

presence of mass or Breast Imaging-Reporting and Data System (BI-RADS) category 5 on imaging, lesions diagnosed by core needle biopsy, and lesions with high nuclear grade. In our previous study, palpability in physical examination, presence of calcification or mass on ultrasonography, suspicious microinvasion in preoperative biopsy, and core needle biopsy as the biopsy method were independent predictors of an underestimation of invasive cancer.⁴ The presence of microinvasion had a 73% possibility of being invasive breast cancer on permanent pathology in a previous study.¹⁴ Several nomograms predicting invasiveness have been published, but no uniform pattern can be noticed overall.^{8,12,13} A possible reason for no significant difference in the value of mass size in the current study is that we only analyzed patients who underwent BCS. We excluded patients who underwent total mastectomy, which is mainly performed in patients with large lesions or multicentric lesions. The small number of enrolled patients may also affect the results of the study. Nevertheless, only the IOF results showed significance predictive information of invasiveness in this study.

IOF showed low sensitivity and high specificity (**Table 4**), and 5 of 6 cases with a positive IOF result for invasive breast cancer were consistent with permanent pathology (**Tables 1 and 2**). Therefore, use of IOF can help to avoid unnecessary axillary surgery in many patients with preoperative DCIS. The use of IOF was helpful for avoiding secondary axillary surgery in about one-third of preoperative DCIS patients diagnosed with invasive cancer in permanent pathology. Our study showed lower sensitivity compared to a previous study by Murphy et al. that also evaluated the performance of IOF in DCIS cases.¹⁵ Their data from 827 patients who underwent either lumpectomy or mastectomy showed that upstaging to invasive breast cancer on permanent pathology was 14.1% (95% CI, 11.8–16.7%).¹⁵ In the lumpectomy group, intra-operative diagnosis had 80% sensitivity and 98.9% specificity with a mean DCIS size of 17.1 mm on preoperative imaging.¹⁵ The difference in sensitivity between the current and previous study may be due to the different sample size. A larger sample size and more IOF-experienced pathologists may increase the sensitivity.

In the past, the majority of patients with preoperative DCIS who underwent BCS at our institution underwent SLNB, because the possibility of upstaging to invasive cancer was over 40%.¹⁶ In this study, the upstaging rate decreased to 23%. This indicates that three-quarters of patients with preoperative DCIS could have avoided SLNB at the time of the definitive surgery if preoperative or intra-operative evaluations could accurately distinguish DCIS and invasive cancer. However, because of the uncertainty of identifying invasiveness in DCIS, axillary staging for patients with DCIS is a controversial issue. The frequency of axillary staging, including SLNB and ALND, in patients with DCIS in the USA increased from 44% to 63% since 1998.¹⁷ This suggests that unnecessary axillary procedures in patients with DCIS are still performed, and this adherence to guidelines might be partly influenced by the uncertainty in identifying invasiveness in preoperative DCIS and the wider application of SLNB. In meta-analysis by Knuttel et al.,¹⁶ one-fifth of patients with preoperative DCIS were underestimated for invasive cancer in final pathology, and they recommended routine use of SLNB in patients with DCIS. However, SLNB is not a risk-free procedure, although it has lower morbidity rates than ALND. The risk of complications such as lymphedema and postoperative pain still remains after SLNB. It is important for patients and surgeons to more accurately estimate the possibility of the upstage to invasive cancer because it can inform the decision whether SLNB should be performed. SLNB can increase patients' complications. Therefore, the ability to predict the possibility of preoperative DCIS upstaging to invasive carcinoma and avoid unnecessary axillary procedures by IOF can reduce the necessity of SLNB at the time of definitive surgery.

Using intra-operative margin assessment in breast surgery facilitates identifying remnant breast disease and can help to decide additional treatment.^{18,19} Applying a similar concept to examine breast lesions intra-operatively could help to avoid unnecessary axillary procedures at the definitive surgery. This may minimize patient stress without axillary pain, operative scar and the continuous outpatient visits and dressing for drainage tube management for pure DCIS patients. Indeed, those patients with DCIS on intra-operative diagnosis had a low probability of harboring invasive breast cancer on final permanent pathology. It may be helpful to use not only IOF but also other predictive risk factors or nomograms to estimate the possibility of the upstaging.

Percutaneous biopsy techniques in DCIS cases are associated with underestimating invasive breast cancer. In our study, the rate of upstaging to invasive breast cancer on final pathology in cases with core needle biopsy was 27.8%, similar to other studies.¹⁶ A previous study reported that a larger needle or amount of tissue obtained are associated with lower rates of underestimation of preoperative DCIS.²⁰ Using vacuum-assisted biopsy methods, the upstaging rates decreased by 31.7% in a previous study.⁴ Therefore, vacuum-assisted biopsy can be used for more accurate diagnosis of preoperative DCIS than core needle biopsy.

A retrospective design and the small number of cases in a single institution are the major limitations of this study. However, to our knowledge, few large-scale studies have used IOF of the main tumor specimen to assess tumor invasiveness. As such, our findings can support the potential utility of IOF in predicting the upstaging of DCIS. Furthermore, the consistency of data from a single institution is also one of the strengths of the study. The results of the biopsy and radiological interpretation were verified with unified criteria and formats. The pathological and imaging interpretation method may vary depending on the institution. Therefore, different institutions may show different results in IOF interpretation. IOF is sometimes difficult and confusing for pathologists; therefore, well-skilled and experienced pathologists are needed to perform IOF accurately. However, experienced pathologists are not always available due to institutional limitations. Machine learning for the interpretation of IOF can help to reduce inter-observer discrepancies among pathologists.

Several trials on de-escalation or omission of axillary surgery, and active surveillance without any surgery, are ongoing in early breast cancer.²¹⁻²⁴ As the studies progress, the status quo in the wide use of axillary surgery for patients with DCIS may change. As part of this, efforts are needed to determine the appropriate extent of surgery necessary for patients to reduce the occurrence of complications. In this regard, this study introduced the role of IOF in reducing axillary surgery in preoperative DCIS.

The use of IOF during BCS showed high specificity and accuracy for detecting invasiveness in cases with preoperative DCIS. However, low sensitivity is a limitation of IOF. Further prospective study is needed to validate the role of IOF during BCS for patients with preoperative DCIS.

In conclusion, IOF can be a potential adjunctive diagnostic tool for identifying invasiveness in patients with preoperative DCIS. This approach may help to reduce the stress of patients by avoiding unnecessary axillary surgery for pure DCIS patients in selected cases.

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