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ORIGINAL ARTICLE

Identifying ductal carcinoma in situ cases not requiring surgery to exclude postoperative upgrade to invasive ductal carcinoma

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Abstract

Background Prospective cohort studies are being conducted worldwide to identify a low-grade group of ductal carcinoma in situ (DCIS) that does not require surgery. However, to do this, it is necessary to predict which cases, diagnosed with preoperative DCIS, will be upgraded to invasive ductal carcinoma (IDC) after surgery.

Methods In this study, we evaluated the frequency of IDC upgrades in patients who were preoperatively diagnosed with DCIS at Showa University using the criteria of ongoing clinical trials. We divided our cases into those that could be enrolled in the ongoing trial and those that could not. Moreover, we evaluated whether CNB, which is allowed only in Japanese clinical trials, is related to the IDC mixture.

Results There were 211 (52.1%) cases that matched the criteria of the U.K. and Netherlands trials, of which 62 (29.4%) were upgraded to IDC. A total of 113 (27.9%) cases met the criteria for clinical trials in Japan and the U.S., 25 (22.1%) of which were upgraded to IDC and 47 (34.6%) which matched when considering biopsy methods. The number of cases upgraded to IDC decreased to four (8.5%).

Conclusions This study demonstrated that there were a certain number of mixed IDC. We will pay attention to the results of ongoing clinical trials regarding how the presence of this mixed IDC affects the prognosis in non-surgery cases. Careful follow-up is recommended for non-surgical treatment.

Keywords Ductal carcinoma in situ · LORETTA trial · Low-grade DCIS · Overtreatment · Active surveillance

Introduction

The introduction of mammography (MMG) screening has increased the incidence of early-stage breast cancer [1–5], but has not reduced advanced breast cancer [6]. Ductal carcinoma in situ (DCIS) can be curable if it is completely removed by surgical operation and has a good prognosis. The standard treatment of DCIS is surgical therapy (± radiation therapy, systemic therapies) [7]. If left untreated, DCIS has a 14–53% chance of progressing to invasive ductal carcinoma (IDC) [8–10]. However, the median prevalence of DCIS was 8.9% (range 0–14.7%) among American women who had not been diagnosed with breast cancer by the time of death [11, 12]. This suggests the existence of a group of low-grade DCIS with no need for surgery [13].

Standard treatments for DCIS have been reviewed worldwide, and prospective phase III clinical trials are ongoing [14–17] to avoid unnecessary interventions. In Japan, the low-risk DCIS with endocrine therapy alone-tamoxifen (LORETTA) trial aims to establish non-surgical treatment for low-grade DCIS. However, among those diagnosed with DCIS by core needle biopsy (CNB) or vacuum-assisted breast biopsy (VAB) before surgery, some cases are upgraded to IDC by postoperative pathological diagnosis [18, 19]. To identify low-grade DCIS that does not require surgery, DCIS that must be upgraded to IDC at the time of diagnosis must be excluded because of which ongoing prospective clinical trials have set some factors as criteria

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(Supplementary Table 1). In this study, we evaluated the frequency of upgrades to IDC in patients who were preoperatively diagnosed with DCIS at Showa University using the criteria of ongoing clinical trials. We also evaluated how well patients eligible for each clinical trial would upgrade to IDC.

Patients and methods

This retrospective study was approved by the Research Ethics Committee in Showa University, Japan. We obtained patients' radiological, clinical, and pathological information from medical records at Showa University Hospital. We reviewed the medical records of 559 women who were diagnosed with DCIS preoperatively and underwent surgery at Showa University Hospital between 2010 and 2017. Those with a history of breast cancer at the time of diagnosis, multiple lesions, and hereditary breast cancer were excluded from the study.

A total of 405 women were evaluated in this study. We retrospectively investigated the presence or absence of seven factors: age ≥ 39 years, mass lesion on MMG, Nuclear grade (NG) 3, comedonecrosis, size ≥ 2.5 cm on MMG and ultrasound (US), estrogen receptor (ER)-negative, and human epithelial growth factor receptor 2 (HER2)-positive. These seven factors are based on the criteria of four phase III trials on IDC that are currently underway in Japan, the U.K., the Netherlands, and the USA [14–17].

In this study, we divided the cases into four stages. First, a case was classified as 'Did not meet the Group A criteria' if it had any of the four common factors, age ≥ 39 years, mass lesion on MMG, NG 3, and comedonecrosis, indicating that the IDC may be mixed. If all four factors did not exist, the case was classified as 'Met the Group A criteria'. Second, cases in which any of the seven factors existed were classified into 'Did not meet the Group B criteria', and cases in which all seven factors did not exist were classified into 'Met the Group B criteria'. Third, in addition to the seven factors, the presence or absence of a high Ki-67 labeling index and findings indicating IDC on magnetic resonance imaging (MRI)—a total of nine factors—were reviewed [20–23]. Cases for which any of the nine factors existed were classified as 'Did not meet the Group C criteria', and those for which none of the nine factors existed were classified as 'Met the Group C criteria'. Finally, among the cases diagnosed with DCIS by VAB or open biopsy, those with any of the seven factors were classified as 'Did not meet the Group D criteria', and those with none of them were classified as 'Met the Group D criteria'. This refers to four clinical trials currently underway. 'Met the group A criteria' is evaluating clinical trials in the Netherlands and the U.K. that do not consider breast cancer subtype and size. 'Met the group B criteria' evaluates clinical trials conducted in Japan and the United States that meet 'Met the group A criteria' and consider subtype and size. In addition, 'Met the group C criteria' has added the Ki67 degree and MRI imaging, which can be evaluated in clinical practice and can be introduced immediately. 'Met the group D criteria' also considers the amount of tissue and evaluates cases collected by VAB or open biopsy that meet the factors of 'Met the group A criteria' and'Met the group B criteria' (Fig. 1).

The ER, HER2, and Ki-67 labeling index status was assessed by immunohistochemistry. ER-positivity was determined based on > 10% nuclear staining. The HER2 status was graded as 0 to 3 + , and a HER2 score of 3 + or

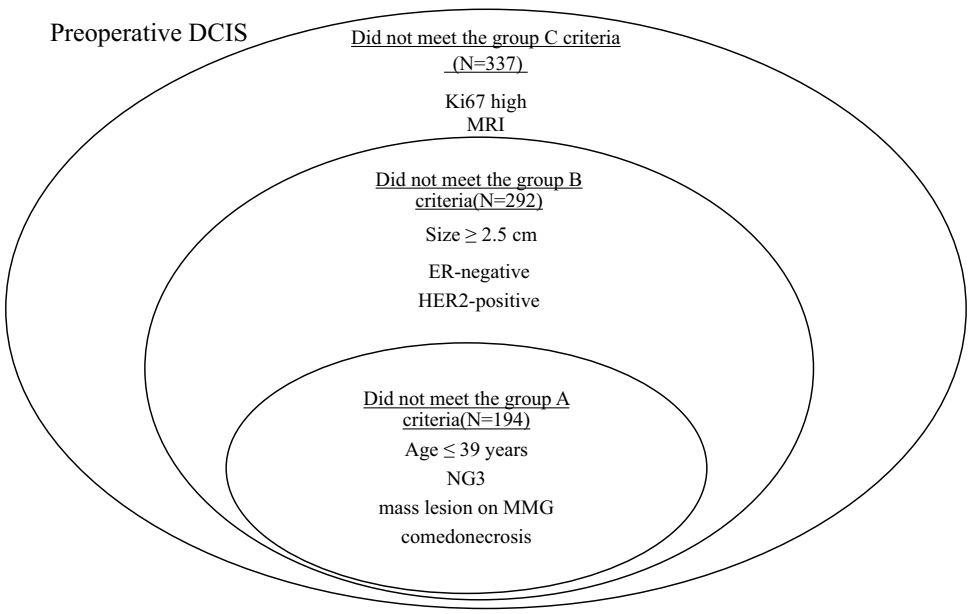

Fig. 1 'Met the Group A criteria', 'B', and 'B' that meet any of the factors. *DCIS* ductal carcinoma in situ, *MRI* magnetic resonance imaging, *ER* estrogen receptor, *HER2* human epithelial growth factor receptor 2, *MMG* mammography, *NG 3* nuclear grade 3

HER2/centrosomal area of chromosome 17 (CEP17) > 2.2 by fluorescence in situ hybridization was defined as positive. The Ki67 labeling index was classified as low (≤ 20%) or high (> 20%). All images were reviewed by two or more breast surgeons. The relationship between the upgrade to IDC and the factors was analyzed by the Chi-square test. A *P*-value < 0.05 was considered statistically significant.

Results

In the final pathological diagnosis after surgery, 117 of 405 cases (28.9%) were upgraded to IDC; 15 cases (3.7%) had T1mi, 44 cases (10.9%) had T1a, 30 cases (7.4%) had T1b, 20 cases (4.9%) had T1c, seven cases (1.7%) had T2, and one case (0.2%) had T3. There were 11 cases (2.7%) that were lymph node-positive, and 150 patients underwent a partial mastectomy. The median age for all patients was 49 years (range 22–91 years). Ten patients (2.5%) were diagnosed with a recurrent malignancy in the breast or distant metastasis within a median follow-up time of 53.1 months. Of the cases diagnosed with DCIS in the final postoperative pathological diagnosis, 1.7% showed local recurrence and 0.3% distant recurrence. Of the cases diagnosed with IDC in the final postoperative pathological diagnosis, 2.6% showed local recurrence and 0.9% distant recurrence. The relationship between the upgrade to IDC and the seven factors is shown in Table 1.

Significantly more cases with large lesions (≥ 2.5 cm) were upgraded to IDC than those with small lesions (Table 2). Of the 211 cases (52.1%) in which all four factors did not exist ('Met the Group A criteria'), 62 cases (29.4%) were upgraded to IDC and 27 cases (12.8%) had T1b or higher invasion exceeding 5 mm (Fig. 2). Of the 113 cases (27.9%) in which all seven factors did not exist ('Met the Group B criteria'), 25 cases (22.1%) were upgraded to IDC, 14 cases (8.8%) had T1b or higher invasion exceeding 5 mm, and one case was lymph node-positive (Fig. 3). Of the 68 cases (16.8%) in which all nine factors did not exist ('Met the Group C criteria'), 13 cases (19.1%) were upgraded to IDC (Fig. 4). Of the 136 of 405 cases (34.6%) diagnosed by VAB or open biopsy, four cases (8.5%) were upgraded to IDC, and one case (2.1%) was found to be T1b or higher (Fig. 5) after re-examining the seven factors.

Discussion

Of the seven factors set by ongoing clinical trials, only lesion size (2.5 cm or larger) was a significant factor in upgrading to IDC. However, it is unimportant that only one factor denies IDC, and it is not necessary to evaluate the intensity of each factor. We believe that multiple factors must be evaluated comprehensively to avoid upgrading IDC. In this study, among the cases preoperatively diagnosed with DCIS, 29.4% without the four factors ('Met the Group A Criteria') were upgraded to IDC. 'Met the Group B criteria' gave better results than Group A; that is, it was better to consider subtypes and sizes. When all nine factors were applied, including Ki67 and MRI evaluation ('Met the Group C criteria'), the probability of mixed IDC reduced to 19.1%. 'Met the Group C criteria' gave better results than Groups A and B; that is, increasing the factors reduced the mix of IDC. The amount of tissue collected at the time of diagnosis was increased in VAB and open biopsy cases, which resulted in a reduction of the probability of mixed IDC to 8.5%. Therefore, it was better to avoid CNB at the time of diagnosis. The overall

Table 1 Patient characteristics

	All study samples (*N* = 405)	DCIS that confirmed after surgery (*N* = 288)	IDC that confirmed after surgery (*N* = 117)	*P*-value
Age, median (range)	49 years (22–91)	50 years (22–88)	48.5 years (30–91)	
Surgery				
Partial lumpectomy	150 (37.0%)	121 (42.0%)	29 (24.8%)	0.001
Total mastectomy	255 (63.0%)	167 (58.0%)	88 (75.2%)	
Node status				
Positive	11 (2.7%)	1 (0.3%)	10 (8.5%)	< 0.0001
Negative	394 (97.3%)	287 (99.7%)	107 (91.5%)	
Recurrence				
Local recurrence	8 (2.0%)	5 (1.7%)	3 (2.6%)	0.59
Distant recurrence	2 (0.5%)	1 (0.3%)	1 (0.9%)	0.51
All recurrence	10 (2.5%)	6 (2.1%)	4 (3.4%)	0.43

Local recurrence + Distant recurrence = All recurrence

DCIS ductal carcinoma in situ, *IDC* invasive ductal carcinoma

Table 2 Factors relevant to upgrade of DCIS to IDC

Factors	All study samples ($N=405$)	DCIS that confirmed after surgery ($N=288$)	IDC that confirmed after surgery ($N=117$)	*P* value
Aged ≦ 39 years				
Yes	42 (10.4%)	27 (9.4%)	15 (12.8%)	0.30
No	363 (89.6%)	261 (90.6%)	102 (87.2%)	
Mass lesion on MMG				
Yes	43 (10.6%)	27 (9.4%)	15 (12.8%)	0.20
No	363 (89.6%)	261 (90.6%)	102 (87.2%)	
NG 3				
Yes	45 (11.1%)	29 (10.1%)	16 (13.7%)	0.30
No	360 (88.9%)	259 (89.9%)	101 (86.3%)	
Comedonecrosis				
Yes	121 (29.9%)	94 (32.6%)	27 (23.1%)	0.06
No	284 (70.1%)	194 (67.4%)	90 (76.9%)	
Size ≧ 2.5 cm on MMG & US				
Yes	164 (40.5%)	103 (35.8%)	61 (52.1%)	0.002
No	241 (59.5)	185 (64.2%)	56 (47.9%)	
ER-negative (< 10%)				
Yes	63 (16.5%)	43 (14.9%)	24 (20.5%)	0.17
No	342 (84.4%)	245 (85.1%)	93 (79.5%)	
HER2-positive				
Yes	63 (16.5%)	43 (14.9%)	24 (20.5%)	0.17
No	342 (84.4%)	245 (85.1%)	93 (79.5%)	

DCIS ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *NG 3* nuclear grade 3, *MMG* mammography, *US* ultrasound, *ER* estrogen receptor, *HER2* human epithelial growth factor receptor 2

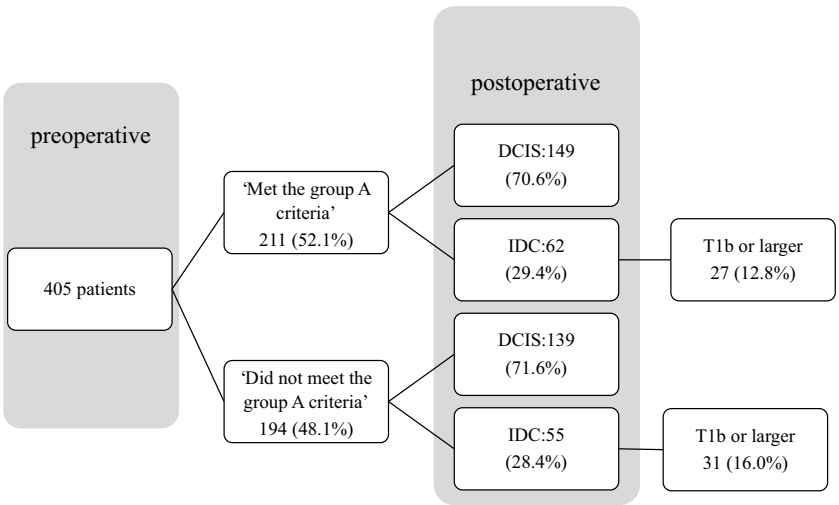

Fig. 2 The rate of DCIS upgraded to IDC when using four factors (age ≥ 39 years, mass lesion on MMG, NG 3, and comedonecrosis). *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *MMG* mammography, *NG 3* nuclear grade 3

recurrence was 2.5% during a median follow-up time of 60.5 months. Of the cases diagnosed with DCIS in the final postoperative pathological diagnosis, 1.7% showed local recurrence and 0.3% distant recurrence. Of the cases diagnosed with IDC in the final postoperative pathological diagnosis, 2.6% showed local recurrence and 0.9% distant recurrence.

All cases who were diagnosed with DCIS preoperatively and underwent surgery had a good prognosis. A certain number of preoperatively diagnosed cases with DCIS were upgraded to IDC in the final postoperative pathological diagnosis. In this study, the frequency of upgrades to IDC was 28.3%, similar to previous reports [21, 24–27]. To avoid upgrading to IDC as much as possible, four ongoing

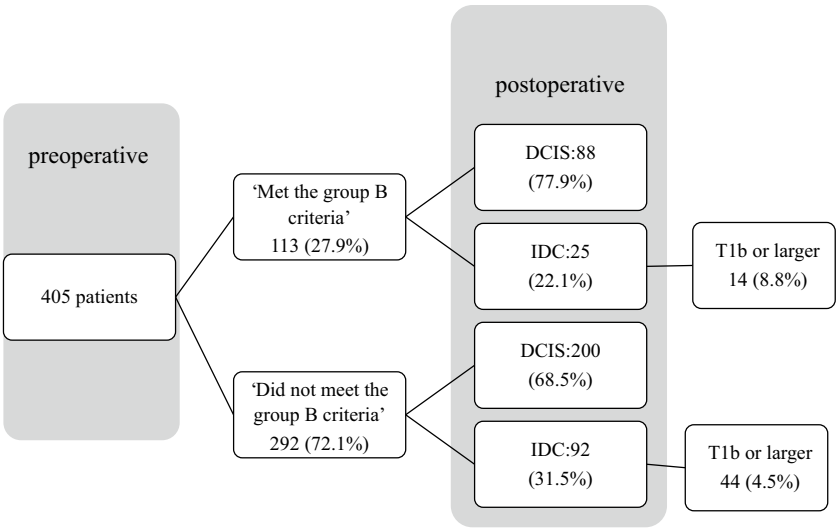

Fig. 3 The rate of DCIS upgraded to IDC when using seven factors (age ≥ 39 years, mass lesion on MMG, NG 3, comedonecrosis, size ≥ 2.5 cm, ER-negative, and HER2-positive). *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *MMG* mammography, *NG 3* nuclear grade 3, *ER* estrogen receptor, *HER2* human epithelial growth factor receptor 2

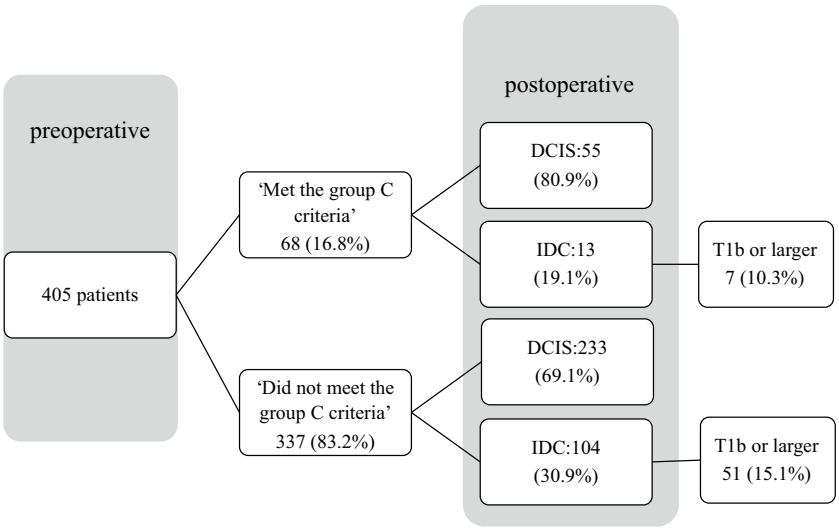

Fig. 4 The rate of DCIS upgraded to IDC when using nine factors (age ≥ 39 years, mass lesion on MMG, NG 3, comedonecrosis, size ≥ 2.5 cm, ER-negative, HER2-positive, high Ki-67 labeling index, and findings indicating IDC on MRI). *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *MMG* mammography, *NG 3* nuclear grade 3, *ER* estrogen receptor, *HER2* human epithelial growth factor receptor 2

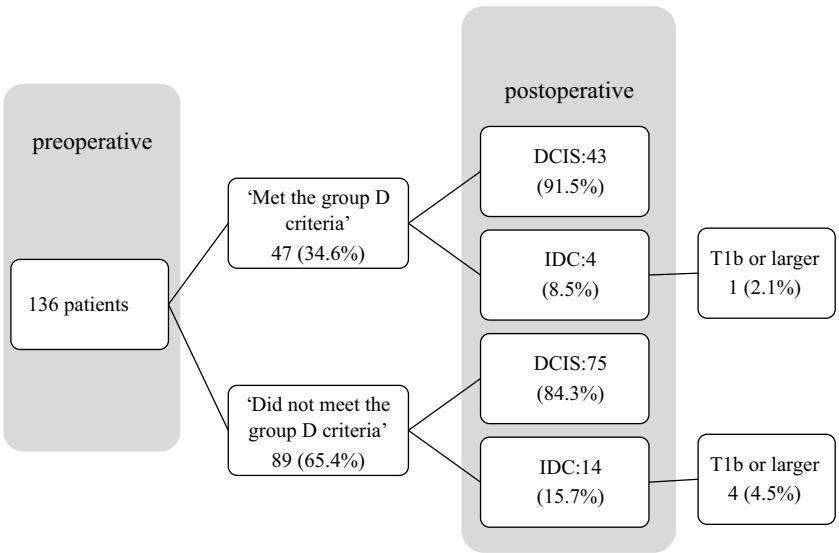

Fig. 5 The rate of upgrading DCIS to IDC by VAB or open biopsy and using seven factors. *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *VAB* vacuum-assisted biopsy

prospective clinical trials have set factors, although each trial has different factors. The LORD and LORIS trials in the Netherlands and the United Kingdom, respectively, have fewer factors and correspond to 'Met the Group A criteria' in this study; they plan to follow up only, without any alternative treatment to non-surgery. The LORETTA trial in Japan plans to use hormone therapy instead of surgery and to compare an operation to monitoring. The COMET trial in the U.S. also allows hormone therapy as an option. Therefore, trials in Japan and the U.S. include only hormone receptor-positive patients, corresponding to the 'Met the Group B criteria' in this study (Supplementary Table 2).

We were able to reduce the probability of upgrades to IDC by 7.3% by increasing the number of factors from 4 to 7. In addition, by examining nine factors, including MRI and the Ki-67 labeling index, we could reduce the probability of upgrades to IDC by 3%. Although the upgrade of DCIS to invasive cancer cannot be eliminated, it should be minimized because the larger the infiltration diameter, the worse the prognosis. Although no clear cutoff has been proposed, our results emphasize that drug treatment regimens should be carefully designed for breast cancers with an infiltration diameter of 5 mm (T1b) or larger [28]. In this study, we could not sufficiently reduce the proportion of IDC above T1b by increasing the factors from 4 to 7 and from 7 to 9. Thus, although the number of eligible cases ('Met the Group criteria') decreased significantly by increasing the number of factors, the validity of this result is not clear because the number of cases upgraded to T1b or higher could not be reduced.

Even if a patient is assigned to the intensive follow-up group, a timely diagnosis of IDC may not affect the prognosis of life, especially with an invasion diameter of 5 mm or less. In prospective clinical trials, the method of intensive follow-up differs from trial to trial (Supplementary Table 2). Hence, it is essential to establish appropriate follow-up methods, a concept that should be investigated in ongoing prospective trials.

Of note, a key difference in the criteria in Japan and other countries is the biopsy method at the time of diagnosis. Only Japanese trials allow the use of core needle biopsy (CNB) for diagnosis, whereas other trials require vacuum-assisted biopsy (VAB) or open biopsy. Owing to physical differences, CNB is often used for diagnosis in Japan; in this study, 269 cases (66.4%) were diagnosed by CNB. Focusing on cases diagnosed by VAB or open biopsy reduced the rate of upgrades to IDC to 8.5% in this study. VAB and open biopsy methods also reduced the number of upgrades to T1b or higher. Although the LORETTA trial in Japan allows diagnosis by CNB, diagnosis is performed with at least three pieces of 14 G needle biopsy samples.

At our hospital, 2–4 pieces of 14 G needle biopsy samples are used for CNB, and 4−6 pieces of 12 G samples are used for VAB. However, in this retrospective study, it was not possible to collect information on the number of biopsies and needle thickness. This study showed that collecting a higher amount of tissue led to a reduction in upgrades to IDC. It is difficult to identify all cases requiring an upgrade to IDC. However, the results of this study suggest that it is possible to exclude cases with T1b and above, key categories that should not be underdiagnosed, by increasing the amount of tissue collected. Thus, the biopsy method is an important approach to achieve this objective [18, 27, 29].

Most of the cases assigned to the surgery group were DCIS. In this study, there were 139 cases of DCIS in 'Did not meet the Group A criteria', 200 cases in 'Did not meet the Group B criteria', and 233 cases in 'Did not meet the Group C criteria'. In this study, increasing the number of factors led to an increase in an increased assignment of DCIS, which does not upgrade to IDC, to the surgery group ('Did not met the Group criteria'). These results highlight the importance of prospective clinical trials to offer patients with DCIS the option of non-surgery. Furthermore, we should consider the possibility that the DCIS included in the surgery group may include cases of DCIS that do not require surgery. It should also be noted that while increasing the number of factors can avoid the underdiagnosis of cases upgrading to IDC, there are still cases where the true objective of overtreatment cannot be avoided. In addition, there are cases in which DCIS is upgraded to IDC during long-term follow-up, and cases in which distant recurrence occurs even with a diagnosis of postoperative DCIS, as was observed in this study.

In this study, we excluded postoperative upgrades to IDC by altering the criteria. Hence, it is crucial to establish a method for identifying high-grade DCIS and a method for intensive follow-up. The factors relevant for upgrading DCIS to IDC include palpable lesions, mass lesion on MMG, lesion size, NG3, and core needle biopsy diagnosis[18, 24–27, 29, 30]. However, the results of this study suggest that only the size of the lesion and the diagnosis by needle biopsy were significant factors. Therefore, the results of ongoing prospective clinical trials are much awaited to examine how the differences in exclusion criteria in each trial affected the trial results. In addition, there are few reports that DCIS with comedonecrosis is easy to upgrade to IDC. However, since they are high-grade DCIS [31] and are included in the exclusion factor in all clinical trials, they were also included in the exclusion factor in this study. Although it would be challenging to reduce the number of exclusion factors, it is important to further reduce the number of cases requiring surgery. New diagnostic methods facilitating the early detection of cases requiring an upgrade to IDC take into account clinicopathological and genetic factors and the use of liquid biopsy will reduce the number of cases requiring surgery.

Few reports have been considered in comparison to ongoing clinical trials. However, this is the first report that considers one ongoing trial and evaluates several ongoing trials. We also evaluated whether MRI imaging and Ki67 are valuable in addition to the several factors used in ongoing studies. We explored whether the amount of tissues is important when evaluating the DCIS. Because of the retrospective design of this study, a limitation of this study was that the missing data were considered to be items, and it was not possible to collect information on palpation and subjective symptoms, which are criteria in ongoing clinical trials in Japan, the U.K., USA, and the Netherlands.

In this study, we examined the factors associated with upgrading patients diagnosed with preoperative DCIS to IDC, based on the criteria of four ongoing prospective clinical trials. Although it is difficult to accurately predict an upgrade to invasive cancer, there are some cases in which it is possible to predict an upgrade to IDC by evaluating relevant factors. In addition, this study showed that increasing the amount of tissue samples, such as with VAB or open biopsy, may reduce upgrades above T1b. New diagnostic approaches based on genetic factors in addition to the existing clinicopathological factors would also help reduce the number of upgrades and hence, the number of cases requiring surgery. Because the criteria and the intervention method for the active surveillance group are different in ongoing trials, information from these clinical trials would help suggest the optimal treatment and diagnostic methods for early-stage breast cancer and long-term prognosis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12282-022-01338-0.

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