Treatment Outcomes and Prognostic Factors of Patients with Breast Cancer: A Retrospective Review

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Objective: *To determine overall survival (OS), disease-free survival (DFS), and prognostic factors for survival in patients with invasive breast cancer treated with combined-modality therapy at BMA Medical College and Vajira Hospital.*

Material and Method: *The authors retrospectively analyzed the patient-tumor characteristic and treatment outcomes of 615 patients with invasive breast cancer who were treated in our radiation oncology division between 1997 and 2006. The authors used the Kaplan-Meier method to describe OS and DFS. The authors analyzed associations of patients and tumor characteristics with OS using the log-rank test and Cox proportional hazards models.*

Results: *The median follow-up time of 60 months, there were 46 loco-regional relapses, 108 distant relapses, and 129 deaths. The 5-year OS and DFS were 77.5% and 73.8%, respectively. The median times to local recurrence (LR) and to distant recurrence (DR) were 23 months (range, 10-67 months) and 24 months (range, 5-91 months). Characteristic statistically significant associated with decreased OS included lymphocascular invasion (LVI), estrogen receptor (ER) and progesterone receptor (PR) status, tumor stage, nodal stage, lymph node involvement $\geq$ 20%, and stage of disease.*

Conclusion: *Overall, the prognosis of patients with breast cancer was good. However, the subgroup of patients who presented with LVI, ER, and PR negative, T3-4 stage, N3-nodal stage, lymph node involvement $\geq$ 20%, and higher stage of disease had a poor long-term outcome.*

Keywords: *Breast neoplasms, Prognosis, Survival analysis, Treatment outcome*

Breast cancer is the most common malignancy in women worldwide, with 1,151,298 new cases identified throughout the world each year [1]. The American Cancer Society estimated that 184,450 new cases of invasive breast cancer will be diagnosed and 67,770 women will die of breast cancer in the United States in 2008[2]. In Thailand, it is the second most common cancer among women with an estimated incidence rate of 20.5 per 100,000 women[1].

Proliferative abnormalities of the breast are limited to the lobular and ductal epithelium.

Approximately 85%-90% of invasive carcinomas are ductal in origin[3]. Breast cancer represents a wide spectrum of tumors with a variety of clinical, biological, and genetic characteristics resulting in a considerable variation in prognosis[4-7]. The prognostic factors include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, tumor hormone receptor status, tumor HER2 status, patient age, and menopausal status[8,9]. Nodal status and tumor size are clearly among the strongest predictors of overall survival and metastasis[10].

Recent advances in the treatment of breast cancer have greatly increased the range of therapeutic options for patients. Combined modality therapy utilizing surgery, radiation, and systemic therapy is

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emerging globally as the standard of care for breast cancer[11]. Postmastectomy radiotherapy (PMRT) reduces the incidence of loco-regional recurrence by 50 to 75 percent[12-15]. The long-term effect of local tumor control in terms of overall survival has remained controversial[16,17], but recent studies reporting that PMRT not only reduced loco-regional recurrence but also improved overall survival[17-22]. Radiotherapy is an integral part of breast conservative therapy (BCT)[23,24]. Randomized clinical trials have established that adjuvant systemic therapy prolongs the survival of patients with breast cancer[25-27]. The reduction in the rates of recurrence and death persists beyond 15 years for all forms of systemic treatment[28-32].

The efficacy of diagnostic and therapeutic approaches has improved, resulting in decreased mortality and in improved palliation for women whose cure is not a possibility. Treatment outcome of breast cancer is so different in survival that it depends on the stage at diagnostic and other prognostic factors.

In the present study, the authors analyzed patients-tumor characteristic and treatment outcome in breast carcinoma patients at the radiation oncology division of the Bangkok Metropolitan Administration (BMA) Medical College and Vajira Hospital. The primary outcome for the presented analysis was overall survival. The secondary outcomes were disease-free survival, local recurrence and distant recurrence as first event and prognostic factors for survival.

Material and Method
Study sample

The authors retrospectively analyzed the data of 675 patients who were diagnosed with breast cancer at the radiation oncology division of the BMA Medical College and Vajira Hospital between January 1997 and December 2006. The authors excluded patients with non-invasive breast cancer and second primary breast tumor (n = 12).

The following patient and tumor factors were collected from the patient's charts, surgical records, and pathology reports, age, laterality, performance status, date of diagnosis, tumor size, number of axillary lymph nodes (ALNs), stage of disease, histology, histologic grade, lymphovascular invasion (LVI), estrogen receptor status (ER), progesterone receptor status (PR), Her-2 status, as well as the initial treatment with surgery, chemotherapy, radiotherapy, and/or hormonal therapy.

Patients were followed until January 31, 2009. Data on survival was collected from the charts; if this was insufficient, the patient's general practitioner was contacted for additional information.

Patients with inadequate records and loss of information for survival (n = 48) were also excluded, leaving only 615 for the analysis.

Outcome

The primary outcome was overall survival (OS), and the secondary endpoints were disease-free survival (DFS), local recurrence (LR), distant recurrence (DR) and prognostic factors for survival. OS was estimated from the date of diagnosis to the date of breast carcinoma-related death. DFS was computed from the date of the diagnosis to the first event of all types of recurrence or breast cancer-related death by the end of follow-up, January 31, 2009. LR was defined as the first site of tumor recurrence involving the ipsilateral chest wall and/or regional lymph node area. DR as the first site of tumor recurrence involving outside loco-regional area.

Treatment-related variables

Surgery was determined into four categories: no surgery, breast-conservative therapy (BCT), modified radical mastectomy (MRM), and unknown. Extent of axillary surgery was categorized as either zero, one to nine, or ten or more ALNs examined at ALN dissection (ALND)[33,34].

Systemic therapy was delivered at the discretion of the oncologist involved in each case. Typically, cyclophosphamide, methotrexate, fluorouracil, and doxorubicin-base regimens were administered. Most patients started chemotherapy after recovering from surgery, and radiation therapy was delivered after the completion of chemotherapy. Endocrine therapy was also delivered at the discretion of the oncologist involved in each case based on hormonal receptor status and menopausal status.

Radiotherapy was determined into two categories: not received radiotherapy and received radiotherapy. In the Radiotherapy group, an axillary field was added if there were four or more nodes positive. Radiotherapy patients were treated with Co-60 machine delivering 50-50.4 Gy in 25 to 28 fractions. Median and lateral tangential fields were used to treat the chest wall or entire breast. The breast tissue extent and treatment coverage of breast tissue were determined clinically. Wedges were the only form of compensation used. Boost dose was delivered in this select group of women. The authors also reviewed the duration of delivered radiotherapy after surgery.

Patients and Tumor-Related Variables

Patients characteristics including age at diagnosis, date of diagnosis, laterality, and menopausal status were analyzed. Tumor characteristics included size, number of positive ALNs, stage of disease[35,36], histology (ductal [including tubular and colloid], lobular [including mixed types], and other [including medullary], histologic grade (I, II, III, unknown) was performed according to the criteria of Bloom and Richardson[37], and LVI (present, absent, unknown)[38]. ER and PR status were determined by immuno-histochemical means on paraffin-embedded tissue and were taken as positive if more than 10% of tumor cells showed staining. Information on Her-2 by immuno-histochemistry was available in a minority of patients, mostly those treated after the year 2003. An immuno-histochemical score of 3 for Her-2 was accepted as Her-2 positively.

Statistical analysis

The Kaplan-Meier method was used to compute freedom from OS, DFS, LR, and DR[39]. Univariate survival analysis was performed using Kaplan-Meier curves and log-rank significance testing. Multivariate analysis of breast cancer related survival was performed using Cox proportional hazards model[40]. All p-values were two sided, and a p value of 0.05 was considered to indicate a statistically significant difference. Statistical tests were performed with SPSS 11.05 for Windows (SPSS, Chicago, IL).

Results
Patient and primary tumor data

The total number of breast cancer patients eligible for inclusion in the present study was 615. The median age at the time of diagnosis was 49 years (range, 25-87 years). Three hundred seventy one (60.3%) patients were premenopausal. Ninety-three percent of patients (n = 574) had invasive ductal carcinoma and 3% had invasive lobular carcinoma (n = 19). The tumor size ranged from 0.3 to 20 cm (median 3 cm). The median number of nodes examined was 14 (range, 3-44), and median number of involved nodes was 4 (range, 1-31). Fifty-six percent were ER positive, 53.5% were PR positive, and 25.3% were Her-2 positive. The majority of tumors were in stage II (47.5%). Sixty-four patients presented with stage I disease (10.4%), 226 with stage III (36.7%), and a small number were in stage IV (5.4%). Ninety-four percent of patients underwent surgery and 74% had adequate axillary lymph node dissection. Eighty-six percent of

Table 1. Patient and tumor characteristics

Characteristic	No. of patients	%
All patients	615	100
Age at diagnosis, years		
< 35	45	7.3
35-39	56	9.1
40-49	215	34.8
50-59	155	25.1
60-69	103	16.7
> 70	41	6.7
Menopausal status		
Pre-menopausal	371	60.3
Post-menopause	244	39.7
Histologic type		
Ductal	574	93.3
Lobular	19	3.1
Other	22	3.6
Tumor Grade		
1	63	10.2
2	251	40.8
3	299	48.6
Unknown	2	0.3
LVI		
Not present	380	61.8
Present	168	27.3
Unknown	67	10.9
ER status		
Negative	187	30.4
positive	238	38.7
Unknown	190	30.9
PR status		
Negative	132	21.5
Positive	152	24.7
Unknown	331	53.8
Her-2 status		
Negative	108	17.6
1+	9	1.5
2+	16	2.6
3+	45	7.3
Unknown	437	71.1
T stage		
T1	96	15.6
T2	354	57.6
T3	78	12.7
T4	87	14.1
N stage		
N0	251	40.8
N1	162	26.3
N2	119	19.3
N3	83	13.5
Positive Lymph nodes		
No. axillary dissection	33	5.4
Negative Lymph nodes	247	40.2
< 20%	124	20.2
≥ 20%	211	34.3

Table 1. (Cont.)

Characteristic	No. of patients	%
Stage		
I	64	10.4
II	292	47.5
III	226	36.7
IV	33	5.4

Fig. 1 Overall survival and disease-free survival by stage of disease

patients underwent radiotherapy, 81.8% received chemotherapy, and 68.3% received hormonal therapy. Stage I breast cancer patients, all patients who underwent BCT received radiotherapy and 74% of patients who underwent MRM received radiotherapy (30% had close-positive margin). See Table 1 for patient and tumor characteristics and Table 2 for treatment.
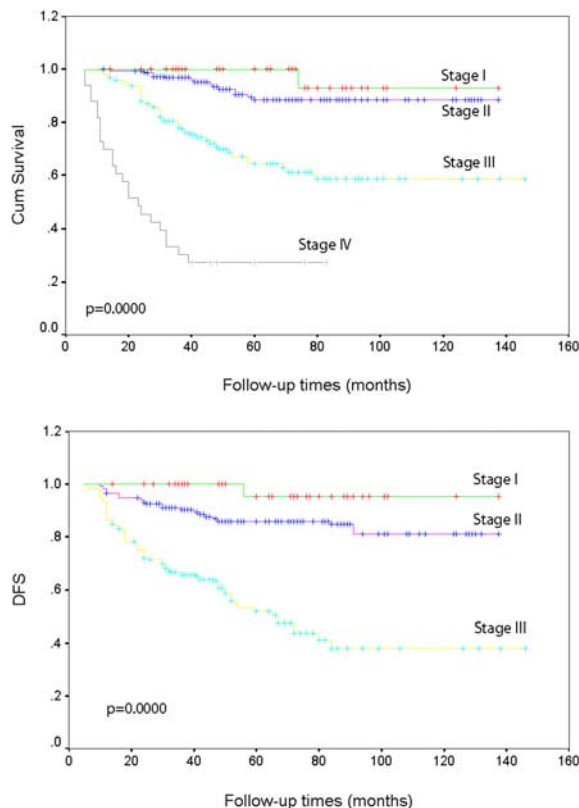
Clinical outcome
Survival

The median follow-up time for all patients was 60 months (range, 6-146 months). One hundred and twenty nine patients (21%) died of breast carcinoma-related cause in the follow-up period: sixty percent of all deaths occurred during the first three years. The 5-year OS was 77.5%, 100%, 88.5%, 64.3%, and 27.3% for all patients, stage I, stage II, stage III, and stage IV, respectively (p = 0.0000) (Fig. 1). Median survival for stage IV was 23 months.

In the MRM patients (n = 543), 5-yr OS was 79.4% and 62.8% for PMRT patients and no PMRT patients, respectively (p = 0.0000) (Fig. 2).

Table 3 shows the overall survival according to various factors. The factors that significantly correlated with lower rate of survival were as follows:

histologic ductal type, higher tumor grade, LVI, ER, and PR negative disease, higher tumor stage, higher nodal stage, lymph node involvement ≥ 20%, higher stage of disease, received radiotherapy, received chemotherapy, and received hormonal therapy.

When these factors were included in a multivariate Cox regression analysis of overall survival

Table 2. Treatment characteristics

Stage	Surgery type			Radiation therapy		Chemotherapy		Hormone Rx	
	No	BCT	MRM	No	Yes	No	Yes	No	Yes
All (n = 615)	25 (4%)	47 (7.7%)	543 (88.3%)	88 (14.3%)	527 (85.7%)	112 (18.2%)	503 (81.8%)	195 (31.7%)	420 (68.3%)
Stage I (n = 64)	-	18	46	12	52	33	31	16	48
Stage II (n = 292)	-	22	270	31	261	59	233	86	206
Stage III (n = 226)	-	5	221	24	202	15	211	78	148
Stage IV (n = 33)	25	2	6	21	12	5	28	15	18
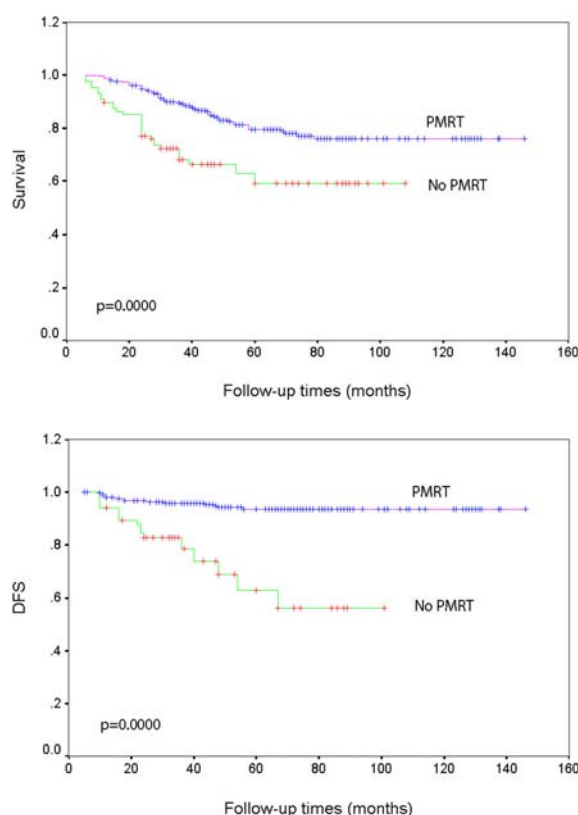
Fig. 2 Overall survival and disease-free survival of the modified radical mastectomy patients by PMRT

(Table 4), whereas LVI, ER, and PR status, tumor stage, nodal stage, lymph node involvement $\geq 20\%$, and stage of disease were statistically significant factors, histologic type and tumor grade no longer provided independent prognostic information.

Recurrence of disease

During the follow-up period, breast cancer recurred in 154 patients (25.1%). Of these, 108 patients (70.1%) had a recurrence in the form of distant disease, while 46 patients (29.9%) had a local-regional relapses (alone or in combination with distant metastases). The results are summarized in Table 5. The median times to LR and to DR were 23 months (range, 10-67 months) and 24 months (range, 5-91 months). The 5-year DFS in all patients was 73.8%, 5-yr DFS was 95.24% in patients with stage I, 85.79% in stage II, and 79% in stage III (p = 0.0000). In the MRM patients (n = 543), 5-yr DFS was 93.4% and 62.8% for PMRT patients and no PMRT patients, respectively (p = 0.0000).

Table 3. Univariate analysis of factors associated

Factor	5-yr rate	p-value
Age	-	NS
Histologic type		0.045
Ductal	77.14	
Lobular	100.00	
Other	80.00	
Tumor grade		0.0000
Grade I	100.00	
Grade II	78.94	
Grade III	70.90	
LVI		0.0000
Absent	84.89	
Present	64.62	
Unknown	68.09	
ER status		0.0001
Negative	73.80	
Positive	86.54	
Unknown	69.65	
PR status		0.0000
Negative	72.89	
Positive	92.92	
Unknown	73.51	
Her-2 status		NS
T stage		0.0000
T1	87.40	
T2	85.05	
T3	78.72	
T4	35.92	
N stage		0.0000
N0	93.55	
N1	71.74	
N2	67.96	
N3	53.03	
Positive lymph nodes		0.0000
No axillary disection	80.00	
< 20%	88.22	
$\geq$ 20%	65.86	
Stage		0.0000
I	100.00	
II	88.48	
III	64.34	
IV	27.27	
Radiation		0.0000
Not received	59.25	
Received	80.47	
Chemotherapy		0.0183
Not received	86.79	
Received	75.14	
Hormonal therapy		0.0149
Not received	73.21	
Received	79.46	

Table 4. Prognosis factors for overall survival in Cox regression analyses

Feature	Multivariate analysis		
	p-value	Relative risk	95% CI
Histologic type (Ductal vs. Lobular)	NS	-	-
Tumor grade (Grade I & II vs. Grade III)	NS	-	-
Lymphovascular invasion (present vs. absent)	<0.00001	1.64	1.28-2.09
ER status (negative vs. positive)	<0.0001	1.29	1.11-1.48
PR status (negative vs. positive)	0.004	1.22	1.06-1.40
T stage (T1-2 vs. T3-4)	<0.0001	1.37	1.12-1.67
N stage (N1-2 vs. N3)	0.002	1.32	1.16-1.46
Positive lymph node $\geq$ 20%	<0.0001	1.16	1.05-1.27
Stage (I vs. II vs. III vs. IV)	<0.0001	1.35	1.24-1.47

Table 5. Site of recurrence

Site	All stage (n = 615)		Stage I (n = 64)		Stage II (n = 292)		Stage III (n = 226)		Stage IV (n = 33)	
	n	%	n	%	n	%	n	%	n	%
None	430	73.6	62	96.9	251	86.0	115	50.9	2*	6.1
Loco-regional	46	7.9	2	3.1	19	6.5	25	11.1		
Distant	108	18.5	-	-	22	7.6	86	38.1		
Bone	40	6.9	-	-	7	2.4	33	14.6		
Liver	23	3.9	-	-	4	1.4	19	8.4		
Brain	8	1.4	-	-	1	0.4	7	3.1		
Lung	35	6.0	-	-	8	2.8	27	12.0		
Other	2	0.3	-	-	2	0.7	-	-		

* In case of complete response after palliative chemotherapy

Discussion

In the present study, the authors focused on the patients-tumor characteristics and outcomes of 615 patients with breast carcinoma. The authors included all patients that were evaluated in our radiation oncology division at initial presentation. The incidence of breast cancer increases with age, but the rate of increase incidence was slow after menopause[41], which indicated the same pattern in the present study. The presented series showed that invasive ductal carcinoma was the most common histological type (93.3%), which is similar to other publications (85%-90%)[3].

In the present study, the 5-year OS and DFS were 77.5% and 73.8%, respectively, in line with other studies[20,35,36,42,43]. On the other hand, several predictive factors have been described to identify breast cancer patients with a relatively worse prognosis. Some of these factors were LVI, ER status, PR status, tumor stage, nodal stage, lymph node involvement $\geq$ 20%, and stage of disease[43,44].

5-yr overall survival for stage I, II, III, and IV were 97.5%, 88.5%, 64.4%, and 27.3%, respectively. The survival outcome favorably compared with 5-year overall survival for stage I, II, III, and IV of 98%, 76-88%, 49-56%, and 16%, respectively as reported by AJCC[35,36].

NSBP trials[45-48] treated primarily with local-regional therapy alone revealed 5-yr survival rates of 82.8%, 73%, 45.7%, and 28.4% for patients with zero, one to three, four to twelve, or > thirteen involved nodes, respectively. The present result is similar to the above mentioned reports showing, worse overall survival in patients with more involved nodes.

In the present series, the majority of patients presented with a T2 stage and a median tumor size of 3 cm. Carter et al found tumor size to be a significant independent prognostic factor for survival[49]. In the present analysis, tumor size based on T stage was significant for overall survival.

LVI was associated with a significance worse overall survival which agreed with several studies[38,50,51]. Also in the present series, 5-year OS of patients with LVI and absent LVI was reported as 64.6% and 84.9%. Patients with ER positive and PR positive tumor in the present study were 38.7% and 24.7%, respectively. Crowe et al found ER/PR positive tumors were significantly better in 10-year OS (p = 0.001)[52]. ER status was a significant prognosticator in the presented analysis.

A similar result was reported by Katz et al[53] who identified patients with less than 20% involved nodes and tumor size less than 5 cm. were a low risk for local recurrence.

In others series, the PMRT reduced the incidence of loco-regional recurrence by 50 to 75%[12-15]. The long-term effect of local tumor control in terms of overall survival has remained controversial[16,17], but recent studies reported that PMRT not only reduced loco-regional recurrence but also improved overall survival[17-22]. In the present study, PMRT improved both OS and DFS. Only 6% of PMRT patient had loco-regional recurrences. The present study confirmed an increase of OS due to improved local control. It seemed possible because of greater benefit from PMRT in node-positive patients, in the present series 60% of patients were node-positive.

During recent decades, breast carcinoma has been accepted as a systemic disease. The results of several studies showing systemic treatment improved survival in breast cancer patients. In the present study, patients who received chemotherapy and hormonal therapy had significantly improved in survival. These results agreed with other studies[28-32].

The present study had certain limitations. First, in any retrospective observation study, unobserved confounders that are correlated with receipt of the invitation and with the outcome of interest may introduce treatment assignment bias. Another possible limitation to the current study related to the relatively small numbers appeared in certain subgroups. Finally, the authors have provided results at only 5 years. Longer follow-up may be needed to assess outcomes.

In conclusion, the authors have demonstrated the 5-year OS for most patients with breast cancer after multimodality treatment. Overall, the prognosis of patients with breast cancer was good. However, a subgroup of patients who presented with LVI, ER, and PR negative, T3-4 stage, N3-nodal stage, lymph node involvement $\geq 20\%$, and higher stage of disease had a poor long-term outcome.

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การศึกษาย้อนหลังถึงผลการรักษาและปัจจัยที่มีผลต่อการรักษาของผู้ป่วยมะเร็งเต้านม

ธนาทิพย์ ตันติวัตนะ, มาริสา จงธนากร, คณิศา รองศรีแย้ม, กันยรัตน์ กตัญญู

วัตถุประสงค์: การศึกษานี้เพื่อศึกษาอัตราการอยู่รอด, อัตราการอยู่รอดโดยปราศจากโรค และ ปัจจัยที่มีผลต่อ การรักษาโรคมะเร็ง ของผู้ป่วยมะเร็งเต้านมที่มาเข้ารับการรักษาที่วิทยาลัยแพทยศาสตร์กรุงเทพมหานคร และวชิรพยาบาล

วัสดุและวิธีการ: ทำการศึกษาย้อนหลังในผู้ป่วย 615 รายที่ได้รับการวินิจฉัยว่าเป็นมะเร็งเต้านมชนิด *Invasive carcinoma* ที่มาเข้ารับการรักษาที่แผนกรังสีรักษาและมะเร็งวิทยา ตั้งแต่ปี พ.ศ. 2540 ถึงปี พ.ศ. 2549 โดยทำการ วิเคราะห์ผลการรักษา และคุณลักษณะของผู้ป่วยและคุณลักษณะของมะเร็ง โดยใช้ *Kaplan Meier* และเปรียบเทียบ ทางสถิติโดยใช้ *log rank test* และ *Cox proportional hazards models*

ผลการศึกษา: ค่ามัธยฐานของการติดตามผลการรักษา คือ 60 เดือน พบว่า ผู้ป่วย 46 ราย พบการกลับเป็นซ้ำ เฉพาะที่ ผู้ป่วย 108 รายพบการแพร่กระจายโรคไปที่อวัยวะอื่น และ ผู้ป่วย 129 ราย เสียชีวิตจากโรคมะเร็งเต้านม อัตราการอยู่รอด และอัตราการอยู่รอดโดยปราศจากโรค 5 ปี ของผู้ป่วยทั้งหมดคือ ร้อยละ 77.5 และ 73.8 ค่ามัธยฐาน ของเวลาการกลับเป็นซ้ำเฉพาะที่ และค่ามัธยฐานของเวลาการแพร่กระจายของโรคไปที่อวัยวะอื่นคือ 23 เดือน และ 24 เดือน ปัจจัยที่มีนัยสำคัญทางสถิติที่มีผลต่อการพยากรณ์อัตราการอยู่รอดที่ต่ำ ได้แก่ *lymphovascular invasion (LVI)*, ภาวะตัวรับฮอร์โมนเอสโตรเจน และ โปรเจสเตอโรน, ระยะขนาดก้อนมะเร็ง, ระยะต่อมน้ำเหลือง, การมีการแพร่ กระจายของตัวโรคไปที่ต่อมน้ำเหลืองมากกว่า ร้อยละ 20 และ ระยะของโรคมะเร็ง

สรุป: โดยภาพรวมนั้น มะเร็งเต้านมนั้นมีพยากรณ์โรคที่ดี แต่อย่างไรก็ตามในกลุ่มของผู้ป่วยที่มีปัจจัยเสี่ยง ได้แก่ *LVI*, ภาวะตัวรับฮอร์โมนเอสโตรเจน และโปรเจสเตอโรนเป็นบวก, ระยะที่ 3 และ 4 ของขนาดก้อนมะเร็ง, ระยะที่ 3 ของต่อมน้ำเหลือง, การมีการแพร่กระจายของตัวโรคไปที่ต่อมน้ำเหลืองมากกว่า ร้อยละ 20 และระยะของโรคมะเร็ง พบว่ามีผลการรักษาที่แย่กว่า