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Acknowledgements—This study was financially supported by Savo Cancer Fund. The technical assistance of Mrs Kaarina Hoffren is gratefully acknowledged. The survival curves were kindly reproduced by Muotomania, Kuopio, Finland.

Pergamon

European Journal of Cancer Vol. 30A, No. 14, pp. 2073–2081, 1994
Elsevier Science Ltd
Printed in Great Britain
0959–8049/94 $7.00+0.00

0959-8049(94)00310-6

Patient Population Analysis in EORTC Trial 22881/10882 on the Role of a Booster Dose in Breast-conserving Therapy

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The changing composition of the patient population in breast cancer, which has been reported over the last decade, has important consequences for prognosis. In the present trial, an analysis of the population in an EORTC trial (22881/10882) on breast-conserving therapy was conducted. A shift towards earlier stages has been seen stage per stage, therefore better survival and local control rates are likely to be expected in comparison to previously published series. The majority of tumours in this trial were small, with a median clinical size of 2 cm and a median pathological size of 1.5 cm. A substantial number of lesions were detected in a pre-clinical stage (17.8%). Nodal involvement was present in only 19% of all patients and usually in only a low number of nodes (only 4% of all patients had four or more nodes invaded). The median number of nodes examined was 12, the difference between institutions was large. There was a significant correlation between the number of nodes examined, the percentage of patients with positive nodes ($P = 0.03$) and the percentage of patients with massive axillary invasion ($P = 0.003$). The correlation between clinical evidence and pathological invasion of the axillary nodes showed that 15% of the clinical examinations were false-negative and 51% were false-positive. Pathological nodal invasion could be clinically predicted in only 31% of patients, and consequently clinical examination of the axilla was a poor predictor of prognosis in this study. Pathological invasion of axillary lymph nodes was better correlated to pathological tumour size than clinical or radiological size.

Key words: breast cancer, radiation therapy, tumorectomy
Eur J Cancer, Vol. 30A, No. 14, pp. 2073–2081, 1994

INTRODUCTION

BREAST-CONSERVING THERAPY (local tumour excision with consecutive radiotherapy) is at present considered to be the standard of care for early breast cancer, making it possible to avoid ablative surgery. During the last decades, evidence has emerged proving the validity of this approach. The first trial which demonstrated the equivalence of mastectomy and breast-conservative treatment was an Italian series, only for tumours less than 2 cm, randomising between Halsted radical mastectomy and quadrantectomy plus radiotherapy to the whole breast (50 Gy) and a booster dose of 10 Gy to the scar [1, 2]. Although the conservative approach proved to be equivalent to radical surgery, it was only confirmed for patients with very small (< 2 cm) tumours. A trial on a similar group of patients in

France produced similar results [3]. However, in the American NSABP study, randomising between mastectomy and lumpectomy with or without radiotherapy (50 Gy without boost), tumours up to 4 cm [4], and in a European multicentre trial from the EORTC (10801), randomising between (modified) radical mastectomy and tumorectomy plus irradiation (50 Gy) with a booster dose administered of 25 Gy, lesions even up to 5 cm were entered [5]. All results were reproducible: no difference in local control and survival could be demonstrated between mastectomy and breast-conserving treatment.

Now that the efficacy of breast-conserving therapy has been demonstrated it is important to optimise this treatment by investigating uncertainties concerning the prognostic influence of pathological subtypes [6], differentiation grade and hormonal receptor status, and optimal radiotherapy dose levels. Currently, this latter question is under study in an EORTC phase III trial (22881/10882) on the role of the booster dose of radiotherapy [7]. It is also still not evident what the maximum tumour size is on which this procedure can be safely performed [6]. Furthermore, it is of prime importance to assess which patients will benefit most from this breast-conserving treatment approach. Differences in local control and survival between subgroups of patients must be judiciously studied, and these are, to a large extent, influenced by the distribution of patients within a series to the various stages of the disease.

This analysis of the patient distribution in the EORTC trial 22881/10882 on breast-conserving therapy has demonstrated a changing trend towards smaller tumours compared to previously published series, a factor which is likely to influence survival and local control of these patients. These data have important consequences for the interpretation of the final outcome and for guidelines for treatment in the future.

MATERIALS AND METHODS

Trial design

The EORTC trial 22881/10882 is a phase III study of the conservative management of breast cancer by tumorectomy and radiotherapy, initiated in May 1989 [7]; it is a joint study of the EORTC Radiotherapy and Breast Cancer Cooperative Groups. The objective is to assess the role of the booster dose in local control and cosmetic outcome.

After tumorectomy and axillary dissection, the whole breast in all patients is irradiated to a dose of 50 Gy given in 25 fractions of 2 Gy in 5 weeks. If the tumour excision is microscopically complete, the patient is randomly assigned to no further irradiation or a boost (16 Gy for external and 15 Gy for interstitial boost modalities). In case of an incomplete resection (microscopical invasion of section margins by invasive cancer), patients receive either a low booster dose (10 Gy) or a higher dose (26 Gy for external or 25 Gy for interstitial therapy). All patients with a breast carcinoma stage T1-2 N0-1 M0 (tumours up to 5 cm) that can be locally excised with an acceptable cosmetic outcome are eligible for this trial. Between May 1989 and November 1992, over 2000 patients were randomised by 26 institutions from nine countries.

Three different case report forms (CRF) have to be completed: an on-study form (two pages), a radiotherapy form and a follow-up form every following year.

Specific information on pre-operative tumour status and pathology is required. The clinical features include dominant site of the lesion in the breast, largest diameter on clinical examination and clinical axillary nodal status. Radiologically, the two largest perpendicular diameters according to pre-operative mammography (not on ultrasound) are requested. The pathological features required are the largest diameter of the dominant lesion, the total number of axillary nodes examined and the number of invaded axillary lymph nodes. Biopsy size, histological type, radicality of excision, microscopical margin from invasive carcinoma and extension of CIS are registered and will be evaluated later.

Analysis of the population

In November 1992, the first analysis of breast tumour characteristics of patients entered in trial 22881/10882 was performed. This analysis included 1458 patients for whom the on-study forms were completed and received at the Data Centre of the EORTC in Brussels (Appendix). The data were first checked for missing items. Information on pre-operative tumour status was quite frequently still lacking, and radiological tumour size was not available in 416/1458 (29%) of the forms (Table 1). This is mainly due to the fact that, in several institutions, patients had surgery elsewhere and were referred thereafter to a radiation oncologist for further treatment. The transfer of sufficient pre-operative clinical information appears to be a problem in such a situation. In the analysis, only the available data on every item were considered so total numbers do not equal 1458, and may differ between analyses (Table 1). For example, information on clinical tumour size was available in 1235 patient files, and information on pathological tumour size in 1388 files (these numbers are presented in parentheses in Table 1). However, for the evaluation of the correlation of clinical and pathological tumour size, information on both was needed and was available in only 1192 patient files. Similarly, correlation of clinical and radiological tumour size was possible in 910 files, correlation of clinical tumour size and clinical nodal status in 1228 files, and of clinical tumour size and pathological nodal status in 1222 files. For classification, the UICC system (1987) was used [8].

The χ^2 test for linear trend was used to assess the correlation between the number of nodes examined and the percentage of positive nodes [9].

RESULTS

Tumour size

Clinical tumour size. The median tumour size as recorded on clinical examination, was 2 cm (Figure 1). While the protocol allowed for randomisation up to 5 cm diameter, in 1136/1235 patients (92%), the tumour was smaller than 3 cm. The largest group of lesions (488 or 39.5%) were between 1 and 2 cm. Sixteen (1.3%) palpable tumours were smaller than 0.5 cm. Only 92 patients (7.4%) with a tumour larger than 3 cm were

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Revised 20 July 1994; accepted 1 Aug. 1994.

Table 1. Number of data available per analysis

TOTAL: 1458	T	pT	RX	N	pN	Number of nodes examined
T	(1235)					
pT	1192	(1388)				
RX	910	965	(1042)			
N	1228	1199		(1430)		
pN	1222	1089		1427	(1427)	
Number of nodes examined					1381	(1385)

Number of patients of whom clinical (T), radiological (RX) or pathological (pT) tumour size and clinical (N) or pathological (pN) nodal status were available for analysis in November 1992. For each separate item, on the diagonal, the number of patients is represented in parentheses, e.g. for the clinical nodal status, information was available on 1430 patients. The other numbers indicate the number of patients for whom data of both parameters for the correlation were available, e.g. for the correlation between clinical nodal status and clinical tumour size, data for both were available in 1228 patients.

Table 2. Correlation of invaded lymph nodes with method of tumour measurement: clinical versus pathological

	pT1		pT2		Total	
	No.*	%	No.*	%	No.*	%
T0	23/207	11.1	4/16	25.0	27/223	12.0
T1	114/602	18.9	22/89	24.7	136/691	19.7
T2	43/198	21.7	43/169	25.4	86/367	23.4
Total	180/1007	17.8	69/274	25.0	249/1281	19.4

*No. with positive nodes/no. per group.

randomised, of which one tumour was clinically larger than 5 cm (6 cm, 2.5 cm on pathological examination). A total of 220 patients (17.8%) with subclinical lesions (T0) have been entered and these tumours were clinically not palpable, but were detected on mammography or ultrasound in a preclinical stage. 7 patients had palpable lesions with unknown size (TX).

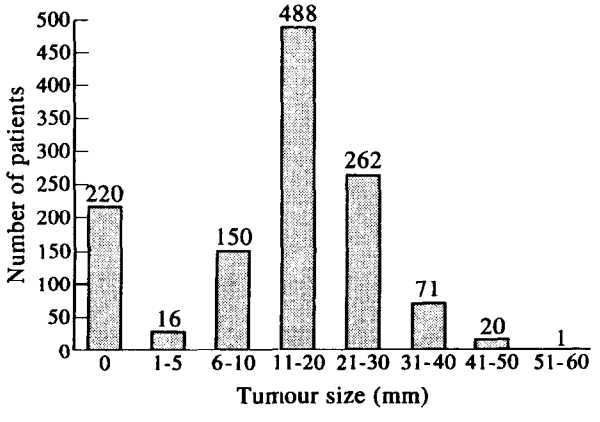

Figure 1. Clinical tumour size distribution in trial 22881/10882. The absolute number for each group is indicated above the columns. Total = 1228 (excluding 7 of unknown size).

Correlation of clinical and radiological tumour size. Of the 227 patients initially reported as presenting with a subclinical tumour (T0), information on radiological size was available in 164. In the remaining 63, either no radiological information was available or the lesion was detected on ultrasound. In the majority of cases (92.1% or 151/164 cases), the lesions were detected on a mammogramme. In 134 (81.7%), the lesions were smaller than 2 cm, and in 17 (10.4%), larger than 2 cm. In 13 T0 cases (7.9%), the tumours were reported as not detected by mammography. For these cases, the institutions were specifically asked how the lesions were detected. In 7/13 patients, the lesion was not subclinical but could be palpated, although it was not seen on a mammogramme, but the exact size was not noted (TX). Thus, the real number of subclinical tumours was 220. In 5/13 patients, the lesion was not palpable, but was visible on mammography, although not measurable. In 1/13, the lesion was discovered during surgery for another (benign) lump.

Of 480 clinical T1 tumours, 440 (91.7%) were visible on mammography, 388 (80.8%) were radiologically smaller than 2 cm and 52 (10.8%) were larger. In 40 (8.3%) cases, the tumour was not visible on the mammogramme. Of 266 clinical T2 tumours, 256 (96.2%) were seen on mammography. In a sizeable group (105, 39.5%), the lesions were smaller than 2 cm on mammography, and in 151 (56.8%) the radiological size was larger than 2 cm. In 10 cases (3.8%), the lesion was not seen on the mammogramme.

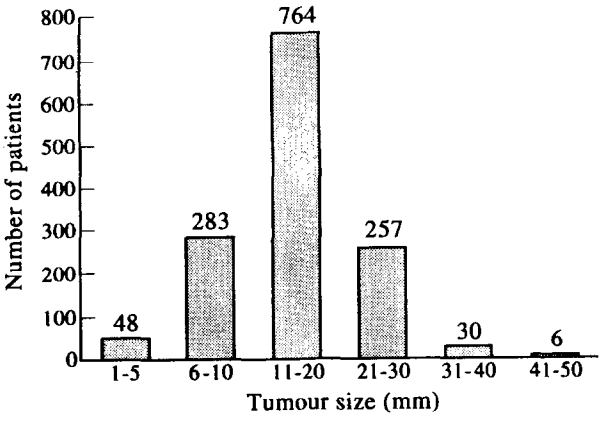

Figure 2. Pathological tumour size distribution in trial 22881/10882. The absolute number for each group is indicated above the columns. Total = 1388.

Pathological tumour size (pT) and correlation with clinical tumour size (T). Tumour size distribution, as recorded on pathological examination is shown in Figure 2. The tumour sizes tended to be somewhat smaller than the clinical estimates (median pT = 1.5 cm compared to median T = 2 cm). In 1304/1388 patients (94%), the lesions were between 0.5 and 3 cm, the majority (764 or 55%) between 1 and 2 cm. 48 (3.5%) patients had tumours between 1 and 5 mm. Only 36 patients (2.6%) had tumours larger than 3 cm. The pathological size of subclinical lesions, detected on mammography or ultrasound, are reported separately in Figure 3. The median size was 1 cm. Of a total of 208 cases, 16 (7.7%) were between 1 and 5 mm, 177 (85.1%) between 6 and 20 mm, 13 (6.3%) between 21 and 30 mm and 2 (0.9%) larger than 31 mm.

The correlation between clinical and pathological tumour size was performed where data for both were available, that is, for 844/874 of all tumours clinically smaller than 2 cm (T1, including the subclinical lesions) and 348/354 of the clinical T2 tumours. Of all T1 tumours, 88% (743/844) were confirmed as smaller than 2 cm on pathological examination, while 12% (101/844) were larger. Of all clinical T2 tumours, 54.3% (189/348) were smaller than 2 cm and 45.7% were larger than 2 cm on pathological examination.

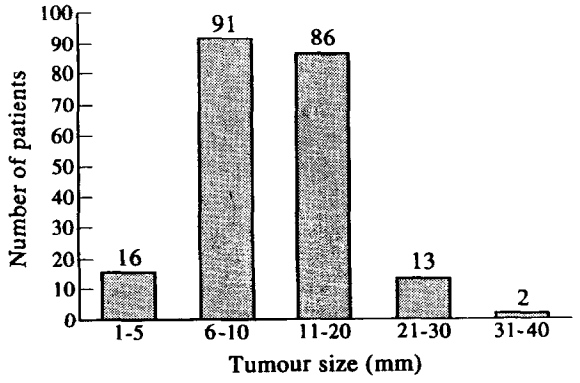

Figure 3. Pathological tumour size distribution of the subclinical lesions (T0) entered in trial 22881/10882. The absolute number for each group is indicated above the columns. Total = 208.

Correlation of pathological and radiological tumour sizes. Of all lesions reported not detectable or measurable on mammography (77 in total), most (90.9% or 70 lesions) were histologically smaller than 2 cm (pT1), whereas 7 (9.1%) were larger (pT2).

Most of the lesions detected by mammography and smaller than 2 cm (645 in total) were also histologically smaller than 2 cm (572, 88.7%), while only 73 (11.3%) lesions were larger than 2 cm. Of all tumours larger than 2 cm detected by mammography (243 in total), 44.9% (109 lesions) were histologically smaller than 2 cm, while 55.1% (134 tumours) were larger.

Nodal involvement

Correlation of clinical nodal involvement and clinical tumour size. While information on clinical invasion of the axillary nodes was available in 1430 patients, information on both clinical nodal involvement and clinical tumour size was available in only 1228 patients. Axillary nodes were reported to be palpable in 138 (11.2%) of these patients. Palpable nodes were found in 89/874 (10.2%) of T1 and in 49/354 (13.8%) of T2 lesions.

Pathological nodal involvement and correlation with tumour size. Information on pathological nodal status was available in 1427 patients, and in 273 (19.1%), invaded nodes were found. Invasion in only one node was found in 127/273 (46.5%), of two nodes in 61 (22.3%), of three nodes in 25 (9.2%), and of four or more nodes in 60 (22%). As a proportion of the total population, 213/1427 patients (15%) had one to three invaded nodes, and 60/1427 (4.2%) had four or more invaded nodes, which is often described as "massive" invasion. Information on both pathological lymph node invasion and clinical tumour size was available in 1222 patients. Axillary nodes were reported to be invaded in 234/1222 (19.1%) of all cases, in 27/218 (12.4%) of T0, in 124/652 (19%) of T1 and in 83/352 (23.6%) of T2 lesions. Correlation of pathological nodal invasion to clinical tumour size showed that nodal invasion occured in 1/15 (6.7%) patients with tumours of 1–5 mm, in 25/149 (16.8%) with tumours of 6–10 mm, in 98/488 (20.1%) with tumours of 11–20 mm, in 58/260 (22.3%) with tumours of 21–30 mm, and in 25/91 (27.5%) with tumours larger than 30 mm (Figure 4).

The correlation of clinical and pathological positive nodes with pathological tumour size was similar to that for clinical tumour size. Clinically enlarged nodes were found in 102/938

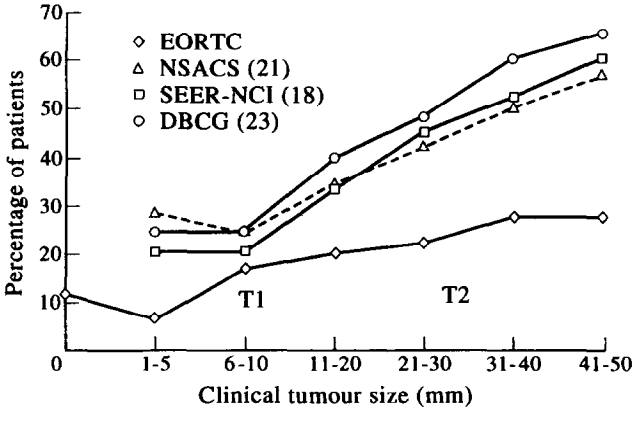

Figure 4. Correlation between clinical tumour size and pathological lymph node invasion, for this trial and for three large pooled series: NSACS, 12 981 patients [21], SEER-NCI, 24 740 patients [18] and the DBCG, 13 851 patients [23].

Table 3. Correlation of invaded lymph nodes with method of tumour measurement: clinical versus radiological

	RX-T0		RX-T1		RX-T2		Total	
	No.*	%	No.*	%	No.*	%	No.*	%
T0	1/13	7.7	17/159	10.7	3/22	13.6	21/194	10.8
T1	7/43	16.3	92/433	21.3	14/65	21.5	113/541	20.8
T2	2/11	18.0	24/120	20.0	42/165	25.5	68/296	23.0
Total	10/67	14.9	133/712	18.7	59/252	23.4	202/1031	19.6

*No. with positive nodes/no. per group.

(10.9%) of pathological T1 lesions and in 33/261 (12.6%) of pathological T2 lesions. Pathological nodal invasion was seen in 165/933 (17.7%) of pT1 and in 64/260 (24.6%) of pT2 lesions.

Correlation of pathologically invaded nodes with method of tumour measurement. Table 2 shows the correlation of pathologically invaded nodes with clinical and pathological tumour size. Of patients with tumours histologically larger than 2 cm, 25% had invaded lymph nodes, irrespective of the clinical tumour size, and of those with smaller lesions, 17.8% had nodal invasion. This difference is related to the fact that the lesions in the pT2 category were nearly all between 2 and 3 cm, with only 36/293 (12.3%) above 3 cm. Clinical tumour size had a limited influence on pT1, although unpalpable tumours had a lower (11%) incidence of nodal invasion. From Table 3, both clinical and radiological measurement of tumour size were similarly correlated to nodal invasion, but to a lesser degree than pathological tumour size.

Number of nodes examined. A median number of 12 examined nodes was reported in 1385 patients (Figure 5), but with a large range which was not evenly distributed between institutions. In 102 patients (7.4%), five or fewer nodes were examined, the majority (77/102, 75.5%) of these were reported by three institutions. In 48 patients (3.5%), exactly 25 nodes (10) or more than 25 nodes (38) were examined in the surgical specimen and these were randomly distributed between institutions. Since the pathologist could be influenced by clinical findings before surgery, the number of lymph nodes examined was analysed in three institutions where patients are seen before surgery and operated upon in the institution itself. The median number of nodes examined in patients with or without clinically enlarged nodes was, however, similar in both groups.

Relationship between the number of nodes examined and patients with positive nodes. The percentage of patients with diagnosis of nodal involvement was correlated to the total number of examined nodes (Figure 6). These percentages differ from 15.8% (16/101) for patients with one to five nodes examined to 20.6% (26/126) for the group with more than 20 nodes examined, a difference which was statistically significant (χ^2 linear trend = 4.51, $P = 0.03$). The diagnosis of massive axillary invasion (defined as four or more invaded lymph nodes) on histological examination was also correlated to the total number of examined lymph nodes. Table 4 shows that the percentage of patients with four or more invaded nodes increased when more nodes were histologically examined, ranging from only 1.7% when a low number (10 or less) to 6.2% when a high number (20 or more) was examined. This increase was highly significant (χ^2 linear trend = 7.65, $P = 0.006$).

Accuracy of the pre-operative clinical axillary examination. The accuracy of the pre-operative clinical examination of the axilla was assessed by analysing the relationship between clinical suspicion and pathological invasion of the axillary lymph nodes (Figure 7).

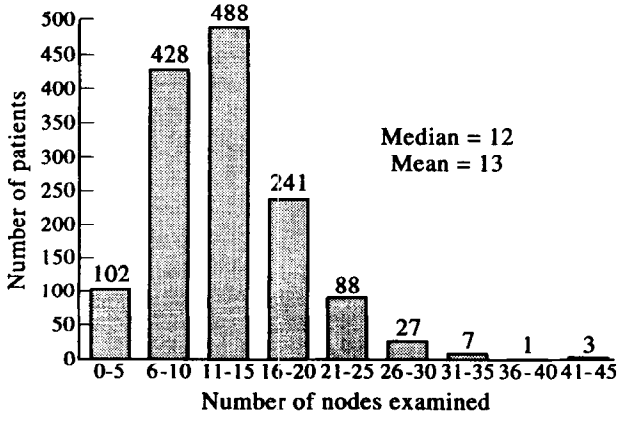

Figure 5. Distribution of the number of nodes examined for all patients. The absolute number for each group is indicated above the columns.

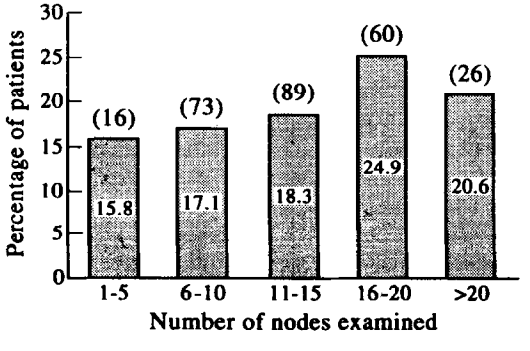

Figure 6. Correlation between patients with positive nodes and the number of nodes examined. Percentage of patients are indicated in the columns and the absolute number is indicated above the columns.

Table 4. Correlation between the number of nodes examined and the percentage of patients with 'massive invasion' of the axillary nodes (> four nodes invaded)

Number of nodes examined	Total no. of patients	Patients with > four nodes invaded No.	%
≤ 10	410	7	1.7
11–15	430	13	3
16–20	219	10	4.6
> 20	113	7	6.2

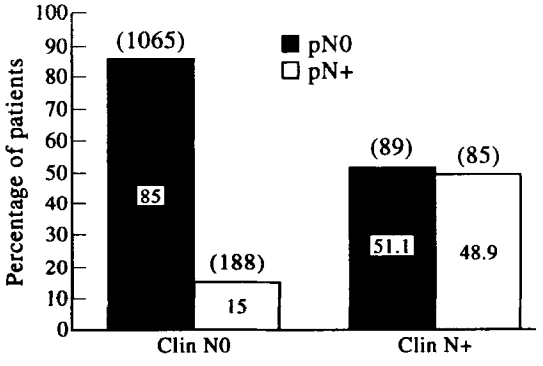

Figure 7. Correlation between clinical (N0/N+) nodal status and pathological nodal involvement (pN0/pN+). The percentage of patients are indicated within the columns and the absolute number is indicated above the columns.

In the patients reported to have no clinical evidence of enlarged nodes in the axilla, 85% (1065/1253) had no invasion of nodes on histological examination, but in 15% (188 patients) tumour invasion of the nodes was seen. These 15% represent 'false-negative' clinical examinations: no clinical evidence for positive nodes, but invasion observed on pathological examination.

In the 174 patients reported to have enlarged, suspicious nodes on clinical examination, nodal invasion was confirmed histologically in 48.9% (85) of patients, but in 51.1% (89 patients) invasion was not confirmed. These 51.1% represent 'false-positive' clinical observations: microscopical examination did not confirm the clinical evidence. Of all 273 patients with histological axillary lymph node invasion, the axilla was normal on clinical examination in 188 (69%) cases.

DISCUSSION

From this initial analysis of the patient population in the EORTC trial on the role of a booster dose in breast-conserving therapy, a number of important findings have emerged.

There is a high proportion of patients with small lesions and subclinical tumours. In reported retrospective and prospective studies in conservative treatment of stage I–II breast carcinoma, the percentage of patients with T1 tumours varies from 38 to 65%, and the percentage of patients with subclinical lesions hardly reaches 4% (Table 5) [10–13]. The exceptionally low percentage of T1 tumours (21%) in the previous EORTC trial on breast-conserving therapy (10801, randomising between mastectomy and conservative treatment), was due to the fact that most institutions only entered patients with tumours larger than 2 cm [5].

There may be several reasons to explain this shift towards smaller tumours. It is possible that some investigators were selective in accepting patients for conservative treatment with a possibility of relatively low radiotherapy doses (50 Gy) and, therefore, randomised only patients with small lesions. However, it may also be the effect of the rise in the incidence of small tumours, as shown by data collected by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute [14–16], which is probably due to screening [14–16] and/or changes in patient behaviour, leading to earlier consultation [16, 17].

The fact that the distribution of the clinical tumour size is normal, around 11–20 mm, except for the subclinical lesions (Figure 1) suggests that these subclinical tumours represent a different type of lesion. There is otherwise no obvious reason why there are only 16 lesions of 1–5 mm and 220 non-palpable tumours.

Another finding of this trial is the very low rate of nodal invasion compared to other published series, where 20–40% of positive nodes are reported for T1 tumours and 40–60% for T2 tumours [18–21]. The logical explanation for this low rate would be that, in this series, the proportion of small tumours is important. In patients from this trial, with tumours detected in a preclinical stage (T0), 12% had histological nodal invasion (Figure 4). Compared to the literature, this is a low rate. Haagensen, in a personal series of 1007 mastectomy patients, found axillary invasion in 19.2% of the patients with subclinical lesions [20]. In another series with 1059 patients, more than 30% (32.9%) of patients with non-palpable breast carcinomas (with a positive mammogramme) were reported to have positive axillary nodes at the time of diagnosis [22]. In the present trial, the percentage of patients with nodal invasion increased from 6.7% in lesions from 1–5 mm up to 27.5% in lesions measuring 31–50 mm. Compared with large, pooled series from the U.S.A. (SEER-NCI, 24740 patients [18] and NSACS, 12981 patients [21]) and from Denmark (DBCG, 13851 patients [23]), it is obvious that for each tumour size, the percentage of patients with positive nodes is lower in this trial (Figure 4). Therefore, the shift towards smaller tumour size can only partially explain the low percentage of patients with nodal invasion.

Patients with poor prognostic features (especially with many positive lymph nodes) may have been excluded from the trial in some institutions or may have been entered in other adjuvant therapy studies. It was decided 2 years after the start of the trial that up front chemotherapy was acceptable. However, this did not change the distribution of tumour size and/or number of

Table 5. Distribution of the percentage of T1-T2 tumours in breast-conserving series

Series	(T0) (%)	T1 (%)	T2 (%)	Total no. of patients
Trial 22881/10882	(18.4)	71	29	1235
Mate *et al.* 1986 [10]		65	35	180
Van Limbergen *et al.* 1987 [13]	(4.1)	38	62	168
Pezner *et al.* 1988 [11]	(2.0)	52	48	102
Solin *et al.* 1988 [12]		57	43	552

patients with positive nodes in patients randomised after that decision in October 1991, although normally one would anticipate that the number of patients with lymph node invasion would increase once pre-operative chemotherapy was permitted.

It is possible that there may have been an underestimation of the number of positive nodes due to a low number of nodes removed and examined. While the median number of examined nodes was 12, usually considered to be adequate [23, 24], there was a considerable difference in the percentage of patients with positive nodes relative to the number of nodes examined: the percentage increased from 16% when one to five nodes were examined to 24% when more than 16 nodes were examined. However, even this reduction of one third (24 to 16%) does not explain the low number of patients with invaded nodes in this study, since usually incidences of 2–2.5 times higher are reported [18–21]. This tendency towards lower incidences of axillary invasion is not yet fully explained, but the same has also been observed in another recent breast cancer trial population (personal communication, Professor Dr H. Stewart, Scottish Cancer Trials Office, 1993).

The high number of small tumours and the low incidence of nodal invasion in this study have important consequences, since this shift will undoubtedly lead to a better prognosis per stage, as local control and survival will increase. In addition, there is an indication that the presently available system for staging (IUCC), which is used to predict prognosis and thereby act as a guideline for comparing treatment results of different institutes, could become less suitable for this purpose if the majority of patients within one stage group have sizeable differences in local control and survival. Therefore, more detailed reporting of tumour size and nodal status has to be established.

Especially the large number of patients (17.8%) with tumours detected in the preclinical stage, is emphasizing the importance of screening. Such subclinical lesions might have a different clinical behaviour and a better prognosis. In view of the increased use of screening programmes, this group will probably increase in the future, and knowledge of the specific clinical behaviour of this group could provide valuable information for future treatment policy.

The shift towards earlier stages hampers comparison of the future results of this study to previously published data: published survival and local control rates in the literature according to the tumour stage are less relevant to the expected results of the present study since most series have, within the same tumour stage, larger tumour sizes and more frequent nodal invasion. Thus, the necessity of randomised studies, and the futility of comparisons with historical series, especially without consideration of the population composition are heavily emphasized.

Furthermore, the shift towards better prognosis can have an influence on the conduct of the trial itself. Since tumours are smaller and nodal invasion reduced, less local recurrences and better survival are expected in comparison to that which has been published before, which implicates that more patients could be needed than originally described in the protocol in order to detect a difference between both treatment arms.

A further consequence is that with decreasing tumour size and less nodal invasion, clinical examination will be less reliable in predicting prognosis. Pathological lymph node invasion is the most important predictor of prognosis in breast cancer [10, 12, 18, 23], and the probability of lymph node invasion is correlated to tumour size [18, 23]. From this study, it is clear that although clinical and radiological measurements of tumour size have some predictive value, pathological tumour size correlates best to lymph node invasion.

The accuracy of pre-operative clinical axillary examination in the literature reports false-positive examinations of 25–38%, and false-negatives of 27–40% (Table 6) [20, 25–28]. These are different from the results reported here, where, when the axilla

Table 6. Accuracy of clinical axillary examination in predicting pathological involvement of axillary lymph nodes

Series	False-positive (%)	False-negative (%)
EORTC trial 22881/10882	51	15
Butcher 1969 [26]	25	32
Bucalossi *et al.* 1971 [25]	29	29
Haagensen 1971 [20]	24	32
Schottenfeld *et al.* 1976 [28]	26	27
Danforth *et al.* 1986 [27]	11	38

was clinically negative, only 15% showed invasion (not 30% as usually reported) and, when nodes were palpable, axillary invasion was confirmed in 48.9% (not 66% as previously reported). In addition, pathological nodal invasion was clinically predicted in only 85/273 (31%) of patients, which is less than previously published data, where more than 50% is reported (56–64%) [25, 28]. Thus, the impact of the findings of clinical examination on the prediction of prognosis is different in this series from that which has been previously assumed.

These data also emphasize that clinical evaluation of tumour status is inferior to pathological examination for predicting prognosis. Staging in breast cancer is based on clinical findings for comparison of series, but pathological staging should be used in parallel for specific goals, such as selection and stratification of patients in prospective studies.

Finally, the correlation between the number of nodes examined and the number of patients with invaded nodes, which was reported to be linear in an investigation from the Danish Breast Cancer Group on 13 851 patients registered with breast cancer [23], is also indicated in our series in which a 50% rise in the percentage of patients with nodal invasion was observed when more than 16 nodes were examined compared to less than five. The probability of detecting massive invasion increased 6-fold when more than 20 nodes were examined compared to less than 10 (Table 4), and therefore, if massive invasion is considered to be an important prognostic factor, a careful examination of nodes by the pathologist is advisable.

The wide range in the number of nodes examined in the axillary resection specimen, reported in the trial, reflects the contemporary confusion and differences in opinion regarding optimal axillary surgery. Even within institutions, willing to co-operate in multicentre trials, no clear consensus is available. However, the consequences of these different treatment options are substantial. Not only is there a correlation between the number of examined lymph nodes and the number of involved nodes and consequently prognosis, but the axillary node status usually serves as a guideline for treatment after surgery, i.e. adjuvant systemic treatment, extent of treatment volumes of radiotherapy to regional lymph node areas. Consequently, not only subsequent local control and ultimate survival rates will be influenced by the extent of axillary surgery, but also treatment morbidity (arm mobility, arm oedema) and cosmetic outcome (amount of breast oedema) [29, 30], which is one of the end points in this trial.

In conclusion, there is a shift towards smaller breast cancer lesions and less nodal involvement in this study, which is likely to result, stage per stage, in better local control and survival in this trial than in other published series. This study suggests that, in the future, it may be necessary to adjust and refine the staging system to changes in population composition. Comparison to other series should be performed with the utmost care, and it could be possible that more patients are needed in this trial than originally planned. Pathological examination of tumour size is superior to other methods, and palpation of the axilla is a poor method for predicting lymph node invasion. Axillary invasion and the number of lymph nodes involved are directly related to the number of nodes examined.

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Acknowledgements—The authors wish to express their gratitude to Dr G. Leunens and Mrs K. Vantongelen for their helpful discussions and support.
For the EORTC Radiotherapy Cooperative Group (Chairman Prof. Dr. H. Bartelink) and Breast Cancer Cooperative Group (Chairman Prof. Dr. R.D. Rubens).
This work was supported by the EORTC Foundation (European Organization for Research and Treatment of Cancer).

APPENDIX

Appendix: Participating institutions in population analysis

Participating institution	Responsible physician	No. of patients
CHU Tivoli La Louviere	A. Renaud	29
UZ St Rafael Leuven	E. van der Schueren	154
AZ VUB Brussel	G. Storme	20
Centre St Yves Vannes	E. Monpetit	7
CHU Henri Mondor Creteil	E. Calitchi	22
CHU La Tronche Grenoble	M. Bolla	21
Centre GF Leclerc Dijon	J.C. Horiot	160
Institut Curie Paris	A. Fourquet	133
NKI Amsterdam	J. Borger	152
DDHK Rotterdam	P. Koper	26
St Radboud Nijmegen	W.J. Hoogenraad	72
AZU Utrecht	H. Struikmans	201
UZ Leiden	J.W. Leer	40
RTIL Heerlen	J.J. Jager	77
B Verbeeten Instituut Tilburg	H. Hamers	93
CRCL Mountpellier	J.B. Dubois	30
UH Geneva	J. Kurtz	22
CHU Vaudois Lausanne	R. Mirimanoff	12
UK Düsseldorf	S. Roth	10
UK Köln	R.P. Müller	80
SK Krefeld	U. Schultz	11
GH Nottingham	D.A.L. Morgan	48
Rambam Haifa	A. Kuten	38
Total		1458

List of participating institutions and number of patients for whom the on-study forms were available at the Data Centre of the EORTC in November 1992.