

## Surgical margins assessment reduces re-excision rates in breast-conserving surgery

### Dear Editor,

Breast-conserving surgery (BCS) followed by radiation therapy for breast cancer offers improved cosmetic results and comparable long-term survival rates as mastectomy.<sup>1</sup> However, BCS is associated with a higher risk for local recurrence, and published literature has reported re-excision rates as high as 20–70% due to positive resection margins of the tumour. The increased re-excision rates are associated with unfavourable consequences, including increased utilisation of healthcare resources and decreased patient satisfaction.<sup>2</sup> An important factor in reducing local recurrence rates in BCS is to achieve a microscopically clear margin absent of tumour cells.<sup>3,4</sup> Intraoperative assessment with frozen section (FS) analysis has been described as a popular method to reduce re-excision rates.<sup>4</sup> FS also offers significant cost savings to patients while improving efficiency in the utilisation of hospital resources through reduced re-operations.<sup>5</sup> On the other hand, opponents of routine use of intraoperative FS cite these reasons as barriers to adoption of the technique: longer operating times; little role for FS evaluation of resection margins that are grossly free of the tumour because of the fatty nature of the margins; diversion of pathologists' resources; and higher patient fees.<sup>6-8</sup> This study aims to audit the effect of intraoperative FS in BCS in a Singapore regional hospital.

After approval from the ethics board, a retrospective study was conducted on consecutive breast cancer patients from Khoo Teck Puat Hospital (KTPH) in Singapore. We identified 186 patients who underwent BCS from January 2012 to February 2020. Eligible patients had either invasive or in situ carcinoma and were deemed to be candidates for BCS after clinical and radiographic evaluation. Patients who had metastases or a history of recurrent breast cancer were excluded. From 2017 onwards, our unit began to perform intraoperative FS routinely, with margins taken from the tumour cavity. Intraoperative ultrasound was also used as an adjunct to aid wide local excision in selected cases where the tumour was small and not well defined by clinical palpation.

The following clinical factors were collected: patient's age, multifocality of the tumour, primary tumour size, staging of the tumour, histological type, and grade.

Additionally, information on the type of surgery performed, duration of the surgery (defined from initial skin incision to skin closure including axillary procedures if any), and data on neoadjuvant therapy were assessed. Our study compared the outcomes of BCS with and without intraoperative FS. Statistical analysis was performed using SPSS Statistics software, version 26.0 (IBM Corp, Armonk, US). All continuous data were expressed as median and compared using two-sample t-tests. All categorical variables were described as percentages and compared using chi-square analysis. Univariate and multivariate logistic regression models were used to analyse the factors associated with the final margin involvement rate. For all analyses, a *P* value of <0.05 was accepted to be statistically significant.

All 186 patients underwent BCS, with about 20% of them performed utilising hookwire localisation or radioguided occult lesion localisation (ROLL), while the remaining were palpable. Intraoperative FS was performed in 145 (78%). The clinicopathologic features were comparable in the 2 groups (Table 1). The use of intraoperative FS in BCS was associated with a longer median operative duration of 115 (91.5–155) minutes compared to 110 (80–125.5) minutes, *P*=0.016. Positive surgical margins were identified in 31 patients (21.4%) during intraoperative FS, and intraoperative re-excision was performed until negative margins were achieved. The final margin involvement rate was lower in the FS group compared to the non-FS group (13.1% versus 26.8%, *P*=0.035). The re-operation rates were lower in the FS group (9% vs 19.5%, *P*=0.060), with no increase in mastectomy rates (3.4% vs 7.3%, *P*=0.965). Patients with positive final margins due to involvement of posterior margins microscopically had excision of the pectoralis muscle fascia. Their tumour bed was also clipped and underwent postoperative radiotherapy with additional boosts to tumour bed; hence repeat surgery for additional margins was not performed. After adjusting for risk factors associated with re-operation, such as larger tumour size (>2cm), multifocality, ductal carcinoma in situ type (DCIS), locally advanced tumours with nodal involvement, or post-neoadjuvant chemotherapy, the use of FS was still found to be an independent predictor for reduced final margin involvement rates, odds ratio 0.37, (confidence interval 0.16–0.89), *P*=0.026.

Table 1. Clinicopathological features of patients and outcomes of patients undergoing breast-conserving therapy, with or without frozen section

| Factors                                                                                             | Without frozen section<br>n=41 | With frozen section<br>n=145 | P value |
|-----------------------------------------------------------------------------------------------------|--------------------------------|------------------------------|---------|
| Age (IQR), years <sup>a</sup>                                                                       | 57 (53–64)                     | 57 (49–63.5)                 | 0.207   |
| Multifocality (%)                                                                                   | 4 (9.8)                        | 7 (4.8)                      | 0.238   |
| Tumour maximal diameter (IQR), cm <sup>a</sup>                                                      | 2.0 (1.5–3.0)                  | 2.0 (1.3–2.5)                | 0.171   |
| T stage (p-staging) (%)                                                                             |                                |                              | 0.060   |
| T0 (pathological complete response)                                                                 | 0                              | 2 (1.4)                      |         |
| Tis                                                                                                 | 7 (17.1)                       | 16 (11.0)                    |         |
| T1                                                                                                  | 14 (34.1)                      | 68 (46.9)                    |         |
| T2                                                                                                  | 15 (36.6)                      | 56 (38.6)                    |         |
| T3                                                                                                  | 1 (2.4)                        | 1 (0.7)                      |         |
| T4                                                                                                  | 4 (9.8)                        | 2 (1.4)                      |         |
| N stage (p-staging) (%)                                                                             |                                |                              | 0.508   |
| N0                                                                                                  | 35 (85.4)                      | 111 (76.6)                   |         |
| N1                                                                                                  | 3 (7.3)                        | 27 (18.6)                    |         |
| N2                                                                                                  | 2 (4.9)                        | 5 (3.4)                      |         |
| N3                                                                                                  | 1 (2.4)                        | 2 (1.4)                      |         |
| Type of surgery (%)                                                                                 |                                |                              | 0.717   |
| Wide local excision                                                                                 | 33 (80.5)                      | 108 (76.8)                   |         |
| Hookwire localisation                                                                               | 4 (9.8)                        | 20 (13.8)                    |         |
| ROLL and excision                                                                                   | 4 (9.8)                        | 17 (11.7)                    |         |
| Histology (%)                                                                                       |                                |                              | 0.179   |
| Invasive ductal carcinoma                                                                           | 33 (80.4)                      | 123 (84.8)                   |         |
| Invasive lobular carcinoma                                                                          | 1 (2.4)                        | 6 (4.1)                      |         |
| Ductal carcinoma in situ                                                                            | 7 (17.1)                       | 16 (11.0)                    |         |
| Grade (%)                                                                                           |                                |                              | 0.994   |
| Low                                                                                                 | 5 (12.2)                       | 17 (11.7)                    |         |
| Intermediate                                                                                        | 14 (34.1)                      | 49 (33.8)                    |         |
| High                                                                                                | 22 (53.7)                      | 79 (54.5)                    |         |
| Operative duration (IQR), min <sup>a</sup>                                                          | 110.0 (80.0–125.5)             | 115.0 (91.5–155.0)           | 0.016*  |
| Neoadjuvant therapy                                                                                 | 1 (2.4)                        | 11 (7.6)                     | 0.236   |
| Outcomes                                                                                            | Without frozen section<br>n=46 | With frozen section<br>n=147 | P value |
| Positive intraoperative frozen section with re-excision till negative margins (%)                   | NA                             | 31 (21.4)                    | NA      |
| Final margin involved (%)                                                                           | 11 (26.8)                      | 19 (13.1)                    | 0.035*  |
| Indeterminate margin rate                                                                           | NA                             | 10.3%                        | NA      |
| Re-operation rate (%)                                                                               | 8 (19.5)                       | 13 (9.0)                     | 0.060   |
| Re-excision (%)                                                                                     | 5 (12.2)                       | 8 (5.5)                      | 0.965   |
| Conversion to mastectomy (%)                                                                        | 3 (7.3)                        | 5 (3.4)                      | 0.965   |
| <b>Multivariate logistic regression analysis for factors associated with positive final margins</b> |                                |                              |         |
| Factors                                                                                             | Odds ratio                     | Confidence interval          | P value |
| Frozen section                                                                                      | 0.37                           | 0.16–0.89                    | 0.026*  |
| Multifocality                                                                                       | 1.16                           | 0.23–5.95                    | 0.855   |
| Neoadjuvant chemotherapy                                                                            | 1.21                           | 0.24–6.04                    | 0.819   |
| Tumour >2cm                                                                                         | 1.27                           | 0.56–2.88                    | 0.576   |
| Nodal involvement                                                                                   | 2.27                           | 0.91–5.64                    | 0.079   |
| Ductal carcinoma in situ                                                                            | 1.45                           | 0.41–5.11                    | 0.563   |

IQR: interquartile range; NA: not applicable; ROLL: radioguided occult lesion localisation

\* $P < 0.05$  is statistically significant<sup>a</sup> Age, tumour maximal diameter and operative duration are measured in median

Our study demonstrated a significant reduction in final margin involvement rates by more than half (13.1% vs 26.8%,  $P=0.035$ ) in the FS group. This reduction extended to a subgroup of patients at higher risk of positive surgical margins and re-operation, including patients with large, multifocal or DCIS-type tumours, nodal involvement and neoadjuvant chemotherapy undergoing BCS.<sup>9</sup> A review of the cases with positive final margin involvement revealed that 26 out of 30 of the cases involved invasive carcinoma, with the remaining 4 being DCIS. Further stratification by tumour biology demonstrated these groups of breast cancer within the invasive carcinoma group: 11 luminal A, 5 luminal B, 2 human epidermal growth factor receptor 2 (HER2)-enriched and 5 triple-negative. The remaining 3 invasive carcinoma cases were not candidates for anti-HER2 therapy; hence fluorescence in situ hybridisation (FISH) was not performed to determine HER2 status. Within the DCIS group, 3 were estrogen receptor-positive, progesterone receptor-positive (ER+PR+), and the remaining 1 was ER-PR-. Furthermore, our FS false-negative rates of 13.1% compared favourably to international studies that reported up to 23% of false-negative rates,<sup>4</sup> thus lowering overall re-excision rates. Our practice is to use the cutting mode on diathermy, or the use of a new blade instead of the coagulation mode on diathermy, when taking margins for intraoperative FS. This is to prevent the creation of charring artefacts that could affect the analysis of margins on frozen sections, which may alter false-negative or false-positive rates.

On the other hand, the drawback to intraoperative FS is its 10.3% “indeterminate” margin rate, which required additional margins of breast tissue to be taken intraoperatively. Indeterminate margins are defined as margins taken during surgery where carcinoma could not be excluded, and which were subsequently found on paraffin assessment to be negative. Among the indeterminate patients, invasive cancer accounted for 12 out of 15 of all indeterminate cases, with the remaining 3 being DCIS. Other drawbacks to intraoperative FS include longer operative times and increased workload for pathology staff.<sup>6</sup> Although the operative duration in the FS group in our study was significantly longer, a median additional duration of 5 minutes (115 minutes in FS vs 110 minutes in the non-FS group) is not clinically significant in real-life practice. The processing time for FS of margins is approximately 20 minutes. However, by performing the wide local resection of the tumour first and sending the

margins for FS analysis before performing any sentinel lymph node biopsy, this sequence of surgery could negate some of the additional time required for FS processing of margins. The availability of a dedicated pathology team to process the specimens in a timely fashion may deliver improved outcomes for patients undergoing BCS with intraoperative FS. Logistical challenges can be further addressed with good pre-planning and deconflict of schedule between surgeons and pathologists prior to surgery for cases that require FS of margins.

Limitations of our study include its inherent retrospective nature, lack of standardisation of the volume of margins taken, lack of data on total specimen volume excised and follow-up of any cosmetic concerns in the postoperative period. Through this audit, it improved understanding and collaboration between the Pathology Department and the Breast Service in our hospital to obtain the common goal of achieving lower re-excision rates for better patient outcomes.

With the increasing adoption of oncoplastic surgery by breast surgeons and the ability to perform wider resection margins without compromising on final cosmetic outcomes,<sup>10</sup> the case for intraoperative FS may be less compelling in selected cases in future. Similarly, breast surgeons from our unit are undergoing formal fellowship training in oncoplastic breast surgery, and this may change the practice of intraoperative FS in our unit in the future.

In conclusion, the use of intraoperative FS for BCS has been shown to decrease re-excision rates significantly by more than half in our unit's audit, and we believe the results of this study could be applicable to other centres with available logistical support.

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