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EJSO
the Journal of Cancer Surgery
ELSEVIER
EJSO 32 (2006) 1082–1088
www.ejso.com

Prognostic significance of total number of nodes removed, negative nodes removed, and ratio of positive nodes to removed nodes in node positive breast carcinoma ☆

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Accepted 14 June 2006
Available online 1 August 2006

Abstract

Background: This study was undertaken to investigate whether total number of nodes (pNtot) removed, negative nodes removed (pNneg), and ratio of positive nodes to total nodes removed (pNratio) are predictors of survival in node positive patients.
Study design: The records of 801 consecutive invasive breast cancer patients with T1-3 tumour and positive axillary lymph node who underwent modified radical mastectomy in our hospital were reviewed. pNtot and pNneg were categorized, and pNratio was computed. The influence of these probable prognostic factors on survival was investigated. Survival curves were generated by Kaplan–Meier method and log-rank test was used for comparisons. Multivariate analyses were performed by Cox proportional hazard model.
Results: Median pNtot, and pNneg are 19 (range 5–54), and 13 (range 0–53), respectively. pNtot $>$ 15, and pNneg $>$ 15 were independently associated with reduced hazard ratios (HRs) of 0.62 (CI 0.48–0.79), and 0.68 (CI 0.52–0.89), respectively. The highest ratio ($>$0.25) of pNratio is associated with the highest hazard ratio for death (HR 3.8, CI 2.74–5.50) compared to the lowest ratio for death ($<$0.001).
Conclusions: pNtot, pNneg, and pNratio appear prognostic factors for survival in node positive breast cancers. Axillary lymph node dissection with more number of nodes removed ($>$15) or negative nodes ($>$15) are associated with increased survival.

Keywords: Breast cancer survival; Number of axillary lymph nodes removed; Ratio of positive nodes to total nodes removed

Introduction

The status of axillary lymph nodes is the most important prognostic factor in breast cancer.[1,2] The absolute number of positive nodes that had also been shown to be an important prognostic factor was reported insufficient for the outcome of node positive patients[3] and ratio of positive nodes to total number of nodes removed (pNratio) has been proposed as a stronger prognostic factor than the number of positive nodes for survival.[4–6] The contribution of axillary lymph node dissection (ALND)[7–9] and the extent of ALND[10–12] to survival in breast carcinoma in relation to the total number of nodes removed (pNtot) are also under debate. Studies that reported survival advantage with more nodes removed in node negative breast cancers[12–15] and 1–3 positive breast cancers[12] have been reported as fraught with potential error of stage migration effect.[16] Vinh-Hung et al. have also proved that survival improved as pNtot,[4] and total number of negative nodes removed (pNneg)[17] increased and pNratio was a significant predictor for survival in node positive patients.[3,4] However, these studies with large databases of (Surveillance, Epidemiology, and end Results) SEER program of USA lack the knowledge of adjuvant systemic therapy and based on data from multicentres with different types of surgery. Thus, to the best of my knowledge, for the first time in literature the effect of pNtot, pNneg, and pNratio on survival in a series of a single institute in node positive patients who underwent a standard surgery by the same team was investigated.

☆ This study was performed at Ankara Oncology Education and Research Hospital, Ankara, Turkey.

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[1] I did not have any financial support, and conflict of interest.

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doi:10.1016/j.ejso.2006.06.005

Patients and methods

Subjects

The records of 801 consecutive invasive breast cancer patients with T1-3 tumour and positive axillary lymph node who underwent modified radical mastectomy between 1994 and 2001 in our hospital were reviewed. Fifteen patients with insufficient histological information were excluded and 7 patients with metachronous contra-lateral breast cancers, and 5 patients with second primary malignancies were included in this study. All patients had histologically proven invasive ductal carcinoma, and metastatic axillary lymph nodes and underwent level 1, 2, and 3 axillary dissections. The same surgical team performed all operations, and all patients received identical axillary treatment. All surviving patients were followed-up at least 60 months with a median follow-up of 72 months (range 60–144 months). No patients were lost to follow-up for the first 6 years, but by 10 years, 17 patients who had been lost to follow-up were censored. Two deaths from traffic accident, and 12 deaths due to diseases other than breast carcinoma were also treated as censored observations. Forty-eight (6%) patients had no adjuvant systemic therapy, 68 (9%) patients received adjuvant tamoxifen alone, 448 (57%) had adjuvant chemotherapy alone and 222 (28%) had adjuvant tamoxifen and chemotherapy. Five hundred and thirty-five patients (68%) received adjuvant radiotherapy to chest wall, to 3 axillary levels and to supraclavicular region within 3 months following operation. Histological grade was assessed using Elston–Ellis modification of Bloom–Richardson grading method.[18] Oestrogen receptor (ER) status was defined by immunohistochemistry and staining of 10% of tumour cells was accepted as ER positive. ER status was known in 57% of the patients. Patients with unknown ER status were included in this study, because the exclusion would introduce selection bias. Each lymph node was sectioned into 4 slides, stained with haematoxylin–eosin, and pathological assessment was performed by two experienced staff pathologists. Informed consent was obtained from the subjects or guardians.

Variables

Information regarding follow-up, adjuvant treatment, and prognostic indicators including age, menopausal status, number of metastatic nodes, total number of the lymph nodes removed (pNtot), tumour size, histological grade and type, presence of peritumoral lymphovascular invasion (LVI), and ER status were obtained from medical records of the patients. The categories for pNtot and pNneg were decided as follows to compare the results with the findings of the referred studies in literature.[3,6,12,17,19] pNtot was categorized as 1–10, 11–15, 16–20, 21–25, >25 nodes and as 1–15, and >15, as 1–20, and >20, and as 1–25, and >25 nodes. Total number of negative nodes removed (pNneg) was categorized as 0–5, 6–10, 11–15, 16–20, >20 and as 0–15, and >15. Because the patients were distributed more homogeneously in each category, the ratio of positive nodes to total number of nodes removed (pNratio) was categorized as ≤0.1, >0.1–0.25, >0.25, and as ≤0.25, and >0.25. Histopathological subtypes were classified according to World Health Organization criteria as invasive ductal (NOS: not otherwise specified), invasive lobular carcinoma, mixed invasive ductal and lobular, atypical medullary; or those with pure special features such as medullary, tubular, mucinous, papillary, comedo, colloid, scirrhous, apocrine, cribriform and adenoid cystic.

Statistical analyses

Overall survival (OS) was the main endpoint of this trial. The follow-up interval for OS was calculated in months and defined as the time between the date of surgery and death from breast carcinoma or last follow-up. Survival analysis was performed using the Kaplan–Meier method, and log-rank test was used for comparison. Stepwise Cox proportional hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for the risk of dying from breast carcinoma.[20,21] The comparisons between pNtot and potential prognostic factors in Table 1, and number of positive nodes were made by Chi-square analysis. Statistical analyses were performed using SPSS 10.05 for windows. p-Values of less than 0.05 were considered significant.

Results

Median pNtot, pNneg, and pNratio are 19 (range 5–54), 13 (range 0–53), and 0.19 (range 0.02–1), respectively. Median age is 47 (range 25–75). Five-year, and 10-year overall survival (OS) rates are 69%, and 48%, respectively. Patient, and tumour characteristics, and treatment factors are shown in Table 1. The comparisons of the categories of pNtot (Table 2) with the categories of age, size, LVI, ER status, histological type, grade, menopausal status, and adjuvant systemic (Table 1) therapy showed no differences. The proportion of patients with 4 or more positive nodes was significantly higher among patients with more than 15 axillary nodes removed compared to 1–15 nodes removed (49%, and 30%, respectively) ($p < 0.001$).

In univariate analysis age, size, menopausal status, grade, LVI, ER status, histological type, systemic treatment, radiotherapy, number of positive nodes, pNtot, pNneg, and pNratio correlated with overall survival (OS) (Tables 1 and 2). Survival gradually improved as the pNneg increased by categories. Ten-year OS was significantly better for patients with pNneg > 15 (66%) compared to patients with ≤15 (34%) ($p < 0.0001$, Fig. 1, and Table 2). A steadily decreased survival was observed across the categories of pNratio where cases with the lowest ratios had highest survival ($p < 0.0001$, Fig. 2, and Table 2). Patients