Local Control of Ductal Carcinoma In Situ Based on Tumor and Patient Characteristics: The Surgeon’s Perspective

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Ductal carcinoma in situ (DCIS) is a disease whose manifestations are largely confined to in-breast pathology. Management strategies therefore focus on various combinations of local therapy: mastectomy, lumpectomy alone, and lumpectomy followed by breast irradiation. Although DCIS does not carry an inherent risk of distant organ metastasis, optimal local control is essential because any in-breast or chest wall recurrence may occur as an invasive lesion. Local recurrence has been reported following breast-conserving surgery as well as mastectomy. Breast radiation is therefore generally recommended following breast-conserving surgery, and in selected circumstances, mastectomy may be the preferred treatment strategy. This article reviews the surgical and associated clinicopathologic issues related to initial biopsy and perioperative planning that should be considered for all DCIS cases to optimize local control.

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Ductal carcinoma in situ (DCIS) is a disease whose manifestations are largely confined to in-breast pathology. Management strategies therefore focus on various combinations of local therapy: mastectomy, lumpectomy alone, and lumpectomy followed by breast irradiation. Clinical trials (1–7) comparing these strategies are summarized in Table 1. In general, all of these trials have demonstrated overall survival rates that are equivalent and quite high for the various randomization arms. Another common denominator between studies, however, is the observation that approximately half of the local recurrences (LRs) following any treatment strategy will be detected as an invasive lesion. It can therefore be argued that proper selection of DCIS cases for breast conservation is even more important than it is with patients who present initially with infiltrating breast cancer because the latter subset faces the risk of needing chemotherapy and experiencing distant organ relapse from the time of diagnosis. For this reason, careful consideration of all surgical perspectives in optimally diagnosing and treating DCIS is extremely relevant. These surgically based considerations can be categorized and will be reviewed sequentially as follows:

1. selection of diagnostic biopsy procedure;
2. selection of breast-conserving surgery vs mastectomy;
3. management of prior core needle biopsy tract(s) at the time of definitive surgery;
4. effect of multiple re-excisions on local control in cases of breast conservation;
5. breast specimen handling.

Selection of Diagnostic Biopsy Procedure

The majority of DCIS patients today present with a nonpalpable abnormality detected mammographically, such as microcalcifications. The initial management approach should include diagnostic imaging such as compression/magnification views to gain full appreciation for the extent of disease. Breast ultrasound may be useful for asymmetric densities. Whenever possible, a percutaneous image-guided needle biopsy should be the initial diagnostic intervention. Percutaneous needle biopsies are preferred over the diagnostic excisional biopsy (which will require wire localization for image-detected abnormalities) because they are less invasive and more efficient diagnostic procedures. Several investigators have also demonstrated that a diagnostic needle biopsy is associated with a higher success rate for subsequent breast-conserving surgery via a single lumpectomy based upon reviews of cases from the National Comprehensive Cancer Network (8); the Surveillance, Epidemiology, and End Results Program (9); and single-institution reviews (10). Needle biopsy as a determinant of successful single lumpectomy breast conservation is predictable because the surgeon will certainly plan a therapeutic partial breast resection with a more aggressive approach when the aim is to achieve margin control compared with when the goal is to sample adequately for a tissue diagnosis.

Stereotactic biopsies are highly accurate for mammographically detected microcalcifications, and ultrasound may be useful to guide the biopsy of an asymmetric mass density. Fine needle aspiration biopsies carry an increased risk of sampling error when compared with core needle biopsies and are unlikely to yield adequate tissue for full histopathologic and molecular characterization of the biopsied lesion. Immunohistochemistry to evaluate estrogen receptor, progesterone receptor, and HER2/neu expression is feasible on the spun down cell blocks from a fine needle aspiration specimen, but in the event that an invasive component is present, it will be unclear whether this molecular marker profile reflects the DCIS or the invasive lesion. Multiple cores should be extracted (10–15 for microcalcifications), and these should be imaged mammographically to confirm the presence of microcalcifications.
Some clusters of microcalcifications are quite small and may be completely resected with cores, especially if vacuum-assisted devices are used. In this setting, a radio-opaque clip should be inserted to facilitate subsequent wire localization lumpectomy for those lesions proven to be cancerous.

When percutaneous core needle biopsies are unavailable, or if the patient cannot tolerate the positioning necessary for the stereotactic approach, then an open biopsy with image-guided wire localization will be required. Specimen mammography should always be performed to document inclusion of the targeted area, and the specimen should be oriented by the surgeon for pathological analysis.

For all biopsy material revealing a diagnosis of DCIS (regardless of biopsy method), scrutiny should focus on ruling out microinvasion and on describing the nuclear grade and the histopathologic pattern. In cases of borderline epithelial lesions, e-cadherin staining may be useful to distinguish DCIS from lobular carcinoma in situ, where expression of this cellular adhesion molecule is lost.

**Selection of Breast-Conserving Surgery vs Mastectomy**

Mastectomy is the oldest treatment for DCIS and is preferred in the following clinical scenarios:

1. patients with diffuse, suspicious-appearing microcalcifications in the breast;
2. inability to obtain margin control by lumpectomy and/or re-excision(s);
3. patients with a medical contraindication to chest wall irradiation (XRT) or who lack access to XRT;
4. suboptimal tumor to breast size ratio, where a margin-negative lumpectomy will yield an unacceptable cosmetic result (as defined by the patient).

Mastectomy and lumpectomy have never been directly compared in a prospective randomized trial designed for DCIS patients. However, comparable survival has been confirmed by indirect comparisons from retrospective studies, and from DCIS patients who were incidentally included in the National Surgical Adjuvant Breast Project B-06 trial (1). The B-06 trial was designed to evaluate the outcome of approximately 1800 stage I and II breast cancer patients treated by breast conserving surgeries (with or without breast irradiation) or by mastectomy. Centralized pathology review subsequently identified 78 cases of DCIS who were randomized as well (1) and were equally divided between the three study arms. As shown in Table 1, the overall survival for all three arms was similar (approximately 96% at 6 years), but the addition of breast irradiation to lumpectomy decreased LR from 43% to 7%.

Past studies of mastectomy performed for DCIS revealed axillary metastases in approximately 2% of DCIS cases. It is commonly assumed that these are related to a focus of invasive disease in the breast that was not readily apparent in pathological tissue sampling. This low risk of detecting nodal disease and the wish to minimize risk of lymphedema prompted most surgeons to abandon the routine practice of performing an axillary lymph node dissection in DCIS patients. For those patients requiring a mastectomy because of diffuse DCIS, the need for axillary staging becomes more relevant because of the associated increased risk of coexisting microinvasion. In these cases, the standard contemporary approach is to perform minimally invasive axillary staging with lymphatic mapping and sentinel lymph node biopsy.

Several retrospective studies (11–24) have reported outcome from DCIS managed by lumpectomy, with or without breast irradiation, and mastectomy. As expected, lumpectomy alone resulted in consistently higher rates of LR (range, 8%–34%) in comparison with patients treated by lumpectomy and breast radiation (range, 0%–17%). Risk factors for LR varied between studies, with involved margin status, young age at diagnosis, and high-grade tumors, with comedonecrosis being the most commonly cited predictors. Although inadequate margin control was frequently implicated in risk for developing LR, there was notable variation between studies regarding the optimal thickness of a negative margin. Furthermore, as noted in a meta-analysis of breast conservation studies for DCIS by Boyages et al. (24), studies published before 1998 often neglected to include margin status in their analyses. In the more recent studies, a negative margin was variously defined as a minimum of 1, 2, or 3 mm of microscopically normal tissue at the inked lumpectomy borders. Regardless of the definition, within studies, the risk of LR was usually lower for subsets where margin control was achieved. Tamoxifen may be added to the therapeutic regimen to further reduce the risk of new and/or recurrent breast events in patients with estrogen receptor–positive DCIS, after a thorough discussion of potential adverse side effects. The National Surgical Adjuvant Breast Project B-24 (6) trial reported that tamoxifen reduced the risk of invasive recurrences after lumpectomy and radiation.

Because of the expense, inconvenience, and potential adverse effects of XRT, its routine use following lumpectomy for “low-risk” DCIS has been questioned. The obvious candidates would be small-volume low-grade DCIS with widely negative margins on lumpectomy. Some groups have developed grading systems that stratify DCIS patients based on the risk of developing LR. The most popular of these is the Van Nuys Prognostic Index, developed by Silverstein et al. (25), and based on the detailed pathology analyses and follow-up of several hundred DCIS patients.

Several groups have implemented studies designed to evaluate the long-term results of treating highly selected subsets of DCIS patients by lumpectomy alone. One such study, conducted by the Dana-Farber/Harvard Cancer Center, used DCIS grade 1 or 2, size up to 2.5 cm, and final margins of at least 1 cm as eligibility criteria. After accrual of 157 patients (out of an accrual goal of 200), the early closure of this study was recently reported (26) because of an excessive LR rate. At a median follow-up of 40 months, 13 patients experienced an LR (nine were invasive recurrences), corresponding to a 5-year rate of 12.5% and a per annum rate of 2.5% per patient-year.

**Management of Prior Core Needle Biopsy Tract(s) at Time of Definitive Surgery**

Surgeons will routinely resect a prior diagnostic open surgical biopsy incision en bloc with the definitive mastectomy or lumpectomy incision because this approach minimizes tunneling and leaves healthier,
Table 1. Results of prospective, randomized clinical trials evaluating treatment for DCIS*

<table>
<thead>
<tr>
<th>Study</th>
<th>NSABP B-06†(1)</th>
<th>EORTC (2,3)</th>
<th>NSABP B-17 (4,5)</th>
<th>NSABP B-24 (6)</th>
<th>UK/AZ (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility requirements</td>
<td>Designed to evaluate the safety of breast conservation for invasive breast cancer; inked margin tumor free</td>
<td>Designed to evaluate lumpectomy with vs without breast XRT; mammographically detected DCIS ≤5 cm; no margin specification</td>
<td>Designed to evaluate lumpectomy with vs without breast XRT; DCIS detected by mammogram or physical examination; inked margin tumor free</td>
<td>Designed to evaluate the added benefit of tamoxifen as adjuvant therapy for DCIS patients treated with lumpectomy and breast XRT; DCIS detected by mammogram or physical examination; inked margin tumor free</td>
<td>Designed to assess the effectiveness of adjuvant tamoxifen and/or XRT after lumpectomy; DCIS respectable by lumpectomy; inked margin tumor free</td>
</tr>
<tr>
<td>Average follow-up (mo.)</td>
<td>83</td>
<td>65</td>
<td>90</td>
<td>74</td>
<td>53</td>
</tr>
<tr>
<td>Randomization arms</td>
<td>Lump</td>
<td>Lump + XRT</td>
<td>Mastectomy</td>
<td>Lump</td>
<td>Lump + XRT</td>
</tr>
<tr>
<td>No. of patients</td>
<td>21</td>
<td>27</td>
<td>28</td>
<td>426</td>
<td>437</td>
</tr>
<tr>
<td>No. of local recurrences, %</td>
<td>5/9 (45)</td>
<td>1/2 (50)</td>
<td>NA</td>
<td>37/83 (44)</td>
<td>23/54 (45)</td>
</tr>
<tr>
<td>Overall survival (all causes), %</td>
<td>96</td>
<td>96</td>
<td>96</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Risk factors for local recurrence</td>
<td>Lack of XRT; age &lt;40 y; symptomatic DCIS; involved margins; solid/cribriform/ comedo patterns</td>
<td>Lack of XRT; age &lt;40 y; symptomatic DCIS; involved margins; solid/cribriform/ comedo patterns</td>
<td>Lack of XRT; calcifications on mammogram</td>
<td>Lack of XRT; calcifications on mammogram</td>
<td>Lack of XRT; age &lt;50 y; involved margins; comedonecrosis; symptomatic DCIS</td>
</tr>
</tbody>
</table>

* DCIS = Ductal carcinoma in situ; EORTC = European Organization for the Research and Treatment of Cancer; Lump = lumpectomy; NA = not applicable; NR = not reported; NSABP = National Surgical Adjuvant Breast and Bowel Project; Symptomatic DCIS = palpable mass, nipple discharge; Tam = tamoxifen; UK/AZ = DCIS trialists in the United Kingdom, Australia, and New Zealand; XRT = breast irradiation.
† Seventy-six cases randomized in NSABP B-06 were found to be pure DCIS on retrospective pathology review.
“fresh” skin edges for definitive closure. However, the need for routine resection of percutaneous core needle biopsy tracts has been questioned. The needle biopsy tract can be quite long and the needle insertion site is occasionally quite remote from the actual target lesion. The surgeon must therefore decide whether to ignore the percutaneous biopsy puncture site, or to include it in the definitive resection, as has been recommended by some investigators (27,28).

The latter strategy can potentially have an adverse impact on cosmesis with either a lumpectomy or a skin-sparing mastectomy. Several investigators have therefore evaluated LR, needle biopsy, and needle tract seeding issues, and most have found no significant evidence of a correlation; however, precise documentation was generally not provided regarding whether the needle biopsy tract and skin insertion sites were completely resected (29–34). Thurfell et al. (35) identified 3 cases of LR out of 303 lumpectomy patients where the recurrence was thought to be related to prior needle tract seeding. In all three of these cases, the patients underwent lumpectomy without breast radiation, and the authors speculated that breast radiation might have added therapeutic value in breast conservation surgery where the prior core needle biopsy tract is left behind. Other investigators have therefore explored the potential impact of needle tract seeding and LR in mastectomy cases, which will typically not require radiation therapy. Although initial percutaneous needle biopsy has certainly not been consistently identified as a risk factor for LR, a few case reports have identified patients with postmastectomy chest wall recurrence detected at a prior needle biopsy site (28,36). Because LR is such a rare occurrence after mastectomy for DCIS, it is probably reasonable for the surgeon to be selective about cases where the needle puncture site and tract are excised, especially with a skin-sparing mastectomy and immediate reconstruction, where the resection of additional skin might substantially compromise the surgical aesthetics.

**Effect of Multiple Re-excisions on Local Control in Cases of Breast Conservation**

The need for re-excision to achieve margin control with lumpectomy is a well-accepted prerequisite for breast conservation. Although multiple re-excisions will likely have a negative impact on cosmesis (especially when followed by the shrinkage that accompanies whole-breast radiation), it is also appropriate to review the data regarding whether number of re-excisions might have an independent association with likelihood of achieving local control. Tartter et al. (37), Aziz et al. (38), and O’Sullivan et al. (39) have all evaluated local control rates following breast-conserving surgery (for both DCIS and invasive cancer) and found no significant correlation. The available data therefore suggest that local control is optimized by adequacy of the lumpectomy, regardless of the number of re-excisions required to achieve margin-negative status.

**Breast Specimen Handling**

The perioperative handling of the breast tissue (whether lumpectomy or mastectomy specimen) can effect subsequent pathology evaluation of margins and can therefore affect treatment decisions regarding re-excisions and/or radiation. As noted above, lumpectomy cases for mammographically detected DCIS should always include specimen mammography to confirm inclusion of the cancerous lesion, and the radiology team should be cautioned against excessive compression of the specimen with distortion of the lumpectomy margin surfaces. Postlumpectomy mammogram should be performed on the patient before proceeding to breast XRT (even if lumpectomy margins were negative) to rule out residual microcalcifications. The surgical and radiology team should confer in advance to insure consistency and appropriateness of mammographic imaging technology used pre- vs postoperatively. Application of specialized mammographic technology (such as digital imaging) in the post-lumpectomy setting can identify additional microcalcifications that may have been missed on conventional imaging performed in the preoperative setting, raising new questions regarding extent and adequacy of surgery. It is also useful to leave 6–10 radio-opaque surgical clips at the perimeter of the lumpectomy cavity. These clips can facilitate subsequent planning of XRT tangents, and they will also serve as targets for diagnostic views on long-term mammographic surveillance looking for recurrence.

Specimen handling with mastectomy cases can also be clinically relevant because, although rare, cases of chest wall recurrence after mastectomy performed for DCIS have been reported (40–44), and these LRs may occur as infiltrating or in situ lesions. Routine resection of the pectoralis fascia can strengthen confidence regarding the adequacy of the posterior margin (even if pathology review demonstrates DCIS approaching the deep surface of the breast tissue) because by definition the DCIS cannot invade adjacent anatomical structures. The anterior skin surface margin of the mastectomy specimen can be more challenging because skin flap thickness will vary according to body habitus and individual anatomy. This can be particularly concerning with the elongated flaps of a skin-sparing mastectomy performed with immediate reconstruction. The skin-sparing approach should be applied cautiously in patients that have diffuse, anteriorly based microcalcifications on mammogram. In these cases, extensive microscopic disease may compromise the superficial margin surface, and leave the patient at risk for residual DCIS and mammary tissue hidden within the subcutaneous fat. Rubio et al. (45) and Young et al. (46) have therefore both advocated in favor of mastectomy specimen mammography to guide intraoperative surgical decisions regarding the need for more aggressive skin and/or tissue resections.

Postmastectomy XRT has been recommended in cases of inadequate margin control for DCIS; however, the optimal margin thickness is not well defined, and whether the margin thickness should differ for anterior vs posterior surfaces is unclear. Vargas et al. (42) and Rashatian et al. (47) have both reported that margin thickness less than 2 mm is associated with risk of LR following mastectomy for DCIS, but collectively these retrospective studies dealt with fewer than 10 cases of chest wall failure, if the results must therefore be interpreted with caution.

**Summary**

Local therapy alone will successfully yield durable control of DCIS, and in-breast failure can be minimized after lumpectomy by obtaining negative margins and utilizing breast radiation. Initial diagnostic needle biopsy can enhance successful single-procedure lumpectomy results. Endocrine therapy for ER-positive DCIS can
also improve local control. Mastectomy performed for DCIS should be accompanied by axillary staging via sentinel lymph node biopsy in the event that an invasive component is identified. Postmastectomy XRT can be considered in cases of suspected inadequate margin control.

References


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