Original Article

Short-Term Survival in Breast Cancer: The Experience of the University of Malaya Medical Centre

Teng Aik Ong and Cheng Har Yip,1 Department of Surgery, Faculty of Medicine and Health Sciences, University Malaysia Sarawak, Kuching, Sarawak, and 1Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

OBJECTIVE: To study the impact of various clinicopathological factors on short-term survival in a cohort of breast cancer patients treated at the University of Malaya Medical Centre (UMMC).

METHODS: All cases of breast cancer treated at UMMC from January 1999 to June 2001, except for stage IV disease, were included in the study. Survival analysis was carried out using Kaplan-Meier for univariate analysis and Cox regression for multivariate analysis. The log-rank test was used to test the significance of differences between the different survival curves.

RESULTS: A total of 385 patients were included. The mean patient age at presentation was 50.3 years (SD, 11.4); 198 (51.4%) patients had lymph node-positive disease, and 187 (48.6%) had node-negative disease. The mean follow-up period was 18.7 months (SD, 8.8). The Malay ethnic group, tumours of larger size, node-positive disease, more than five positive lymph nodes, oestrogen receptor (ER) negativity and the presence of lymphovascular invasion were significant prognostic factors for shorter recurrence-free survival (RFS) in the univariate analysis. In the multivariate analysis, ER negativity was the only independent adverse prognostic factor for RFS. For overall survival (OS), tumours of larger size, node-positive disease, more than five positive lymph nodes, ER negativity and high grade tumours were associated with significantly shorter OS. However, more than five positive lymph nodes was the only independent prognostic factor for shorter OS in the multivariate analysis. Further multivariate analysis of the patients with node-positive disease showed that the Malay ethnic group, ER negativity and more than five positive lymph nodes were independent prognostic factors for shorter RFS. On the other hand, ER negativity and more than five positive lymph nodes were independent negative prognostic factors for OS in this subgroup of patients.

CONCLUSION: The evaluation of various prognostic factors would provide useful information on disease progression in local patients, especially for the planning of adjuvant therapies and follow-up protocols. Differences in the pattern of breast cancer among the different ethnic groups in Malaysia warrant further studies. [Asian J Surg 2003;26(3):169–75]

Introduction

Breast cancer is a “lifelong” diagnosis that irreversibly changes the lives of patients affected and their families.1 It is a disease in which “cure” is often a relative term2 as recurrences can appear many years after an apparent “cure”. While the study of long-term prognostic factors is of great interest, knowledge about prognostic variables affecting short-term outcome is no less important to clinicians and patients. The peak incidence of recurrence is in the first 2 to 5 years after diagnosis.3 This is a demanding period as decisions on adjuvant therapies are made and complications of the disease and its treatment are...
tackled accordingly.

Prognostic factors are useful to clinicians and patients because they help to prognosticate individual cases and serve as a guide in the planning of adjuvant therapies. The presence of certain prognostic factors also predicts the patients’ response to specific hormonal or novel immunotherapies, e.g. oestrogen receptor (ER) response to tamoxifen and c-erbB-2 response to trastuzumab. Because there is still no universal follow-up protocol for breast cancer patients,4 clinicopathological variables of prognostic significance could serve as useful guides for planning the most cost-effective and optimum follow-up strategy.

While axillary nodal status has been the traditional mainstream predictor for recurrence and survival in primary breast cancers,5 many clinicopathological and molecular factors have been extensively studied in the search for the “best” prognostic marker. Apart from the problem of different patient selection criteria and methodologies in various studies, the matter is further complicated by the fact that clinicopathological variables change in their prognostic importance during follow-up,6 as some factors have their greatest prognostic value immediately after primary treatment, whereas others may retain their prognostic significance after the first recurrence and even during long-term follow-up. Data on prognostic indicators for breast cancer in Malaysia are lacking.

This study aimed to determine the impact of various clinicopathological variables of prognostic significance on short-term outcomes in a cohort of breast cancer patients, treated in the Breast Clinic of the University of Malaya Medical Centre, who have no evidence of distant metastases at presentation, i.e. stage I to III disease. Cases with stage IV disease at presentation often have very poor outlook and, thus, were excluded from the current analysis.

Methods

This was a retrospective study of all breast cancer cases treated in the Breast Clinic of the University of Malaya Medical Centre from January 1999 to June 2001 (over a 30-month period). Clinical and follow-up data were obtained from case records, and pathological information from the individual patients’ histopathological reports. These data made up the database of patients of the Breast Clinic. Cases of carcinoma in situ, malignant phylloides tumours and sarcomas were excluded. For the purpose of this study, cases with distant metastases at presentation (which generally have dismal prognosis) were excluded from the analysis. The clinicopathological variables included in the analysis were ethnic group, age at presentation, tumour size, nodal status, number of positive lymph nodes, tumour grade, ER status and presence of lymphovascular invasion (LVI).

The SPSS (Statistical Package for the Social Sciences) software, version 10.0 (SPSS Inc., Chicago, IL, USA), was used for statistical analyses. The information was entered into an SPSS database. Unavailable information was treated as missing data and the respective cells in the database were left blank. Univariate analyses were performed using the Chi-squared test to test for the association of categorical variables. The short-term outcomes analysed were recurrence-free survival (RFS) and overall survival (OS). RFS was defined as the period from the date of diagnosis to the date of diagnosis of recurrence, for either locoregional or systemic recurrences. OS was defined as the period from the date of diagnosis to the date of death from any cause. In this study, all deaths were attributed to breast cancer. All the time periods were calculated in months. Univariate analyses for prognostic significance of various variables were done using the Kaplan-Meier procedure. Statistical differences between the survival curves were analysed using the log-rank test. Cox regression analysis was used for multivariate analysis.

Results

A total of 460 breast cancer cases were seen over the study period, of which 385 (83.7%) had no evidence of distant metastases at presentation (stages I–III). The characteristics of the 385 patients who presented with stage I to III disease are listed in Table 1. The primary and adjuvant treatments received by the patients are summarized in Table 2.

The mean follow-up for this cohort of patients was 18.7 months (median, 19 months; standard deviation, SD, 8.8 months). During the follow-up period, 33 patients had recurrences and 15 patients died from breast cancer.

In the univariate analysis for RFS, the following factors were associated with shorter RFS, either locoregional or systemic: Malay ethnicity ($p = 0.012$), tumours larger than 2 cm in diameter ($p = 0.001$) lymph node-positive tumours ($p < 0.001$), more than five positive lymph nodes ($p < 0.001$), ER negativity ($p < 0.001$) and presence of LVI ($p = 0.007$). Age at diagnosis and tumour grade had no significant relationship with RFS. Further multivariate analyses considering age and various significant variables showed that ER negativity was the only significant independent prognostic factor for short-term RFS (Table 3; Figure 1).
In the OS study, univariate analyses revealed that tumours larger than 2 cm in diameter \( (p = 0.003) \), lymph node-positive tumours \( (p = 0.002) \), more than five positive lymph nodes \( (p = 0.004) \), ER negativity \( (p = 0.005) \) and high-grade (grade 3) tumours \( (p = 0.020) \) were associated with shorter OS. Ethnicity, age and LVI did not appear to have a significant impact on short-term OS. In the multivariate analyses, more than five positive lymph nodes was the only significant independent prognostic factor for OS (Table 4; Figure 2).

When the cases were analysed based on lymph node status, it was obvious that patients with node-negative disease had a much lower incidence of recurrence or death from breast cancer. During follow-up, only four cases of recurrence and one death were noted in the node-negative group of patients.
whereas 29 cases of recurrence and 14 deaths occurred in the node-positive group.

In a separate analysis of survival in node-positive patients, Malay patients (\(p = 0.014\)), tumour size larger than 2 cm (\(p = 0.026\)), more than five positive lymph nodes (\(p < 0.001\)) and ER negativity (\(p = 0.005\)) were associated with shorter RFS in univariate analyses. In multivariate analyses, Malay ethnicity, more than five positive lymph nodes and ER negativity were the independent prognostic factors for short-term RFS in node-positive patients (Table 5; Figure 3).

Univariate analyses for OS in node-positive patients showed that younger age (< 40 years) at diagnosis (\(p = 0.046\)), more than five positive lymph nodes (\(p = 0.004\)) and ER negativity (\(p = 0.028\)) were associated with shorter OS. In multivariate analyses, more than five positive lymph nodes and ER negativity were the independent prognostic factors for short-term OS (Table 6).

The above analyses reveal that there are differences in survival among different ethnic groups, specifically in the event of recurrence. Thus, further study of the differences in characteristics of breast cancers in the various ethnic groups are warranted. When all the breast cancer cases are taken into consideration, i.e. stages I to IV, Malay patients appeared to present at a younger age (< 40 years) (Chi-squared; \(p = 0.002\)), with a higher disease stage (stage III or IV) (\(p = 0.001\)), have larger tumours (> 5 cm) (\(p = 0.003\)) and a higher incidence of node-positive disease (\(p = 0.001\)). However, when only patients with stage I to III disease are analysed, there were no significant differences in disease stage at presentation among the various ethnic groups (\(p = 0.096\)). In this group of patients (with stage I–III disease), Malay patients seemed to present at a younger age (< 40 years) (\(p = 0.001\)) and have a higher incidence of node-positive disease (\(p = 0.019\)).

**Discussion**

In this study, a number of key clinicopathological variables were examined in a cohort of local patients with breast cancer in a Malaysian population, from a single institution, with a team specializing in breast cancer care. As the analyses concentrated on short-term outcomes, the information derived is helpful for the planning of management strategies for patients during the first 2 years of follow-up after diagnosis.
Based on the results, lymph node status played a critical role in determining the outlook for breast cancer patients. This issue has been extensively evaluated and nodal status has become the “standard” prognostic factor. The number of lymph nodes involved with metastases appears to be a very important variable because it stands out as a prominent independent prognostic factor for RFS and OS in the cohort of patients in this study, especially for node-positive patients. This observation is consistent with other studies on this aspect of breast cancer management. There is evidence that nodal metastasis is not only a marker of diagnosis at a later point in the natural history of breast cancer (chronological age of the individual cancer), but is also a marker of an aggressive breast cancer phenotype. This finding supports the role of axillary lymph node dissection in the management of breast cancer. Besides the role for locoregional disease control for node-positive breast cancer, the number of dissected lymph nodes is also of prognostic value in node-negative cases. It is clear that, in order to provide optimum care, clinicians should work closely with pathologists to give the most informative nodal assessment.

In the current study, ER status was an independent prognostic factor for RFS regardless of nodal status, as it was for OS in node-positive patients as well. This gives ER status a prominent role as a prognostic indicator in the first 1 to 2 years after breast cancer diagnosis. The prognostic role of ER was first noted in 1977. It is now a well-established fact that the absence of ERs is related to a poorer outcome. More specifically, there is evidence that the ER content in breast cancer seems to be an indicator of growth rate rather than of metastatic potential, and accordingly, a predictor of the pattern of recurrence and length of disease-free survival rather than of long-term survival. This is consistent with the results of our study. On the other hand, progesterone receptor (PR) status appears to be more closely associated with OS. Further studies on PR expression in local breast cancer patients might provide extra prognostic information. In the long run, it would be interesting to see if ER status maintains its prognostic value since it appears to lose its prognostic significance in long-term follow-up.

Controversy abounds regarding the role of age in the prognosis of breast cancer. There is evidence that younger patients have worse outcomes compared to patients who present with breast cancer at an older age, because younger patients are believed to have more aggressive disease. However, the evidence on this matter is not conclusive. In our study, age younger than 40 years was a significant adverse prognostic factor for OS in node-positive patients in univariate analysis. In other survival analyses, age did not appear to have a significant impact on outcomes. However, there was a trend for younger patients to have poorer survival in terms of recurrence and death from disease, even though it did not reach statistical significance. This is an aspect that should be further studied and kept in mind when managing local breast cancer patients.

Tumour size, a “traditional” core prognostic factor, was only a significant prognostic factor in the univariate analyses for RFS and OS, but not in the multivariate analyses for RFS and OS. This is not a total surprise. Primary breast cancer can often be controlled with surgery or radiotherapy. With proper surgical technique, complete excision of a primary tumour with good margins can be consistently achieved. Furthermore, some studies have shown that patients with extremely large tumours tend to have better outcomes than those with tumours of intermediate size. It was postulated that tumours that have grown to a large size without killing the patient or causing nodal spread might have a lower metastatic potential.

One striking finding in our study was that there were significant differences in RFS among the different ethnic groups in this cohort of patients. Compared to the other ethnic groups, Malay patients appeared to have shorter RFS in the univariate analysis. In the node-positive subgroup of patients, Malay ethnicity was an independent adverse factor for RFS in the multivariate RFS analysis. Is this association real? A total of 90 Malay patients with stage I to III disease were included in the study (23.4% of the total patients), of which 41 were available for RFS analysis in the node-positive subgroup. Although the number of patients is modest, it is adequate to show any statistically significant difference compared to the other ethnic groups. Is this tendency for Malay patients to develop recurrence due to unique tumour pathology or is it secondary to sociocultural differences? There is no clear answer to this question. A review of tumour characteristics (taking all cases into consideration, stages I–IV) showed that Malay

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**Table 6. Results of Cox regression analysis: overall survival for node-positive, stage I–III breast cancers**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Wald Chi-squared</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive lymph nodes &gt; 5</td>
<td>4.761</td>
<td>0.029</td>
</tr>
<tr>
<td>Oestrogen receptor negative</td>
<td>5.084</td>
<td>0.024</td>
</tr>
<tr>
<td>Tumour size &gt; 2 cm</td>
<td>1.854</td>
<td>0.173</td>
</tr>
<tr>
<td>Age &lt; 40 yr</td>
<td>1.091</td>
<td>0.296</td>
</tr>
</tbody>
</table>
patients tended to present at a younger age, with higher disease stage, larger tumour size, and tended to have node-positive breast cancer. When only stage I to III cancers are considered, Malay patients appeared to present at a younger age and with node-positive disease. Taken together, it appears that a larger proportion of Malay patients had adverse prognostic variables. A review of the literature showed that differences in recurrence and survival exist between different ethnic groups, whether in the same country or between different countries. For instance, Japanese patients with breast cancer show a 5% to 15% 10-year survival advantage over Caucasian patients, and African-Americans have lower survival rates compared to other American patients, even after adjusting for disease stage. Besides tumour pathology, many other factors can affect disease progression in breast cancer. Are Malay patients presenting late to the hospital? Do they prefer traditional therapy (herbal medicine and massage) to hospital-based treatment? These questions need to be answered if we aim to provide the best care to all breast cancer patients in Malaysia.

The pathological variables of tumour grade and LVI did not appear to have a significant impact on survival in this cohort of patients. Higher grade tumours were associated with shorter OS in univariate analyses, and LVI was associated with shorter RFS. Inter-observer variation is a major problem in interpretation of tumour grade and LVI, and has made histopathological grading of low prognostic value in individual patients. Unless a standardized method of interpretation is agreed on by specialists in this field, inconsistency in interpretation will prove to be an obstacle to the use of tumour grade and LVI in the prognosis of breast cancer.

Summary

The number of positive lymph nodes and ER status are the most important prognostic variables for OS and RFS, respectively. Both variables are also independent prognostic factors for OS and RFS in the subgroup of node-positive patients. Knowledge of these two variables is of great clinical importance in prognosticating and in the planning of adjuvant therapies and follow-up strategies for breast cancer patients. We emphasize that the information for the current study is concentrated on short-term outcomes, i.e. in the first 1 to 2 years after the diagnosis of breast cancer, when the level of stress for both patients and clinicians is intense in looking for the best treatment plan. We hope that our data are of use in the planning of local treatment and follow-up protocols.

Suggestions could be made to extend the current study to yield further information regarding longer-term survival. This would be helpful in long-term follow-up because the value of various prognostic factors changes dynamically with time. Other markers, e.g. c-erbB-2, p53, Ki-67 and others, should also be explored to study their prognostic values in local patients. As the database expands and the follow-up period lengthens, meaningful analysis of survival in the node-negative subgroup could be done. This work is important because significant prognostic factors could help in the decision-making process for adjuvant therapies in this group of patients, who generally have a better outlook. Furthermore, the study of ethnic differences in breast cancers in the multiracial society of Malaysia would give a different perspective on the pathology of breast cancers.

References

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