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Research Article

Ductal Carcinoma *In situ* Manageable by Active Surveillance

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- Ductal carcinoma *in situ*; Invasive ductal carcinoma; Overdiagnosis; Active surveillance

Abstract

Background: The widespread use of mammography for breast cancer screening has increased the detection of ductal carcinoma *in situ* (DCIS), leading to breast cancer overdiagnosis. In this study, we investigated the clinicopathological characteristics of DCIS to determine whether it could be managed by active surveillance.

Methods: We analyzed 613 invasive ductal carcinomas (IDCs) and 220 DCIS removed by surgery in 2012. Using cancer mapping diagrams of the surgical specimens, we classified the IDC lesions into four groups according to the proportion of intraductal components: group A (≤25%), group B (>25%–≤50%), group C (>50%–≤75%), and group D (>75%). We characterized group D and identified the DCIS cases with the same characteristics.

Results: There were 273 IDC lesions in group A (44.5%), 112 in group B (18.3%), 74 in group C (12.1%), and 154 in group D (25.1%). Compared with the other three groups, the group D included significantly more nuclear grade 1 lesions ($P = 0.006$), more comedo-type ($P = 0.030$), and more hormone receptor-negative and HER2-positive subtypes ($P < 0.001$). Only one DCIS lesion had all these three characteristics.

Conclusions: In this study, we assumed that IDCs with a predominant intraductal component had taken a long time to invade, and we used the proportion of intraductal components as an index of the time for invasion. Since the number of DCIS lesions exhibiting the same characteristics as the IDC lesions was too small, we could not make any conclusion on DCIS overdiagnosis.

ABBREVIATIONS

DCIS: Ductal Carcinoma *in situ*; IDC: Invasive Ductal Carcinoma; USPSTF: The U.S. Preventive Service Task Force; NG: Nuclear Grade; ER: Estrogen Receptor; PgR: Progesterone Receptor; HR: Hormone Receptor; HER2: Human Epidermal Growth Factor Receptor 2; BCT: Breast-Conserving Therapy; VNPI: Van Nuys Prognostic Index; SEER: Surveillance, Epidemiology, and End Results; USC/VNPI: University of Southern California/Van Nuys Prognostic Index

INTRODUCTION

Breast cancer screening with mammography is effective in reducing mortality in women between 50 and 74 years of age (relative risk, 0.78; 95% confidence interval [CI], 0.70–0.85) and in those in their 40s (relative risk, 0.85;95% CI, 0.73–0.98) [1,2]. The U.S. Preventive Service Task Force (USPSTF) has stated that the effectiveness of mammography screening in reducing mortality is the same for women in their 40s and 50s. However, false positive results are most common among women in their 40s, and the number of women who need to undergo mammography to avoid a single death from breast cancer is highest for women between 39 and 49 years of age [3]. In 2009, the USPSTF changed its recommendation grade for mammographic screening for women in their 40s from "recommended for all" to "recommended for selective cases" [4]. In 2012, Bleyer et al., reported that although the number of early-stage breast cancers detected in women before the age of 40 had approximately doubled in the United States over 30 years after the introduction of mammographic screening, there was no corresponding decrease in the number of advanced cancers [5]. This study raised the issue that most of the cases of breast cancer discovered during screening may be overdiagnosed, triggering a subsequent debate [6]. In 2015, the USPSTF stated that screening mammography for women in their 40s entails the risk of overdiagnosis, that is, the detection and treatment of breast cancers that would have no effect on survival, if left untreated [7].

Overdiagnosed breast cancers can include ductal carcinoma *in situ* (DCIS), in which metastasis and recurrence are extremely rare. Two Phase III trials are currently underway in Europe with the aim of identifying cases of DCIS that are considered to undergo overtreatment based on overdiagnosis [8,9]. These trials are designed to verify the non-inferiority of active

surveillance compared with standard therapy for women older than 45 years, who have low nuclear grade (NG) DCIS detected from microcalcifications in screening mammography. These studies verify the validity of no surgical intervention in cases of DCIS assumed to have a low likelihood of invasion in a short term.

In the current study, we hypothesized that DCIS cases that require a long time to invade the stroma can be managed by long-term active surveillance and are likely to be overdiagnosed. The aim of this study was to identify the characteristics of DCIS manageable by active surveillance through investigation of the characteristics of invasive ductal carcinomas (IDCs) with a predominant intraductal component.

SUBJECTS AND METHODS

Subjects

In the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, 862 IDC or DCIS patients underwent surgery as an initial treatment between January and December 2012. Among them, 29 lesions (28 lesions removed by open biopsy at another hospital and one lesion removed after chemotherapy for another primary cancer) were excluded. The subjects of this study were 833 breast cancer patients, including 613 IDC and 220 DCIS cases. The patients' median age was 51 (range: 23–91) years. The surgical procedure was mastectomy in 440 cases (52.8%) and partial mastectomy in 393 (47.2%). The median diameter of invasive components in the IDC lesions was 1.1 (range: 0.1–8.0) cm.

Using cancer mapping diagrams of the surgical specimens, we classified the IDC lesions into four groups according to the proportion of intraductal components: group A, ≤25%; group B, >25%–≤50%; group C, >50%–≤75%, and group D, >75%. We compared these four groups in terms of age, NG, comedo necrosis, and immunohistological subtype, and identified the characteristics of group D. Then we investigated the cases that exhibited the same characteristics in the DCIS group.

Histopathological evaluation

According to the 17th edition of the *General Rules for Clinical and Pathological Recording of Breast Cancer*, edited by the Japanese Breast Cancer Society [10], NG was divided into three grades in order of increasing atypia: NG1, low nuclear atypia; NG2, moderate nuclear atypia; and NG3, high nuclear atypia. Intraductal components were classified as comedo type if even a small amount of comedo necrosis was evident, and as non-comedo type if it was absent. IDC lesions with no intraductal component were classified as the non-comedo type. Estrogen receptor (ER) and progesterone receptor (PgR) were evaluated by immunohistochemical testing using clone 1D5 (Dako Japan Inc., Tokyo, Japan) or clone SP1 (Roche Diagnostics K.K., Tokyo, Japan) as the ER antibody, and clone PgR636 (Dako Japan Inc.) or clone 1E2 (Roche Diagnostics K.K.) as the PgR antibody. ER and PgR were assessed as positive if positive cells were ≥10% of the entire lesion, and as negative if they were <10%. Lesions were defined as hormone receptor (HR) positive if they were positive for ER and/or PgR. Human epidermal growth factor receptor 2 (HER2) was investigated by immunohistological testing for protein expression, and was graded as 0, 1+, 2+, or 3+ according to the American Society of Clinical Oncology/College of American Pathologists guidelines on HER2 testing [11]. HER2 immunostaining was carried out using the Hercep Test staining kit (Dako Japan Inc.) or the clone 4B5 HER2 antibody (Roche Diagnostics K.K.). HER2 was assessed as negative if the lesion was graded 0, 1+, or 2+, and as positive if the lesion was graded 3+. Histological factors were evaluated in invasive components of IDC and *in situ* components of DCIS.

Statistical analysis

StatMate III (ATMS, Tokyo, Japan) was used for statistical analysis. Differences between the four IDC groups were assessed by using a non-parametric test for age and a χ^2 test for all other factors. A P value < 0.05 was considered statistically significant.

Ethical considerations

All the subjects provided comprehensive consent for the use of specimens prior to surgery. The study was approved by the institutional review board of the Japanese Foundation for Cancer Research (No. 2015-1053).

RESULTS

Clinicopathological characteristics of the IDC groups

The IDC lesions were classified into four groups according to the proportion of intraductal components (Table 1). The numbers of lesions were 273 in group A (44.5%), 112 in group B (18.3%), 74 in group C (12.1%), and 154 in group D (25.1%). There was no significant difference between the median ages of patients in each group (P = 0.259). Group D included significantly more NG1 lesions (P = 0.006), comedo-type (P = 0.030) and more HR-negative and HER2-positive (P < 0.001) lesions than the other groups. Only one of the 154 lesions in group D exhibited all the three characteristics that were significantly more common in this group.

We investigated the distribution of the three characteristics within group D and found that 77 lesions (50.0%) were NG1, 52 (33.8%) were comedo type, and 23 (14.9%) were HR negative and HER2 positive. Half of the lesions in group D were NG1, and the other half were comedo-type and/or HR-negative and HER2-positive lesions that showed NG2 or NG3.

DCIS characteristics

Then we investigated whether the characteristics more common in group D—with a predominant intraductal component—were exhibited in the DCIS group. We found that 164 lesions (74.5%) were NG1, 35 (15.9%) were comedo type, and 11 (5.0%) were HR negative and HER2 positive. Only one DCIS lesion exhibited all the three characteristics.

DISCUSSION

In this study, we showed that a group of IDCs (group D) had a higher prevalence of NG1, comedo-type, or HR-negative and HER2-positive lesions than the other groups. However, these three characteristics contradict each other as indicators of tumor malignancy based on the proliferative potential. Namely, NG1 is a low malignancy factor associated with low proliferative potential, whereas the comedo type and HER2 positivity are

Table 1: Clinicopathological characteristics of the lesions.

	IDC All	IDC group A	IDC group B	IDC group C	IDC group D	DCIS
Case number	613	273	112	74	154	220
Median age (years)	51	53	51	52	50 *	51
Nuclear grade						
1	249 (40.6%)	94 (34.4%)	49 (43.7%)	29 (39.2%)	77 (50.0%) **	164 (74.5%)
2	240 (39.2%)	110 (40.3%)	47 (42.0%)	35 (47.3%)	48 (31.2%)	42 (19.1%)
3	124 (20.2%)	69 (25.3%)	16 (14.3%)	10 (13.5%)	29 (18.8%)	14 (6.4%)
Comedo necrosis						
Present	166 (27.1%)	60 (22.0%)	30 (26.8%)	24 (32.4%)	52 (33.8%) #	35 (15.9%)
Absent	447 (72.9%)	213 (78.0%)	82 (73.2%)	50 (67.6%)	102 (66.2%)	185 (84.1%)
HR/HER2 status						
$HR^{(+)}HER2^{(-)}$	479 (78.1%)	215 (78.8%)	91 (81.2%)	62 (83.8%)	111 (72.1%)	189 (86.0%)
$HR^{(+)}HER2^{(+)}$	30 (4.9%)	11 (4.0%)	5 (4.5%)	4 (5.4%)	10 (6.5%)	10 (4.5%)
$HR^{(-)}HER2^{(-)}$	61 (10.0%)	35 (12.8%)	11 (9.8%)	5 (6.8%)	10 (6.5%)	10 (4.5%)
$HR^{(-)}HER2^{(+)}$	43 (7.0%)	12 (4.4%)	5 (4.5%)	3 (4.0%)	23 (14.9%) ##	11 (5.0%)

Abbreviations: IDC: Invasive Ductal Carcinoma; DCIS: Ductal Carcinoma i*n situ*; HR: Hormone Receptor; HER2: Human Epidermal Growth Factor Receptor 2

Results of statistical analyses between group D and the other groups

*Age, $P = 0.259$; ** Nuclear grade 1 vs. 2, 3, $P = 0.006$; # Comedo necrosis, $P = 0.030$; ## HR/HER2 status, $HR^{(-)}HER2^{(+)}$ vs. others, $P < 0.001$

high malignancy factors associated with high proliferative potential. In fact, only one of the DCIS lesions exhibited all the three characteristics. The distribution of these characteristics in group D revealed that lesions in this group can be split into two types, NG1 lesions and comedo-type and/or HR-negative and HER2-positive lesions. Group D therefore consisted of two types of lesions with different proliferative potential.

Although it is easy to understand that DCIS with low invasive potential can be NG1 lesions, the number of studies validating this issue is small. Eusebi et al., reported the natural histories of 80 patients with DCIS initially diagnosed as benign by surgical biopsy [12]. They found that a lower proportion of low-NG DCIS cases developed into IDC compared with high-NG DCIS cases, and the prognosis was better for the former than the latter. Silverstein et al., investigated local recurrence risk after breast-conserving therapy (BCT) for DCIS using the Van Nuys Prognostic Index (VNPI), which combines tumor size, surgical margin width, degree of NG and presence or absence of comedo necrosis [13]. In the study, local recurrence-free survival after BCT was highest for low-NG tumors (NG1 or NG2) without necrosis, followed by low-NG tumors with necrosis and then by high-NG tumors. For patients with low-NG DCIS showing a low VNPI score, there was no significant difference in local recurrence-free survival between those who underwent breast-conserving surgery with and without irradiation. Therefore, they concluded that patients with low-NG DCIS showing low VNPI scores can be treated with breast-conserving surgery alone. Warren et al., also reported that patients with low-NG DCIS developed significantly less ipsilateral second tumors after BCT compared with those with high-NG DCIS (hazard ratio 1.76) [14]. Sagara et al., investigated the survival benefit of surgery using the large-scale Surveillance, Epidemiology, and End Results (SEER) database [15]. They compared prognosis between the surgery group and non-surgery group for DCIS. For DCIS with NG1, there was no significant difference between the two groups in either the weighted 10-year breast cancer-specific survival (98.6% vs 98.8%, $P = 0.95$) or overall survival (87.9% vs 91.0%, $P = 0.60$). The survival benefit of surgery was lower for DCIS with NG1 compared with NG2 or NG3. Although this was a retrospective study, its results suggested that DCIS with NG1 has extremely low effect on survival prognosis. In our study, NG1 was identified as a characteristic of IDC with a predominant intraductal component, and it was also reported to be an indicator of low-malignant DCIS. Therefore, NG1 may be one of the characteristics of overdiagnosed DCIS.

In the study by Eusebi et al., about DCIS natural history [12], the 80 subjects included only two comedo-type lesions. Although both cases developed into invasive carcinoma within 5 years, the sample size was small, and nine of the 78 non-comedo-type tumors also developed into invasive carcinoma. Therefore, it is too difficult to compare between the comedo and non-comedo types in terms of natural history. Studies of local recurrence include the NSABP B-17 trial, which investigated the significance of radiotherapy after breast-conserving surgery for DCIS [16], and the combined long-term outcomes of the NSABP B-17 trial

and the NSABP B-24 trial, which investigated the efficacy of tamoxifen after BCT for DCIS [17]. In the NSABP B-17 trial, multivariate analysis of clinicopathological factors identified the comedo type as a predictive factor of ipsilateral local recurrence [16]. The NSABP B-24 trial showed that ipsilateral local recurrence of DCIS was significantly more frequent for the comedo-type lesions (hazard ratio 2.21, $P < 0.01$). However, when local recurrence was confined to lesions with invasive components, there was no significant difference between the comedo and non-comedo types (hazard ratio 0.87, $P = 0.41$) [17]. On the other hand, Li et al., investigated the risk of ipsilateral local recurrence with invasive components in cases of DCIS and lobular carcinoma *in situ* using the SEER database. They reported that the recurrence with invasive components was significantly more frequent for comedo-type DCIS (hazard ratio 1.4, $P < 0.05$) [18]. Although in our study the comedo subtype was identified as a characteristic of IDC with a predominant intraductal component, we considered it as a risk factor for local recurrence of DCIS. The comedo carcinoma subtype is a high-grade carcinoma associated with high proliferative potential. However, in our study, the group D—assumed to have a low proliferative potential—had a high prevalence of comedo-type lesions: a paradoxical situation.

HER2 positivity has been reported as a risk factor for the recurrence of DCIS, either alone or in combination with other biomarkers such as Ki67 [19]. However, no study has described the natural history of HR-negative and HER2-positive DCIS. Ringberg et al., reported that HR-positive DCIS tumors included fewer high-NG or comedo-type lesions compared with HR-negative DCIS [20]. Kepple et al., investigated predictive factors for DCIS recurrence in terms of receptor expression patterns. They showed that the overall recurrence rate for HER2-positive DCIS was significantly higher and disease-free survival was significantly lower even if the lesions were ER positive [21]. Barnes et al. also reported that the cumulative 5-year disease-free survival was significantly lower for HER2-positive DCIS than for HER2-negative DCIS ($P = 0.0102$) [22]. These results suggested that both HR negativity and HER2 positivity were indicators of DCIS malignancy. It is inconsistent with our result that HR-negative and HER2-positive DCIS may be overdiagnosed DCIS.

No study concerning natural history of DCIS has investigated age. Silverstein et al., reported that local recurrence-free survival significantly improved in patients older than 60 years of age ($P \leq 0.01$). Therefore, they added age as a factor to the VNPI and formulated the University of Southern California/Van Nuys Prognostic Index (USC/VNPI) to predict local recurrence risk after BCT in patients with DCIS [23]. According to a report of a Phase III trial investigating the significance of radiotherapy after breast-conserving surgery for DCIS by the European Organization for Research and Treatment, multivariate analysis showed that women younger than 40 years of age had a significant risk for local recurrence [24]. Wapnir et al., also found that patients aged <45 years had significantly higher rates of both ipsilateral local recurrences with and without invasive components after breast-conserving surgery for DCIS compared with those aged ≥65 years [17]. In our study, we found no significant difference in age among the four IDC groups.

CONCLUSION

The aim of this study was to identify characteristics of DCIS that showed a low probability of stromal invasion in a short term and that could be managed by active surveillance over a long term. We assumed that IDC with a predominant intraductal component had taken a long time to invade. Then we investigated the IDC characteristics and identified NG1, comedo-type and HR-negative and HER2-positive lesions. However, considering our results together with those of other studies on tumor malignancy of DCIS, the factors—except for NG1—were inconsistent with characteristics of DCIS showing a low likelihood of invading the stroma in a short term. We also confirmed that the IDC comprised two types of lesions with different degree of malignancy, i.e., IDC with a low capability of invasion and that with a high capability of ductal spread. Therefore, we concluded that the IDC characteristics cannot be used as conditions of overdiagnosed DCIS.

Our study has several limitations. We attempted to investigate the characteristics of invasive carcinomas that may have taken a long time to invade in order to identify the characteristics of DCIS. Then, we assumed that the invasive carcinomas would have a predominant intraductal component. We used the proportion of intraductal components as an index of the time required for invasion. However, the time from carcinogenesis to clinical detection, the speed and acceleration of intraductal growth and stromal invasion are all uncertain. Furthermore, there is an opinion that IDC with a synchronous intraductal component is not suitable study group for answering our research question about DCIS, since the lesion is already invasive. Retrospective studies using DCIS cases already resected cannot drive characteristics of DCIS which can be followed without treatment. Now we are wondering what study design appropriate for the research question.

Prospective trials of active surveillance for DCIS with low risk of invasion or recurrence are now underway both in Japan and overseas to address the problem of overdiagnosed early-stage breast cancer detected from cancer screening. The results of these trials will optimize the management strategy for early-stage breast cancer, including DCIS.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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