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Does radical surgery to the axilla give a survival advantage in more severe breast cancer?

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Abstract

There is some evidence that more radical treatment of the axilla may improve survival in node-positive disease, but there are concerns about the resultant morbidity from axillary surgery and radiotherapy. The aim of this study was to compare the outcome of axillary node clearance with axillary sampling in similar patients by comparing loco-regional recurrence and overall survival. Patients with invasive breast cancer undergoing axillary surgery between 1986 and 1997 were included. The axillary procedure performed in these patients was either an axillary sample or a level III axillary clearance. To compare like with, the patients were separated into good, moderate and poor prognostic groups by the Nottingham Prognostic Index (NPI) and overall survival was compared by a Kaplan–Meier life table analysis and the log rank test. 734 consecutive patients with operable invasive breast cancer were treated by axillary clearance $n=350$ or sampling $n=384$. The mean follow-up in the clearance group was 65 months versus 66 months in the sampled group. Local recurrence in the clearance group was 11% versus 6% in the sampled group, regional recurrence 2% versus 3% and distant metastasis 28% versus 13%. Kaplan–Meier analysis of the three prognostic groups for the clearance versus sampled groups showed no differences in the absolute survival (log rank: $P=0.3$, $P=0.8$ and $P=0.6$ for the good, moderate and poor prognostic groups, respectively). A conservative surgical approach to the axilla did not significantly increase the incidence of local or regional recurrence and the expected survival benefit from a radical axillary clearance was not apparent.

1. Introduction

The best management of the axilla in patients with invasive breast cancer remains uncertain, but staging of the disease is important for the prognostic value, as well as to plan adjuvant treatment. The three most important prognostic factors used to determine treatment are tumour grade, lymph node status and to a lesser extent tumour size [1]. However, axillary surgery to determine the lymph node status is associated with side-effects which include nerve damage, sensory loss, lymphoedema and decreased shoulder mobility. There has therefore been a move to reduce the extent of axillary surgery since a large proportion of women do not have spread to the axilla and therefore do not benefit from the procedure. For this reason, axillary node sampling, which is a limited surgical procedure, has been used in preference to full axillary clearance. In some centres, sentinel node biopsy is being evaluated in clinical trials to see if this more limited procedure can predict axillary involvement as effectively [2].

Recent Danish studies have shown a survival advantage from radical radiotherapy in high-risk (stage II and III) pre- and postmenopausal breast cancer [3,4]. However, radical axillary radiotherapy increases the morbidity of axillary surgery and can be distressing for patients. It is most unlikely that a randomised trial of axillary clearance versus sampling would recruit sufficient numbers since few surgeons have equipoise and it is unlikely that many patients would be prepared to be randomised. However, any observational study is likely to be confounded by treatment bias, since patients with more severe disease are more likely to have more radical surgery. Nevertheless, if allowance is made for known prognostic factors and if axillary surgery is equivalent to axillary radiotherapy, one would expect to see some survival advantage for axillary clearance in patients with more severe disease, in view of the size of the effect

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seen in the Danish radiotherapy trials, a 9% difference in survival [3,4] at 10 years.

It has been the practice in this unit since 1986 to perform an axillary node sample to assess the axilla in patients undergoing conservative breast surgery. Axillary clearance was performed in patients with clinically involved axillary nodes and in most patients who had a mastectomy.

In order to compare like with like as far as possible, the Nottingham Prognostic Index (NPI) seemed the best available instrument to separate patients into those with a good, moderate or poor prognosis [5].

The aim of this study was to compare the outcome of axillary node clearance with a sampling technique in patients with similar disease by comparing loco-regional recurrence and overall survival.

2. Patients and methods

All patients with invasive breast cancer undergoing axillary surgery between January 1986 and December 1997 were retrieved from a validated database. This was a consecutive series of patients with operable breast cancer referred to a dedicated breast unit in a district general hospital whose primary treatment is outlined in Table 1. The axillary procedure performed in these patients was either an axillary node sample or an axillary clearance.

Axillary sampling was performed by dissecting out four separate lymph nodes which were sent for histological assessment in four separate specimen pots. The majority of the sampled patients underwent conservative breast surgery and had less severe disease. Postoperatively, this group of patients received radiotherapy to the breast and the lower axilla by two glancing fields with the arm extended to the level of the humeral head, not including the axillary apex or the supraclavicular nodes.

Radiotherapy dose: 45 Gy was given in 15 fractions over 5 weeks and a boost of 9 Gy was given to the tumour site in three fractions over 1 week. Treatment was given on a cobalt unit until 1994 and thereafter on a 5 MD linear accelerator.

Axillary clearance was performed to level III and the majority of these patients had a mastectomy. Patients did not receive radiotherapy to the chest wall or axilla after mastectomy, except in 8 cases.

In all patients, the tumour size, tumour grade and lymph node status were available. Patients undergoing mastectomy and axillary clearance had more severe disease and the patients were therefore separated into good, moderate and poor prognostic groups by the NPI [5]. The NPI has proved to be a robust predictor of survival outcome and is now well-validated [6]. Overall survival was compared in patients in the three prognostic groups by a Kaplan–Meier life table analysis and the log-rank test.

Table 1
Primary Treatment in the clearance and sampled groups

	Clearance $n=350$	Sampled $n=384$
WLE	3	89
WLE + RT	20	254
Mastectomy only	319	41
Mastectomy + RT	8	0

WLE, wide local excision; RT, radiotherapy.

3. Results

734 patients with invasive breast cancer who presented between January 1986 and December 1997 were treated by axillary clearance ($n=350$) or sampling ($n=384$). In the sampled group, four or more nodes were retrieved in 83% of cases. Sampled patients had less severe disease: 89% ($n=343$) were treated by wide local excision and 11% ($n=41$) with a mastectomy. In the sampled group, 254 patients treated by wide local excision also received radiotherapy (74%) to the breast and low axilla. In the clearance group 93% ($n=327$) of the patients had a mastectomy and 7% ($n=23$) a wide local excision. In the clearance group, 8% ($n=28$) of patients received radiotherapy, 20 after wide local excision and 8 after mastectomy (Table 1).

Mean follow-up in the clearance group was 65 months versus 66 months in the sampled group. Local recurrence in the clearance group was 11% ($n=38$) versus 6% ($n=24$) in the sampled group, regional recurrence 2% ($n=7$) versus 3% ($n=13$) and distant metastasis 28% ($n=97$) versus 13% ($n=50$). Local recurrence after mastectomy + clearance without radiotherapy occurred in 37/319 patients (11.6%), but in half of the cases local and metastatic recurrence presented at approximately the same time.

Prognostic factors in the two groups were compared and are shown in Table 2. Kaplan–Meier curves were plotted for the three NPI prognostic groups between the radical and conservative groups and there was no difference in absolute survival (log rank test: $P=0.3$, $P=0.8$ and $P=0.6$, respectively) (Figs. 1–3). In each

Table 2
Prognostic factors for clearance versus sampled groups

	Clearance ($n=350$)	Sampled ($n=384$)
Grade 3	110 (31%)*	71 (18%)
Involved nodes	167 (48%)*	103 (27%)
Mean size of tumour	2.49 cm*	2.02 cm

*$P<0.001$.

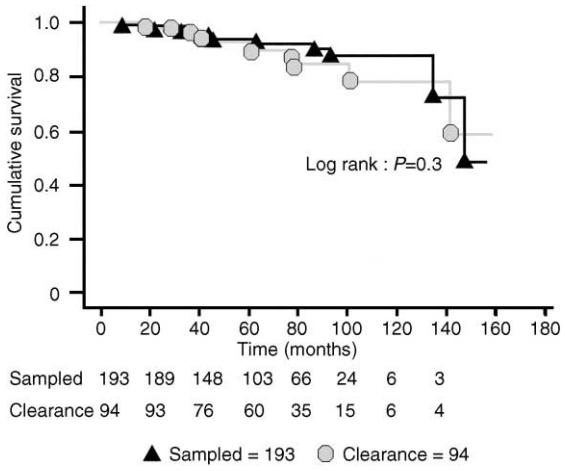

Fig. 1. Kaplan–Meier curves comparing overall survival of good prognostic groups: clearance versus sampled.

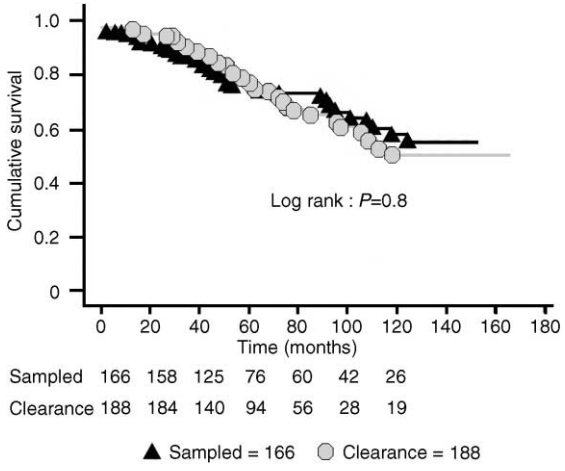

Fig. 2. Kaplan–Meier curves comparing overall survival in the moderate prognostic groups: clearance versus sampled.

analysis, there was a non-significant trend towards better survival in the sampled group.

4. Discussion

It is generally agreed that axillary node status in potentially curable breast cancer is the best predictor of outcome and the main determinant of benefit from adjuvant therapy [7]. At the present time, there is no non-invasive technique which can accurately stage the axilla since those imaging techniques and molecular markers which have been investigated have not proved successful. Surgical removal of the axillary lymph nodes for histological examination still remains the cornerstone for such an evaluation. Unfortunately, the extent of axillary surgery is proportional to the severity of postoperative morbidity and, although much of the morbidity is short term, some patients have debilitating impairment of shoulder mobility, lymphoedema or,

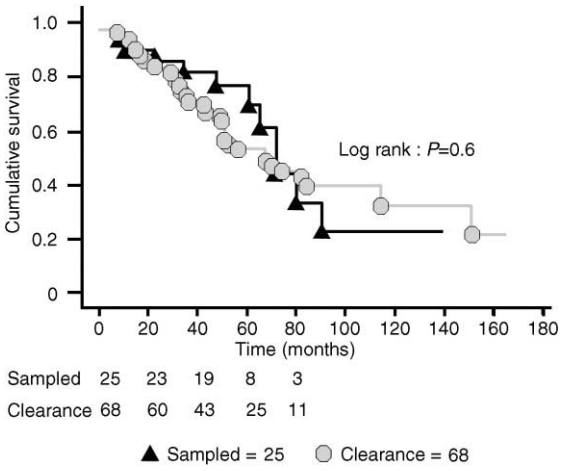

Fig. 3. Kaplan–Meier curves comparing overall survival in the poor prognostic groups: clearance versus sampled.

rarely, a brachial plexopathy. Such complications have a significant physical, as well as pychological, impact on an already anxious patient. The Danish randomised studies have shown an improved survival after radiotherapy to the axilla in node-positive disease [3,4], but the addition of this treatment does cause an increase in morbidity. This morbidity is clearly radiation dose-dependent and the late endpoints are steep [8]. Furthermore, morbidity after radiotherapy is strongly influenced by concomitant surgery.

Three levels to the dissection of the axilla are described and, although there is no uniform agreement as to the appropriate extent of dissection, if the objective of the procedure is to treat the axilla adequately, a level III clearance is most likely to achieve this [7].

With the introduction of the breast screening programme in 1988 in the UK and an increased awareness in the population, breast carcinoma is being detected earlier. It is for this reason that a lesser operative procedure on the axilla has been preferred in patients suitable for conservative surgery in the present series, but most patients undergoing mastectomy had a level III axillary clearance. It was expected that patients in the former group would have less severe disease and this was confirmed as significantly more patients in the clearance group had grade 3 disease, lymph node positivity and larger tumours (Table 2).

To adequately sample the axilla, it has been suggested that at least four nodes should be analysed [9] and this was achieved in 83% of patients during the study period.

Contrary to expectations, the adoption of a policy of axillary sampling did not significantly increase the regional recurrence compared with the clearance group. The present study is a retrospective, observational study which is prone to bias, but the findings are similar to those of the randomised control trial from the Edinburgh group [9]. In their study, 466 patients were randomised to level III axillary clearance or four-node

axillary sample. Radiotherapy to the axilla was given selectively and at follow-up there was no difference in local, regional or distant metastasis or in 5-year survival between the two groups.

In order to compare like with like in the present series, patients in the two groups were separated into good, moderate and poor prognostic groups using the NPI. At a mean follow-up of over 5 years, there was no significant difference in overall survival between those patients treated by axillary node clearance or sampling. Similar results have been reported by the Trafford database experience in a study of 379 patients [10]. The non-significant trend towards a survival advantage in the sampled group probably reflects a bias towards a more favourable prognosis which may not have been completely adjusted for by separating the two groups into NPI categories. However, the trend is the same for each category and is not reversed by axillary clearance in the worst prognosis group (Fig. 3).

The relative morbidity after the two procedures has not been formally assessed since the present study is retrospective, but other reports on the assessment of morbidity have found that it is least in patients who underwent node sampling without radiotherapy to the axilla [9,11]. The Uppsala-Orebro Breast Cancer Study Group from Sweden performed a prospective randomised control trial to assess morbidity after axillary surgery [12] and concluded that the extent of the surgical procedure and young age are the main determinants of arm morbidity after breast-conserving treatment.

The present study is not randomised and it is likely that within each NPI prognostic group there is an uncorrected bias in favour of the sampled patients. However, in view of the size of the survival advantage from radical radiotherapy in the two Danish randomised trials [3,4], it is surprising that no effect is seen from axillary node clearance in the poor prognostic group.

It is concluded from the present study that a conservative surgical approach to the axilla did not increase the incidence of regional recurrence and the expected survival benefit from the more radical approach was not apparent.

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