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The Prognostic Significance of the Axillary Apex Biopsy in Clinically Operable Breast Cancer

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To evaluate the prognostic significance of the axillary apex biopsy and its impact on clinical practice, a retrospective analysis was performed in 875 patients with clinically operable breast cancer who underwent this procedure from 1977 to 1985 (165 TNM stage I; 512 TNM stage II; 198 TNM stage IIIA). Apex biopsy is performed as a staging procedure. Apex biopsy positive patients are treated by radiotherapy alone, while apex biopsy negative patients are treated with breast conserving therapy or mastectomy, both including complete axillary dissection. The apex biopsy was tumour positive in 4% of TNM stage I patients; 17% of stage II patients and 40% of stage IIIA patients. Among patients with clinically node-negative disease, the apex biopsy was positive in 12%; in patients with palpable suspected lymph nodes this figure was 45%. Actuarial 8 y survival rates for patients with stage I, II and III disease and a negative apex biopsy were 83, 70 and 50%, respectively. The corresponding figures for patients with a positive apex biopsy were 60, 28 and 14%. In a multivariate analysis, a positive apex biopsy, clinical N classification and T classification were independent prognostic factors for survival ($P < 0.0001$). We conclude that a positive apex biopsy is rare in clinical stage I breast cancer, and that in patients with TNM stage II and III disease the procedure is an important tool to assess prognosis pre-operatively.

Key words: breast neoplasm, clinically operable breast cancer, axillary apex biopsy, prognostic factor
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INTRODUCTION

IN 1956, the axillary apex biopsy was introduced in the Netherlands Cancer Institute as a staging procedure for patients with clinically operable breast cancer. This was based on the experience that patients with lymph node metastases in the axillary apex had a very poor prognosis despite ablative radical surgery. Furthermore, the combination of radical surgery and radiotherapy to the axilla in these particular patients was associated with a high risk of arm oedema. The goal of the apex biopsy procedure was therefore to identify a subset of patients with a poor prognosis before surgery, in order to avoid mutilating surgery and the combination of axillary dissection and radiotherapy to the axilla in this patient group. Patients with a tumour positive apex biopsy at frozen section were considered inoperable and treated with radiotherapy alone [1]. In the same period, Haagensen introduced a similar staging procedure. He performed not only an axillary apex biopsy, but also internal mammary chain biopsies as a criterion for acceptability for surgery [2]. Indeed, an international comparison of treatment techniques of 1962 demonstrated that, due to a better selection with this staging procedure, a 10–15% improved 5 year survival was seen in his mastectomised patients with Columbia Clinical Classification stage A and B [3]. Supraradical procedures, including supraclavicular and internal mammary node dissection were introduced in order to improve the prognosis [4]. However, no difference in 5 year survival was found in a randomised study comparing this supraradical operation with simple mastectomy plus postoperative irradiation [5].

During the last 15 years, major changes have taken place in treatment policy, especially for patients with stage I and II breast cancer. For the majority of these patients, the mutilating radical mastectomy according to Halsted and supraradical procedures have now been abandoned. Breast conserving therapy is increasingly the treatment of choice for these patients. An EORTC randomised clinical trial showed recently that breast conservation is a safe alternative for radical surgical procedures in patients with tumours up to 5 cm [6, 7]. For patients treated with breast conserving therapy, the avoidance of mutilating radical mastectomy is no longer a reason to perform the apex biopsy. Yet, the prevention of arm oedema and other late sequelae of combined surgery and radiotherapy to the axilla remains important. Furthermore, patients with a positive apex biopsy are currently being asked to participate in a randomised trial investigating the role of neoadjuvant very high-dose chemotherapy with peripheral stem cell reinfusion in this patient category [8].

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The purpose of the present study was to assess the relevance of the apex biopsy as a staging procedure. The first aim was to establish to what extent a positive apex biopsy is a prognostic factor for survival, independent of well known pre-operative prognostic factors, T and N classification and TNM tumour stage [9]. The second aim was to assess the relative frequency of a tumour positive apex biopsy per tumour stage and its consequences for general surgical practice.

PATIENTS AND METHODS

875 patients with clinically operable invasive breast cancer (T1 to T3a; N0 to N1b) underwent an axillary apex biopsy in the Netherlands Cancer Institute as a staging procedure from 1 January 1977 to 31 December 1985. Data concerning TNM classification, axillary apex biopsy and survival were obtained from the tumour registry department. Uncertainties concerning TNM classification or survival were updated using the patient charts. The median follow-up of the 729 patients still alive was 74 months. The distribution of clinical TNM stages in all 875 cases was: 165 (19%) clinical stage I, 512 (58%) stage II and 198 (23%) stage IIIA. The majority of patients (76%) had clinically node-negative disease (Table 1).

Patients with a tumour negative axillary apex biopsy were treated either by a (modified) radical mastectomy or by breast conserving therapy, consisting of wide tumour excision and complete axillary clearance followed by whole breast irradiation to 50 Gy plus a boost of 25 Gy. This procedure was chosen according to the protocol of EORTC trial 10801 [6, 7]. Internal mammary lymph node chain irradiation was added when axillary lymph nodes were positive and/or in case of a central or medial tumour localisation. Patients with a tumour positive axillary apex biopsy were treated with radiotherapy to breast and adjacent lymph nodes to a normalised total dose of approximately 60–70 Gy in 2 Gy fractions to areas containing macroscopic tumour. Details of the radiotherapy are described elsewhere [10]. During the period of investigation, two subsequent randomised trials were running, investigating the role of adjuvant systemic treatment in inoperable breast cancer. The majority of patients with a positive axillary apex biopsy were entered in one of these trials [11, 12].

Survival data were analysed according to the product-limit method of Kaplan and Meier [13]. Survival curves were compared using the log-rank test [14]. The independent prognostic significance of clinical T classification, N classification, TNM stage grouping and of the outcome of the axillary apex biopsy were tested using a stepwise proportional hazard regression analysis described by Cox [15].

TECHNIQUE OF THE AXILLARY APEX BIOPSY

The skin is incised at the level of the sulcus between the clavicular and the sternal part of the major pectoral muscle, followed by splitting the muscle fibres between these parts. The clavipectoral fascia is incised and the fatty tissue in the space bordered by the subclavian vein, the medial border of the minor pectoral muscle and the thoracic wall (level III of the axilla) is removed, taking care not to extend the dissection to level II, i.e. dorsal from the minor pectoral muscle. The specimen is sent for histology by frozen section prior to histological analysis. If mastectomy is planned, a part of the mastectomy incision is often used to reach the subclavicular space [1].

Table 1. Distribution of patients according to clinical TNM classification (UICC 1978)

	T_1	T_2	T_3	Total
N0-1a	165	390	111	666
N1b	15	107	87	209
Total	180	497	198	875

Table 2. Positive apex biopsy by clinical tumour stage

Stage	Number of patients	Number apex + (%)
I	165	6 (4)
II	512	89 (17)
III	198	80 (40)
Total	875	175 (20)

Table 3. Percentage of positive apex biopsy by clinical TNM classification

%	T_1	T_2	T_3	Total
N0-1a	4	12	26	12
N1b	33	36	59	45
Total	6	17	40	20

RESULTS

Overall, 175 of the patients (20%) had a tumour positive axillary apex biopsy: 4% in stage I patients, 17% in stage II and 40% in stage IIIA (Table 2). There was a clear positive correlation between more advanced clinical TNM classification and a higher incidence of positive apex biopsies (Table 3). Patients with suspicious palpable axillary nodes had a 45% chance of a positive apex biopsy (Table 3).

The estimated 5 year survival for patients with stage II apex biopsy positive disease was 42%—half that of the patients with the same clinical stage tumour with a negative apex biopsy (84%) (Figure 1). This difference was similar in stage IIIA patients

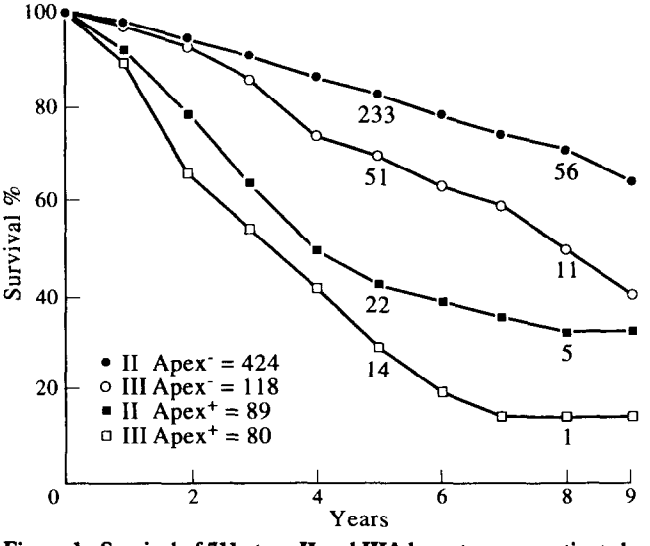

Figure 1. Survival of 711 stage II and IIIA breast cancer patients by clinical tumour stage and the outcome of the apex biopsy (numbers of patients at risk at 5 and 8 years indicated).

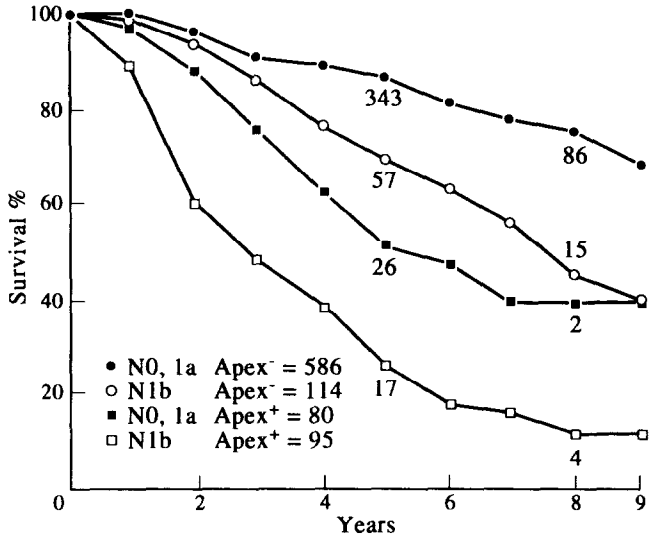

Figure 2. Survival of 875 clinically operable breast cancer patients by clinical N classification and the outcome of the apex biopsy (numbers of patients at risk at 5 and 8 years indicated).

(29% 5 year suvival for apex biopsy positive patients and 69% for apex biopsy negative ones). Median survival for apex biopsy positive patients with stage II and IIIA breast cancer was 49 and 41 months, respectively. Similarly, the survival curves for patients with clinically node-negative or positive disease and a negative or positive apex biopsy showed a marked difference (Figure 2). Patients with suspicious palpable nodes had an estimated 5 year survival of 69% if their apex biopsy was negative and 26% if it was positive. The acturial 8 year survival rates for patients with stage I, II and III disease with a negative apex biopsy were 83, 70 and 50%, respectively. The corresponding figures for patients with a positive apex biopsy were 60, 28 and 14%. The estimated 8 year survival of patients in all T, N and apex biopsy categories indicated a deterioration of prognosis with increasing TNM classification and with a positive apex biopsy in all categories (Table 4).

T classification, N classification, TNM stage and the outcome of the apex biopsy were all significant prognostic factors ($P < 0.0001$) for survival in a univariate analysis. In the consecutive multivariate analysis, the outcome of the apex biopsy, N classification and T classification all remained strong, independent, prognostic factors (all $P < 0.0001$), whereas tumour stage did not remain an independent prognosticator, because it was too closely correlated with T classification. For the proportional hazard analysis, using T classification ($T_1/T_2/T_3$), N classification ($N_0/N_{1a}/N_{1b}$) and apex biopsy outcome (positive/negative) as linear covariates the estimated $\ln_{(\text{hazard ratio})}$s for two adjacent categories are given in Table 5. When using T classification and N classification as stratification variables,

Table 4. Actuarial 8 year survival in percentage by TNM classification and outcome of the apex biopsy

	N0-1a		N1b	
%	apex⁻	apex⁺	apex⁻	apex⁺
T_1	83	60	58	0
T_2	74	47	55	18
T_3	61	13	23	9

Table 5. $\ln_{(\text{hazard ratio})}$ in proportional hazard model

Variable	$\ln_{(\text{hazard ratio})}$	Standard error	Coeff./ S.E.
Apex biopsy outcome	1.1475	0.1346	8.5245
T classification	0.5459	0.1018	5.3617
N classification	0.6622	0.1301	5.0898

thereby avoiding the proportional hazard, linearity and no interaction assumption for these two variables, the $\ln_{(\text{hazard ratio})}$ for apex biopsy outcome remains 1.1475 (SE 0.1346). We also tested in this model whether the prognostic value of apex biopsy outcome differed between the nine combinations of T- and N-classification (i.e. a classification *apex biopsy outcome interaction). There appeared to be no evidence for this ($P = 0.67$). From Table 5, it can be seen that the prognostic effect of a positive apex biopsy is almost as large as the prognostic difference between T3 and T1 or between N1b and N0.

DISCUSSION

This study confirmed that the axillary apex biopsy procedure is able to identify a significant subset of clinically operable breast cancer patients (20%) with an unfavourable prognosis. The proportion of patients with a positive apex biopsy increased with TNM classification. In patients with stage I breast cancer, the proportion of apex biopsy positive cases was low (4%), whereas among patients with clinical stage II and IIIA breast cancer 24% had a positive axillary apex biopsy. In multivariate analysis, the result of the apex biopsy was a strong prognostic factor, independent of clinical N classification and T classification.

Solitary involvement of the axillary apex, or level III of the axilla, is very rare [16, 17]. Pigott and colleagues [16] found solitary level III metastasis in only 1 of 80 cases with axillary involvement, whereas in the other 32 cases with level III metastases they also found involvement of level II (3 cases), I (2 cases) or both (27 cases). Danforth and colleagues [17] described 65 patients with axillary metastases, of whom 18 (28%) had level II involvement. Only 2 of these (3%) had solitary level III metastases. Thus, a positive apex biopsy generally indicates axillary involvement of at least two levels with a large number of positive nodes. Consequently, the survival of the apex biopsy positive patients in our series is similar to that of patients with more than 16 positive lymph nodes in the United States National Survey of 1982 [18] and of comparable patient groups in other series [19, 20]. Similarly the apex biopsy, together with an internal mammary chain biopsy, tumour size and grade was an important prognostic factor in the Nottingham Prognostic Index that was originally developed in 1982 [21]. Its value was recently confirmed in a large patient series [22]. Clinical examination alone is unreliable in predicting axillary involvement. False negative percentages up to 39% have been reported [17, 19]. The axillary apex biopsy thus identifies patients with extensive axillary involvement before complete axillary dissection is performed. Recently, a retrospective study in 209 inoperable patients and 289 clinically operable apex biopsy positive patients was performed in our institution [10]. In univariate analysis, survival was better in apex biopsy positive patients compared with those with clinically inoperable disease. However, in multivariate analysis, clinical tumour size, clinical lymph node size and age were the only significant independent prognostic factors for survival. This indicates that, indeed, a positive apex biopsy

predicts a prognosis comparable with that of a patient with locally advanced breast cancer.

In our patients with stage I breast cancer, the proportion of apex biopsy positive cases was low (4%). Despite their early clinical tumour stage, these patients will also ultimately have an unfavourable outcome; all six had distant metasatases by the time they were last seen. Since patients with stage I disease are usually treated with breast conserving therapy, one of the main reasons to perform the apex biopsy, the avoidance of unnecessary mutilating surgery, is not relevant in this patient group. Performing the apex biopsy would mean an extra scar in the infraclavicular region in 100% of these women in order to avoid the late sequela of combined surgery and radiotherapy to the axilla in less than 2% of them. For this reason, the apex biopsy procedure has been abandoned for stage I patients.

Among patients with clinical stage II and IIIA breast cancer, a large proportion (169/710; 24%) had a positive apex biopsy, their 5 and 8 year survival rates being less than half that of apex biopsy negative patients in the same clinical tumour stage (Figure 1). If the apex biopsy had not been performed, many of these patients, especially those with stage III disease, would have undergone a (modified) radical mastectomy. In addition, they would have undergone postoperative locoregional radiotherapy because of positive "level III" (or axillary apex) lymph nodes. In addition, in patients treated with breast conserving therapy, the axilla would have been treated with a combination of surgery and irradiation. This combination increases arm and shoulder toxicity to an unacceptable level [23–25]. The avoidance of toxicity of the combination of axillary surgery and irradiation is the reason for retaining the procedure of apex biopsy, even in patients with stage II disease who are initially selected to receive breast conserving therapy. The results of our treatment policy in terms of local and regional control and toxicity are beyond the scope of this paper and are subject to further study. From our previous study [10] and the literature [26–28], it can be stated that local regional control is mainly dependent upon tumour size, node classification (or size) and radiation dose.

The results of conventional adjuvant chemotherapy in this patient group have been shown to be disappointing in randomised clinical trials [11, 12]. Hopefully, intensification of chemotherapy with autologous bone marrow support or peripheral stem cell support will improve these results. For the last few years, patients with a positive apex biopsy have been asked to participate in a study to investigate this question. Following a feasibility study [8], a randomised phase III study is currently being performed. Until the results of these studies are known, optimal local regional control with minimal mutilation and minimal treatment toxicity is the main treatment goal in this patient group.

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