Factors predictive of invasive ductal carcinoma in cases preoperatively diagnosed as ductal carcinoma in situ

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DOI: 10.21203/rs.2.19211/v1

SUBJECT AREAS
   Oncology    Cancer Biology

KEYWORDS
   invasive ductal carcinoma, ductal carcinoma in situ, invasion, platelet-lymphocyte ratio, biopsy, surgery
Abstract

Background

Invasion is often found in the postoperative pathological examination of cases diagnosed as ductal carcinoma in situ (DCIS) by histological examinations such as core needle biopsy (CNB) or vacuum-assisted biopsy (VAB). A meta-analysis reported that 25.9% of invasive ductal carcinoma (IDC) cases are diagnosed as DCIS preoperatively by CNB. Risk factors for invasion by postoperative examination have been studied, but no factors have been found that could be assessed preoperatively from blood tests. In this study, we investigated factors predictive of invasion based on preoperative blood tests in patients diagnosed with DCIS by preoperative biopsy.

Methods

In this study, 118 patients who were diagnosed with DCIS by preoperative biopsy were included. Biopsies were performed with 16-gauge CNB or VAB. Peripheral blood was obtained at the time of diagnosis. This study evaluated absolute platelet count, absolute lymphocyte count, lactate dehydrogenase, carcinoembryonic antigen, and cancer antigen 15-3 (CA15-3). The platelet-lymphocyte ratio (PLR) was calculated by dividing the absolute platelet count by the absolute lymphocyte count, and patients were grouped into high PLR (≥160.0) and low PLR (<160.0) groups.

Results

Invasion was found more frequently after surgery in pathologically high-grade cases than in pathologically not-high-grade cases (p = 0.015). The median PLR was 138.9, and 48 patients (40.7%) were classified into the high PLR group. The high PLR group was significantly more likely to have invasion in the postoperative pathology than the low PLR group (p = 0.018). In multivariate analysis of factors predictive of invasion in postoperative pathology, a high PLR (p = 0.007, odds ratio [OR] = 3.212), larger tumor size (p = 0.044, OR = 2.758), and biopsy method (VAB vs CNB, p = 0.001, OR = 0.206) were independent risk factors.

Conclusions

The PLR may be a predictor of invasion in the postoperative pathology for patients diagnosed with DCIS by preoperative biopsy.
Background
Because ductal carcinoma in situ (DCIS) is not an invasive malignant tumor, it does not have the ability to metastasize. Therefore, the necessity of surgical treatment and sentinel lymph node biopsy for DCIS has been studied [1–4]. However, DCIS is diagnosed by histological examinations such as core needle biopsy (CNB) or vacuum-assisted biopsy (VAB), and invasion is often found in the postoperative pathological examination. A meta-analysis reported 25.9% (18.6–37.2%) of invasive ductal carcinomas (IDCs) are preoperatively diagnosed as DCIS by CNB [5]. Although risk factors have been examined, there are no factors that can be identified easily using blood tests.

Cancer affects the general condition as it progresses. In particular, changes in the blood are often observed from an early stage. Tumor markers often correlate with progression and have been reported to change earlier than other symptoms and other tests after recurrence [6–8]. Carcinoembryonic antigen (CEA) and cancer antigen 15 – 3 (CA15-3) are commonly used as tumor markers for breast cancer. The white blood cell population and blood chemistry can also change. Lactate dehydrogenase (LDH) is one of the most important metabolic enzymes involved in glycolysis [9]. An increase in serum LDH is observed with tissue destruction caused by cancerous growth [10], and serum LDH values have been reported to be consistent with clinical TNM staging [10, 11]. Furthermore, the peripheral blood platelet-lymphocyte ratio (PLR) has been reported to be useful for predicting prognosis [12–14], and results from a meta-analysis suggest a correlation between the PLR and progression in breast cancer [12]. Therefore, we hypothesized that there may be a difference in blood test results if there is invasion in patients diagnosed with DCIS by preoperative biopsy. In this study, we identified predictors of invasion from preoperative blood tests in patients diagnosed with DCIS by preoperative biopsy.

Methods
Patients
In this study, one hundred and eighteen patients who were diagnosed with DCIS by preoperative biopsy from August 2007 to January 2018 at the Osaka City University Hospital were included. The grade of DCIS was based on the World Health Organization classification [15]. Patients with multiple breast cancers were excluded, as were patients with a history of cancer regardless of breast cancer.
Biopsies were performed with 16-gauge CNB or VAB at the discretion of the attending physician. All patients underwent mastectomy or breast-conserving surgery. In both preoperative biopsy and postoperative pathological examination, invasion was examined by Hematoxylin-Eosin staining and immunohistochemical staining. Furthermore, the expression of the estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki67 was evaluated by immunohistochemical staining in the biopsy tissue. Tumor size was measured by imaging evaluation such as ultrasonography, computed tomography, and magnetic resonance imaging. Cases that are suspected of having lymph node metastases in the image are diagnosed IDC even if they are diagnosed with DCIS by biopsy, and are excluded from this study.

**Blood Sample Analysis**

Peripheral blood was obtained at diagnosis, before surgery. This study evaluated absolute platelet count, absolute lymphocyte count, LDH, CEA, and CA15-3. Patients in whom any of these variables was not measured were excluded from the study. The number of blood cells was determined using a hemocytometer. Percentages of different cell types were determined using a Coulter LH 750 Hematology Analyzer (Beckman Coulter, Brea, CA, USA). The PLR was calculated from the preoperative blood sample by dividing the absolute platelet count by the absolute lymphocyte count. On the basis of previous studies, a PLR value of 160.0 was used as the cutoff value to discriminate between a high PLR (≥ 160.0) and a low PLR (< 160.0) [16]. For LDH, CEA, and CA15-3, each upper limit of normal range (ULN) was set as a cut-off value (LDH: 120–242 IU/L, CEA: ≤5.0 ng/mL, CA15-3: ≤25.0 U/mL).

**Statistical Analysis**

All statistical analysis was performed with the JMP software package (SAS, Tokyo, Japan). The relationship between each factor was examined using Pearson’s chi-square test. The odds ratio (OR) and 95% confidence interval were calculated by logistic analysis. Multivariable analysis was performed using the multivariable logistic regression model. Significance was defined as a p-value less than 0.05.

**Results**

**Clinicopathological features**
Their clinicopathological features of one hundred and eighteen patients who were diagnosed with DCIS by preoperative biopsy and met the conditions of this study are shown in Table 1. The median age was 51 (range, 30–78) years, and the median tumor diameter was 17.7 mm (range, 3.0–50.0 mm).

| Parameters                                      | Number of patients (n = 118) (%) |
|------------------------------------------------|----------------------------------|
| Age at operation (years old)                   | 51 (30–78)                       |
| Palpability Impalpable / Palpable               | 33 (28.0%) / 85 (72.0%)          |
| Tumor size (mm)                                 | 17.7 (3.0–50.0)                  |
| Biopsy device                                   | 67 (56.8%) / 51 (43.2%)          |
| Estrogen receptor Impalpable / Positive         | 22 (18.6%) / 96 (81.4%)          |
| Progesterone receptor Impalpable / Positive     | 37 (31.4%) / 81 (68.6%)          |
| HER2 ≤2 / 3                                     | 101 (85.6%) / 17 (14.4%)         |
| Ki67 ≤14% / >14%                                | 98 (83.1%) / 20 (16.9%)          |
| Grade of DCIS Low, intermediate / High          | 98 (83.1%) / 20 (16.9%)          |
| Postoperative pathology DCIS only / Invasive ductal carcinoma | 70 (59.3%) / 48 (40.7%) |
| Platelets–lymphocyte ratio Low / High           | median 138.9 (range, 55.0–292.0) |
| LDH ≤ULN / >ULN                                 | median 170 (range, 121–452)      |
| CEA ≤ULN / >ULN                                 | median 1.6 (range, < 0.5–12.4)   |
| CA15-3 ≤ULN / >ULN                             | median 6.6 (range, < 0.5–40.8)   |

DCIS: ductal carcinoma in situ, HER2: human epidermal growth factor receptor 2, LDH: lactate dehydrogenase, CEA: carcinoembryonic antigen, ULN: upper limit of normal.

In 85 patients (72.0%), a tumor was palpable. VAB was selected in 51 patients (43.2%), but 67 patients (56.8%), more than half, were diagnosed preoperatively by 16-Gauge CNB. Ninety-six patients (81.4%) had ER-positive tumors, and 81 patients (68.6%) had PgR-positive tumors.

Seventeen patients (14.4%) had a score of 3 + for HER2. Ki67 expression was >14% in 20 patients (16.9%). Twenty preoperative biopsy specimens (16.9%) were pathologically high-grade. Forty-eight patients (40.7%) were found to have invasion by postoperative pathological examination.

The median LDH was 170 IU/L (range, 121–452 IU/L), with 13 patients (11.0%) having higher than the ULN. The median CEA was 1.6 ng/mL (range, <0.5–12.4 ng/mL), with 7 patients (5.9%) having higher than the ULN. In addition, the median CA15-3 was 6.6 U/mL (range, <0.5–40.8 U/mL), with 3 patients (2.5%) having higher than the ULN. The median PLR was 138.9 (range, 55.0–292.0), and 48 patients (40.7%) had a PLR > 160 and were placed into the high PLR group.
Correlations between clinicopathological features and postoperative pathology

The correlations between clinicopathological features and postoperative pathology are listed in Table 2. In cases in which the tumor was palpable before surgery, the postoperative pathology tended to be IDC (p = 0.065). In cases in which the tumor diameter was larger than 20 mm, the probability of the postoperative pathology being IDC was significantly higher (p = 0.024). Cases biopsied by VAB were significantly more likely to be diagnosed as DCIS by postoperative pathology than those biopsied by CNB (p = 0.003). Although no significant difference was observed based on immunohistochemical staining, invasion was found more frequently after surgery in pathologically high-grade cases than in pathologically not-high-grade cases (p = 0.015) (Fig. 1).

Table 2
Correlation between postoperative pathology and clinicopathological features

| Parameters                  | Postoperative pathology | p value |
|-----------------------------|-------------------------|---------|
|                             | DCIS only (n = 70)      | Invasive ductal carcinoma (n = 48) |
| Age at operation (years old)| ≤ 60 20 (28.6%)         | > 60 50 (71.4%) |
|                             | 33 (68.8%)              | 15 (31.3%) |
| Palpability Impalpable      | 9 (18.8%)               | 24 (45.7%) |
| Palpable                    | 39 (81.3%)              | 46 (65.7%) |
| Tumor size (mm) ≤ 20.0      | 35 (72.9%)              | 32 (45.7%) |
| > 20.0                      | 19 (39.6%)              | 22 (31.4%) |
| Biopsy device               | 52 (74.3%)              | 38 (54.3%) |
| Core needle biopsy          | 19 (39.6%)              | 32 (45.7%) |
| Vacuum-assisted biopsy      | 29 (60.4%)              | 13 (27.1%) |
| Estrogen receptor Negative  | 13 (27.1%)              | 9 (18.8%) |
| Positive                    | 35 (72.9%)              | 61 (87.1%) |
| Progesterone receptor       | 29 (60.4%)              | 52 (74.3%) |
| Negative                    | 19 (39.6%)              | 18 (25.7%) |
| HER2 ≤ 2                    | 35 (72.9%)              | 63 (90.0%) |
| HER2 > 3                    | 13 (27.1%)              | 7 (10.0%)  |
| Ki67 ≤ 14%                  | 10 (20.8%)              | 60 (85.7%) |
| Ki67 > 14%                  | 38 (79.2%)              | 10 (20.8%) |
| Grade of DCIS Low, intermediate | 35 (72.9%)              | 63 (90.0%) |
| High                        | 13 (27.1%)              | 7 (10.0%)  |
| Platelets-lymphocyte ratio  | 24 (50.0%)              | 50 (71.4%) |
| Low                         | 24 (50.0%)              | 20 (28.6%) |
| High                        | 6 (12.5%)               | 63 (90.0%) |
| LDH ≤ ULN                   | 42 (87.5%)              | 20 (28.6%) |
| > ULN                       | 7 (10.0%)               | 10 (14.3%) |
| CEA ≤ ULN                   | 45 (93.8%)              | 66 (94.3%) |
| > ULN                       | 4 (5.7%)                | 4 (5.7%)  |
| CA15-3 ≤ ULN                | 46 (95.8%)              | 69 (98.6%) |
| > ULN                       | 2 (4.2%)                | 1 (1.4%)  |

DCIS: ductal carcinoma in situ, HER2: human epidermal growth factor receptor 2, LDH: lactate dehydrogenase, ULN: upper limit of normal, CEA: carcinoembryonic antigen.
Examination of preoperative blood sampling results showed no significant difference in LDH or tumor markers based on pre- and postoperative concordance. However, the high PLR group was significantly more likely to show invasion in postoperative pathology than the low PLR group (p = 0.018). The correlations between the PLR and other clinical factors were examined, but there was no clear correlation (Table 3). In univariate analysis of factors predictive of invasion in postoperative pathology, a high PLR (p = 0.018, OR = 2.500) was a factor, as were larger tumor size (p = 0.024, OR = 2.372), non-Low Grade of DCIS (p = 0.015, OR = 3.343) and biopsy method (VAB vs CNB, p = 0.003, OR = 0.313) (Fig. 1). Moreover, in multivariate analysis of factors predictive of invasion in postoperative pathology, a high PLR (p = 0.007, OR = 3.212) was an independent factor, as were larger tumor size (p = 0.044, OR = 2.758) and biopsy method (VAB vs CNB, p = 0.001, OR = 0.206) (Table 4).
| Parameters                              | Platelets–lymphocyte ratio |      | p value |
|----------------------------------------|----------------------------|------|---------|
|                                        | Low (n = 74)               | High (n = 44) |         |
| Age at operation (years old) ≤ 60     | 51 (68.9%)                 | 32 (72.7%)          | 0.661   |
|                                        | 23 (31.1%)                 | 12 (27.3%)          |         |
|                                        | 22 (29.7%)                 | 11 (25.0%)          | 0.580   |
|                                        | 52 (70.3%)                 | 33 (75.0%)          |         |
| Palpability                            | Impalpable                 | Palpable           |         |
|                                        | 45 (60.8%)                 | 26 (59.1%)          | 0.854   |
|                                        | 29 (39.2%)                 | 18 (40.9%)          |         |
| Tumor size (mm) ≤ 20.0 > 20.0         | 42 (56.8%)                 | 25 (56.8%)          | 0.995   |
|                                        | 32 (43.2%)                 | 19 (43.2%)          |         |
| Biopsy device                          | Core needle biopsy         | Vacuum-assisted biopsy |     |
|                                        | 15 (20.3%)                 | 7 (15.9%)           | 0.556   |
|                                        | 59 (79.7%)                 | 37 (84.1%)          |         |
| Estrogen receptor                      | Negative                   | Positive           |         |
|                                        | 25 (33.8%)                 | 12 (27.3%)          | 0.461   |
|                                        | 49 (66.2%)                 | 32 (72.7%)          |         |
| HER2                                    | ≤ 2                        | ≥ 3                |         |
|                                        | 63 (82.4%)                 | 40 (90.9%)          | 0.205   |
|                                        | 13 (17.6%)                 | 4 (9.1%)            |         |
| Ki67                                    | ≤ 14%                      | > 14%              |         |
|                                        | 62 (83.8%)                 | 36 (81.8%)          | 0.783   |
|                                        | 12 (16.2%)                 | 8 (18.2%)           |         |
| Grade of DCIS                          | Low, intermediate          | High               |         |
|                                        | 60 (81.1%)                 | 38 (86.4%)          | 0.460   |
|                                        | 14 (18.9%)                 | 6 (13.6%)           |         |
| LDH                                     | ≤ ULN                      | > ULN              |         |
|                                        | 67 (90.5%)                 | 38 (86.4%)          | 0.484   |
|                                        | 7 (9.5%)                   | 6 (13.6%)           |         |
| CEA                                     | ≤ ULN                      | > ULN              |         |
|                                        | 70 (94.6%)                 | 41 (93.2%)          | 0.753   |
|                                        | 4 (5.4%)                   | 3 (6.8%)            |         |
| CA15-3                                  | ≤ ULN                      | > ULN              |         |
|                                        | 71 (95.9%)                 | 44 (100.0%)         | 0.176   |
|                                        | 3 (4.1%)                   | 0 (0.0%)            |         |
| Postoperative pathology                | DCIS only                  | Invasive ductal carcinoma |     |
|                                        | 50 (67.6%)                 | 20 (45.5%)          | 0.018   |
|                                        | 24 (32.4%)                 | 24 (54.5%)          |         |

DCIS: ductal carcinoma in situ, HER2: human epidermal growth factor receptor 2, LDH: lactate dehydrogenase, ULN: upper limit of normal. CEA: carcinoembryonic antigen.
Table 4
Univariate and multivariate analysis with upstaging preoperatively DCIS to invasive cancer.

| Parameters                      | Univariate analysis |           |         | Multivariate analysis |           |         |
|---------------------------------|---------------------|-----------|---------|-----------------------|-----------|---------|
|                                 | Odd ratio           | 95% CI    | p value | Odd ratio             | 95% CI    | p value |
| Age at operation (years old) ≤ 60 vs > 60 | 1.136               | 0.510–2.531 | 0.754       | 1.662                 | 0.588–4.923 | 0.342   |
| Palpability Impalpable vs Palpable | 2.261               | 0.941–5.434 | 0.065       | 1.662                 | 0.588–4.923 | 0.342   |
| Tumor size (mm) ≤ 20.0 vs > 20.0 | 2.372               | 1.111–5.063 | 0.024       | 2.758                 | 1.028–7.925 | 0.044   |
| Biopsy device CNB vs VAB        | 0.313               | 0.142–0.690 | 0.003       | 0.206                 | 0.075–0.516 | 0.001   |
| Estrogen receptor Negative vs Positive | 0.397            | 0.154–1.023 | 0.051       | 0.689                 | 0.187–2.550 | 0.572   |
| Progesterone receptor Negative vs Positive | 0.528         | 0.240–1.163 | 0.111       |                       |           |         |
| HER2 ≤ 2 vs 3                   | 2.368               | 0.832–6.744 | 0.100       |                       |           |         |
| Ki67 ≤ 14% vs > 14%             | 1.579               | 0.601–4.149 | 0.352       |                       |           |         |
| Grade of DCIS Low, intermediate vs High | 3.343          | 1.221–9.155 | 0.015       | 2.599                 | 0.717–9.973 | 0.146   |
| Platelets - lymphocyte ratio Low vs High | 2.500       | 1.160–5.386 | 0.018       | 3.212                 | 1.370–7.866 | 0.007   |
| LDH ≤ ULN vs > ULN              | 1.286               | 0.404–4.094 | 0.670       |                       |           |         |
| CEA ≤ ULN vs > ULN              | 1.100               | 0.235–5.152 | 0.904       |                       |           |         |
| CA15-3 ≤ ULN vs > ULN           | 3.000               | 0.264–34.052 | 0.353       |                       |           |         |

DCIS: ductal carcinoma in situ, CNB: core needle biopsy, VAB: vacuum-assisted biopsy, HER2: human epidermal growth factor receptor 2, LDH: lactate dehydrogenase, ULN: upper limit of normal, CEA: carcinoembryonic antigen, CI: confidence intervals.

Discussion
IDC may be misdiagnosed as DCIS by preoperative biopsy. As mentioned above, 25.9% (18.6–37.2%) of cases preoperatively diagnosed as DCIS have been reported to be IDC according to a meta-analysis.
However, the ratio in this study was 40.7%, higher than that previously reported. This is greatly influenced by the biopsy method. The meta-analysis found that one of the risk factors of underestimation was sampling by 14-Gauge CNB instead of 11-Gauge CNB. In contrast, more than half of the cases in this study used 16-Gauge CNB for biopsy. As a result, in patients diagnosed with DCIS by VAB, the rate of postoperative invasion was 27.1%, but that in patients diagnosed by CNB, it was 52.2%. Certainly, VAB has stronger pain and higher medical costs than CNB. However, in the future, CNB with a thicker puncture needle or VAB is considered necessary for more accurate preoperative diagnosis.

There are various factors other than biopsy devices that are risk factors for underestimation. High grade, tumor size larger than 20 mm, and palpability have been previously identified as risk factors [5]. One study also reported hormone receptor negativity as a risk factor [17]. Similar results were found in this study regarding these clinical factors. However, this study focused on preoperative blood test results, and invasion in postoperative pathology was found significantly more frequently in patients with a high PLR than in patients with a low PLR. Platelets and growth factors such as platelet-derived growth factor and transforming growth factor-β are known to promote tumor growth [18–22]. In addition, immunity is involved in the progression of cancer, and lymphocytes play a key role in the host anti-tumor immune function [23]. In recent years, one report has reported changes in the immune microenvironment around tumors in DCIS and IDC. According to the report, immune escape is progressing in the invasion part [24]. This study was started with the hypothesis that blood test changes may occur as cancer progresses. LDH and tumor markers showed no significant difference based on pre- and postoperative concordance, but invasion was significantly more likely showed in the high PLR group than in the low PLR group. This result may indicate that PLR is not elevated as cancer progresses, but that a systemic immune state with a high PLR involved in the change from DCIS to IDC.

One limitation in this study is that there were many cases in which biopsy was performed with 16-Gauge CNB, so the rate of IDC after surgery was higher than that of previous reports. In addition, since the absolute platelet count and lymphocyte count are easily affected by liver diseases and
inflammation, it is also a limitation that the comorbidities are not included in the study. However, randomized trials are currently underway to investigate follow-up for low-grade DCIS [25, 26]. One strength of this study is that the PLR can be evaluated relatively easily in clinical practice, and changes in DCIS can be found by evaluating the PLR over time.

Conclusions

The PLR may be a predictor of invasion in postoperative pathology for patients diagnosed with DCIS by preoperative biopsy.

List Of Abbreviations

CA15-3, cancer antigen 15 – 3
CEA, carcinoembryonic antigen
CNB, core needle biopsy
DCIS, ductal carcinoma in situ
ER, estrogen receptor
HER2, human epidermal growth factor receptor 2
IDC, invasive ductal carcinoma
LDH, lactate dehydrogenase
OR, odds ratio
PgR, progesterone receptor
PLR, platelet-lymphocyte ratio
ULN, upper limit of normal
VAB, vacuum-assisted biopsy

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all subjects. This research conformed to the provisions of the Declaration of Helsinki in 2013. All patients were informed of the investigational nature of this study and provided their written, informed consent. The study protocol was approved by the Ethics Committee of Osaka City University (#926).

Consent for publication
Not applicable.

**Availability of data and materials**

The datasets supporting the conclusions of this article is included within the article.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This study was supported in part by Grants-in Aid for Scientific Research (KAKENHI, Nos. 17K10559 and 19K18067) from the Ministry of Education, Science, Sports, Culture and Technology of Japan.

**Authors’ contributions**

KTakad participated in the design of the study and drafted the manuscript. SK participated in the design of the study and manuscript editing. YA, WG, TM and TT helped with study data collection and manuscript preparation. HF, KTakah and ST helped with study data collection and participated in its design. KH and MO conceived the study, and participated in its design and coordination and helped to draft the manuscript. All authors have read and approved the final manuscript.

**Acknowledgements**

We thank Yayoi Matsukiyo and Tomomi Okawa (Department of Surgical Oncology, Osaka City University Graduate School of Medicine) for helpful advice regarding data management.

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Figures

![Figure 1](image)

Forrest plot. Forest plot showed odd ratios for the univariate association of the clinicopathological features on postoperative pathology changes to invasive ductal carcinoma. In univariate analysis of factors predictive of invasion in postoperative pathology, a high PLR (p = 0.018, OR = 2.500) was a factor, as were larger tumor size (p = 0.024, OR = 2.372), non-Low Grade of DCIS (p = 0.015, OR = 3.343) and biopsy method (VAB vs CNB, p = 0.003, OR = 0.313).