p53 and c-erbB-2 but Not bcl-2 are Predictive of Metastasis-free Survival in Breast Cancer Patients Receiving Post-mastectomy Adjuvant Radiotherapy in Taiwan

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Background: Patients with breast cancer often receive radiotherapy after mastectomy if they are at a high risk of local recurrence, but the prognosis varies among patients. We conducted a study to evaluate p53, bcl-2 and c-erbB-2 as predictors of prognosis in breast cancer patients receiving post-mastectomy radiotherapy, which has not been well defined in the Taiwanese population.

Methods: We recruited 74 consecutive patients with primary operable breast cancer who were treated with mastectomy followed by locoregional radiotherapy and studied the presence of p53, bcl-2 and c-erbB-2 expressions in tumor tissues by immunohistochemical staining. Associations between the protein expressions and clinical outcomes, including local recurrence-free survival (LRFS), metastasis-free survival (MFS) and overall survival (OS), were evaluated.

Results: The median follow-up time was 55 months. Expressions of p53, bcl-2 and c-erbB-2 were observed in 14 (19%), 28 (38%) and 39 (53%) patients, respectively. Both p53 and c-erbB-2 were significant predictors of MFS. The 5-year MFS for p53-negative and p53-positive tumors were 61.2 and 35.7% (P = 0.01) and 5-year MFS for c-erbB-2-negative and c-erbB-2-positive tumors were 71.3 and 42.4% (P = 0.01). Whereas expression of bcl-2 protein is associated with favorable clinicopathological features, it was not related to LRFS, MFS or OS. Multivariate analyses confirmed c-erbB-2 and p53 expressions as predictors of MFS independent of tumor size, histological grading and lymph node involvement.

Conclusion: Expressions of p53 and c-erbB-2 are independent predictors of MFS in this Taiwanese population. Further research should be conducted on their application in the treatment and follow-up of patients.

Key words: breast neoplasms – c-erbB-2 – p53 – bcl-2 – radiotherapy – immunohistochemistry

INTRODUCTION

Radiotherapy plays an important role in the treatment of breast cancer and the benefits of post-mastectomy radiotherapy in locoregional control in high-risk breast cancer patients has been confirmed by many randomized clinical trials (1,2). Recent randomized studies also showed that post-operative radiotherapy prolonged the survival of pre- and post-menopausal women with high-risk lymph-node-positive breast cancer (3–5). In general, patients with lymph node metastasis, tumors larger than 5 cm or positive surgical margins are advised to receive local radiotherapy after mastectomy (6). However, even when treated with the same modalities, patients with similar pathological characteristics may have different clinical courses. In addition to the metastatic status of lymph nodes, a well-documented indicator of prognosis, there is a need to seek other biological markers that may identify subgroups of patients with a more aggressive course for more intensive follow-up and treatment.

Activation of the p53-dependent signal transduction pathway is one of the responses of cancer cells to the damage caused by ionizing radiation (7). It may regulate induction of radiation-induced apoptosis (8). Several recent studies have shown that breast cancers harboring p53 mutations are more likely to recur, have a more aggressive phenotype and poor survival (9) and are associated with increasing local failure in patients treated with post-mastectomy radiotherapy (10). bcl-2
is an oncogene that protects cells from apoptosis, allowing genetically damaged cells to continue to replicate. Breast cancer with bcl-2 expression is usually associated with a prognostically favorable phenotype (11). An inverse relationship of bcl-2 with over-expression of p53 has been reported (12). An association between bcl-2 expression and better prognosis in terms of disease-free survival and overall survival in breast cancer was observed (13). The c-erbB-2 gene, also known as HER-2/neu, encodes a trans-membrane glycoprotein that is homologous to the epidermal growth factor receptor (14). Patients with strong c-erbB-2 expression seem to have a poor response to hormonal agents such as tamoxifen and also as nonanthracyclin chemotherapy (15). A negative association with disease-free survival has been reported (16).

Several studies have examined the associations of p53, bcl-2 or c-erbB-2 protein expression with clinical outcome or response of treatment in breast carcinoma, but different findings were observed on different populations. Most of them focused on patients receiving surgical treatment, chemotherapy or both. To date, there are few data on the association between prognostic factors and clinical outcome in breast cancers treated with post-mastectomy radiotherapy. Breast cancer in Taiwan is particularly characterized by its low incidence rate (about 15–18 cases per 100 000 per year) and younger age at tumor onset (more than 50% of breast cancers diagnosed annually are in subjects younger than 50 years) (17). These unique features may suggest that Taiwanese breast cancers have racial differences in survival. In Taiwan, about 50% of total breast cancers were composed of patients in stage II and III, and most of them were treated with post-mastectomy adjuvant radiotherapy. For these patients biological markers need to be sought to select a high-risk subgroup for more aggressive adjuvant chemotherapy.

The aim of this study was to evaluate the association between p53, bcl-2 and c-erbB-2 expressions and clinical outcome in breast cancer patients with tumors larger than 5 cm or more than four axillary lymph node metastases who were treated with adjuvant radiotherapy after receiving mastectomy.

PATIENTS AND METHODS

Patients

From 1990 to 1996, we recruited consecutive patients with operable breast cancers who underwent primary mastectomy followed by locoregional radiotherapy in the Department of Radiation Oncology, National Cheng Kung University Hospital. All patients were referred for radiotherapy because they had histologically confirmed metastases in axillary lymph nodes or a tumor larger than 5 cm in diameter. All patients underwent modified radical mastectomy and axillary node dissection up to level III by the same surgical team at the hospital. We excluded patients referred from other hospitals owing to the lack of paraffin blocks from their primary tumors. Patients with locally advanced disease who received chemotherapy before the surgery were also excluded. As a result, 74 patients were included in the analyses.

Radiotherapy with 50–60 Gy (median, 50 Gy) to the chest wall and regional lymph nodal areas was given. Radiotherapy was performed with similar techniques to similar fields. The chest wall was given 50 Gy in 25 fractions using two tangential fields by cobalt-60 or 6–8 MV X-rays. Six patients received a scar boost of another 10 Gy with electrons (total dose: 60 Gy/30 fractions). The draining lymph node regions (supraclavicle and axilla) were treated by a separate field with 50 Gy in 25 fractions. The internal mammary nodal areas were treated with 45–50 Gy with 1.8–2 Gy per fraction for mediially located tumors only.

Adjuvant chemotherapy was administered either by medical oncologists or surgeons within about 3 weeks after surgery. The decision regarding chemotherapy was made on the physician’s judgment and the patient’s preferences, often on the basis of the presence of risk factors, such as numbers of axillary lymph nodes involved, size of primary tumor, menopausal status and patient’s performance status. Anthracycline-based polychemotherapy containing cyclophosphamide, epirubicin and 5-fluorouracil (CEF) was frequently administered for 4–6 months. For patients of older age, poor performance status and unwillingness to take potentially toxic treatments, other regimens, such as cyclophosphamide, methotrexate and fluorouracil (CMF), were administered intermittently at intervals of 3–4 weeks for 6–8 cycles. Most patients with metastasis to axillary nodes received chemotherapy followed by radiotherapy administered to the chest wall and regional lymph node areas. In addition to radiotherapy, hormone therapy was recommended to all patients with hormone receptor-positive tumors and to some with hormone receptor-negative tumors, because a small number of patients with estrogen receptor (ER)-negative tumors may respond to a hormonal intervention (18). Hence, hormone therapy with tamoxifen was prescribed to most patients for a minimum period of 2 years, mostly 5 years.

Histological typing was determined according to the World Health Organization classification. Histological grading for invasive ductal carcinoma was performed following the modified Scarf–Bloom-Richardson combined histological grading. All specimens were evaluated without knowledge of the clinical data.

IMMUNOHISTOCHEMICAL STAINING

For bcl-2 and p53 immunostaining, 4 μm thick sections were obtained from formalin-fixed, paraffin-embedded tumor tissues removed by modified radical mastectomy. Tissue sections were deparaffinized in xylene and rehydrated through graded alcohols. After blocking endogenous peroxidase activity with 3% H2O2 in methanol for 10 min, the sections were heated in a microwave oven at 750 W in 10 mM citrate buffer at pH 6.0 for 25 min periods and kept at room temperature for 20 min. After microwave antigen retrieval, the sections were incubated overnight at 4°C with a 1:100 dilution of monoclonal antibody to...
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bcl-2 protein (clone 124, DAKO, synthetic peptide sequence comprising amino acids 41–54 of bcl-2 protein) and monoclonal antibody to p53 protein (Pab1801, Oncogene Science, amino acid residues 46–55 of human p53, reacts with both mutant and wild-type human p53 protein). The antigens were detected with a biotin-labeled anti-mouse secondary antibody and ABC complex (DAKO LSAB kit) according to the manufacturer’s instructions. Peroxidase was detected with an aminoethylcarbazole substrate kit (AEC kit; Zymed Laboratories, San Francisco, CA) and the sections were lightly counterstained with hematoxylin. Positive and negative controls were included in all runs. Sections from a normal tonsil served as positive controls for bcl-2 protein staining and sections from colonic adenocarcinoma with a known positive staining served as positive controls for p53 protein. Incubation of parallel slides omitting the primary antibodies was performed as negative controls. The bcl-2 staining was interpreted as positive when >25% of the tumor cells showed distinct cytoplasmic staining and the p53 staining was interpreted as positive when >10% of the tumor cells showed distinct nuclear staining (19,20).

Immunostaining for c-erbB-2 was performed as described above, but the procedure of microwave irradiation was omitted. The primary antibody was CB11 monoclonal antibody

Table 1. Patients’ characteristics and relationships of p53, bcl-2 and c-erbB-2 over-expression to clinicopathological features and hormone receptors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total patients (%)</th>
<th>Patients with positive p53</th>
<th>Patients with positive bcl-2</th>
<th>Patients with positive c-erbB-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>P</td>
<td>No. (%)</td>
<td>P</td>
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<tr>
<td>-------------------------------</td>
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<td>-------</td>
</tr>
<tr>
<td>Total patients</td>
<td>74</td>
<td>14 (19)</td>
<td>28 (38)</td>
<td>39 (53)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>38 (52)</td>
<td>9</td>
<td>0.28</td>
<td>13</td>
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<tr>
<td>Postmenopausal</td>
<td>36 (48)</td>
<td>5</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>1 (1)</td>
<td>0</td>
<td>0.24</td>
<td>0</td>
</tr>
<tr>
<td>Ductal</td>
<td>68 (92)</td>
<td>13</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Lobular</td>
<td>2 (3)</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Mixed ductal &amp; lobular</td>
<td>2 (3)</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1 (1)</td>
<td>1</td>
<td></td>
<td>1</td>
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<tr>
<td>Histological grade</td>
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<tr>
<td>Grade I</td>
<td>15 (20)</td>
<td>2</td>
<td>0.20</td>
<td>11</td>
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<tr>
<td>Grade II</td>
<td>41 (55)</td>
<td>6</td>
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<td>13</td>
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<tr>
<td>Grade III</td>
<td>18 (25)</td>
<td>6</td>
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<td>4</td>
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<td>Tumor size (cm)</td>
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</tr>
<tr>
<td>&lt;5</td>
<td>40 (54)</td>
<td>7</td>
<td>0.74</td>
<td>21</td>
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<tr>
<td>≥5</td>
<td>34 (46)</td>
<td>7</td>
<td></td>
<td>7</td>
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<tr>
<td>No. of involved nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>16 (21)</td>
<td>3</td>
<td>0.85</td>
<td>8</td>
</tr>
<tr>
<td>4–9</td>
<td>28 (38)</td>
<td>4</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>≥10</td>
<td>30 (41)</td>
<td>7</td>
<td></td>
<td>6</td>
</tr>
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<td>ER status</td>
<td></td>
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<tr>
<td>Positive</td>
<td>39 (57)</td>
<td>11</td>
<td>0.02</td>
<td>19</td>
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</tr>
<tr>
<td>p53</td>
<td></td>
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</tr>
<tr>
<td>Positive</td>
<td>14 (19)</td>
<td>–</td>
<td></td>
<td>5</td>
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<tr>
<td>Negative</td>
<td>60 (81)</td>
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<td>Bcl-2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>28 (38)</td>
<td>5</td>
<td>0.85</td>
<td>–</td>
</tr>
<tr>
<td>Negative</td>
<td>46 (62)</td>
<td>9</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>c-erbB-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>39 (53)</td>
<td>10</td>
<td>0.11</td>
<td>10</td>
</tr>
<tr>
<td>Negative</td>
<td>35 (47)</td>
<td>4</td>
<td></td>
<td>29</td>
</tr>
</tbody>
</table>
(BioGenex, synthetic peptide corresponding to a site on the internal domain of the c-erbB-2 protein) at 1:50 dilution. Negative controls were performed without the primary antibodies and a positive control was included in all runs. The c-erbB-2 staining was interpreted as positive when >80% of the tumor cells showed distinct cell membrane staining (19).

**Statistical Analysis**

Associations between immunostaining results and conventional prognostic factors, including histological type, histological grade, tumor size, lymph node involvement and ER status, were evaluated using the chi-squared test. Actuarial curves for local recurrence-free survival (LRFS), metastasis-free survival (MFS) and overall survival (OS) were constructed using the Kaplan–Meier method. LRFS was defined as the time from the day of mastectomy until the discovery of local recurrence, which was defined as a recurrence on the chest wall or in the axillary or supraclavicular nodal regions within the previously irradiated fields. MFS was defined as the time from the day of mastectomy until the discovery of distant metastasis. OS was defined as the time from the day of mastectomy until the day of death or last follow-up. Log-rank tests were carried out to evaluate differences between different groups. Associations between prognostic factors and survivals were evaluated by both univariate and multivariate Cox’s proportional hazard models.

**Results**

**Patients’ and Tumor Characteristics**

The follow-up period ranged from 1 to 11.8 years (median, 4.6 years). Patients’ characteristics are reported in Table 1. The ages of the patients ranged from 28 to 76 years (median, 49 years). Among the patients, 38 (52%) were premenopausal, 68 (92%) had invasive ductal carcinoma and 36 (46%) had a tumor larger than 5 cm in diameter. There were 15 patients in histological grade 1, 41 in grade 2 and 18 in grade 3. Lymph node metastasis was noted in 68 (92%) patients and the number of positive axillary nodes ranged from 0 to 42 (mean, 9). Among the 74 patients 62 (84%) had adjuvant chemotherapy and 67 (91%) received hormone therapy with tamoxifen. The regimens of adjuvant chemotherapy consisted of CMF in 30 patients (48.4%), CEF in 26 (41.9%) and other regimens in six (9.7%).

**Expressions of p53, bcl-2 and c-erbB-2**

Of the 74 patients, positive immunohistostaining was observed for p53 in 14 (19%), bcl-2 in 28 (38%) and c-erbB-2 in 39 (53%). Table 1 also presents the relationships between expressions of p53, bcl-2 and c-erbB-2 and clinicopathological features, including tumor size, number of involved lymph nodes and ER status.

bcl-2 immunoactivity was significantly correlated to small (<5 cm) tumor size ($P = 0.004$), low histological grade ($P = 0.005$), less nodal involvement ($P = 0.01$) and positive ER status ($P = 0.01$) (Table 1). p53 immunoactivity was significantly associated with positive ER status only ($P = 0.02$). The c-erbB-2 immunohistostaining was correlated with a large number of
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There was an inverse correlation between bcl-2 and c-erbB-2 expressions ($P = 0.02$). There was no association between bcl-2 and p53 or between p53 and c-erbB-2.

SURVIVAL AND OTHER CLINICAL OUTCOMES

By the end of follow-up, local recurrence was observed in 12 (16%) patients from 10 months to 5.5 years after mastectomy. The cumulative local recurrence-free survival rate (LRFS) was 85.4 and 77.3% for 5 and 10 years, respectively. There was no...
increase in local failure after radiotherapy for larger tumors (≥5 cm) or more involved nodes (all P > 0.05). No association was found between p53, bcl-2 or c-erbB-2 expression and LRFS (P = 0.46, 0.32 and 0.92 for log-rank test, respectively) (Fig. 1).

Thirty-nine (53%) patients developed distant metastasis in 2 months to 8.5 years. The MFS rate was 56.2% at 5 years and 30.2% at 10 years. There was no difference in MFS between patients receiving CEF and patients receiving CMF in our study (P = 0.50). In univariate analyses (Fig. 2), there was no association between bcl-2 expression and MFS (P = 0.55), but both the c-erbB-2 and p53 expressions were significant predictors for MFS. For those patients without p53 protein expression, the MFS at 5 years was 61.2%, whereas for those with p53 expression, the MFS at 5 years was only 35.7% (P = 0.01). A similar association with MFS was found for c-erbB-2 over-expression. Patients without c-erbB-2 protein expression had a 5-year MFS of 71.3%, whereas those with c-erbB-2 protein expression had a 5-year MFS of 42.4% (P = 0.01).

The OS among the patients was 72 and 58.1% for 5 and 10 years, respectively. No associations between the expression of p53, bcl-2, c-erbB-2 and OS were observed (P = 0.15, 0.31 and 0.53 for log-rank test, respectively) (Fig. 3).

In multivariate analysis using the Cox’s proportional hazard models, only c-erbB-2 [relative risk (RR) = 2.06, 95% confidence interval (CI) = 1.00 to 4.30] and p53 immunoreactivities (RR = 2.25, 95% CI = 1.01–5.04) appeared to be independent predictors for MFS after adjusting the effects of tumor size, histological grade and involvement of lymph nodes (Table 2). Non-statistically significant associations were found between p53 over-expression and LRFS (RR = 2.59, 95% CI = 0.62–10.71) and OS (RR = 1.93, 95% CI = 0.60–6.21), and also between bcl-2 over-expression and LRFS (RR = 0.42, 95% CI = 0.10–1.79) (Table 2).

### DISCUSSION

Breast cancer ranks as the second most common malignancy among Taiwanese women (21). In contrast to the early detection and successful treatment of breast cancer in Western countries, a substantial proportion of patients with breast cancer in Taiwan note their disease late in the course and require post-mastectomy adjuvant radiotherapy (22,23). All the 74 patients included in our study had either a large number of lymph node involvement, large tumors or both. Although many researchers had reported the prognostic or predictive values of p53, bcl-2 and c-erbB-2 in breast cancer, there were substantial controversies. Because the patients in our study received mastectomy performed by the same surgical team and adjuvant treatment modalities according to international guidelines, the effects of the heterogeneity in treatment were minimized. Therefore, the roles of these biological markers as prognostic indicators for patients receiving radiotherapy could be better elucidated.

Our study showed that the molecular heterogeneity of breast cancer was evident even in a highly selected group. The frequencies of p53 and bcl-2 over-expression in this study were consistent with other reports on breast cancer with lymph node metastasis (24). However, over-expression of c-erbB-2 of 53% was high in comparison with the 20–30% rates reported in breast carcinoma in general (25,26). One possible explanation may be that patients in our study were a high-risk group, of whom 92% had lymph node involvement and 41% had >10 positive lymph nodes. Other reports also demonstrated that the level of c-erbB-2 protein was well correlated with unfavorable tumor features (27). In fact, a correlation between c-erbB-2 expression and regional lymph node metastases in breast carcinoma had been reported (28). Although patients with over-expression of c-erbB-2 were reported to be resistant to hormone therapy or non-anthracycline therapy (29), there was no difference in MFS between patients receiving CEF and patients receiving CMF in our study (P = 0.50). Previous meta-analyses of randomized trials regarding polychemotherapy for early breast cancer also failed to demonstrate which regimens are the most effective or which women derive most benefit (30,31). Thus, the possibility of biases of the clinical outcome occurring between the two regimens in this study should be low, if any.

Expression of bcl-2 was reported to be a favorable biological predictor (11) and, in some studies, a predictor of better clinical outcome in breast cancer (32). A better tumor response to radiotherapy in cervical cancer patients with bcl-2 expression has been reported (33). Our results confirm bcl-2 as a potential indicator of favorable clinical outcomes. In our study, bcl-2 expression was significantly more frequent in patients with steroid receptors, well-differentiated tumors, smaller tumors
and smaller number of axillary lymph nodes being invaded. We did not observe an association between good local disease control and bcl-2 over-expression. One possible explanation might be that all the patients received local irradiation. With the local control rate of 83.9 and 80.4% at 5 and 10 years, respectively, the possible benefits of bcl-2 on local control might be masked by the effectiveness of local radiotherapy.

The question of whether over-expression of p53 protein could serve as a prognostic marker in breast cancer has drawn the attention of many investigators. Some studies showed that p53 over-expression was associated with early disease recurrence and poor survival (34,35), but some failed to observe such associations (36). Wild-type p53 is involved in the balance between cell proliferation and apoptosis, playing a ‘braking’ role in tumor growth (37). In our study, whereas p53 over-expression was not a statistically significant indicator for local disease control and OS, it appeared to be a good indicator for MFS, suggesting a relationship between p53 immunocactivity and capability of developing distant metastasis.

Over-expression of the c-erbB-2 oncoprotein was considered as an independent predictor of poor disease-free survival and OS rates in patients with breast carcinoma (38). Co-expression of c-erbB-2 and p53 has also been reported as a predictor of poor prognosis in breast cancer patients (39). Our study showed that p53 and c-erbB-2 were independent predictors of unfavorable MFS for patients treated with post-mastectomy radiotherapy, which is in agreement with a previous study (40). The value of p53 and c-erbB-2 in the evaluation of radiotherapy response seemed to be limited, as they did not correlate well with local control.

In a study of 635 breast cancer patients without lymph node metastasis who were treated by surgery alone or by surgery followed by radiotherapy, local recurrence was more frequent in patients with tumors exhibiting p53 and low or no bcl-2 among those who received surgery alone. Conversely, in patients who received surgery followed by radiotherapy, the predictive relevance of such markers was not observed (41). Such results support an association between radiation sensitivity and the expression of markers involved in apoptosis and DNA damage repair. Another study on the application of neo-adjuvant therapy by either chemotherapy or radiotherapy before surgery in T2/T3–N0/N1–M0 breast tumor also revealed that neither p53 nor c-erbB-2 had an association with response to primary chemotherapy or radiotherapy (42). In contrast, in a cohort of 1530 breast cancer patients treated with mastectomy, p53 over-expression was independently associated with an increased local failure rate in patients with or without radiation (10). However, the retrospective design and uncontrolled treatment preferences could have biased the results. In our study, the patients had good local control survival and we failed to observe a prognostic role of p53, bcl-2 and c-erbB-2 in local control. These results may derive from the benefit of adjuvant radiotherapy in preventing local recurrence. Therefore, the results for p53 and c-erbB-2 with a predictive role in distant metastasis will be helpful in these patient groups.

In conclusion, we have described the clinicopathological variables and immunohistochemical expression of p53, bcl-2 and c-erbB-2 in a selected group of stage II–III breast cancer patients receiving mastectomy followed by locoregional radiotherapy in Taiwan. This subgroup of breast cancer patients had more lymph node involvement or large tumors in general. The results suggest that bcl-2 protein is associated with favorable clinicopathological features but is of no prognostic value for LRFS, MFS or OS. Over-expressions of p53 and c-erbB-2 protein are strong prognostic factors for MFS independent of other clinical factors such as tumor size, histological grade and lymph nodal status. These findings may help to identify subsets of breast cancer patients with aggressive biological behavior who need more aggressive chemotherapy.

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