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*Original Article*

# Pathologic evaluation of lumpectomy resection margins for invasive breast cancer: a single institution's experience

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**Abstract:** Objectives: Breast conservation therapy (BCT) or lumpectomy followed by radiation has been established as a preferred treatment for most patients with early-stage invasive breast cancer. About 20-40% of patients after initial lumpectomy will have to undergo re-excision due to a positive margin. Methods: To determine the factors predicting higher risk of positive resection margin, we retrospectively analyzed 409 patients who underwent initial lumpectomy for invasive breast cancer from January 2019 through November 2022. Based on microscopic examination, the samples were divided into 3 subgroups with positive, close, or clean margins. Results: Positive margin was more frequently associated with larger tumor size (P<0.0001), specified histologic type (P<0.0001), higher tumor grade (P=0.004), multifocality (P<0.0001), positive lymph node status (P=0.0005), and lymphovascular invasion (P=0.0007). Other factors were not significantly associated with margin status including HER2/ER/PR status, presence of carcinoma in situ component, age at diagnosis, and history of neoadjuvant chemotherapy. Conclusions: From the clinical practice of individual institution, identification and comprehensive assessment of these pathologic predictors will be useful for clinical management and intraoperative surgical-decision-making to reduce the rate of re-excision.

**Keywords:** Lumpectomy, margin status, pathologic factors, invasive breast cancer

## Introduction

Breast cancer (BC) remains the second leading cause of cancer-related death among women with ~ 255,000 new diagnosed cases per year in the US [1]. Over the last decades, the wide application of routine mammography screening has successfully facilitated the early detection of breast tumors, even when they are very small and non-palpable [2, 3]. Breast conservation therapy (BCT) or lumpectomy followed by radiation has been established as a preferred standard treatment for most patients with early-stage invasive breast cancer. Large randomized clinical trials have shown that lumpectomy provided a long-term equivalent survival compared to mastectomy [4, 5]. For the purpose of surgical procedure, the appropriate extent of resection generally should be placed closed to the tumor to avoid extensive tunneling at the time of lumpectomy. Unfortunately, about 20-40% of patients will have to undergo re-excision due to positive microscopic margin, or warrant subsequent mastectomy to achieve a definitive negative margin [6]. A positive microscopic margin also demonstrated higher risk of local recurrence in association with residual tumor in the breast [6-8]. In addition, re-excision and reoperation may generate more discomfort and significant anxiety for both the patient and family, increase healthcare cost, and lead to a delay of adjuvant treatment such as systemic chemoradiation therapy [3]. Hence, to ensure the best clinical outcomes of breast conserved therapy, the main goal at the first lumpectomy operation is to obtain tumor-free resection margins, while maximally maintaining the cosmetic appearance of the remaining breast.

Pathologic assessment of margin status has become the standard practice in evaluation of

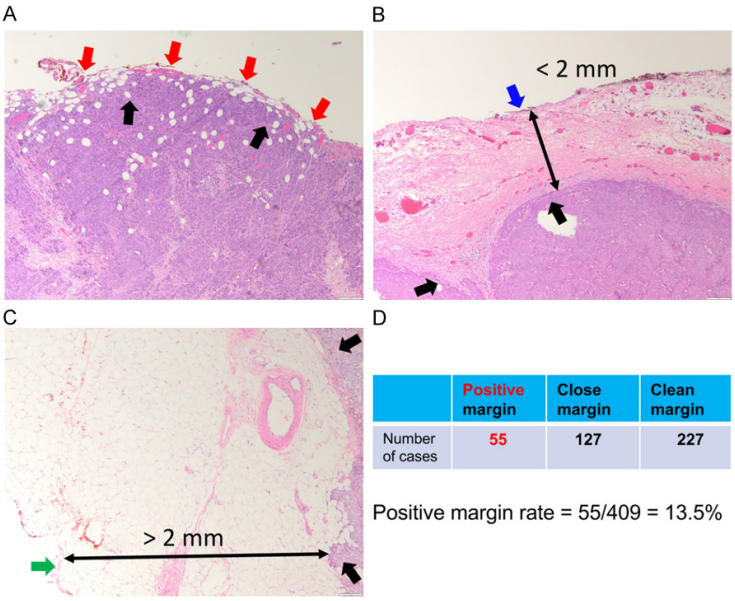


**Figure 1.** Categories of lumpectomy margin status, and positive margin rate. A. Positive margin: invasive ductal carcinoma (black arrow) on the inked resection margin (red arrows), H&E 4× magnification. B. Close margin: invasive ductal carcinoma (black arrows) <2 mm (double headed arrow) from the inked margin (blue arrow), H&E 4× magnification. C. Clean margin: invasive ductal carcinoma (black arrows) >2 mm (double headed arrow) from the inked margin (green arrow), H&E 4× magnification. D. Number of cases within the 3 categories, and positive margin rate.

lumpectomy specimens, compliant with the College of American Pathologists (CAP) breast cancer reporting protocol. Microscopic margin status has been the primary determinant for local breast cancer control after surgical management [9]. At Penn State Health Hershey Medical Center, we routinely applied a multicolor inking system to stain indicating the superior, inferior, anterior, posterior, lateral, and medical surfaces of the resection specimen, allowing orientation of the individual margin to the corresponding surgical cavity in the patient. By identifying the microscopic distance between cancer cells and the inked surface, margin status can be divided into three major categories: positive, close, and negative margins following the SSO-ASTRO-ASCO consensus guidelines for invasive breast cancer [3]. A positive resection margin was defined as tumor on the ink (**Figure 1A**). Close margin was defined as identifying tumor cells <2 mm from the inked edge (**Figure 1B**). Clean margin was verified as having tumor cells ≥2 mm away from the ink (**Figure 1C**). When margins are ink-negative ('no tumor on the ink'), re-excision is not recommended.

In order to optimize the balance between negative margin achievement and the cosmesis requirement, surgeons, pathologists, and radiologists all play critical roles to reduce positive margins [10, 11]. Positive margins have been reported to be associated with multiple variabilities, including surgeon volume, patient, imaging, and tumor-related factors [12]. Previous studies have shown several independent risk factors associated with positive margins following lumpectomy, including high tumor grade, lobular histology, larger tumor size, lymphovascular invasion, presence of ductal carcinoma in situ (DCIS), multifocality, and presence of mammographic microcalcifications [10, 13, 14]. In this study from our single institution's experience based on the patient population from central Pennsylvania, we evaluated variable pathological factors to determine their impact on higher risk of margin positivity after initial lumpectomy.

## Materials and methods

We retrospectively analyzed 409 patients who underwent initial lumpectomy for invasive breast cancer from January 2019 through November 2022 at Hershey Medical Center, PA, USA. This retrospective cohort study was approved by the institutional review board at Hershey Medical Center. Based on the microscopic histologic examination reviewed by two of the authors (Y.Z., B.H.) to confirm resection margin status, the pathologic specimens were divided into 3 subgroups with positive, close, or clean margins following the SSO-ASTRO-ASCO consensus guidelines. According to the CAP Breast Cancer and Biomarker reporting protocols, multiple clinicopathologic characteristics were evaluated to identify which predictive factors may influence margin status. These included patient age, tumor histologic type, tumor grade, size, hormone receptor status (ER/PR/HER2), multifocality, presence of carcinoma in situ components (DCIS/LCIS), lymphovascular

**Table 1.** Summary of patient and tumor characteristics

| Characteristic | Positive margin (N=55) Values (%) | Close margin (N=127) Values (%) | Clean margin (N=227) Values (%) | *p* value |
|---|---|---|---|---|
| Age (mean ± SD) | 65.9 ± 10.6 | 64.7 ± 11.9 | 64.3 ± 10.8 | 0.38 |
| Tumor size (mean ± SD) | 21.4 ± 12.5 | 16.5 ± 10.6 | 11.9 ± 7.9 | <0.0001 |
| Histologic type | | | | <0.0001 |
| Ductal | 23 (42%) | 95 (75%) | 198 (87%) | |
| Lobular | 17 (31%) | 16 (12%) | 16 (7%) | |
| Mixed | 5 (9%) | 5 (4%) | 5 (2%) | |
| Other specified | 10 (18%) | 11 (9%) | 8 (4%) | |
| Tumor grade | | | | 0.004 |
| Grade I | 7 (13%) | 30 (24%) | 83 (37%) | |
| Grade II | 38 (69%) | 73 (57%) | 112 (49%) | |
| Grade III | 10 (18%) | 24 (19%) | 32 (14%) | |
| Tumor deposits | | | | <0.0001 |
| Single | 40 (73%) | 111 (87%) | 212 (93%) | |
| Multiple | 15 (27%) | 16 (13%) | 15 (7%) | |
| Hormone receptor status | | | | 0.37 |
| ER+ and/or PR+ | 51 (93%) | 105 (82%) | 199 (87%) | |
| HER2+ | 3 (5%) | 11 (9%) | 15 (7%) | |
| ER-/PR-/HER2- | 1 (2%) | 11 (9%) | 13 (6%) | |
| Carcinoma in situ component | 45 (82%) | 88 (69%) | 155 (68%) | 0.13 |
| LN status | | | | 0.0005 |
| Negative | 40 (73%) | 98 (77%) | 204 (90%) | |
| Positive | 15 (27%) | 29 (23%) | 23 (10%) | |
| LVI status | | | | 0.0007 |
| Negative | 45 (82%) | 110 (87%) | 217 (96%) | |
| Positive | 10 (18%) | 17 (13%) | 10 (4%) | |
| Neoadjuvant chemotherapy | 5 (9%) | 9 (7%) | 13 (6%) | 0.64 |

Abbreviations: ER, Estrogen Receptor; PR, Progesterone Receptor; LN, Lymph Node; LVI, Lymphovascular Invasion.

invasion (LVI), and axillary nodal status. Standard immunohistochemical (IHC) techniques were performed for ER/PR/HER2 staining in our clinical IHC lab on the selected block from each case. A triple-negative breast cancer (TNBC) was defined as ER negative, PR negative, and HER2 negative.

*Statistical analysis*

Chi-square test, one-way ANOVA, or Student's *t* test were used to compare these pathologic features in association with margin status. Statistical significance was set at $P<0.05$.

## Results

Of the 409 breast cancer cases, positive margin rate was 13.5% (**Figure 1D**) after the initial lumpectomy. For the positive margin group, the mean age at diagnosis was 65.9 years (range, 39 to 88 years). The close margin group showed a mean age at 64.7 years (range, 36 to 95 years), while the mean age at diagnosis for clean margin group was 64.3 years (range, 29 to 88 years) (**Table 1**). Positive margin group was associated with a significantly larger tumor size, compared to close and clean margin groups ($P<0.01$ and $P<0.0001$, respectively, **Figure 2A**). The mean tumor size at the time of resection was 21.4 mm for margin positive specimens, 16.5 mm for close margin specimens, and 11.9 mm for margin negative specimens (**Table 1**).

Positive margin was more frequently associated with invasive lobular carcinoma, mixed type (invasive carcinoma with ductal and lobular features), or other specified types including mucinous, medullary, tubular, apocrine, and papil-

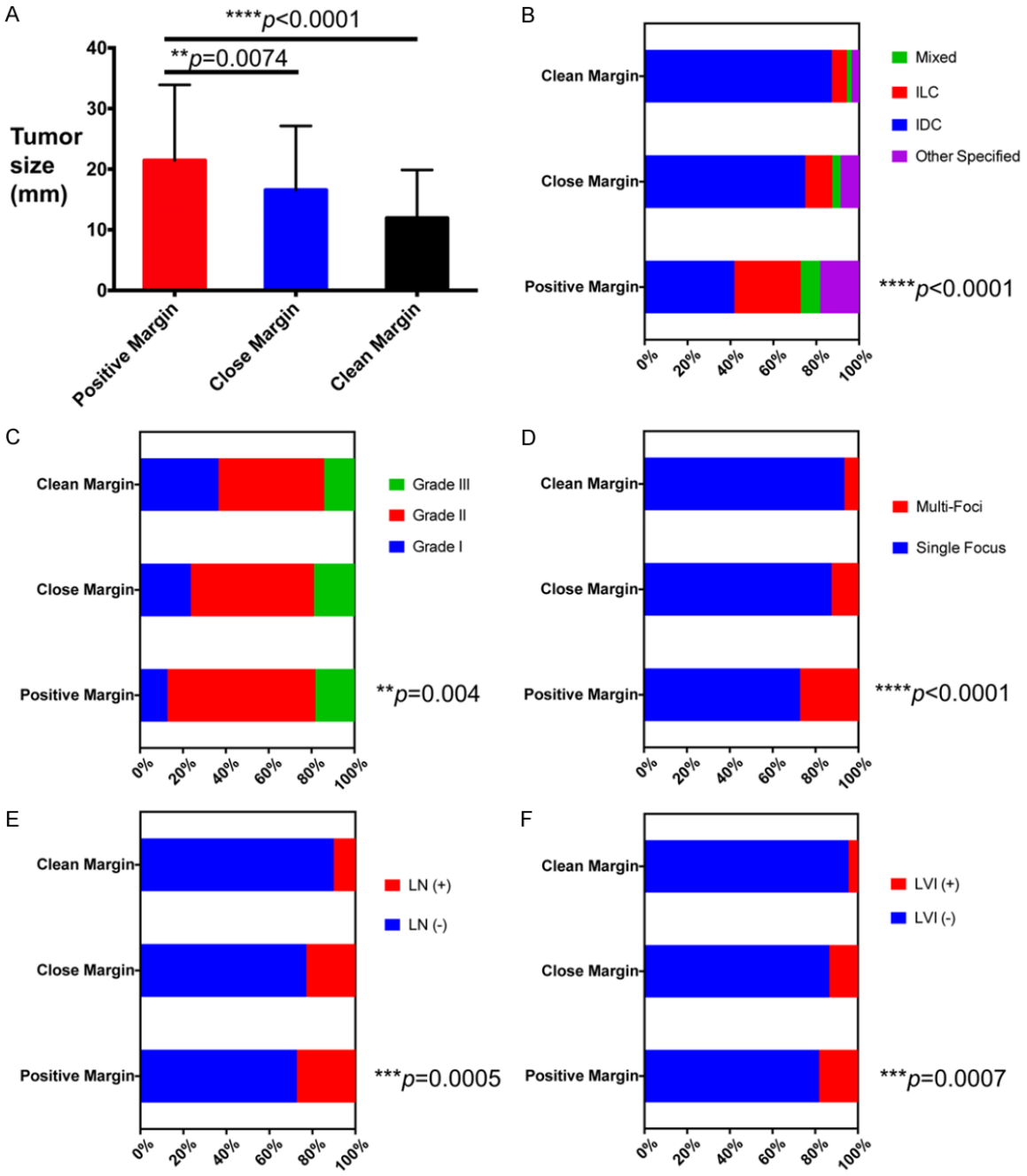


**Figure 2.** Evaluated pathologic factors for lumpectomy margin status. (A) Tumor size of invasive breast cancer specimens with positive, close, or clean margins. Results are presented as mean ± SD. (B-D) Graph of the distribution of histologic subtypes (B), tumor grade (C), and multifocality (D) per positive, close, and clean margins. Mixed: invasive carcinoma with ductal and lobular features; ILC: Invasive Lobular Carcinoma; IDC: Invasive Ductal Carcinoma; Other specified includes subtypes of mucinous, medullary, tubular, apocrine, and papillary carcinoma. (E, F) Graph of the distribution of pathologic lymph node status (E), and lymphovascular invasion (F) per positive, close and clean margins.

lary carcinomas (*P*<0.0001, **Figure 2B** and **Table 1**). Positive margin also demonstrated the trend to be significantly associated with higher tumor grade (*P*=0.004, **Figure 2C** and **Table 1**), multifocal tumor deposits (*P*<0.0001, **Figure 2D** and **Table 1**), positive lymph node (LN) status (*P*=0.0005, **Figure 2E** and **Table 1**), and lymphovascular invasion (LVI) (*P*=0.0007,

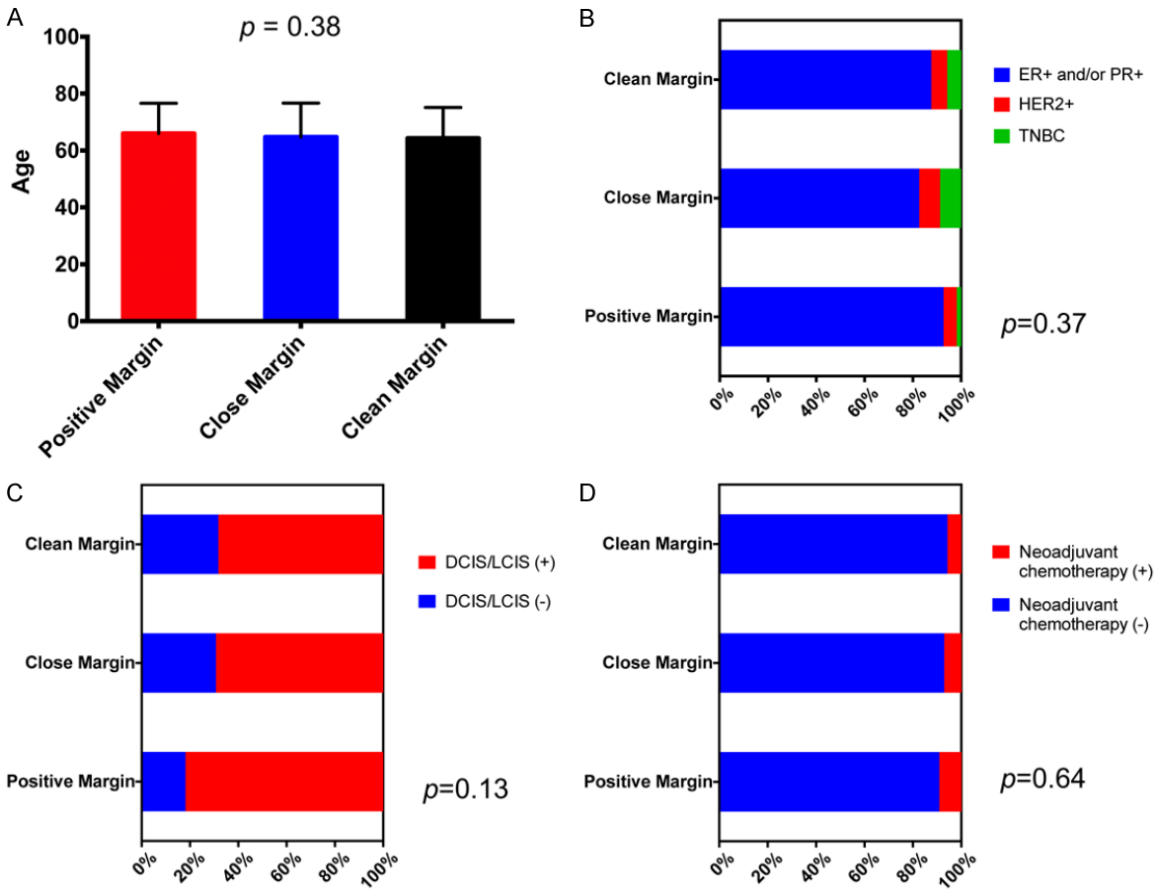


**Figure 3.** Other evaluated risk factors for resection margin status. (A) Age at diagnosis of 3 groups. The mean ± SD is depicted graphically. (B-D) Graph of the distribution of hormone receptor status (B), carcinoma in situ components (C), and history of neoadjuvant chemotherapy (D).

**Figure 2F** and **Table 1**). No significant difference in age was noted between three groups ($P$>0.05, **Figure 3A**). Other factors not significantly associated with margin status included HER2/ER/PR status ($P$=0.37, **Figure 3B** and **Table 1**), presence of DCIS and/or LCIS component ($P$=0.13, **Figure 3C** and **Table 1**), and history of neoadjuvant chemotherapy before the lumpectomy ($P$=0.64, **Figure 3D** and **Table 1**).

## Discussion

Reducing the re-excision rate is a practical clinical goal of initial lumpectomy for management of invasive breast cancer. Positive tumor cells on the surface ink indicates higher likelihood of residual disease in the breast and significant rate of local recurrence, which may warrant a re-excision or multiple procedures to achieve negative margins [7, 8, 15-18]. Therefore, pathologists play an important role in the multidisciplinary teamwork guiding surgeons to ensure a negative lumpectomy margin by intraoperative frozen section, rapid cytologic analysis, and pathologic evaluation on permanent resection specimens [19-21]. Understanding the predictive pathologic factors of positive resection margins may be useful for surgical planning, preoperative patient counselling to help them choose an option surgery leading to a better outcome from breast-conserving therapy.

Our analysis on lumpectomy is representative of a typical high-volume breast surgical practice composed of more than 4 dedicated breast surgeons and 5 breast surgical pathologists for the patient population at the area of central Pennsylvania. In our current study, the rate of positive margin was slightly low at 13.5%, as the majority of studies have demonstrated a rate of positive margins ranging from 20% to

40% [22, 23]. Due to the complexity of various clinicopathologic factors from multidisciplinary teams and different patient populations, the definitive risk factors that affect margin status are not clearly elucidated in the literature. Few studies have examined several risk factors that may contribute to margin positivity at the time of lumpectomy including tumor size, lobular histologic type, stage, multifocality, lymphovascular invasion, co-existing ductal carcinoma in situ (DCIS), microcalcifications, and patient age at the time of lumpectomy [10, 13, 14]. However, the conclusions are generally controversial between different studies regarding the risk factors to be investigated. For example, some research found that larger tumor size was highly associated with positive margins [24-27], while other research did not identify this to be the case [28, 29]. Histologic subtypes, especially with lobular features, have also been reported to affect margin positivity in some research [24, 27, 30], but not found to be contributory factor in other publications [25, 26, 31]. As with Keskek et al. [24] and Chagpar et al. [32], we found that tumor size and histologic subtypes were the significant risk factors associated with margin status. Miller et al. and Jia et al. found that HER2/neu positivity [33, 34] and the co-existing of DCIS may correlate with margin positivity [14], but their findings were not confirmed in other publications including our study. In recent studies by Angarita et al. and Aziz et al., positive resection margins were less common in elderly women than young women [35, 36]. In comparison, a correlation of patient age with margin positivity was not identified in the current study.

Therefore, from the practice of individual institution, the independent investigation of predictive risk factors appears to be important for breast conserving therapy. Our study adds to the growing literatures on the evaluation of lumpectomy margin status in a contemporary cohort of patient population. We found that there were 6 predictive tumor-related factors significantly associated with positive margins in the lumpectomy pathologic specimens. These features include tumor size, lobular histology and other specified carcinoma types, higher tumor grade, multifocal tumor deposits, lymphovascular invasion, and positive lymph node status. Our data can help a clinical team and patients in our institution to make better personalized treatment decisions. In patients with a combination of multiple key predictive factors, surgeons should take into consideration that these features are associated with a higher risk of positive resection margins, and therefore may warrant a wider initial excision, or additional resection margins during the operation.

Further research is needed to focus on the integration of pathologic risk factors, radiologic imaging, and adjunctive use of novel technologies for intraoperative margin assessment such as MarginProbe, optical spectroscopy, bioimpedance, and mass spectrometry [37]. This may ultimately help guide the breast surgeons to remove only necessary breast tissue, and facilitate the crucial surgical decision-making to obtain both clear margins and better cosmesis at the time of lumpectomy.

## Conclusion

Over the past decades, management of breast cancer has evolved from a radical mastectomy procedure to combined techniques including routine mammographic screening of early detection, limited extent of surgical excision while maintaining breast cosmesis and improving disease-free survival of breast cancer patients. Therefore, the trend toward lumpectomy has increased the need for accurate assessment of resection margins both intraoperatively and postoperatively for surgical pathologists. The definitive risk factors that affect margin status are not entirely elucidated due to the complexity of clinical variables from specialized surgical teams with their own practice habits, various radiologic correlations, and different patient populations. In the setting of our single-intuitional experience, we have defined 6 predictive pathologic factors associated with margin status after the initial lumpectomy. Identification and comprehensive evaluation of these pathologic predictors are important for clinical management at the individual institution not only providing information to multidisciplinary team, but also facilitating surgeons to make personalized pre-operative and intraoperative surgical decisions and ultimately reduce the rate of re-excision.

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## Disclosure of conflict of interest

None.

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