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ORIGINAL ARTICLE

Predictors of Recurrent Ductal Carcinoma *In Situ* after Breast-Conserving Surgery

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Purpose: Local recurrence is a major concern in patients who have undergone surgery for ductal carcinoma *in situ* (DCIS). The present study assessed whether the expression levels of hormone receptors, human epidermal growth factor receptor 2 (HER2), and Ki-67, as well as resection margin status, tumor grade, age at diagnosis, and adjuvant hormonal therapy and radiotherapy (RT) are associated with recurrence in women with DCIS. **Methods:** In total, 111 patients with DCIS were included in the present study. The invasive and noninvasive recurrence events were recorded. The clinicopathological features; resection margins; administration of hormonal therapy and RT; expression statuses of estrogen receptor (ER), progesterone receptor (PR), and HER2; Ki-67 expression; and molecular subtypes were evaluated. Logistic regression analysis was performed to examine the risk factors for recurrence. **Results:** Recurrence was noted in 27 of 111 cases (24.3%). Involvement of resection margins, low tumor grade, high Ki-67 expression, and RT were independently associated with an increase in the recurrence rate ($p<0.05$, Pearson chi-square test). The recurrence rate was not significantly associated with patient age; ER, PR, and HER2 statuses; molecular subtype; and hormonal therapy. **Conclusion:** The results of the present study suggested that the involvement of resection margins, low tumor grade, high Ki-67 index, and the absence of adjuvant RT were independently associated with increased recurrence in patients with DCIS. Future studies should be conducted in a larger cohort of patients to further improve the identification of patients at high-risk for DCIS recurrence.

Key Words: *Breast, Carcinoma, Intraductal, Recurrence*

INTRODUCTION

Breast screening programs such as mammography or biopsy have resulted in the increase in the detection of ductal carcinoma *in situ* (DCIS) [1,2]. DCIS is the most common type of noninvasive breast cancer [1]. Patients with DCIS have excellent survival rates; however, invasive recurrence is associated with mortality. Therefore, local recurrence is a major concern in patients with DCIS [3,4]. The need to identify patients at risk for recurrence of DCIS is a significant priority. Surgical biopsy provides useful information on the extent of a lesion, its margins, and multifocality or multicentricity, along with histopathological grading and immunohistochemical information such as estrogen receptor (ER) and progesterone receptor (PR) statuses, human epidermal growth factor receptor 2 (HER2) status and the proliferative potential of the lesion, often measured by the Ki-67 index. Detailed histopathological findings on DCIS help the clinicians to determine additional treatment options [5]. The Van Nuys prognostic index (VNPI) was initially established in 1996. The tumor size, margin width, and pathological classification are the three significant predictors of local recurrence, and they are combined to form a final score for the prognostic index [6,7]. The updated University of Southern California/VNPI, which also incorporated patient age, was developed after 7 years, and the DCIS treatment range was determined based on the combined score. For patients with intermediate scores, excision is considered as the treatment option, whereas for patients with high scores, further treatment is considered [8]. DCIS can be classified into the same molecular subtypes as invasive breast cancer via gene expression analysis [9]. In addition, a pivotal role for the prognostic characterization of DCIS has been to support the newly established Oncotype DX® Breast Cancer assay for DCIS (DCIS Score) [10]. This is the first multigene assay that

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generates individualized estimates for the 10-year risk of any local recurrence. The DCIS score was significantly associated with the risk of invasive local recurrence, separate from the overall risk of local recurrence [10]. After the validation of the DCIS score assay, the ability of a given test result to influence patient management was referred to as "clinical utility" [11, 12]. The aim of the present study was to identify the biological markers or molecular predictors for local recurrence, which might potentially stratify women with DCIS into high- and low-risk populations, and further improve risk stratification and treatment recommendations for women with DCIS [13]. However, conflicting results have been published, as some studies suggested that biological markers are associated with recurrence rates [14,15], whereas other studies did not [16]. In this context, the present study aimed to determine the clinicopathological and molecular characteristics associated with recurrence rates in women with DCIS after breast-conserving surgery (BCS).

METHODS

In total, 111 patients treated and followed up for DCIS at Inje University, Sanggye Paik Hospital between 1990 and 2010 were included in the present study. All patients were treated with BCS. After the surgery, adjuvant hormonal therapy and radiotherapy (RT) were considered. When the patients were diagnosed as ER- or PR-positive, we routinely considered adjuvant hormonal therapy such as tamoxifen or anastrozole irrespective of whether the patients received RT to the ipsilateral breast. A positive resection margin was defined by a distance of < 1 mm from the tumor cells. DCIS was divided into three tumor grades according to the nuclear grade and necrosis. Tumors with nonhigh nuclear grade and without necrosis were classified as low-grade, those with nonhigh nuclear grade with necrosis were classified as intermediate-grade, and those having high nuclear grade with or without necrosis were classified as high-grade disease. The following antibodies were used for the immunohistochemistry (IHC) analysis: ER (SP1; Dako, Carpinteria, USA), PR (SP2; Dako), HER2 (A0485; Dako), Ki-67 (MIB-1; Dako), CK5/6 (D5/16; Dako), and epidermal growth factor receptor (EGFR) (E30; Dako). Patients with HER2 IHC grades of 2+ subsequently underwent HER2 fluorescence *in situ* hybridization (PathVysion™; Abbott Molecular Inc., Des Plaines, USA), in order to determine the HER2 status of the patient. The patients were classified as ER, PR, and HER2 positive or negative, and the latest American Society of Clinical Oncology (ASCO) guidelines for the detection and scoring of ER, PR, and HER2 statuses were followed [17,18]. The Ki-67 expression was classified as low (< 14%) or high (≥ 14%). Based on the results of the IHC analysis, the molecular subtypes were defined as luminal A (ER+ and/or PR+, HER2 and Ki-67 low), luminal B (ER+ and/or PR+, HER2+/ER+ and/or PR+, HER2 and Ki-67 high), HER2 positive (ER–, PR–, and HER2+), and the basal-like (ER–, PR–, HER2–, EGFR+ and/or CK5/6+). All patients underwent mammography, physical examination, chest radiography, and breast ultrasonography during the follow-up period. The total number of invasive and noninvasive recurrence events was monitored. This study was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (SGPAIK 2016-02027).

Statistical methods

The following clinical and pathological factors were assessed: age at diagnosis (in 10-year increments); the Van Nuys tumor grade (a one level increase in the 1–3 scale); ER expression (positive vs. negative); PR expression (positive vs. negative); HER2 amplification (positive vs. negative); Ki-67 expression (high vs. low); tumor margin (involved vs. clear); hormonal therapy (performed vs. not performed); and RT (performed vs. not performed). The molecular subtypes were also analyzed. The associations between clinicopathological variables and tumor recurrence were examined. Pearson chi-square and Student t-tests were used to analyze discrete and quantitative variables, respectively. Potential risk factors for tumor recurrence were further examined using univariate and multivariate logistic regression analyses. All statistical analyses were performing using the IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, USA). All p-values < 0.05 were considered statistically significant.

RESULTS

The patients consisted of 111 women with DCIS. The median ages at diagnosis and recurrence were 48 years (range, 17–73 years) and 50 years (range, 36–70 years), respectively. After the BCS, adjuvant RT was performed in 47 of 111 patients (42.3%). Among the 88 ER- or PR-positive patients, 67 (76.1%) received adjuvant hormonal therapy and 36 (40.9%) received both hormonal therapy and RT. The involvement of resection margins was noted in 25 cases (22.5%). In these cases, additional sequential resection was not performed. Of 25 patients, 10 (40.0%) received RT, and four of whom (40.0%) showed tumor recurrence. On the other hand, among the 15 patients who did not receive RT, 10 patients (66.7%) showed tumor recurrence. RT was not performed in patients with low grade DCIS, those aged < 25 years old or aged > 70 years old, the presence of phobia on the side effects of RT, the presence

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of cardiovascular disease or systemic disease, and poor performance status. The DCIS tumor grade was low in 25 (22.5%), intermediate in 35 (31.6%), and high in 51 (45.9%) patients. The ER and PR statuses were positive in 88 (79.3%) and 82 (73.9%) cases, respectively. Ki-67 expression was low and high in 84 (75.7%) and 27 (24.3%) cases, respectively. The molecular subtypes of the majority of cases were luminal A (43.2%), followed by luminal B (37.0%), HER2 positive (18.0%), and basal-like (1.8%). The median follow up was 48 months (range, 6–162 months). Recurrence was noted in 27 of 111 cases (24.3%) (Table 1). Among these 27 cases, 12 (44.4%) showed noninvasive recurrences, and 15 (55.6%) showed invasive recurrences. The recurrence rates were 40.8%, 33.3%, 22.2%, and 3.7% for luminal B, luminal A, HER2 positive and basal-like subtypes, respectively. When the original status of the hormone receptors and HER2 were compared, 12 of 15 (80.0%) invasive recurrent carcinoma cases showed the same status and the most common initial subtype was ER+/PR+/HER2– (46.7%). Among the 12 noninvasive recurrences, nine cases (75.0%) had the same hormone receptor and HER2 statuses as the primary tumor. In contrast to the invasive recurrent cases, the most common initial subtype

Table 1. The clinicopathological characteristics

Categorical variable	No. of case (%) (n=111)
Recurrence	
Negative	84 (75.7)
Positive	27 (24.3)
Resection margin	
Negative	86 (77.5)
Positive	25 (22.5)
Tumor grade	
I	25 (22.5)
II	35 (31.6)
III	51 (45.9)
ER	
Negative	23 (20.7)
Positive	88 (79.3)
PR	
Negative	29 (26.1)
Positive	82 (73.9)
HER2	
Negative	56 (50.5)
Positive	55 (49.5)
Ki-67	
Low	84 (75.7)
High	27 (24.3)
Molecular subtype	
Luminal A	48 (43.2)
Luminal B	41 (37.0)
HER2-positive	20 (18.0)
Basal-like	2 (1.8)
RT	
Negative	64 (57.7)
Positive	47 (42.3)
Endocrine treatment*	
Negative	21 (23.9)
Positive	67 (76.1)
Endocrine treatment and RT*	
Negative	52 (59.1)
Positive	36 (40.9)

ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; RT=radiotherapy.
*For the patient with positive ER or PR.

Table 2. Univariate logistic regression analysis of tumor recurrence and clinicopathological factors

	Tumor recurrence, No. (%)		*p*-value	HR (95% CI)
	No	Yes		
Resection margin			0.000	
Negative	73 (86.9)	13 (48.1)		Ref
Positive	11 (13.1)	14 (51.9)		7.15 (2.67–19.15)
Tumor grade			0.001	
I	18 (21.4)	7 (25.9)		Ref
II	26 (31.0)	9 (33.3)		0.08 (0.02–0.34)*
III	40 (47.6)	11 (40.7)		0.30 (0.11–0.81)*
RT			0.024	
No	43 (67.2)	21 (32.8)		Ref
Yes	41 (87.2)	6 (12.8)		0.31 (0.12–0.86)
Hormonal treatment†			0.867	
No	16 (76.2)	5 (23.8)		Ref
Yes	52 (77.6)	15 (22.4)		0.91 (0.29–2.88)
HT and RT†			0.161	
No	37 (71.2)	15 (28.8)		Ref
Yes	32 (88.9)	4 (11.1)		0.32 (0.06–1.61)
ER			0.706	
Negative	17 (19.8)	6 (24.0)		Ref
Positive	69 (80.2)	19 (76.0)		0.82 (0.28–2.36)
PR			0.508	
Negative	21 (24.49)	8 (32.0)		Ref
Positive	65 (75.6)	17 (68.0)		0.72 (0.27–1.91)
HER2			0.910	
Negative	42 (50.6)	14 (50.0)		Ref
Positive	41 (49.4)	14 (50.0)		1.00 (0.40–2.27)
Ki-67			0.010	
Low	70 (82.4)	14 (53.8)		Ref
High	15 (17.6)	12 (46.2)		3.56 (1.35–9.37)
Molecular subtype			0.588	
Luminal A	39 (46.4)	9 (33.3)		Ref
Luminal B	30 (35.7)	11 (40.7)		1.59 (0.58–4.33)‡
HER2(+)	14 (16.7)	6 (22.2)		1.86 (0.56–6.17)‡
Basal-like	1 (1.2)	1 (3.7)		4.33 (0.25–76.05)‡

HR=hazard ratio; CI=confidence interval; RT=radiotherapy; HT=hormonal treatment; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2.
*Versus grade I; †Treatment for ER(+) or PR(+) patients; ‡Versus luminal A.

(41.7%) was ER−/PR−/HER2+ and the second most common initial subtype (33.3%) was ER+/PR+/HER2+. Univariate and multivariate analyses showed that recurrence rates were significantly associated with low tumor grade ($p=0.001$ and $p=0.004$, respectively), Ki-67 ($p=0.010$ and $p=0.026$, respectively), and the resection margin ($p=0.000$ and $p=0.034$, respectively). However, recurrence rates were not associated with age; ER, PR, and HER2 statuses; or the molecular subtype (Tables 2, 3).

Table 3. Multivariate logistic regression analysis of tumor recurrence and clinicopathological factors

	Tumor recurrence, No. (%)		*p*-value	HR (95% CI)
	No	Yes		
Resection margin			0.034	
Negative	73 (86.9)	13 (48.1)		Ref
Positive	11 (13.1)	14 (51.9)		10.90 (3.30–35.99)
Tumor grade			0.004	
I	18 (21.4)	7 (25.9)		Ref
II	26 (31.0)	9 (33.3)		0.08 (0.02–0.34)*
III	40 (47.6)	11 (40.7)		0.30 (0.11–0.81)*
RT			0.025	
No	43 (67.2)	21 (32.8)		Ref
Yes	41 (87.2)	6 (12.8)		0.22 (0.06–0.83)
Hormonal treatment†			0.957	
No	16 (76.2)	5 (23.8)		Ref
Yes	52 (77.6)	15 (22.4)		0.96 (0.20–4.67)
HT and RT†			0.283	
No	37 (71.2)	15 (28.8)		Ref
Yes	32 (88.9)	4 (11.1)		0.24 (0.02–3.23)
ER			0.706	
Negative	17 (19.8)	6 (24.0)		
Positive	69 (80.2)	19 (76.0)		
PR			0.508	
Negative	21 (24.49)	8 (32.0)		
Positive	65 (75.6)	17 (68.0)		
HER2			0.910	
Negative	42 (50.6)	14 (50.0)		
Positive	41 (49.4)	14 (50.0)		
Ki-67			0.026	
Low	70 (82.4)	14 (53.8)		Ref
High	15 (17.6)	12 (46.2)		5.47 (1.31–22.74)
Molecular subtype			0.358	
Luminal A	39 (46.4)	9 (33.3)		Ref
Luminal B	30 (35.7)	11 (40.7)		0.62 (0.14–2.78)‡
HER2(+)	14 (16.7)	6 (22.2)		1.40 (0.22–9.17)‡
Basal-like	1 (1.2)	1 (3.7)		9.91 (0.50–198.46)‡

HR = hazard ratio; CI = confidence interval; RT = radiotherapy; HT = hormonal treatment; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.
*Versus grade I; †Treatment for ER(+) or PR(+) patients; ‡Versus luminal A.

DISCUSSION

BCS is a method that is widely acknowledged in the management of DCIS. However, the risk of ipsilateral recurrence after BCS is up to 30%, half of which accounts for the invasive breast cancer cases [19,20]. In the present study, 24.3% of the cases showed recurrence, and 55.6% of the recurrences were invasive cancers. One large study demonstrated that the excision margin is the most important factor in predicting the recurrence of DCIS after local excision, indicating that a margin of 1 mm is probably insufficient, and that an excision margin of 5 mm should be the aim [21]. Therefore, if the margins are positive, re-excision is definitely indicated. However, a recent series from four high-volume breast centers varied between 74% and 94% in the re-excision rates for positive margins [22]. Although the case-specifics cannot be known, such variation suggested that clear evidence supporting re-excision for positive margins is not always obtained. In the present study, a resection margin <1 mm was a significant risk factor. Adding whole breast irradiation to the treatment followed by BCS reduced the relative risk of local recurrence; however, this treatment has not been shown to have an impact on survival [23]. Univariate and multivariate analyses showed that RT reduced tumor recurrence. However, hormonal therapy was not statistically significant even in hormone receptor positive patients. The role of adjuvant endocrine therapy remains uncertain [5]. The role of a high-grade tumor in the prognosis of DCIS recurrence is also consistent with the University of Southern California/VNPI framework [8,9]. We showed that low tumor grade was significantly associated with recurrence. The results pertaining to the aggravating role of Ki-67 expression in the present study are consistent with those reported in a recent study [24], showing that Ki-67 is a risk factor for invasive recurrence. We observed a significant correlation between high Ki-67 expression and tumor recurrence. Ki-67 is expressed during the active phases of the cell cycle, but not during the G0 resting phase [25]. Therefore, Ki-67 expression might indicate a potential for future recurrence.

The risk of local recurrence after BCS for DCIS was related to a high tumor grade, close or involved resection margins, and age <50 years [20]. In the present study, we showed independent associations between the recurrence rate and low tumor grade and involved resection margins. Furthermore, young age was not associated with recurrence. Meta-analyses reported varying results [26,27]. Wang et al. [26] confirmed significant associations between DCIS recurrence and comedonecrosis, focality, margin status, the method of detection, tumor grade, and tumor size. Zhang et al. [27] highlighted ipsilateral recurrence of DCIS and positive margins as risk factors deter-

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mined via the symptomatic nonscreen detection method; however, no associations were found between nuclear grade, comedonecrosis, tumor size, multifocality, hormonal status, or HER2 positivity and tumor recurrence. One study showed that there was no association between the molecular subtype and risk of recurrence [28]. On the other hand, another study suggested that luminal B, HER2 positive, and basal-type DCIS subtypes were associated with recurrence, compared to the luminal A DCIS [24]. In the present study, we did not identify a significant relationship between molecular subtype and recurrence. However, our results were hampered by a small patient cohort and definitive conclusions could not be reached. In 12 noninvasive recurrent cases, the conversion rates of hormone receptors and HER2 were three cases (25.0%) and two cases (16.7%), respectively. In 15 invasive recurrent cases, the conversion rates of hormone receptors and HER2 were three cases (20.0%) and three cases (20.0%), respectively. Previous studies demonstrated variations in the receptor status between the primary tumor and the recurrent lesion as 40% for PR, 36% for ER, and 20% for HER2 [29]. The reasons for these discrepancies could indicate that the molecular profile of breast cancers evolves over time and that biomarkers are heterogeneously expressed within the tumor [30]. We found no definitive data on the prognostic significance of receptor expression status in the literature.

In conclusion, the present study attempted to trace the pathogenesis of DCIS to tumor recurrence based on risk factors. Resection margin involvement, low tumor grade, high Ki-67 expression, and RT were the key prognostic factors for tumor recurrence. In-depth knowledge of the biological components and additional molecular markers could reveal additional predictive elements for the recurrence of DCIS.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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