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Original Paper

Arm Morbidity After Sector Resection and Axillary Dissection With or Without Postoperative Radiotherapy in Breast Cancer Stage I. Results from a Randomised Trial

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The incidence and time course of arm morbidity after sector resection and axillary dissection with or without postoperative radiotherapy to the breast was assessed in a prospective randomised trial among 381 patients with stage I breast cancer. At 3–12 months, arm symptoms were reported by 59/110 of the patients who had ≥10 lymph nodes found in the axillary specimen versus 85/253 in whom <10 lymph nodes were found ($P = 0.002$); at 13–36 months, the corresponding figures were 35/106 versus 44/225 ($P = 0.001$). Postoperative wound complications increased the incidence of arm symptoms at 3–12 months from 104/283 to 39/79 at 3–12 months ($P = 0.03$). Employed patients and patients <65 years of age reported arm symptoms at 3–12 months in 86/161 and 94/191 compared to 58/207 and 50/177 among retired patients and patients ≥65 years of age, respectively ($P = 0.0001$ and $P = 0.0002$, respectively). In a multivariate logistic regression analysis at 3–12 months, only young age (relative risk = 0.93 per year of increasing age, 95% CI 0.91–0.97) and the number of lymph nodes found in the axillary specimen (relative risk = 1.11 per lymph node found, 95% CI 1.05–1.18) remained statistically significant. No negative impact on arm morbidity was found by the addition of postoperative radiotherapy only to the breast, either in univariate or multivariate models. We conclude that factors directly related to the extent of the surgical procedure and young age are determinants of arm morbidity after breast preserving treatment for stage I breast cancer. Arm symptoms are most common during the first year after treatment and are reduced over the subsequent 2–3 years by around 40–50%. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: breast cancer, axillary dissection, arm morbidity, randomised trial, conservative treatment

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INTRODUCTION

ARM PROBLEMS such as arm swelling, pain, numbness, weakness and impaired shoulder mobility are negative side-effects after axillary dissection [1–5]. Attempts have been made to correlate the occurrence of arm morbidity to a variety of factors, such as the extent of axillary dissection [6–12], the addition and timing of postoperative radiotherapy [7, 13–20] and the type of operation performed in the breast, i.e. mastectomy versus breast preservation [20–22]. Postoperative wound complications have been shown to increase the risk of arm oedema after mastectomy [23]. Increased incidence of arm oedema has also been associated with the administration of radiotherapy to the breast only after breast conserving surgery and axillary dissection [9, 24].

The objective of this study was to describe the incidence and time course of arm morbidity in a prospective, randomised trial evaluating standardised sector resection and axillary dissection of level I and II in the axilla with or without postoperative radiotherapy only to the breast among 381 patients with stage I breast cancer.

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PATIENTS AND METHODS

Study design

The study design has been described in detail previously [25]. Women with a maximum age of 80 years with a unifocal breast cancer and a maximal tumour diameter of 20 mm on the pre-operative mammogram were eligible. All patients were subjected to a standardised sector resection, as described earlier [26]. In short, the mammary gland was dissected free to its periphery in the plane of *Scarpas fascia* and down to the pectoralis muscle, with the pectoral fascia included in the specimen. The axilla was dissected to levels I and II [27]. The axillary nodes should be histopathologically free from metastases. The radiotherapy technique has also previously been described in detail [25]. In short, the breast parenchyma plus 1 cm was defined as the target volume. Two opposing tangential fields with an open angle of 185° were applied. Radiotherapy was delivered by photons from a 4–10 MV linear accelerator or from ^{60}Co. A total dose of 54 Gy in 27 fractions, five fractions a week was given to the breast. Full informed consent was required. The study was approved by the regional ethics committee.

Randomisation

After stratification for participating centre, mode of detection (screening or clinical diagnosis), and tumour size (equal or less than 10 mm or otherwise), patients were randomised to receive postoperative radiotherapy (XRT group) or surgery along (non-XRT group). Allocation to treatment group was stratified in blocks of four within each centre and stratum.

Patient accrual

Patient accrual started in October 1981. Six central county hospitals enrolled a total of 381 eligible patients into the study. Patient accrual terminated in September 1988. 11 women who did not accept postoperative irradiation were analysed according to the assigned treatment as were four women who never began this treatment because of complications (postoperative infection, two; cerebrovascular incident, one; and suicide, one).

Evaluation procedures

The study protocol stipulated that arm swelling was estimated by measuring the arm circumference 10 cm above and 10 cm below the elbow on both arms. Measurement was to be performed at 3 months, 12 months, 24 months and 36 months after surgery. At the same points in time, patients were asked for subjective arm symptoms (e.g. pain, numbness, impaired shoulder mobility and weakness) from the arm at the operated side. The symptoms were graded as no arm symptoms, moderate arm symptoms or severe arm symptoms. In the analysis, moderate and severe arm symptoms were grouped together and classified as any arm symptoms. The most severe report in the time period 3–12 months, 13–24 months and >36 months, respectively, was used. The evaluation variables are given in Table 1.

Patient characteristics

Age was analysed in the univariate analysis according to age <65 years of age or ≥65 years of age at the day of operation. In the multivariate analysis, age was used as a continuous variable. Data were collected from the patient records concerning occupation: employment in or outside the home or retirement from work. For non-retired patients, data were collected from the local insurance registry on the number of off-work days 0–6 months after surgery both for the primary tumour and in the event of a recurrence.

Table 1. Risk factors for arm morbidity tested by uni- and multivariate analyses

Patient characteristics
Age
Occupation
Tumour characteristics
Size
Site
Side
Treatment characteristics
Radiotherapy
Number of dissected axillary lymph nodes
Complications to treatment
Postoperative seroma, haematoma or wound infection
Skin or tissue reaction to radiotherapy
Arm swelling

Tumour characteristics

Tumour size was categorised according to histopathological tumour diameter ≤10 mm or 11–20 mm. Site of the tumour was categorised as tumour in the upper outer quadrant versus other location in the breast. Relation to location on the left or right side was also explored.

Treatment characteristics and complication to treatment

An association with postoperative radiotherapy was tested by comparing reported arm symptoms in the XRT group with those reported in the non-XRT group. Reported arm symptoms among patients who experienced postoperative seroma, haematoma or wound infection in the breast and/or axilla were compared with reported arm symptoms among patients not experiencing any postoperative complication. We also compared arm symptoms among patients in the XRT group who developed moderate to severe skin or tissue reaction during radiotherapy (e.g. reactions necessitating local treatment or a pause in the radiotherapy) with those without any adverse reaction to radiotherapy. The yield of lymph nodes in the axillary specimen was used as a proxy for the extent of the axillary dissection, and categorised in the univariate analysis in two ways: as ≤5 versus >5 lymph nodes or as <10 versus ≥10 lymph nodes reported in the histopathological report. In the multivariate analysis, the number of lymph nodes was used as a continuous variable. Arm swelling was calculated by using the measures of arm circumference (O) 10 cm above and 10 cm below the elbow. Using the formula $O = 2\pi\, xr$, r_1 (above the elbow) and r_2 (below the elbow) were calculated. The formula for calculation of the volume of frustrum of a cone, $V = \frac{1}{3}\, h \cdot \pi(r_1^2 + r_2^2 + r_1 r_2)$ was used to calculate arm volume from 10 cm above to 10 cm below the elbow. The difference in ml between the operated and non-operated side was used as a measure of arm swelling.

Statistical analysis

The association between patient characteristics, treatment characteristics, complications to treatment and moderate/severe arm symptoms were explored univariately in a PC

Table 2. Proportion of any arm symptoms (pain, numbness, impaired shoulder mobility or arm swelling) in relation to age and occupation at 3–12 months, 13–36 months and >36 months after surgery

	3–12 months $n = 368$ (%)	(P)	13–36 months $n = 335$ (%)	(P)	>36 months $n = 115$ (%)	(P)
Employed	86/161 (53)	$P < 0.0001$	38/141 (27)	$P = 0.02$	13/44 (30)	n.s.
Retired	58/207 (28)		42/194 (22)		9/71 (13)	
Age <65	94/191 (49)	$P < 0.0002$	46/171 (27)	$P = 0.04$	16/57 (28)	n.s.
Age ≥65	50/177 (28)		34/164 (21)		6/58 (10)	

n.s., not significant.

computer program (Statistica®). The chi-square test, log rank test and t-test were used for test of equality. Multivariate analysis was based on logistic regression using the Logistic Procedure in the SAS System [28]. 0.05 was considered as the level of statistical significance.

RESULTS

Of the 381 patients in the study, 184 were randomly assigned to receive postoperative radiotherapy (XRT group) and 197 to follow-up only (non-XRT group). Reports of arm symptoms were completed for 368 patients at 3–12 months after surgery, for 335 patients at 13–36 months after surgery and for 115 patients beyond 36 months after surgery. Complete reports on arm circumference were available from 273 patients (118 in the XRT group and 155 in the non-XRT group) at 3–12 months and from 270 patients (117 in the XRT group and 153 in the non-XRT group) at 13–36 months. Beyond 36 months, <50 reports on arm circumference were complete. Because of the low number of reports, arm swelling was not analysed beyond 36 months after surgery.

Patient characteristics (Table 2)

There was a strong and statistically significant association to both age <65 years of age and occupation during the first 12 months after surgery. 53% of the employed patients and 49% of the patients <65 years of age reported any arm symptoms during the first postoperative year compared to 28% of those retired from work or 28% those 65 years of age ($P < 0.0001$ and $P < 0.0002$, respectively). Only 5 patients reported severe arm symptoms. During the time period 13–36 months after surgery, the difference by occupation and age group diminished ($P < 0.02$ and $P < 0.004$, respectively). However, beyond 36 months, the number of patients <65 years of age or employed reporting arm symptoms was not statistically different to the number of older or employed patients reporting symptoms. The average number of off-work days among patients occupied was 64 days among patients reporting no arm symptoms and 74 among patients reporting any arm symptoms. The difference was not statistically significant. The type of arm symptoms reported were pain (40%), numbness (20%), weakness (20%), arm swelling (16%) and impaired shoulder mobility (4%).

Treatment characteristics, tumour characteristics and complication to treatment (Table 3)

A statistically significant association was found according to the number of lymph nodes found in the axillary specimen. The median number of lymph nodes found was 7. At

Table 3. Proportion of any arm symptoms (pain, numbness, impaired shoulder mobility and arm swelling) related to tumour characteristics, treatment characteristics and complications to treatment at 3–12 months, 13–36 months and >36 months after surgery

	3–12 months (%)	P	13–36 months (%)	P	>36 months (%)	P
XRT	64/177 (36)	n.s. ($n = 368$)	42/167 (25)	n.s. ($n = 335$)	12/52 (23)	n.s. ($n = 115$)
Non-XRT	80/191 (42)		38/168 (23)		10/63 (16)	
≤5 lymph nodes	31/113 (27)	$P = 0.004$ ($n = 363$)	16/102 (16)	$P = 0.005$ ($n = 331$)	4/36 (11)	n.s.
>5 lymph nodes	113/250 (45)		63/229 (28)		18/77 (23)	
<10 lymph nodes	85/253 (34)	$P = 0.002$ ($n = 363$)	44/225 (20)	$P = 0.001$ ($n = 331$)	12/76 (16)	n.s.
≥10 lymph nodes	59/110 (54)		35/106 (33)		10/37 (27)	
No wound complication	104/283 (37)	$P = 0.03$ ($n = 362$)	59/260 (23)	n.s. ($n = 331$)	15/95 (16)	n.s.
Wound complication	39/79 (49)		20/71 (28)		6/18 (33)	
No complication to XRT	53/144 (37)	n.s. ($n = 170$)	32/136 (24)	n.s. ($n = 160$)	10/41 (24)	n.s. ($n = 50$)
Complication to XRT	9/26 (35)		8/24 (33)		1/9 (11)	

n.s., not significant.

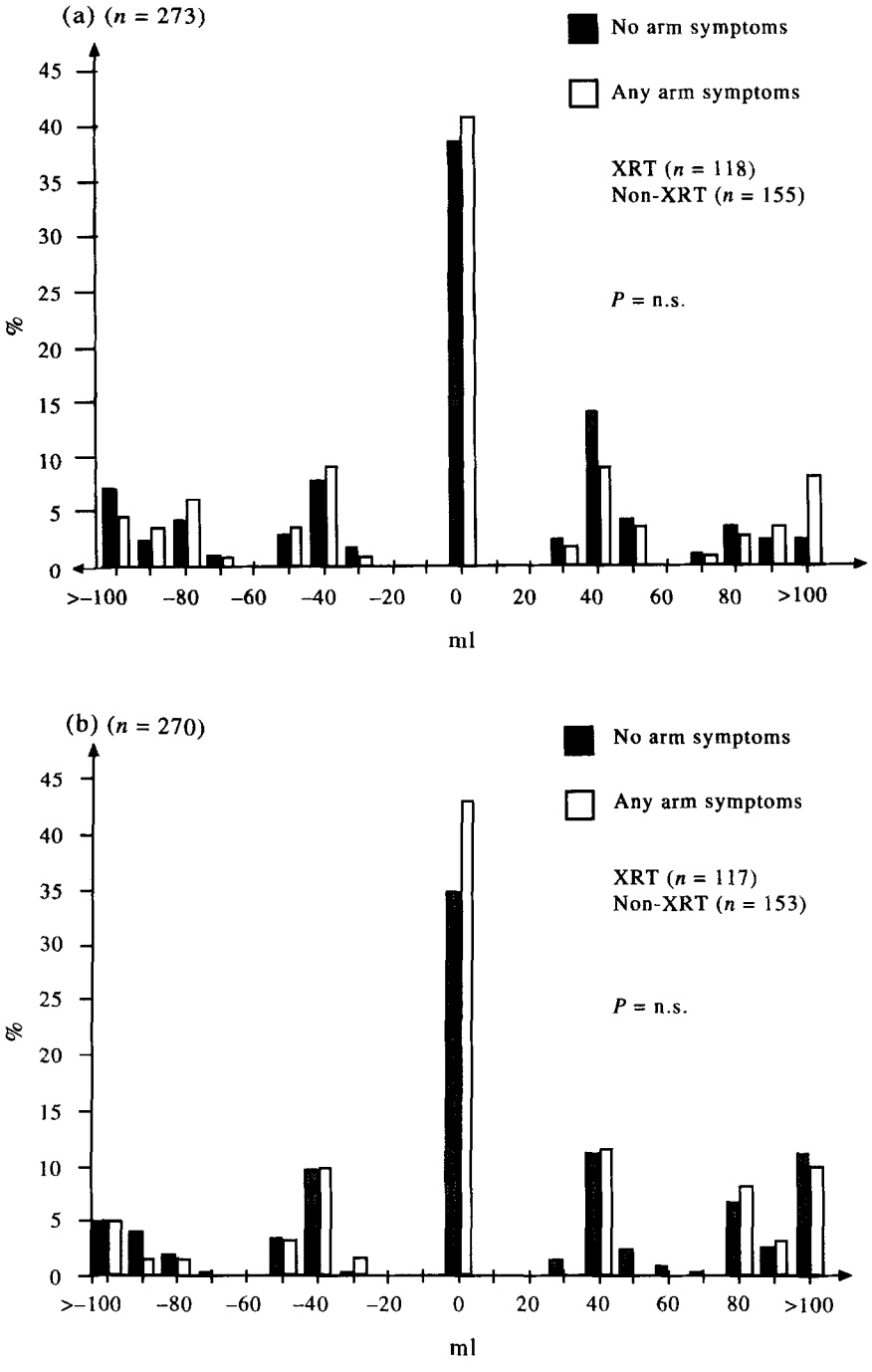

Figure 1. Difference in arm volume (ml) between the arm on the operated and the other side among patients with no arm symptoms and patients with any arm symptoms (pain, numbness, arm swelling or impaired shoulder mobility) at 3–12 months (a) and 13–36 months (b) after surgery. Closed bars—no arm symptoms. Open bars—any arm symptoms.

3–12 months, patients with ≤5 lymph nodes had a lower incidence of any arm symptoms compared to patients with >5 lymph nodes found ($P = 0.004$). If the cut-off point was increased to ≥10 lymph nodes found, an even more distinct difference was seen ($P = 0.002$). At 13–36 months, the association was still statistically significant both if the cut-off point was >5 or ≥10 lymph nodes ($P = 0.005$ and ($P = 0.001$, respectively) A statistically significantly increased incidence in reported arm symptoms was also observed at 3–12 months among patients suffering from seroma, haematoma or wound infection postoperatively in the breast or the axilla compared to patients without postoperative wound complication ($P = 0.03$). If only wound complications in the axilla were considered, the level of statistical significance was strengthened, but did not reach beyond the first postoperative year (data not shown). There was no association between any arm symptoms and radiotherapy to the breast only, nor was there any association found between moderate/severe skin and tissue reaction as a side-effect of radiotherapy and any arm symptoms (data not shown). Tumour size ≤10 mm versus tumour size 11–20 mm, right-sided tumours versus left-sided tumours and lo-

Table 4. Mean difference in arm volume (ml) between the arm on the operated and the other side related to treatment characteristics, tumour characteristics and complications to treatment

	Difference 3–12 months (n = 273)	Difference 13–36 months (n = 270)
XRT	−2	14
Non-XRT	3	23
Upper outer quadrant	2	15
Other quadrants	−5	22
≤5 lymph nodes	7	20
>5 lymph nodes	2	19
<10 lymph nodes	9	15
≥10 lymph nodes	−7	29
No wound complications	2	26
Wound complications	−7	−1
No XRT complications	9	19
XRT complications	4	15

n.s., not significant. For all categories, the mean difference in arm volumes was non-significant.

cation of tumour in the upper outer quadrant versus other quadrants did not influence the incidence of any arm symptoms at any point in time studied (data not shown).

Arm swelling

The difference in arm volume (ml) between the operated and the other side is shown in Figure 1(a) (3–12 months) and Figure 1(b) (13–36 months). No statistically significant difference was found irrespective of whether any arm symptoms were reported, nor was there any statistically significant association found between mean difference in arm volume and treatment characteristics, tumour characteristics or complications to treatment (Table 4). However, there was a trend of increasing difference over time. The proportion of patients with >100 ml difference between the operated and the other side increased from 3–12 months to 13–36 months from 2.4% to 11.2% among patients with no arm symptoms and from 8.1% to 10.2% among patients with any arm symptoms. Compliance to the protocol that stipulated measurement of arm circumference at fixed intervals was less strictly followed than for registration of arm symptoms, particularly in the XRT group where only 2/3 of the patients had complete data. The reason has not been possible to find retrospectively.

Multivariate analysis (Table 5)

The multivariate logistic regression showed that only the number of lymph nodes found in the axillary specimen and age remained statistically significantly associated with any arm symptoms at 3–12 months. The 7% risk reduction/year with increased age implies that a 60 year old woman has a 65% lower risk at 3–12 months and a 35% lower risk at 13–36 months after surgery having any arm symptoms than a 40 year old woman. If 5 lymph nodes are found in the axillary specimen instead of 10, the risk reduction will be 40% at 3–12 months and 30% at 13–36 months after surgery.

DISCUSSION

Radiotherapy as delivered in this study, with two tangential fields at an open angle of 185°, might result in a spill over of radiation to the lower part of the axilla. Two authors have found an increased incidence in arm morbidity after radiotherapy only to the breast [9, 23]. In the Royal Marsden Hospital study [9], the difference was not statistically significant in the multivariate analysis. In the study by Moffat and associates [23], the difference was only borderline significant in a univariate analysis. No such association was found in this study either by uni- or multivariate analysis. Instead, different patient characteristics, other treatment characteristics than radiotherapy and complications to the surgical procedure, were found to influence arm symptoms.

Both age and employment were strongly associated with any arm symptoms during the first postoperative year in the univariate analysis. 86% of patients <65 years of age in this study were employed. Having a job might accentuate arm symptoms. However, the multivariate analysis showed that arm symptoms were age-dependent rather than associated

Table 5. Multivariate analysis of the relation between any arm symptoms at 3–12 months and at 13–36 months after treatment and patient characteristics, treatment characteristics, tumour characteristics and complications to treatment. The table shows relative risks (RR) obtained in logistic regression

	RR (95% confidence interval)	
	3–12 months (n = 368)	13–36 months (n = 335)
XRT versus non-XRT	0.69 (0.42–1.12)	1.07 (0.61–1.83)
No. of lymph nodes dissected	1.11 (1.05–1.18)	1.07 (1.02–1.14)
Age (years)	0.93 (0.91–0.97)	0.96 (0.92–0.99)
Employed (no versus yes)	0.74 (0.37–1.49)	0.53 (0.24–1.18)
Wound complication (yes versus no)	1.71 (0.98–2.93)	1.53 (0.82–2.85)
Complication to XRT (yes versus no)	1.00 (0.39–2.55)	1.83 (0.69–4.84)
Outer upper quadrant (yes versus no)	1.33 (0.84–2.12)	1.59 (0.93–2.73)

with employment. Kiel and Rademacker [12] and Keramopoulos and associates [20] also reported an association with age and arm symptoms. In their studies, patients >55 years and >60 years of age had more arm symptoms (arm swelling and pain) than younger patients.

The extent of axillary dissection in this study had a clear relation to any arm symptoms up to 36 months in this study, both in the uni- and multivariate analysis. However, there was a trend towards less frequent arm symptoms with increasing time since surgery. The extent of axillary dissection has been shown by other authors to influence arm morbidity [6–12]. This illustrates the existing conflict between, on the one hand, having an adequate yield from the axilla in order to maximise local control and the reliability of staging, and, on the other, minimising arm morbidity. One practical example of this conflict is that Sacks and associates [27] recommend full axillary clearance in all premenopausal women. This may be the optimal surgery, but our data indicate that younger women and those with the most extensive dissections have the highest rate of arm morbidity. The number of axillary nodes found in the axillary specimen as a proxy for the extent of the axillary dissection is both surgery and pathologist dependent. However, we know of no better retrospective method of evaluating the extent of axillary dissection. Our own data on 358 consecutive patients operated at the Örebro Medical Centre Hospital in 1992–1993 show that the yield of the axillary dissection is more dependent on the surgeon than on the pathologist [29].

Postoperative wound complications were related to any arm symptoms, but only during the first postoperative year and only in the univariate analysis. Mozes and associates [23] have previously described wound infection after mastectomy as increasing the risk of arm oedema. Hoe and associates [21] did not find any association between postoperative wound complications and arm oedema. Thus, postoperative wound complication does not seem to be a major contributor to the development of postoperative arm symptoms after breast cancer treatment.

Arm swelling—expressed as the difference in arm volume between the operated and the other side—was not a common finding in this study. Less than 2–8% of the patients had an increase in arm volume of >100 ml, irrespective of whether they reported any arm symptoms at 3–12 months. There was a small increase of 10–11% at 13–36 months, but still no difference between patients with and without any arm symptoms. However, measurement of arm circumference may be too imprecise to evaluate adequately arm swelling after breast cancer treatment [30].

From this analysis, we conclude that radiotherapy only to the breast after breast-conserving surgery and axillary dissection for stage I breast cancer does not negatively influence arm symptoms over the first 3 postoperative years. Instead, young age and increasing extent of the axillary dissection are the factors of greatest importance for the development of any arm symptoms. However, the results from this study cannot be a strong argument to abandon level I and II dissection of the axilla in early breast cancer, especially not in young women who might be candidates for postoperative chemotherapy if the axillary nodes we found to be histopathologically positive for metastasis. However, if chemotherapy would be administered routinely even in node-negative patients, the need for axillary dissection in young women without clinical evidence of involved axillary nodes could be questioned. In that case, a watch policy with selective axillary clearance only when clinically involved nodes are detected among patients with small tumours (≤10 mm) might be a more appropriate alternative to axillary dissection in all cases.

ADDENDUM

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