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Evaluation of Resection Margin by Intraoperative Frozen Section Biopsy in Breast Conservative Surgery for Early Breast Carcinoma

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Abstract | **Original Research Article**

***Background*:** Breast cancer is currently the second leading cause of cancer deaths in women. Early detection and accurate classification of suspicious masses as benign or malignant is important for arriving at an appropriate treatment plan. ***Aims*:** To evaluate the resection margin by intra-operative frozen section in breast conserving surgery for early breast carcinoma. ***Methods*:** This cross sectional study was carried out in the department of general surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. A total of 20 patients with early stage breast carcinoma underwent surgery were included in this study. Admitted patients with diagnosis of invasive ductal carcinoma of the breast, patient who gave consent for research purpose, patients diagnosed with stage I & II breast cancer, small (up to 4 cm) unifocal tumor and clinically negative axillary nodes were enrolled in this study. Statistical analyses of the results were obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-22). ***Results*:** It was observed that more than one third (40.0%) patients belonged to age 41-50 years. The mean age was 45.55±10.94 years with ranged from 28 to 75 years. Half (50.0%) patient's educational level was primary. Majority (85.0%) patient's occupational statuses were housewife. Majority (90.0%) patients had lump size >2-≤5 cm. The mean lump size was 2.89±0.66 cm with ranged from 1.5 to 4 cm. Three fourth (75.0%) patients had lump in the right breast. Almost two third (60.0%) patients had lump in the upper outer quadrant of breast. Two (10.0%) patients had Grade I and 18(90.0%) had Grade II tumor. Three fourth (75.0%) patients had resected tumor of T2 >2-≤5 cm size. The mean size of resected toumour was 2.65±0.62 cm with ranged from 1.4 to 3.8 cm. The frequency of positive resection margin on frozen section was 3 (15%). Among them 1 (33.3%) patient had positive superior margin and 2 (66.7%) had positive lateral margin. These three (15.0%) patients had also positive margin on histopathology. In frozen section margin evaluation for BCS, true positive 3 cases, false positive 0 case, false negative 0 case and true negative 17 cases in identification by histopathological diagnosis. The validity of frozen section evaluation for early breast carcinoma was correlated by calculating sensitivity, specificity, accuracy, positive and negative predictive values. ***Conclusion*:** The frozen section is highly sensitive, specific and useful method in intraoperative margin assessment in breast conserving surgery. It can also be used as a planning strategy for the surgeons as to which direction requires a greater excision margin for safety by using the pathologist's report.

Keywords: Breast cancer, Intra-operative margin evaluation.

INTRODUCTION

Globally, breast cancer is the most common cancer and the second leading cause of death amongst women [1]. Breast cancer represents 29% of all newly diagnosed cancers in females [2]. Even though the incidence of breast cancer in developing countries is lower than in their Western counterparts, it is rising

rapidly. According to GLOBOCAN, more than half (52.9%) of 1.67 million new breast cancer cases were diagnosed in developing countries in 2012 [3], while the corresponding figure for 1980 was only 35% [4]. Most early-stage breast cancers can manage with breast conserving surgery (BCS) followed by radiation therapy [5]. In the last 30 years, local treatment combining wide breast conserving resection and radiotherapy (Breast-Conserving Therapy) has become the standard treatment for early stage breast cancer [6]. Breast conserving surgery (BCS), also referred to as lumpectomy or wide local excision, is currently the most widely used surgical procedure for resection of breast cancer [7]. The main goal of BCT is complete tumor excision with adequate safety margins and maintaining acceptable cosmetic appearance. The positive margin at initial lumpectomy was reported to range between 15% and 47% [3]. This therapy has enabled breast conservation and long term safety in cancer [8, 9]. The principal risk of the conservative option is local recurrence, ranging between 0.6% and 1.5% per year [10]. As described, local recurrence is the main risk of BCT, varying from 6 to 24% depending on the length of the series, with an annual rate of 1%, even when radiotherapy is administered [8-11]. With an extensive in situ component, invasion of the margins around the lumpectomy cavity is the main factor of local recurrence after conservative treatment [8-12]. There are at least three methods for intra operative margin assessment, including gross examination after slicing the specimen, frozen section analysis, and imprint cytology. Intraoperative Frozen Section Analysis is a relatively simple procedure with a high sensitivity and specificity [13]. Intra-operative frozen section can also be used as a planning strategy for the surgeon as to which direction requires a greater excision margin for safety by using the pathologist's report. Surgical resection margin status of a tumor is important for any malignant condition. When this occurs in conjunction with efforts to preserve or conserve the afflicted organ, these margins become extremely important. It is therefore important to have a clear understanding of what constitutes a positive margin or negative margin, the impact of disease factors in margin assessment [14]. Mammary tissue is notoriously technically difficult to cryosection because of its adiposity. Freezing also introduces tissue artifact in the form of architectural distortion and resistance of adipose tissue to sectioning. In addition, if the tissue submitted for evaluation is more than 1 cm in largest dimension, there is the added risk of sampling error. Surgeons, like the intraoperative frozen section method because it enables rapid microscopic examination of tissue during surgery and it can be used to determine the extent of surgery to be performed in a single operative setting [14]. Negative surgical margins minimize the risk of local recurrence after breast conserving surgery. Intra-operative frozen section analysis (FSA) is one of the preferable methods for margin evaluation. Olson *et al*., (2007) [15], concluded that intra-operative frozen section analysis allows resection of suspicious or positive margins at the time of wide local excision and results in low rates of local recurrence and re-excision. So, this study will focus on the resection margin by intra-operative frozen section biopsy in wide local excision for early breast carcinoma.

OBJECTIVES

General Objective

- To evaluate the resection margin by intra-operative frozen section in breast conserving surgery for early breast carcinoma.

Specific Objectives

- To see measurement of clear margin in first surgery.
- To see frequency of cavity shaving after initial surgery.
- To see margin status following cavity re-shaving.

METHODOLOGY

This was a Cross Sectional Observational study. The patients were selected purposively. A total of 20 patients were included in this study. The study was conducted in the department of general surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. At September 2018 to March 2021.

Inclusion Criteria

- Patients admitted in Department of surgery with diagnosis of invasive ductal carcinoma of the breast.
- Who were given consent for research purpose
- Patients diagnosed with stage I & II breast cancer.
- Small (up to 4 cm) unifocal tumor.
- Clinically negative axillary nodes.

Exclusion Criteria

- Diagnosed with stage III and IV cancer.
- Locally advanced carcinoma.
- Inflammatory breast carcinoma.
- Multifocal tumor.
- Lobular carcinoma

Study Procedure

This hospital based prospective study was conducted in the Department of General Surgery, BSMMU. Patients present with breast carcinoma were diagnosed by core biopsy were included in the study. About 20 patients were selected as sample according to inclusion and exclusion criteria by purposive sampling. Aims, objectives, procedure, risks and benefits of the study were explained to the patients. They were encouraged for voluntary participation. They were assured about secrecy of information and records. Written informed consent was taken from each patient. Different aspects of tumor were evaluated by triple assessment. Location and size of the tumor in breast and

axillary lymphnode status were evaluated by clinical examination and imaging techniques. Tumors were measured by measuring tape clinically. USG and mammogram both were done to define the extent of the lesion and to see multi focality and multi centricity. As patients have stage I-II disease, so metastatic workup was not done. Then operation was performed under general anesthesia in the supine position with the patient's arm abducted at ninety degrees. Initially about 5 ml Gention violet was injected into subdermal plexus around the nipple. After injection of dye breast was massaged continuously to enhance uptake. Then operation was started with natural crease line skin incision over the lump. The breast tumor was widely excised with 1 cm macroscopic margin. After resection the tumor was oriented by using suture as lateral margin with long suture, deep margin with double suture, superior margin with short suture. Then the size of resected tumor was measured by scale and the fresh specimen without preservatives was sent for frozen section biopsy to Pathology department for margin assessment. Fresh tissue was then placed in a cryostat, frozen and sectioned with a microtome into 4-5 mm sections that are fixed in alcohol and stained with hematoxylin eosin and microscopically examined by experienced pathologists. Frozen section was performed for five margins of tumor: superior, inferior, lateral, medial and deep. Margins with tumor within a 1 mm band were regarded as positive and more than 1 mm were negative. The cavity of the resected tumor was further reexcised about 1 cm on that direction margin was positive on frozen section by diathermy. The reexcised tissue was also oriented by suture and sent for histopathology. Axilla was opened through a separate incision for SLNB when tumor was sent for frozen section. When 2 SLN was positive no axillary dissection was done and when more than 2 SLN was positive axillary dissection was done upto level ii. Then skin was closed in layers as cosmetically as possible. After surgery the entire specimen is submitted for routine histopathological analysis. The results of frozen section were compared with the definitive routine histopathological report.

Data Analysis

Data was processed and analyzed by using computer based software SPSS-22 (Statistical package for Social Science) (IBM Corp, NY, USA). Different statistical method was applied for data analysis. For presentation of quantitative data, mean ± SD and for qualitative data frequency and percentage was used. The validity of frozen section was correlated by calculating sensitivity, specificity, accuracy, positive and negative predictive values.

Ethical Clearance

Ethical clearance of study was taken from the Ethical Review Committee of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Written consent was taken from the participant of the study.

RESULTS

Table I: Distribution of the study patients by socio-demographic characteristics. (N=20)

Socio-demographic characteristics	Frequency	Percentage
Age (in years)		
≤30 yrs.	2	10.0
31-40 yrs.	5	25.0
41-50 yrs.	8	40.0
51-60 yrs.	3	15.0
>60 yrs.	2	10.0
Mean±SD	45.55±10.94	
Range(min-max)	(28 - 75)	
Education		
Primary	10	50.0
Secondary	4	20.0
Others	6	30.0
Occupation		
Housewife	17	85.0
Service holder	3	15.0

Table I showed the distribution of the study patient by socio-demographic characteristics. It was observed that more than one third (40.0%) patients belonged to age 41-50 years. The mean age was 45.55±10.94 years with ranged from 28 to 75 years. Half (50.0%) patient's educational level was primary. Majority (85.0%) patient's occupational statuses were housewife.

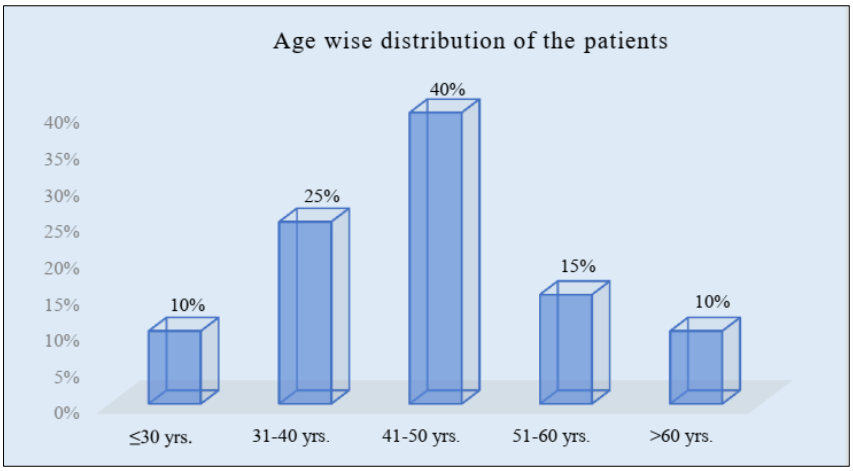

Figure 1: Column chart showed age wise patients distribution (N=20)

Table II: Distribution of the study patients by lump size (cm). (N=20)

Lump size (cm)	Frequency	Percentage
T1 ≤2	2	10.0
T2 >2-≤5	18	90.0
Mean ±SD	2.89±0.66	
Range(min-max)	(1.5 - 4)	

Table II showed the distribution of the study patient by lump size. It was observed that majority (90.0%) patients had lump size T2 >2-≤5 cm. The mean lump size was 2.89±0.66 cm with ranged from 1.5 to 4 cm.

Table III: Distribution of the study patients by site of tumor. (N=20)

Lump location	Frequency	Percentage
Right	15	75.0
Left	5	25.0
Site of Tumor		
Upper outer quadrant (UOQ)	12	60.0
Upper inner quadrant (UIQ)	6	30.0
Lower inner quadrant (LIQ)	2	10.0
Lower outer quadrant (LOQ)	0	0.0

Table III showed the distribution of the study patient by site of tumor. It was observed that three fourth (75.0%) patients had lump in the right breast. Almost two third (60.0%) patients had lump in the upper outer quadrant.

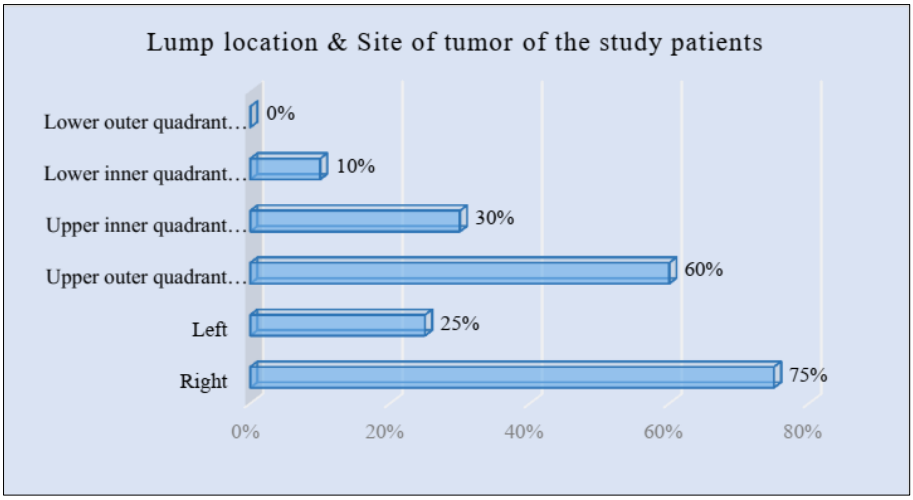

Figure 2: Bar chart showed lump location & site of tumor wise patients. (N=20)

Table IV: Distribution of the study patients by tumor grading (N=20)

Tumor grading	Number	Percentage
Grade I	2	10.0
Grade II	18	90.0
Grade III	0	0.0

Table IV showed the distribution of the study patient by tumor grading. It was observed that 2 (10.0%) patients had Grade I tumor and 18(90.0%) had Grade II tumor.

Table V: Distribution of the study patients by frozen section margin. (N=20)

Frozen section margin	Frequency	Percentage
Positive	3	15.0
Negative	17	85.0

Table V showed the distribution of the study patient by frozen section margin. It was observed that 3 (15.0%) patients had resection margin positive on frozen section.

Table VI: Frequency of margin reexcision after initial surgery. (N=20)

Margin reexcision	Frequency	Percentage
Required	3	15.0
Not required	17	85.0

Table VI showed frequency of margin reexcision after initial surgery. It was observed that 3(15.0%) patients had required margin reexcision after initial surgery and 17(85.0%) had not require.

Table VII: Distribution of the positive resection margin status of lumpectomy specimen. (n=3)

Resection margin status	Frequency	Percentage
Superior	1	33.3
Inferior	0	0.0
Medial	0	0.0
Lateral	2	66.7
Deep	0	0.0

Table VII showed the positive resection margin status of the study patient. Resection margin was positive in 3 cases. 2 cases (66.7%) positive in lateral margin and 1 (33.3%) case positive in superior margin. All cases underwent reexcision and they were negative on histopathology.

Table VIII: Distribution of the study patients by margin by histopathology (N=20)

Histopathology	Frequency	Percentage
Positive	3	15.0
Negative	17	85.0

Table VIII showed the distribution of the study patient by margin by histopathology. It was observed that 3 (15.0%) patients had resection margin positive on histopathology.

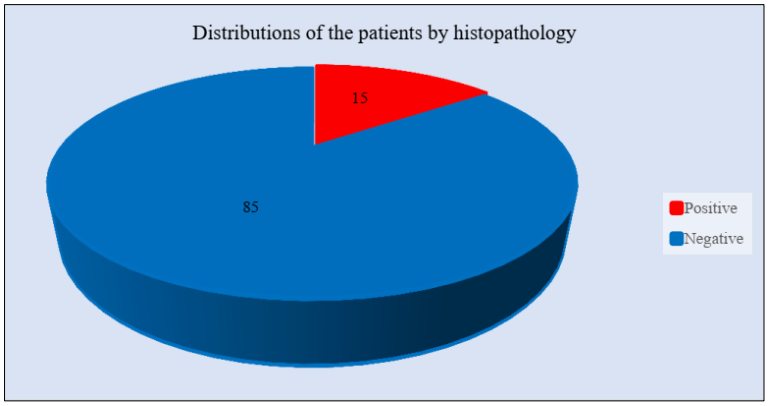

Figure 3: Pie chart showed histopathology of the patients (N=20)

Table IX: Distribution of the study patients by size of resected tumor (cm). (N=20)

Size of resected tumor (cm)	Frequency	Percentage
T1 ≤2	5	25.0
T2 >2-≤5	15	75.0
Mean±SD	2.65±0.62	
Range(min-max)	(1.4 - 3.8)	

Table IX showed the distribution of the study patient by size of resected tumor (cm). It was observed that three fourth (75.0%) patients had resected tumor of T2 >2-≤5 cm size. The mean size of resected tumor was 2.65±0.62 cm with ranged from 1.4 to 3.8 cm.

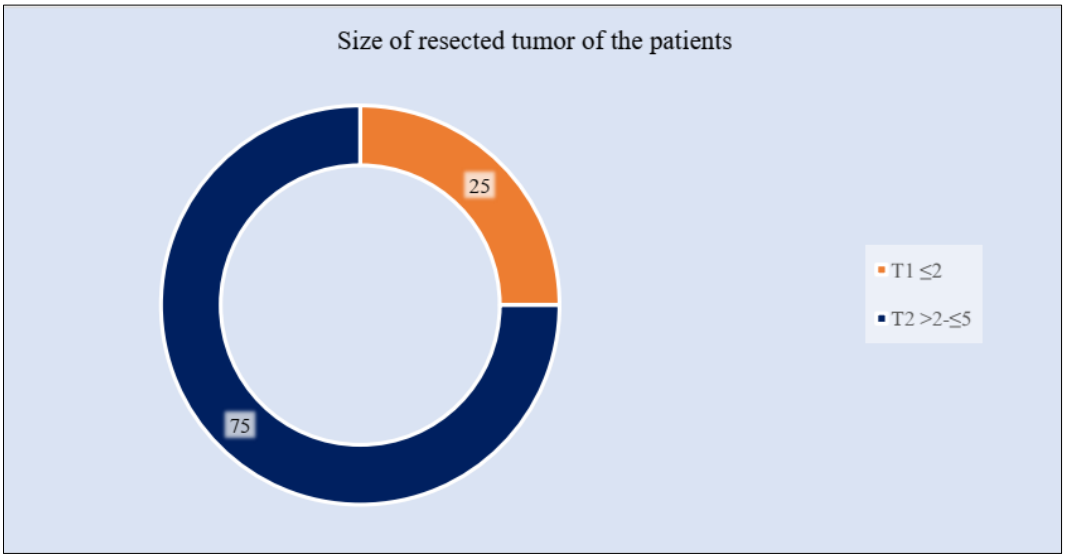

Figure 4: Ring chart showed size of resected tumor (cm) wise patients (N=20)

Table X: Comparison between histopathological diagnosis and intraoperative frozen section margin evaluation in BCS (N=20)

Frozen section margin	Histopathological diagnosis	
	Positive	Negative
Positive (n=3)	3 (True positive)	0 (False positive)
Negative (n=17)	0 (False negative)	17 (True negative)

Table X showed in intraoperative frozen section margin evaluation for BCS, true positive 3 cases, false positive 0 case, false negative 0 case and true negative 17 cases in identification by histopathological diagnosis.

Table XI: Sensitivity, specificity, accuracy, positive and negative predictive values of the intraoperative frozen section margin evaluation in BCS (N=20)

Validity test	Percentage
Sensitivity	100.0
Specificity	100.0
Accuracy	100.0
Positive predictive value	100.0
Negative predictive value	100.0

Table XI showed the validity of intraoperative frozen section evaluation in BCS was correlated by calculating sensitivity, specificity, accuracy, positive and negative predictive values.

DISCUSSION

Globally, breast cancer is the most common cancer and the second leading cause of death amongst women [16]. Most early-stage breast cancers can be managed with breast conserving surgery (BCS) followed by radiation therapy [5]. Breast conserving surgery (BCS), also referred to as lumpectomy or wide local excision, is currently the most widely used surgical procedure for resection of breast cancer [7]. There are at least three methods for intraoperative margin assessment, including gross examination after slicing the specimen, frozen section analysis, and imprint cytology. Intraoperative frozen section analysis is a relatively

simple procedure with a high sensitivity and specificity [13]. Intra-operative frozen section can also be used as a planning strategy for the surgeon as to which direction requires a greater excision margin for safety by using the pathologist's report. In this present study it was observed that 40.0% patients belonged to age 41-50 years. The mean age was 45.55±10.94 years varied from 28 to 75 years. Kumar and Prasad (2019) [17], found most (80.0%) of the patients were in the age group of 15-35 years and the youngest patient was of 15 years and oldest was of 62 years. Fayed *et al*., (2018) [18], study was done on 40 patients with breast cancer in which the patients´ age range from 26 to 65 years. In another study Atabey *et al*., (2014) [19], done on 96 patients, where mean age of their patients was 50 years with ranged varied from 19 to 87 years, which is higher than the present study. Similarly, higher mean age and age ranged also observed by Chang *et al*., (2013) and Alam *et al*., (2008) [16-20]. In this current study it was observed that half 50.0% patient's education level was primary. In this present study it was also observed that majority 85.0% patient's occupational statuses were housewife. In this current study it was observed that 75.0% patients had lump location on right side. Almost two third 60.0% patients had lump in the upper outer quadrant of breast followed by 30.0% in upper and inner quadrant and 10.0% in lower and inner quadrant. Fayed *et al*., (2018) [18], study observed that 72.5% patients had lump in upper outer quadrant followed by 10.0% upper inner, 10.0% lower outer, 2.5% lower inner and 5.0% central. Rusell *et al*., (2000) [21], documented that 72.0% of malignant tumors in the breast were located into the upper quadrant (upper outer 60% and upper inner 12%), which is consistent with the present study. In this present study it was observed that 10.0% patients had Grade I tumor, 90.0% had Grade II and grade III was not found in this study. Rubio *et al*., (2014) [22], study found that 31.6% patients had Grade I, 63.2% Grade II and 5.3% had grade III tumor in their study. In another study Dener *et al*., (2009) [23], showed 12.4% patients had Grade I, 68.7% Grade II and 18.7% had grade III tumor, which is comparable with the present study. In this current study it was observed that 15.0% patients had resection margin positive on frozen section and 85.0% had negative. Fayed *et al*., (2018) [18] study found 26.6% and 73.4% were positive and negative respectively in frozen section, which is comparable with the present study. Among the positive resection margin 2 cases (66.7%) positive in lateral margin and 1 (33.3%) case positive in superior margin. All cases underwent reexcision and they were negative on histopathology. In this present study it was observed that 3(15.0%) patients required cavity shaving after initial surgery and 17(85.0%) did not require cavity shaving. Final cavity margin status was obtained from the final histopathology report and all are free of tumor. In this present study it was observed that 15.0% patients had resection margin positive on histopathology and 85% had negative. Fayed *et al*., (2018) [18], study found 22.8% were positive and 77.2% were negative on histopathology, which is comparable with the current study. In this current study it was observed that 75.0% patients had size of resected tumor T2 >2-≤5 cm and 25.0% had ≤2 cm. The mean size of resected tumor was 2.65±0.62 cm with ranged from 1.4 to 3.8 cm. Morrow *et al*., 2012; Houssami *et al*., 2014; Nowikiewicz *et al*., 2018; van Deurzen, (2016) [24-27], study enrolled breast carcinoma, size of primary lesions over 2 cm. In this present study it was observed that frozen section evaluation in BCS, true positive 3 cases, false positive 0 case, false negative 0 case and true negative 17 cases in identification by histopathological diagnosis. Nowikiewicz *et al*., (2019) [28], study observed that the number of true-positive results 4 cases, true-negative results 429 cases, false-positive not found and false-negative results was 72 cases. Fayed *et al*., (2018) [18], study compared results of frozen section for the 259 margins with the results of paraffin section for the same number of margins. There were 57 true positive margins (22.01%) that were positive on both frozen section and paraffin section. There were 188 true negative margins (72.59%) that were negative on both frozen section and paraffin section. There were two false negative margins (77.0%) that were negative on frozen section and positive on paraffin section. There were 12 false positive margins (4.63%) that were positive on frozen section and negative on paraffin section. The literature reported that frozen section might give a false positive margin ranging between 0% and 0.4%, and a rate of false negative results between from 0.5% and 3.4% [29]. In this current study it was observed that the sensitivity was 100.0%, specificity 100.0%, accuracy 100.0%, positive predictive values 100.0% and negative predictive values 100.0% for frozen section for identification of intraoperative resection margin for early breast carcinoma. Nowikiewicz *et al*., (2019) [28], study observed that the specimen frozen section pathologic analysis was characterized by specificity of 100%, a positive predictive value (PPV) of 100%, and negative predictive value (NPV) of 85.6%. In terms of diagnostic accuracy, frozen section was found on meta-analysis to have a pooled sensitivity of 0.86 (95% CI 0.78-0.91) and a specificity of 0.96 (95% CI 0.92-0.98), but with significant heterogeneity observed by Dumitru *et al*., (2018) [30]. In another study Fayed *et al*., (2018) [18], found the sensitivity of frozen section was 96.91% and its specificity was 94%. The positive predictive value was 82.61%, and the negative predictive value was 98.95%. The overall accuracy rate for this method was 94.59%. Frozen section examination was proved to be a reliable and accurate method [32], It has a sensitivity of 91.7% to 97.9%, and a specificity of 89.5% to 100% [15-33].

CONCLUSION

Several emergent technologies exist which can potentially improve intraoperative margin assessment and reduce rates of reexcision, but further technological developments are required to augment image processing and facilitate routine clinical usage. Moreover, these will need to compare favorably with direct tissue-based

methods, such as frozen section and cytology, which are notably more sensitive and specific than most other methods of margin assessment. This study was undertaken to evaluate the resection margin by intra-operative frozen section in breast conserving surgery for early breast carcinoma. It can be concluded that frozen section is highly sensitive, specific and useful method in breast conserving surgery.

Limitations of the Study

- The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not be reflect the exact picture of the country.
- The present study was conducted at a very short period of time.
- During the study period the estimated sample couldn't be collected, therefore small sample size was also a limitation of the present study. Therefore, in future further study may be under taken with large sample size.

RECOMMENDATIONS

Frozen section analysis is highly specific and sensitive for intraoperative margin assessment in breast conserving surgery for early breast carcinoma. Further studies can be undertaken by including large number of patients.

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