

# Intraoperative pathological monitorization of surgical margins: a method to reduce recurrences after conservative treatment for breast cancer

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## Summary

**Introduction:** Local recurrences after conservative surgical treatment for breast cancer are not uncommon and cause negative influences on the oncological prognosis and quality of life of the patients. Aiming to avoid this problem, we have developed a method of intraoperative pathological monitoring of surgical margins (IPMSM), in order to assure adequacy of resection.

**Materials and Methods:** IPMSM is based on radiological, macroscopic, cytological and histological examination of frozen sections of the breast specimens in the operating room during the surgery. We evaluated 98 women with 100 tumors clinical stage I-II breast cancer for whom we planned conservative surgery. The margins were oriented by the surgeon and inked by the pathologist in different colors to retain orientation.

**Results and Discussion:** According to the histological or cytological results, immediate re-excision was indicated and performed in 40 (40.8%) cases. In six of these, we had to perform a mastectomy. The indications for additional resections were: insufficient margins in 23 cases, extensive intraductal component in eight, multifocality in four, atypical proliferative lesion at the margin in four and diffuse tumor in one. Permanent histological sections confirmed all intraoperative results. These patients were followed by a median period of 42 months (range 3 to 99 months) and we observed 1% of local recurrence and 5.1% of distant metastasis. We compared this group of patients with a control group represented by 149 cases of breast cancer stages I-II treated by conservative surgery, but not submitted to IPMSM. In the control group, we observed 17 (11.4%) local recurrences and 49 (32.9%) distant metastases after a follow-up period from 14 to 213 months (median of 126 months).

**Conclusion:** The IPMSM proved to be a safe and accurate method to prevent additional surgery for insufficient margins and to reduce the recurrence rate.

**Key words:** Breast cancer; Conservative surgery; Frozen section examination.

## Introduction

In the last decades we have observed a tendency towards conservative methods of surgical management of many neoplasms, including breast cancer. Breast-conserving surgery became the standard therapy for most early invasive breast cancers. The aim of surgical treatment is to remove the amount of breast tissue necessary and sufficient for the best cosmetic results while ensuring the lowest rates of recurrence as possible.

Local recurrence after conservative surgery can be related to persistence of cancer cells (true recurrence) or biological aggressiveness of the neoplasia. It is important to observe that only true local recurrences can potentially be prevented by the quality of local surgery, although it is possible that the reduction of local recurrences can alter the prognosis, even of the more aggressive tumors.

The impact of local recurrence in overall survival was not evident in the first reports of results of breast-conserving surgery [1-3]. Actually, after longer periods of follow-up, there is evidence that women with local recurrences have an increased risk of distant metastasis and prognosis [4-7]. Fortin *et al.* [7] evaluated the role of local failure in the survival of 2,030 patients treated with lumpectomy and postoperative radiotherapy. Local failure was a powerful predictor of mortality. The relative risk associated with local failure was 3.6 for mortality and 5.1 for distant metastasis, which is statistically significant.

Today, the importance of obtaining negative margins is well recognized [8-10]. There is no consensus about the exact amount of tissue to be removed, or the optimal method for assessing margins, as well as the

definition of clear margin. Certainly, the ideal extension of breast resection in conserving-surgery cannot be the same for all cases, but rather depends on the characteristics of the tumor, such as histological type, extensive intraductal component (EIC) and vascular involvement, as well on the characteristics of the surrounding tissue, determined by age of patient, breast density and histological characteristics.

Although some workers have tried to find preoperative indicators of the ideal extension of the surgery in order to guarantee clear margins [10], we do not as yet have any.

Given the importance of microscopic margin evaluation, we propose a method to reduce the risk of local recurrence: intraoperative pathological monitorization of surgical margins (IPMSM), based on radiological, macroscopic, cytological and histological examination of the breast specimens in the operating room.

## Patients and methods

From 1990 to 1998 we studied 98 consecutive women with 100 clinical stage I and II infiltrating carcinomas of the breast; two of them with bilateral tumors: one simultaneously and other after 18 months of follow-up. The age of the patients ranged from 26 to 93 years old (mean 53.7,  $\sigma=12.5$ ). The patients were followed for a period of 3 to 99 months (mean 42,  $\sigma=22$ ).

The histological diagnosis was made preoperatively by core biopsy or by surgical biopsy of the lesion at the same time of the treatment. Histologic type was classified according the World Health Organization [11] (Table 1). All patients were submitted to conservative surgery under general anesthesia. The classical quadrantectomy described by Veronesi [12] was applied in the initial cases. Afterwards, we developed more conservative surgeries with preservation of skin and peri-areolar incisions [13].

After excision of the breast segment, the surgeon oriented the breast tissue excised by sutures, often in conjunct with the pathologist. In selected cases, such as those with microcalcifications for example, we performed a radiography of the specimen (Figure 1). The external surface of the specimen was grossly examined and dense areas were submitted to scrapes for cytological examination. The surgical margins were inked in different colors to retain orientation and to permit identification on histopathological examination (Figure 2). Peripheral areas without adipose tissue were peeled. Peeled tissue corresponding to suspicious areas, either from gross inspection or from cytological examination, was submitted to frozen section examination. Following inking and peeling, the specimen was sectioned perpendicular to the inked surface every 4 or 5 mm. The cut surfaces were grossly examined and the tissues around the tumor and close to margins were submitted to scrapes for cytological examination to identify microscopic neoplastic extension (Figure 3). An additional cytological preparation was done in the tumor to be used as a positive control for comparison with the slides of the periphery and the margins. Grossly or cytological suspicious areas were selected for frozen section examination. Histological section of the tumor was performed in all the cases without preoperative histological diagnosis to determine the histologic type, nuclear grade and the existence of EIC. The slides were stained with the hematoxylin-eosin method. Routinely, we made histological sections of the closest margin and the areolar border of all the cases, independent of the gross or cytological aspects.

Margins were considered involved when tumor was identified at an inked surface of the specimen (Figure 4). The deep margin of pectoral fascia was considered negative, unless tumor was identified directly at the inked surface. For tumors with circumscribed borders and without signs of intraductal extension beyond the

Table 1. — *Histologic type.*

Histologic type	N
Invasive duct carcinoma	81
Infiltrative lobular carcinoma	8
Mucinous carcinoma	4
Infiltrative cribriform carcinoma	2
Apocrine carcinoma	1
Metaplastic carcinoma	1
Malignant fibrous histiocytoma	1
Tubular carcinoma	1
Mixed infiltrative ductal and lobular carcinoma	1
Total	100

Table 2. — *Results of intraoperative pathological monitorization of surgical margins (IPMSM) in 100 breast cancer cases considered candidates for breast-conservation.*

Indications for widening	Final surgery		Total
	Conservative	Mastectomy	
Insufficient margins	23	0	23
EIC	6	2	8
Multifocal tumors	1	3	4
Proliferative lesion at the margin	4	0	4
Diffuse tumor	0	1	1
Total	34	6	40

limits of the invasive component of the lesion, we considered a margin of 2 mm sufficient. We defined “close margins” as those of 2 mm or less for these cases. For the tumors with spiculated borders, EIC or high nuclear grade, we defined free margins as those with histological representation of, at least, two lobular units morphologically normal between the margin and the tumor (Figure 5).

If the margin was considered insufficient, the surgeon excised additional tissue from the portion indicated by the pathologist. The new margin was oriented by the surgeon, inked and studied by means of cytology scrapes and frozen section. If clear margins could not be obtained after the additional resection a mastectomy was performed.

The intraoperative pathological evaluation was compared with the final pathology report.

The behavior of these patients in respect to the recurrence rate was compared to that of a control group composed of 149 patients, age range from 26 to 70 years old (mean 49,  $\sigma = 9.7$ ) with breast cancer at clinical stage I and II, who were submitted to conservative surgery by the same surgeon (JAP), but not to IPMSM. This group was followed for a period of 14 to 213 months (median = 126 months).

The Kaplan Meier method was used to estimate event-free survival curves and the Log-rank test was used to compare the two groups. Significance level was established at 0.05.

## Results

The immediate re-excision was indicated in 40 of the 100 tumors, six of which were submitted to mastectomy. The indications for additional resections were insufficient margins in 23 cases (9 positive margins and 14 close margins), EIC involving margins in eight, multifocality in four, atypical proliferative lesions at the margin in four and diffuse tumor in one. In all the 23 cases of insufficient margins we were able to make additional resections and maintain the conservative surgery. Of the eight cases of EIC at the margins, two were submitted to mastectomy because we could not achieve free margins (Table 2). One of the four cases that had multiple tumors was submitted to conservative surgery because the patient, although requiring mastectomy, did not consent to this. All the results of intraoperative examination were confirmed in the final report. The final diagnoses in the cases of atypical proliferative lesions at the margins were: ductal carcinoma in situ in three cases and atypical ductal hyperplasia in one.

Local recurrence was observed in one case after 45 months, and was not related to localization of the first tumor. The histological type of the primary and the recurrent tumor were both infiltrative lobular carcinomas. In the control group there were 17 (11.4%) local recurrences. The differences between the two groups were significant ( $p = 0.04$ ) (Figure 6).

Metastases were detected in five patients and four of these died of disease. In the control group we had 49 cases with metastasis and 43 deaths. The differences in the metastasis-free survival curve were significant (Figure 7) ( $p = 0.0078$ ), although we could not detect significant differences in overall survival (Figure 8).

## Discussion

The intraoperative evaluation of margins is a common practice in many tumors for which, like the breast, margins play an important role in the prevention of recurrence, for example, some tumors of the skin, head and neck regions and gastrointestinal tract [14]. We began this project to investigate the value of intraoperative evaluation for prevention of involved or insufficient margins.

After a long experience with conservative treatment of breast cancer, we know how dramatic a local recurrence is for the patient. After being convinced that the ideal surgical treatment should have free margins and that better results with radiotherapy are obtained with free margins [15-20], we make every effort to clear the margins, preferably at one time.

Microscopic margin evaluation is difficult because the surface area of the specimens is often quite large and highly complex and irregular. A further problem is the lack of uniformly-accepted definitions of “positive”, “negative” and “close” margins. Nonetheless, the surgeon needs to know if the margin is sufficient or not, be-



Fig. 1

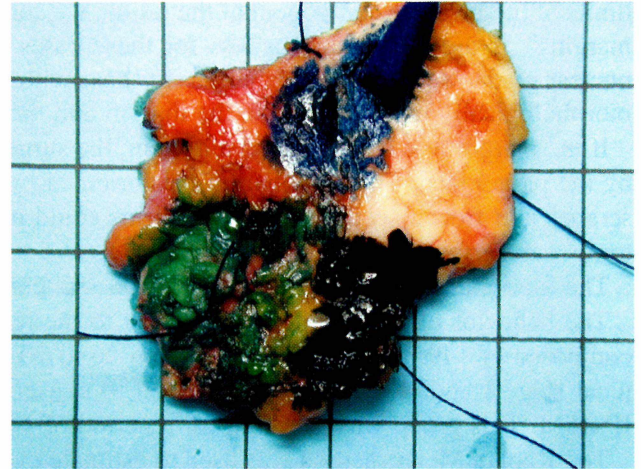
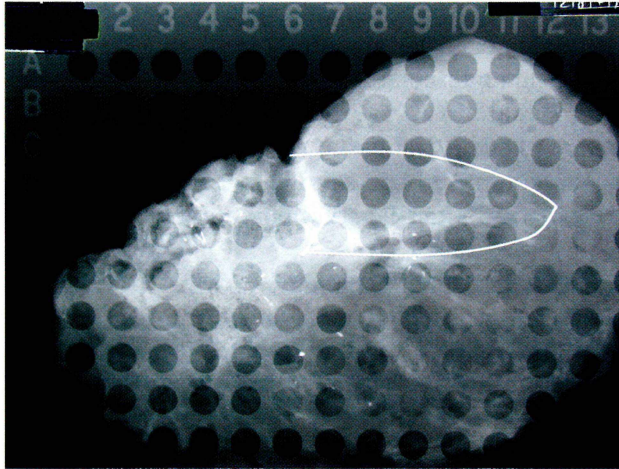


Fig.

Fig. 3

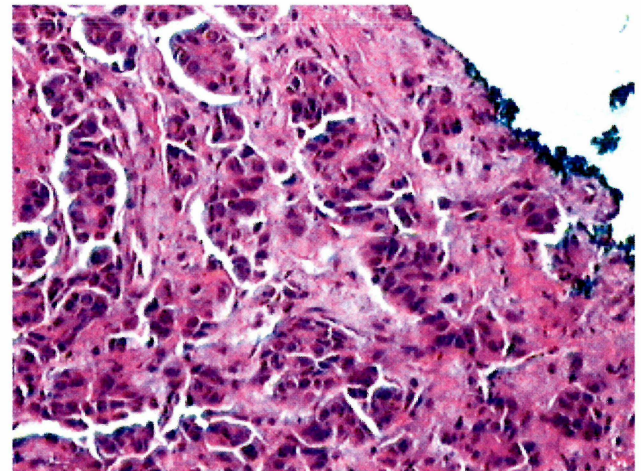
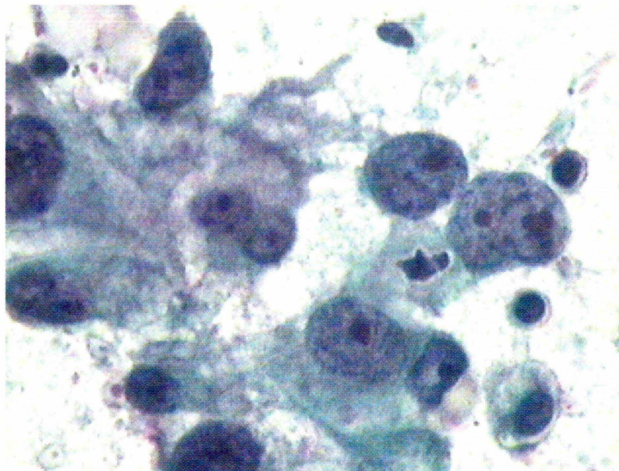


Fig.

Fig. 5

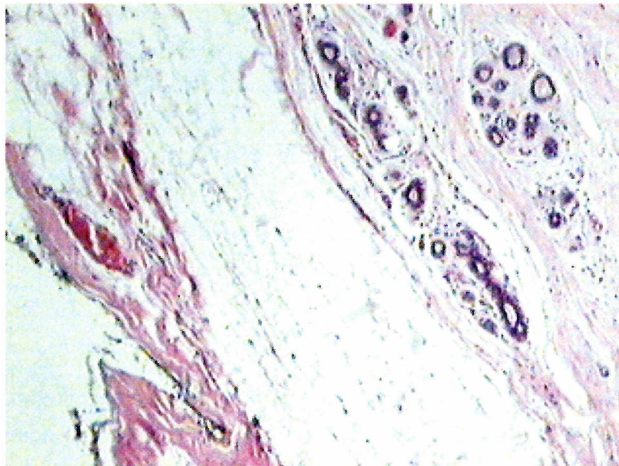


Figure 1. — X-ray of the specimen.

Figure 2. — Surgical margins inked in different colors.

Figure 3. — Cytological scrape showing malignant cells (HE - x400).

Figure 4. — Positive margin: tumor reaching the border of the lesion (HE - x100).

Figure 5. — Free margin: uninvolved lobules between the tumor and the border (HE - x40).

cause there is no doubt that the involvement of margins, irrespective of the technique used to assess them, has an important impact on local recurrence, although the magnitude of risk is variable [1, 8, 9, 16, 17, 20-23]. Obedian and Haffty [23] determined the impact of the final pathologic margin status on relapse-free survival in patients undergoing conservative surgery and radiation therapy for invasive breast cancer. Breast relapse-free survival at ten years was 98% for patients with negative or close margins and 83% for patients with positive margins. These authors evaluated 984 patients and re-excision was carried in 294 of these patients, almost 30%. Besides being traumatic for the patient, the re-excision is difficult for the surgeon who has to localize an involved margin. It is not uncommon to perform a mastectomy after involved margins are found because we cannot

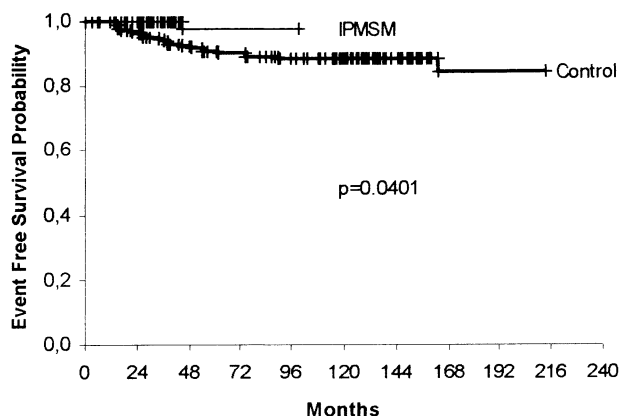


Figure 6. — Relapse-free survival curve for groups IPMSM (intraoperative pathological monitorization of surgical margins) (1 event/98 patients) and Control (17 events/149 patients).

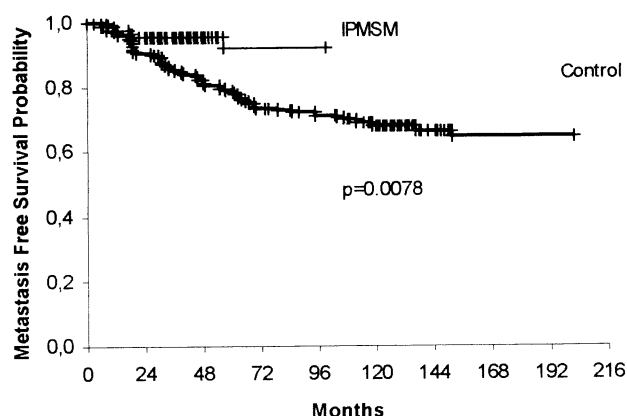


Figure 7. — Metastasis free survival curve for groups IPMSM (5 events/98 patients) and Control (49 events/149 patients).

surely assess the local diffusion. Another important consequence with the two-step procedure is the impossibility of performing immediate plastic surgery at the time of the first surgery.

Intraoperative evaluation of breast margins has been suggested by many authors [8, 9, 24-28] and widely criticized [29]. Weber *et al.* also found a good accuracy of frozen section examination of the surgical margins followed by reduction of the recurrence rate. These authors have 5% of recurrence among the patients managed by lumpectomy with frozen section analysis. In general, particularly among North Americans, frozen section is not recommended, but cytological assessment is well accepted [9, 10]. In our study we combined histological and cytological analysis with emphasis on the cytology since this method permits a wider area of study. Obviously, intraoperative monitorization in cases of breast cancer is not as simple as making a benign/malignant diagnosis; however an experienced pathologist in breast pathology is required. The IPMSM of breast-conserving surgery is an example of how the conventional pathological procedures are changing as a function of different specimens and broader objectives of examination. Our proposal of IPMSM takes into account not only the margins *per se*, but certain pathological factors that may influence the outcome, such as the extensive intraductal component (EIC) for example, planning the surgery individually for each patient. Although breast tumors with EIC have increased risk of recurrence after conservative surgery [30, 31], particularly if associated with others factors, such as high-grade histology [32] and involved margins [17], the EIC is not considered a contraindication of conservative surgery since the margins are free.

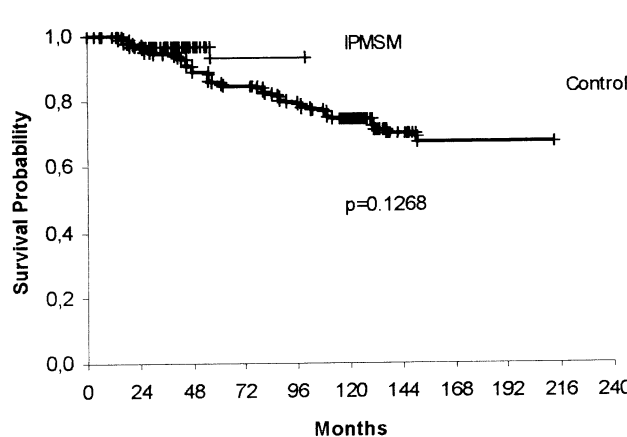


Figure 8. — Overall survival curve for groups IPMSM (4 events/98 patients) and Control (43 events/149 patients).

The concept of sufficient margins is becoming recognized. New preoperative imaging methods like nuclear magnetic resonance and intraoperative ultrasound are being developed and perhaps they will have a place in the determination of the real extension of the tumor and the presence of multicentric disease. Some histological characteristics indicating local aggressiveness can be obtained in the preoperative biopsy, among which are the EIC, nuclear high grade, peritumoral vascular involvement and expression of HER2 protein. The more preoperative information, we have, the more secure the surgery will be and the easier the IPMSM.

**Conclusion**

The intraoperative pathological evaluation of surgical margins has proved to be a safe and accurate method. Additional surgery for insufficient margins could be avoided 40% of the time and reduce the recurrence rate.

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