

# Operable Breast Cancer: a Clinical Analysis of 6,263 Cases

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**OBJECTIVE** In Europe and America breast cancer commonly occurs in women of middle and old age, with a median age of about 57 years. Modified radical mastectomy now called standard radical mastectomy, has taken the place of traditional radical mastectomy. Patients with breast cancer at an early stage commonly receive BCT (breast conservative therapy). The TNM stage (especially the lymph node status) affects the prognosis, and adjuvant therapy can improve survival. In China, only a few reports have been published studying large numbers of breast cancer patients. This study was designed to analyze the clinical features, surgical pattern and treatment outcome of resectable breast cancer, as well as to explore the prognostic factors and the effect of adjuvant therapy, with a goal to improve the level of diagnosis and treatment.

**METHODS** Records of the 6,263 patients with resectable breast cancer who had been admitted into our hospital from June 1964 to June 2003 were analyzed retrospectively.

**RESULTS** Of the 6,263 cases, 98.8% were female. Breast cancer occurred most frequently in patients of ages 40~49 years (41.0%), especially in patients 45~49 years old (25.2%). A breast lump, which occurred in 96.2% of the patients, was the main clinical manifestation. The overall 5- and 10-year survival rates were 75.16% and 40.44%. Of the patients in TNM stages 0-I, II, and III, the 5-year survival rates were 96.8%, 73.7% and 46.4% respectively and the 10-year survival rates were 78.7%, 64.6% and 33.5% respectively. The 5-, and 10-year survival rates were higher in the lymph node negative group than in the lymph node positive group (80.3% vs. 55.6%, and 59.2% vs. 31.9%,  $P < 0.01$ ). Since the 1980s there was no significant difference in survival rates of patients who received a radical mastectomy compared to a modified radical mastectomy ( $P > 0.05$ ). Of the 73 patients who underwent breast conservative therapy, no local recurrence or metastasis occurred during a maximal follow-up of 17 years. Of the patients in stage T2-T4, the 5-, and 10-year survival rates were significantly higher in the group treated with adjuvant chemotherapy compared to the non-chemotherapy group (78.2% vs. 60.1%, and 48.9% vs. 30.7%,  $P < 0.01$ ).

**CONCLUSION** According to our data, breast cancer most frequently occurred in patients of ages 45~49 years. The TNM stage (especially the lymph node status) relates to breast cancer prognosis. The prognosis was worse in patients with positive lymph nodes compared to the patients with negative lymph nodes. The efficacy of a modified radical mastectomy is equal to that of a radical mastectomy, and breast conservative therapy can be applied to patients in an early stage. Adjuvant chemotherapy and endocrine therapy can improve the survival of resectable breast cancer patients.

**KEYWORDS:** breast neoplasms, surgery, adjuvant therapy, prognosis.

In Europe and America, breast cancer is the number one cause of female malignancy and in China, and depending on the city, the incidence is either first or second. Furthermore it is on the increase every

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year. Presently, the etiology of breast cancer is unknown and there is no effective means for its prevention. In order to improve the efficacy of breast cancer therapy, it is necessary obtain a better understanding of its clinical aspects as well as to summarize our clinical experience with this malignancy. Over the period from June 1964 to June 2003 the records from 6,263 patients with operable breast cancer who had been admitted into our hospital were analyzed retrospectively. By studying the clinical features of breast cancer in China we hope to improve breast cancer therapy.

## MATERIALS AND METHODS

### General data

A retrospective analysis was conducted of the records from 6,263 patients with operable breast cancer who had been admitted to our hospital from June 1964 to June 2003. Of the 6,263 patients, 65 were male, 6,198 were female, ranging in age from 17 to 90 years with a median age of 47. Classifying the patients' age, 10 were 15~19 (0.2%), 40 were 20~24 (0.6%), 183 were 25~29 (2.9%), 279 were 30~34 (4.4%), 694 were 35~39 (11.1%), 990 were 40~44 (11.6%), 1,579 were 45~49 (25.2%), 974 were 50~54 (15.6%), 669 were 55~59 (10.7%), 369 were 60~64 (5.9%), 236 were 65~69 (3.8%), 140 were 70~74 (2.2%), 62 were 75~79 (11.0%), 31 were 80~84 (0.5%), 5 were 85~89 (0.1%) and 2 were  $\geq 90$  (0.03%). The breast cancer occurred most frequently in patients of 40~49 years old (41.0%). Over the past 30 years, the age distribution of breast cancer has not significantly changed (Table 1). Of the total cases, 3,145 cancers were in the left breast and

3,118 were in the right breast. The chief complaint of the 6,024 patients was a breast lump; 182 cases displayed lactation; 15 cases had an axillary lump; 42 cases were noted at the time of an examination. The duration of symptoms were from 3 days to 42 months with a median time of 6.5 months.

### Treatment

There were 142 cases who underwent an extensive radical mastectomy, 3,648 cases received a radical mastectomy, 2,201 cases were treated by a modified radical mastectomy, 199 cases received a mastectomy and 73 cases underwent BCT (breast conserving treatment). From the 1980's, patients received adjuvant chemotherapy (chemotherapy regimen: CMF or CAF or CEF), if they were diagnosed in stage II or higher. They received endocrine therapy, if they were positive for hormone receptors, and adjuvant radiotherapy if they displayed 4 or more positive lymph nodes. Patients who underwent BCT also received radiotherapy to the whole breast as well as adjuvant chemotherapy and endocrine therapy if they were positive for hormone receptors.

### Pathology and TNM stage

Non-invasive carcinoma occurred in 395 cases, 5,316 cases were non-specific invasive carcinoma (including 874 cases of early invasive carcinoma) and 552 cases were specific carcinoma. Of the 6,263 cases, 3,009 cases had positive axillary lymph nodes (48.0%). According to the TNM classification standards of the UICC 2002, 125 cases were in stage 0, 584 cases were in stage I, 4,335 cases were in stage II, 1,219 cases were in stage III.

Table 1. Age Distribution of 6,263 patients with resectable breast cancer [ n(%)].

Age(years)	1964~1969	1970~1979	1980~1989	1990~1999	2000~2002	Total
10~19	1(0.4)	2(0.2)	2(0.2)	3(0.1)	2(0.2)	10(0.2)
20~29	5(2.2)	24(2.2)	43(3.4)	110(4.3)	41(3.8)	223(3.6)
30~39	36(15.6)	168(15.3)	201(15.7)	396(15.4)	172(15.8)	973(15.5)
40~49	91(39.4)	436(39.8)	500(39.1)	1079(42.0)	463(44.4)	2569(41.0)
50~59	64(27.7)	350(32.0)	315(24.6)	642(25.0)	272(24.9)	1643(26.2)
60~69	21(9.1)	84(7.7)	159(12.4)	238(9.3)	103(9.4)	605(9.7)
70~79	10(4.3)	23(2.1)	44(3.4)	89(3.5)	36(3.3)	202(3.2)
80~89	3(1.3)	8(0.7)	13(1.0)	10(0.4)	2(0.2)	36(0.6)
$\geq 90$	0(0)	0(0)	2(0.2)	0(0)	0(0)	2(0.0)
Total	231	1095	1279	2567	1091	6263

## Follow-up and statistical methods

Follow-up data from all of the patients were collected when the patients came back to the hospital for examination or by contacting through the mail. The follow-up data were computer analyzed using Life-table statistical software SPSS 10.0 for windows.

## RESULTS

Considering all of the 6,263 patients, the 5-year and 10-year overall survival rates were 75.16% and 40.44% respectively. Of the patients in TNM stages 0-I, II and III, the 5-year overall survival rate was 96.82%, 73.66% and 46.45% respectively ( $P<0.01$ ) and the 10-year overall survival rate was 78.72%, 64.56% and 33.46% respectively ( $P<0.01$ ). As the decade advanced, the survival of the breast cancer patients in every TNM stage increased (Table 2). The 5- and 10-year overall survival rates of the lymph node negative group were better than the lymph node positive group (80.33% vs. 55.62%, and 59.16% vs. 31.93%,  $P<0.01$ ). There was no statistically significant difference between the overall survival rate of patients receiving a radical mastectomy versus a modified radical mastectomy since the 1980's (Table 3). Seventy-three patients who underwent BCT developed no local recurrence or metastasis during a follow-up period from 3 months to 17 years. Among the patients with 4 or more positive lymph nodes, the local recurrent rate was significantly lower in the adjuvant-radiotherapy group than in the non-radiotherapy group (5.4% vs. 21.3%,  $P<0.01$ ). The 5- and 10-year survival rates in the adjuvant-radiotherapy group were similar to the radiotherapy-treated group (45.6% vs. 47.1%; 22.9% vs. 23.2%,  $P>0.05$ ). Of the patients in stage T<sub>2</sub>-T<sub>4</sub>, the 5- and 10-year survival rates were significantly higher in the chemotherapy group than in the non-chemotherapy group (78.24% vs. 60.12%; 48.87% vs. 30.68%,  $P<0.01$ ).

## DISCUSSION

### Age distribution of breast cancer

The age distribution of breast cancer in China is quite different compared to America and Europe. In America and Europe, breast cancer usually occurs in women of middle and old age, but in China it commonly occurs in middle age. Nab et al.<sup>[1]</sup> studied 2,052 breast cancer cases and found a median age of 56.5 years. In our study, the median age was 47 years. In Rutqvist's<sup>[2]</sup> report of 14,731 cases, 60.6% were  $\geq 55$  years of age, but in our study of 6,263 cases, only 24.2% were  $\geq 55$  years old. According to our data, among the groups with a 5-year interval, breast cancer occurred most frequently in the 45-49 year-old group (25.2%), then in the 40-44 year-old group (15.8%) and less in the 50-54 year-old group (15.6%). Among the 10-year interval groups, breast cancer occurred mostly in the 45-49 year-old group (41.0%), then in the 50-59 year-old group (26.2%) and less in the 30-39 year-old group (15.5%). Within the decade of the 1970's, 1980's and 1990's, the age distribution of breast cancer incidence in the first 3 age groups in had not changed. A further study is needed to answer the question as to why the median age of breast cancer in China is nearly 10 years earlier than in America and Europe.

### Relationship between the TNM stage and prognosis

Prognosis of all malignant tumors, including breast cancer, was affected by the TNM stage with the more advanced TNM stages correlating with the worst prognosis. According to a report from the Tianjin Cancer Hospital, of 4,230 patients with breast cancer, the 10-year survival rates in the TNM stages I, II, III and IV were 83.0%, 72.1%, 39.0% and 14.7% respectively.<sup>[3]</sup> In our study, of the patients in TNM stages 0-I, II and III, the 10-year overall survival rates were 78.72%, 64.56% and 33.46% respectively. The survival of patients in an early stage was significantly higher than that with ad-

Table 2. Survival Rates of 6,263 patients with resectable breast cancer.

TNM stage	Survival rate (%)							
	1970~1979		1980~1989		1990~1999		1964~2003	
	5-year	10-year	5-year	10-year	5-year	10-year	5-year	10-year
0-I	90.4	73.7	91.5	77.0	95.8	90.5	92.3	78.7
II	70.1	56.6	72.3	61.4	73.9	65.3	73.7	64.6
III	43.2	32.6	44.7	34.7	50.1	36.3	46.5	33.5

**Table 3. Survival rates of patients receiving a radical mastectomy or a modified radical mastectomy for breast cancer since 1980's [% (n)].**

TNM stage	5-year survival rate		10-year survival rate		P value
	Radical mastectomy	Modified radical mastectomy	Radical mastectomy	Modified radical mastectomy	
0-I	92.8(323/348)	92.9(195/210)	87.1(303/348)	86.7(182/210)	>0.05
II	73.0(1556/2132)	73.0(940/1287)	62.0(1321/2132)	62.0(798/1287)	>0.05
II	44.9(269/599)	45.2(163/361)	35.9(215/599)	36.0(130/361)	>0.05

vanced stage ( $P<0.01$ ). Obviously an early diagnosis and treatment are crucial in improving the efficacy of breast cancer therapy.

### Relationship between axillary lymph node status and prognosis

In our study, the rate of positive axillary lymph nodes was 48.04%, which was similar to the result of 47.9% reported by Shen et al.<sup>[4]</sup> Apparently, nearly half of the patients with breast cancer in China have had axillary lymph node metastases when they visited the doctor for the first time. In China, it is necessary that a great effort be made in the field of early diagnosis of this malignancy. It had been reported that from 1969 to 1978, the positive rate of axillary lymph nodes from invasive breast carcinoma was 45%~50%. However, with the promulgation of public information concerning breast cancer and development of techniques for early diagnosis (such as mammograms etc.), from 1984 to 1993 the positive rate of axillary lymph node declined to 34%~31%.<sup>[5]</sup> Now, it is generally accepted that axillary lymph node status is an important factor which influences the prognosis of breast cancer. Shen et al.<sup>[4]</sup> reported that the 5-year survival rate of patients with negative axillary lymph nodes was 88.6%. The 5-year survival rates of patients with 1 to 3 positive lymph nodes, 4 to 6 positive lymph nodes and  $\geq 7$  positive lymph nodes were 71.3%, 60.9% and 44.9% respectively. In our study, the 5-year survival rates of the negative lymph node group and positive lymph node group were 80.3% and 55.6%, and the 10-year survival rates were 59.2% and 31.9%. The survival rate of the negative lymph node group was significantly higher than the positive lymph node group ( $P<0.01$ ).

### Relationship between modality of surgery and prognosis

Halsted designed a radical mastectomy in 1889 and in 1894 reported his first follow-up results from 50 patients who underwent this operation. His report of a local recurrent rate of 6% made a big impact in the field

of surgical oncology, for in those days, the breast cancer local recurrent rate of after an operation was about 51%~82%. Halsted's radical mastectomy was considered to be a milestone of surgical oncology. With a furthering of the knowledge about the biological behaviour of breast cancer, oncologists found that the main cause of treatment failure was not the insufficiency of the surgical operation, but the distant tumor cell metastases. Over the past 30 years, many retrospective and random clinical studies have shown that the efficacy of modified radical mastectomy is similar to that of radical mastectomy.<sup>[6-8]</sup> So a modified radical mastectomy has become the standard mastectomy. In our study, there was also no significant statistical difference in the 5- and 10-year survival rates of patients between radical mastectomy and modified radical mastectomy since the 1980's ( $P>0.05$ ).

During the past 20 years, with the development of radiotherapy and chemotherapy, BCT has been used for patients in early stage disease in America and Europe, and has achieved efficacy similar to radical mastectomy. In 1995, the EBCTCG (early breast cancer trialists collaborative group) of America produced a meta-analysis of 28,405 patients who received BCT before 1985. The result showed that the 10-year local recurrent rates of the patients after radical mastectomy or BCT were 6.2% and 5.9%, there being no significant difference.<sup>[9]</sup> Actually, in 1990, a breast cancer conference concerning early treatment convened by the American National Cancer Institute, drew the conclusion that BCT treatment was preferable for patients with early breast cancer. In our study, 73 patients who underwent BCT and no local recurrence or metastasis, over a 17-year follow-up. That showed the feasibility of BCT being applied for patients in an early stage.

### Adjuvant therapy after operation

It is generally accepted that adjuvant chemotherapy can improve therapeutic efficacy. The EBCTCG<sup>[10]</sup> presented an updated overview of 18,000 patients with breast cancer from 47 random trials. The results were as fol-

lows: among the patients under the age of 50, polychemotherapy improved the 10-year survival from 71.9% for those with negative nodes to 77.6%, an absolute benefit of 5.7% ( $P=0.02$ ), and for those with positive nodes polychemotherapy improved the 10-year survival from 41.4% to 53.8%, an absolute benefit of 12.4% ( $P<0.001$ ); among the patients of age 50–69 years, polychemotherapy improved the 10-year survival from 64.8% for those with negative nodes to 71.2%, an absolute benefit of 6.4% ( $P=0.005$ ), and for those with positive nodes polychemotherapy improved the 10-year survival from 46.3% to 48.6%, an absolute benefit of 2.3% ( $P=0.002$ ).

The efficacy of endocrine therapy has also been confirmed. The EBCTCG<sup>[11]</sup> analyzed 37,000 patients with breast cancer from 55 random trials with the results showing: among the axillary-negative lymph node patients, the 10-year survival rate was 5.6% higher in patients who had taken tamoxifen for 5 years compared to patients receiving no tamoxifen (78.9% vs. 73.3%,  $P<0.001$ ); among the axillary-positive lymph node patients, the 10-year survival rate was 10.9% higher in the patients who had taken tamoxifen for 5 years compared to patients received no tamoxifen (61.4% vs. 50.5%,  $P<0.001$ ). The NSABP B-14 test also confirmed the efficacy of tamoxifen: the 15-year overall survival rates of patients in a tamoxifen group and in a placebo group were 71% and 65% respectively, the former being significantly better than latter ( $P=0.001$ ).

The efficacy of adjuvant chemotherapy plus endocrine therapy has also been confirmed, but it appears to have some relationship with patients age. Some results of the NSABP B-20 test showed the following: of the patients < 60 years old, the 12-year overall survival rates in the tamoxifen-treated group and in the tamoxifen plus CMF-chemotherapy group were 84% and 90%; of the patients  $\geq$  60 years old, 12-year overall survival rates in the tamoxifen-treated group and in the tamoxifen plus CMF-chemotherapy group were 81% and 77%. Obviously the efficacy of CMF-chemotherapy was better for the patients < 60 years old than for those  $\geq$  60 years old ( $P=0.027$ ).<sup>[12]</sup>

Adjuvant radiotherapy applied regularly to patients receiving BCT has been generally used, but for patients who underwent a modified radical mastectomy, the application of radiotherapy has been controversial. The practice guidelines from NCCN 2004, suggested the following: for patients with 1–3 positive axillary nodes might receive chemotherapy followed by RT (radiotherapy) to the chest wall and supraclavicular area; if RT is given, internal mammary RT could be considered; for

the patients with  $\geq$  4 positive axillary nodes, chemotherapy followed by RT to the chest wall and supraclavicular area should be applied, and internal mammary RT could be considered; for the patients with a tumor size > 5 cm, chemotherapy followed by RT to the chest wall should be applied.

The EBCTCG produced a meta-analysis of 10- and 20-year survival results from 40 randomized trials of radiotherapy for early breast cancer. It involved 20,000 patients, half with positive axillary nodes. After 2 years, radiotherapy reduced the annual mortality rate from breast cancer by 13.2% (SE 2.5), but increased those from other causes by 21.2% (SE 5.4). After subgroup analyses, they considered radiotherapy to be favorable only for younger women with a relatively high risk of local recurrence, but it was unfavorable for older women and for women of any age who were at particularly low risk for a local recurrence (such as those with small screen-detected cancers or with no evidence of nodal involvement after mastectomy with axillary clearance).<sup>[13]</sup> In an analysis by Hage et al.<sup>[14]</sup> of 4,018 early breast cancer cases from different trials, the median follow-up was 6.1–13.4 years. The results showed that in patients who underwent mastectomy and had 1–3 positive nodes, radiotherapy was associated with significantly improved survival rates ( $P<0.001$ ); however, in patients with 4 or more positive nodes, no significant association between radiotherapy and overall survival was found. The questions of how to choose patients for radiotherapy and how to improve the application of radiotherapy, requires further research for the answers.

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