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Original Paper

The Dissection of Internal Mammary Nodes does not Improve the Survival of Breast Cancer Patients. 30-Year Results of a Randomised Trial

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The lymph nodes of the internal mammary chain represent a primary station draining the lymph from the breast and their removal or their irradiation has been considered an important step in breast cancer treatment. From January 1964 to January 1968, 737 patients with breast cancer were randomised at the National Cancer Institute in Milan to undergo either Halsted mastectomy or extended mastectomy with internal mammary node dissection. Patients with non-disseminated carcinoma classified as T1, T2, T3, N0, N1 were eligible for the study. No patients received postoperative radiotherapy or systemic therapy. After 30 years of follow-up, the overall survival curves and the specific survival curves do not show any difference between the patients of the two groups. Among the 558 patients who died in the 30 year interval period, 395 (71%) died from breast carcinoma (201 in the Halsted group and 194 in the extended mastectomy group) and 163 from other causes. This study shows that the removal of internal mammary nodes does not improve the survival of patients treated for breast carcinoma. This finding supports the theory that treatment of regional nodes does not influence the survival of cancer patients. The prognostic value of internal mammary node status is, however, high and a biopsy on a selected lymph node should be considered for staging purposes.

Key words: breast cancer, internal mammary nodes, surgical treatment
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INTRODUCTION

SINCE THE first attempts to treat breast cancer surgically a century ago, dissection of axillary nodes was always included in the surgical procedure [1, 2] whilst for many decades the internal mammary lymph nodes were ignored. It was only in the 1950s that the removal of internal mammary nodes interested a few surgeons becoming a not uncommon treatment in some centres with results that seemed to improve survival compared with the classic Halsted mastectomy [3]. To evaluate correctly the possible role of the dissection of the internal mammary nodes, an international randomised trial was started in 1963 and the preliminary results, published in 1976, showed no survival advantages in removing the internal mammary nodes [4]. The data obtained from the patients randomised at the Milan Cancer Institute were separately published in 1981 [5]. The issue of treatment of internal mammary nodes has, however, remained a matter of controversy especially with regard to the indication for radiotherapy and we consider it useful to report the long-term results of the Milan randomised trial conducted in the years 1964–1968 which compared patients treated by 'Halsted mastectomy' with patients treated by the same operation plus removal of the internal mammary nodes.

PATIENTS AND METHODS

From January 1964 to January 1968, 737 patients with breast cancer were randomised to undergo either conventional Halsted mastectomy or extended radical mastectomy

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(i.e. with internal mammary nodes dissection); 716 were considered evaluable. As previously reported, this series was part of an international cooperative trial whose results were published in 1976. Patients with non-disseminated breast cancer classified as T_1, T_2, T_{3a}, N_0, or N_1 were eligible for the study.

The classical Halsted mastectomy with removal of the breast, pectoralis muscles, and axillary contents *en bloc* was performed in 374 (52%) patients. Extended radical mastectomy was carried out in 342 (48%) patients. The internal mammary dissection was done *en bloc* and in continuity with the breast tissue and included internal mammary vessels and lymph nodes from the first to the fourth intercostal space, the corresponding portion of the pleura also being removed.

Patients in the two series were comparable in age, menopausal status, tumour site and size, and frequency of axillary metastases (Table 1).

No patients received postoperative radiotherapy and no other specific anticancer drugs or hormonal manipulation were applied in the absence of documented evidence of primary treatment failure. After mastectomy, all patients were followed in the Out-patient Clinic of the Institute. Follow-up studies and secondary treatments administered upon relapse were detailed in a previous publication [5].

STATISTICAL METHODS

Main patient and tumour characteristics were described separately for the Halsted and extended radical mastectomy trial options by means of contingency tables.

The primary outcome considered was death from any cause. However, the long follow-up duration for many patients implied the occurrence of a sizeable number of deaths unrelated to breast cancer. Therefore, we also restricted the analysis to breast cancer-specific death, as ascertained during follow-up or by search for death certificates, to improve the estimate of the treatment effect, under the assumption that the cause of death was reliably classified. The analyses for the two above described outcomes are henceforth referred to under the title of 'overall' and 'specific' survival.

Overall survival curves were estimated with the Kaplan–Meier method [6]. The two trial options were compared in terms of overall and specific survival by using Cox regression models [7], after verifying the proportional hazard assumption by means of log-minus log-survival plots. All patients were included in the analysis according to the intention-to-treat principle. The analyses were adjusted for the following covariates: patient age at the time of surgery, tumour site (medial, lateral quadrants) and size (<2.0, 2.1–5.0, >5.0 cm), axillary nodes status (negative, positive). Surgical treatment and the above covariates were entered into Cox models by means of 0–1 indicator variables, with the exception of age, which was modelled as a continuous variable by means of a restricted three-knot cubic spline [8]. To investigate the joint prognostic role of axillary and internal mammary nodal status, a Cox model containing these two factors and tumour size was fitted to the subset data from the extended mastectomy group.

Bayesian posterior distribution of the hazard ratio (HR) has been traced by assuming a uniform prior and that log HR is normally distributed [9].

The analysis was carried out using the S-plus library supplied by Harrell [10]. The conventional 5% significance level was adopted.

Table 1. *Patient and tumour characteristics*

	Extended (342 pts) *n* (%)	Halsted (374 pts) *n* (%)	Total (716 pts) *n* (%)
Age (years)			
≤35	16 (4.7)	17 (4.5)	33 (4.6)
36–45	81 (23.7)	87 (23.3)	168 (23.5)
46–55	113 (33.0)	125 (33.4)	238 (33.2)
56–65	101 (29.5)	114 (30.5)	215 (30.0)
>65	31 (9.1)	31 (8.3)	62 (8.7)
Menopausal status			
Premenopause	140 (40.9)	145 (38.8)	285 (39.8)
Menopause	202 (59.1)	229 (61.2)	431 (60.2)
Tumour site (quadrant)			
Medial	145 (42.4)	141 (37.7)	286 (39.9)
Lateral	197 (57.6)	233 (62.3)	430 (60.1)
Tumour size (cm)			
≤2.0	38 (11.1)	47 (12.6)	85 (1.9)
2.1–5.0	264 (77.2)	284 (75.9)	548 (76.5)
>5.0	40 (11.7)	43 (11.5)	83 (11.6)
Axillary nodal status			
Negative	161 (47.1)	174 (46.5)	335 (46.8)
Positive	181 (52.9)	200 (53.5)	381 (53.2)
Positive internal mammary nodes			
Negative	272 (79.5)		
Positive	70 (20.5)		

RESULTS

Involvement of internal mammary nodes was recorded in approximately 20.5% (70/342) of the women who underwent extended mastectomy.

Patient observation time varied from 4–398 (median: 126) months. Table 2 reports the number of first neoplastic events and deaths observed during follow-up. The cause of death was breast cancer for 395 (71%) of the 558 women who died.

Overall survival

Overall survival curves are reported in Figure 1. These curves were substantially overlapping in the two treatment options.

Table 2. *First events and cause of deaths*

	Extended *n*	Halsted *n*	Total *n*
Neoplastic events (type of recurrence)			
Local	44	46	90
Distant	130	131	261
Local + distant	18	24	42
Contralateral	4	2	6
Causes of deaths			
Breast cancer	194	201	395
Another tumour	5	14	19
Not tumour	52	53	105
Unknown	13	26	39
Total	264	294	558

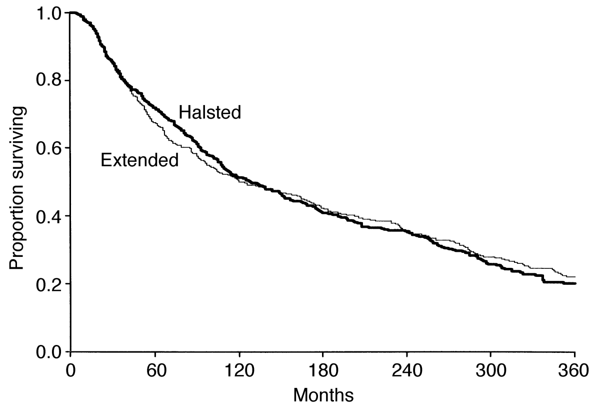

Figure 1. Overall survival curves for extended and Halsted treatment options.

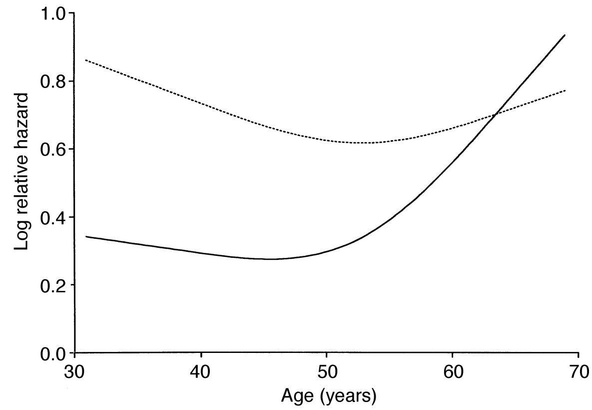

Figure 2. Log relative hazard plot according to age for overall (—) and breast cancer specific survival (·····).

The results obtained with the Cox model are reported in Table 3. Adjusting for patient age, tumour site and size and nodal status, the hazard ratio estimate for surgery was 0.98 ($P=0.859$). By contrast, out of the covariates considered, significant results ($P<0.001$) were obtained for patient age, tumour size and nodal status. In particular, as expected, a higher risk of death was associated with large tumour size and the presence of metastatic axillary involvement. To describe the effect of age, the log-relative hazard curve was plotted (Figure 2, solid line). The curve showed a slight increase in the death hazard in young patients and a much more evident upsurge after the age of 50 years.

No interaction of clinical importance was detected between surgery and the covariates considered.

Considering the subset of 342 patients treated with extended mastectomy, the HR estimate for internal mammary nodal involvement, adjusted for tumour size and axillary nodal status, was 1.9 (95% confidence interval, CI: 1.42–2.53; $P<0.001$), not very different from that reported in Table 3 for axillary nodal status (HR 2.60). The interaction between internal mammary and axillary nodal involvement was negligible and statistically not significant ($P=0.5334$). Therefore, the involvement of internal mammary nodes seems to have a prognostic value both in axillary node negative and positive patients.

To make the findings clear, the distribution of cases with axillary and internal mammary nodes involvement is reported in Table 4. An involvement of the internal mammary nodes was evident in 70 cases (20.5%), in 55 (16%) associated with axillary metastases and in 15 (4%) without axillary involvement. An increase in the annual death rate for internal mammary node positive women was observed for axillary node negative (from 0.031 to 0.055) and positive (from 0.077 to 0.163) patients. The survival curves according to presence or absence of metastases in the axillary and in the internal mammary nodes show the similar prognostic effect of internal mammary and axillary nodes (Figure 3).

Specific survival

When considering specific survival, the Cox model (Table 3) yielded for surgery a hazard ratio estimate (1.11, $P=0.311$). A significant prognostic effect was again detected for tumour size and nodal status. The corresponding hazard ratio estimates were higher than those obtained in analysing overall mortality; thus suggesting that underestimation of prognostic effects may actually occur when a substantial proportion of the observed mortality (some 30%) is unrelated to the disease under investigation. In contrast, significant results were no longer obtained for age. In particular, the log-relative hazard curve (Figure 2, broken line) no longer showed the

Table 3. Results of the Cox models in terms of hazard ratio (HR), corresponding 95% confidence interval (95% CI) and Wald's P value (P)

Variable	Reference category	Overall survival			Specific survival‡		
		HR	95% CI	*P*	HR	95% CI	*P*
Surgery							
Extended	Halsted	0.98	0.83–1.17	0.859	1.11	0.91–1.35	0.311
Age							
59 years	45 years	1.28*	1.14–1.44	<0.001	0.97	0.84–1.12	0.425
Tumour site							
Medial	Lateral	1.04	0.87–1.23	0.673	0.99	0.80–1.21	0.910
Tumour size							
2.1–5.0 cm	≤2.0 cm	1.55	1.16–2.08	<0.001†	1.72	1.18–2.49	<0.001
>5.0 cm	≤2.0 cm	2.14	1.56–2.93		2.53	1.71–3.75	
Axillary nodal status							
Positive	Negative	2.60	2.17–3.08	<0.001	3.64	2.91–4.56	<0.001

*Hazard ratio estimate corresponding to the interquartile range of age (from 45 to 59 years). †*P* value for testing the overall association between tumour size and survival. ‡Analysis restricted to breast cancer deaths.

Table 4. Distribution of 342 patients submitted to internal mammary dissection according to involvement of axillary and internal mammary nodes. Number of deaths and annual rates for each subgroup are reported

	n	Deaths	Annual death rates (95% CI)
Axillary nodes negative and internal mammary nodes negative	146	91	0.031 (0.025–0.038)
Axillary nodes negative and internal mammary nodes positive	15	12	0.055 (0.031–0.097)
Axillary nodes positive and internal mammary nodes negative	126	107	0.077 (0.063–0.093)
Axillary nodes positive and internal mammary nodes positive	55	54	0.163 (0.125–0.213)
Total	342	264	

CI, confidence interval.

sharp increment in the death hazard after the age of 50 years previously described for overall survival. This peak was thus likely to be due to the background mortality in older women.

In order to enable the surgeon to extrapolate to clinical practice findings given in terms of statistical significance, it appeared useful to consider the Bayesian posterior distribution of the two surgery hazard ratios. Estimates of these distributions are shown in Figure 4 for overall survival (Figure 4a) and for specific survival (Figure 4b). Values of the HR < 1 indicate that extended surgery was better than Halsted mastectomy whereas values of HR > 1 indicate the contrary. The message emerging from Figure 4a suggests a similarity of the two outcomes as the area under the curve on the left of one is almost equal to that on the right. In contrast, Figure 4b shows that the probability that the true mortality on Halsted surgery is lower than that on extended mastectomy is some 85% of cases.

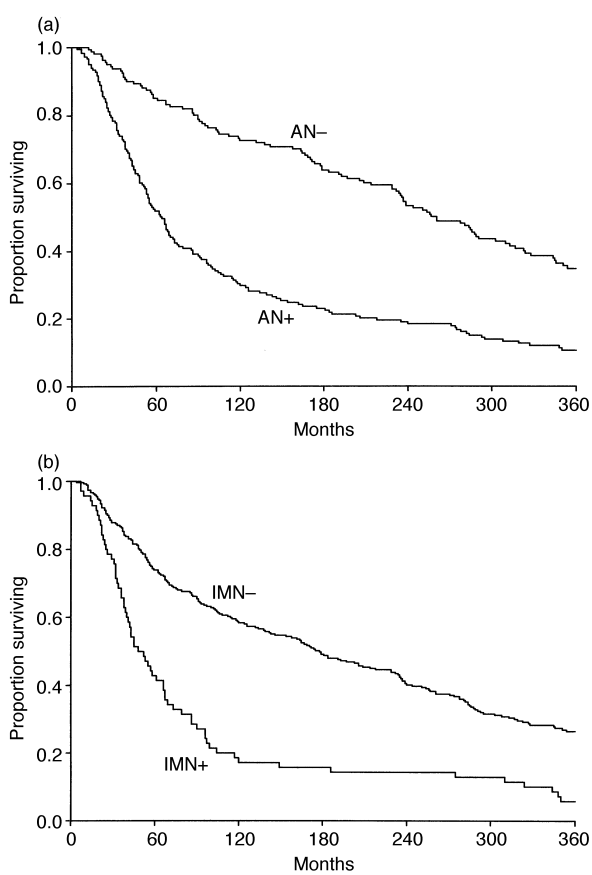

Figure 3. Overall survival curves according to (a) axillary involvement (among 342 patients treated with extended mastectomy): node negative (AN −) and node positive (AN +). (b) Internal mammary nodes involvement (among 342 patients treated with extended mastectomy): node negative (IMN −) and node positive (IMN +).

DISCUSSION

The present analysis shows no difference in overall and specific survival in patients treated with Halsted radical mastectomy and in patients treated with the same operation plus dissection of internal mammary nodes. The type of operation employed in this trial was a radical one with complete dissection of the internal mammary node chain from the first to the fourth intercostal space, leaving no doubt about the fact that removing or not removing these nodes does not affect the prognosis.

The prognostic value of the information on the internal mammary nodes is, however, high [11]. The present study shows that the annual death rates were very high when both axillary and internal mammary nodes were involved whilst the involvement of internal mammary nodes alone had a prognostic value similar to that of axillary metastases alone. It appears, therefore, that a possible role of the internal mammary dissection is that of better staging to improve the choice of adjuvant treatments, similar to what happens with axillary node dissection [12].

The fact that the dissection of internal mammary nodes does not improve the prognosis poses the problem of the indication of radiotherapy to the internal mammary chain. The proposal of prophylactic regional node irradiation is put forward from time to time, although recent information on the natural history of breast carcinoma clearly indicates that the final outcome of a patient with breast cancer is determined by the presence or absence of occult metastases in distant organs [13] and that a local or regional recurrence represents more an indicator of grave prognosis than a source of further spread of disease. Various studies have been published on the results of trials involving local-regional radiotherapy after surgery, showing a significant reduction in loco-regional recurrences with postoperative radiotherapy but no improvement in long-term survival [14–16]. Further, the meta-analytical conclusion of the Early Breast Cancer Trialists' Collaborative Group was that axillary lymphadenectomy conferred no survival advantage [17]. They used data from 58 randomised trials involving 12 000 deaths among 28 405 women with early breast cancer, and recognised that either clearance of or radiotherapy to the axilla, when used as an adjunct to mastectomy, yielded equivalent 10-year survival rates. Equivalent survival was also found in patients with undissected axillae when compared with those who had undergone axillary dissection. This lack of survival advantage

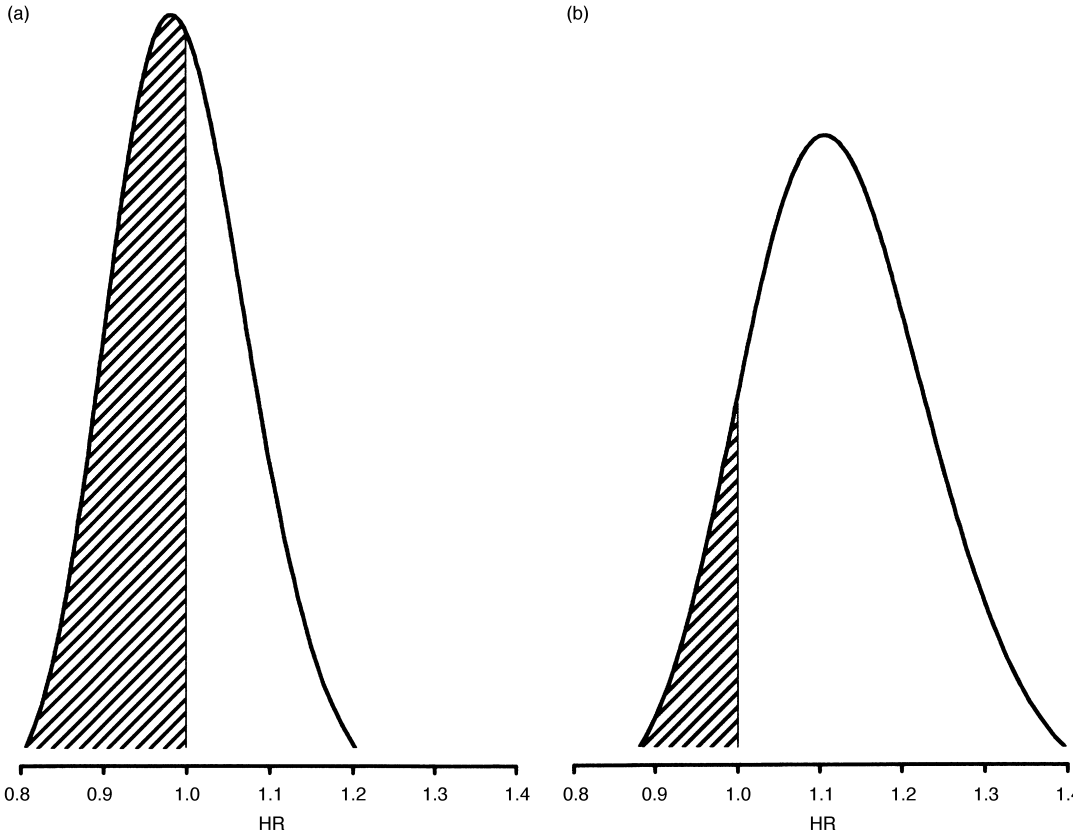

Figure 4. Bayesian posterior distribution of surgery hazard ratio (HR) for overall (a) and breast cancer specific survival (b).

supports the concept that regional lymph node metastases are an expression rather than a determinant of a poor prognosis [18–21].

However, two recent papers [22, 23] have again reproposed the problem of extensive postoperative loco-regional radiotherapy showing an advantage due to the radiotherapy not only in terms of reduced local regional recurrences but also in terms of improved survival. The two studies deserve some comments. The first study [22], on 318 premenopausal women treated with modified radical mastectomy with positive axillary nodes, showed a limited, although non-significant advantage in overall survival, in patients treated with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and postoperative radiotherapy compared with patients treated with CMF alone. The study was a multicentric one involving different surgical departments: the average number of removed axillary nodes was eleven.

The second paper [23] reported on a much larger series of 1708 premenopausal patients with breast cancer with severe prognosis randomised to CMF or to CMF and postoperative radiotherapy after mastectomy and axillary dissection. The main weak point of the study is the fact that it was a multicentric trial involving 79 hospitals some of them of small size, certainly with an uneven type of surgical treatment. The average number of cases per centre was 22, spread over 7 years. It is not surprising that the average number of axillary nodes removed was seven and that in some 15% of the patients only three or less nodes (sometimes no nodes) were removed. This type of surgery is certainly not the surgery generally applied in most Surgical Departments where the average number of nodes removed varies between 20 and 30 and the radiotherapy applied in this trial may be considered more therapeutic than adjuvant. Independently of these considerations, the studies do not clarify the possible role of internal mammary nodes radiotherapy, as in both trials radiotherapy included four different fields (chest wall, supra-infraclavicular, axillary, internal mammary nodes) and it is not possible to isolate an hypothetical advantage of internal mammary irradiation. To prove or disprove the efficacy of internal mammary radiotherapy, a trial should be conducted, where one arm should receive internal mammary radiotherapy after surgery on primary carcinoma to be compared with another arm without such radiotherapy. Suggestions in such a direction were given in the conclusion of a recent paper by Zucali and colleagues [24], based on the evidence of the prognostic role of tumour site on survival after breast conservation surgery. The status of internal mammary nodes bears a considerable prognostic significance [11, 12]. A biopsy of one internal mammary node, possibly guided by a gammaprobe after the dermal or subdermal injection of radiolabelled (T99) colloid albumin (sentinel node), could represent a simple method to obtain the maximum prognostic information to improve the indication of adjuvant systemic treatments. Moreover, a positive sentinel node biopsy would represent an indication for radiotherapy on the internal mammary node chain.

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