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Review

Ductal carcinoma in situ current trends, controversies, and review of literature

Young K. Hong, Kelly M. McMasters, Michael E. Egger, Nicolas Ajkay*

[a] Division of Surgical Oncology, Department of Surgery, University of Louisville, USA

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ABSTRACT

Ductal carcinoma in situ (DCIS) is a non-obligate precursor, non-invasive malignancy confined within the basement membrane of the breast ductal system. There is a wide variation in the natural history of DCIS with an estimated incidence of progression to invasive ductal carcinoma being at least 13%–50% over a range of 10 or more years after initial diagnosis. Regardless of the treatment strategy, long-term survival is excellent. The controversy surrounding DCIS relates to preventing under-treatment, while also avoiding unnecessary treatments. In this article, we review the incidence, presentation, management options and surveillance of DCIS. Furthermore, we address several current controversies related to the management of DCIS, including margin status, sentinel node biopsy, hormonal therapy, the role of radiation in breast conservation surgery, and various risk stratification schemes.

Introduction

Ductal carcinoma in situ (DCIS) is a precursor, non-invasive lesion of malignant epithelial cells confined within the basement membrane of the terminal duct lobar units of the breast.[1] The development model of invasive ductal carcinoma (IDC) is the sequential progression of hyperplasia, atypical ductal hyperplasia, DCIS and ultimately IDC. However, the progression from DCIS to IDC is not absolute. There will be a progression to IDC in at least 13%–50% of cases, but predicting which DCIS lesions will progress is difficult.[2] DCIS-associated mortality is low, with the expected cumulative breast cancer mortality ten years after DCIS estimated to be 2.3% for women <50 years of age and 1.4% for women >50 years of age after treatment.[3] Because of these excellent long-term outcomes, there are various prognostic variables including genetic profiling, grade, necrosis, morphology, and size that are routinely evaluated to guide the management of DCIS in efforts to minimize over-treatment. It is especially important as the incidence of DCIS has increased in the last 20 years for all races and all ages as a result of the increased utilization of screening mammography.[4] The incidence in 1994 was 22.31 per 100,000 and increased to 34.43 per 100,000 by 2014, with nearly 15–30% of the breast disease detected in screening mammography being DCIS. The increase in incidence is higher for black females, with 20.10 per 100,000 females in 1994 to 37.38 per 100,000 at all ages in 2014, compared to white females, with 22.87 per 100,000 in 1994 to 33.57 per 100,000 in 2014. The most significant rise in incidence for DCIS was in black females older than 50 years of age with 52.96 per 100,000 in 1994 to 103.88 per 100,000 by 2014.[5]

Presentation and histologic diagnosis

Patients with DCIS are typically diagnosed by screening mammography that detects atypical calcifications rather than by having a palpable lesion. A recent analysis of pure DCIS identified by various imaging techniques revealed that 44% were visible by both mammography and sonography, 46% were detectable by mammography only, 8% by sonography only, and 2% were not detected by either mammography or sonography.[6] Nuclear grade or comedo necrosis did not impact the ability to visualize these lesions.

The management of breast disease is critically dependent upon the pathologist who diagnoses the breast core biopsies. Unfortunately, there may be a wide range of discordance in the accuracy and consistency of breast biopsy results between different centers due to variable case volumes and private versus academic settings. This discordance may be greater in DCIS than IDC. In a study by Elmore et al. the level of diagnostic agreement between expert pathologists and those with lesser expertise was high at 96% (95%

* Corresponding author. Breast Surgical Oncology, University of Louisville, 315 East Broadway (M10), Louisville, KY 40202, USA.
E-mail address: nicolas.ajkay@louisville.edu (N. Ajkay).

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CI, 94–97%) for invasive carcinoma, but lower for DCIS at 84% (95% CI, 82–86%). There were 3% (95% CI, 2–4%) incidence of over-interpretation of DCIS to IDC, 13% (95% CI, 12–15%) incidence of under-interpretation of DCIS to atypia and 17% (95% CI, 15–21%) incidence of over-interpretation of atypia to DCIS.[7] Therefore, it is important to recognize the possibility of under or over-interpretation for DCIS within pathologist of different levels of expertise. Obtaining a second opinion may be one prudent way to avoid the risk of unnecessary treatments.

Current studies by Holland and Hendricks demonstrate that DCIS is usually confined to a single segment of the breast and rarely multifocal.[8] However, Faverly studied the growth pattern of DCIS within the duct system and demonstrated that in 63% of the cases, there is a discontiguous pattern with uninvolved gaps, usually up to 5 mm.[9] There was a continuous pattern of DCIS in 90% of the high grade, but only 30% and 45% of intermediate and well-differentiated DCIS demonstrated a continuous pattern. Therefore, it is essential to assess adequate margin after resection of DCIS as there are discontiguous lesions. Overall, an accurate histologic diagnosis—including grade, histologic type, the presence of calcifications, estrogen, and progesterone—as well as understanding the distribution of DCIS, is paramount to adequate treatment planning.

Treatment options

Multiple treatment options exist for patients with DCIS ranging from no surgery,[10] lumpectomy alone, lumpectomy with radiation,[11] unilateral mastectomy with sentinel lymph node biopsy, and bilateral mastectomy with ipsilateral sentinel lymph node biopsy. A recent SEER database analysis reported the utilization of these treatment options for DCIS from 1991 to 2010 with 43% treated by lumpectomy and radiation, 26.5% with lumpectomy alone, 23.8% with unilateral mastectomy, and 4.5% with a bilateral mastectomy. There was a significant increase of lumpectomy with radiation (24.2%–46.8%), bilateral mastectomy (0–8.5%) and no treatment (1.2–3.2%) over time. There were significant reductions in unilateral mastectomy (44.9–19.3%) and lumpectomy alone (29.8–22.3%).[12]

Surgical management

Mastectomy

Total mastectomy is a very valid option for any patient with DCIS because of its low local recurrence rate of 1–3% at ten years.[13] The current clinical indications for mastectomy are high-risk features of DCIS, i.e., multicentricity and diffuse involvement requiring extensive breast parenchymal resection with prohibitive cosmetic results. Nipple-sparing mastectomy is also selectively used in patients with DCIS without increased recurrence.[14] However, the local recurrence rate after skin-sparing mastectomy was higher (8-year local-recurrence rate 5.6% vs. 0%) when compared to simple mastectomy in a cohort of 199 patients undergoing mastectomy for DCIS.[15] Therefore, total mastectomy is an effective treatment for those who have extensive or multicentric DCIS, that would result in cosmetically unacceptable results after lumpectomy, and for those who are unwilling or unable to undergo radiation therapy.

Breast conservation and radiation therapy

The management of breast conservation with lumpectomy in combination with, or without radiation had also prompted a great debate about the benefit of adjuvant radiation therapy after lumpectomy. As a result, four randomized trials (NSABP B-17,[16] EORTC,[17] UK/ANZ,[18] and Swedish Breast Cancer Group)[19] were performed to answer this question. These studies demonstrated a consistent benefit of radiation therapy in combination with breast conservation compared with breast conservation alone (Table 1.).[20,21] A meta-analysis by the Early Breast Cancer Trialists Collaborative Group [EBCTCG] found radiotherapy to decrease the 10-year risk of ipsilateral breast event of DCIS or invasive carcinoma by 15.2% (12.9% vs. 28.1% $p < 0.0001$) regardless of age of diagnosis, extent of breast-conserving surgery, tamoxifen, method of DCIS diagnosis, margin status, focality, grade, comedo necrosis, architecture, or tumor size.[22] Therefore, we recommend routine use of adjuvant radiation therapy after breast conservation therapy for DCIS.

Sentinel node biopsy

The examination of the axillary contents for DCIS is indicated only for selected patients given that axillary involvement without invasion of the basement membrane is rare,[23] and the risk of lymphedema after sentinel lymph node biopsy is not negligible (5%).[24] However, a recent meta-analysis reported a risk of discordance of core needle biopsy results with the final surgical specimen. Knuttel et al. demonstrated a nearly 19.1% (95% CI, 18.1–21.3) under-estimation and 9.3% (95% CI, 7.7–11.4%) over-estimation of grade with core needle biopsy compared to final pathology.[25] Researchers at Memorial Sloan-Kettering looked at the incidence of positive sentinel nodes after DCIS in 470 high-risk patients and noted 43 patients (9%) had positive sentinel lymph nodes.[26] As a result, there is a risk for upstaging DCIS to invasive carcinoma on final pathology and a need to rule out axillary lymph node involvement in these patients. The American Society of Clinical Oncology Clinical Practice Guideline recommends sentinel lymph node biopsy (SLNB) for women with DCIS planning to receive a mastectomy, large size of DCIS (>5 cm), multicentric disease, or mass lesion diagnosed by imaging study or clinical exam that is suspicious for invasive cancer. SLNB performed after mastectomy is technically challenging and potentially inaccurate because of disruption of the lymphatic drainage.[27,28] Only 1%–2% of patients with pure DCIS will have axillary nodal metastasis, undoubtedly from invasive occult cancer.[27] Patients from NSABP B-17 and B-24 had an ipsilateral nodal recurrence risk of less than 1%, regardless of the use of radiation or tamoxifen.[29] Thus, routine assessment of axillary staging for DCIS is unnecessary except for high-risk cases when the risk of occult IDC is high or planned mastectomy. The reason to perform SLN biopsy for patients undergoing mastectomy is the inability to perform it later in the event invasive cancer is detected.

Hormonal therapy

NSABP B-24 demonstrated the benefit of adjuvant hormone therapy for DCIS after breast-conserving surgery with lumpectomy and radiation.[30] Patients with estrogen-receptor- (ER) or progesterone-receptor (PR)-positive DCIS were administered tamoxifen as adjuvant therapy (76% of eligible patients enrolled in the study). At ten years, patients receiving adjuvant tamoxifen who had positive hormone DCIS demonstrated a significant decrease in the risk of breast cancer recurrence (HR 0.49; $p < 0.001$). However, for patients with ER-negative DCIS, there was no benefit to adjuvant tamoxifen.[30] In post-menopausal women, NSABP B-35 assessed the benefit of anastrozole versus tamoxifen as adjuvant hormone therapy after breast conservation surgery. For patients older than 60 years of age, there was similar efficacy in the two drug treatments. However, when compared to patients younger than 60 years of age, there was a lower risk of ipsilateral breast tumor recurrence with anastrozole.[31] To assess the individual role of hormonal therapy and radiation therapy versus observation, the UK/ANZ study randomized in 2×2 factorial design for observation, adjuvant radiation with tamoxifen, radiation alone, or tamoxifen alone for patients with DCIS treated with lumpectomy. A total of

Table 1
Summary of the effect of radiotherapy on breast conservation for DCIS.
NSABPB-17[16] and EORTC[17]UK/ANZ[18], NSABP B-17[16], EORTC[17], UK/ANZ[18], Swedish Breast Cancer Group[19] trials demonstrate the importance of reduction of ipsilateral breast cancer recurrence for patients who undergo breast conservation therapy.

			% Ipsilateral Breast Cancer Recurrence				% Breast Cancer Specific Survival	
			Lumpectomy Alone		Lumpectomy + Radiotherapy			
Trial	N	Median F/U (years)	All	Invasive	All	Invasive	Lumpectomy	Lumpectomy + RT
NASBP B-17	813	17.25	35%	20%	20%	11%	96.9%	95.3%
EORTC 10853	1010	10.5	26%	13%	15%	8%	96%	96%
UK/ANZ	1030	12.7	19%	9.1%	7.1%	3.3%	97.3%	98.5%
SweDCIS	1046	8.4	27%	12%	12%	7.2%	97.1%	96%

1694 patients were randomized with a median follow-up of 12.7 years. Radiation therapy was noted to have a risk reduction of ipsilateral breast events (HR 0.41, 95%CI 0.30–0.56; $p < 0.0001$) but did not have any effect on contralateral breast events. However, tamoxifen demonstrated an all-breast-risk reduction, with a decrease of ipsilateral DCIS recurrence (HR 0.70, 0.51–0.86; $p = 0.03$) and contralateral events (HR 0.44, 0.25–0.77; $p = 0.005$), but no effect on ipsilateral invasive disease (HR 0.95, 0.66–1.38; $p = 0.80$).[18] Despite the clear benefit of hormone therapy for ER-positive DCIS, hormone therapy is recommended in fewer than 40% of patients, and less than a third of the patients will comply with this therapy.[32]

Controversies

Lumpectomy alone vs. lumpectomy and radiation

The growing concern of over-treatment for DCIS has raised the possibility of observation alone after lumpectomy for low-risk DCIS. The NSABP B-17 trial randomized patients to lumpectomy alone versus lumpectomy and radiation to assess ipsilateral breast tumor recurrence (IBTR) and survival benefit.[33] After a median follow up of 207 months, there was a significant 52% risk reduction of IBTR in the lumpectomy with radiation group compared to lumpectomy alone.[33] The recent prospective randomized trial RTOG 9804, evaluated 636 patients who had less than 2.5 cm of low to intermediate grade DCIS and greater than 3 mm margin width. They were randomized to lumpectomy alone versus lumpectomy with radiation. The local failure rate for observation after lumpectomy was 6.7% (95% CI, 3.2%–9.6%) compared to 0.9% (95% CI, 0.0%–2.2%) in the adjuvant radiation therapy arm at median follow-up of 7 years.[34] Silverstein et al. argued that the recurrence rates of patients after wide local excision of DCIS alone versus those with wide local excision and radiation were similar. This argument raised the question of the role of radiation therapy in DCIS for low-risk DCIS excised with wide margins.[35] However, Wong JS. et al. conducted a prospective, single-arm trial of 158 patients with 2.5 cm or less, grade 1 or 2, DCIS with a final margin of 1 cm or greater treated with wide excision alone. The trial closed to accrual early due to a significant increase in local recurrence of 2.4% per patient per year, and a 5-year local recurrence rate of 12%.[36] Wong et al. had higher recurrence rates than the study by Silverstein et al., and have been criticized for not accounting for DCIS with necrosis. According to the Van Nuys criteria, DCIS with necrosis should have been considered as a high recurrence risk factor.[37]

The ECOG-ACRIN E5194 Study was a non-randomized, prospective clinical trial that evaluated the 12-year risk of developing an ipsilateral breast event (IBE) for women with DCIS after lumpectomy without radiation. Unlike the RTOG 9804 which only included low-intermediate grade DCIS, the E5194 group stratified by low-intermediate grade DCIS <2.5 cm versus high-grade DCIS 1 cm or smaller. The 12-year risk of IBE was 14.4% for the low-intermediate group versus 24.6% for the high-grade DCIS group with no evidence of plateau reached at the 12-year endpoint ($p = 0.003$).[38] Similarly, Wai et al. evaluated a group of patients treated with lumpectomy alone and confirmed a higher 10-year local recurrence risk of 15%–30% with comedo histology, high nuclear grade, tumor size > 5 cm or indeterminate size, and positive margins.[39]

The preponderance of the evidence, which includes level 1 randomized clinical trials, has yet to be able to identify a low-risk group in whom adjuvant radiation therapy can be omitted after segmental mastectomy for DCIS with acceptable ipsilateral breast recurrence rates. Until such a group has been identified, adjuvant

radiotherapy should be strongly considered in all patients with reasonable life expectancy and acceptable medical comorbidities after segmental mastectomy for DCIS.

Risk stratification

The Van Nuys Prognostic Index (VNPI) was first described in 1996 as a decision-making tool for the management of DCIS using four prognostic factors which include age, tumor size, margin width, and pathologic classification (nuclear grade and presence of comedo necrosis).[40] The initial scoring system correlated with treatment recommendations of excision only for low scores of 3 or 4, radiation therapy for intermediate scores of 5, 6, or 7, and consideration for mastectomy for high scores of 8 or 9. However, the scoring system was later changed to a higher threshold for radiation with scores of 7–9 and mastectomy for 10–12. The reason for the adjustment was because of no change in recurrence rates at 12 years for those with or without radiation for scores 4–6 compared to 15% local recurrence reduction for those receiving radiation for scores 7–9. Mastectomy is recommended for scores in the high-risk group of 10–12 due to recurrence of nearly 50% at 5 years.[41] The VNPI continues to change to the actual cutoff for risk assessment management as the number of patients in the database increases.[42] However, there has been some criticism of the VNPI due to lack of assessment of estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2) and endocrine therapy in their risk assessment, which could have affected the local recurrence rates in their analysis.[43]

The Memorial Sloan-Kettering Nomogram for DCIS by Rudloff et al. in 2010 used 10 clinicopathologic variables (age at diagnosis, family history, initial presentation, radiation, adjuvant endocrine therapy, nuclear grade, necrosis, margins, number of excisions, year of surgery) to predict 5- and 10- year IBTR in 1868 patients from 1991 to 2006. The variables deemed to have the highest influence on predicting IBTR included adjuvant radiation therapy or endocrine therapy, age, margin status, number of excisions, and treatment period.[44] This nomogram was the first to attempt to predict the IBTR after resection of DCIS based on several risk factors. Critics of this nomogram cite the of lack external validation, not including the size of DCIS as a variable, and inclusion of endocrine therapy (given it is not currently standard practice outside of the US).[45,46] Since then, several external validations of the nomogram have been performed in several retrospective analyses of patient databases with excellent correlation of predicted compared to observed local recurrences (10-year risk estimate c-statistic range of 0.61–0.68), and therefore it is a useful treatment decision aid for patients with DCIS.[47,48]

Another strategy to stratify patients with variable levels of aggressive DCIS is to analyze their molecular prognostic markers using a 12-gene Recurrence Score assay or Oncotype Dx DCIS (Genomic Health, Redwood CA). The test is designed to give prognostic information of risk for local tumor recurrence over ten years following breast-conserving therapy. In a study of patients from ECOG E5194, Oncotype Dx DCIS score stratified patients as low, intermediate, and high risk. There was an associated 10-year risk of developing ipsilateral DCIS recurrence of 10.6%, 26.7%, and 25.9% and ipsilateral invasive breast cancer recurrence of 3.7%, 12.3%, and 19.2%, respectively, after breast conservation alone for DCIS.[49] A similar study from Toronto, Canada with 718 patients demonstrated a strong correlation between Oncotype Dx DCIS score, and local DCIS and invasive breast cancer recurrence.[50] A recent study has shown a lack of cost-effectiveness of the test for patients with low/intermediate vs. high-grade DCIS using a Markov model for evaluating outcomes at 10-years.[51] A survey of physicians at ten different centers noted a clinically significant 33% (95% CI: 23.0–40.6%) change for a recommendation for radiation from pre-assay to post-assay of Oncotype Dx DCIS.[52]

Margins

There is ongoing controversy over the optimal margin width needed for patients treated with lumpectomy for DCIS. As 40–50% of DCIS recurrences are invasive, adequate margin width is of paramount importance to decrease local recurrence of IDC. In retrospective studies, there is a definite local recurrence advantage of obtaining negative margins compared to positive margins (10-year ipsilateral breast tumor recurrence [IBTR] 11% vs. 23%),[39] but the margin width for DCIS has been debated. In a joint consensus statement, the Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology recommends the margin for breast conservation surgery with whole breast radiation for DCIS to be 2 mm.[53,54] In their report, a meta-analysis of studies looking at various margin widths (>0 or 1 mm, 2 mm, 3 mm, 10 mm) analyzed their IBTR risk. The relative odds ratio of IBTR was 0.99 (CI 0.61–1.64) when margins of 2 mm were compared to 10 mm, signifying no statistical difference in recurrence of a wider negative margin. A 2 mm margin was determined after comparison to narrower margins (>0 mm or 1 mm) demonstrated a statically significant decrease in IBTR (OR 0.51, 95%CI 0.31–0.85; $p = 0.01$). Therefore, the current recommendation is at least 2-mm margins for breast conservation with whole breast radiation for DCIS. However, the panel recommends exercising clinical judgment when determining the need for re-excision for margins <2 mm.

Lastly, in a subset of women choosing not to undergo radiation therapy, the 10-year IBTR rate for wide excision alone is higher than compared with wide excision with radiation for both negative (26.0% vs 12.0%; $p < 0.0001$) and positive margins (48.3% vs 24.2%; $p = 0.0004$) [22]. When patients who undergo mastectomy have close margins, the 10-year local recurrence rates are 5% for margins < 1 mm, 3.6% for margins 1.1–2.9 mm, and 0.7% for margins > 3 mm; $p < 0.001$).[55]

Surveillance

Given the spectrum of aggressiveness of DCIS, there are some proponents of active surveillance rather than surgery for those with low-grade DCIS. The rationale for surveillance arises from the notion that DCIS is over-diagnosed from screening mammography, leading to surgical excision of all DCIS (regardless of the presence or absence of prognostic features), and potentially to over-treatment.[56] The LORIS trial from the United Kingdom aims to compare the current surgical management of DCIS to active surveillance for these lesions. Of 225 DCIS patients in a retrospective analysis by Soumian et al., there was no progression to invasive cancer for those patients who met the strict definition of low-grade DCIS under the LORIS inclusion criteria (female age > 46 years, screen-detected or incidental microcalcifications, large-volume vacuum-assisted biopsy, no previous breast cancer or DCIS, and patients fit for surgery).[57] Another clinical trial in the US that is randomizing low-grade DCIS patients to determine if surgery can be avoided altogether. The trial randomizes low-grade DCIS patients to surgery with or without radiation plus choice of endocrine therapy versus non-operative active surveillance with the only choice of endocrine therapy is the COMET trial (Comparison of Operative to Monitoring and Endocrine Therapy Trial for Low-Risk DCIS).[58] The primary outcome of the trial is the incidence of ipsilateral invasive cancer after two years of follow-up. However, critics of this strategy argue that the 20% incidence of synchronous invasive carcinoma found at surgical excision for those with heterogeneous grade, size, and

receptor status for LORIS-eligible women may lead to under-treatment.[59] Furthermore, given that the 10-year ipsilateral breast tumor recurrence (IBTR) rate for LORIS-eligible women was 6% with surgical excision without radiation therapy, critics of the LORIS trial anticipate a higher rate of IBTR in those under the active monitoring arm of the trial.[60]

Conclusion

DCIS is a prevalent disease with therapeutic strategies ranging from observation, lumpectomy, lumpectomy with radiation, lumpectomy with radiation plus hormone therapy, or mastectomy. Definitive predictive tools to identify patients who will proceed to invasive carcinoma remain elusive. While there is a difference in local-recurrence rates among various treatments, the similar overall survival rates in these patients drive the continuing discussions about the optimal treatment for DCIS. Despite the landmark studies performed thus far, the management of DCIS is still controversial and should be individualized, taking into account the available evidence.

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