Prognostic Factors of Local-Regional Recurrence in Patients with Operable Breast Cancer in Asia: A Meta-Analysis

Wirisma Arif Harahap1, Ricvan Dana Nindrea2,3

1Surgical Oncology Division, Faculty of Medicine, Universitas Andalas, Dr M Djamil, General Hospital Padang, West Sumatera Province, Indonesia; 2Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta City, Indonesia; 3Department of Public Health, Faculty of Medicine, Universitas Andalas, Padang City, Indonesia

Abstract

BACKGROUND: Cause of recurrence of breast cancer is multifactorial. Also, the occurrence of breast cancer in Asian patients has some different factors from the recurrence of breast cancer in western countries.

AIM: This study aims to determine the prognostic factors of local-regional recurrence in patients with operable breast cancer in Asia.

METHODS: The authors conducted a meta-analysis of published research articles published in an online database of PubMed, ProQuest and EBSCO between January 2000 and July 2018. Pooled risk ratios (RR) were calculated using fixed and random-effect models. Data were processed by using Review Manager 5.3 (RevMan 5.3).

RESULTS: This study reviewed 879 articles. There were 11 studies conducted a systematic review then continued by meta-analysis of relevant data with total patients involved were 5,213 patients. The prognostic factors found of local-regional recurrence in patients with operable breast cancer were Nodal (N) stage with the highest risk ratio (RR = 6.35 [95% CI 3.78-10.67]) followed by HER2 positive (RR = 2.14 [95% CI 1.16-3.97]), stage of cancer (RR = 1.82 [95% CI 1.44-2.31]), tumor size (RR = 1.55 [95% CI 1.04-2.31]), tumor grade (RR = 1.43 [95% CI 1.23-1.65]), PR status (RR = 0.65 [95% CI 0.48-0.88]) and the least was ER status (RR = 0.60 [95% CI 0.39-0.91]). Homogeneity of variance was found in N stage, tumor size and tumor grade for recurrence of operable breast cancer.

CONCLUSION: This meta-analysis confirmed the correlation of N stage, HER2, stage of cancer, tumour size, tumour grade, ER and PR status with recurrence in patients with operable breast cancer in Asia.

Introduction

Breast cancer, the most common cancer in women, is highly heterogeneous with various clinical courses and outcomes [1], [2]. The disease recurrence and prolong survival have been reduced by several proven adjuvant systemic therapies, including chemotherapy, hormonal treatment, and anti-HER2 (human epidermal receptor). Breast cancers are classified into genomically defined subgroups, including subtypes: luminal A, luminal B, HER2+, and triple-negative (TN) tumours. Clinical courses, patterns of metastasis, and prognosis of these subgroups may be various. Most relapses happen during the first 5 years after diagnosis, even though the late recurrence of luminal breast cancer has been reported.

Breast cancer may recur 5-10 years after first treatment. High-bulk disease, high proliferative index, and HER2-positive malignancies correlated to recurrence earlier than 10 years, whereas progesterone receptor-positive (PR+) group was associated with relapse later than 10 years [3], [4]. The term of local-regional recurrence refers to recurrence either in ipsilateral breast structure after lumpectomy, in chest wall recurrence after mastectomy or recurrence in axillary or supraclavicular lymph nodes (less common intraclavicular and/or internal mammary nodes).
Approximately, local recurrence develops in 10-15% of stage I-II of breast cancer after breast-conserving surgery and 10-20% chest wall recurrence in the cancer stage I-IIIA after mastectomy [4].

Annual follow-up visits are usually scheduled for patients who have five disease-free years or completed hormonal treatment. Some of those patients develop rapid and extensive metastasis during the follow-up intervals; with few of these patients can not undergo chemotherapy due to organ dysfunction or unwell performance status as a result of systemic metastasis. In spite of the decrease of recurrence risk by adjuvant chemotherapy in the first 5 years, the effect of the therapy beyond 5 years is still unknown. Patients with estrogen receptor-positive (ER+) breast cancer have benefited from adjuvant tamoxifen, with the greatest benefit is in the first 4 years and an additional decline of recurrence risk carryover for more than 5 years [5]. Tamoxifen use extended to 10 years in women with early-stage breast cancer reportedly reduces the risk of late recurrence [6].

The cause of recurrence of breast cancer is multifactorial. Nowadays, several risk factors for breast cancer recurrence have been reported. The risk factors known are age, menopausal status, clinical T (tumor), clinical N (nodal involvement), LN (lymph-node), lymphovascular invasion, margin status, histologic grade, nuclear grade, hormonal status, HER2 status, chemotherapy, and antihormonal treatment [6], [7]. Also, the occurrence of breast cancer in Asian patients has some different factors from the recurrence of breast cancer in western countries.

This study determined prognostic factors of local-regional recurrence in patients with operable breast cancer in Asia by performing a meta-analysis study in which the conclusion had drawn have better accuracy. The result in this study will be useful and assist physicians in determining prognostic factor of recurrence in Asian patients with operable breast cancer.

Material and Methods

Study design and research sample

This research was a quantitative study performed by using meta-analysis study design. The meta-analysis followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement [8]. Meta-analysis was used to find prognostic factors of local-regional recurrence in patients with operable breast cancer in Asia. The research samples consisted of published research articles published in online article databases of PubMed, ProQuest and EBSCO between January 2000 and July 2018.

Operational definitions

The variables of this study included several independent variables of prognostic factors, i.e: age, menopausal status, clinical T (tumor), clinical N (nodal involvement), LN (lymph-node), lymphovascular invasion, margin status, histologic grade, nuclear grade, hormonal status, HER2 status, chemotherapy, and antihormonal treatment; and a dependent variable, i.e: local-regional recurrence of operable breast cancer.

Research procedure

This study was conducted by collecting data through the identification of published research articles on prognostic factors of recurrence in patients with operable breast cancer in Asia in online article databases of PubMed, ProQuest and EBSCO (Figure 1).

![Flow diagram research procedure](https://www.id-press.eu/mjms/index)

Figure 1: Flow diagram research procedure

Identification process of 913 articles was held by identifying the title of the articles, continued by abstract and full-text review of the articles. The article excluded if: (a) irrelevant to subject outcome, (b) the methods was neither case-control nor cohort study (c) the data provided in the results section of the article was insufficient for extraction and (d) duplicate studies.
Data collection technique

The search was limited to English language articles. The article type was limited to research articles. The research subject was limited to research involved human subject. The time of publication was limited for January 2000 to July 2018 period. The abstract of articles with relevant title continued to review process, and the articles with the irrelevant title were excluded. After that, articles with relevant abstract were continued to be reviewed in full-text, while the others were excluded. The inclusion criteria of the sample included published research on prognostic factors of recurrence in patients with operable breast cancer in Asia. The exclusion criteria were either the research was not available in the full-text form, or the criteria were not satisfied or if the information provided was insufficient for data extraction. These data were obtained from the articles: name of the first author and publication date, study location, study type, total samples and risk factors identified.

The information fulfilled criteria of inclusion from the studies obtained were extracted carefully by two independent investigators by a standardised protocol. Three other investigators resolved the disagreements. Quality assessment was performed by using the Newcastle – Ottawa Quality Assessment Scale (NOS) and studies with a NOS score ≥ 7 were considered as high quality [9].

Table 1: Systematic review of prognostic factors for local-regional recurrence in operable breast cancer patients in Asia

| First Author, Year | Region | Type of Study | Number of Samples | Risk Factors | NOS |
|--------------------|--------|---------------|-------------------|-------------|-----|
| Eikum et al [10]   | Saudi Arabia | Prospective | 867              | Grade        | 8   |
| Son et al [11]     | South Korea | Prospective  | 523              | Stage        | 7   |
| Tanioka et al [12] | Japan   | Prospective  | 88               | HER2, axillary | 7   |
| Chen et al [13]    | China   | Retrospective | 540              | Positive nodes | 7   |
| Akbari et al [14]  | Iran    | Prospective  | 258              | LVI, stage   | 7   |
| Song et al [15]    | South Korea | Prospective | 95               | Stage, grade, p53, HER2 | 7   |
| Ahn et al [16]     | South Korea | Prospective | 677              | Tumour size, N stage, Grade, ER, PR, HER2 | 7   |
| Wei et al [17]     | South Korea | Prospective  | 1698             | Tumour size, N stage, Grade, ER, PR, HER2 | 7   |
| Wangchinda and Ithimakin [18] | Thailand | Retrospective | 300              | Tumour size, N stage, Grade, ER, PR, HER2 | 7   |
| Ditsatham et al [7] | Thailand | Retrospective | 185              | ER status, PR status | 7   |
| Ahmad et al [19]   | Iran    | Retrospective | 182              | Grade, ER, PR status | 7   |

NOS, Newcastle-Ottawa Quality Assessment Scale.

Data analysis

The analysis was conducted to obtain the value of pooled risk ratio as the combined risk ratio value from the collected research. Data analysis was held by using the Mantel-Haenszel method with a fixed effect model and the DerSimonian-Laird random-effect model. Meta-analysis was carried out by using Review Manager 5.3.

Results

The selection of studies was conducted to identify 11 studies related to prognostic factors of recurrence in patients with operable breast cancer in Asia with total sample of 5,213 patients [7, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19] (Table 1).

We found 11 studies through the systematic review (7 cohort study and 4 case-control) which then analysed by meta-analysis. The research variables analysis was based on the systematic review that has been done included stage of cancer, grade of the tumour, HER2, tumour size, N stage, ER and PR status (Figure 2).

Table 2: Meta analysis of risk factors for recurrence in patients with operable breast cancer in Asia

| Risk Factors | OR (95% CI) |
|--------------|-------------|
| N stage      | 2.31 (1.49-3.60) |
| Tumour size  | 1.55 (1.35-1.78) |
| Stage        | 1.24 (1.12-1.36) |
| Grade        | 1.07 (1.05-1.10) |
| ER status    | 1.00 (0.97-1.03) |
| PR status    | 1.00 (0.97-1.03) |
| HER2         | 0.79 (0.69-0.90) |

It was shown in Figure 2, based on prognostic factors known, N stage has the highest risk ratio (RR = 2.31 [95% CI 1.49-3.60]) followed by HER2 (RR = 0.79 [95% CI 0.69-0.90]), stage of cancer (RR = 1.24 [95% CI 1.12-1.36]), tumour size (RR = 1.55 [95% CI 1.35-1.78]), grade (RR = 1.07 [95% CI 1.05-1.10]), ER status (RR = 1.00 [95% CI 0.97-1.03]) and PR status (RR = 1.00 [95% CI 0.97-1.03]).
Discussion

Local recurrence is the reemergence of tumour in the ipsilateral breast chest wall or overlying skin. The incidence of local-regional recurrence after mastectomy is 9%-28% in early breast cancer. Approximately 40% of isolated local-regional recurrences are detected during routine examinations in symptomatic or asymptomatic patients. Identifying and management of local recurrence is important because 30-40% of local-regional recurrence will develop distant metastasis. The peak of annual hazard for recurrence occurs in 1 to 2 years after treatment and then declines slowly after 12 years. Therefore, the factors correlated to local-regional recurrence are essential to identify to provide adequate therapy so that metastasis can be prevented. Breast cancer in Asia seems to be different from western countries since it occurs at a younger age with an average age of 40 to 50 years and with smaller breast sizes leading to more difficult conservative surgery [20].

In this study, we compiled a total of 5,213 patients from 11 studies (7 cohort study and 4 case-control) that are appropriate for this systematic review. The races included in this study are Arabic, Japan, China, Korea and Malay. The basis of prognostic factors of recurrence in patients with operable breast cancer in Asia, consecutively, are N stage has the highest risk ratio (RR = 6.35 [95% CI 3.78-10.67]) followed by HER2 (RR = 2.14 [95% CI 1.16-3.97]), stage of cancer (RR = 1.82 [95% CI 1.44-2.31]), tumor size (RR = 1.55 [95% CI 1.04-2.31]), tumor grade (RR = 1.43 [95% CI 1.23-1.65]), PR status (RR = 0.65 [95% CI 0.48-0.88]) and ER status (RR = 0.60 [95% CI 0.39-0.91]). N stage, stage of cancer, tumour size and tumour grade have homogeneity of variance for recurrence of operable breast cancer.

The previous study known in Arab population has identified that young age (< 40) is an independent risk factor for relapse in operable Saudi breast cancer patients [10]. Another study in Japan found that HER2 status and axillary metastases are independent predictors of recurrence in breast cancer patients [12]. In China population, it has been reported that axillary lymph nodal status is the only risk factor of significant impact on 10-year [13]. In Thailand population, ER+/PR+ and HER2 patients have a higher risk of recurrence in later than 5 years, especially in patients with high ER titer and low nuclear grade. Tumour with larger and node-positive have a higher risk of early recurrence [18].

The first and second influential factor of recurrence in breast cancer patients is the involvement of axillary lymph nodes and HER-2 positive, respectively [12]. This systematic review also proves that the presence of lymph node metastasis plays a significant role as a predictive factor for local recurrence. By a report from the United States which Saphner et al., reported that the hazard for the recurrence is particularly high for those with 4 or more involved axillary lymph nodes during the first to 6 years of follow up as well as those with fewer nodes involved [21].

Following metastasis to the axillary lymph nodes, the HER2 type has the second highest hazard rate at local recurrence. The presence of HER2 positivity will be a major factor in recurrence if patients do not receive adjuvant trastuzumab therapy [22]. HER2 is transmembrane tyrosine kinase receptor regulating cell growth, proliferation. Amplification of this gene observed in 15 – 30 % of breast cancer patients and is a strong prognostic biomarker for aggressive disease. The prominence of HER2 positive factors as a second order risk factor in this study is interesting since this is different from the risk factor for local-regional recurrence of western countries. This phenomenon can be explained by the high percentage of young age breast cancer in Asia who have aggressive behaviour as well as a high percentage overexpression of HER2.

Stage of cancer is strongly correlated with tumour size. In this study, it was found that the stage and size of the tumour as a third and fourth risk factor for the occurrence of local-regional breast cancer recurrence in Asia. If the tumour size of more than 2 cm, positive lymph nodes axillary, histopathologic grading, the incidence of recurrence in stage III (25%)

Figure 3: Funnel plots prognostic factors of local-regional recurrence in patients with operable breast cancer in Asia
is higher than stage I and II (5% and 12%) [23]. Many studies have demonstrated a linear correlation between the diameter of the primary tumour and both the presence of lymph node metastasis and clinical outcome. Among node-negative patients, tumour size is the only important prognostic factor [24].

The estrogen receptor impact in prognosis was significant in lymph node-positive patients [10]. In the first three years after diagnosis, estrogen receptor positivity affects prognosis significantly, but after three years this effect is not present. However, estrogen or progesterone receptor positive tumours will respond better to treatment with anti-estrogen drugs like Tamoxifen. A large study conducted in 37000 women in 1998 indicated that Tamoxifen treatment in estrogen receptor-positive patients would decrease recurrence and mortality rate for 47% and 26%, respectively [25]. In study patients with negative lymph nodes, estrogen receptor positivity has been associated with better prognosis [26].

Type of cancer and its grade, presence of tumour emboli, endolymphatic invasion, negative estrogen receptor, increased expression of HER-2 and positive P53 are all variables that have been associated with risk of local recurrence [27]. A study reported that early recurrence associated with unregulated stress response signalling and certain clinical parameters, such as molecular subtypes, tumour size, and grade; while late recurrence correlated with mesenchymal characteristics of the tumour epithelium and gene expression alterations in the adjacent tumour stroma [28].

Local-regional recurrence may be associated with more aggressive tumour biology. Several factors have been associated with increased risk for local-regional recurrence in western. These factors are a lymphovascular invasion, young age, increasing tumour size, closed or involved margin status, positive nodal, high grade, extensive intraductal component, multifocal/centric disease, negative hormone receptors, lack of adjuvant systemic therapy [23], [27], [29]. The NSABP B-06 trial found a 3 times greater incidence of distant relapse in patients with local recurrence and 2.5 times higher increased risk of death. One-third of these patients have synchronous distance disease and another one-third subsequently develop metastatic disease, so re-staging of the patient with local-regional recurrence is important. Patients who have nodal recurrence has a higher risk than those with chest wall recurrence. Nodal recurrence may be a source of distant metastasis or a marker of systemic dissemination [30].

There were a few limitations in this meta-analysis. First, two studies seemed potentially eligible to be included in this meta-analysis, but the full texts were not accessible. This issue may raise the possibility of selection bias. Second, the number of cases sample in one study is relatively small (12), which can reduce statistical power.

Several studies have analysed and compared patients who died with the recurrent disease with those without recurrent disease. However, less attention has been paid to evaluating factors associated with the recurrence.

In conclusion, the development of recurrent breast cancer has been investigated as an effort to achieve successful breast cancer therapy and better clinical outcome as well as more number of breast cancer survivors. Loads of the number of follow up patients in this large population requires efficient, timesaving and cost-effective monitoring. Assessment for recurrence risk of the disease could be performed by the integration of the anticipated natural history of breast cancer based on its anatomic and biologic prognostic factors and the anticancer treatment administered.

This analysis confirmed the correlation of N stage, HER2, stage of cancer, tumour size, tumour grade, ER and PR status with recurrence in patients with operable breast cancer. We suggest that these patients should have proper treatment and be followed up frequently.

References

1. Nindrea RD, Aryandono T, Lazuardi L. Breast cancer risk from modifiable and non-modifiable risk factors among women in Southeast Asia: a meta-analysis. Asian Pac J Cancer Prev. 2017; 18:3201–6. PMid:29281867 PMCID:PMC5980871
2. Nindrea RD, Harahap WA, Aryandono T, Lazuardi L. Association of BRCA1 Promoter methylation with breast cancer in Asia: a meta-analysis. Asian Pac J Cancer Prev. 2018; 19:885–9. PMid:29693332
3. Sestak I, Dowsett M, Zabaglo L, Lopez-Knowles E, Ferree S, Cowens JW, et al. Factors predicting late recurrence for estrogen receptor-positive breast cancer. J Natl Cancer Inst. 2013; 105:1504–11. https://doi.org/10.1093/jnci/djt424 PMid:24029245
4. Nishimura R, Osako T, Nishiyama Y, Tashima R, Nakano M, Fujisue M, et al. Evaluation of factors related to late recurrence—later than 10 years after the initial treatment—in primary breast cancer. Oncology. 2013; 85:100–10. https://doi.org/10.1159/000353099 PMid:23867253
5. Early Breast Cancer Trialists Collaborative Group, Davies C, Godwin J, Gray R, Clarke M, Cuzick J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011; 378:771–84. https://doi.org/10.1016/S0140-6736(11)60993-8
6. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013; 381:805–16. https://doi.org/10.1016/S0140-6736(12)61963-1
7. Ditsatham C, Somwangprasert A, Watcharachan K, Wongmaneerung P, Khorana J. Factors affecting local recurrence and distant metastases of invasive breast cancer after breast-conserving surgery in chiang Mai University hospital. Breast Cancer (Dove Med Press). 2016; 18:47-52. https://doi.org/10.2147/BCTT.S99184
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC,
20. de Bock GH, Bonnema J, van der Hage J, Kievit J, van de Velde CJ. Effectiveness of routine visits and routine tests in detecting isolated locoregional recurrences after treatment for early stage invasive breast cancer: meta-analysis and systematic review. J Clin Oncol. 2004; 22:4010-8. https://doi.org/10.1200/JCO.2004.06.080 PMid:15459225

21. Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol. 1996; 14:2738-46. https://doi.org/10.1200/JCO.1996.14.2738 PMid:8874335

22. Thürlimann B. Reducing the risk of early recurrence in hormone-responsive breast cancer. Annals of oncology. 2007; 18(Suppl 8):viii-17.

23. Cheng SHC, Tsai SY, Yu BL, Horng CF, Chen CM, Jian JJ, et al. Validating a Prognostic Scoring System for Postmastectomy Locoregional Recurrence in Breast Cancer. Int J Radiat Oncol Biol Phys. 2013; 85:953-8. https://doi.org/10.1016/j.ijrobp.2012.08.042 PMid:23122982

24. Carter CL, Allen C, Henson DE. Relation of tumor size lymph node status and survival in 24,730 breast cancer cases. Cancer. 1989; 63:181-7. https://doi.org/10.1002/1097-0424(19890101)63:1<181::AID-CNCR2820630129>3.0.CO;2-H

25. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998; 90:1371-88. https://doi.org/10.1093/jnci/90.18.1371 PMid:9747868

26. Fisher B, Redmond C, Fisher ER, Caplan R. Relative worth of estrogen or progesterone receptor and pathologic characteristics of differentiation as indicators of prognosis in node negative breast cancer patients: findings from National Surgical Adjuvant Breast and Bowel Project Protocol B-06. J Clin Oncol. 1988; 6:1076-87. https://doi.org/10.1200/JCO.1988.6.7.1076 PMid:2858862

27. Noguchi S, Koyama H, Kasugai T, Tsukuma H, Tsuji N, Tsuda H, et al. A case-control study on risk factors for local recurrences of distant metastases in breast cancer patients treated with breast-conserving surgery. Oncology. 1997; 54:468-74. https://doi.org/10.1159/000227605 PMid:9394843

28. Cheng Q, Chang JT, Gwin WR, Zhu J, Ambs S, Geradts J, et al. A signature of epithelial-mesenchymal plasticity and stromal activation in primary tumor modulates late recurrence in breast cancer independent of disease subtype. Breast Cancer Res. 2014; 16:407. https://doi.org/10.1186/s13058-014-0407-3 PMid:25060555 PMCID:PMC4187325

29. Nindrea RD, Payandeh M, Sadeghi M. The recurrence experience. BMC Cancer. 2007; 5:2. https://doi.org/10.1186/1471-2407-7-22 PMid:18053234

30. Wangchinda P, Ithimakin S. Factors that predict recurrence rates and survival in operable breast cancer patients: the Saudi Arabia experience. BMC Cancer. 2007; 5:222. https://doi.org/10.1186/1471-2407-7-22 PMid:18053234

31. Son BH, Ahn SH, Kwak BS, Kim JK, Kim HJ, Hong SJ, et al. The recurrence rate, risk factors and recurrence patterns after surgery in 3700 patients with operable breast cancer. J Breast Cancer. 2007; 10:33-44. https://doi.org/10.4048/jbc.2006.10.2.334

32. Tanioka M, Shimizu C, Yonemori K, Yoshimura K, Tamura K, Kuono T, et al. Predictors of recurrence in breast cancer patients with a pathologic complete response after neoadjuvant chemotherapy. Br J Cancer. 2010; 103:297-302. https://doi.org/10.1038/sj.bjc.6605769

33. Chen ZJ, Yan MY, Zhuang HQ, Hao JL, Li RY, Yuan ZY, et al. Prognostic and Predictive Factors of Early Breast Cancer. Clin Oncol Cancer Res. 2010; 7:246-52. https://doi.org/10.1007/s11805-010-0526-8

34. Akbari ME, Mozaffar M, Heidari A, Zirakzadeh H, Akbari A, Akbari M, et al. Recurrence and Survival Effect in Breast Conserving Surgery: What are the Predictive and/or Prognostic Factors? Iran J Cancer Prev. 2011; 4:49-53.

35. Song WJ, Kim KII, Park SH, Lee TH, Park HK, et al. The Risk Factors Influencing between the Early and Late Recurrence in Systemic Recurrent Breast Cancer. J Breast Cancer. 2012; 15:218-23. https://doi.org/10.4048/jbc.2012.15.2.218 PMid:22807940

36. Ahn SG, Lee HM, Cho SH, Bae SJ, Lee SA, Hwang SH, et al. The Difference in Prognostic Factors between Early Recurrence and Late Recurrence in Estrogen ReceptorPositive Breast Cancer: Nodal Stage Differently Impacts Early and Late Recurrence. PloS One. 2013; 8:e63510. https://doi.org/10.1371/journal.pone.0063510 PMid:23717438 PMCID:PMC3661516

37. Wei XQ, Li X, Xin XJ, Tong ZS, Zhang S. Clinical Features and Survival Analysis of Very Young (Age<35) Breast Cancer Patients. Asian Pac J Cancer Prev. 2013; 14:5949-52. https://doi.org/10.7314/APJCP.2013.14.10.5949 PMid:24289606

38. Wangchinda P, Ithimakin S. Factors that predict recurrence later than 5 years after initial treatment in operable breast cancer. World J Surg Oncol. 2016; 14:223. https://doi.org/10.1186/s12957-016-0988-0 PMid:27557365

39. Ahmadi SA, Arabi M, Payandeh M, Sadeghi M. The recurrence frequency of breast cancer and its prognostic factors in Iranian patients. Int J Appl Basic Med Res. 2017; 7:40-43. https://doi.org/10.4103/2229-516X.198521 PMid:29251106