The Prognostic Significance of Pathologic Characteristics of Breast Cancer Patients in Taiwan

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*To investigate the prognostic significance of pathologic characteristics of breast cancer patients, we retrospectively studied 514 patients with operable cancer from 1978 through 1987. The mean age of the patients was 50.2±12.4 years. Tumor sizes ranged from 0.7 to 13.0 cm, with a mean size of 4.26±2.4 cm. Axillary node metastases were found in 56.4% of the patients. Univariate analysis on the survival rate revealed that the number of positive nodes, tumor size, lymphatic permeation, tumor necrosis, histologic type, histologic grade, and age were significant prognostic factors. Multivariate Cox regression analysis showed that the number of positive nodes ($p<0.00005$), histologic grade ($p=0.0002$), and tumor size ($p=0.0108$) were independent prognostic factors. Our study confirms the importance of pathologic characteristics in predicting the prognosis of breast cancer patients. (**Tzu Chi Med J** 1998; **10**: 265-271)*

Key words: ***breast cancer, pathology, prognosis***

INTRODUCTION

The incidence of breast cancer in Taiwan is relatively low in comparison with the industrialized nations of Europe and North America. However, it is rapidly increasing and has become the second most common form of cancer in women [1]. Studies have shown that several pathologic factors possess prognostic significance [2]. Although there is a large amount of literature on the subject of prognostic factors, they are sometimes contradictory. To investigate the prognostic significance of pathologic characteristics of breast cancer patients in Taiwan, we performed a retrospective study on 514 patients with primary operable cancers.

MATERIALS AND METHODS

Patients were identified retrospectively from the pathologic records at Department of Pathology at National Taiwan University Hospital from 1978 through 1987. There were 905 patients with primary breast cancer. Patients were excluded from the study if they had the following conditions; patients whose primary tumors

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were totally excised outside our hospital and underwent subsequent mastectomy at our hospital and patients who did not have adequate pathologic data to review. A total of 514 patients who had primary breast carcinoma with no evidence of systemic metastasis and underwent surgery at our hospital were included in this study. Axillary node dissections in addition to mastectomy were performed on 488 patients.

For histopathologic analyses, specimens were fixed in 10% formalin, embedded in paraffin and stained using hematoxylin and eosin. The tumors were classified according to the World Health Organization (WHO) nomenclature [3]. The microinvasive ductal carcinoma was defined as tumors with earliest invasion limited to no more than a few fields of microscopic invasion. The invasive ductal carcinoma was graded according to the modified Scarff-Bloom-Richardson method [4] using the following three parameters; degree of tubule formation, nuclear pleomorphism and mitotic index. The presence of tumor necrosis, lymphatic permeation, perineural invasion and the degrees of lymphocytic infiltration in the tumor were also recorded. Tumor necrosis was defined as any identified area of tumor necrosis or comedo-type necrosis.

Data were analyzed using the Chi-square test to evaluate the significance of the categorical variables. Univariate survival rate analysis of the pathologic characteristics was assessed using Kaplan-Meier method. Statistical differences between survival rate curves were evaluated using the log rank test. A two-tailed $p<0.05$ was regarded as statistically significant. Those parameters showing significant differences in univariate analyses were included in multivariate Cox regression models. All statistical analyses were performed using the SPSS statistical program (SPSS Inc. Chicago, IL) on a microcomputer.

RESULTS

The pathologic characteristics of these 514 patients are listed in Table 1. The mean follow-up period was 63.4±39.9 months. There were 39 patients classified with ductal carcinoma in situ (DCIS), including comedo DCIS in 14 patients and non-comedo DCIS in 25 patients. The number of positive nodes in each patient varied from 0 to 57. Tumor necrosis, unequivocal lymphatic permeation and perincural invasion were found in 42.2%, 21.8% and 7.8% of the patients, respectively. The histologic grades of 423 invasive ductal carcinomas were: grade I (well differentiated), 22.9%; grade II (moderately differentiated), 53.4%; and grade III (poorly differentiated), 23.7%.

Univariate survival rate analysis of patients according to pathologic characteristics is listed in Table 2. Figures 1 and 2 illustrate the effects of lymph node status and tumor size on the survival rate. As expected, both increased tumor size and increased number of positive nodes have a negative influence on the patients' survival rate.

Table 1. Clinicopathologic Characteristics of 514 Patients with Primary Operable Breast Cancers

Age (mean, yr.)	50.1±12.4 (23 to 87)
Size (cm)	4.26±2.4 (0.7 to 13)
<2	44 (8.5%)
2-5	297 (57.8%)
>5	173 (33.7%)
Histologic type	
Ductal carcinoma in situ	39 (7.6%)
Microinvasive ductal carcinoma	15 (2.9%)
Invasive ductal carcinoma	423 (82.3%)
Mucinous carcinoma	12 (2.3%)
Medullary carcinoma	5 (1.0%)
Invasive lobular carcinoma	9 (1.8%)
Others	11 (7.2%)
Number of positive node*	
0	213 (43.6%)
1	49 (10.0%)
2-3	74 (15.2%)
4-9	80 (16.4%)
≥10	72 (14.8%)

*: total 488 patients underwent axillary node dissection

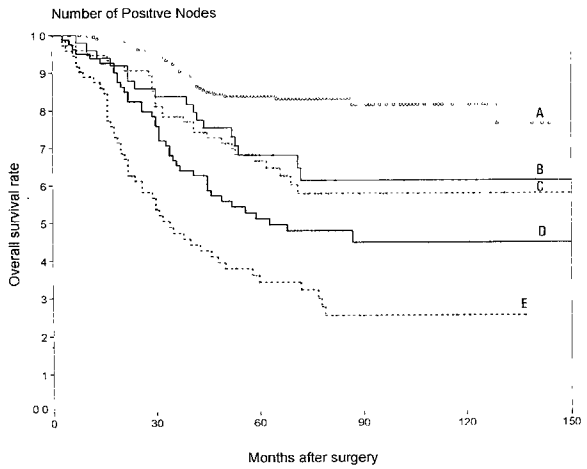

Fig. 1. Survival rate curves of 488 patients stratified according to nodal status (p<0.00005). A: Negative node (n=213); B: 1 positive node (n=49); C: 2 -3 positive nodes (n=74); D: 4-9 positive nodes (n=80) and E: ≥10 positive nodes (n=72).

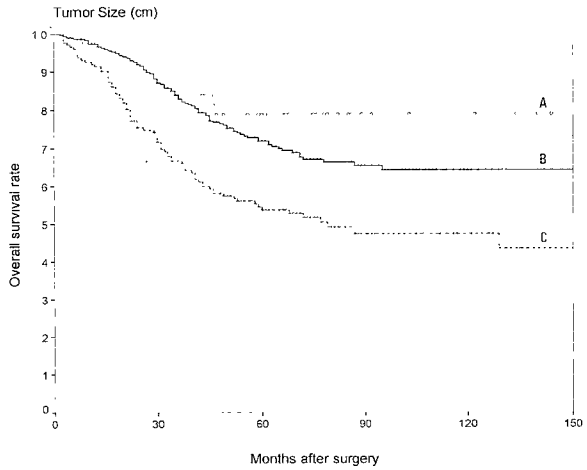

Fig. 2. Survival rate curves of 514 patients stratified according to tumor size (p<0.00005). A: <2 cm (n=44); B: 2-5 cm (n=297) and C: >5 cm (n=173).

Table 2. Univariate Survival Rate Analysis of Patients According to the Pathological Characteristics

Variables	Classification	p values
Age (yr.)	≤30, >30	0.0409
	≤45, >45	>0.1
Tumor size (cm)	<2, 2-5, >5	<0.00005
Number of positive nodes	0, 1, 2-3, 4-9, >10	<0.00005
Histologic type@	DCIS&MIDC, IDC, MUCC, MEDC, ILC, OTHERS	0.0001
Histologic grade †	Grade I, II, III	<0.00005
Degree of tubule formation †	Well, Moderately, Poorly	0.0002
Nuclear pleomorphism†	Mild, Moderate, Marked	0.0059
Mitotic index (/10 HPF*) †	<10, 10-19, ≥20	0.0407
Lymphatic invasion	Absent, Present	<0.00005
Lymphocytic infiltration	Absent & Mild, Moderate & Marked	>0.1
Tumor necrosis	Absent, Present	<0.00005
Perineural invasion	Absent, Present	>0.1

@DCIS: ductal carcinoma in situ; MIDC: microinvasive ductal carcinoma; IDC: invasive ductal carcinoma; MUCC: mucinous carcinoma; MEDC: medullary carcinoma; ILC: invasive lobular carcinoma
† for 423 invasive ductal carcinoma only
*HPF: high power fields

The effects of histologic type on the survival rate is illustrated in Table 3. Patients with tumors classified as ductal carcinoma in situ and microinvasive ductal carcinoma had a better prognosis than those with invasive carcinoma. Patients with medullary carcinoma and mucinous carcinoma also had better prognoses.

The overall survival rate curves of patients with invasive ductal carcinoma stratified among three histologic grades are shown in Fig. 3. The differences of the survival rate is statistically significant.

The prognosis also significantly correlated with lymphatic permeation, tumor necrosis, and patient age below 30 years. The same trends were also seen when the patients were classified by single histologic parameter of grading system, mainly, degree of tubule formation, nuclear pleomorphism and mitotic index. There was no significant effect of lymphocytic infiltration or perineural invasion on the survival rate.

The number of positive nodes, tumor size, histologic grade, lymphatic permeation, tumor necrosis and age were combined in multivariate Cox regression analysis for an overall survival rate (Table 4). The variables showing independent prognostic effects were the number of positive nodes, histologic grade, and tumor size.

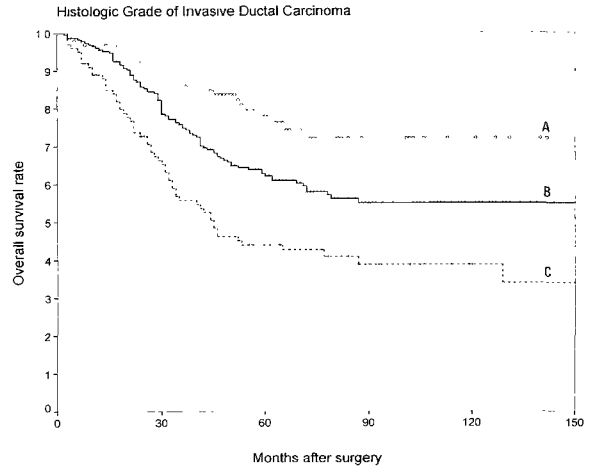

Fig. 3. Survival rate curves of 423 patients with invasive ductal carcinoma according to histologic grade (p<0.00005). A: grade I (n=97); B: grade II (n=226) and C: grade III (n=100).

Table 3. The effect of histologic type on the survival rate

Histologic Type	Number of Patients	No. Events	No. Censored	Percent Censored	Cumulative survival (%) 5-year	Cumulative survival (%) 10-year	Node metastasis (%)
Ductal carcinoma in situ & Microinvasive ductal carcinoma	54	6	48	88.9%	90.1±4.2%	82.6±8.2%	5/49 (10.2%)
Invasive ductal carcinoma	423	171	252	59.6%	61.3±2.4%	54.9±2.7%	254/405 (62.7%)
Invasive lobular carcinoma	9	3	6	66.7%	64.8±16.5%	64.8±16.5%	7/9 (77.8%)
Medullary carcinoma	5	0	5	100%	100%	100%	1/5 (20%)
Mucinous carcinoma	12	2	10	83.3%	91.7±8.0%	61.2±25.5%	3/10 (30%)
Others	11	0	11	100%	100%	100%	5/10 (50%)

Table 4. Results of Multivariate Cox Regression Analysis of the Variables Significant in Univariate Survival Rate Analyses

Variable	Coefficient	Standard error	Relative risk	95% confidence interval	p value
Number of positive nodes	0.0517	0.0092	1.0530	1.0343-1.0721	<0.00005
Histologic grade	0.4902	0.1315	1.6326	1.2616-2.1126	0.0002
Tumor size	0.0853	0.0335	1.0890	1.0199-1.1629	0.0108
Tumor necrosis	0.3353	0.1677	1.3984	1.0066-1.9426	0.0456

Tumor necrosis was a weak independent factor while age ≤ 30 and lymphatic permeation were not independent factors.

Patients age ≤ 30 years had a higher frequency of axillary node metastases than those age > 30 years. Fifteen of 20 (75%) patients age ≤ 30 years had axillary node metastasis whereas 260 of 468 (55.6%) age > 30 years had node metastases (p=0.086). Age did not correlate with tumor size, or histologic grade.

Lymphatic permeation also significantly correlated with axillary node metastasis (p<0.00005), large tumor size (p<0.00002), and high histologic grade (p<0.03).

DISCUSSION

Breast cancer is a widespread disease. As the range of treatments for patients with breast cancer widens, it becomes increasingly important that the pathologists provide accurate prognostic information. Our present study confirms the prognostic significance of pathologic characteristics of breast cancer patients.

Several pathologic factors have been shown to possess prognostic significance. Among them, axillary node metastasis is considered to be the most important. Others include tumor size, histologic grade, nuclear grade, mitoses, lymphatic permeation and tumor necrosis.

The relation between the extent of axillary node involvement and survival rate has been investigated in detail [5-7]. Other data, as well as ours, confirm that axillary node status is the most important prognostic factor. Increased number of positive nodes has a negative effect on the survival rate.

Most breast cancers are invasive carcinoma [8]. Among them, invasive ductal carcinoma is the most commonly seen with a frequency of 70 to 85%. The reported frequencies of invasive lobular carcinoma, medullary carcinoma, and mucinous carcinoma vary considerably, ranging from 1 to 10% [8]. It is generally thought that the patients with the latter two histologic types of carcinomas possess better prognoses. Although the number of cases in our study is limited, our results support that patients with medullary carcinoma or mucinous carcinoma seem to have better prognoses than patients with invasive ductal or lobular carcinomas.

Since histologic grading for breast cancer was first reported in 1925, several different prognostic classifications have been introduced. Histologic grading has been criticized because of its poor reproducibility, due in part to subjective evaluation. However, pathologists who used the same criteria for a grading system have shown that the system has excellent reproducibility [9,10]. If a routine histologic grading system shows prognostic significance, this would be an advantage for most clinical situations when complex procedures cannot be done. Several studies have shown a significant correlation between the histologic grade and the survival rate [4,11,12]. In addition, the prognostic importance was independent of nodal status [4]. However, some reports have shown histologic grade has no practical prognostic value after 1 year of follow-up [13] or are of rather low value [14]. In this study, we confirmed the prognostic significance of histologic grade independent of nodal status.

Tumor size was a practical parameter for estimating survival rate [5,15,16] independent of nodal status [15,16]. We also confirmed the prognostic significance of tumor size. We found tumor necrosis was weakly associated with survival rate which is in accordance with the results of other studies [17,18].

The relationship of patients age with the breast cancer survival rate is controversial. Some researchers found that age was a significant factor in patients prognosis [16,19,20]. A higher frequency of tumors with poorly differentiated, axillary node positive and negative hormone receptor status was observed in patients under 35 years [19]. We found that patients under 30 years had tumors with a higher frequency of axillary node metastases. This explains the lower survival rate of patients under 30 years in our study.

In conclusion, we found that axillary node status, tumor size and histologic grade of invasive ductal carcinoma were independent pathologic factors which can

be used for predicting the prognosis of breast cancer patients.

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乳癌的病理特徵在預後的重要性

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為了探討乳癌的病理特徵所具有的預後意義，我們回溯性收集1978至1987年間514位接受手術治療，有組織證明的乳癌病例。其平均年齡是50.2±12.4歲。腫瘤大小由0.7至13.0公分，平均是4.26±2.4公分。腋下淋巴結轉移可見於56.4%病人。單一變數存活分析結果顯示腋下淋巴結轉移，腫瘤大小，淋巴管侵襲，腫瘤壞死，腫瘤組織分類，組織學惡性度，及年齡少於30歲是有意義之預後因子。多變數存活分析結果顯示腋下淋巴結轉移($p<0.00005$)，腫瘤組織學惡性度($p=0.0002$)，及腫瘤大小($p=0.0108$)，是獨立有意義之預後因子。我們的研究顯示乳癌的病理特徵在評估病人預後的確具有相當的重要性。(**慈濟醫學** 1998; **10**: 265-271)

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