EVALUATIONS OF MARGINS

Ayşegül Şahin

One of the most important contributions of a pathologist in the management of breast cancer is the performance of an accurate evaluation of resection margins of breast excision specimens. The local treatment of breast cancer has undergone major revisions in the last two decades, and breast-conserving therapy (segmental resection and radiotherapy) has become the standard treatment for many patients with breast cancer. Many retrospective and prospective studies have demonstrated that patients treated with breast-conserving therapy have similar disease-free and overall survival rates, compared to patients who have total mastectomy. However, complete excision of tumor is necessary to achieve satisfactory local tumor control. Therefore, accurate assessment of surgical margins of breast resection specimens is an essential component of successful local treatment of breast cancer.

Evaluation of surgical excision margins of breast specimens is one of the most difficult and complex tasks that a pathologist has to deal with, and it requires a multidisciplinary effort and close collaboration between surgeon and radiologist. Several different methods of evaluating margins have been described, and it is important to realize that all these methods are subject to sampling error.
There is no single or optimal method that will apply to all cases.

The main difficulty in the evaluation of margins is related to the growth patters of breast cancer. Except for a small percentage of special histologic types such as medullary and mucinous carcinomas, breast cancers form masses with irregular borders and show fingerlike projections into adjacent breast parenchyma. They are also associated with varying amounts of an in situ carcinoma component that is not apparent on gross examination. Evaluation of margins for carcinoma in situ is more problematic because in the majority of cases, carcinoma in situ does not form a mass; therefore, it is not feasible to depend on gross evaluation of the resection specimen. Specimen radiography is essential to guide the pathologist in the evaluation of extent of the disease and margin status. Another unresolved issue related to the assessment of margins is the concept of "negative" margin. The definition of negative margins for invasive and carcinoma in situ is not well established in the literature.

Depending on the size and histologic type of the tumor, the size of the excision specimen, and the size of the breast in relation to the excised specimen and imaging findings, different approaches should be considered when evaluating surgical excision margins in an individual specimen. Therefore, it is vital for a pathologist to be familiar with the clinical and imaging findings of each case before he or she decides how to evaluate breast resection specimens.

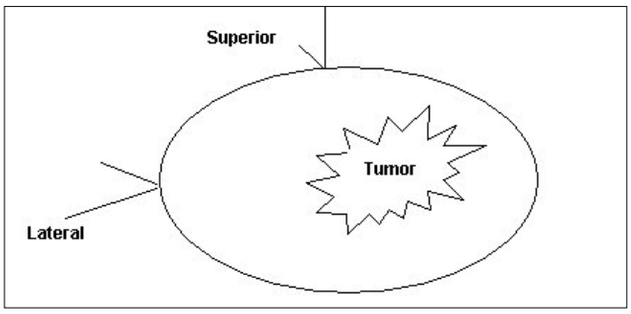
The treatment of breast cancer has undergone a marked shift toward less invasive procedures. The recent 20-year follow-up data from the NSABP's B-06 study has confirmed a lack of survival difference between Stage 1 and II breast cancers treated with lumpectomy and radiotherapy versus mastectomy.1 Local recurrence rates in modern series with contemporary radiation protocols are quite acceptable.2 However, the issue of surgical margins in breast conserving therapy (BCT) remains problematic for many treating physicians.

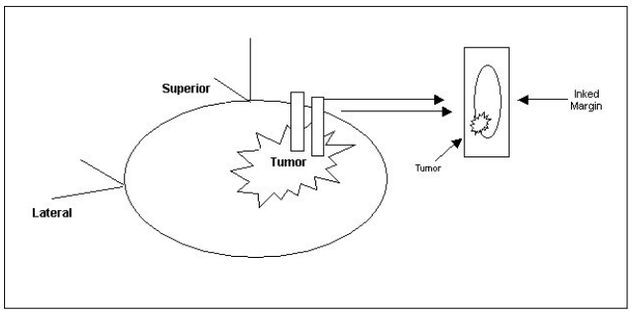
There are several practical and technical issues in margin assessment. Ink may seep into cracks or crevices in the surface of the tissue, including those created by tissue handling intraoperatively.3 In addition, all margin evaluation is subject to sampling error, as complete sampling of the margin of a 2 cm specimen would require over 3000 sections.4 Specimen radiography may distort the margins,5 and even without compression, the specimen may lose volume during imaging.6

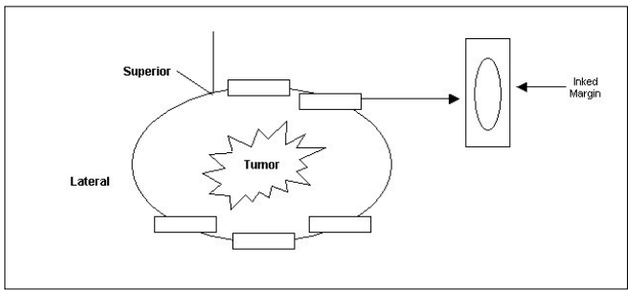
Margin status is related to local recurrence. Local recurrence is more frequent in patients with positive margins than those with negative margins.7 The definition of an adequate margin, however, remains somewhat subjective. Schnitt and colleagues reported similar 5-year rates of recurrence for patients with negative, close, and even focally positive margins, with higher rate of local recurrence for those with greater than focally positive margins.8 Age may also be a factor, with young women with positive margins being at the highest risk for local failure.9

A certain percentage of patients will have positive margins and require re-excision. Negative margins are obtained after the initial excision in 50-90% of cases. Several studies have evaluated strategies to improve this initial negative margin rate. Certainly mastectomy could be used more often, but this would be a step backward and conventional criteria are accurate for selection appropriate BCT candidates. 9-12

Magnetic resonance (MR) imaging has been proposed to reveal cancer that is more extensive that evident by traditional imaging and come authors recommend MR as a routine step in the evaluation of patients for BCT candidacy.13 Bedrosian and colleages reported 267 patients who underwent MR imaging prior to their definitive surgical therapy and found that this led to additional







biopsy or treatment with mastectomy in 26%.14 However, 20 of those patients (29%) did not have additional cancer identified by the MRI. This group also evaluated 82 cancers excised with close or positive margins with MRI prior to re-excision. In this setting, MRI had a sensitivity of 61% and a specificity of 69% for residual disease.15 Hlawatsch and colleages reported 104 women with findings suggestive of malignancy evaluated with mammography, sonagraphy, and MR imaging with histologic correlation.16 They found that the use of MR imaging benefited 7 patients and 8 patients had false-positive MR findings.

The concept that there is residual disease following lumpectomy, however, is not new. Holland and colleagues performed extensive histologic evaluation of mastectomy specimens from tumors that would have met criteria for BCT.17 Only 39% of cases had tumors that were confined to the primary mass. Forty-one percent of patients had foci of tumor more than 2cm beyond the edge of primary tumor mass. Even with 4 cm of margin around the primary tumor, 10% of patient would still have residual foci of invasive or in situ carcinoma. Clearly postoperative radiotherapy has the capacity to control the majority of these residual microscopic foci of disease, given that local recurrence rates for BCT in modern series do not reflect this known residual tumor. How, then, does one decide who will benefit from re-excision? In a study of 260 invasive tumors, over half of which were re-excised, 30% of all cases had some residual cancer on re-excision, regardless of the initial margin status.18 This included those with negative margins. A more pertinent question is how much disease remains - clearly if a large residual tumor burden remains, the patients will be best served by additional surgery whereas microscopic residual disease responds to radiotherapy. Wazer et. Al. evaluated 265 State I and II tumors with margins < 2 mm or unknown margins who underwent re-excision.19 Among those with positive margins, those with moderate or extensive positivity were more likely to have medium or large amounts of residual tumor than those with focal or minimal margin positivity. Close, focally positive, and minimal margin positive were all statistically similar for the likelihood of finding a medium or large amount of residual disease.

The goal of radiotherapy, therefore, is to render this residual disease biologically insignificant. This is quite effective, with modern series showing local recurrence rates of 2-6% at 10 years. Thus, demonstration of this residual disease, whether by MRI or other methods, is unlikely to improve local recurrence rates and will increase the costs associated with treating breast cancer as well as decreasing the use of BCT. A measurable benefit needs to be demonstrated before MR should be incorporated into the routine evaluation of patients with early stage breast cancer.

In summary, the evaluation of surgical margins provides important information because it provides our best indication of the adequacy of surgical excision. Patients with truly positive margins should undergo additional surgical therapy. However, caution needs to be exercised in the clinical application of margin evaluation to avoid surgically over treating women for microscopic residual disease that has already been proven effectively managed by postoperative radiotherapy.

References

1. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N. Twenty-year follow-up of a randomized trial comparing mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment f invasive breast cancer. N Engl J Med 347:1233-1241, 2002.
2. Morrow M, Harris JR. Local management of invastive breast cancer. In Harris JR, Lippman ME, Morrow M, Osborne CK (eds). Diseases of the Breast. Williams & Wilkins; 515-560, 2000.
3. Schnitt SJ, Connolly JL. Processing and evaluation of breast cancer excision specimens. A clinical oriented approach. Am J Clin Pathol 98:125-137, 1992.
4. Carter D. Margins of "lumpectomy" for breast cancer. Hum Pathol 17:330-332, 1996.
5. Clingan R, Griffin M, Phillips J, Coberly W, Jennings W. Potential margin distortion in breast tissue by specimen mammography. Arch Surg 138:1371-1374, 2003.

6. Graham RA, Homer MJ, Katz J, Rothschild J, Safaii H, Supran S. The pancake phenomenon contributes to the inaccuracy of margin assessment in patients with breast cancer. Am J Surg 184:89-93, 2002.
7. Spivack B, Khanna MM, Tafra L, Juillard G, Giuliano AE. Margin status and local recurrence after breast-conserving surgery. Arch Surg 129:952-956, 1994.
8. Schnitt SJ< Abner A, Gelman R, Connolly JL, Recht A, Duda RB, Eberlein TJ, Mayzel K, Silver B, Harris JR. The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. Cancer 74:1746-1751, 1994.
9. Jobsen JJ, va der PJ, Ong F, Meerwaldt JH. The value of a positive margin for invasive carcinoma in breast-conservative treatment in relation to local recurrence is limited to young women only. Int J Radiat Oncol Biol Phys 57:724-731, 2003.
10. Morrow M, Bucci C, Rademaker A. Medical contraindications are not a major factor in the utilization of breast conserving therapy. J Am Coll Surg 186:269-274, 1998.
11. Gae I, Schnitt SJ, Nixon AJ, Silver B, Recht A, Troyan SL, Eberlein T, Love SM, Gelman R, Harris JR, Connolly JL. Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. Cancer 78:1921-1928, 1996.
12. Staradub VL, Rademaker AW, Morrow M. Factors influencing outcomes for breast conservation therapy of mammographically detected malignancies. J Am Coll Surg 196:518-524, 2003.
13. Hata T, Takahashi H, Watanabe K, Takahashi M, Taguchi K, Itoh T, Todo S. Magnetic resonance imaging for preoperative evaluation of breast cancer: a comparative study with mammography and ultrasonography. J Am Coll Surg 198:190-197, 2004.
14. Bedrosian I, Mick R, Orel SG, Schnall M, Reynolds C, Spitz FR, Callans LS, Buzby GP, Rosato EF, Fraker DL, Czerniecki BJ. Changes in the surgical management of patients with breast carcinoma based on preoperative magnetic resonance imaging. Cancer 98:468-473, 2003.
15. Lee JM, Orel SG, Czerniecki BJ, Solin LJ, Schnall MD. MRI before re-excision surgery in patients with breast cancer. AJR Am J Roentegenol 182:473-480, 2002.
16. Hlawatsch A, Teifke A, Schmidt M, Thelen M. Preoperative assessment of breast cancer: sonography versus MR imaging. AJR Am J Roentgenol 179:1493-1501, 2002.
17. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer 56:979-990, 1985.
18. Swanson GP, Rynearson K, Symmonds R. Significance of margins of excision on breast cancer recurrence. Am J Clin Oncol 25:438-441, 2002.
19. Wazer DE, Schmidt-Ullrich RK, Schmid CH, Ruthazer R, Kramer B, Safaii H, Graham R. The value of breast lumpectomy margin assessment as a predictor of residual tumor burden. Int J Radiat Oncol Biol Phys 38:291-299, 1997.
20. Chapgar A, Yen T, Sahin A, Hunt KK, Whitman GJ, Ames FC, Ross MI, Meric-Bernstam F, Babiera GV, Singletary SE, Kuerer HM. Intraoperative margin assessment reduces reexcision rates in patients with ductal carcinoma in situ treated with breast-conserving surgery. Am J Surg 186(4):371-377, 2003.
21. Creager AJ, Shaw JA, Young PR, Geisinger KR. Intraoperative evaluation of lumpectomy margins by imprint cytology with histologic correlation: a community hospital experience. Arch Path & Lab Med 126(7):864-848, 2002.
22. Millar EK, Leong AS. Significance of assessment of margin status in ductal carcinoma in situ of the breast. [Review] Adv Anatom Pathol 8(6):338-344, 2001.
23. Florell SR, Layfield LJ, Gerwels JW. A comparison of touch imprint cytology and Mohs frozen-section histology in the evaluation of Mohs micrographic surgical margins. J Am Acad Derm 44(4):660-664, 2001.
24. Abraham SC, Fox K, Fraker D, Solin L, Reynolds C. Sampling of grossly benign breast reexcisions: a multidisciplinary approach to assessing adequacy. Am J Surg Pathol 23(3):316-322, 1999.
25. Saarela AO, Paloneva TK, Rissanen TJ, Kiviniemi HO. Determinants of positive histologic margins and residual tumor after lumpectomy for early breast cancer: a prospective study with special reference to touch preparation cytology. J Surg Oncol 66(4):248-253, 1997.
26. Cox CE, Hyacinthe M, Gonzalez RJ, Lyman G, Reintgen D, Ku NN, Greenberg H, Nicosia SV. Cytologic evaluation of lumpectomy margins in patients with ductal carcinoma in situ: clinical outcome. Ann Surg Oncol 4(8):644-649, 1997.
27. Guidi AJ, Connolly JL, Harris JR, Schnitt SJ. The relationship between shaved margin and inked margin status in breast excision specimens. Cancer 79(8):1568-1573, 1997.