Pergamon

European Journal of Cancer, Vol. 35, No. 6, pp. 908–912, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00056-8

Original Paper

The Prognosis of Small Primary Breast Cancers

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The Nottingham Prognostic Index (NPI) is an integrated prognostic index used to predict patient survival for women with invasive breast cancer. The index is based on invasive tumour size, histological lymph node stage and tumour grade. The value of such an index has been questioned in small invasive breast cancers and it has been suggested that size is the only necessary prognostic determinant. The aims of this study were to determine the extent of regional lymph node involvement and survival in women with small invasive breast cancers and to assess the value of the NPI. Between 1976 and 1994, 2684 women aged ≤70 years were treated for primary operable invasive breast cancers of ≤5 cm in maximum diameter, of which 318 measured ≤1 cm. Follow-up data were evaluated to determine histological factors important in predicting survival outcomes in women with cancers ≤1 cm in diameter and comparing their survival according to the NPI with all women treated for primary operable breast cancers ≤5 cm in maximum diameter. Histological lymph node involvement was demonstrated in 56/318 (18%) of cancers of ≤1 cm in diameter. Significant survival differences were demonstrated for small breast cancers according to lymph node stage, vascular invasion and histological tumour grade. Only lymph node stage and histological tumour grade were independent prognostic indicators using a multivariate Cox model. The survival curves for small tumours stratified by the NPI were similar to those of cancers up to 5 cm in diameter. The results indicate that lymph node staging and histological grading are still important prognostic determinants for breast cancers ≤1 cm in diameter. An axillary node staging procedure should be performed for all invasive breast cancers ≤1 cm in diameter. The NPI remains relevant for small breast cancers. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: breast cancer, size, histological grade, lymph node status, prognosis
Eur J Cancer, Vol. 35, No. 6, pp. 908–912, 1999

INTRODUCTION

THE DEMONSTRATION of regional lymph node metastases has important prognostic and therapeutic implications in primary operable breast cancer. However, the role of axillary surgery has been questioned in the management of small breast cancers ≤1 cm in diameter where the risk of axillary nodal involvement is thought to be low [1]. Furthermore, the prognosis of women with small breast cancers is good overall, such that the value of other prognostic parameters (i.e. histological tumour grade) has been questioned [2].

The purposes of this study were to determine the incidence of regional lymph node involvement in small invasive breast cancers and to determine the prognostic significance of histological tumour grade in small breast cancers and the relevance of the Nottingham Prognostic Index (NPI) to such cancers [3].

PATIENTS AND METHODS

The group consisted of a consecutive series of 2684 women aged ≤70 years treated at the Nottingham City Hospital (Nottingham, U.K.) between 1976 and 1994 with primary operable invasive breast cancer with a histological tumour diameter of ≤5 cm. Of these, 318 had tumours of ≤1 cm in diameter.

Surgical treatment

Complete tumour excision was achieved by mastectomy or subcutaneous mastectomy in 1854 cases (69.1%) and by lumpectomy in 830 (30.9%). For tumours ≤1 cm in

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Received 19 Oct. 1998; revised 5 Feb. 1999; accepted 8 Feb. 1999.

diameter, complete tumour excision was achieved by mastectomy or subcutaneous mastectomy in 152 patients (48%) and by lumpectomy plus intact breast radiation in 166 (52%). The lymph node sampling technique consisted of triple node biopsy for all patients undergoing mastectomy before 1989. Nodes were sampled from the lower axilla, the apex of the axilla and the internal mammary chain [4, 5]. Staging then depended on the level of axillary node involvement and/or involvement of the internal mammary chain, and has been previously reported [6]. If all three nodal areas sampled were negative, the stage was A; if only the lower axillary node or the internal mammary node was positive, the stage was B; if the apical axillary node or both lymph node chains were positive, the stage was C. From 1989 patients underwent sampling of 4 lower axillary nodes together with internal mammary node sampling for medially located tumours only. In this instance, stage A denoted no involvement of regional nodes; stage B denoted involvement of ≤ 3 axillary nodes or involvement of the internal mammary node; stage C denoted involvement of > 3 axillary nodes or both internal mammary and axillary node involvement.

Histopathology

The method of tumour fixation and the measurement of histological tumour size (cm) and grade (I, II, III) has been previously described by Elston and Ellis [7]. Careful attention was paid to specimen preparation. The tumour was sliced in a cruciate manner and the histological size was measured in two planes of which the larger value was recorded. The presence or absence of lymphovascular invasion was assessed according to the criteria described by Pinder and colleagues [8].

NPI

The previous Nottingham–Tenovus studies on all patients who underwent locoregional treatment alone for primary operable invasive breast cancer have shown that tumour size, histological grade and lymph node stage are independent prognostic indicators for breast cancer-specific survival in retrospective [9] and prospective patient groups [10, 11]. These three histological factors are used to determine the NPI which identifies three different prognostic groups (good prognostic group, moderate prognostic group and poor prognostic group in terms of breast-cancer specific survival. The NPI is calculated using the following equation:

$$\text{NPI} = 0.2 \times \text{tumour size (cm)} + \text{grade (I} - \text{III)} + \text{lymph node score (1} - \text{3 according to stage A} - \text{C).}$$

A score of ≤ 3.4 gives a good prognosis, 3.41–5.4 a moderate prognosis and > 5.4 a poor prognosis.

Overall, women in the good prognostic group have a 15-year survival approaching 85%. A subgroup of women within the good prognosis group with NPI scores ≤ 2.4 have an excellent prognosis with a 15-year survival of 94%, thus representing a group of patients potentially cured by locoregional treatment alone. By definition, all patients in the poor prognostic group have histologically involved nodes at presentation. Patients in the good and moderate prognostic group comprise both lymph node positive and negative patients, depending on histological tumour size and grade.

Adjuvant systemic therapy

Patients were not routinely given adjuvant systemic therapy before October 1988. Thereafter systemic therapy was given to all patients with an NPI > 5.4 (poor prognostic group). Our current protocol is to offer adjuvant systemic therapy to all patients in the medium and poor prognostic groups. Postmenopausal patients with oestrogen receptor (ER) positive tumours are treated with tamoxifen for 5 years. Patients with ER negative tumours are offered chemotherapy using cyclophosphamide, methotrexate and 5-fluorouracil (CMF) for 6 months or tamoxifen for 5 years. Premenopausal patients with ER negative tumours are treated with CMF for 6 months and those with ER positive tumours are offered CMF for 6 months or randomisation to the Zeneca Zebra Study 118630/2802 which compares CMF for 6 months with monthly Zoladex injections for 2 years in premenopausal node positive breast cancer patients. In this series, adjuvant systemic therapy was given to 478/2684 (17.8%) patients of which 27 had tumours of ≤ 1 cm in diameter.

Follow-up

All patients were followed-up in the Primary Breast Clinic at regular intervals for at least 10 years. Those developing a locoregional recurrence continued to be followed-up for at least 10 years after the event. Those developing distant metastases were managed in the advanced breast cancer clinic until death. Those discharged from the clinic or who moved to another vicinity were followed-up by regular inquiry to the relevant general practitioner or clinic.

Statistics

Analyses are presented for all patients entered into the Nottingham primary breast series between 1976 and 1994, for those with tumours of ≤ 1 cm and for all patients with tumours up to 5 cm in diameter. Actuarial survival was determined using the life tables method [12]. Differences in survival curves were evaluated by univariate analysis using the Wilcoxon rank test [13]. Prognostic factors found to be significant in univariate analysis were entered into a Cox proportional hazards model [14]. Parameters other than survival were compared using the standard χ^2 test.

RESULTS

Histopathology

A steady increase in regional node involvement was demonstrated with increasing tumour size (Table 1, $\chi^2 = 155.7$, $P < 0.0001$, 5 d.f.). Overall, 56/318 (18%) of cancers ≤ 1 cm had histologically involved regional nodes. Furthermore, a significant association between histological

Table 1. *Results of histological tumour size according to lymph node status for* 2684 *women* ($\chi^2 = 155.7$, $P < 0.0001$, 5 *d.f.)*

	Lymph node involvement (%)	
Tumour size (mm)	Negative	Positive
1–5	44 (88)	6 (12)
6–10	218 (81)	50 (19)
11–15	419 (74)	151 (26)
16–20	466 (66)	237 (34)
20–30	437 (56)	341 (44)
30–50	133 (42)	182 (58)
Total	1717	965

Table 2. Results of histological tumour size according to tumour grade for 2684 women ($\chi^2 = 226.8$, P < 0.0001, 10 d.f.)

	Histological grade (%)		
Tumour size (mm)	I	II	III
1–5	21 (42)	19 (38)	10 (20)
6–10	98 (37)	114 (43)	56 (21)
11–15	171 (30)	202 (35)	197 (35)
16–20	142 (20)	248 (35)	313 (45)
20–30	88 (11)	262 (34)	428 (55)
30–50	24 (8)	99 (31)	192 (61)
Total	544	944	1196

tumour grade and tumour size was demonstrated (Table 2; $\chi^2 = 226.8$, $P < 0.0001$, 10 d.f.). A significant difference in degree of lymph node involvement was demonstrated for tumours ≤1 cm according to histological tumour grade. Twenty-nine per cent of grade III cancers were found to be lymph node positive compared with 11% of grade I and 18% of grade II cancers. ($\chi^2 = 14.4$, $P = 0.006$, 4 d.f.).

Survival

In the follow-up period, 32 patients with cancers ≤1 cm developed distant metastases and there were 29 recorded breast cancer deaths. Actuarial survival at 10 and 14 years was 87% and 83%, respectively (Figure 1). Survival curves according to histological tumour grade, lymph node status and lymphovascular invasion are illustrated in Figure 2. A significant survival difference in actuarial survival was demonstrated according to histological tumour grade ($\chi^2 = 21.6$, $P < 0.0001$, 2 d.f.), lymph node stage ($\chi^2 = 51.4$, $P < 0.0001$, 2 d.f.) and lymphovascular invasion ($\chi^2 = 5.0$, $P = 0.03$, 2 d.f.). No differences in survival were demonstrated according to patient age (< 50 or 50 years; $\chi^2 = 0.31$, $P = 0.6$, 1 d.f.) or tumour size (1–5 mm or 6–10 mm; $\chi^2 = 0.8$, $P > 0.05$, 2 d.f.). For 263 lymph node negative patients, 8 deaths were recorded in the follow-up period, with over 91% survival noted for all three tumour grade categories ($\chi^2 = 1.2$, $P = 0.06$; Figure 3). There were no deaths recorded for grade I lymph node negative patients (which corresponds to the Nottingham excellent prognostic group).

Cox multivariate analysis was used to test for independent prognostic significance in cancers ≤1 cm using histological tumour grade, lymph node status and lymphovascular invasion. The model of best fit involved 289 cases available for analysis. Histological tumour grade and lymph node stage continued to be independent prognostic indicators (Table 3). According to the higher value of the β coefficient, histological lymph node status was of greater prognostic significance than tumour grade. Lymphovascular invasion was not an independent prognostic indicator in this model.

NPI

The association between small tumour size, lymph node negativity and low tumour grade indicated a higher proportion

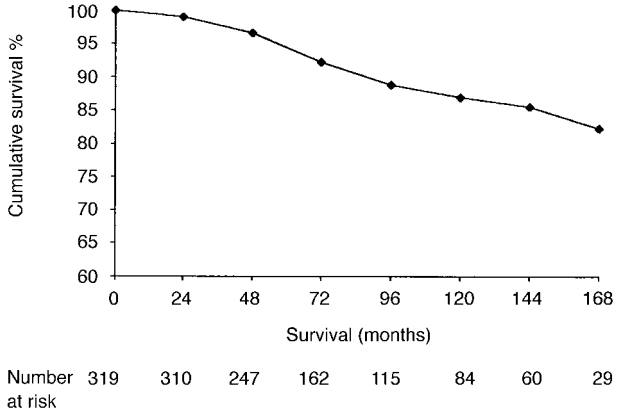

Figure 1. Actuarial survival for patients with breast cancers ≤1 cm in diameter.

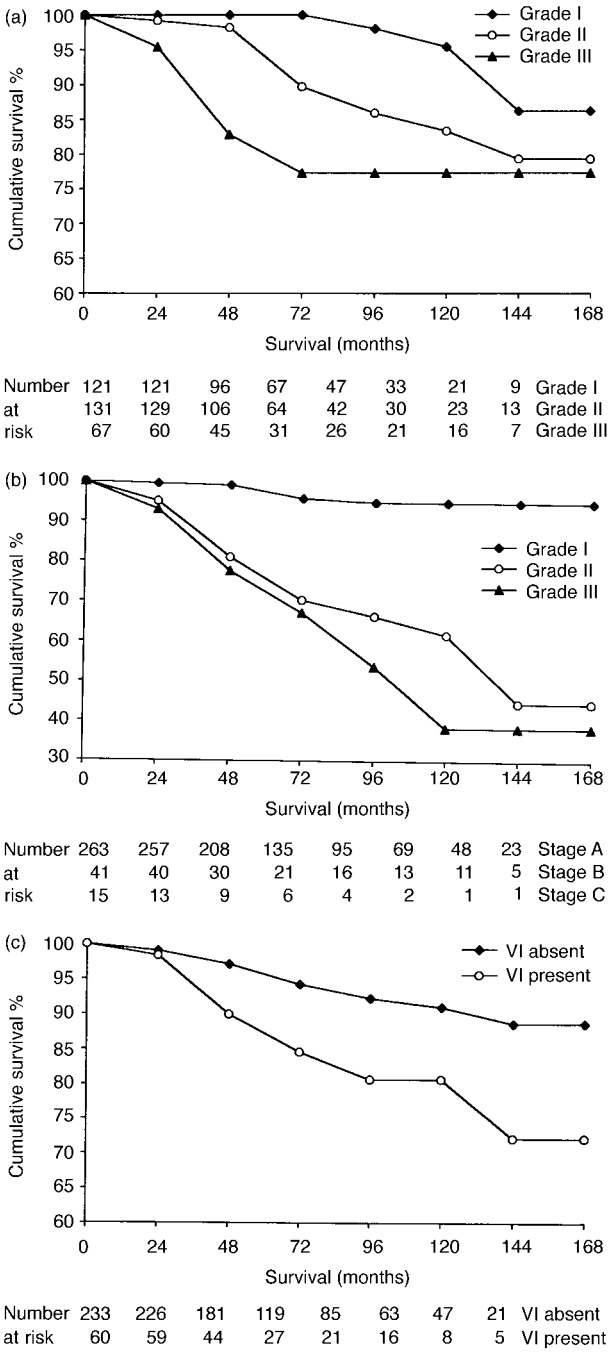

Figure 2. Actuarial survival for small breast cancers with tumour diameter ≤1 cm according to (a) histological grade, (b) lymph node stage, (c) lymphovascular invasion.

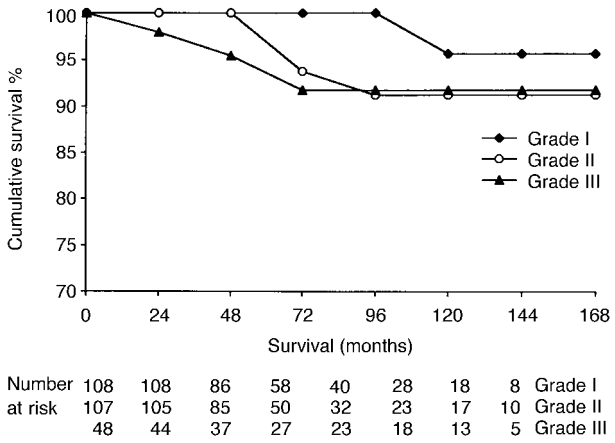

Figure 3. Actuarial survival for lymph node negative breast cancers with tumour diameter ≤1 cm according to histological grade.

of patients with small breast cancer falling into the excellent and good prognostic groups according to the NPI (Table 4); ($\chi^2 = 974.2$, $P < 0.0001$, 10 d.f.). Only 7 patients with cancers ≤1 cm fell into the poor prognostic group.

Survival curves according to the NPI for all cancers in the series and for cancers ≤1 cm are illustrated in Figure 4. Prognostic stratification was demonstrated for cancers ≤1 cm according to the Nottingham prognostic group, although survival in the good and moderate prognostic groups improved somewhat with small tumour size (which is in accordance with the absolute index values for all cancers ≤5 cm in diameter). Pairwise comparisons between cancers ≤1 cm and all cancers ≤5 cm demonstrated no significant survival differences within each Nottingham prognostic group (good prognostic group $\chi^2 = 3.8$ $P = 0.06$; moderate prognostic group $\chi^2 = 2.1$, $P = 0.15$; poor prognostic group $\chi^2 = 0.01$, $P = 0.93$). Only 7 patients with cancers ≤1 cm in diameter were in the poor prognostic group, of which 2 were alive after 48 months of follow-up, but their survival to this stage was similar to all poor prognostic group cases.

DISCUSSION

Increased patient awareness and the introduction of population-based screening programmes has resulted in the earlier detection of breast cancer. As such, the detection of small cancers of ≤1 cm in diameter has increased to 30% in some series [2, 15]. In general, the prognosis of patients diagnosed with small breast cancer is favourable, such that the majority will not benefit from the effects of adjuvant systemic therapy. Nevertheless, the identification of a subgroup of women diagnosed with breast cancers ≤1 cm in diameter with a moderate or poor prognosis is important in order to recommend adjuvant systemic therapy.

Table 3. Results of Cox multivariate analysis

Variable	β value	χ^2	RR	*P* value	95% CI
Histological grade I–III	0.61	3.8	1.8	0.05	1.00–3.31
Lymph node stage (A, B, C)	1.34	29.7	3.8	< 0.0001	2.36–6.20
Lymphovascular invasion (present, absent)	0.37	0.72	1.4	0.4	0.030–1.61

RR, relative risk; CI, confidence interval.

Table 4. Results of histological tumour size according to Nottingham prognostic group for 2684 women ($\chi^2 = 974.2$, P < 0.0001, 15 d.f.)

	Nottingham prognostic group (%)			
Tumour size (mm)	Excellent	Good	Moderate	Poor
1–5	19 (38)	19 (38)	11 (22)	1 (2)
6–10	87 (32)	103 (38)	72 (27)	6 (2)
11–15	142 (25)	169 (30)	245 (43)	14 (2)
16–20	104 (15)	179 (25)	387 (55)	33 (5)
20–30	0	54 (7)	500 (64)	224 (29)
30–50	0	18 (6)	158 (50)	139 (44)
Total	352	542	1373	417

A direct correlation between tumour size and regional lymph node involvement predicts a low incidence of involved regional nodes for tumours ≤1 cm in diameter [16]. The results of this study demonstrated that 18% of tumours ≤1 cm in diameter had histological evidence of axillary nodal involvement, using standard histological techniques. It has been suggested that consideration should be given to eliminating axillary node dissection for T1a (≤5 mm) tumours [1]. In this series, six of 50 tumours ≤5 mm in diameter (12%) were associated with histologically involved axillary nodes. The incidence of axillary lymph node positivity in this series was higher than in the study of Silverstein and colleagues [1] (12% versus 3%).

For breast cancers ≤1 cm, the incidence of nodal involvement correlated with histological tumour grade, with 11, 18 and 29% of cases demonstrating positive nodes for grade I, II and III tumours, respectively. Both histological tumour grade and lymph node status were important prognostic indicators in univariate and multivariate analyses. In the Cox multivariate model for cancers ≤1 cm in diameter, the results of the β coefficient indicate that the prognostic significance of lymph node status is approximately twice that of histological grade. This differs from that of the β values depicted for the NPI for all invasive tumours ≤5 cm in diameter for women

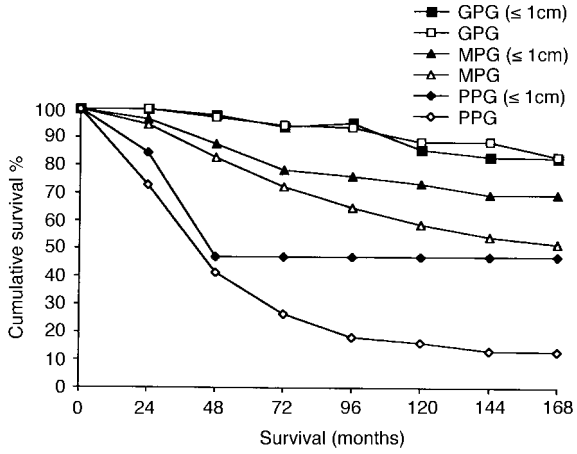

Figure 4. Actuarial survival for breast cancers ≤1 cm and all cancers ≤5 cm in diameter according to Nottingham prognostic groups (□, good prognostic group ($n = 894$); ■, good prognostic group tumour size ≤1 cm ($n = 228$); △, moderate prognostic group ($n = 1374$); ▲, moderate prognostic group tumour size ≤1 cm ($n = 83$); ◇, poor prognostic group ($n = 416$); ◆, poor prognostic group tumour size ≤1 cm ($n = 7$).

aged ≤70 years [9, 10] where histological tumour grade and lymph node status were of equal prognostic significance. These results suggest that the proportionality of the hazard is not preserved across the entire size range. Although the survival of patients with small breast cancers was slightly better than that for all patients with cancers ≤5 cm according to Nottingham prognostic groups, the differences in survival were not significant, suggesting that the NPI is still relevant for small breast cancers.

After 14 years, the cumulative breast cancer-specific survival for lymph node negative small breast cancers was 93% compared with only 40% for lymph node positive cases. Although there was stratification for survival according to histological tumour grade for lymph node negative cases, the cumulative survival was >90% for all tumour grades. These findings are in keeping with those of Leitner and colleagues [17] and Rosner and Lane [18] where the actuarial survival of all patients with lymph node negative breast cancers ≤1 cm was approximately 90% after 7 years of follow-up. This further illustrates the case for not advocating adjuvant systemic therapy for lymph node negative tumours ≤1 cm irrespective of histological grade or Nottingham prognostic group. According to the NPI, patients with small, high grade cancers with no lymph node involvement would fall into the moderate prognostic group and, as such, would be offered adjuvant systemic therapy. In this particular instance, the use of the NPI is limited due to the improved survival demonstrated for this subgroup of patients in the moderate prognostic group. Adjuvant systemic therapy should, therefore, be considered in cases of axillary nodal involvement, which comprised 18% of the patients in this series. The omission of an axillary staging procedure would not permit the identification of this significant group who only have a moderate prognosis and excludes approximately 80% of patients with a very good prognosis who would not otherwise be recommended adjuvant systemic therapy.

In summary, the results indicate that lymph node status and histological grade are still important prognostic determinants for breast cancers ≤1 cm in diameter. In this series, 18% of small breast cancers were found to have histologically involved regional nodes using standard histological techniques. Adjuvant systemic therapy is likely to benefit those with nodal involvement who lie in the moderate and poor prognostic groups according to the NPI. An axillary nodal staging procedure should, therefore, be advocated for all invasive breast cancers ≤1 cm to identify those with nodal involvement. The majority of patients who constitute those with uninvolved nodes have a 14-year survival greater than 90%, irrespective of histological tumour grade or Nottingham prognostic group. The benefit of adjuvant systemic therapy in this group of patients is negligible such that its use cannot be recommended. The NPI remains relevant for small breast cancers, although its relevance is limited to women within the moderate or poor prognostic groups where regional lymph node involvement is demonstrated.

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