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Survival of Spinal Metastasis Disease based on Immunohistochemistry Subtype of Breast Cancer: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: Breast cancer is categorized as a slow-growth tumor in the spinal metastases disease (SMD) scoring system. Based on immunohistochemistry, breast cancer has four subtypes: Luminal A (LumA), luminal B (LumB), human epidermal growth factor 2 (Her-2) type, and triple-negative breast cancer (TNBC). TNBC has the poorest prognosis.

AIM: This study aimed to describe the survival time of breast cancer with SMD based on immunohistochemistry subtypes through systematic review and meta-analysis.

METHODS: This is a systematic review and meta-analysis study. This study used electronic articles published in PubMed and CENTRAL online database. We used keywords ([breast] AND [cancer] AND [spine] AND [metastasis]) to find eligible studies. Articles included were full-text studies in English. Survival time as the outcome was pooled according to the immunohistochemistry subtype of breast cancer. Statistical analysis was performed using software Stata.

RESULTS: Five articles met our inclusion and exclusion criteria. LumA, LumB, Her-2 type, and TNBC have a survival time of 32.84 months, 35.20 months, 60.8 months, and 14.27 months, respectively.

CONCLUSION: TNBC has the lowest survival time in the pooled analysis. We proposed TNBC be categorized as a moderate growth primary tumor.

Introduction

Breast cancer is one of the most common cancers to metastasize to the spine and is the second leading cause of death in women associated with cancer [1]. Spinal metastasis is a significant cause of severe morbidity and decreasing quality of life due to severe pain, pathological fractures, spinal cord compression, and hypercalcemia [2]. Patients with spinal metastases have short remaining life; thus, over-treatment is a concern. Therefore, treatments are focusing on symptoms and the expected quality of life or survival [3], [4].

As many as, 20–30% of breast cancers will be metastasized, of which 9.7% cases are to the spine. The diagnosis can be delayed up to 2 months from the moment a patient comes to the doctor for the 1st time [5], [6]. Patients diagnosed with spinal metastases shows spinal pain as a symptom in 63.3%, and neurological deficits are seen in only 1.4% of cases [7].

Breast cancer has four phenotypes that play an essential role in routine clinical management: Luminal A (LumA), luminal B (LumB), human epidermal growth factor 2 (Her-2) positive, and basal-like/triple-negative breast cancer (TNBC). These phenotypes are assessed based on immunohistochemical pathological markers consisted of estrogen receptor, progesterone receptor, and Her-2 [1], [8]. Positive hormone receptor breast cancer has the best prognostic with the lowest relapse rate, whereas negative hormone receptor is associated with poor survival outcome [6].

Several scoring systems can predict spinal metastases patient's survival, for example, Tokuhashi *et al*., Tomita *et al*., Bauer and Wedin, Van der Linden *et al*., and Katagiri *et al*. These scoring systems can determine the preoperative evaluation of the prognostic spinal metastases but do not differentiate breast cancer phenotype itself [9], [10], [11], [12], [13], [14]. This study aimed to evaluate every subtype of breast cancer's nature according to patients' survival with spinal metastases.

Methods

Eligibility criteria

This review included all studies of spine metastases of breast cancer with immunohistochemistry results. We included all publications in English. However, articles in other languages were translated using Google translate and decided by the author to be included. The outcome of interest in this review was the survival time (month) of each subtype of breast cancer in spinal metastasis patients.

Search strategy

In this study, we used keywords ([breast] AND [cancer] AND [spine] AND [metastasis]) in online databases to find eligible studies. The study selection process was performed by two authors (IHH and PEM) to reduce the possibility of discarding relevant studies. The decision of another author (TGBM) was used when disagreement occurred. Duplicate records were removed. Titles and abstracts were screened, and irrelevant studies were removed. Studies that passed the first screening were further evaluated to comply with the inclusion and exclusion criteria of this review. Finally, the studies were further evaluated for their quality before included in this review.

Data collection process

An electronic data collection form was used to collect data by each author. The collected data by each author will be merged and be managed with software Stata.

Data items

The data items were the author's name, year of publication, method, sample size, diagnosis of participant, age, immunohistochemistry profile of breast cancer, and survival time (months). They were pooled and analyzed.

Assessment of quality of study

Studies that complied with inclusion and exclusion criteria were assessed for their quality to ensure the studies' validity and reliability. This process was done independently by two authors using a standardized critical appraisal tool to minimize the possibility of bias in study selection. The critical appraisal tool was Joanna Briggs Institute (JBI) critical appraisal tool based on study design. The decision of the third author was used when disagreement occurred.

A cutoff point was used to determine the quality of the study. Cutoff point in this review was half of the total score in each JBI critical appraisal checklist. A low-quality study was defined as a score below the cutoff point while conversely was termed a high-quality study.

Synthesis of result

The outcome of interest was pooled and analyzed. Meta-analyses were performed using software Stata. The random effect model was used regardless of heterogeneity.

Results

We found five articles describing the survival time of different immunohistochemistry of spinal metastasis disease Table 1. Five articles described the survival time of TNBC, and only three articles described the survival time of LumA, Lum B, and Her-2 type Table 2. The study selection process according to the PRISMA flow diagram is shown in Figure 1.

LumA

There are three studies reporting survival time of subtype LumA spinal metastasis. The meta-analysis of survival of subtype LumA showed survival of 32.8 months (95% CI 30.9–34.7; $I^2 = 92.5\%$). The forest plot is shown in Figure 2.

LumB

There are three studies reporting survival time of subtype LumB spinal metastasis. The meta-analysis of survival of subtype LumB showed survival of 35.2 months (95% CI 29.5–40.9; $I^2 = 85.9\%$). The forest plot is shown in Figure 3.

Her-2 type

There are three studies reporting survival time of subtype Her-2 type spinal metastasis. The meta-analysis of survival of subtype Her-2 type showed survival of 60.85 months (95% CI 53.4–68.3; $I^2 = 95.1\%$). The forest plot is shown in Figure 4.

TNBC

There are five studies reporting survival time of subtype TNBC spinal metastasis. The meta-analysis of survival of subtype TNBC showed survival of 14.27 months (95% CI 12.4–16.15; $I^2 = 91.3\%$). The forest plot is shown in Figure 5.

Table 1: Summary of findings of included studies

Study author	Type of study	Level of evidence	Participant	Outcome
Amelot *et al.*,[15] 2020	Prospective cohort	2b	Total 123; LumA 46; LumB 25; Her-2 type 23; TNBC 29	LumA 35.6 (7.5); LumB 48.8 (23.2); Her-2 type 76.1 (21.5); TNBC 17.4 (6.2)
Bollen *et al.*,[3] 2014	Retrospective cohort	2b	Total 111; LumA 67; LumB 9; Her-2 type 11; TNBC 24	LumA 22.5 (17.9–27.0); LumB 26.9 (9.1–44.7); Her-2 type 20.9 (1.1–40.8); TNBC 5.5 (2.0–9.0)
Chan-Seng *et al.*,[4] 2014	Retrospective cohort	2b	Total 140; LumA 67; LumB 16; Her-2 type 4; TNBC 12	LumA 30.5; LumB 26.25; Her-2 type 22.25; TNBC 39
Tan *et al.*,[16] 2017	Retrospective cohort	2b	Total 185; ER (+) 51; ER (−) 0; PgR (+) 62; PgR (−) 1; Her-2 (+) 100; Her-2 (−) 36; HR (+) 42; HR (−) 0; Not triple (−) 161; Triple (−) 24	ER (+) 13 (1–72); PgR (+) 15 (1–80); Her-2 (+) 20 (1–125); Her-2 (−) 26.5 (3–96); HR (+) 12 (1–72); Not triple (−) 30 (1–204); Triple (−) 11 (1–27)
Wang *et al.*,[7] 2014	Retrospective cohort	2b	Total 151; ER (+) 96; ER (−) 16; PgR (+) 28; PgR (−) 25; HR (+) 113; HR (−) 17; Her-2 (+) 22; Her-2 (−) 49; TNBC 8	ER (+) 21.5 (15.9–27); ER (−) 10.6 (1.3–33.3); PgR (+) 18.8; PgR (−) 16.6 (10.6–27.1); HR (+) 21.5 (15.5–26.8); HR (−) 10.6 (1.3–33.3); Her-2 (+) 23.1 (13.8–27.3); Her-2 (−) 21.3 (13.4–27); TNBC 9.9 (1.1–46.8)

LumA: Luminal A, LumB: Luminal B, Her-2: Human epidermal growth factor 2, HR: Hormone receptor, ER: Estrogen receptor, PgR: Progesterone receptor, TNBC: Triple-negative breast cancer.

Table 2: Characteristics of included studies

Methods	Retrospective cohort
Survival in breast cancer patients with spine metastases: Prognostic assessment involving molecular markers (Amelot *et al.*,[15] 2020)	
Participants	Inclusion criteria: All consecutive patients treated for spinal metastases breast cancer; patients with spinal metastases and breast cancer were synchronously diagnosed; patients with previously diagnosed and treated breast cancer Exclusion criteria: Missing data or lost during the follow-up period
Comparison	LumA 46; LumB 25; Her-2 type 23; TNBC 29
Outcome	Mean survival in months
Molecular phenotype is associated with survival in breast cancer patients with spinal bone metastases (Bollen *et al.*,[3] 2014)	
Participants	Inclusion criteria: All consecutive breast cancer patients presenting with symptomatic spinal metastases
Comparison	LumA 67; LumB 9; Her-2 type 11; TNBC 24
Outcome	Median survival in months
Spinal metastases in breast cancer: Single center experience (Seng *et al.*,[4] 2017)	
Participant	Inclusion criteria: Patients with spinal metastases from breast cancer; In asymptomatic patients (35%), spine metastases were diagnosed during systematic routine follow-up (bone scintigraphy [single photon emission CT-CT], whole-body CT scan, or MRI)
Comparison	LumA 67; LumB 16; Her-2 type 4; TNBC 12
Outcome	Mean survival in months
Evaluation of prognostic factors and proposed changes to the modified Tokuhashi score in patients with spinal metastases from breast cancer (Tan *et al.*,[16] 2017)	
Participant	Inclusion criteria: All cases of histologically-confirmed breast cancer spinal metastases patient who presented Exclusion criteria Incomplete clinical/radiological findings or loss of follow-up with an unknown time of death
Comparison	ER (+) 51; ER (−) 0; PgR (+) 62; PgR (−) 1; Her-2 (+) 100; Her-2 (−) 36; HR (+) 42; HR (−) 0; Not triple (−) 161; Triple (−) 24
Outcome	Median survival in months
Survival analysis of breast cancer subtypes in patients with spinal metastases (Wang *et al.*,[7] 2014)	
Participant	Inclusion criteria: All patients with pathologically confirmed breast cancer with spinal metastases who had undergone surgical treatment
Comparison	ER (+) 96; ER (−) 16; PgR (+) 28; PgR (−) 25; HR (+) 113; HR (−) 17; Her-2 (+) 22; Her-2 (−) 49; TNBC 8
Outcome	Median survival in months

LumA: Luminal A, LumB: Luminal B, Her-2: Human epidermal growth factor 2, HR: Hormone receptor, ER: Estrogen receptor, PgR: Progesterone receptor, TNBC: Triple-negative breast cancer.

Discussion

Prognostic scoring systems were designed to assist the practitioner during the decision-making process, whether a patient should be offered surgical treatment or not [17]. Based on immunohistochemistry, breast cancer was divided into four subtypes. In this study, the Her-2 type has the most extended survival with a surprising 60.8 months of survival time. LumA and B subtypes have similar survival with 32 and 35 months of life expectancy, respectively. Meanwhile, TNBC showed the shortest survival with 14 months of life expectancy.

According to Tokuhashi *et al*., 0 points are given to the primary lesion with survival found to be <6 months, and 5 points are given to the primary lesion with a survival of more than 1 year [10]. In this study, we found 14 months of life expectancy in spinal metastases with the TNBC subtype. Considering the survival is <1 year on the three studies by Foerster *et al*., Tan *et al*., and Wang *et al*.; 6.7 months, 11 months, and 9.9 months, respectively, we propose to include TNBC as primary lesion to point three or moderate growth in another scoring system.

TNBC is a poor prognostic factor; one reason is there is no specific targeted therapy available for TNBC [18]. The heterogeneity of detection of spinal metastasis was found in the studies included in this meta-analysis (Table 2). Studies in the center that routinely perform systematic follow-up (bone scintigraphy [single photon emission CT-CT], whole-body CT scan, or MRI) will detect spinal metastases faster than the other, thus makes survival seems longer.

Another consideration should be taken about the treatment provided in every study. The ideal management of spinal metastases breast cancer consisted of multiple aspects of specialties, including surgical oncology, spine surgery, medical oncology, radiation, pain management, and rehabilitation [19]. There is no clear distinction between what modalities of therapy given in the studies

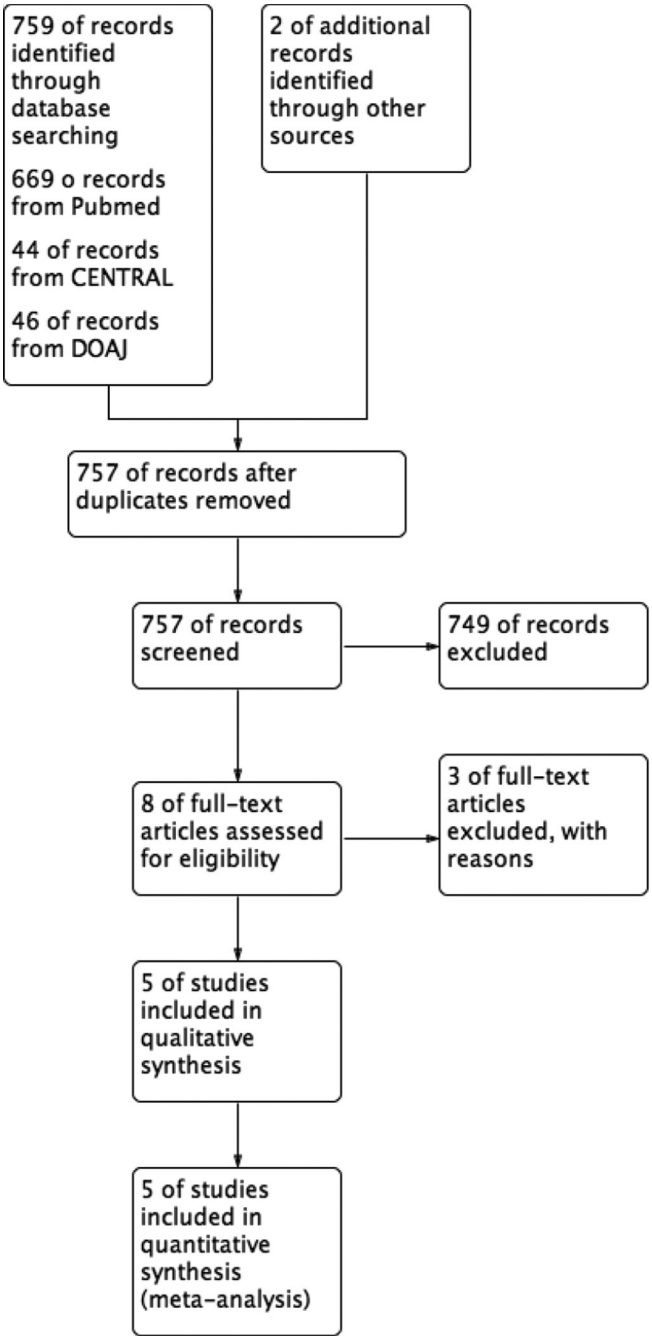

Figure 1: PRISMA flow diagram

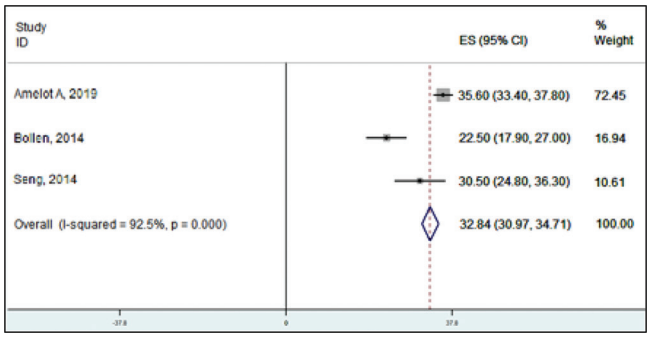

Figure 2: Forest plot of survival time of spinal metastasis disease with subtype luminal A

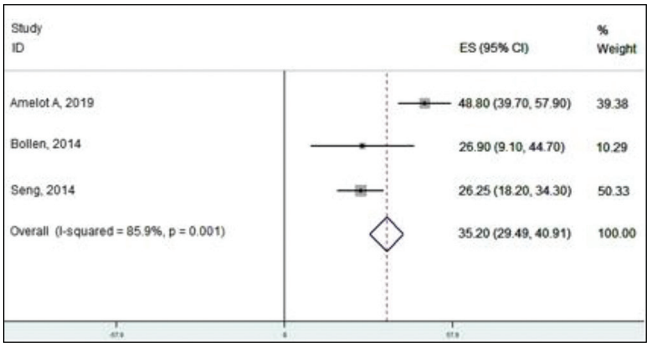

Figure 3: Forest plot of survival time of spinal metastasis disease with subtype luminal B

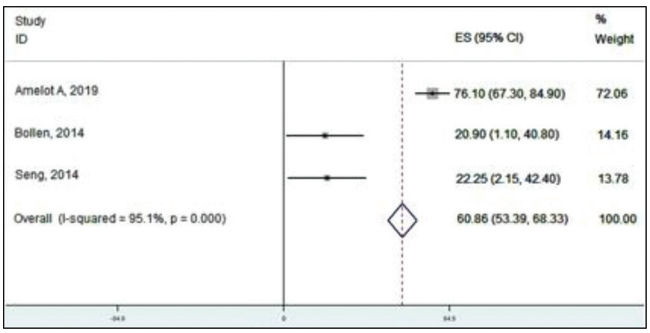

Figure 4: Forest plot of survival time of spinal metastasis disease with subtype human epidermal growth factor 2 type

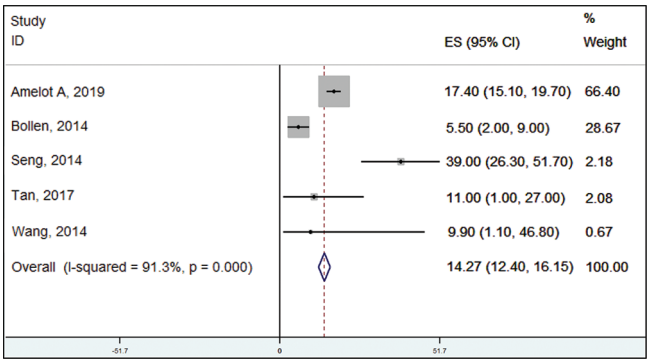

Figure 5: Forest plot of survival time of spinal metastasis disease with subtype triple-negative breast cancer

were analyzed. Zadnik *et al*. stated that dual therapy (chemotherapy and radiotherapy) was associated with significantly higher survival than single modality post-operative adjuvant therapy (p = 0.042) [20].

Conclusion

Each breast cancer with its immunohistochemistry subtype has a different survival on patients with spinal metastases. Aggressive treatment can be performed in the patient with long-term survival. Meanwhile, we should reconsider subtype TNBC due to its aggressiveness and unavailability of targeted treatment. We proposed TNBC

should be categorized as a moderate growth tumor in the metastasis scoring system.

Author Contribution

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Tjokorda Mahadewa, Ivan Hugo Hadisaputra, and Putu Eka Mardhika. Tjokorda Mahadewa acted as a decision-maker during the screening of articles. Tjokorda Mahadewa wrote the first draft of the manuscript and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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