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Local recurrence in lumpectomy patients after imprint cytology margin evaluation

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Abstract

Background: This is a follow-up study to our previously reported data on local recurrence rates in patients whose lumpectomy margins were evaluated by intraoperative imprint cytology (IIC^M). The purpose of this study was to compare local recurrence rates for patients whose lumpectomy margins were evaluated with IIC^M with local recurrence rates of those not evaluated by IIC^M.

Methods: A total of 1713 patients underwent lumpectomy treatment for breast cancer from 1988 to 2001 were prospectively entered into a computerized database and subsequently included in this study. Of the patients, 520 (group 1) had their surgery performed at an outside institution where conventional margin analysis was performed. Another 1193 (group 2) had their surgery performed at our institution where margins were evaluated by IIC^M. For each histologic type and for the overall sample, probabilities of recurrence with time were estimated using the method of Kaplan and Meier.

Results: IIC^M overcomes sampling error inherent in the frozen section analysis and results in a diminished incidence of overall 5-year local recurrence from 8.8% to 2.8% ($P < 0.0001$). The recurrence rates for each respective histologic subtype are reported for both absolute recurrences and probability of recurrence with time.

Conclusions: IIC^M provides an accurate evaluation of lumpectomy margins for patients undergoing breast-conservation treatment. IIC^M was associated with an overall lower local recurrence rate. This series defined the utility of intraoperative imprint cytology for evaluation of margins in patients undergoing breast-conservation treatment.

Keywords: Breast cancer; Imprint cytology; Lumpectomy margins; Recurrence

During the last 20 years, breast-conservation therapy (BCT) has come to the forefront of treatment options for breast cancer. The success of BCT depends not only on appropriate patient selection but also on adequate surgical margins combined with a cosmetically pleasing result. The goal of BCT should be to remove the smallest amount of tissue possible but still remove the tumor with adequate negative margins. Although the majority of patients will receive radiation therapy to the preserved breast, radiation cannot completely compensate for inadequate surgery. The appropriate margin width is debated in the literature, but most studies have demonstrated unacceptably high local recurrence rates when tumor cells are present at the cut surface of the specimen [1]. The first operation provides the best opportunity to achieve an acceptable cosmetic outcome over subsequent operations to clear positive margins, thereby establishing the need to accurately assess the margin status intraoperatively.

Frozen section has been the traditional method of microscopic analysis of margins and is widely used at many institutions. The use of frozen section unfortunately causes permanent loss of tissue, sampling errors, and histologic artifacts related to tissue preparation [2]. The use of intraoperative imprint cytology ($IIC^{M)}$ allows for rapid analysis of the entire margin surface without loss of diagnostic material or histologic freezing artifacts. In 1991, we reported on the sensitivity, specificity, and diagnostic accuracy of IIC^M at our institution.

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Table 1
Procedure used in standard intraoperative imprint cytology

A. Thoroughly air dry slides.
B. Stain with Diff-Quik solution as follows:
Step 1: Fix for 15–20 seconds in solution 1. Drain excess solution onto a paper towel.
Step 2: Dip slides repeatedly for 15–20 seconds in solution 2 until slides are uniformly coated and turn reddish-pink. Drain excess stain.
Step 3: Dip slides repeatedly for 10–15 seconds into solution 3. Rinse in tap water.
Step 4: Drain excess water. Examine slide smears for quality of stain (purple). If the stain is too pale or too intense (deep blue), it may be restained by repeated immersion in solution I for 20–30 seconds.
Step 5: Intraoperative/stat reading may be performed on uncoverslipped wet slides. Mount in resin and coverslip slides when dry.

* Performed on margins by cytopathologists at H. Lee Moffitt Cancer Center.

We reported a sensitivity of 100%, a specificity of 97.1%, and a diagnostic accuracy of 97.7% based on the evaluation of 90 patients [3]. Klimberg et al's data supported these findings after evaluating 428 patients and finding a sensitivity and specificity of 100% [4]. Another benefit of IIC^M is that its use does not preclude the addition of frozen section analysis if there is any question regarding margin status.

An accurate intraoperative assessment of margin status spares many patients a return trip to the operating room for margin re-excision. Does a more accurate initial intraoperative assessment of margin status have any impact on local recurrence rates? IIC^M has been used routinely at the H. Lee Moffitt Cancer Center (MCC) since April 1987 when it was first initiated. Many patients undergo their surgical procedure at MCC, but because this is a referral center, a number of BCT patients had their surgical excision performed at an outside facility and were referred to MCC for radiation treatment. Most of these facilities are community-based hospitals at which routine use of IIC^M is not employed. By comparing these two groups of BCT patients for local recurrence after careful review of their pathologic slides, one can begin to make conclusions about the utility of IIC^M in decreasing local recurrence rates for all histologic subtypes of breast cancer.

Table 2
Absolute local recurrences (mean follow-up 5 years) for patients who received BCT at an outside institution and were subsequently referred to MCC versus those who received BCT at MCC

Recurrence	Group 1 (n = 520) Referred	Group 2 (n = 1193) Moffitt
% Overall recurrence	10.9 (57/520)	2.8 (33/1193)
% DCIS recurrence	14.7 (5/34)	4.6 (8/171)
Mean time to local recurrence (y)	4.5	2.9
% IDC recurrence	11.2 (48/428)	2.6 (23/879)
Mean time to local recurrence (y)	3.8	3.4
% ILC recurrence	10.5 (4/38)	1.1 (1/91)
Mean time to local recurrence (y)	7.9	2.8
% Mixed recurrence	0 (0/20)	1.9 (1/52)
Mean time to local recurrence (y)	N/A	3.3

BCT = breast-conserving therapy; MCC = H. Lee Moffitt Cancer Center; DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; mixed = mixed ductal and lobular carcinoma.

Methods

Patients

Following current compliance guidelines, Institutional Review Board approval (no. 6304) was obtained for the review of this series of patients. Between 1988 and 2001, 1713 breast cancer patients treated at MCC with BCT were prospectively entered into a computerized database and their data reviewed, under Institutional Review Board approval, for information on pathologic variables, margin status, and local recurrence rates. A total of 520 patients (group 1) had their initial surgery done at an outside institution and were referred to our center for radiation therapy and/or chemotherapy. A total of 1193 patients (group 2) had their initial surgery and margin analysis performed at our institution.

Surgical therapy

BCT was defined as lumpectomy plus either sentinel lymph node biopsy or complete axillary lymph node dissection. Complete axillary lymph node dissection included levels I and II lymph nodes with >10 nodes evaluated. Some patients from both groups had to undergo re-excision of margins if the margins were found to be positive or <1 mm on final histologic evaluation.

Pathologic evaluation

All patients who had their initial surgical procedure performed at an outside institution had their original pathology reports and slides reviewed by our pathologists to confirm that the margins were negative. Outside facilities used conventional margin analysis such as frozen sections and permanent analysis. If margins were found to be positive on our review, patients were taken for re-excision of margins before undergoing radiation treatment. All patients who had their initial surgical procedure performed at our institution had their margins initially evaluated by IIC^M (Table 1) and supplemented in certain cases with frozen-section analysis. Then margins were determined to be negative ($\geq$1 mm) by final histologic review.

Follow-up

Patients were followed-up every 6 months to 1 year with routine physical examination and mammograms, and all

Table 3
Kaplan-Meier estimates of 5-year local recurrence rates for patients who received BCT at an outside institution and were subsequently referred to MCC and those who received BCT at MCC*

Recurrence	Referred (n = 520)	Moffitt (n = 1193)	*P* value
% Overall recurrence	8.8 (1.4)	2.8 (0.6)	<0.0001
% DCIS recurrence	8.8 (4.9)	4.0 (1.9)	0.105
% IDC recurrence	9.5 (1.7)	2.7 (0.7)	<0.0001
% ILC recurrence	5.1 (3.5)	1.5 (1.5)	0.166
% Mixed recurrence	0 (0)	2.9 (2.8)	0.558

BCT = breast conserving therapy; DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; MCC = H. Lee Moffitt Cancer Center; mixed = mixed ductal and lobular carcinoma.

* Values in parentheses are standard errors.

local recurrences were entered into the computerized database. Mean follow-up time for group 1 was 5.6 years, and mean follow-up time for group 2 was 5 years. Follow-up time spanned 1 to 13 years.

Statistical analysis

Groups 1 and 2 were broken down into various histologic subtypes including ductal carcinoma in situ (DCIS), invasive ductal carcinoma, invasive lobular carcinoma, and mixed ductal and lobular carcinoma. The 2 groups were then compared for overall local recurrence rates. For each histologic type and for the overall sample, probabilities of recurrence with time were estimated using the method of Kaplan and Meier. Standard errors of these estimates were computed using Greenwood's formula. Comparisons of these 2 groups with respect to recurrence over time were based on the log rank test. All *P* values reported are 2-sided. All calculations were performed using SAS statistical software (version 8.2; SAS, Cary, North Carolina).

Results

Five hundred twenty patients (group 1) treated with BCT had their lumpectomy margins evaluated by conventional histology, and 1193 patients (group 2) had their lumpectomy margins evaluated with IIC^M. In group 1, 7.3% (38 of 520) patients underwent a re-excision to obtain clear margins on another date after their original lumpectomy surgery. For group 2, this number was 6.2% (74 of 1193). Probability of overall local recurrence rates with time for group 1 was 8.8%, whereas the local recurrence rate for group 2 was 2.8%. The absolute overall recurrence rate for group 1 was 10.9% and for group 2 was 2.8%. The mean follow-up time for group 1 was 5.6 years and for group 2 was 5 years. The range of follow-up time was up to 13 years because patients were studied from 1988 to 2001. Patients were further subdivided into different histologic subtypes, and absolute local recurrence rates and Kaplan and Meier estimates of recurrence rates with time are reported (Tables 2 and 3). Recurrence over time is shown graphically (Fig. 1). An analysis of the histologic subgroups showed a significantly higher recurrence rate in all subgroups of group 1. The only exception was in the mixed subgroup secondary to lack of patients in that subgroup of group 1.

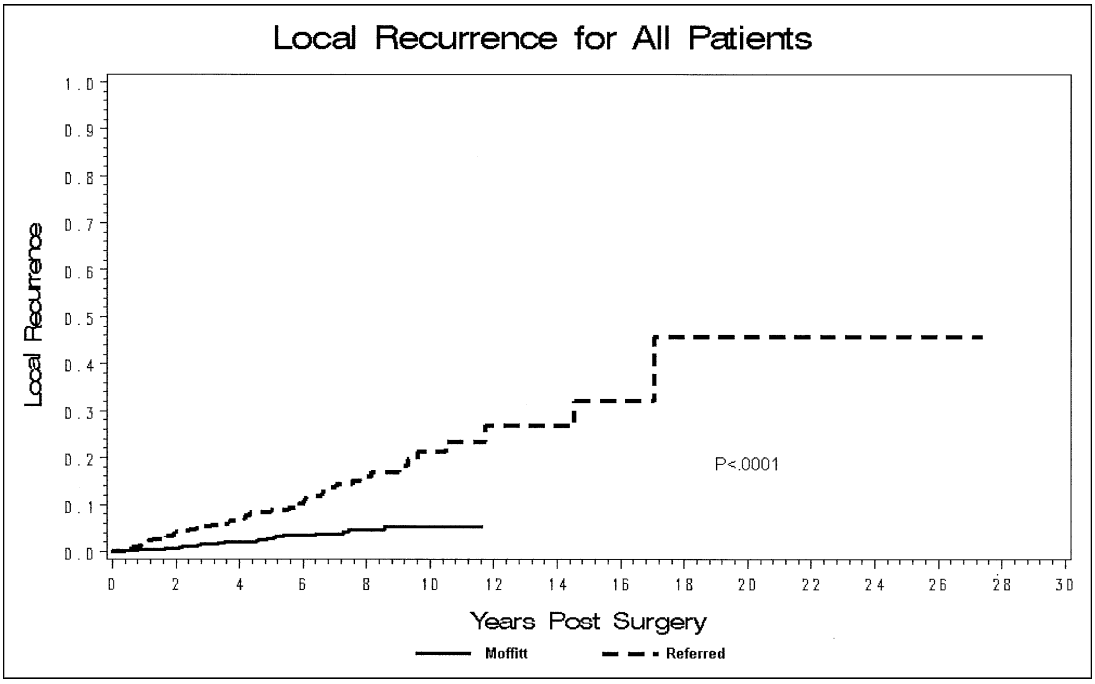

Fig. 1. Recurrence rates with time for all patients in this series.

Table 4
Studies reporting on local recurrences in patients receiving conventional histologic evaluation on lumpectomy margins

Investigators	No. of patients	Follow-up (mo)	Local recurrence with negative margins (%)	Local recurrence with positive margins (%)
Peirce et al. [5]	396	60	3	13
Van Dongen et al. [6]	431	96	9	20
Heimann et al. [7]	869	60	2	11
Burke et al. [8]	306	60	2	15
Fourquet et al. [9]	518	103	8	29
Clarke et al. [10]	436	120	4	10
Mansfield et al. [11]	704	120	8	16
Slotman et al. [12]	514	68	3	10
Veronesi et al. [13]	289	79	9	17
DiBiase et al. [14]	453	120	13	31
LeBorgne et al. [15]	817	75	9	6

Discussion

Many studies have examined the different variables that may lead to local recurrence after lumpectomy. The impact of factors such as extensive intraductal component, age, tumor size, and lymph node involvement on local recurrence rates is debated in the literature. However, a review of studies that have examined the relationship between margin status and local recurrence rates leaves no doubt that margin positivity clearly correlates with increased local recurrence rates [5–15] (Table 4). Most studies demonstrated that the degree of margin width does not correlate with local recurrence rates as long as there is not gross tumor at the inked margin [1]. One might suggest that a potential bias exists in our study because the total volume of resection may be more important than the use of imprint cytology. If this bias exists, it is undoubtedly a bias toward group [1]. Without the use of intraoperative imprint cytology (group 1), surgeons would inevitably take wider excisions because they will want to insure clear margins. These patients, in turn,

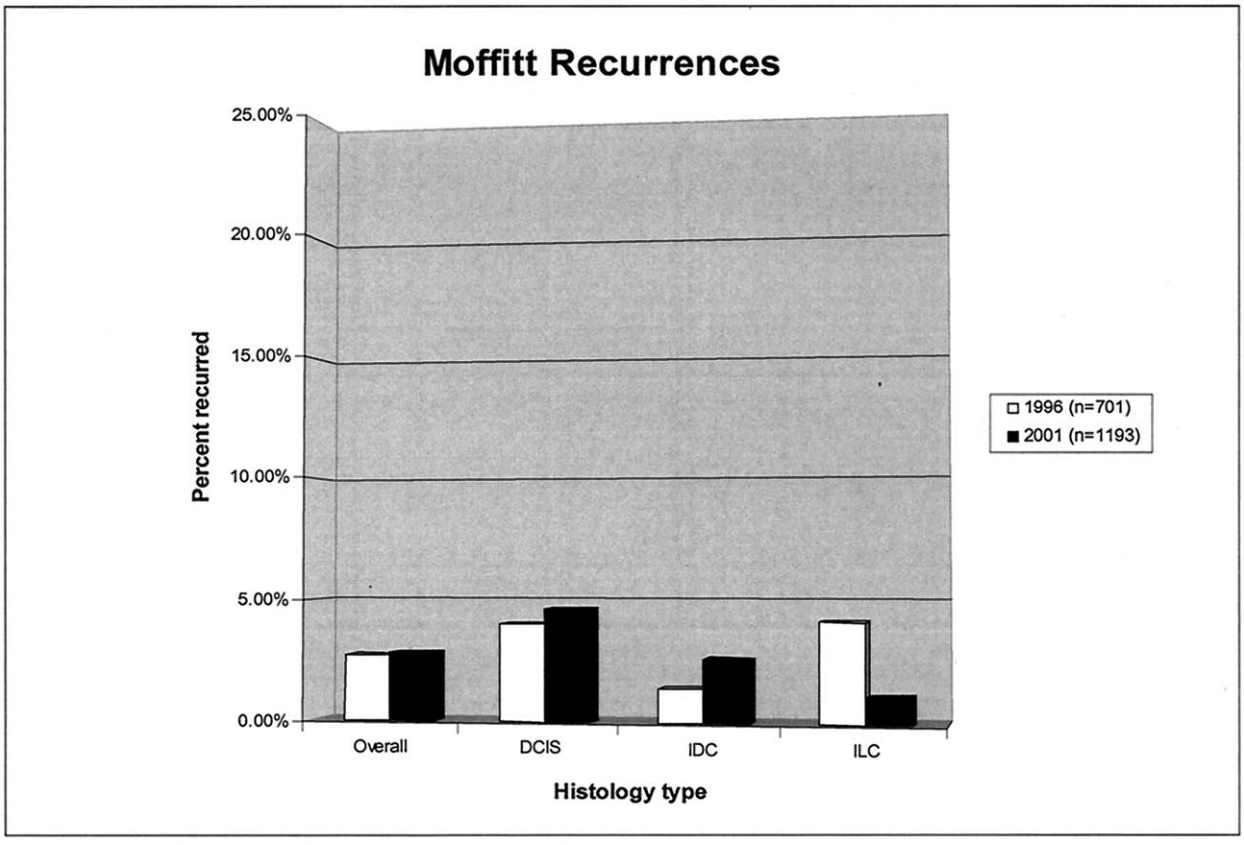

Fig. 2. Comparison of Moffitt recurrences (based on histologic subtype) in our original study conducted in 1996 with recurrences in our current study conducted in 2001. Abbreviations as in Table 3.

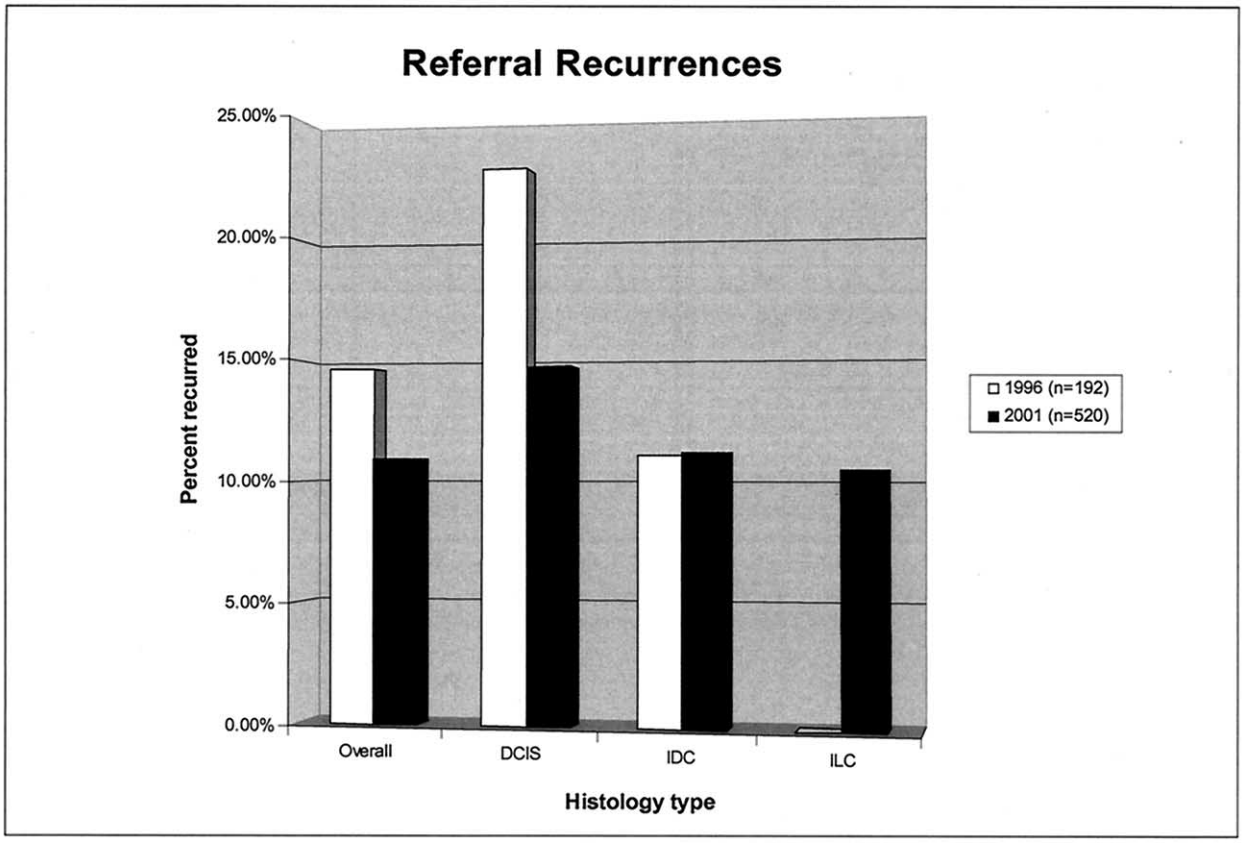

Fig. 3. Comparison of referral recurrences (based on histologic subtype) in our original study conducted in 1996 with recurrences in our current study conducted in 2001. Abbreviations as in Figure 2.

would have had a lower recurrence rate because they would have had a larger volume of excision. Therefore, this suggested bias is contradicted by the outcome. It cannot be concluded that obtaining a large lumpectomy volume will decrease the rate of local recurrence after BCT [1], rather that clear margins are the most critical aspect of recurrence. The bias in group 2 is to do minimal excision with re-excision to negative margins, which—according to the results of this study—support the conclusion that minimal excision to negative margins is the critical requirement for better outcomes.

Achieving a negative margin is paramount to decreasing local recurrence rates. Furthermore, achieving a negative margin at the initial lumpectomy is cost-efficient, time-conserving, and improves cosmetic outcome. The studies listed in Table 4 all used conventional histopathologic methods for determining margin status; none used IIC^M. The range of local recurrences for patients with negative margins varied from 2% to 13%, and the mean local recurrence rate was 8%.

In 1991, we reported on our experience with IIC^M with regard to sensitivity, specificity, and diagnostic accuracy. In 1 study, the use of IIC^M in 90 lumpectomy specimens yielded a sensitivity of 100%, a specificity of 97.1%, and a diagnostic accuracy of 97.7% [3]. A second study of 114 lumpectomy specimens yielded a sensitivity of 100%, a specificity of 96.6%, and a diagnostic accuracy of 97.3% [2]. A review of 5 other studies that examined IIC^M demonstrated sensitivities of 80% to 100%, specificities of 83% to 100%, and diagnostic accuracies of 73% to 100% [16]. Over the years, IIC^M has proven to be as accurate as frozen section but without the loss of tissue and creation of artifact. Furthermore, it is rapid and reliable while allowing frozen-section verification if necessary. One limitation to IIC^M is that cytopathology training and certification, along with a desire to perform rapid intraoperative assessment, is a requirement for success of the procedure. Furthermore, errors in interpretation based on specimen surface irregularity, cauterization, dryness, or overinterpretation of atypical cells are pitfalls of the technique [17].

In previously published data on local recurrence of breast cancer after IIC^M, 701 patients were evaluated with IIC^M at MCC and compared with 192 patients who were evaluated at outside facilities with conventional histologic methods. The follow-up time was 3.5 years, and the local recurrence rates were significantly higher in the patients evaluated by conventional histology [17,18]. The overall local recurrence rates were 2.7% in the IIC^M group and 14.6% in the referred patients. This new study has accrued an additional 820 patients (328 in group 1 and 492 in group 2), and the mean

follow-up time has been extended from 3.5 years to 5 years with no significant change in outcome.

The local recurrence rates amongst the various histologic subgroups in each group were similar to the current data presented here (Figs. 2 and 3). Of particular interest is the DCIS subgroup. The local recurrence rate in group 1 was 14.7% (5 of 34) compared with 4.6% (8 of 171) in group 2, i.e., those evaluated with IIC^{M}. Patients with DCIS have high local recurrence rates, and therefore a mastectomy is often recommended out of fear of inability to acquire negative margins. In 1997, we reported on our experience in using IIC^{M} to evaluate the margins of DCIS patients [19]. In this study, BCT was attempted in 104 patients and was successful in 93% (97 of 104) [19]. Only 6.6% (7 of 104) patients required mastectomy, and the local recurrence rate in the lumpectomy group was only 6.1% (6 of 97). Since that data was published, the local recurrence rates for DCIS treated with BCT at MCC has essentially remained the same: 4% in 1996 and 4.6% in 2001.

Another histologic subgroup that warrants further discussion is that of invasive lobular carcinoma. These cells are difficult to analyze with conventional histologic methods as well as with IIC^{M} because the cells are small, monomorphic, and difficult to differentiate from normal cellular component. Our recurrence rate in this subgroup is very low, 1.1% (1 of 52); however, these specimens often undergo frozen section analysis as well as IIC^{M}. The slight but apparent increase in the recurrence rate of IDC from 1996 to 2001 may represent the maturity of the data from a 3.5-year to a 5-year follow-up because there would be no unfavorable bias to avoid BCT in this population.

Comments

IIC^{M} has proven to be a sensitive, reliable, rapid, and topographically accurate method for the evaluation of lumpectomy margins in breast cancer patients. Because local recurrence rates are likely attributable to undiagnosed microscopic disease, it is crucial that margin status is correctly evaluated. It is ideal that the margins be correctly analyzed at the initial operation to spare patients a second procedure for re-excision of margins and also to provide better cosmetic outcomes. The current study represents the largest series with the longest follow-up to evaluate the use of IIC^{M} and its impact on local recurrence since our first description of the technique in 1987. Based on the experience at MCC, IIC^{M} proved to be superior to conventional histopathologic methods alone in evaluating lumpectomy specimens for negative margins to prevent local recurrence of disease.

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