to the risk of locoregional recurrence, i.e. patients with negative and positive axillary nodes. The effect of radiotherapy in axillary node-negative patients was negligible in terms of distant recurrence or overall survival. However, there was a beneficial effect of radiation in axillary node-positive patients, with a significant decrease in distant recurrence rate ($p = 0.001$) and a marginally significant improvement in overall survival ($p = 0.06$). The main results are summarized in Table 3.

A more detailed analysis was carried out in the Stockholm material. Radiotherapy produced a fivefold decrease in the risk of local recurrence ($p < 0.0001$). In axillary node-positive patients, the treatment decreased the risk of distant dissemination with a relative risk of 0.63. The multivariate analysis using local recurrence as a time-dependent covariate suggests that the decrease in distant metastases was related to local recurrence prevention (12). A similar effect was found in models that used overall death as the endpoint. These results are in line with those published by Whelan & Fisher (14, 15) in a breast-conserving surgery series. In the analysis of pattern of failure, it would be important to take into account different endpoints as competing events. Without this kind of analysis, it would be more appropriate to consider the total incidence of distant metastasis. For instance, in the Danish trial on premenopausal patients, the total incidence of distant failure was 52% in the control group compared with 42% in the irradiated group.

In summary, the largest randomized trials on post-mastectomy radiotherapy showed an important reduction in locoregional recurrence. Reduction effects on distant metastasis and overall death were suggested in modern

megavoltage trials, when fine-tuned analyses were done, and in the Danish trials in the presence of systemic adjuvant treatments.

OVERVIEWS

The main advantage of overviews (or meta-analyses based on individual patient data) is the increase of statistical power to detect moderate effects. Trials included in the overview should be unconfounded, i.e. the only difference between trial arms should be the evaluated treatment. Another advantage is to decrease the publication bias, as all related trials are included after an exhaustive search. The main disadvantage is the heterogeneity between trials. This heterogeneity is not generally detected by formal statistical tests that have a low sensitivity. This drawback is more pronounced in treatments in which many parameters can vary from one trial to the next. More specifically, in the overviews of post-mastectomy radiotherapy, the evaluation has generally not taken into account factors such as lymph node status, energy (kilo- or megavoltage), total radiation dose (from 18 to 60 Gy), dose per fraction, technique (dose to critical organs), different volumes treated (chest wall or lymph nodes).

Cuzick et al. (66, 67) published two overviews, including 7 941 patients, focused on long-term mortality. The first overview was published in 1987 (66) and showed an overmortality after 10 years of follow-up in the postoperative radiotherapy group. The overview included 2 873 patients alive after 10 years of follow-up, for the irradiated patients the overmortality was estimated at a relative risk of 1.30. These results had a major impact on treatment policies and focused attention on the potentially lethal effects of adjuvant radiotherapy. The second overview was published in 1994 (67) and gave more information on the late cause of death related to cardiac toxicity. With a longer follow-up, there were 4 309 long-term survivors, the overall mortality for the irradiated group was estimated to a non-significant relative risk of 1.07 (95% confidence interval (CI): 0.96–1.18). Breast-cancer-specific mortality was non-significantly decreased to 0.90 (CI: 0.76–1.11), but cardiac mortality was significantly increased to 1.62 (CI: 1.25–2.1).

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has conducted overviews every five years. The results of the 1985 and 1990 overviews were published with a 5-year delay (3, 68) and main results are summarized in Table 4. The last published overview included more than 17 000 patients and confirmed a significant increase in intercurrent deaths ($RR = 1.24$, $p = 0.002$) compensated by a beneficial effect on breast-cancer-specific mortality ($RR = 0.94$, $p = 0.03$).

Overall, recent overview results are compatible with a beneficial effect of radiotherapy in terms of a reduction in breast cancer deaths, but also show that late complications may be lethal and could delete the beneficial effect with a resulting null effect on overall survival.

TOXICITY OF RADIOTHERAPY

In the 1970s it was suggested that postoperative radiotherapy could induce immune-depression leading to an increase in distant metastases (69, 70). However, it was shown that the analyses were biased (71) and that induced immune changes did not have a clinical impact (72–74).

However, late toxicity has again become a subject of major interest at the present time. It was thought many years ago that adjuvant radiotherapy at moderate doses, i.e., 45 to 50 Gy, would not cause major late thoracic complications. However, the report of the Oslo trial published in 1986 (47) showed that treated Stage I patients had a higher risk of cardiovascular complications. These results were also concordant with those published in other populations such as patients with Hodgkin's disease (75) irradiated on the mediastinum, in which a higher rate of acute infarction was reported. The lungs and heart are the most important organs at risk and may be a major problem in the long-term follow-up.

Table 3

Main results of the Oslo–Stockholm joint study on the role of post-mastectomy radiotherapy

Axillary status	No. of patients	10-year metastasis-free rate (%)	RR (95% CI)	10-year overall survival (%)	Relative risk (95% CI)
N (−)					
Control	386	80	1.0	77	1.0
RT	375	82	0.97 (0.70–1.33)	76	1.10 (0.85–1.43)
N (+)					
Control	211	40	1.0	46	1.0
RT	213	57	0.63 (0.48–0.83)	53	0.78 (0.61–1.00)
All					
Control	597	66	1.0	66	1.0
RT	588	73	0.75 (0.61–0.92)	67	0.92 (0.77–1.10)

Adapted from Auquier et al. (65).

Table 4

EBCTCG overviews evaluating the effect of postoperative radiotherapy on mortality

Overview, publication year (reference)	N	Death odds reduction (± SD)	Breast-cancer-specific mortality (95% CI)	Intercurrent deaths (95% CI)
EBCTCG, 1990 (68)	9 933	1% ± 4	0.94*	1.24*
EBCTCG, 1995 (3)	17 273	2.6% ± 2.5	(0.88–1.00)	(1.09–1.42)

* Hazard ratio.

The lung is a radiosensitive organ that can develop clinically acute pneumonitis or late radiation fibrosis. The lung and mediastinal irradiation has recently been shown to be deleterious in a postoperative radiotherapy overview of lung cancer (76). Symptomatic acute pneumonitis is unusual in breast cancer; the occurrence rate should be kept below 1% if an adequate technique is used (77). More recently, Lind et al. (78) correlated intensity of post-radiotherapy CT scan abnormalities with lung function and extension of treated volumes. Bentzen et al. (79) reported enhanced radiation-induced pulmonary fibrosis in patients treated with concomitant tamoxifen.

Moderate radiation doses should be given to a limited part of the heart to decrease complications (80–82). In the 1980s, it was reported that the use of postoperative radiotherapy was related to electrocardiographic changes (83). In the Oslo trial (47), a direct Co60 beam was used to irradiate the internal mammary chain and the supraclavicular area. The field was 6 cm wide from the midline and delivered 50 Gy in 4 weeks at 3 cm depth. The total dose received by a large part of the heart was then over 35 Gy. Similar results were reported by the CRC trial (54). Rutqvist et al. (63, 64) showed that the radiation technique was important and that the risk was higher for patients with left breast cancer (63, 84). The latter finding has been reproduced in other surveys (85) and raises the question of whether the treatment of the internal mammary chain is necessary (86–89).

The Stockholm Breast Cancer Group has performed detailed analyses on cardiovascular complications and their possible causes (90–95). Hojris et al. (96), in a recent analysis of the Danish trials, did not find any significant difference in the 12-year cumulative morbidity and mortality from either ischemic heart disease or acute myocardial infarction among patients treated with systemic treatment alone compared with patients receiving the same systemic treatment plus locoregional irradiation. A multivariate analysis showed that age and previous heart disease were significant predictors of death from cardiac diseases, but there was no effect of irradiation or tumor laterality.

Another unusual but dreadful complication is the development of radiation-induced sarcoma. The study conducted in the IGR material (97) showed that the actual risk is very low, i.e. 0.2% at 10 years.

TECHNICAL IMPROVEMENTS TO CIRCUMVENT TOXICITY

The previous findings commented on have produced a series of publications that show interest in improving radiation techniques to decrease late toxicity. (93, 98–106). Even if there is no consensus on the ideal technique, most authors agree in some general recommendations such as:

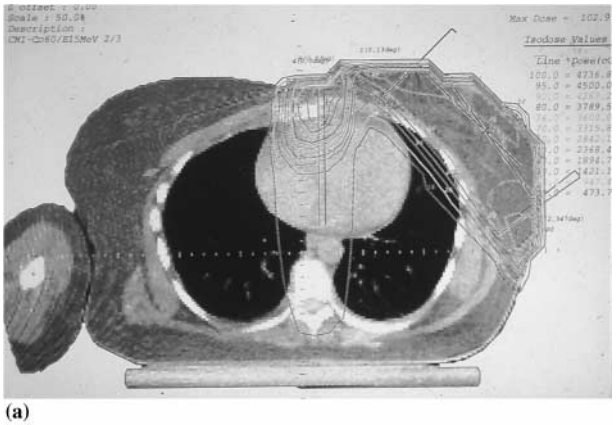
(a) Avoid treating critical volumes: e.g. it seems useless and harmful to treat the axilla when an axillary dissection has been performed (42, 43).
(b) Avoid field overlapping: the overlapping of the supraclavicular and posterior axillary fields may cause an increased risk of brachial plexopathy (41).
(c) Reduce to the minimum the lung volume treated by tangential fields, 2 cm of lung in a central CT-scan slice is the maximum acceptable.
(d) If the internal mammary chain is to be treated, the use of a mixed beam (photons-electrons of adequate energy) is mandatory. Localization procedures such as internal mammary chain scintigraphy to visualize the lymph nodes may be useful (107). An example of a treatment plan is presented in Fig. 1a.
(e) Multiple (or three-dimensional) CT-scan slices to detect dose variations should be routinely performed. The production of dose-volume histograms may be useful to provide guidelines on treated volumes.

LOCOREGIONAL RECURRENCE RATE AS A GUIDE TO TREATING LYMPH NODE AREAS

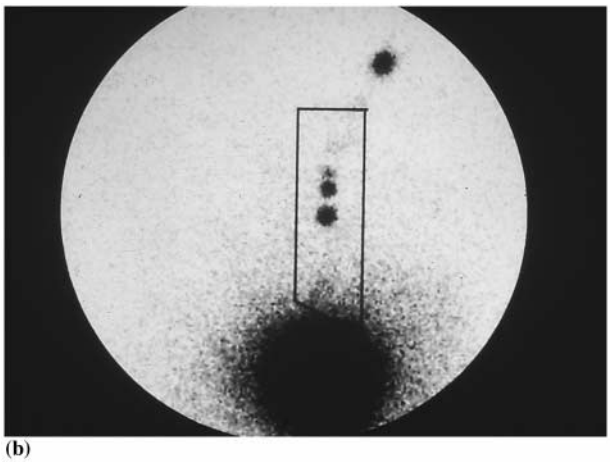
The main guideline indicating the need for postoperative radiotherapy is the risk of locoregional recurrence in a determined population. Indications of post-mastectomy radiotherapy may be modulated according to the level of risk of locoregional recurrence. A locoregional recurrence rate of approximately 10% at 10 years can be considered as acceptable, taking into account that this is the risk for patients with negative axillae not receiving post-mastec-

tomy radiotherapy and also for patients with small tumors treated with breast-conserving surgery and postoperative radiotherapy on the breast. If the 10% locoregional recurrence rate is an acceptable risk, all patients with node-positive axillae should receive postoperative radiotherapy, as overall, the 10-year risk is increased by more than 20% where there is no adjuvant treatment (4, 12).

We analyzed the IGR database of patients treated with radical or modified radical mastectomy, including 1 949 patients with positive axillary nodes (108). The multivariate analysis showed that the two independent prognostic factors of locoregional recurrence are the number of positive axillary nodes and the histoprognostic grade, as described by Bloom et al. (109, 110). In the same population, the effect of radiation therapy was analyzed according to the number of involved axillary nodes; in each category post-mastectomy radiotherapy gave a threefold decrease in the risk of recurrence. Patients with 1 to 3 positive axillary nodes had a 23% risk of locoregional recurrence at 10 years, reduced to 8% when radiation was given. The corresponding figures for patients with 4 to 9 and 10 or more involved axillary nodes, were 35% and 12%, and 56% and 20%, respectively.



(a)



(b)

Fig. 1. a) Tangential radiation fields to treat the breast and chest wall and a direct mixed beam with 60% of 9 MeV electrons and 40% of Co60 photons. Radiation isodoses are displayed in one CT-scan slice. The anterior part of the heart receives a total radiation dose of less than 26 Gy in 5 weeks. b) To help the determination of depth and location of the IMC; an IMC scintigraphy was performed previously.

DISCUSSION AND PERSPECTIVES

Recent results strongly suggest that adjuvant radiotherapy may give a beneficial effect in terms of overall survival (23). This effect could be explained by the prevention of secondary dissemination from residual tumor left in the tumor bed (12, 14). Recently, Koscielny & Tubiana (111) described a mathematics model tested in a population of more than 5 000 patients; the results are consistent with the hypothesis of secondary dissemination. Moreover, this effect would be independent of the use of adjuvant chemotherapy, as shown in three recent published trials (29–31). The results of these trials are particularly relevant, as they used more modern radiotherapy techniques, and at the present time they do not show a deleterious radiation effect with a follow-up longer than 12 years (94). Furthermore, the results shown in the Danish, the Vancouver and the IGR database contradict the limitation of adjuvant radiotherapy to patients with 4 or more involved nodes (5, 112). It has been argued (23) that the high risk of locoregional recurrence in this subset of patients in the Danish and Vancouver trials is related to suboptimal axillary surgery. However, this was not the case in the IGR series in which a systematic complete axillary dissection was performed, and probably the high rate of recurrence is related more to the closed long-term follow-up. Even if the beneficial treatment effects shown in the recent published randomized trials are only explained by the suboptimal axillary surgery, this fact would only stress the importance of a complete locoregional treatment to improve overall results. The impact of axillary clearance on overall survival is also a matter of controversy, despite published randomized trials. However, the results of a recent meta-analysis (113), based on six randomized trials including 2 936 patients, on the role of prophylactic axillary node dissection suggest that axillary dissection improves survival in women with operable breast cancer, the potential benefit being about 5.4% (CI: 2.7–8.0%). These considerations give more weight to the proposition of using the locoregional recurrence rate as a guideline for indication of adjuvant radiotherapy. Each center could use this endpoint, taking into account its own long-term results.

This subject is not just of academic interest, as it can be argued that radical surgery has become an exceptional indication in the treatment of early breast cancer. The results of lymph node irradiation in N(+) patients obtained in post-mastectomy trials can be extrapolated to those treated with breast-conserving surgery, as it can be hypothesized that the treatment of microscopically involved lymph nodes may similarly decrease the risk of

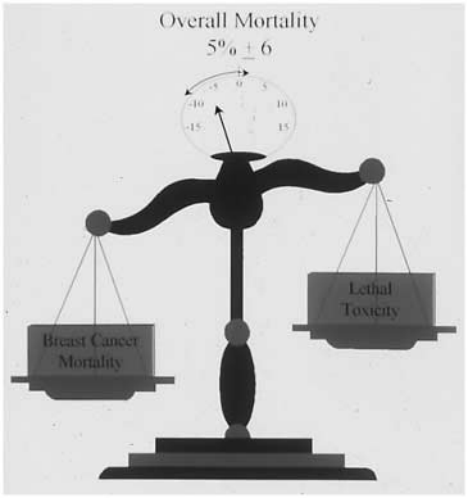


Fig. 2. Schedule of the balance between the decrease in breast-cancer-specific mortality and the increase in mortality due to other diseases, both determining the overall effect on survival. Hypothetically, improved radiation techniques could decrease toxicity and obtain a net therapeutic gain on overall survival.

secondary dissemination. However, the potential radiation-related late complications make it necessary to balance the indications for radiation treatment, as shown in Fig. 2. More specifically, the exact role of the IMC irradiation using modern techniques merits further investigation because of its potential toxic effect (23). A French trial, performed in Lyon, including more than 1 000 patients has recently terminated, while a large European Organization for Research and Treatment of Cancer (EORTC) randomized trial has been launched on this subject to include more than 3 000 patients.

In summary, recent evidence (12, 29–31, 65) shows that an improved locoregional control after breast surgery may have a significant impact on overall survival by decreasing the risk of secondary dissemination. The exact definition of subgroups to be treated by lymph node irradiation, as well as the lymph node volumes to be irradiated, are currently the subjects of further clinical research. However, the main practical guideline may be the actual long-term risk of locoregional recurrence in each category of patients.

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