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Review Article



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

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Abstract

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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 infraclavicular 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 (tumour), 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).

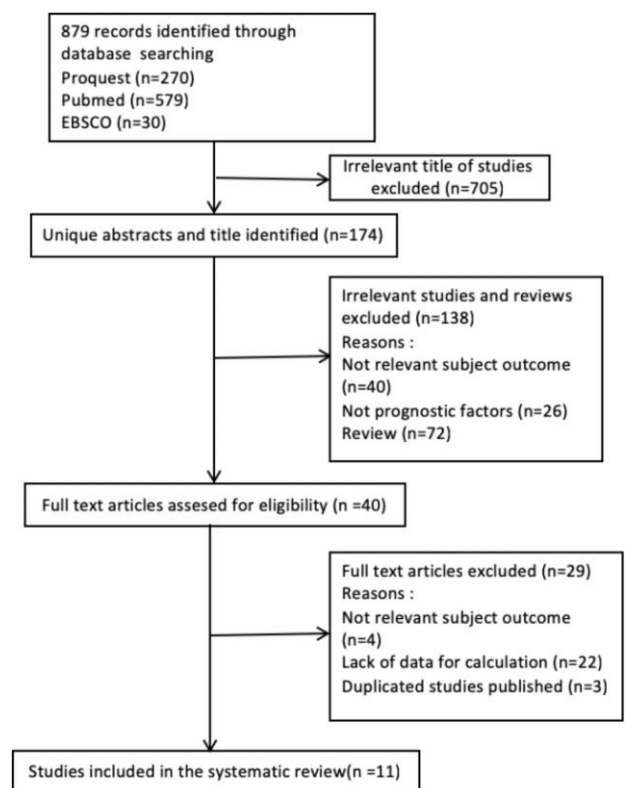


Figure 1: Flow diagram research procedure

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 involving 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
Elkum 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 lymph nodes	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, Ki67	7
Ahn et al. [16]	South Korea	Prospective	677	N stage, grade,	7
Wei et al [17]	China	Prospective	1498	Stage, tumor size, ER, PR, HER-2	8
Wangchinda and Ithimakin [18]	Thailand	Retrospective	300	Tumour size, N stage, Grade, ER, HER2	7
Ditsatham et al. [7]	Thailand	Retrospective	185	ER status, PR status	7
Ahmadi 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).

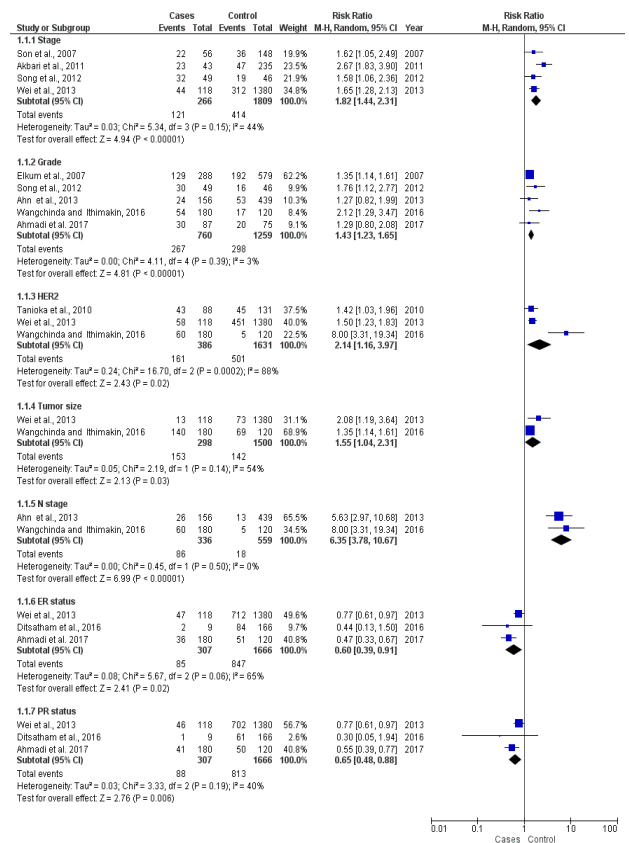


Figure 2: Forest plots prognostic factors of local-regional recurrence in patients with operable breast cancer in Asia

It was shown in Figure 2, based on prognostic factors known, 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]). Funnel plots was performed to identify publication bias among publication on recurrence in patients with operable breast cancer in Asia (Figure 3).

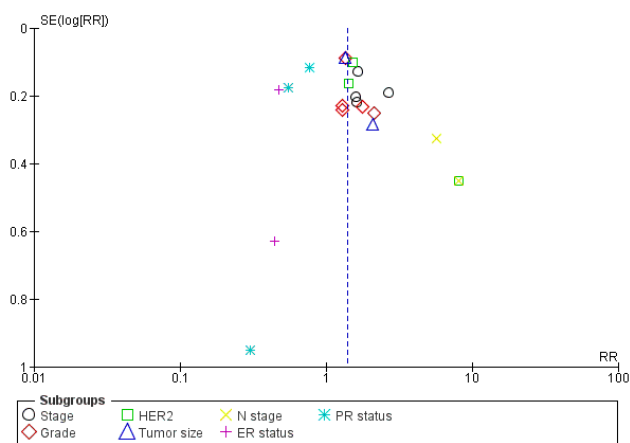


Figure 3: Funnel plots prognostic factors of local-regional recurrence in patients with operable breast cancer in Asia

Figure 3 shows that N stage, stage of cancer, tumour size and tumour grade have homogeneity of variance for recurrence of operable breast cancer resulted by the symmetrical plot based on the vertical line which means if the analysis conduct on a different population, time, place, and conditions, the results will be consistent. This is different from HER2, ER and PR status.

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%)

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 distant 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.

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