The Breast 18 (2009) 248–253

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Intra-operative touch preparation cytology following lumpectomy for breast cancer: A series of 400 procedures

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ARTICLE INFO

Article history:
Received 14 July 2008
Received in revised form
2 April 2009
Accepted 2 May 2009

Keywords:
Breast conservation
Intra-operative margin assessment
Frozen section
Imprint cytology

ABSTRACT

Aims: Achieving negative margins is essential in conservative treatment for breast cancer. The conventional method for intra-operative assessment of resection margins is gross or histological examination of frozen sections. We describe and evaluate the contribution of an original intra-operative touch preparation cytology (IOTPC) technique (400 procedures) performed on 396 patients.

Materials and methods: IOTPC consists of touching glass slides to the surfaces of interest after gently pressing the spatially localized specimen taken according to predetermined conditions. The result is conveyed to the surgeon immediately and compared with the conventional histological findings after embedding in paraffin.

Results: The average response time is 10 min, which renders the technique compatible with standard operating room procedures and its cost is reasonable. The method has a sensitivity of 88.6%, specificity of 92.2%, positive predictive value of 73.6%, negative predictive value of 97%, and correlation with paraffin section histology of 91.5%. Only 5 true false negatives were found in this series and the technique prevented 11.75% of secondary re-excision procedures for positive margins.

Conclusion: IOTPC is a reliable extemporaneous method for assessing surgical margins in conservative treatment for breast cancer and a useful tool for surgeons.

Introduction

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.[1] This therapy has enabled breast conservation and long-term safety in cancer.[2,3] 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.[2,4] With an extensive in situ component, invasion of the margins around the lumpectomy cavity is the main factor of local recurrence after conservative treatment.[2,5] The difficulty with breast-conserving treatment is therefore reconciling an objectively satisfactory cosmetic result[6] with excision to healthy tissue.[4,7] This explains why a large number of patients undergo surgical re-excision for inadequate margins (up to 20 or 30%), in particular young patients with a clinically palpable lesion, and presenting with an extensive in situ component or a lobular subtype.[8,9] An intra-operative assessment of resection margin status must enable directed resections to be made, thus reducing the deferred surgical re-excision rate and cosmetic, psychological and economic prejudice.[8] The most widely used technique in clinical practice is gross examination, which is sometimes verified by an X-ray examination, with a margin of clearance of healthy tissue at least 1 cm thickness. Frozen section margin assessment is gradually falling into disuse as it is time-consuming, costly and difficult to perform in an adipose region and is also a source of material loss.[10,11] We present an imprint cytology technique (intra-operative touch preparation cytology, IOTPC) and correlate findings for a series of 400 procedures with conventional analysis of paraffin-embedded operative specimens which remains the gold standard.

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doi:10.1016/j.breast.2009.05.002

Materials and methods

Materials

This controlled prospective study was conducted at the Eugène Marquis Comprehensive Cancer Center between January 1, 2004 and December 31, 2005. Seven hundred and thirty-six patients underwent breast-conserving treatment for unifocal breast cancer. Patients with multifocal lesions presenting with ipsilateral recurrence and having received neo-adjuvant treatment were excluded from the study. Four hundred procedures were thus performed on 396 patients (4 cases of bilateral BCT), which led to the collection of 1665 slides for cytological investigation, all of which were examined during the procedures.

The characteristics of the operated patients were comparable with other series of women having received breast-conserving treatment. The average age was 58.6 years (range: 29–88), 260 of the 384 patients whose hormonal status was known were menopausal (65%), 117 were premenopausal (29.25%), 7 had disorders associated with the perimenopausal period (1.75%), and 28 patients had a personal history of contralateral breast cancer (4 of which during the study period). The procedures were divided into 258 breast-conserving procedures for clinically palpable lumps (64.5%) and 142 lumpectomies for nonpalpable lesions (35.5%). The mean volume of operative specimens was 104.1 cm^3 (range: 1.5–701.25 cm^3). The mean size of invasive lesions (pT, histological measurement of the operative specimen by the pathologist) was 16 mm (range: 2–50 mm), and the size of in situ lesions was 18.9 mm (range: 4–70 mm). Histologically, the distribution was 89% ductal lesions (pure IDC 19%, pure DCIS 11%, IDC with in situ component 59%) and 11% lobular lesions (pure ILC 3%, associated with in situ lesions 5%, and pure LCIS 3%). The size of the tumors according to the histological characteristics is summarized in Table 1. Deferred surgical re-excision was performed when, on final examination, the minimum margin was less than or equal to 2 mm, based on a local recurrence rate of 7% at 10 years after conservative treatment followed by radiation therapy.[12]

The statistical analysis was conducted using the SAS® software package (Statistical Analysis System, SAS Institute Inc. Cary, USA). The X^2 test was used for qualitative variables and the Student test was applied for comparison of mean values. The tests were considered positive when $p \leq 0.05$.

Methods

Surgical resection of operative specimens included en bloc skin excision of the lesion (palpable or localized by ultrasound or radiological examination the day before the procedure by hook wire left in contact with the radio signal) to the *pectoralis major*. The operative specimen was localized by the surgeon in the 3 spatial planes and referred to the pathologist who dried it on absorbent paper. A numbered glass slide was applied to each surface of interest (superior, inferior, anterior–posterior, lateral) after a gentle press on the specimen. If the side measured more than 5 cm or thickness exceeded 2 cm, 2 glass slides were used to cover the entire surface. The slides were room-dried and stained with Toluidine blue prior to interpretation. The results reported to the surgeon were expressed as: (a) acellular slides corresponding to healthy tissue (due to absence of normal epithelial cell desquamation[13]); (b) presence of benign cells (macrophages, columnar or apocrine metaplasia cells, Fig. 1); or (c) suspect positive slide in the presence of malignant cells (Fig. 2). The precise site of the lesions was deduced from their localization on the slide with anatomical mapping to the specimen for performing guided resection. In the case of resection, also oriented by the surgeon, the cytological procedure was reproduced until standardization of the imprint cytology technique was achieved.

Histological examination was performed after fixing and embedding in paraffin. The specimen was inked with different colors (1 color per specimen surface), then sectioned into 3-mm slices in a frontal plane to enable us to best analyze the 4 surfaces of interest. The inked resection margins were analyzed in 3-mm slices perpendicular to the lumpectomy bed.

Table 1
Characteristics of the tumors (histological type, grade, histological size of the tumor and the margins).

	SBR1[a]	SBR2[a]	SBR3[a]	Size of the tumor (mm – min–max)	Distance between tumor and margins (mm)
DCI & DCIS	97[a]	89[a]	49[a]	28.5 (1–55) 35.4 (2–70)	7.9 7.1
DCI	40	18	17	21.5 (3–55)	14
DCIS	11	16	14	23.5 (0.9–70)	4.5
LCI & LCIS	9[a]	6[a]	4[a]	14.5 (1–28) 27.5 (8–35)	5.9
LCIS	6	1	1		

DCI/IS: ductal carcinoma invasive and in situ. LCI/LCIS: lobular carcinoma invasive and in situ.
[a] Scarff-Bloom-Richardson Grade of the invasive component.

Results

The pathologists analyzed 1665 slides corresponding to a total of 400 breast-conserving procedures and lumpectomies performed, and compared their cytological findings with those of the histological examinations on paraffin sections.

The total time of the procedure was on average 10 min (range: 7–17 min). Correlation between IOTPC and histological examination was 91.5%, with sensitivity and specificity of 88.6% and 92.2%, respectively. The positive predictive values (PPV) and negative predictive values (NPV) were respectively 73.6% and 97.0% (Table 2). In 9 in 400 cases, the cytological finding was falsely negative, representing 2.31% of total findings. For 4 patients, the final histological examination showed tumor cells in contact with at least one margin of the specimen (true false negatives). In the other 5 cases, the margins of the analyzed paraffin-embedded specimen were less than or equal to 2 mm, resulting in deferred surgical re-excision. Ductal carcinoma in situ was significantly more represented in the false negatives than in the other cases ($p < 0.005$), particularly when its size was greater than or equal to 30 mm ($p < 0.005$). In addition, the histological grade of ductal carcinoma in situ influenced the results. The IOTPC technique recognized all the cases of pure grade 3 ductal carcinoma in situ with involved margins, whereas sensitivity was only 72% in grade 1 and 2 ductal carcinoma in situ cases (Table 2). IOTPC was falsely positive (positive imprint cytology with in sano margins on paraffin specimen examination) in 6.25% of cases (25/400). We observed twice as many false positives in the lobular carcinoma population (10.2%) as in the ductal carcinoma ones and particularly in the case of histological grade 3 (5.6%) although the results were not statistically significant given the small size of the population (Table 2). On the other hand, the presence of fibrocystic mastopathy lesions in the tumor significantly increased ($p < 0.001$) the percentage of false positives (48% versus 17%). We also observed IOTPC requiring more than 4 slides to be linked to a statistically higher false positive rate ($p = 0.0019$). Finally, the pathologists observed that the imprint cytology cases considered "difficult" (no objective classification could be put forward) were a source of false positives. This was particularly the case when the