Omitting Axillary Surgery for Low-risk Breast Cancer Patients

A Swedish Prospective Cohort Study

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Acta Oncologica Vol. 39, No. 3, pp. 291–294, 2000

The effects of mammography screening are a decrease in the sizes of tumours and a shift in stage. Very few small breast cancers (≤ 10 mm) have lymph node metastases when screening-detected, the rate being as low as 7%. Axillary clearance is not necessary for all such small tumours. A Swedish prospective cohort study, scheduled for 1 500 patients, is being launched, where axillary surgery is omitted for screening-detected breast cancers of ≤ 10 mm showing Elston grade I or II/and/or S-phase $\leq 10\%$. Axillary surgery, with the associated disadvantages, will not be performed in 970 women out of 1 000 expecting an axillary recurrence rate of 3%. Nordic breast cancer centres are welcome to join the study, which has already recruited around 500 patients.

Received 3 May 1999
Accepted 18 October 1999

Axillary surgery is the main reason for decreased quality of life in surgical breast cancer treatment. Postoperatively, some patients have permanent restriction in shoulder mobility, impaired muscle function in the arm, arm oedema and sensibility disturbances, all of which create problems in daily life activities (1, 2). Breast-preserving surgery has been introduced as being equally as effective regarding survival as mastectomy in breast cancer stages I and II. The question of the type of axillary surgery that should be performed has been discussed for decades and different techniques have been established in different parts of Europe, starting with the Halstead concept with full clearance of all nodes below the clavicle, to more of a staging procedure performed as clearance or sampling.

Today there are several prognostic factors available from the primary tumour for calculation of the risk for recurrence and/or decreased survival (3). Adjuvant medical treatment prolongs the disease-free interval and also significantly decreases breast-cancer-related mortality (4, 5). Prognostic and also predictive factors for adjuvant treatment are increasingly indicated from the primary tumour (6).

When mammography screening was introduced for public health systems, an increasing number of breast cancer patients had axillary lymph nodes without metastases. Routinely performed axillary dissection for some subgroups with a low risk of metastatic nodes is questionable (7–11). Instead of having local and individual exceptions for axillary surgery, we created a study where we could omit axillary surgery for a defined group of breast cancer patients with a low risk for lymph node involvement.

DEFINITION OF LOW-RISK PATIENTS

From two regions in Sweden, the southeast region with Linköping as the University Hospital and the Uppsala/Örebro region, both with ongoing general mammography screening, we analysed size distribution and the correlation with lymph node metastases in screen- and clinically detected small breast cancers. For cancers ≤ 10 mm, 91% were node negative in the southeast region and 6.5% (30/464) of screening-detected cancers were node positive in the Uppsala/Örebro region. In the southeast region, for 1 035 screening-detected cancers ≤ 10 mm, 7% were node positive, most of them with involvement of only one node, while the clinically detected cancers of the same size showed node positivity in 14% of cases. The corresponding figure in Uppsala/Örebro was 16%. In the 11–15 mm group, 24% were node positive (Table 1.) In the latter group we tried to define a subgroup with a lower incidence of axillary metastases by using S-phase, receptors and ploidy, but we could not identify a definitive low-risk

 ISSN 0284-186X

Table 1

Node positivity for different sizes and detection mode

	Size	
	1–10 mm n = 1 135	11–15 mm n = 1 190
Screen detected (%)	7	18
Clinical detected (%)	14	31
All inv. Cancers (%)	11	24

n = 2 325.

subgroup by these factors. In another study from Östergötland we evaluated Elston grade by nodal status in 247 small breast cancers ≤ 10 mm and grade I and II showed a nodal positivity in 8% of cases while grade III showed 16% (Table 2.). Low S-phase ($\leq 5\%$) in cancers ≤ 10 mm showed node positivity in 9% of patients but in this subgroup we excluded the very small tumours because of lack of material, so this value is mainly calculated on tumour sizes of 7–10 mm (Table 3.)

Size and tumour grade, available for all small breast cancers in combination with diagnosis by screening, turned out to be clinically the most valuable parameters for calculating and establishing a subgroup with low risk of node metastases.

Screening-detected invasive breast cancer ≤ 10 mm constitutes 1/3 of the screening cancers, i.e. a total of 20% of all breast cancers detected in Sweden. This means that around 850 cancer patients per year might be available for a study on the omitting axillary surgery. Such a low-risk group has a $>95\%$ probability of a 10-year disease-free survival (12, 13).

STUDY DESIGN

Screening-detected clinically node-negative patients with tumours of 10 mm or less on the mammogram are candidates for the study. These patients will be treated mainly with breast-preserving surgery and at this stage there will be no axillary exploration. At the final histopathology, evaluable tumours with Elston grade III and/or high S-phase ($\geq 10\%$) and a final tumour size above 10 mm will be treated with axillary surgery in a second step, as will all multifocal invasive cancers and cases with positive margins

Table 2

Node positivity for different tumour grades (size 1–10 mm) n = 247

Grade 1 (%) n = 118	5
Grade 2 n = 91	11
Grade 1+2 (%)	8
Grade 3 (%) n = 38	16

Table 3

Node involvement for different S-phase values

S-phase	$\leq 5\%$	$>5\%$
Size 1–10 mm (%) n = 391	9	17 ($p<0.025$)
Size 11–15 mm n = 668	24	31 (n.s.)

at the first operation. Adjuvant treatment can be performed according to local treatment programmes but will generally not be performed in this low-risk group of patients. We are conducting this study as a prospective cohort study with randomization for a small subgroup in order accurately to evaluate the post-and perioperative morbidity and costs. We do not expect any increase in mortality. Theoretical calculation of a randomized study for detecting a 1% difference in disease-free survival must include 15 000 patients in each arm in order to have enough power to produce significant results. This cannot be done in practise, which is why we have chosen a prospectively recruited cohort of 1 500 patients with a probable 9% node positivity. We expect 3% axillary events giving around 50 patients in whom we can analyse primary tumour data with reference to progressive axillary disease. Primary endpoints in this cohort study are incidence and morbidity of axillary recurrences and the correlation to distant disease. We also intend to analyse the correlation of age and histopathological grade with axillary relapses. Secondary endpoints, which will be addressed by randomization of a small group of patients, are morbidity and costs of axillary surgery compared to costs of relapses. Actual numbers of events hypothetically calculated from the known data today are presented in Table 4.

The study has been discussed in the Swedish Breast Cancer Study Group and has the full support of the members of the group.

Table 4

Number of events expected/1 000 patients. Breast cancer-related mortality 5% at 10 years. Total mortality 10 year 20% (annual death rate 2%); 9% node positivity

	No axillary surgery	Axillary surgery as today
No. of women	1 000	1 000
Death breast cancer—all	40	40
Death breast cancer node positive (n = 60 alive 10 years)	15	15
Death breast cancer node negative (n = 770 alive 10 years)	25	25
Axillary relapse	30?	5
No axillary surgery	970	0

FOLLOW-UP SCHEDULE

Clinical examination will be conducted every 6 months and mammography once a year for the first two years, then clinical examination and mammography once a year within a 6-month interval of each other for a further 3 years.

DISCUSSION

It is known from studies where axillary surgery has not been performed that less than the expected numbers in fact progress to relapse in the axilla. For instance, NSABP-B04 (14) randomized patients with clinically negative axilla for axillary surgery or not. In the axillary dissected group, 40% were pathologically node positive while only 22% of not operated axillas, if all are included, had axillary relapses within a 10-year follow-up period. Some non-randomized studies support this observation (15). Other studies have shown a higher proportion of axillary relapses when surgery was omitted, but in those trials large tumours were included (16) and in one study patients also had clinically positive axilla (17). None of the randomized studies where axillary surgery is omitted has shown any difference regarding survival.

In an overview article (11) Ruffin says that, today, adequate staging is the main reason for axillary dissection, the highest possible prognostication and, when a full axillary surgical procedure is performed, to achieve the best local control of the disease in the axilla but no survival benefit can be found.

Patients with an axillary recurrence as first event have a relatively good prognosis with a 5-year survival from the recurrence of around 50% (18), even in cases with larger primary tumours than those discussed in our study. In some of the patients with axillary recurrences, distance metastases will develop within a short time.

Most of the cancers ≤ 10 mm will be treated with breast-preserving surgery and will have radiotherapy to the breast and the lower nodal stations will also be irradiated, even if the axilla is not formally included in the target volume.

Several studies have sought to define a subgroup of breast cancer patients in which axillary surgery can be avoided by using predictive factors in the primary tumour (7, 19). Our choice of criteria (diagnosis by screening, tumour size ≤ 10 mm and Elston grade I–II) is based on the fact that these parameters are available in all patients.

CONCLUSION

Axillary clearance is the procedure with the highest physical morbidity in the surgical treatment of breast cancer. The surgical procedure in small, screening-detected breast cancers results in a high proportion of node-negative axillae being dissected, in many cases as a second surgical procedure. To avoid local and individual criteria for omitting axillary surgery, a protocol has been created by a Swedish study group for avoiding axillary surgery in invasive unifocal breast cancers ≤ 10 mm. In most Swedish regions only Elston grades I and II and/or tumours with S-phase lower than 10% are included in the study cohort. The goal for the study is 1 500 patients. The study cohort will be actively evaluated for 5 years in a follow-up programme; 80% of Swedish hospitals will take part in the study and other breast cancer centres in the Nordic countries are welcome to join in. In April 1999 approximately 500 patients were brought into the study. Even if sentinel node biopsy can be established as a primary procedure in the surgical treatment of breast cancer, there is most probably a sizeable low-risk group where no surgery in the axilla is needed at all, which it is hoped can be established through this study.

ACKNOWLEDGEMENTS

This study was funded by the Swedish Cancer Union.

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