Original Article

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Does a 40% Cut-off Point for Ki-67 Expression Have a Role in Identifying the Development of Distant Metastasis Within 2 Years in Locally Advanced Triple Negative Breast Cancer Patients?

Kelvin Setiawan[1], Ida Bagus Suryawisesa[2], I Ketut Widiana[2], I Wayan Sudarsa[2]

[1]Department of General Surgery, Udayana University Faculty of Medicine, Prof. Dr. I.G.N.G. Ngoerah General Hospital, Bali, Indonesia
[2]Division of Oncology Surgery, Department of Surgery, Udayana University Faculty of Medicine, Prof. Dr. I.G.N.G. Ngoerah General Hospital, Bali, Indonesia

ABSTRACT

Objective: Triple negative breast cancer (TNBC) has a higher proportion of patients with distant recurrence or metastasis. Ki-67 has been suggested as an essential factor in cancer grading and prognostic evaluation, although there is still a debate regarding the Ki-67 cut-off value in TNBC. The aim of this study was to determine the role of Ki-67 expression using a 40% cut-off point as a risk factor for developing distant metastasis within two years in patients with TNBC.

Materials and Methods: This analytical observational study was conducted with a case-control design from January 2021-2022. Subjects were divided into two groups (metastasis within two years or more than two years after diagnosis). Bivariate analysis was conducted using chi-square test and odds ratio (OR) was also analyzed.

Results: A total of 66 subjects were included. In patients with metastasized TNBC and a Ki-67 expression of ≥40%, 29 patients (55.8%) had metastasis occurring in ≤2 years and 23 patients (44.2%) had metastasis occurring in >2 years; in patients with metastasized TNBC and a Ki-67 expression of <40%, 4 patients (28.6%) had metastasis occurring in ≤2 years and 10 patients (71.4%) had metastasis occurring in >2 years. Chi-square analysis (p = 0.071) indicated no significant association between patients with Ki-67 expression of ≥40% and <40% with metastasis within 2 years [OR 3.152 (confidence interval: 95% 0.875–11.362)].

Conclusion: Ki-67 protein expression of over 40% in patients with locally-advanced TNBC does not indicate a greater risk of distant metastasis in the first two years after diagnosis.

Keywords: Triple negative breast cancer; breast cancer; Ki-67; metastasis

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Key Point

- Based on our study's analysis result, it could be concluded that Ki-67 protein expression of over 40% in patients with locally-advanced triple-negative breast cancer does not provide a risk of distant metastasis in under 2 years. There were still inconsistencies between Ki-67 expression and the impact on survival in patients with breast cancer due to the ongoing debate regarding the inaccurate assay's precision, the difference in methods in measuring Ki-67 and different cut-off values in differentiating tumors with high and low concentrations of Ki-67 expression.

Introduction

Triple negative breast cancer (TNBC) is defined as a tumor that does not express the three prognostic and predictive biomarkers typically used for routine clinical management, which are estrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor type 2. TNBC is more commonly found in younger patients across varied ethnicities and races. Patients with TNBC typically have a larger tumor, with a higher grade and more rapid growth. TNBC is also associated with a greater likelihood of distant recurrence or metastasis compared to local recurrence. TNBC with metastasis usually involves visceral organs, such as the lung and brain and is less likely to involve bones, in contrast to tumors with positive ER. Thus,

Corresponding Author:
Kelvin Setiawan; kelvin.setiawana.a@gmail.com

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TNBC is regarded as a more aggressive tumor with a worse prognosis compared to other subtypes (1).

Patients with TNBC are also more likely to develop typical distant and local recurrence sequelae, within 1–3 years of initial diagnosis. Tseng et al. (2) showed that the median overall survival (OS) duration in TNBC patients with lung metastases was 16.6 years but only 4.3 years in cases with brain metastases. The median time to death in patients with TNBC is shorter compared to other subtypes. Furthermore, in addition to a more likely distant recurrence, patients with TNBC are also more likely to develop an earlier recurrence. The mean time to distant metastases in a cohort of patients diagnosed with TNBC in a single institution in Toronto was 2.6 years, compared to 5 years in other subtypes (3). The risk of relapse and mortality in patients with TNBC is the highest within the first 3–5 years of diagnosis. All deaths in TNBC occurred more rapidly and within a period of 10 years after diagnosis. In comparison, deaths due to other breast cancer subtypes occur up to 18 years after diagnosis (1).

Protein Ki-67 is an antigen that occurs in two protein isoforms with a molecular weight of 345 and 395 kDA; it was first identified by Scholzen and Gerdes (4) in the early 1980s. Ki-67 is strictly associated with proliferation and studies have suggested that Ki-67 is an essential factor in cancer grading and prognostic evaluation. Xiong et al. (5) showed that the Ki-67 index is associated with the prognosis of patients with advanced-stage cancer. A study by Wang et al. (6) in 2016 reported that TNBC patients with lower Ki-67 expression (<40%) had a better 3-year disease-free period compared to those with Ki-67 expression of >40% (90.8% compared to 78.4%, with a log-rank *p*-value of 0.001).

The consistent relationship between high Ki-67 index and poor outcomes in patients with breast cancer is conclusive, despite the uncertain precision of laboratory results, the difference in methods of measuring Ki-67 and different cut-off values in differentiating tumors with a high and low concentration of Ki-67 expression (7). The higher Ki-67 expression in TNBC is considered to play a role in the development of a more rapid metastasis, although there is still a debate regarding the standardization of the cut-off value for Ki-67 expression in TNBC. Considering the high risk of early distant metastasis in TNBC patients, the aim was to conduct a study comparing patients with TNBC and distant metastases either before or after two years of diagnosis and Ki-67 indexes either above or below a 40% cut-off.

Materials and Methods

This analytical observational study was conducted with a case-control design. This study was conducted in the Department of Oncology Surgery, Faculty of Medicine, University of Udayana in the Prof. Dr. I Gusti Ngoerah Gde Ngoerah Hospital, Denpasar, Bali for a duration of one year, from January 2021 to January 2022.

This study included all patients diagnosed with local-advanced TNBC and recorded in the medical records. The sample was divided into two groups, the case and control groups. The case group included locally-advanced TNBC patients with distant metastasis occurring less than two years after diagnosis, while the control group included locally-advanced TNBC patients with distant metastasis occurring over two years after diagnosis. TNBC patients under 18 years old, patients with incomplete clinical and histopathology medical records, patients who were not monitored for disease progression and patients diagnosed during pregnancy were excluded. Both groups received therapy (chemotherapy and/or radiotherapy) based on each patient's indications. Total consecutive sampling was conducted; therefore, patients who met the inclusion and exclusion criteria during the study period were considered as study samples until the minimum sample was met. This study was approved by the Research Ethics Committee of the Faculty of Medicine, University of Udayana (no: 2021.02.1.1086, date: 09.09.2021).

Ki-67 expression was counted in patient tumor samples, which were freshly obtained by incisional biopsy. Tumor samples were fixed using 10% formal saline in under 30 minutes and were delivered straight into the pathology department. Calculation of Ki-67 expression was done by counting total number of Ki-67-positive tumor cells in each field from immunohistochemistry (IHC) hotspot areas divided by the total number of tumor cells. This Ki-67 expressions was presented as percentages.

The independent variable in this study was the Ki-67 expression in the tumor sample. Ki-67 expression was startified into Ki-67 expression ≥40% as a positive risk factor and Ki-67 expression <40% as a negative risk factor. The instrument for measuring this variable was the IHC examination conducted by staff of the histopathology department. Time measurement of under or over 2 years of distant metastasis was started after a locally-advanced TNBC diagnosis based on the IHC examination from distant metastatic tissue samples was made. The control variables in this study were age, menopausal status, staging, histopathology features, tumor grading, tumor-infiltrating-lymphocytes (TIL), and lymphovascular invasion (LVI). The study's procedure is shown in Figure 1.

Statistical Analysis

Data analysis in this study consisted of univariate analysis (descriptive statistics) and bivariate analysis. Descriptive analysis aims to describe the study subjects' characteristics. The categorical variable is presented as the frequency of total (percentage), while numerical data are presented as mean and standard deviation. Bivariate analysis is conducted by making a cross-tabulation 2x2 (row x column) and measuring the effect size in odds ratio (OR). The used hypothesis

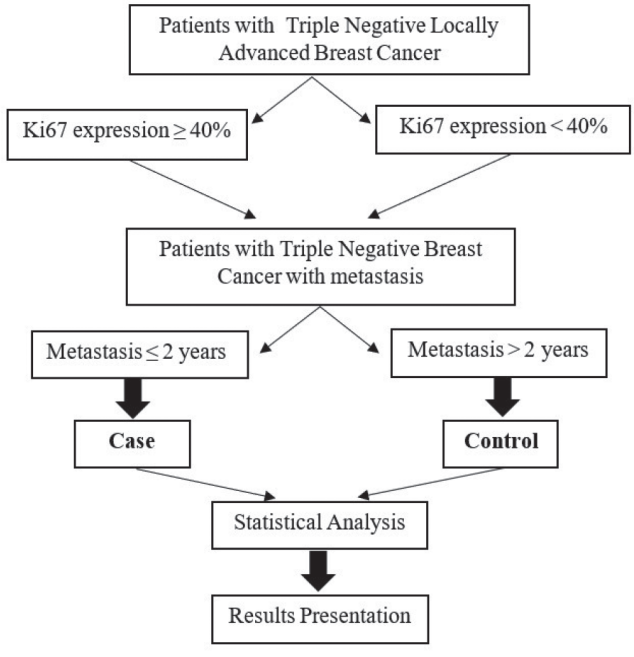

Figure 1. Procedural steps of the study

test was chi-square, in which a $p<0.05$ was considered statistically significant. All data analysis in this study was performed using the statistical program SPSS, version 25.0 (IBM Inc., Armonk, NY, USA).

Results

A total of 66 locally-advanced TNBC patients with metastasis who met the inclusion and exclusion criteria were included in this study. The subjects were divided into two groups: locally-advanced TNBC patients with distant metastasis occurring in less than 2 years from diagnosis (n = 33); and locally-advanced TNBC patients with distant metastasis occurring later than 2 years after diagnosis (n = 33). The variables of interest were age, menopausal status, histopathology type, staging, tumor grading, TIL and LVI. All these variables were comparable between the two groups (Table 1).

Then the association between Ki-67 using the 40% cut-off and metastasis of TNBC patients with a cut-off of 2 years after diagnosis was analyzed with a cross-tab using a 2x2 table with a chi-square test and a significance level of <0.05. Based on Table 2, in patients with metastasized TNBC and a Ki-67 expression of ≥40%, there were 29 patients (55.8%) with metastasis occurring in ≤2 years and 23 patients (44.2%) with metastasis occurring in >2 years. In patients with metastasized TNBC and a Ki-67 expression of <40%, there were 4 patients (28.6%) with metastasis occurring in ≤2 years and 10 patients (71.4%) with metastasis occurring >2 years. The chi-square statistical analysis result was $p = 0.071$, indicating that there was no significant association between patients with Ki-67 expression of ≥40% and <40% with metastasis within 2 years with an OR value of 3.152 [confidence interval (CI) 95% 0.875–11.362].

Table 1. Study subjects' characteristics

Variable	Metastasis ≤2 years, n (%)	Metastasis >2 years, n (%)	*p*
Age			
>50 years	13 (48.1)	14 (51.9)	0.802
≤50 years	20 (51.3)	19 (48.7)	
Menopausal status			
Post Menopause	17 (53.1)	15 (46.9)	0.708
Pre-Menopause	16 (48.5)	17 (51.5)	
Histopathology type			
No specific type (NST)	26 (49.1)	27 (50.9)	
Invasive lobular carcinoma	3 (33.3)	6 (66.7)	0.170
Metastatic carcinoma NST	1 (100)	0 (0)	
Special type carcinoma	3 (100)	0 (0)	
Staging			
IIIA	2 (50)	2 (50)	0.197
IIIB	24 (45.3)	29 (54.7)	
IIIC	7 (77.8)	2 (22.2)	
Tumor grading			
Grade 3	22 (52.4)	20 (47.6)	0.609
Grade 1-2	11 (45.8)	13 (54.2)	
TIL			
Moderate – strong positive	9 (40.9)	13 (59.1)	0.296
Negative – positive mild	24 (54.5)	20 (45.5)	
LVI			
Positive	18 (62.1)	11 (37.9)	0.083
Negative	15 (40.5)	22 (59.5)	

Discussion and Conclusion

Generally TNBC is characterized as an aggressive breast tumor and has poor prognosis compared with the luminal subtype. Moreover, TNBC has a tendency to develop distant metastasis, particularly brain metastasis, which significantly reduces the OS of patients with this form of breat cancer (1). Ki-67 expression, as one of the proliferation indices, was been widely used as a breast cancer prognostic factor in previous studies (4-7). However, in contrast to the luminal subtype which is divided into luminal A and B based on teh Ki-67 value, TNBC has no different classifications according to Ki-67 expression. Whether higher Ki-67 expressions in TNBC results in a worse prognosis or not is still a matter for ongoing debate. Hence the rationale behind the present study. The Ki-67 index cut-off of 40% was derived from the meta-analysis of Wu et al. (8) in 2019. These authors reported that Ki-67 expression ≥ 40% in resected TNBC patients was linked with a higher chance of recurrence and death (8). The present study focused on locally advanced TNBC and the relationship between Ki-67 expression levels and distant metastasis events inside two years of diagnosis.

Several studies, including retrospective evaluations from randomized clinical trials and meta-analyses, have shown that increased Ki-67 expression is independently associated with poor outcomes in patients with breast cancer. One of the studies, that included the most patients, was conducted by Petrelli et al. (9) in 2015 who undertook a systematic literature review and meta-analysis of several studies. A total of 41 studies, including 64,196 patients, were identified. Although the cut-off value of Ki-67 in the study varied, ranging from 10 to over 25%, the strongest prognostic significance in determining OS was shown in Ki-67 measurement with a cut-off value of over 25% [with a hazard ratio (HR) of 2.05; CI 95% 1.7–2.5; $p<0.00001$] (9). However, the low cut-off value of Ki-67 was not based on scientific evidence and research; rather, it was based on expert opinions. Until standardized research is available, Ki-67 measurement should adhere to previously published recommendations from the International Ki-67 in Breast Cancer Working Group (10).

Bivariate analysis in the present study showed a non-significant association between Ki-67 expression with a cut-off value of 40% and metastasis within two years ($p = 0.071$) and OR 3.152 (95% CI 0.875–11.362). Another study using Ki-67 expression in TNBC patients in order to attempt to predict progression of the breast cancer was performed by Hao et al. (11) in 2016. These authors used a Ki-67 cut-off value of 35%, which was the median value of Ki-67 expression from their sample. Overall, Ki-67 expression of over 35% had a similar disease-free survival (DFS) with patients with Ki-67 expression of ≤35% ($p = 0.481$). Although their study reported a similar result to the present study, their were several methodological differences: (1) the 35% cut-off value; (2) the use of survival analysis for determining prognostic factors of Ki-67 expression; (3) classifications of survival analysis based on age group; and (4) outcome in relation to breast-cancer-specific survival, which was not described in detail.

Table 2. The association between Ki-67 with a cut-off value of 40% and metastasis timing

Ki67 Expression	Metastasis ≤2 years (n; %)	Metastasis >2 years (n; %)	OR (95% CI)	*p*-value
≥40%	29 (55.8%)	23 (44.2%)	3.152 (0.875–11.362)	0.071
<40%	4 (28.6%)	10 (71.4%)		

OR: odds ratio; CI: confidence interval

Munzone et al. (12) peformed a study investigating Ki-67 expression, and drew a similar conclusion to the present study. Munzone et al. (12) used a cut-off value of 35% and compared DFS between patients with Ki-67 >35% and ≤35% in the six years following diagnosis. Over this period the DFS was similar between these two groups [p = 0.192 and HR 1.3 (95% CI 0.7–2.3)] (12). Another study that reported a similar analysis result using Ki-67 cut-off value of 30% was performed by Pistelli et al who compared DFS and OS between Ki-67 >30% and ≤30% within a median of 52.4 months. In this observational period, Ki-67 expression of over 30% had a statistically similar DFS [p = 0.71 and HR 0.8 (95% CI 0.23–2.71)] and OS (p = 0.99 and HR 1; 95% 0.21–4.73) with Ki-67 of ≤30% (13). Both of these studies used a survival analysis study design.

A retrospective study analyzing the association between Ki-67 and local recurrence and metastasis was conducted by Wang et al. (14) in 2019. This study used a cut-off value of >30% and ≤30%. Ki-67 expression of >30% had a statistically similar recurrence-free survival rate with Ki-67 expression of ≤30% (p = 0.112) (14). Another retrospective study by Gonçalves et al. (15) in 2018 with a cut-off value of 25% reported that Ki-67 of >25% had a statistically similar recurrence-survival with Ki-67 of <25% (HR 0.91; 95% CI 0.39–2.11; p = 0.83).

Previously, Wang et al. (6) in 2016 used the same Ki-67 expression cut-off as our study of 40% in the same population, although with a different analysis conclusion. They analyzed OS and DFS in patients with TNBC with Ki-67 expression of over and under 40%. Wang et al. (6) concluded that patients with Ki-67 expression of ≤40% had a significantly better DFS compared to Ki-67 >40% within 3 years (90.8% compared to 78.4%, log-rank p = 0.001) (6). Another study by Masuda et al. (16) in 2011 evaluated DFS in pre- and post-chemotherapy TNBC patients, stratified by Ki-67 of < and ≥50%. In both pre-chemotherapy TNBC patients and post-chemotherapy patients who did not achieve pathological complete response, both survival analyses showed a similar result, in which patients with a higher Ki-67 expression (≥50%) had a worse DFS compared to those with low Ki-67 expression (<50%) within two years with p values of 0.04 and 0.002 (16).

Other potential prognostic biomarkers have recently been investigated. One of these was circular RNAs (circRNA). circRNAs are known to be involved in TNBC cell proliferation, apoptosis, migration, and invasion, and have also been found to be involved in colorectal cancer and prostate cancer (17, 18). Recent studies have also shown the correlation between disease specificity and clincial relevance in TBCA and the expression of circRNAs. circRNAs are highly stable and thus have a long half-life, are resistant to Rnase R digestion, and can be detected by cost-effective methods (quantitative real-time PCR). Tian et al. (17) reviewed the use of circRNAs as a potential prognostic biomarker for TNBC. These authors showed that several upregulated circRNAS were associated with poor survival in TNBC patients but further studies are still required to standardized the collection timing and cut-off values. Another potential prognostic biomarker is the epidermal growth factor receptor (EGFR), which has been shown to be an independent indicator of prognosis for worse DFS and OS. Immunotherapy biomarkers, such as the programmed cell death protein 1, have also been shown to be commonly expressed in TNBC patients and are associated with poor prognoses (18). Furthermore, besides biomarkers, other prognostic factors also include clinical and radiological findings. Costa et al. (19) found that clinical findings such as large tumor size, angiolymphatic invasion, axillary node involvement, smoking and advanced clinical stage, were significantly related to lower OS and/or DFS and recurrence in patients with TNBC. Moreover, certain MRI features of TNBC have been shown to be useful in determining the prognosis of patients. Choi et al. (20) reported that MRI features, including heterogeneous/rim enhancement, very high intratumoral signal intensity on T2 images and peritumoral edema were significantly associated with standarized uptake value maximum from 18F-fluorodeoxyglucose positron emission tomography/computed tomography, indicating poor prognosis for TNBC.

The present study had several limitations. First, the study design was retrospective observational with case-control hypothesis testing. Based on literature review, there are only a few case-control retrospective studies that assessed Ki-67 expression as a risk factor for metastasis in patients with TNBC. Most of the available studies used a prospective survival analysis as their design and so the conclusions of this study have a poorer evidence base. Second, due to incomplete data in medical records, there were fewer study participants who met the inclusion criteria, which may have biased the results further. This missing data included details of chemotherapy agents and duration of chemotherapy or radiotherapy, which constitutes substatial data omission.

In conclusion, in this cohort Ki-67 protein expression of over 40% in patients with locally-advanced TNBC did not indicate a greater risk of distant metastasis in under two years of diagnosis compared to patients with a Ki-67 level of <40%. It should be noted that there are still inconsistencies between Ki-67 expression and the impact on survival in patients with breast cancer. These may be due to the assay precision, the difference in methods in measuring Ki-67 and different cut-off values in differentiating tumors with high and low concentrations of Ki-67 expression. Until standardized research is available, Ki-67 measurement should adhere to previously published recommendations from the International Ki-67 in Breast Cancer Working Group.

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Faculty of Medicine, University of Udayana (no: 2021.02.1.1086, date: 09.09.2021).

Informed Consent: Written informed consent forms were obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.S., I.B.S.; Concept: K.S.; Design: K.S., I.K.W., I.W.S.; Data Collection or Processing: K.S., I.B.S.; Analysis or Interpretation: K.S., I.B.S., I.W.S.; Literature Search: K.S., I.K.W.; Writing: K.S., I.B.S., I.K.W., I.W.S.

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