

# The Impact of Surgery on Ductal Carcinoma In Situ Outcomes: The Use of Mastectomy

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Mastectomy has been the historical mainstay of treatment for ductal carcinoma in situ (DCIS), but over time, there have been significant changes in its use for preinvasive breast cancer. Although there was an early reduction in mastectomy rates for DCIS with the introduction of breast-conserving surgery, in some groups, the rates of both mastectomy and contralateral mastectomy for DCIS have increased in recent years. Due to advances in breast cancer screening as well as improvements in breast reconstruction, mastectomy will continue to be an important and acceptable treatment option. Recurrence is rare following mastectomy for DCIS. Nevertheless, there remains a need to follow patients for in-breast, nodal, or contralateral breast events, which can occur long after the index DCIS has been treated. Since up to 70% of women with newly diagnosed DCIS have disease that can be managed with breast-conserving surgery, patient counseling is imperative to ensure the best use of this option for DCIS, given that mastectomy does not significantly impact survival in this setting.

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Genomic and phenotypic similarities between ductal carcinoma in situ (DCIS) and invasive breast cancer support that DCIS is likely a nonobligate precursor of invasive ductal cancer. Because it remains difficult to predict which individuals with DCIS will develop invasive cancer without excision, surgery has long been the mainstay of treatment for women diagnosed with DCIS. Presently in the United States, 97% of patients with DCIS undergo surgical excision, of which one-third will involve mastectomy (1,2). The most recent *NCCN Clinical Practice Guidelines in Oncology* (v.2.2010) recommend total mastectomy as one treatment option for DCIS (3). General guidelines for the use of mastectomy in DCIS have been suggested by an expert panel convened by the American College of Radiology (4) and recommend that patients with extensive and/or multifocal DCIS involving 4–5 cm of disease or more than one quadrant should be offered mastectomy. In addition to these patients, women with potential contraindications to breast irradiation or a strong preference for mastectomy over breast conservation have been considered appropriate candidates for this procedure.

In the United States, the use of mastectomy for treatment of DCIS has declined steadily. Among the cancer registries participating in the Surveillance, Epidemiology, and End Results (SEER) Program, 43% of women with DCIS underwent mastectomy in 1992 compared with 28% in 1999 (1). However, significant variations in surgical treatment patterns for DCIS persist among SEER sites: between 1997 and 2000, those treated with mastectomy for DCIS ranged from the highest rate of 50.5% in Utah to the lowest rate of 23.1% in Connecticut (5). Factors reported to be associated with a higher likelihood of mastectomy for DCIS have included young age at diagnosis, geographic site, and white race (5,6). Following treatment for DCIS, the risk of contralateral breast events has been shown to be 4.5/1000 person-

years (7). Despite this increased contralateral breast cancer risk, few women have previously undergone contralateral prophylactic surgery for DCIS. However, there has been a recent surge in the prevalence of contralateral prophylactic mastectomy (CPM), and between 1998 to 2005, the CPM rate in women with DCIS increased from 2.1% to 5.2% (8). Factors contributing to this increase most certainly include the inaccurate perception many women with DCIS harbor regarding their future risk for invasive cancer (9), although improved reconstructive outcomes and more widespread use of magnetic resonance imaging have also been proposed as contributing causes.

Various surgical approaches for mastectomy are currently used and include simple mastectomy (excision of breast tissue and overlying skin), skin-sparing mastectomy (removal of breast with preservation of the skin envelope), and most recently, nipple-preserving mastectomy techniques. None of these approaches appear to confer increased risk of local recurrence over the others, provided that conscientious attention is given to performing a complete excision of all apparent breast tissue (10–12). Nipple-sparing procedures have been more widely reported in the last few years, including for DCIS, and with short-term follow-up, the local recurrence risk has not exceeded 3% (13–15) with one study showing no recurrences in 15 cases of DCIS treated with nipple-sparing mastectomy at a median follow-up of 41 months (14). DCIS, as an intraductal lesion, may be expected to more frequently extend into the nipple. In fact, however, DCIS has been shown to less frequently involve the nipple–areolar complex than either invasive ductal carcinoma or invasive lobular carcinoma (16). The low recurrence rates reported in these studies may in part be attributed to appropriate selection criteria for nipple-sparing procedures and a low threshold to exclude patients with centrally located disease, extensive DCIS, or radiographic abnormalities in proximity to the nipple–areolar

complex. In aggregate, the studies reporting outcomes for DCIS treated with nipple-sparing mastectomy have shown that the procedure is oncologically safe; however, longer follow-up is required to confirm durable recurrence-free survival with this approach.

Reconstruction is often used following mastectomy for DCIS. Considerations regarding breast reconstruction do not differ substantially from those for patients with invasive breast cancer, with the one notable exception being that women with DCIS less frequently undergo postmastectomy radiation therapy (PMRT). Indications for postmastectomy radiation in the setting of DCIS remain controversial and limited, with no DCIS group shown to derive consistent clinical benefit from PMRT. Few patients are considered to have sufficiently high risk to justify PMRT, but based on clinical parameters such as extent of disease, high grade, positive margins, or young age, radiation may occasionally be given. This recommendation is supported by two studies, which reported long-term recurrence rates of 16% and 11% for mastectomy margins of less than or equal to 2 mm (11,17). In contrast, we have found an 8-year locoregional recurrence rate below 2% in women with close or positive margins after mastectomy without radiation (18). These few and discrepant studies support a selective use of PMRT for DCIS. The resulting low rate of PMRT in women treated with mastectomy for DCIS makes this group especially well suited for immediate reconstructive options, possibly combined with nipple-sparing techniques in carefully selected candidates.

Clinical outcomes following mastectomy for DCIS are excellent, with both clinical trial and population-based studies consistently reporting a 1%–2% rate of local recurrence with long-term follow-up compared with approximately 10%–15% following breast conservation and radiation (19–22). The increased local recurrence risk with breast conservation has not been shown to affect breast cancer–specific survival when compared to patients undergoing mastectomy for DCIS, with both groups exhibiting up to a 99% long-term breast cancer–specific survival (19,23). The National Surgical Adjuvant Breast and Bowel Project has reported that in their DCIS trials, women with DCIS who recur with invasive cancer after treatment have a twofold greater mortality risk relative to those without invasive recurrence (hazard ratio = 2.08, 95% confidence interval = 1.46% to 2.98%) (24). Thus, although the risk of local recurrence is low, there is some evidence to suggest that suboptimal locoregional therapy may affect long-term outcome if there is progression to invasive cancer.

Although isolated nodal recurrences and distant recurrences are occasionally encountered following mastectomy for DCIS, the majority of local recurrences present as an invasive focus on the chest wall detected by palpation (11). To date, no comprehensive studies of local recurrences after mastectomy for DCIS have been reported. A small review of 10 chest wall recurrences in this setting has suggested that young age and multifocality are associated with increased risk of locoregional failure (25). One recent study reported a series of 80 patients who had undergone mastectomy for DCIS and had margins <10 mm (17). At a median follow-up of 61 months, six patients (7.5%) had a local recurrence. In this study, recurrences were associated with high grade and margin of less than or equal to 2 mm. Young age (defined as <60 years) was again identified as a risk factor for recurrence. However, as discussed

above, PMRT is rarely recommended even in “high-risk” patients, and indications for its use in the setting of DCIS have not been established. Fortunately, in women with isolated locoregional recurrence after mastectomy for DCIS, surgical excision combined with chest wall radiation has been an effective treatment strategy and has been associated with excellent long-term disease-free survival (25).

Because of the low risk of nodal extension in DCIS, routine axillary dissection is no longer recommended in this setting. Nevertheless, until recently, more than 30% of mastectomies for DCIS still included axillary lymph node dissection (1). Many advocate for the use of sentinel node biopsy in patients undergoing mastectomy for DCIS because subsequent sentinel node biopsy may be technically difficult following division of lymphatic channels in the axillary tail. The 10%–20% upstaging of DCIS to invasive stage I or II breast cancer following definitive surgery further supports sentinel node biopsy in women undergoing mastectomy for DCIS as it obviates the need for a second surgery if invasive cancer is identified upon excision (26). In one study of 470 patients with DCIS who underwent sentinel node biopsy, 9% of patients were found to have a positive sentinel node. The majority (84%) had isolated tumor cells only ( $\leq 0.2$  mm), which were not detected on H and E staining (27). The clinical significance of such a finding remains in doubt. At this time, sentinel node biopsy should be considered for those patients with increased likelihood of invasive cancer, including those with multiquadrant disease, extensive comedonecrosis, or radiographic findings suspicious for invasive cancer. If a positive node is identified, the patient is likely at increased risk for distant disease as nodal involvement suggests the presence of undetected invasive cancer. Consequently, most women with DCIS and nodal metastases will be recommended both axillary dissection and systemic therapy. It remains to be seen whether the long-term prognosis for patients with node-positive DCIS differs from that of other DCIS patients.

Systemic hormonal therapy has a limited role following mastectomy for DCIS. In National Surgical Adjuvant Breast and Bowel Project B-24, a randomized controlled study of tamoxifen following lumpectomy and radiation for DCIS, there was a 2% incidence of contralateral breast events at a median follow-up of 74 months. Women treated in the tamoxifen arm had 74% fewer invasive cancer events and 78% fewer contralateral DCIS compared with the placebo group (21). This benefit appeared to be confined largely to the estrogen receptor (positive) group (28), although these data await validation. Cuzick et al. (29) have recently reported a 29% reduction in recurrent ipsilateral DCIS with tamoxifen (hazard ratio = 0.71, 95% confidence interval = 0.58%–0.88%) (29). Given the low rate of ipsilateral breast events in women following mastectomy for DCIS, tamoxifen does not confer a significant benefit to the ipsilateral breast. Thus, the greatest impact of systemic hormonal therapy after mastectomy for DCIS may be to the contralateral breast, with younger women with longest life expectancy likely to benefit most.

## Conclusions

Although mastectomy is the most invasive surgical treatment for DCIS, it remains the gold standard for long-term locoregional

control. Mastectomy is the recommended surgical option for women with extensive or multicentric disease. However, it has not been shown to improve breast cancer-specific survival in women with DCIS. It is possible that improvements in surgical technique, including better outcomes from breast reconstruction, have recently led to an unintended consequence of increased rates for both ipsilateral and contralateral prophylactic mastectomy. Thus, even as we gain greater insight into strategies to reduce the risk of invasive cancer in DCIS, it is imperative that efforts also be focused on understanding how women make surgical treatment decisions for DCIS to maximize the benefit and minimize the morbidity resulting from treatment. This is particularly important as DCIS continues to be a disease for which invasive potential and clinical impact are as yet poorly defined. Fundamental to progress in this regard will be a greater emphasis on identifying tools to more accurately communicate the risk associated with both the disease and its treatment in patients diagnosed with DCIS.

## References

- Baxter NN, Virnig BA, Durham SB, Tuttle TM. Trends in the treatment of ductal carcinoma in situ of the breast. *J Natl Cancer Inst.* 2004;96(6):443–448.
- Burstein HJ, Polyak K, Wong JS, Lester SC, Kaelin CM. Ductal carcinoma in situ of the breast. *N Engl J Med.* 2004;350(14):1430–1441.
- NCCN Clinical Practice Guidelines in Oncology: Breast Cancer v.2.2010. National Comprehensive Cancer Network; 2010.
- Rabinovitch R, Solin L, Shank B, et al. Expert Panel on Radiation Oncology-Breast Work Group. Ductal carcinoma in situ. [online publication]. Reston, VA: American College of Radiology; 2006.
- Joslyn SA. Ductal carcinoma in situ: trends in geographic, temporal, and demographic patterns of care and survival. *Breast J.* 2006;12(1):20–27.
- Nassar H, Sharafaldeen B, Visvanathan K, Visscher D. Ductal carcinoma in situ in African American versus Caucasian American women: analysis of clinicopathologic features and outcome. *Cancer.* 2009;115(14):3181–3188.
- Li CI, Malone KE, Saltzman BS, Daling JR. Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988–2001. *Cancer.* 2006;106(10):2104–2112.
- Tuttle TM, Jarosek S, Habermann EB, et al. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. *J Clin Oncol.* 2009;27(9):1362–1367.
- Partridge A, Adloff K, Blood E, et al. Risk perceptions and psychosocial outcomes of women with ductal carcinoma in situ: longitudinal results from a cohort study. *J Natl Cancer Inst.* 2008;100(4):243–251.
- Fisher DE, Schnitt SJ, Christian R, Harris JR, Henderson IC. Chest wall recurrence of ductal carcinoma in situ of the breast after mastectomy. *Cancer.* 1993;71(10):3025–3028.
- Carlson GW, Page A, Johnson E, Nicholson K, Styblo TM, Wood WC. Local recurrence of ductal carcinoma in situ after skin-sparing mastectomy. *J Am Coll Surg.* 2007;204(5):1074–1078; discussion 8–80.
- Gerber B, Krause A, Dieterich M, Reimer T, Kundt G. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. *Ann Surg.* 2009;249(3):461–468.
- Garwood ER, Moore D, Ewing C, et al. Total skin-sparing mastectomy: complications and local recurrence rates in 2 cohorts of patients. *Ann Surg.* 2009;249(1):26–32.
- Crowe JP, Patrick RJ, Yetman RJ, Djohan R. Nipple-sparing mastectomy update: one hundred forty-nine procedures and clinical outcomes. *Arch Surg.* 2008;143(11):1106–1110.
- Kim HJ, Park EH, Lim WS, et al. Nipple areola skin-sparing mastectomy with immediate transverse rectus abdominis musculocutaneous flap reconstruction is an oncologically safe procedure: a single center study. *Ann Surg.* 2010;251(3):493–498.
- Brachtel EF, Rusby JE, Michaelson JS, et al. Occult nipple involvement in breast cancer: clinicopathologic findings in 316 consecutive mastectomy specimens. *J Clin Oncol.* 2009;27(30):4948–4954.
- Rashtian A, Iganej S, Amy Liu IL, Natarajan S. Close or positive margins after mastectomy for DCIS: pattern of relapse and potential indications for radiotherapy. *Int J Radiat Oncol Biol Phys.* 2008;72(4):1016–1020.
- Chan LW, Rabban J, Fowble B, et al. Is radiation indicated in patients with DCIS and close/positive mastectomy margins? *Int J Radiat Oncol Biol Phys.* 2008;72:S151.
- Lee LA, Silverstein MJ, Chung CT, et al. Breast cancer-specific mortality after invasive local recurrence in patients with ductal carcinoma-in-situ of the breast. *Am J Surg.* 2006;192(4):416–419.
- Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol.* 1998;16(2):441–452.
- Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet.* 1999;353(9169):1993–2000.
- Schouten van der Velden AP, van Vugt R, Van Dijck JA, Leer JW, Wobbes T. Local recurrences after different treatment strategies for ductal carcinoma in situ of the breast: a population-based study in the East Netherlands. *Int J Radiat Oncol Biol Phys.* 2007;69(3):703–710.
- Silverstein MJ, Buchanan C. Ductal carcinoma in situ: USC/Van Nuys Prognostic Index and the impact of margin status. *Breast.* 2003;12(6):457–471.
- Wapnir I, Dignam J, Julian TB, et al. Long-term outcomes after invasive breast tumor recurrence (IBTR) in women with DCIS in NSABP B-17 and B-24 [2007 ASCO Annual Meeting Proceedings Part I]. *J Clin Oncol.* 2007;25(18S):520.
- Kim JH, Tavassoli F, Haffty BG. Chest wall relapse after mastectomy for ductal carcinoma in situ: a report of 10 cases with a review of the literature. *Cancer J.* 2006;12(2):92–101.
- Dominguez FJ, Golshan M, Black DM, et al. Sentinel node biopsy is important in mastectomy for ductal carcinoma in situ. *Ann Surg Oncol.* 2008;15(1):268–273.
- Moore KH, Sweeney KJ, Wilson ME, et al. Outcomes for women with ductal carcinoma-in-situ and a positive sentinel node: a multi-institutional audit. *Ann Surg Oncol.* 2007;14(10):2911–2917.
- Allred DC. Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: findings from NSABP Protocol B-24. *Breast Cancer Res Treat.* 2002;76(suppl 1):S36.
- Cuzick J, Sestak I, Pinder S, et al. Beneficial effect of tamoxifen for women with DCIS: long-term results from the UK/ANZ DCIS trial in women with locally excised DCIS. *Cancer Res.* 2009;69(suppl):493s.

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