

# The Effectiveness of Intraoperative Frozen Section Analysis of Safety Margins in Breast Conserving Surgery and the Role of Surgeon in Decreasing the Rate of Positive Margins

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## Abstract

**Introduction:** Nowadays the more accepted surgical option for treating early breast cancer is breast conserving surgery. The main challenge in this type of surgery is to get free safety margins without need of second surgical operation, so many breast surgeons have started to depend on intraoperative frozen sections to ensure free safety margins. **Aim of work:** To assess our policy that we prefer to depend on intraoperative frozen section analysis to get free safety margin in breast conserving surgery from the 1<sup>st</sup> surgery, and its oncologic outcome. **Patients and Methods:** This is a retrospective study conducted in Oncology Center—Mansoura University (OCMU), where the data of 219 patients with breast cancer, who were managed by breast conserving surgery with intraoperative frozen section analysis of the safety margins, was analyzed. **Results:** The intraoperative frozen section analysis of safety margin was negative from the start in 183 (83.6%) patients, while it was positive in 36 patients (16.4%). Intraoperative decision of margin re-excision was applied for 29 patients (13.2%) in order to reach negative margin, modified radical mastectomy was offered for 4 patients (1.8%), while nipple sparing mastectomy with immediate breast reconstruction using latissimus dorsi flap was offered for 3 patients (1.4%). The postoperative paraffin results were typical with intraoperative frozen section analysis results in 216 patients (98.6%) and different results were obtained in only 3 patients (1.4%) who were managed by modified radi-

cal mastectomy in a second operation. Only 4 patients had local recurrence (1.8%) during the period of follow-up duration which was ranged from 1 to 86 months with mean  $\pm$  SD (22.3  $\pm$  14.1). **Conclusion:** The intraoperative frozen section analysis of safety margins in breast conserving surgery has very high-rate typical results with the paraffin section analysis and it is very helpful in decreasing the rate of second surgical operation in cases of infiltrated margins. It should be used routinely in all cases of breast conserving surgery.

## Keywords

Breast Conserving Surgery, Intraoperative Frozen Section Analysis, Safety Margins, Breast

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## 1. Introduction

The result of progress in radiological diagnosis of breast cancer leading to early detection of breast cancer, more breast cancers is detected at a smaller sized breast. This makes breast conserving surgery an accessible and preferable choice for many patients; this is due to the improved cosmetic and Psychic effect over the patient to preserve her breast. The breast recurrence after BCS is related to age of women, grade and size of the neoplasm, and presence of multifocality or multicentricity [1] [2] [3] [4], whilst safety margin is the tremendous foreseeable of breast cancer local recurrence [5] [6] [7] [8].

As a routine, the paraffin histopathological result following the breast conserving surgery will be received after few days, so if patient is in need for another operation to re-excise the residual tumor proved by positive safety margin, it will be cared out after many days later on the 1<sup>st</sup> one. The mentioned rates of re-excision in the literature ranged from 7% to 73%, with most of them reporting range between 15% - 50% [9] [10] [11] [12].

Unfortunately, in unlucky cases the 2<sup>nd</sup> margin examined by paraffin is non-conclusive obligating the patient and surgeon to go for the 3<sup>rd</sup> time to the operating room. Imagine, the patient decision in these situations while we discuss her for the 3<sup>rd</sup> or even second operation she ask for mastectomy to avoid going again to operation if still positive margin after ongoing operation this is in spite of the early stage of her disease. Another problem for depending on paraffin, that delay in the other oncological, non-surgical lines for the patient, psychological burden over the patient and surly affecting the cosmosis of the breast [13].

Our policy is to depend on the result of intraoperative frozen section analysis of the marginal status of the excised tumor, and if positive margins are found re-excision at same scene is done. Although, this may increase the cost and duration of the surgical operation but mostly it avoids the patient to be subjected to another operation. [13]

At Oncology Center—Mansoura University [OCMU], we have a policy to use frozen section to ensure the marginal status of the tumor resected to decrease the

necessity for a second operation in case of residual tumor proved by positive marginal status. In this study, we want to estimate the validation of our policy to depend on the frozen section to ensure negative safety margin and assess the role of surgeon in decreasing the rate of positive margins.

## 2. Patient and Methods

This is a retrospective study conducted between 1 January 2010 till 29 February 2017, in Oncology Center—Mansoura University (OCMU), where the data of all patients with breast cancer who were exposed to BCS (Breast Conserving Surgery) with intraoperative frozen section analysis of the safety margins (219 patients) were reviewed. Patients with phylloides tumors and patients with indeterminate results or missing data were excluded from this study. The design of this study was approved by the Institutional Research Board (IRB) of the Faculty of Medicine in Mansoura University and written informed consent was obtained from all patients before enrolment.

The tumor safety margins were marked by stitches and send for frozen section analysis with an extra safety margin for more confirmation in cases when the resection margin was near to the tumor (**Figure 1**). If there were any positive safety margins for residual tumor so another intraoperative re-safety margin was excised.

We abstracted and recorded the following data; clinical characteristics (like age, side, site, size), radiologic findings (like microcalcifications), pathological characteristics (like preoperative biopsy, intraoperative frozen section status, paraffin section status, pathologic types, grade, staging, receptor status, surgical procedures (conventional breast conserving surgery or oncoplastic volume displacement techniques or reconstructive procedures with autologous flaps),



**Figure 1.** Resection of retroareolar breast tumor with safety margins marked by one stitch for the upper margin and two stitches for the medial margin with an extra-medial safety margin for more confirmation because the resection margin was near to the tumor.

number of surgical operations for each patient in order to calculate the percentage of second operation and how intraoperative frozen section analysis avoid this and follow-up visits for any local recurrent or distant metastasis and survival.

### 3. Results

This study evaluated 219 patients with breast cancer with mean  $\pm$  SD age  $48 \pm 10$  ranging from 23 - 76 years. The tumor affected right breast in 109 patients (49.8%) and the left breast in 110 patients (50.2%). Regarding the site; the upper outer quadrant was the affected area in 129 patients (58.9%), upper inner quadrant in 38 patients (17.4%), lower inner quadrant in 17 patients (7.8%), lower outer quadrant in 22 patients (10.0%) and retro areolar area in 13 patients (5.9%). Tumor size was ranged from 10 to 70 mm with mean  $\pm$  SD ( $25 \pm 9$  mm).

Sixteen patients (7.3%) have no preoperative biopsy, 34 (15.5%) patients underwent fine needle aspiration cytology (FNAC) as preoperative biopsy, 154 patients (70.3%) subjected to core needle biopsy (CNB), 2 patients (0.9%) had an incisional preoperative biopsy and 13 patients (5.9%) had an excisional one. The preoperative pathological findings were found as follow; malignant with invasive type in 175 patients (79.9%), highly suspicious for malignancy in 16 patients (7.43%), atypical proliferative lesion in 4 patients (1.8%), ductal carcinoma in situ (DCIS) in one patient (0.5%), Paget's disease in one patient (0.5%), fibroadenosis with sclerosis in one patient (0.5%), fibroadenosis in one patient (0.5%), benign breast lesions in 4 patients (1.8%) but highly suspicious in radiologic assessment and lastly there were 16 patients with no preoperative biopsy but highly suspicious in radiologic assessment. The demographic data of the patients were shown in **Table 1**.

The intraoperative frozen section analysis of safety margin was negative from the start in 183 (83.6%) patients, while it was positive in 36 patients (16.4%) (**Figure 2** & **Figure 3**). Intraoperative decision of margin re-excision was applied for 29 patients (13.2%) in order to reach negative margin, modified radical mastectomy was offered for 4 patients (1.8%), while nipple sparing mastectomy with immediate breast reconstruction using latissimus dorsi flap was offered for 3 patients (1.4%).

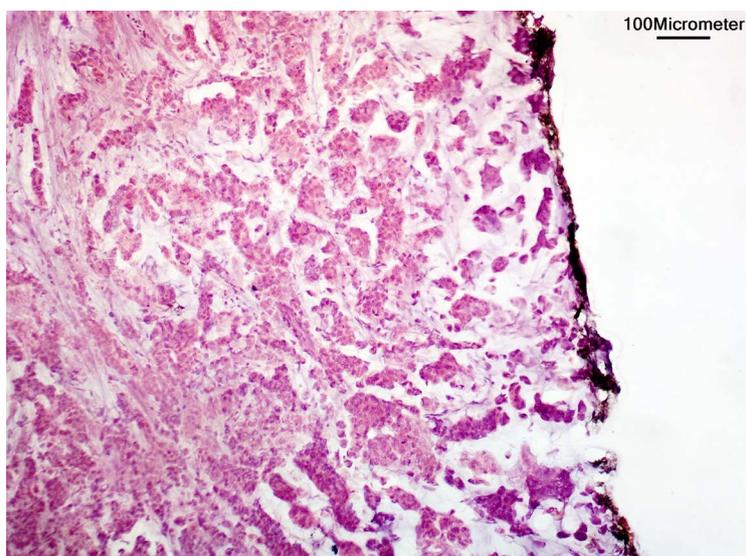
The postoperative paraffin results were typical with intraoperative frozen section analysis results in 216 patients (98.6%) and different results were obtained in only 3 patients (1.4%) as follow: two patient (0.9%) with infiltrated all margins by DCIS, and one patient (0.5%) with infiltrated depth. Those 3 patients were managed by modified radical mastectomy in a second operation.

Final pathological types after paraffin section analysis were invasive ductal carcinoma (IDC) in 199 (90.9%), invasive lobular carcinoma (ILC) in 10 patients (4.6%), mixed invasive type in one patient (0.5%), mucinous adenocarcinoma in 2 patients (0.9%), medullary carcinoma in 3 (1.4%), colloid carcinoma in 2 patients (0.9%) and ductal carcinoma in situ (DCIS) in 2 patients (0.9%)

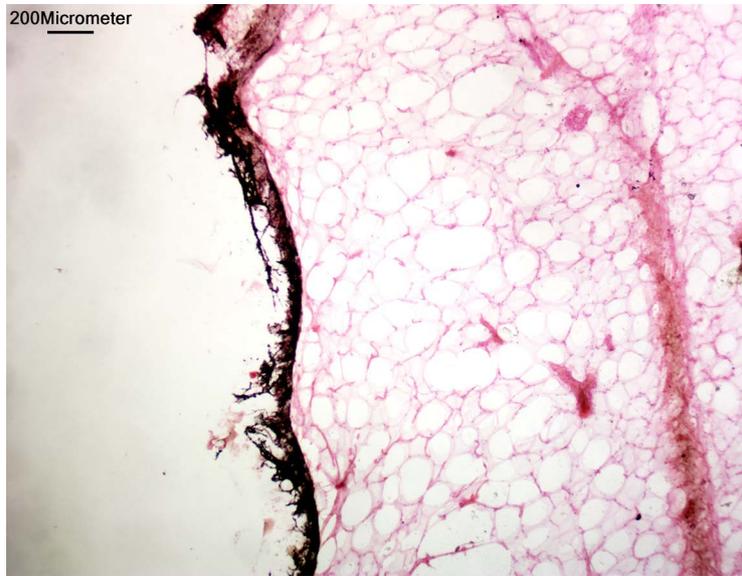
**Table 1.** Patient demographics.

Item	Number	%	
<b>Age</b>	Mean $\pm$ SD	48 $\pm$ 10 years	
	Range	23 - 76 years	
<b>Breast side</b>	Right	109	49.8%
	Left	110	50.2%
<b>Tumor site</b>	Upper outer quadrant	129	58.9%
	Upper inner quadrant	38	17.4%
	Lower inner quadrant	17	7.8%
	Lower outer quadrant	22	10%
<b>Tumor size</b>	Mean $\pm$ SD	25 ( $\pm$ 9) mm	
	Range	10 - 70 mm	
<b>Preoperative biopsy technique</b>	None	16	7.3%
	FNAC*	34	15.5%
	CNB**	154	70.3%
	Incisional	2	0.9%
	Excisional	13	5.9%
	None	16	7.3%
<b>Preoperative pathologic diagnosis</b>	Atypical proliferative lesion	4	1.8%
	Highly suspicious	16	7.3%
	Malignant or invasive	175	79.9%
	Benign breast lesions	4	1.8%
	Fibroadenosis	1	0.5%
	Fibroadenosis with sclerosis	1	0.5%
	DCIS***	1	0.5%
Paget disease of nipple	1	0.5%	

\*Fine Needle Aspiration Cytology; \*\*Core Needle Biopsy; \*\*\*Ductal Carcinoma *In-Situ*.



**Figure 2.** Positive surgical margin in intraoperative frozen section, black line indicate inked margin touched by tumor cells (Hematoxylin & eosin staining, 200x).



**Figure 3.** Negative surgical margin in intraoperative frozen section, black line indicate inked margin (Hematoxylin & eosin staining, 100x).

and pathological grade was grade 2 in 139 patients (63.5%), grade 1 in 7 patients (3.2%) and grade 3 in 59 patients (26.9%) and no available grade in 14 patients (6.4%). The results of intraoperative frozen section analysis and pathological outcome were shown in **Table 2**.

Breast conserving surgery was done in 212 patients (96.8%) with various techniques according to the breast volume and tumor size and its site. These surgical techniques are summarized in **Table 3**. Four patients (1.8%) had modified radical mastectomy and 3 patients (1.4%) had nipple sparing mastectomy with immediate breast reconstruction using latissimus dorsi flap.

The intraoperative frozen section analysis avoids second surgical operation in 216 patients (98.6%) while second surgical operation in the form of MRM was done for 3 patients (1.4%) who had different paraffin section analysis results of safety margins.

Only 4 patients had local recurrence (1.8%) during the period of follow-up duration which was ranged from 1 to 86 months with mean  $\pm$  SD ( $22.3 \pm 14.1$ ). Distant metastasis was developed in 11 patients during this period of follow-up as the following; 4 patients (1.8%) had bone distant metastasis, one patient (0.5%) had liver metastasis, one patient (0.5%) had pleural effusion, one patient (0.5%) had bone and liver metastasis, local recurrence & contralateral nodal metastasis was developed in 2 patients (1.8%), local and regional recurrence was noticed in one patient (0.5%) and krukensberg tumor was developed in one patient (0.5%).

#### 4. Discussion

Oncology Center—Mansoura University (OCMU) is a referral oncology center, we receive referral cases of breast cancer from Egyptian delta governments, as to

the last data received from The International Agency for Research on Cancer (GLOBOCAN 2012), the breast carcinoma is considered the most common one affecting female all over the world with some increased incidence with the developing countries [14].

**Table 2.** The results of intraoperative frozen section analysis and pathologic outcome.

	Item	Number	%
<b>Intraoperative frozen section analysis of safety margins</b>	Positive (infiltrated)	36	16.4%
	Negative	183	83.6%
<b>Intraoperative infiltrated margins (36 patients)</b>	Medial & depth	4	1.8%
	Depth & lower	1	0.5%
	Lateral & lower	3	1.4%
	Lower	2	0.9%
	Upper	11	5.0%
	Depth	2	0.9%
	Medial	11	5.0%
	All	2	0.9%
<b>Intraoperative surgical decision making</b>	No further excision	183	83.6%
	Re-excision with negative further margins	29	13.2%
	MRM*	4	1.8%
	NSM & IBR-LDF**	3	1.4%
<b>Paraffin pathologic results</b>	Typical with intraoperative frozen section analysis	216	98.6%
	Different	3	1.4%
<b>Types of paraffin section analysis difference</b>	Typical	216	98.6%
	Infiltrated all margins by DCIS	2	0.9%
	Infiltrated depth	1	0.5%
<b>Final pathological types after paraffin section analysis</b>	DCIS	2	0.9%
	IDC	199	90.9%
	ILC	10	4.6%
	Mixed IDC & ILC	1	0.5%
	Mucinous adenocarcinoma	2	0.9%
	Medullary carcinoma	3	1.4%
	Colloid carcinoma	2	0.9%
	Not available	14	6.4%
<b>Pathologic grade</b>	Grade 1	7	3.2%
	Grade 2	139	63.5%
	Grade 3	59	26.9%

\*Modified Radical Mastectomy; \*\*Nipple Sparing Mastectomy with Immediate Breast Reconstruction using Latissimus Dorsi Flap.

**Table 3.** Surgical and oncologic outcome.

		<b>Item</b>	<b>Number</b>	<b>%</b>
<b>Type of surgical techniques used in the first surgical operation[</b>	BCS (212 patients)	Conventional wide local excision	101	46.1%
		Round block periareolar incision	11	5.0%
		Medial racquet mammoplasty	5	2.3%
		Lateral racquet mammoplasty	21	9.6%
		Grisotti technique	5	2.3%
		Batwing technique	3	1.4%
		Parallelogram technique	4	1.8%
		Comma shaped mammoplasty	3	1.4%
		Central quadrantectomy	1	0.5%
		Upper inner quadrantectomy	1	0.5%
		Upper outer quadrantectomy	3	1.4%
		S-shaped mammoplasty	1	0.5%
		Le Jour Mammoplasty	1	0.5%
		J-mammoplasty	2	0.9%
		Inferior pedicle mammoplasty	17	7.8%
		Medial pedicle mammoplasty	14	6.4%
		Superior pedicle mammoplasty	2	0.9%
		Supero-medial pedicle mammoplasty	4	1.8%
		superior and inferior bi-pediced mammoplasty	1	0.5%
		Inverted T-reduction mammoplasty	7	3.2%
		Volume replacement using latissimus dorsi mini-flap	3	1.4%
		Matrix rotational flap	1	0.5%
		medial and inferior bi-pedicle mammoplasty	1	0.5%
<b>Type of second operation for positive margins</b>	MRM NSM & IBR-LDF		4	1.8%
			3	1.4%
		No	216	98.6%
<b>Recurrence</b>	No	MRM	3	1.4%
		Local	204	93.2%
<b>Follow-up duration (months)</b>	Distant (11 patients)	Liver metastasis	4	1.8%
		Bone metastasis	1	0.5%
		pleural effusion	4	1.8%
		bone & liver metastasis	1	0.5%
		local recurrence & contralateral nodal metastasis	1	0.5%
		Loco-regional recurrence	2	0.9
		Krukenberg's tumor	1	0.5%
			1	0.5%
Mean ± SD		22.3 ± 14.1		
Range		1 - 86		

Conserving the osmosis of the patient breast is now the corner stone for treating breast cancer. That is why breast conserving surgery became more popular either among surgeons and patients. Breast conserving surgery resects the tumor with safety margin but what is the warranty that is no residual tumor? Some surgeons may depend on the preoperative radiological diagnosis and gross resection intraoperative with waiting the result of the paraffin histopathological about safety margins. Some prefer wide margin, however it may be difficult to gain due to size of the breast and tumor site [13]. The other strategy is to depend on the intraoperative frozen section analysis.

The disadvantage of depending on paraffin section analysis are that we may need another operation with more risk of anesthesia, delay to start adjuvant therapy lines for the patients, psychological trauma to the patient that she need another operation and surly more cost and the patient's work disturbance [15].

In our work we depend mainly on the preoperative radiological and clinical assessment for intraoperative resection guide and frozen section to be sure of clear safety margin with discussion of other surgical option with patient preoperatively if we need it. Our result revealed that intraoperative frozen section analysis confirmed negative margin for residual malignancy in 183 patients (83.6%) positive for residual malignancy need more remargin in 36 patients (16.4%). For other patients with positive margins; intraoperative decision for re-excision was applied for 29 patients (13.2%) for attempt to gain another negative safety margin guided by intraoperative frozen section analysis which was successful in this issue, modified radical mastectomy was offered for 4 patients (1.8%) due to either patient desire or extensive DCIS or due to the breast being small in volume not allowing more resection of margins, while nipple sparing mastectomy with immediate breast reconstruction using latissimus dorsi flap was offered for 3 patients (1.4%). Our rate of positive margin was low (16.4%) in comparison to other authors in literature e.g. 57% [13], 30.3% [16] and 25% [15].

This low rate for re-excision in our work could be explained as we are usually resecting from the start margins being grossly free as possible as we can surly with the balance of cosmetic outcome. The postoperative paraffin results corresponded with intraoperative frozen in 216 patients (98.6%) and different results had occurred only in 3 patients (1.4%), this is little less than mentioned by Osako *et al.* (4%) [16].

The benefit of our strategy in surgical planning that is patient subjected only to one surgery, one anesthesia risk and one hospital admission as possible, moreover psychological suffering of one operation is less than two operations. Limitations are the need for special surgical training, expertise pathologist, equipment for frozen and apparently more cost but in total we think it is less cost.

## 5. Conclusion

The intraoperative frozen section analysis of safety margins in breast conserving

surgery has very high-rate typical results with the paraffin section analysis and we can depend on it in decreasing the rate of second surgical operation in cases of infiltrated margins. It should be used routinely in all cases of breast conserving surgery.

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### Competing Interests

Authors disclose no potential conflicts of interest.

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