RESEARCH ARTICLE

Higher Ki67 Expression is Associates With Unfavorable Prognostic Factors and Shorter Survival in Breast Cancer

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Abstract

Background: The prognostic value of the Ki67 expression level is yet unclear in breast cancer. The aim of this study was to investigate the association between Ki67 expression levels and prognostic factors such as grade, Her2 and hormone receptor expression status in breast cancers. **Materials and Methods:** Clinical and pathological features of the patients with breast cancer were retreived from the hospital records. **Results:** In this study, 163 patients with breast cancer were analyzed, with a mean age of 53.4 ± 12.2 years. Median Ki67 positivity was 20% and Ki67-high tumors were significantly associated with high grade ($p < 0.001$), lymphovascular invasion ($p = 0.001$), estrogen receptor (ER) negativity ($p = 0.035$), Her2 positivity ($p = 0.001$), advanced stage ($p < 0.001$) and lymph node positivity ($p < 0.003$) . Lower Ki67 levels were significantly associated with longer median relapse-free and overall survival compared to those of higher Ki67 levels. **Conclusions:** High Ki67 expression is associated with ER negativity, Her2 positivity, higher grade and axillary lymph node involvement in breast cancers. The level of Ki67 expression is a prognostic factor predicting relapse-free and overall survival in breast cancer patients.

Keywords: Breast cancer - Ki67 expression - hormone receptor - Her2 - prognosis

Introduction

Breast cancer is the most common malignancy in females in the world. In 2008, it accounted for 23% of the new cancer cases in females (Jemal et al., 2011). Breast cancer also leads to 14% of the total cancer death. However, prognosis of breast cancer is very good especially in early stage disease. To date, a number of prognostic and predictive factors including axillary lymph node involvement, hormone receptor negativity, Her2 positivity, and large tumor size have been described in breast cancer patients. Many other markers such as Ki67 have also been assessed in order to use as a prognostic or predictive marker in breast cancer patients.

Ki67 is classically described as a nuclear protein expressed in proliferating cells with expression levels being altered throughout the cell cycle (Gerdes et al., 1984). Ki67 is expressed in all phases of the cell cycle except the G0 and peaks in the M phase (Beresford et al., 2006). The half-life of the Ki67 antigen is 1-1.5 hours (Heidebrecht et al., 1996). Although some authors suggested that high levels of Ki67 were associated with unfavorable prognosis, the prognostic and predictive value of Ki67 expression level is yet unclear in breast cancer (DeCensi et al., 2011; Tanei et al., 2011).

The aim of this study was to investigate the association between Ki67 expression levels and prognostic factors such as grade, Her2 and hormone receptor expression status in breast cancers.

Materials and Methods

The subjects included patients who were treated due to invasive breast cancer at Cumhuriyet University Faculty of Medicine, Department of Medical Oncology until 31 December 2011. Demographic, clinical and pathological features of the patients were retreived from the hospital records. Menapousal status, grade, hormone receptor status, perineural and lymphovascular invasion, stage, and nodal status of the patients were recorded to the study database. RFS is defined as the length of time after primary treatment for a cancer ends that the patient survives without local relapse, distant metastasis, and contralateral breast cancer. And Overall survival is defined as the length of time from the date of diagnosis for a disease that patients diagnosed with the disease are still alive.

Estrogen and progesterone receptor (ER and PgR) expressions were defined as positive when nuclear staining was >1%. cErbB2 receptor expression was described as positive either with a 3+ immunohistochemical staining or positivity using the FISH method. For Ki67 staining, 4μm sections were dewaxed in xylene and then hydrated by means of a series of graded ethanol baths and rinsed in water. After blocking the endogenous peroxidase activity,

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antigen retrieval was performed by microwaving at 750W in pH 6.0 citrate buffer for 10 min. Sections were then incubated for one hour at room temperature with MIB-1 primary antibody (Dako, Denmark) at 1:50 dilution. Biotinylated rabbit anti-mouse immunoglobulin was used as the secondary antibody, followed by the application of avidin-biotin complex (ABC) (Dako). Peroxidase activity was developed with diaminobenzene (DAB) (Sigma, USA) and counterstaining was conducted with haematoxylin. All washes and dilutions were performed with phosphate-buffered saline (PBS). Stained sections were then examined using a standard light microscope, with the observer blinded to patient outcome. Ki67 score was defined as the percentage of nuclear staining positive cells (at least 1000) among the totalnumber of malignant cells counted in 10 high-power fields (940). The same staining procedure that was described for MIB-1 was used for ER, with microwave antigen retrieval. Sections were incubated for two hours at room temperature with 6F11 primary antibody (Novocastra, UK) at 1:40dilution. All pathological reports of tumor specimens obtained at surgery were retrospectively evaluated. ER, PgR, cErbB2, and Ki 67 proliferation indices were recorded to a database. This study was approved by the Ethical Committe of Cumhuriyet University Faculty of Medicine (Decision Number: 2011-01/19).

Statistical analyses

The optimal cutoff value for Ki67 was selected by use of the Time-dependent ROC (receiver operating characteristic) curves analysis for censored survival data with R software version 3.0.2 (Heagerty et al., 2000). The SPSS software package version 15.0 (Chicago, IL) was used for all the remaining statistical analyses. The association between the Ki67 index and clinicopathological parameters was analyzed by the chi-square test. The changes of Ki67, ER and PR populations, or FISH scores of HER2 were assessed by the Wilcoxon signed rank test. We also performed logistic regression analysis and Cox-regression analysis to determine whether Ki67 value was independent prognostic factor for breast cancer survival or not. Overall survival and relaps-free survival were calculated with the Kaplan-Meier method. Statistical significance was assumed for $p<0.05$ from two-sided tests.

Results

In this study, data from 163 patients with breast cancer were analyzed. The mean age of the patients was 53.4±12.2 years. The patients' characteristics were summarized in Table 1. 67% of the study population was postmenopausal. The most common histological subtype was the invasive ductal carcinoma (76%). Immunohistologically, 65% of the patients were defined as ER positive, 61% were PgR positive and 28% were Her2 positive by the evaluation of two independent investigators (ET, SE). The patients were classified as Luminal A or B (72%), Her2 positive but hormone receptor negative (13%), and triple negative (14%). In 56% of the cases, at least one axillary lymph node was positive.

Table 1. The Patients' Characteristics

		n	%
Age (mean±sd)		53.4±12.2	
Menopausal status (%)	Premenopausal	54	33
	Postmenopausal	109	67
Histology	Invasive Ductal	124	76
	Invasive Lobular	14	9
	Mixt	21	13
	Other	4	2
Stage	I	27	17
	II	75	46
	III	48	29
	IV	13	8
ER (+)		106	65
PR (+)		100	61
Her2 (+)		46	28
Grade	I	53	33
	II	60	37
	III	45	28
LVI (+)		80	49
PNI (+)		48	29
Node (+)		91	56
Triple negative		23	14
Relapse		23	14
Exitus		29	18

*ER: Estrogen receptor; PR: progesterone receptor; LVI: lymphovascular invasion; PNI: perineural invasion

Table 2. The Relationship between Expression Level of Ki67 and the Patients' Characteristics

		Ki67 ≤20	Ki67 >20	p
Age (mean±sd)		54.1±11.9	53.0±12.3	0.629
Age n(%)	<50	35 (52)	33 (48)	0.885
	≥50	50 (53)	45 (47)	
Menopausal status n (%)				
	Premenopausal	17 (32)	37 (68)	0.360
	Postmenopausal	45 (40)	66 (60)	
Grade n (%)	I	39 (74)	14 (26)	<0.001
	II	33 (55)	27 (45)	
	III	11 (24)	34 (76)	
Lymphovascular invasion n (%)				
	Absent	49 (67)	24 (33)	0.001
	Present	32 (40)	48 (60)	
Perineural invasion n (%)				
	Absent	60 (57)	45 (43)	0.124
	Present	21 (44)	27 (56)	
Estrogen receptor n (%)				
	Negative	23 (41)	33 (59)	0.035
	Positive	62 (59)	44 (41)	
Progesteron receptor n(%)				
	Negative	27 (44)	35 (56)	0.073
	Positive	58 (58)	42 (42)	
Her2 n (%)	Negative	70 (60)	46 (40)	0.001
	Positive	15 (33)	31 (67)	
Lymph node involvement n (%)				
	Negative	44 (67)	22 (33)	0.003
	Positive	39 (43)	52 (57)	
Stage n (%)	I	21 (78)	6 (22)	<0.001
	II	44 (59)	31 (41)	
	III	18 (38)	30 (62)	
	IV	2 (15)	11 (85)	
Luminal A or B n (%)	No	17 (37)	29 (63)	0.008
	Yes	69 (59)	48 (41)	
Triple negative n (%)	No	57 (40)	83 (60)	0.261
	Yes	7 (30)	16 (70)	

Relationship of Ki67 with other pathological factors and biomarkers

Median Ki67 positivity was 20% in this study. By using the median value as the cut-off value, patients were divided into Ki67-high and Ki67-low groups. The mean age was similar between these two groups (54.1±11.9 *vs* 53.0±12.3; p=0.629). The relationship of Ki67 with other pathological factors and biomarkers was displayed in Table 2.

Ki67-high tumors were significantly associated with high grade (p<0.001), lymphovascular invasion (p=0.001), ER negativity (p=0.035), Her2 positivity (p=0.001), advanced stage (p<0.001) and lymph node positivity (p<0.003) of the tumor. There was no relationship between the age, menopausal statuses, perineural invasion, PR staining and Ki67 positivity. Ki67 proliferation index was significantly higher in patients with histologically Luminal A or B (p<0.001) tumors. Although the Ki67 index was higher in cases with triple negative disease, this relationship could not reach statistical significance (p=0.269).

Time-dependent ROC curve analysis was also performed in this study population for Ki67 positivity. According to the analyses, the cut-off value was 20% for Ki67 (p=0.005) (Figure 1). For this cut-off value, the sensitivity was 72% and the specificity was 65%.

Survival analysis

The median follow-up was 52 months (3-140 months) among study subjects. Lower Ki67 levels were significantly associated with longer median relaps-free survivals compared to those of higher Ki67 levels for cut-off level 20% (p=0.008) (Figure 2). The 5-year relaps-free survival was 93% *vs* 66% respectively. The overall survival was longer in patients with lower Ki67 levels than those with higher levels for cut-off level 20%
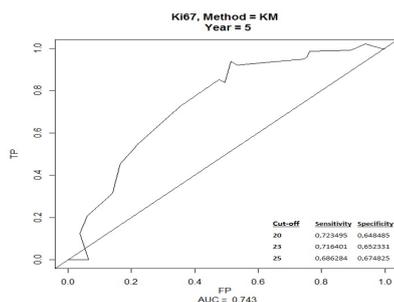

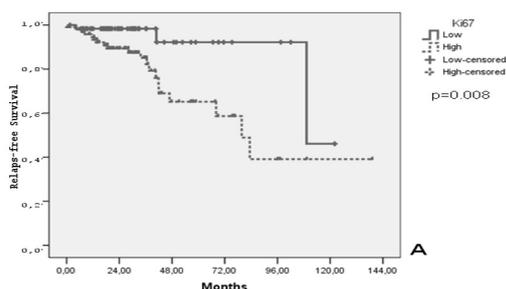**Figure 1. Time-dependent ROC Curve Analysis for Ki67 Expression (p=0.005)**

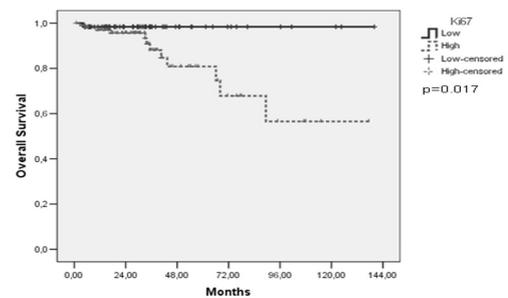**Figure 2. Relapse-free Survival Curve (p=0.008 for Ki67 Cut-Off Level 20%)**

Figure 3. Overall Survival Curve (p=0.017 for Ki67 Cut-off level 20%)

(p=0.017 (Figure 3). The 5-year overall survival was 98% for patients with Ki67 levels below 20%, and 80% for patients with higher Ki67 levels.

Discussion

Herein our group suggested a significant association between the high Ki67 antigen proliferation index and other prognostic factors including high grade, ER negativity, Her2 positivity, advanced stage, and positive lymph node involvement in breast cancer patients. Furthermore, the overall survival and relaps-free survival rates were improved in patients with lower Ki67 levels.

Ki67 is a proliferation marker that is expressed in all cell-cycle phases. However, it is expressed at levels below 3% in breast tissues from healthy subjects. Although Ki67 expression in breast cancer cells was previously reported, assessment of cellular proliferation by Ki67 expression is not yet recommended in routine pathological evaluation by the existing guidelines of the American Society of Clinical Oncology and European Society of Medical Oncology. In fact, investigators have previously argued that a higher Ki67 proliferation index has both a prognostic and a predictive significance in breast cancer (van Diest et al., 2004; Urruticoechea et al., 2005; de Azambuja et al., 2007; Dowsett et al., 2007). The 2013 St Gallen Consensus has recommended using markers of proliferation, such as Ki67, in determining the optimum treatment strategy for early breast cancers (Untch et al., 2011).

Hormone receptor expression level is associated with Ki67 expression in breast tissue. While Ki67 is highly expressed in ER negative tumor cells, its expression is lower in patients with ER positive tumors. Also, a significant association between Ki67 expression and ER negativity was observed (Faratian et al., 2009). However, hormone replacement therapy with anastrozole or letrozole is known to result in a decreased Ki67 expression (Fabian et al., 2007). In another study, a significant association between higher Ki67 expression levels and ER negativity was reported (Klintman et al., 2010). Ki67 expression following neoadjuvant hormone replacement therapy was identified to be significantly associated with a favorable prognosis and lower recurrence rate (Dowsett et al., 2007; Ellis et al., 2008). However, the reports demonstrating the relationship between Ki67 expression and tumor grade in breast cancer has been inconsistent. While many studies suggested that higher Ki67 levels were positively correlated with high grade tumors (Gasparini et al., 1991;

Sahin et al., 1991; Klintman et al., 2010), others could not detect any association (Jalava et al., 2006; Faratian et al., 2009; Tanei et al., 2011). Tan et al. showed that histological grade in breast cancers was significantly correlated with Ki67 immunohistochemical staining (Tan et al., 2005). Likewise, higher Ki67 expression was significantly associated with high grade in our study.

Her2 status is a prognostic and predictive factor for breast cancer. Breast tumors which are Her2 positive tend to have higher proliferation rates. Several studies demonstrated an association between higher Ki67 levels and Her2 positivity (Bottini et al., 2001; Viale et al., 2008; Faratian et al., 2009; Klintman et al., 2010). In contrast, Some authors reported that there was not any significant association between Ki67 levels and Her2 status (Tanei et al., 2011; Gudlaugsson et al., 2013). We also evaluated the relationship between Ki67 expression levels and Her2 status in this study, and found that Ki67 expression was higher in Her2 positive patients.

Lymp node involvement is proven to be the most important prognostic factor for breast cancer. The overall and progression-free survivals in lymph node positive patients are shorter than those without lymph node involvement. Hovewer, the association between lymph node status and the level of Ki67 expression has not been adequately investigated. It was suggested in a study where the prognostic significance of Ki67 expression was evaluated in premenopausal node negative breast cancer patients that the prognostic value of Ki67 was restricted only to the ER-positive and grade 2 patients (Klintman et al., 2010). In contrast, no significant association between the Ki67 expression levels and lymph node involvement could be demonstrated in another study (Tanei et al., 2011).

Many studies have investigated the use of Ki67 as a prognostic marker for breast cancer (Colozza et al., 2005; de Azambuja et al., 2007; Stuart-Harris et al., 2008; Jones et al., 2009; Yerushalmi et al., 2010; Tanei et al., 2011). In the majority of those studies, it was reported that higher Ki67expression was associated with poor prognosis. de Azambuja et al published a meta-analysis of 35 studies involving 12500 early stage breast cancer patients, evaluating the prognostic value of the level of Ki67 expression in breast cancers (de Azambuja et al., 2007). They indicated that high Ki67 expression was associated with worse prognosis, with decreased overall survival (OS) (HR: 1.95) and disease-free survival (DFS) (HR: 1.93) rates. In addition, significantly worse DFS and OS outcomes were reported independently in both node-negative and node-positive patients compared with those who had lower Ki67 expression scores. Moreover, the DFS and OS were decreased in patients with higher Ki67 scores regardless of the treatment status. These results were confirmed by a recently published meta-analysis with a larger sample size (Stuart-Harris et al., 2008). In this meta-analysis, the OS was siginficantly shorter in patients with high Ki67 expression. It was also reported in these two meta-analyses that a statistically significant association existed between high Ki67 expression levels and increased risk for breast cancer relapse (de Azambuja et al., 2007; Stuart-Harris et al., 2008). Jones at al, in their study, suggested that post-therapy Ki67 was the only

significant independent prognostic factor for relaps-free survival (Spyratos et al., 2002). The authors showed that higher Ki67 level may be useful to distinguish luminal A from luminal B breast cancer subtypes. In our study, the relaps-free and overall survival have significantly prolonged in patients with higher Ki67 expression level. The results of our study confirmed that higher Ki67 expression level was a prognostic factor for breast cancer.

Recently, Inwald et al. demonstrated in a large cohort that Ki-67 level is an important prognostic factor for breast cancer (Inwald et al., 2013). They reported that higher levels of Ki-67 were significantly associated with premenopausal status, lymph node positivity, higher tumor size, lymphatic and vascular invasion, ER negativity as well as Her2 positivity. According to Ki67 staining pattern in tumor cells, five levels for Ki67-labeling were defined in this study and the study population was categorized into 5 different groups according to those Ki67 levels. In comparison to the baseline group (Ki67<15%), higher Ki67 was associated with worse prognosis and was an independent poor prognostic factor for DFS and OS. However, this association could not be shown for the group of patients with Ki67 levels between 16 and 25%. It was also reported in the study that the survival curves were prominently different between the patients with a Ki67 labeling of <25% and ≥26%.

There are some limitations of this study, however. First, the optimal cut-off level for Ki67 expression in breast cancer has not yet been universally established. Some authors defined 20% or more Ki67 staining as a high expression level, while others justified the median value of percent positively stained cells as the distinguishing value to segregate high expression from low (Spyratos et al., 2002; Talley et al., 2002). Herein, 20% staining was defined as the cut-off value for Ki67 expression. In addition, we also performed the Time-dependent ROC curve analysis to determine the cut-off value for Ki67 expression level. According to the ROC curve analysis, 20% was the value demonstrating the highest specificity and sensitivity. Another limitation was that this study was planned as a retrospective study. Although the association between Ki67 expression and other prognostic factors was not negatively affected, the overall and progression-free survivals might be affected from the retrospective data.

In conclusion, high Ki67 expression was associated with ER negativity, Her2 positivity, higher grade and axillary lymph node involvement in breast cancers. The level of Ki67 expression was also presented as a prognostic factor predicting the relaps-free and overall survival in breast cancer patients. Ki67 expression level in tumor tissue might be used in decision making, regarding the treatment and risk stratification of breast cancer patients in future.

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