Recurrence and Death from Breast Cancer after Complete Treatments: An Experience from Hospitals in Northern Thailand

Rungnapa Chairat MNS*,***, Adisorn Puttisri MD**, Asani Pamarapa MD***, Nongnoot Wongrach MNS****, Chamaiporn Tawichasri MSc*****, Jayanton Patumanond MD, PhD******, Apichat Tantraworasin MD, PhD*******, Chaiyut Charoentum MD********

** PhD Program in Clinical Epidemiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*
*** Department of General Surgery, Sawanpracharak Hospital, Nakorn Sawan, Thailand*
**** Department of General Surgery, Uttaradit Hospital, Uttaradit, Thailand*
***** Department of General Surgery, Lampang Hospital, Lampang, Thailand*
****** Clinical Epidemiology Society at Chiang Mai, Chiang Mai, Thailand*
******* Clinical Research Center, Faculty of Medicine, Thammasart University, Bangkok, Thailand*
******** Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*
********* Department of Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

Objective: *To describe the pattern of disease progression and to describe locoregional recurrence, distant recurrence, and death rates in breast cancer patients after complete treatment.*
Material and Method: *Medical records of women diagnosed with breast cancer at two university affiliated tertiary care hospitals in the Northern Thailand that had complete treatments between 2006 and 2010 were traced. Extracted key information included patient clinical profiles and documented recurrence of cancer. The causes of death were verified from breast cancer case registration database, death certificates through The Ministry of Internal Affairs' civil registration, by direct telephone contact, or by distributed prepaid postcards.*
Results: *Medical records of 829 women diagnosed with breast cancer without prior evidence of distant metastasis, and had complete recommended treatment were included. Six hundred thirty seven women had not experienced any events up to the end of the follow-up (76.8%). The first occurring events were focused and categorized into three distinct types, locoregional recurrence (n = 83, median follow-up time = 34.2 months), distant recurrence (n = 78, median follow-up time = 35.4 months), and death without any evidences of locoregional or distant recurrences (n = 12, median follow-up time = 36.7 months). Distant recurrence after locoregional recurrence was reported (n = 33). There were109 patient who had died (breast cancer related death) up to the end of the follow-up (13.2%). The three types of consecutively occurring deaths were death after locoregional recurrence without any distant recurrences (n = 15), death after distant recurrence with locoregional recurrence (n = 21), and death after documented distant recurrence without any locoregional recurrences (n = 61).*
Conclusion: *The trend was that the rate of the first occurring locoregional recurrence was slightly higher than that of distant recurrence. The death rate in patients without any recurrences was much lower than in those experiencing prior recurrences. The rates of disease progression from local recurrence to distant recurrence and to death were approximately 5 to 7 times faster in patients who had experienced earlier progressions.*

Keywords: *Breast cancer, Locoregional recurrence, Distant recurrence, Survival, Death*

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Breast cancer is still one of the leading causes of death among women worldwide. The incidence of breast cancer varies from region to region, but there is an upward trend in developing countries[1]. In Thailand, breast cancer is becoming the most common cancer in women. The incidence increased from 37.9/100,000 to 40.8/100,000 between 2007 and 2011[2].

The effective treatment of early breast cancer is consisted of surgery, chemotherapy, hormonal therapy, HER-2 targeted therapy and radiation. Surgery is considered very crucial due to its removal of the cancer and the ability to stage the cancer. The majority of patients were operated on with a modified radical mastectomy (MRM) or breast conservation surgery (BCS) combined with radiation, or surgery followed

Correspondence to:
Tantraworasin A, Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.
Phone: 053-945-767
E-mail: ohm_med@hotmail.com

by adjuvant chemotherapy and/or hormonal therapy, HER-2 targeted therapy and/or radiation. Decision on types of treatment depends on the stage of the cancer, its prognosis, the hormone, and HER-2 receptor status of the tumor[3,4]. The treatment was aimed at local control of the cancer and prevention or reduction of local recurrence, distant recurrence (or metastasis) and mortality[4,5].

Even with the advance of breast cancer treatments, many studies reported locoregional recurrence of the cancer at the original sites, mainly the chest wall and ipsilateral regional lymph nodes, which could be as high as 11 to 27%[6,7]. Distant recurrence or metastasis to other sites was reported in 11% of cases, mainly to the lungs, liver, bones and brain[6]. Isolated reports of cancer recurrence after completion of the treatment varied vastly. This was thought to be due to the prognostic patterns[8].

Survival is the most important long-term outcome of cancer treatments. The mortality rates in under-developed or developing countries are much higher than in developed countries[9]. In Thailand, breast cancer mortality was 6.8/100,000 to 8.4/100,000 between 2007 and 2011, showing a rising trend[2]. Even with many statistical reports on mortality/survival of breast cancer, which varies vastly from region to region[7,10], very few studies combined the overall perspectives of the disease progression of breast cancer, from treatments to recurrence until death.

The authors explored the complete pattern of disease progression of breast cancer after complete treatment in order to predict the timing of tumor recurrence or tumor progression.

Material and Method

Patients were women diagnosed with breast cancer (ICD-10), who had complete treatment at two university-affiliated tertiary-care hospitals in Lampang and Uttaradit located in the Northern Thailand between 2006 and 2010. Patients presented with breast lumps and verified as breast cancer by tissue pathology (biopsy or operative specimen), and/or mammography, and/or ultrasonography and/or FNAC. All patients were followed-up for breast cancer surveillance to monitor for recurrence. The routine surveillance of breast cancer comprise of 1) history eliciting of symptom and physical examination, 2) mammography, and 3) breast self-examination. Computed tomography scan (CT scan) or ultrasonography of the liver, bone scan, tumor marker investigation were not recommended as a routine test, but were recommended for confirmation of the suspected recurrence. The exclusion criteria were patients who were diagnosed with breast cancer presenting with metastasis at first diagnosis (n = 8), or women with a history of other cancer. Medical records of the patients were reviewed and traced until the last day of follow-up. Key information included patient characteristics and history (age, type of surgery, tumor size, positive axillary lymph nodes, receptor status (ER, PR and HER2 receptor), stage, treatment, and prognosis). Locoregional recurrence is defined as any reappearance of cancer in the ipsilateral regio mammaria, i.e. residual breast, chest wall, or skin overlying the chest wall and refers to tumor involving the ipsilateral axillary lymph nodes, supra/infraclavicular lymph nodes, or internal mammary lymph nodes. Locoregional recurrence, distant recurrence, and death were taken from the cancer case registration database. The causes of cancer related death were verified from the breast cancer case registration database, death certificates through The Ministry of Internal Affairs' civil registration, by direct telephone contact, or by distributed prepaid postcards. The study was approved by The Research Ethics Committee, Faculty of Medicine, Chiang Mai University and The Research Ethics Committee of Lampang and Uttaradit Hospitals. Informed consent was not required in this retrospective data collection. Patient identification or traceable information were kept confidential and omitted in all parts of analysis.

Statistical analysis

The rates of locoregional recurrence, distant recurrence, and death were calculated based on individual patient follow-up time, and were described in a flow chart. The incidence rate was calculated by the number of specific events divided by total person-times of follow-up in that specific event category. This was used instead of the usual median survival time calculation due to the relatively short follow-up time in the study. The time to the first occurring events was calculated by Nelson-Aalen's estimates of cumulative hazards and was graphically displayed.

Results

The medical records of 829 women diagnosed with breast cancer without prior evidences of distant metastasis, and had been completely treated were included. Patient age varied from 25 to 90 years (mean = 53.0±11.5 years). Modified radical mastectomy (MRM) was the most common type of surgery

performed in the present study (n = 711, 85.8%). Tumor size was between 0.5 and 15 cm (mean = 3.1±1.8 cm). Breast cancer staging was stage I, stage II and stage III in 29.7%, 55.4% and 14.9% respectively. The majority of patient had ≤3 positive axillary lymph nodes (n = 630, 79.0%). The percentage of positive ER receptor was 61.3%, positive PR receptor was 54.2%, and positive HER2 receptor by IHC was 42.6% (Table 1). The most common adjuvant chemotherapy given were FAC regimen (5-Fluorouracil, Adriamycin and Cyclophosphamide), CMF regimen (Cyclophosphamide, Metotrexate and 5-Fluorouracil), and AC regimen (Adriamicin and Cyclophosphamide). Adjuvant chemotherapy was given to 87.2% of patients. Seventy-nine patients were treated with neo-adjuvant chemotherapy. The most common neo-adjuvant chemotherapy given were FAC regimen (n = 46, 58.2%) and AC regimen (n = 18, 22.8%). Fifty patients in the present study received adjuvant taxanes (paclitaxel or docetaxel) and six patients received adjuvant anti HER-2 monoclonal antibody (trastuzumab). Adjuvant hormonal therapy was given to 63.6% of patients. The most common adjuvant endocrine therapy given was tamoxifen. All of breast-conserving surgery and eighty patients in stage III had radiotherapy (65.6%) (Table 1).

Six hundred thirty seven women had not experienced any events up to the last follow-up days (76.8%). The first occurring events were focused and categorized into three distinct types, locoregional recurrence (n = 83, rate = 3.35% per year, median follow-up time = 34.2 months), distant recurrence (n = 78, rate = 3.12% per year, median follow-up time = 35.4 months), and death without any evidences of locoregional or distant recurrences (n = 12, rate = 0.46% per year, median follow-up time = 36.7 months). Distant recurrence after locoregional recurrence was reported (n = 33, rate = 22.11% per year). Site of distant recurrence were lung, liver, bone, brain and multiple organs in 25.2%, 23.4%, 12.6%, 8.1% and 30.7% respectively. Three types of consecutively occurred deaths were; death after locoregional recurrence without any distant recurrences (n = 15, rate = 15.19% per year), death after distant recurrence with locoregional recurrence (n = 21, rate = 87.33% per year), and death after documented distant recurrence without any locoregional recurrences (n = 61, rate = 100% per year) (Table 2, Fig. 1).

Comparing among first occurring events showed that survival from death was the highest. Survival from locoregional recurrence and survival from distant recurrence were somehow similar, although the survival from distant recurrence seemed to be higher (Fig. 2).

Table 1. Characteristics of patients

Characteristics	Total n = 829 mean ± SD or number (%)
Age (years)	53.0±11.5
Type of surgery	
MRM	711 (85.8)
Simple mastectomy	58 (7.0)
BSC	60 (7.2)
Tumor size (cm)	3.1±1.8
Positive axillary lymph nodes (n = 797)	
≤3	630 (79.0)
>3	167 (21.0)
Receptor status	
ER receptor (n = 812)	
Positive	498 (61.3)
Negative	314 (38.7)
PR receptor (n = 813)	
Positive	441 (54.2)
Negative	372 (45.8)
HER2 receptor (n = 752)	
Positive	320 (42.6)
Negative	432 (57.4)
Stage and treatment received	
Stage 1 (n = 246)	
Chemotherapy	188 (76.4)
Hormonal therapy	171 (69.5)
Radiation therapy	56 (22.8)
Stage 2 (n = 459)	
Chemotherapy	414 (90.6)
Hormonal therapy	290 (63.2)
Radiation therapy	166 (36.2)
Stage 3 (n = 124)	
Chemotherapy	117 (95.9)
Hormonal therapy	66 (53.2)
Radiation therapy	80 (65.6)
Prognosis (first occurred event)	
Survive/censored	637 (76.8)
Recurrence	161 (19.4)
Locoregional	83 (10.0)
Distant	78 (9.4)
Death	31 (3.8)
Cancer	12 (1.5)
Other causes	19 (2.3)

% calculated from non-missing data

MRM = modified radical mastectomy; BCS = breast-conserving surgery; ER receptor = estrogen receptor; PR receptor = progesterone receptor; HER2 receptor = human epidermal growth factor receptor 2

Table 2. Follow-up time and incidence rate of first occurring events; locoregional recurrence (LRR), distant recurrence (DR) or death (n = 829)

Parameters	LRR	DR	Death
Total follow-up time: patient-months	29,749.1	30,013.5	30,977.1
Average follow-up time (months) (mean ± SD)	35.9±19.1	36.2±19.2	37.4±19.0
Median follow-up time (months) (IQR)	34.2 (20.9-51.7)	35.4 (20.8-51.9)	36.7 (22.9-52.7)
Number of events	83	78	12
Incidence rate (% per months) (95% confidence interval)	0.28 (0.23-0.35)	0.27 (0.21-0.33)	0.04 (0.02-0.07)

Discussion

The present study showed that when confined to the first occurring events, the rate of locoregional recurrence and that of distant recurrence were very similar, although the rate of locoregional recurrence appeared to be insignificantly higher. Very few studies reported such comparisons within the same studies[6,7,10-27].

Locoregional recurrence was a common pitfall in breast cancer treatments. It was also a direct predictor for mortality[28]. Even after the standard cancer treatments, the present study showed that locoregional recurrence was still reported with the rate of 3.35% per year. The corresponding figures from previous studies varied from 5.2 to 39.8%[6,7,10-17].

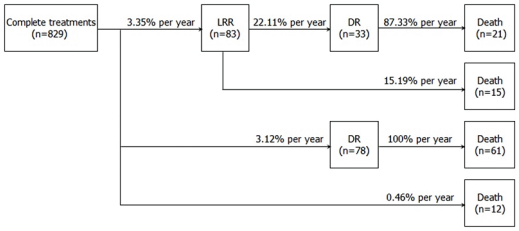

Fig. 1 Types and rates of disease progression; locoregional recurrence (LRR), distant recurrence (DR), or death after complete treatments.

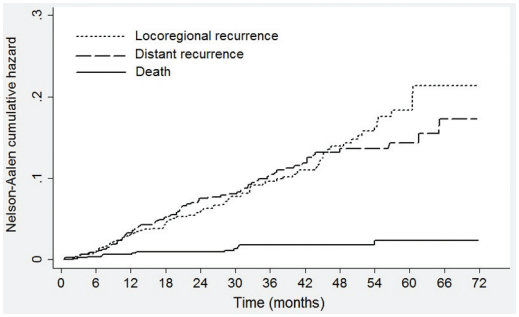

Fig. 2 Locoregional recurrence (LRR), distant recurrence (DR) or death after complete treatments (first occurring events).

Distant recurrence was the major cause of death in breast cancer. When confined to the first occurring events, the rate was much lower than from that occurring as subsequent events after locoregional recurrence (3.12 vs. 22.11% per year). The rate of distant recurrence in other studies varied from 11.4 to 43.3[6,16,18,19]. After modified radical mastectomy (MRM) or breast conservation surgery (BSC), 10.0 to 25.0% of the patients experienced locoregional and distant recurrence[20]. Distant recurrence was reported in patient experiencing prior locoregional recurrence with a rate of 56.8 to 66.0%[18,21]. Factors predicting locoregional and/or distant recurrence have not been fully identified at present[21].

Mortality/survival is the finite clinical endpoint in breast cancer after complete treatment. Our study reported 76.8% of patients experienced no event, or progression free survival, until the last day of follow-up (median follow-up time = 38.6 months). One previous study also reported 5-year progression free survival in 76.0% of the cases[22]. However, the rate of death in those without any documented recurrence (0.46% per year) was much lower than those who experienced only locoregional recurrence (15.19% per year), those experiencing distant recurrence after locoregional recurrence (87.33% per year) or those experiencing only distant recurrence without prior locoregional recurrence (100% per year). The death rate of patients experiencing locoregional recurrence (15.19% per year) was approximately five times higher than those without locoregional recurrence. Distant recurrence and death after distant recurrence seemed to be superimposing as one may see that the rate of death after distant recurrence was 100%. It seemed that death and distant recurrence in these patients occurred at almost the same time or at least within a very close time interval, which may imply that distant recurrence was the "surrogate" for death[19]. This may infer that the rate of death without any documentation of recurrence (0.46% per year) was somehow similar to

the rate of distant recurrence (3.12% per year). One study reported 48.0% mortality after locoregional recurrence without documented distant recurrence[23]. The fact that the mortality rate in those experiencing only distant recurrence (100% per year) was higher than in those experiencing both locoregional and distant recurrence (87.33% per year) might be explained by relatively poorer prognosis of patients experiencing early locoregional recurrence[28]. On the other hand, patients with locoregional recurrence might be treated and monitored more closely for disease progression[17], resulting in a consequent lower mortality rate. Previous studies reported very wide ranges of mortality rates and very wide ranges of median survival times, from as short as weeks to as long as many years[7,10,22-27].

The present study demonstrated that cancer progression (locoregional recurrence, distant recurrence, and death) varied in specific disease progression patterns. This could be due to the fact that breast cancer is not only a single disease identity, but a heterogeneous disease representing a broad spectrum of biologic potential[8,13,29]. Any clinical outcome therefore, depended on different prognostic patterns[8] and on individual patient response to treatment[10]. Rapid disease progression in patients experiencing recurrence may reflect aggressive disease phenotypes[21]. The most interesting key finding in our study was that the mortality rate in patients with locoregional recurrence was as high as five fold compared to those without locoregional recurrences. A study on prognostic indicators for such recurrence and death should be encouraged in order to identify patients where cancer is more likely to progress rapidly. More specific, more selective or more aggressive treatment may be required in such patients[30].

Conclusion

One observed trend was that the rate of first occurring locoregional recurrence was higher than that for distant recurrence. The death rate in patients without any type of documented recurrence was much lower than those experiencing any type of recurrence. The rates of disease progression from local recurrence to distant recurrence and to death were approximately 5 to 7 times faster in patients who had experienced earlier progression.

What is already known on this topic?

The death rate in patients without any recurrences was much lower than in those experiencing prior recurrences.

What this study adds?

The rate of distant recurrence in patients with prior local recurrence was approximately seven times more than those without prior local recurrence. The death rate in patients with prior local recurrence was approximately five times more than those without prior local recurrence.

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Potential conflicts of interest

None.

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การกลับเป็นซ้ำและการเสียชีวิตของผู้ป่วยมะเร็งเต้านม

รุ้งนภา ชัยรัตน์, อดิศร พุทธิศรี, อัสนี ภมะราภา, นงนุช วงศ์ราษฎร, ชไมพร ทวิชศรี, ชยันตร์ธร ปทุมานนท์, อภิชาติ ตันตระวรศิลป์, ชัยยุทธ เจริญธรรม

วัตถุประสงค์: *เพื่ออธิบายรูปแบบการดำเนินโรคและศึกษาอัตราการเกิดกลับเป็นซ้ำและอัตราการเสียชีวิตของผู้ป่วยมะเร็งเต้านมภายหลังการรักษา*

วัสดุและวิธีการ: *ศึกษาผู้ป่วยหญิงที่ได้รับการวินิจฉัยว่าเป็นมะเร็งเต้านมภายหลังการรักษา ที่โรงพยาบาลศูนย์ลำปาง และโรงพยาบาลอุตรดิตถ์ ระหว่าง พ.ศ. 2549 ถึง พ.ศ. 2553 รวบรวมข้อมูลที่สำคัญ ได้แก่ ข้อมูลการรักษา การกลับเป็นซ้ำ การเสียชีวิตจากเวชระเบียน และมีการตรวจสอบสาเหตุของการเสียชีวิต วิเคราะห์และแสดง follow-up time, incidence rate และ 95% confidence interval ของการกลับเป็นซ้ำและการรอดชีพ/การตาย แสดง failure curve ของการเกิดเหตุ ภายหลังการรักษาด้วย Nelson-Aalen's estimates of cumulative hazards*

ผลการศึกษา: *ผู้ป่วยมะเร็งเต้านมจำนวน 829 ราย มีผู้ป่วยที่อยู่รอดโดยไม่เกิดเหตุการณ์ใด ๆ เลย จำนวน 637 ราย (ร้อยละ 76.8) ที่เหลือการดำเนินของโรคแบ่งผู้ป่วยกลุ่มเกิดเหตุออกเป็น 3 กลุ่ม คือ กลุ่มที่หนึ่งผู้ป่วยกลับเป็นซ้ำเฉพาะที่จำนวน 83 ราย มีการแพร่กระจายของโรคไปอวัยวะอื่นจำนวน 78 ราย ผู้ป่วยเสียชีวิตจากมะเร็งเต้านมโดยไม่มีการบันทึกไว้ในเวชระเบียนว่ามีการกลับเป็นซ้ำ 12 ราย มีผู้ป่วยพัฒนาไปเป็นมีการแพร่กระจายของโรคไปอวัยวะอื่นโดยที่เคยมีการกลับเป็นซ้ำเฉพาะที่มาก่อน 33 ราย ส่วนการเสียชีวิตที่ไม่ใช่ first occurred events ได้แก่ เสียชีวิตหลังกลับเป็นซ้ำเฉพาะที่โดยไม่มีการแพร่กระจายของโรคไปอวัยวะอื่น 15 ราย เสียชีวิตหลังการแพร่กระจายของโรคไปอวัยวะอื่นที่มีการกลับเป็นซ้ำเฉพาะที่มาก่อน 21 ราย และเสียชีวิตหลังการแพร่กระจายของโรคไปอวัยวะอื่นโดยไม่มีการกลับเป็นซ้ำเฉพาะที่ 61 ราย*

สรุป: *อัตราการกลับเป็นซ้ำเฉพาะที่ที่เกิดขึ้นครั้งแรกมีแนวโน้มสูงกว่าการแพร่กระจายของโรคไปอวัยวะอื่นที่เกิดขึ้นครั้งแรก อัตราการเสียชีวิตของผู้ป่วยมะเร็งเต้านมที่ไม่มีการกลับเป็นซ้ำเกิดขึ้นมาก่อนมีแนวโน้มต่ำกว่าคนที่มีการกลับเป็นซ้ำมาก่อน และอัตราความก้าวหน้าของโรคจากการกลับเป็นซ้ำเฉพาะที่ไปสู่การแพร่กระจายของโรคไปอวัยวะอื่นและการเสียชีวิตของผู้ป่วยมะเร็งเต้านมมีแนวโน้มเกิดขึ้นเร็วกว่าประมาณ 5 ถึง 7 เท่า ในคนที่มีการกลับเป็นซ้ำมาก่อนเมื่อเทียบกับผู้ป่วยที่ไม่มีการกลับเป็นซ้ำ*