Analysis of 346 Chinese patients with breast cancer

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Three hundred and forty-six patients who underwent surgical treatment for primary breast cancer at the Prince of Wales Hospital were studied retrospectively. Their mean age was 52.3 years and 38.6% were younger than 45 years. With a median follow up interval of 42.3 months, the five-year survival rates were: stage I, 100%, stage II, 78.8%, and stage III, 67.6%. The overall five-year survival for all stages was 84.2%. Univariate analysis showed that T stage, N stage, and histologically-positive lymph node status were significant factors affecting survival and disease-free survival ($P < 0.05$). Multivariate analysis showed that a histologically-positive lymph node status was associated significantly with lower survival probability ($P << 0.01$) and lower disease-free survival probability ($P << 0.01$). The most important prognostic factor for Chinese patients is the histological status of their axillary lymph nodes.

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Introduction

Breast cancer has been recognised as a life-threatening disease since the time of the ancient Egyptians. Early reports of breast cancer can be traced to the 1930s.[1] Breast cancer management has become important because the incidence in women has been increasing, especially in developed countries.

In Hong Kong, the annual incidence of breast cancer has increased to more than 1000 cases, which is three times more than the figure observed 30 years ago. In 1991, there were 1133 new cases of lung cancer and 1106 new cases of breast cancer in women. In the same year, 881 women died from lung cancer and 333 women died from breast cancer.[2]

Breast cancer is now the second most common cancer and the second leading cause of cancer death in Hong Kong women. Breast cancer in Chinese women has not been as extensively studied as it has been in the West. Previous studies suggest a relationship between breast-feeding and breast cancer and state the need for early detection.[3,4] Hence, it is imperative to conduct an in-depth analysis of breast cancer in Hong Kong Chinese patients.

Clinical studies are largely based on the prospective or retrospective analysis of clinical information and the tumour characteristics related to breast cancer.[5-8] Researchers in this area are interested in identifying prognostic factors according to clinical and tumour characteristics. By studying the patient's survival and disease-free interval, clinicians and researchers can identify and confirm the optimal methods for managing breast cancer patients. We have conducted a retrospective analysis of 346 patients with breast cancer who received surgical treatment at the Prince of Wales Hospital (PWH), Hong Kong, over a nine-year period.

Subjects and methods

Three hundred and forty-six patients who received surgical treatment for breast cancer at the PWH from July 1984 through June 1993 were retrospectively analysed in this study. The clinical characteristics, tumour characteristics, surgical treatment, and the clinical outcome were analysed in terms of survival and disease-free survival.

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Table 1. Clinical stage distribution of patients with breast cancer

	No. of patients (%)
Carcinoma in situ	22 (6.4)
I	35 (10.8)
II	191 (59.0)
III	90 (27.8)
IV	4 (1.2)
Not stated	4 (1.2)
Tumour T stage	
T_1	37 (11.4)
T_2	189 (58.3)
T_3	92 (28.5)
T_4	3 (0.9)
Not stated	3 (0.9)
Tumour N stage	
N_0	226 (69.7)
N_1	93 (28.8
N_2	2 (0.6)
Not stated	3 (0.9)

Tumour classification was based on the descriptions of Spiessl and pre-operative staging was according to Rogers and Bland i.e. stage I (T1 N0 M0) referred to invasive tumours without metastases[10,11]; stage II (T1 N1 M0, T2 N1 M0, and T3 N0 M0) described small tumours with axillary metastases and larger primary tumours (T3 N0) without axillary metastases; stage III (T1 N2 M0, T2 N2 M0, T3 N1 M0, T3 N2 M0, and T4 with any N M0), included tumours of any size that were associated with matted or fixed regional lymph nodes and tumours with skin or chest wall invasion.[8-10] Stage IV (any T, any N with M1) was reserved for cases with documented distant metastases or supraclavicular lymph node involvement. The tumour characteristics were determined from a review of the pathology reports. Follow up information was obtained from hospital records and telephone interviews with patients and their families.

All recorded data were entered into a dBase IV (Borland International Inc., Scotts Valley, Ca,US) program and analysed using an SPSS for Windows (Release 6) [SPSS Inc., Chicago, Ill, US] program. Kaplan-Meier survival analysis was used to estimate the survival probability of patients with different characteristics.[12] The survival probability by time since surgery was analysed as five-year survival rates and five-year disease-free survival rates.

Table 2. Clinical characteristics of the 346 patients with breast cancer

	No. of patients (%)
Patient age distribution	
< 45 y	133 (38.6)
45-65 y	88 (25.4)
> 65 y	125 (36.0)
Menopausal status	
pre-menopausal	161 (46.5)
post-menopausal	168 (48.6)
not stated	17 (4.9)
Marital status	
single	35 (10.1)
married	271 (78.3)
not stated	40 (11.6)
Parity status	
yes	262 (75.7)
no	48 (13.9)
not stated	36 (10.4)
Breast-feeding history	
yes	140 (40.5)
no	134 (38.7)
not stated	72 (20.8)
Oral contraceptive history	
yes	59 (17.1)
no	174 (50.3)
not stated	113 (32.6)
Family history of breast cancer	
yes	22 (6.4)
no	304 (87.9)
not stated	20 (5.7)

The outcome measure method for survival rate as described by Rosen et al was calculated as the number of years from surgery for the original breast cancer until death or until the date of the last time the patient was known to be alive.[13] Disease-free survival was calculated as the number of years after surgery until the recurrence of breast cancer and death or until the date of the last time the patient was known to have no evidence of disease.

Due to the small number of patients in stage IV, T4 stage, and N2 stage (4, 3 and 2, respectively, Table 1), the survival probabilities of the patients with these tumour stages were not estimated as

meaningful interpretation was not possible. Four stage IV patients had suspicious supraclavicular lymph node disease. In addition, 22 patients with carcinoma-in-situ were not included in the analysis of survival by clinical stage.

Three hundred and sixteen patients (90%) received a total mastectomy and either axillary sampling or axillary dissection. From November 1991 onwards, complete axillary dissection in the form of enbloc removal of level I or II lymph nodes—and if involved by disease—removal of level III nodes was the routine surgical treatment for the axilla. Thirty patients received either a lumpectomy or partial mastectomy followed by radiotherapy. A few patients, however, did not receive radiotherapy due to advanced age. Lumpectomy was typically carried out for tumours less than 3 cm in size with the breast tumour excised with a normal tissue margin of 1.5 cm. Microscopic clearance of disease was routinely confirmed on paraffin section. Chemotherapy was routinely given to women with positive axillary nodes and who were younger than 65 years. Post-operative radiotherapy to the chest wall was usually given to women with advanced stage disease.

Results

Our 346 breast cancer patients had a mean age of 52.6 years (age range, 23 to 92 years). One hundred and thirty-three (38.6%) patients were younger than 45 years. Eighty-eight (25.4%) were aged from 45 to 65 years and 125 (36%) patients were older than 65 years. The clinical characteristics of patients with breast cancer are shown in Table 2.

Pre-menopausal and post-menopausal women were equally likely to be affected by breast cancer (46.5% and 48.6%, respectively); 10% of the patients were single, 13.9% were nulliparous, 38.7% had no history of breast-feeding, and 17.1% had previously used oral contraceptives. Overall, only 6.6% had a family history of breast cancer.

The clinical stage distribution of 346 patients with invasive breast cancer is shown in Table 2. A majority of the patients had clinical stage II (59.0%, n = 191) or stage III (27.9%, n = 90) disease. Only 10.8% of the patients had stage I disease and 12.2% of the patients had T1 tumour. Similarly, a majority of the patients

Table 3. Five-year survival and disease-free survival rates of patients by clinical stage*

	No. of patients	Five-year survival rate (%)[1]	P value[2]	Five-year disease-free survival rate (%)[1]	P value[2]
Clinical stage[3]					
I	35	100.0		88.5	
II	191	78.8	0.23	68.0	0.12
III	90	67.6		54.5	
T stage (by tumour size)[4]					
T_1 (< 2 cm)	37	100.0		89.4	
T_2 (2-5 cm)	189	78.8	0.04†	68.8	0.01‡
T_3 (> 5 cm)	92	59.7		47.5	
N stage (by axillary lymph node status)[5]					
N_0 (-)	226	80.9		74.9	
N_1 (+)	93	64.3	0.04	40.6	<< 0.01

[1] Five-year survival and disease-free survival rates estimated by the Kaplan Meier method
[2] five-year survival and disease-free survival rates estimated by the Log-rank test method
[3] results from four patients with stage IV disease were excluded
[4] results from three patients with stage T_4 were excluded
[5] results from two patients with N_2 stage were excluded
* Patients with carcinoma in situ were excluded (22)
† P-value for T_1 vs T_2 = 0.19, T_1 vs T_3 = 0.02, T_2 vs T_3 = 0.07
‡ P-value for T_1 vs T_2 = 0.38, T_1 vs T_3 = 0.03, T_2 vs T_3 = 0.01

Table 4. Five-year survival and disease-free survival rates of patients by histological characteristics

	No. of patients	Five-year survival rate (%)*	P value†	Five-year disease-free survival rate (%)*	P value†
Tumour histology					
carcinoma in situ (1)	22	91.7		86.3	
invasive cancer (2)	292	74.8	0.31	63.8	0.13
other cancer (3)‡	32	79.1		65.9	
No. of involved lymph nodes					
0 (1)	212	86.7		77.7	
1-3 (2)	74	64.7	<< 0.01§	55.1	<< 0.01‖
> 3 (3)	60	54.6		39.1	

* Five-year survival and disease-free survival rates estimated by the Kaplan Meier method
† five-year survival and disease-free survival rates estimated by the Log-rank test method
‡ Other cancer = other invasive carcinoma
§ P-value for 1 vs 2 = 0.0002, 1 vs 3 < 0.0005, 2 vs 3 = 0.5
‖ P-value for 1 vs 2 = 0.0001, 1 vs 3 < 0.00005, 2 vs 3 = 0.2

had either T2 tumour (58.3%, n = 189) or T3 tumour (28.5%, n = 92). Ninety-five patients (29.4%) had clinically suspicious axillary lymph node involvement (Table 1).

The median follow up time of the 346 patients was 42.3 months (range, 12 to 125 months). Of these patients, 249 were alive with no evidence of cancer, 32 were alive with a history of recurrence during the follow up period, 55 had died due to recurrence cancer and 10 had died due to other causes.

Table 3 shows the five-year survival and disease-free survival analysis according to clinical stage. As expected, patients with advanced tumour had a poor clinical outcome. The five-year survival probability by clinical stage was 100% (stage I), 78.8% (stage II), and 67.6% (stage III), respectively, and the five-year disease-free survival probability was 88.5% (stage I), 68.0% (stage II) and 54.5% (stage III), respectively. However, there was no statistically significant difference between survival and disease-free survival according to clinical stage (Table 3, P = 0.23 and 0.12, respectively), yet tumour size (T stage) significantly correlated with the survival and disease-free survival probability (P = 0.04 and 0.01, respectively). Patients with T3 stage tumour (≥ 5 cm in diameter) had a consistently lower survival and disease-free survival rate (59.7% and 47.5%) than did those with T1 (100% and 89.4%) and T2 (78.8% and 68.8%) stage tumours.

Patients with positive axillary lymph nodes (N1) had significantly lower five-year survival rates (64.3%) compared with patients with negative lymph node findings (80.9%, P = 0.04, Table 3). The disease-free survival rate of patients with positive axillary lymph nodes was also significantly different from that of patients with negative results. At five years, the percentage surviving disease-free was only 40.6% for patients with positive lymph nodes, compared with 74.9% for patients with negative lymph nodes; these differences were statistically significant (P << 0.01, Table 3).

Tumours were classified into three histopathological categories—ductal and lobular carcinoma-in-situ (CAIS), other cancers (other invasive carcinomas, medullary carcinoma, mucinous carcinoma, etc.) and invasive carcinoma (invasive ductal and lobular carcinomas). Lymph node involvement status was categorised according to the number of positive lymph nodes—0, 1 to 3, and more than 3, respectively.

Table 4 shows that patients with invasive carcinoma had a lower survival rate (74.8%) and disease-free survival rate (63.8%) at five years compared with the other patient groups. However, these differences were not statistically significant (P = 0.3, P = 0.13, respectively).

The lymph node involvement status was an important factor in determining the prognosis of breast cancer patients. Histologically proven disease in one or more axillary lymph nodes was present in 134 patients

Table 5. Five-year survival and disease-free survival rates of patients by type of operation

Type of operation	No. of patients	Five-year survival rate (%)*	P value†	Five-year disease-free survival rate (%)*	P value†
Modified radical mastectomy	125	72.1		65.8	
Mastectomy and node sampling	191	80.6		67.2	
Conservation surgery	30	80.0	0.29	53.0	0.78

* Five-year survival and disease-free survival rates estimated by the Kaplan-Meier method
† five-year survival and disease-free survival rates estimated by the Log-rank test method

(39.3%, Table 4). Patients with negative lymph node results had significantly better five-year survival rates (86.7%) than did patients with one to three positive lymph nodes (64.7%, P « 0.01) and patients with more than three positive nodes (54.6%, P « 0.01, Table 4). The five-year disease-free survival rate of patients with negative lymph nodes was 77.7%, which was significantly more than that of patients with one to three positive lymph nodes (55.1%, P « 0.01) and that of those with more than three positive lymph nodes (39.1%, P « 0.01). Although patients with positive lymph nodes had a significantly poorer prognosis (P < 0.01), the relationships between patient survival probability and disease-free survival probability according to the number of involved lymph nodes were not statistically significant (for $N_{(1-3)}$ vs $N_{(>3)}$: P = 0.5 and 0.2, Table 4).

One hundred and twenty-five patients received a modified radical mastectomy (total mastectomy and axillary dissection), 191 patients received a total mastectomy plus axillary node sampling, and 30 patients received a partial mastectomy or lumpectomy (breast conservation surgery). There was no significant difference in their five-year survival rates and five-year disease-free survival rates (P = 0.29 and 0.78, respectively). The five-year survival rates in these three patient groups were 72.1%, 80.6%, and 80.0%, respectively; their five-year disease-free survival rates were 65.8%, 67.2%, and 53.0%, respectively (Table 5).

The results from this study showed that tumour T stage and lymph node involvement status are prognostic factors for Hong Kong women with breast cancer. The five-year disease-free survival rates of our breast cancer patients according to tumour T stage and the number of positive lymph nodes are similar to the results of studies from Japan, the United States and the United Kingdom (Table 6).[14-16]

The factors that were shown to affect patient clinical outcomes were further analysed by the Cox's regression model. After all parameters were adjusted for each other, histologic lymph node involvement status was the only parameter associated with the risk of dying from breast cancer at any time (P « 0.01). Patients with more than three positive lymph nodes were 1.68 (1.15 to 2.74) times more likely to die from breast cancer than were patients with negative lymph nodes.

The disease-free survival results show that histological lymph node status and N stage correlate with the risk of dying or developing recurrent disease (P < 0.01 and 0.01, respectively). The hazard rate (95% CI) for patients with more than three positive lymph nodes was 1.59 times (1.15 to 2.20) greater than that for patients with negative lymph nodes. Similarly, patients with clinically positive nodes had a 1.37 times greater risk of dying or developing recurrent breast cancer than did those with negative lymph nodes.

Discussion

Although the incidence of breast cancer has increased in many countries recently, many of these patients with breast cancer have early stage disease due to early diagnosis. Consequently, mortality due to breast cancer in recent decades has remained stable. It has been suggested that regular breast self-examination, physician breast examination, and

Table 6. Comparison of disease-free survival rates of Hong Kong breast cancer patients with the rates of other regions

	Five-year disease-free survival rate (%)			
	Hong Kong*	Japan[14]	USA[15]	UK[16]
T stage				
T_1	89	91	79	75
T_2	69	71	69	68
T_3	48	47	50	30
Positive lymph node				
N_0	78	94	71	82
N_{1-3}	55	77	62	56
$N_{>3}$	39	42	40	30

* Results from this study

screening mammography are important for the early diagnosis of breast cancer.[17,18]

The survival rates of our study patients were similar to those found elsewhere (Table 6). Patients with T1 or N0 stage tumour had a better prognosis than did patients with advanced breast cancer. In this study, however, only 12% (n = 37) of the patients had tumours smaller than 2 cm in diameter and these patients had a significantly better prognosis ($P < 0.05$, Table 3). Other countries, such as Japan (47%), the United States (50.5%) and the United Kingdom (34%), had three to four times more patients with tumours smaller than 2 cm in diameter.[14-16] Hence, Hong Kong Chinese women tend to have their disease diagnosed relatively late and consequently, relatively fewer women are suitable candidates for breast conservation surgery. In this series, only 8.7% of patients received breast conservativon surgery whereas approximately 33% of patients in the United States in 1988 elected to receive breast conservation surgery and radiotherapy for treatment of their breast cancer.

Factors other than tumour size may explain the lower rate of breast conservation surgery, including patient preference, doctor preference, and the fact that breast conservation surgery in our hospital was only routinely available after 1 November 1991. In this study, 98% of patients presented with a self-palpated breast lump. Therefore, regular self-examination or physician breast examination plus screening with mammography may increase the number of patients seen with small tumours and improve the prognosis of patients with breast cancer.

Tumour characteristics are important aids in predicting the clinical outcome of breast cancer patients. Two of the most important prognostic indicators for breast cancer are tumour size and the extent of axillary lymph node involvement.[19]

Rosen and colleagues investigated a group of 644 breast cancer patients who had been treated by mastectomy with a median follow up interval of 20 years.[13] Their results show that the probability of recurrence is directly related to the initial extent of the disease (tumour size and lymph node involvement status). Similar results from Berg and Robbins show that factors such as tumour size and axillary lymph node status are useful prognostic factors.[20] The longest follow up study of breast cancer patients has been conducted by Adair.[21] Their 30-year results show that axillary node involvement is the most reliable index for prognosis. The probability of long-term survival among women with negative axillary nodes is greater than it is for those with positive nodes, the ratio being three to two.

Tumour size and the status of axillary lymph nodes played a significant role in the prediction of patient outcome in terms of the survival rate or disease-free survival rate. The presence of a large tumour (> 5 cm in diameter) and the axillary lymph node involvement status can be used to predict the probable survival and disease-free survival of patients at five years.

Patients with histologically negative lymph nodes had better survival rates than did patients with histologically positive lymph nodes.[22] Because prognosis is clearly related to the extent of involved lymph node, it has become conventional to categorise patients according to the number of nodes involved. To enable comparison of this study with others, patients were divided into three groups according to the number of involved lymph nodes (0, 1 to 3, and more than 3, respectively).[17]

Fisher and coworkers conclude that the extent of axillary node involvement correlates with the prognosis and remains the best prognostic indicator available.[23] Our results are similar to those of others as patients with positive lymph nodes had a poor clinical outcome. Single factor statistical analysis showed a significant difference in the survival rate and disease-free survival rate between patients with histologically negative lymph nodes and those with positive lymph nodes.

When analysed using a multivariate method (Cox regression model), tumour lymph node involvement

status also showed a significant association with patient prognosis. It was also found that patients with more than three positive lymph nodes had the worst prognosis. This result was similar to the findings of others in that the prognosis was related to the level of positive lymph node involvement and the number of positive lymph nodes.[17] Hence, a high recurrence rate was associated with an increased number of positive nodes. Cox regression analysis showed that more than three positive lymph nodes could be used as a prognostic determinant of the survival rate and disease-free survival rate of patients. Tumour N stage could also be used as a prognostic determinant of the disease-free survival rate of breast cancer patients. Therefore, the prognostic factors derived from the clinical characteristics of Hong Kong Chinese patients are similar to those reported in the literature. This similarity in the pattern of breast cancer among different regions allows the comparison of treatment programmes and treatment results between regions.

Aaronson and colleagues thought that breast conservation surgery could replace radical mastectomy in stage I and II breast tumours and the subsequent disease-free survival rates were almost the same between patients with breast conservation surgery and mastectomy.[24,25] However, patients with breast conservation surgery have a higher rate of recurrent disease due to the presence of breast tissue at risk of new tumour formation.[25,26] It is also possible that breast conservation surgery does not remove all microscopic disease at the time of surgery.[27] It has been suggested that additional radiotherapy is required to increase the disease-free survival rate of patients undergoing breast conservation surgery.[24,27]

Our study shows that patients with total mastectomy plus axillary dissection and those with mastectomy plus axillary node sampling have similar five-year disease-free survival rates (65.8% and 67.2%, Table 5). Although patients with mastectomy had a higher disease-free survival rate (65.8%) than did patients treated with lumpectomy (53.0%), the difference was not significant. The lower five-year disease-free survival rate of patients with lumpectomy can be explained by the fact that some of these were elderly patients who were treated by partial mastectomy only and did not receive radiotherapy as part of the treatment programme. Recent reports suggest that radiotherapy is important in reducing the local recurrence rate in patients treated by lumpectomy. Any analysis of the treatment results of modified radical mastectomy versus breast conservation surgery is limited by the small sample size for the breast conservation group and the absence of a prospective randomised study.

The clinical and histological characteristics of breast cancer in Hong Kong Chinese women are largely similar to those observed in the West. Of major concern is the fact that breast cancer in Hong Kong is being seen increasingly in women younger than 45 years. As our lifestyle continues to become more urban, it is expected that breast cancer will increasingly be a serious health problem for Hong Kong women. Hence, a programme for the early detection of breast cancer is essential to address this major health concern of Hong Kong women.

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