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Ductal Carcinoma in Situ of the Breast: Evaluating the Role of Radiation Therapy in the Management and Attempts to Identify Low-Risk Patients

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Abstract

Ductal carcinoma in-situ (DCIS) of the breast has rapidly increased in incidence over the past several decades secondary to an increased use of screening mammography. Local treatment options for women diagnosed with DCIS include mastectomy or breast-conserving therapy (BCT). While several randomized trials have confirmed a greater than 50% reduction in the risk of local recurrence with the administration of radiation therapy (RT) compared to breast-conserving surgery (BCS) alone, controversy persists regarding whether or not RT is needed in selected 'low-risk' patients. Over the past two decades, two prospective single-arm studies and one randomized trial have been performed and confirm that the omission of RT after surgery alone is associated with higher rates of local recurrence even after selecting patients with the most optimal clinical and pathologic features. Importantly, these trials have failed to consistently and reproducibly identify a low-risk cohort of patients (based on clinical and pathologic features) that does not benefit from RT. As a result, adjuvant RT is still advocated in the majority of patients, even in these low-risk cases. Future research is moving beyond traditional clinical and pathologic risk factors and instead employing more modern approaches such as multi-gene assays and biomarkers with the hopes of identifying truly low-risk patients who may not require RT. However, recent

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studies confirm that even low-risk patients identified from multi-gene assays have higher rates of local recurrence with local excision alone than would be expected with the addition of radiation therapy.

Keywords

breast cancer; DCIS; radiation therapy; breast-conserving surgery

Introduction

Ductal carcinoma in situ (DCIS) of the breast represents up to one quarter of all new breast neoplasms diagnosed in the United States, with an increasing incidence noted over the past three decades secondary to increases in mammographic screening¹. The local management of DCIS has traditionally paralleled that of early-stage invasive cancer as no randomized trials have directly compared mastectomy versus breast-conserving therapy (BCT). Currently, BCT, consisting of breast-conserving surgery (BCS) with adjuvant radiation therapy (RT), is considered the standard of care with regards to local management for eligible patients; while use of BCT in DCIS has increased over the past few decades, recent data has demonstrated a trend for increased rates of mastectomy utilization despite equivalent outcomes and improved quality of life with breast conservation^{2–6}. Further, among those patients that elect for BCS, up to 50% do not receive adjuvant RT^{5, 7, 8}. Therefore, the purpose of this systematic review is to examine the evidence supporting adjuvant RT, attempts to identify low-risk subsets of patients, and to examine various local treatment options in the contemporary management of DCIS.

Materials & Methods

This systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁹. No official review protocol was created for this systematic review. Eligibility criteria for this review included published studies in English evaluating patients with DCIS treated with or without radiotherapy published between 1992 and 2012; required information included the number of patients, length of follow-up, radiation therapy (yes/no, detailed analysis not required for studies to be reviewed), outcomes (local control outcomes at a minimum), and institution/source of data (to ensure no duplication). A twenty year interval of publication was chosen in order to focus on more recent literature which included modern surgical and radiation techniques. Sources of information for the review included Medline/PubMed, those found in references from the major articles identified, and known articles to the authors. The PubMed search was conducted by a single author (CS) to identify any and all articles addressing DCIS and radiation therapy with the following MeSH headings: DCIS, ductal carcinoma in situ, radiation therapy, excision, mastectomy, outcomes, low risk. When multiple updates from a single institution were available, the most recent data were utilized unless results presented were unique to each study. All searches were completed by January 2, 2014.

Four separate searches were performed: (1) BCT (BCS + RT), (2) BCS alone, (3) studies of low-risk patients (including BCT and BCS studies), and (4) mastectomy for DCIS. When

evaluating long term (greater than 10 years) outcomes following breast-conserving therapy in DCIS a total of 149 articles were identified including 10 known to the authors; after review by a single author (CS), 103 were excluded. The remaining 46 studies were evaluated and 16 were found to have documented methodology and sufficient data to be incorporated into the review including 6 randomized trials, 1 meta-analysis, and 9 retrospective studies (Figure 1). With regards to data on the omission of radiation therapy (BCS), due to the quality of evidence available, focus was placed on randomized trials, prospective single arm studies, meta-analyses, and large retrospective series. A total of 1394 articles were identified; after review, 7 randomized trials, 2 prospective single arm trials, 2 meta-analyses, and 3 large retrospective series were felt to be of sufficient quality to include in the review. As quality meta-analyses were already available and published in peer-reviewed journals, data were not pooled. The search for publications evaluating low risk DCIS patients (treated with BCT or BCS) identified 153 articles with 104 excluded. The remaining 49 articles were reviewed and 21 appropriate including 2 randomized trials, 2 single arm prospective trials, 2 meta-analyses, 3 evidence based guidelines, 1 nomogram, and 11 retrospective studies. The search evaluating mastectomy for DCIS identified a total of 557 articles with 450 excluded. The remaining 107 studies were evaluated and 17 were found to have documented methodology and sufficient data to be incorporated into the review including 2 meta-analyses, and 15 single institution/retrospective studies.

Results

Breast-conserving Therapy for DCIS with Radiotherapy: Long-Term Results

As noted above, no randomized trials directly comparing mastectomy versus BCT (BCS + RT) have been performed in patients with DCIS. Therefore, the efficacy of BCT is often extrapolated from randomized trials in patients with early-stage invasive cancers that have confirmed that BCT is not associated with inferior outcomes and provides equivalent survival to mastectomy^{10–12}. There are numerous retrospective studies that have directly evaluated the long-term efficacy of BCS with adjuvant RT in patients with DCIS. Solin et al followed 1,003 patients that were treated at 10 institutions with all patients receiving whole breast irradiation. With a median follow-up of 8.5 years, 10% of patients developed local failures (15 year rate: 19%) and the 15 year cause-specific survival was 98%¹³. Similar results have been noted from several institutions; data from William Beaumont Hospital, with a median follow-up of 19.3 years found the 10, 15, and 20 year local recurrence rates following BCS with RT to be 12.2, 13.7, and 17.5%, respectively which was confirmed by several studies with long-term follow up that are presented in Table 1^{14–22,24–28}.

Additional data on the long-term efficacy of BCT in patients with DCIS can be found in the control arms of the four randomized trials evaluating the role of radiation therapy in patients treated with BCS^{23–29}. More recent efficacy data on BCT for DCIS are available from the NSABP B-24 study which evaluated the role of Tamoxifen in patients with DCIS undergoing BCT and the RTOG 9804 phase III trial which evaluated the omission of RT in patients with low-risk DCIS^{27,28}. In the four randomized trials that examined the efficacy of adjuvant RT following BCS, patients treated with RT had a local recurrence rate of 10–15% at 10 years with 15 year outcomes from NSABP B-17 and EORTC 10853 finding local

recurrence rates of 18–20%^{23–27}. The Early Breast Cancer Trialists Group meta-analysis of these four trials found the 10 year rate of ipsilateral breast tumor recurrence (IBTR) to be 13% for those patients undergoing BCT with adjuvant RT²⁹. In the NSABP B-24 trial, the 15 year rates of IBTR were 8.5–10% for the two arms which both underwent BCT²⁷. More recently, the RTOG 9804 trial randomized 636 patients to observation alone or RT with or without Tamoxifen following BCS. As this represents a lower-risk cohort of patients than the previously discussed studies, the five-year rate of IBTR was 0.4% with adjuvant RT²⁸.

It should be noted that recent local control outcomes for patients undergoing BCT appear to be improved compared with the older trials. For example, a retrospective review of 246 patients with DCIS undergoing BCT between 2001 and 2007 at Harvard University demonstrated a 0% rate of IBTR with 58 months of follow-up³⁰. Similar findings were noted by Nelson et al. when evaluating a modern cohort of 609 patients with 10 year local recurrence rates of only 4.2–7.2%³¹. In summary, patients undergoing BCS with the addition of adjuvant RT have 10 year rates of IBTR of 10–15% based on older series (retrospective and prospective studies) and 0–7% based on more recent data. With 15 years of follow-up, older series have found the rate of IBTR to be in the range of 15–20% (Table 1).

Breast-conserving Therapy for DCIS without Adjuvant Radiotherapy

As previously discussed, four randomized trials have been conducted evaluating the role of RT following BCS, enrolling a total of 4,596 patients with DCIS. Women enrolled on these trials are different than most patients with DCIS evaluated today in that none received endocrine therapy (except for the UKCCR trial), negative margins were not required in all series, and a larger percentage of cases were clinically detected compared with current series. NSABP B-17 randomized 818 patients following BCS to observation alone or WBI (50 Gy); at 15 years, WBI significantly reduced the rate of IBTR (17.7% v. 35.1%) with no difference in survival reported²³. Similar findings were noted from the EORTC 10853 trial and Swedish DCIS trials which found that WBI reduced the rate of IBTR with no survival benefit^{24,25}. It should be noted a small randomized trial from Hungary that accrued patients between 2000 and 2007 found no difference in recurrence rates though only 29 patients were accrued³². The UKCCR trial was different from the first three trials in that it incorporated hormonal therapy (Tamoxifen), included micro-invasive disease, and was a 2 × 2 randomization such that patients following BCS could undergo observation, WBI, Tamoxifen, or WBI plus Tamoxifen. The results of this trial demonstrated that WBI reduced the rates of IBTR (19.4% v. 7.1%) at 12 years with similar reductions noted for invasive and non-invasive IBTRs²⁶. A recently published meta-analysis of these four trials confirmed the findings of each individual trial; adjuvant WBI reduced rates of IBTR compared with observation (13% v. 28%)²⁹. These findings were confirmed by a second meta-analysis that identified a 50% reduction in local recurrences with similar rates of decrease noted for invasive and non-invasive recurrences³³.

More recently, two single-arm studies examining excision alone and one randomized trial have been conducted to further evaluate the efficacy of omitting adjuvant RT after BCS in highly selected, “low-risk patients” as defined by pathologic characteristics (i.e., tumor size,

margin status, nuclear grade). The first trial was performed at the Dana Farber Cancer Institute (DFCI) and enrolled 158 patients with low/intermediate-grade DCIS measuring 2.5 cm or less with surgical margins greater than 1 cm; of note, no endocrine therapy was allowed on this trial. This study was closed early due to a higher than expected rate of local recurrence (5-year IBTR rate of 12%) with subsequent follow-up demonstrating 8 and 10 year local recurrence rates of 13% and 15.6% respectively³⁴. The Eastern Cooperative Oncology Group (ECOG) E-5194 trial enrolled 670 patients with low/intermediate-grade DCIS that was 2.5 cm or smaller or high-grade DCIS that was 1 cm or smaller with all cases requiring 3 mm or wider surgical margins. Unlike the DFCI study, Tamoxifen use was allowed following a protocol amendment in 2000 (30% of cases). At five years, the rates of IBTR were 6.1% and 15.3% and at 10 years 15.4% and 15.1% respectively for the low/intermediate and high-grade cohorts³⁵. A recent analysis was performed using the ECOG criteria and compared outcomes between those receiving RT (single institution retrospective cohort) and those treated with excision alone (ECOG cohort); in the low/intermediate grade (4.4% v. 10.5%) and high grade (2.0% v. 18.0%) subsets, RT reduced the rates of IBTR³⁶. The RTOG 9804 trial was a Phase III study, which utilized eligibility criteria similar to the ECOG study (mammographically detected, low/intermediate grade DCIS, 2.5 cm or less, and 3 mm or greater margins) and randomized patients to observation alone or followed by RT after excision with or without Tamoxifen. This trial closed in 2006 secondary to poor accrual enrolling only 35% of its intended goal (636/1790 patients). At five years, RT was associated with a significant reduction in the rate of IBTR (0.4% v. 3.2%). Evaluating patterns of failure in this study found that two-thirds of recurrences in the observation alone arm were true recurrences (in the same quadrant as the initial tumor) while none of the recurrences in the RT arm were true recurrences²⁸.

Multiple retrospective studies have also evaluated outcomes with BCS alone. One of the largest retrospective series comes from a pooled analysis of the French Regional Cancer Centers; 705 patients were treated with excision alone or with RT between 1985 and 1995. With a median follow up of seven years, the IBTR rate was 32.4% for excision alone compared with 12.6% with RT³⁷. Higher rates of local recurrence were also noted in a review from Ontario that found a 19% rate of local recurrence compared with 13% with adjuvant RT, with over 3,500 patients evaluated¹⁸. One of the most complete long-term studies on excision alone for DCIS comes from the University of Southern California. Findings from this study resulted in the development of the Van Nuys Prognostic Index (VNPI). In the initial study, 333 patients were treated with BCS with (n=138) or without the addition of RT (n=195) and were assigned VNPI scores of 3–9 based on tumor size, margin, and histologic classification. The initial analysis found that for patients with VNPI scores of 3–4, no benefit to RT following BCS was noted, while for patients with VNPI scores of 5–7, a 17% benefit in local control was observed with the addition of RT. Patients with VNPI scores of 8–9 had large benefits with RT but were recommended to undergo mastectomy due to high rates of IBTR regardless of treatment³⁸. Subsequent updates of these results have led to the addition of patient age to the VNPI with comparable findings noted in terms of low-risk (VNPI 4–6, excision alone equivalent to BCT), intermediate-risk (VNPI 7–9, RT reduces local recurrences) and high-risk patients (VNPI 10–12, mastectomy recommended)^{39–40}. A recent update from the group evaluated 205 patients 50 years or

older with grade 1–2 tumors less than 2 cm treated with excision alone; the 6 and 12 year rates of local recurrence were 6.6% and 7.8% respectively⁴¹.

Identifying a “Low-Risk” Patient

Multiple attempts have been made to identify a low-risk subset of patients with DCIS that would require excision only. It should be noted that the randomized trials and EBCTG meta-analysis have failed to identify a low risk subset that did not benefit from adjuvant radiation therapy with respect to local control; analysis of NSABP B-17 did find that comedonecrosis, solid tumor type DCIS, moderate/marked lymphoid infiltrate, and multifocality were associated with IBTR with a trend for uncertain/involved margins^{23–25, 29, 42}. Further, the recently published RTOG 9804 which enrolled “low-risk” patients still found a significant benefit to the addition of adjuvant radiation therapy despite being underpowered and having short follow up at this time while single arm prospective trials have demonstrated unacceptably high rates of LR, even with “low-risk” patients^{28, 34, 35}. To this end, there exists no standardized or universally accepted pathologic definition of ‘low-risk’ as it pertains to the omission of RT for patients with DCIS. Currently, neither the National Comprehensive Cancer Network DCIS guidelines nor the American College of Radiology specify a set of criteria to identify low-risk patients suitable for observation alone following BCS which has been confirmed by a recently updated German evidence based guideline^{2, 43, 44}.

Initial attempts to identify low-risk patients were based on patient and clinical/pathologic characteristics based on data demonstrating associations between such factors (size, margin, grade, age) and local recurrence^{45, 46}. One such attempt discussed above is the use of the VNPI^{38–40}. However, the VNPI has not successfully been validated and its external reproducibility and applicability remain controversial^{47–50}. Another risk-stratification model comes from a nomogram developed at the MSKCC which incorporates age, clinical presentation, tumor grade, necrosis, margin status, receipt of RT, family history, receipt of endocrine therapy, and year of treatment into a composite score between 0 and 500; each factor is weighted based on its impact on rates of IBTR with the key factors being receipt of RT and receipt of endocrine therapy⁵¹. Unfortunately, no evaluation of outcomes for patients receiving BCS alone compared with adjuvant RT by nomogram score has been performed to date to identify a low-risk score and the nomogram’s ability to accurately predict the rate of recurrence has been questioned⁵². When looking at older patients (> 66 years old) who have traditionally been associated with lower rates of local recurrence, Smith et al still found a benefit to adjuvant RT amongst low risk patients with an 8.2% rate of local recurrence without radiation therapy compared with 1% with RT^{45, 46, 53}.

A future direction in the identification of a low-risk subset of DCIS patients is to move beyond traditional clinical and pathologic risk factors and utilize tumor genetics to better identify patients at low risk for local recurrence. Previously, multi-gene assays have been developed for patients with invasive cancers; initially, these assays were not designed to be utilized in patients with DCIS^{54–56}. However, a recent analysis of a new 21-gene assay designed for patients with DCIS has been performed incorporating data from the ECOG

E-5194 trial and was associated with rates of IBTR with the low and intermediate-risk groups having an IBTR rate of 4% and 12% respectively at 10 years^{35,57}.

An alternative methodology is to build upon current prognostic models by incorporating biomarkers; such a technique was performed by Altintas et al by utilizing the VNPI and evaluating the impact of Ki-67 and genomic grade index; the genomic grade index when used in conjunction with the VNPI was found to more accurately identify high risk cases⁵⁸. However, several series have failed to identify biomarkers that are associated with local recurrence^{46, 59}. HER2 is also being evaluated as a biomarker for prognosis and response to adjuvant therapy; currently, the NSABP is enrolling patients with DCIS to undergo centralized HER2 testing and subsequent randomization for those that are HER2+ to radiation therapy with or without trastuzumab⁶⁰. Moving forward, more studies are required to confirm the prognostic ability of these assays and biomarkers; should they be confirmed, patients with low-risk molecular/genetic profiles will have to be prospectively evaluated to determine if excision alone results in acceptable rates of long-term local control. Table 3 summarizes studies that have attempted to identify a low-risk cohort and the results of such stratifications.

The Role of Mastectomy in DCIS

Mastectomy represents the traditional local management technique for DCIS and still remains an appropriate therapeutic option in selected cases. Currently, the utilization of mastectomy in DCIS is often limited to patient preference, cases where the patient is unable to undergo BCS (i.e., diffuse microcalcifications, multi-centric disease, and/or persistently positive margins, etc.), and, at some institutions, patients that are felt to have “high-risk” DCIS^{2, 38}. Long-term outcomes following mastectomy have consistently demonstrated local recurrence rates less than 5% and cause specific survival rates greater than 95% (Table 4)^{61–74}.

As previously noted, no randomized trials are available directly comparing mastectomy and BCT for DCIS, with limited published data of any type directly comparing the two techniques. A meta-analysis from Boyages et al. found that the recurrence rates after mastectomy, BCS with RT, and BCS alone were 1.4%, 8.9%, and 22.5% respectively; however, this included a wide variety of trials and studies and no control for clinical or pathologic features by treatment technique was attempted⁷⁵. While local control rates are inconsistent between studies, a second meta-analysis and several analyses have confirmed no difference in survival or cancer mortality between techniques^{64,66,71–74, 76,77}. Taken together, no difference in survival or cancer specific survival have been noted with BCT and based on the data available BCT remains the standard of care in the management of DCIS^{75–77}.

Discussion/Conclusions

At this time, BCT, consisting of BCS followed by adjuvant RT, represents the standard of care in the management of patients with DCIS based on the publication of several randomized trials documenting improvement in local control with adjuvant RT after surgery. Over the past two decades, several trials have attempted to identify a “low-risk” cohort of

DCIS patients who may be safely treated with excision alone but have consistently demonstrated an increase in the rate of local failure with the omission of RT and failed to identify a consistent and reproducible subset of patients that does not benefit from adjuvant radiation. Genetic assays and biomarkers are the prognostic tools of the future but require further study and validation prior to widespread clinical use. Unfortunately, up to 50% of patients are not receiving adjuvant radiation therapy despite clinical guideline recommendation. At this time, adjuvant RT should be advocated for most women who present with DCIS based on the consistent benefit in local control it provides and the inability to accurately identify truly low-risk patients; omitting radiation therapy should only be offered on-protocol with an increased focus placed on ensuring radiation therapy access for women that desire breast conservation. Future research will need to evaluate not only local control but to examine the long-term survival and the balance between survival outcomes and quality of life following treatment.

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Figure 1.

Table 1

Breast Conserving Surgery with Adjuvant Radiation Therapy for DCIS

	Years	Number of Patients	Follow-Up (months)	Local Recurrence Rate (Time Point)
NSABP B-17	1985–1990	411	206	19.8% (15 years)
EORTC 10853	1986–1996	507	128	18% (15 years)
Swedish DCIS	1987–1999	526	102	12% (10 years)
UKCCR	1990–1998	583	151	7.1% (12 years)
NSABP B-24	1991–1994	1804	162	8.5–10% (15 years)
RTOG 9804	1999–2006	287	84	0.4% (5 years)
Solin et al. (Multi-institutional)	1973–1995	1003	102	19% (15 years)
Netherlands (Multi-institutional)	1989–2003	798	59	9% (RFS at 5 years)
William Beaumont Hospital	1980–1993	145	231	17.5% (20 years)
University of Michigan	1985–2002	198	74	9.8% (10 years)
Harvard University	2001–2007	246	58	0% (5 years)
Nelson et al. (Multi-institutional)	--	609	62	4.2–7.2% (5 years)
Ontario	1994–2003	1,895	120	12.7% (10 years)
MD Anderson Cancer Center	1973–1994	22	132	13% (10 years)
National Cancer Center Hospital (Tokyo, Japan))	1962–1995	336	180	10% (15 years)
Chiari Hospital (Trento, Italy)	1980–1990	139	81	14% recurrences (10 years)
Yale	1973–1998	230	98	13% (10 years)

Abbreviations: NSABP= National Surgical Adjuvant Breast and Bowel Project, EORTC= European Organisation for Research and Treatment of Cancer, DCIS= Ductal Carcinoma in Situ, UKCCR= United Kingdom Coordinating Committee on Cancer Research, RTOG= Radiation Therapy Oncology Group, WBH= William Beaumont Hospital

Table 2**Breast Conserving Surgery Alone for DCIS**

	Years	Number of Patients	Follow-Up (months)	Local Recurrence Rate (Time Point)
NSABP B-17	1985–1990	407	206	35.1% (15 years)
EORTC 10853	1986–1996	503	128	31% (15 years)
Swedish DCIS	1987–1999	520	102	27% (10 years)
UKCCR	1990–1998	1111	151	19.4% (12 years)
RTOG 9804	1999–2006	298	84	3.2% (5 years)
Dana Farber	1995–2002	158	40	13%/15.6% (8 years/10 years)
ECOG E-5194	1997–2002	670	74/79	15.4%/15.1% (low grade/high grade, 10 years)
France (Multi-Institutional)	1985–1995	705	84	32.4% (7 years)
University of Southern California	1996–2003	426	81	24% (10 years) VNPI 4–6: 3% (10 years) VNPI 7–9: 27% (10 years) VNPI 10–12: 66% (10 years)
Ontario	1994–2003	1,867	120	20.0% (10 years)

Abbreviations: NSABP= National Surgical Adjuvant Breast and Bowel Project, EORTC= European Organisation for Research and Treatment of Cancer, DCIS= Ductal Carcinoma in Situ, UKCCR= United Kingdom Coordinating Committee on Cancer Research, RTOG= Radiation Therapy Oncology Group, ECOG= Eastern Cooperative Oncology Group

Table 3**Techniques to Identify Low-Risk Patients with DCIS**

	Criteria	Treatment Decision	Data Utilized to Generate	Validation
VNPI	1) Tumor size (1.5 cm, 1.5–4.0 cm, > 4 cm) 2) Margin status (1 cm, 1–9 mm, < 1 mm) 3) Grade (Grade 1–2, Grade 1–2 with necrosis, Grade 3) 4) Age (>60, 40–60, < 40)	VNPI 4–6: Excision Alone VNPI 7–9: Excision with adjuvant RT VNPI 10–12: Mastectomy	University of Southern California series, rates of IBTR: VNPI 4–6: 3% VNPI 7–9: 27% VNPI 10–12: 66%	Controversial; multiple series have failed to confirm (MacAusland et al, Di Saverio et al), some series have confirmed some parts (Gilleard et al)
MSKCC	Age, presentation, tumor grade, necrosis, margin status, receipt of RT, family history, receipt of endocrine therapy, and year of treatment	--	MSKCC series (1,681 patients); features scores based on rates of IBTR at 5/10 years; RT and endocrine therapy dominant factors	MDACC identified concordance index of 0.63, suggesting low discrimination and calibration
ECOG E-5194	1) Low/intermediate-grade, 2.5 cm or smaller 2) High-grade, 1 cm or smaller Surgical margins 3 mm or greater	Excision Alone	Consensus opinions and data from Lagios et al.	5/10 year IBTR: 1) 6.1%/15.4% 2) 15.3%/15.1%
Dana Farber	Low/intermediate-grade, 2.5 cm or smaller, surgical margins greater than 1 cm	Excision Alone	Based on University of Southern California Series	8/10 year IBTR 13%/15.6%
RTOG 9804	Mammographically detected, low/intermediate grade, 2.5 cm or smaller, and 3 mm or greater margins	Randomized: Excision + Tamoxifen with or without RT	Based on Lagios et al, Schwartz et al, Silverstein et al, Solin et al. Van Zee et al, and Consensus Cancer Committee	5 year IBTR: 3.2% (no RT) v. 0.4% (RT)
Oncotype	12 genes: Ki-67, STK15, Survivin, Cyclin B1, MYBL2, PR, GSTM1, Beta-actin, GAPDH, RPLPO, GUS, TFRC	Excision Alone (ECOG E-5194)	NSABP B-14, Kaiser Permanente data	10 year IBTR: low (score<39), intermediate (39–54), and high (>55)-12.0%, 24.5%, and 27.3%
VNPI with Ki-67 & Genomic grade index	VNPI + genomic grade index (GGI, replaced nuclear grade) + Ki-67	VNPI subgroups	VNPI series	Ki-67 not prognostic; use of GGI increased prognostic value, detection of high – risk DCIS relapse (HR 18.14, p=0.02)

Abbreviations: VNPI= Van Nuys Prognostic Index, MSKCC= Memorial Sloan-Kettering Cancer Center, ECOG= Eastern Cooperative Oncology Group, RTOG= Radiation Therapy Oncology Group, IBTR= Ipsilateral Breast Tumor Recurrence, RT= radiation therapy, MDACC= MD Anderson Cancer Center

Table 4

Mastectomy for DCIS

	Years	Number of Patients	Follow-Up (months)	Local Recurrence Rate (Time Point)
British Columbia	1990–1999	637	144	1.0% (10 years)
University of California San Francisco	1985–2005	193	96	1.7% (8 years)
Beth Israel Medical Center	1997–2007	207	55	0.9% (10 years)
University of Southern California	1972–2005	430	72	0.5% (12 years)
Emory University	1991–2003	223	82	3.3% (7 years)
William Beaumont Hospital	1981–1999	43	84	4.7% (7 years)
Institute Bergonie	1971–1995	250	94	2.6% (8 years)
Harvard University	1998–2005	142	90	1.4% (crude)
Wake Forest University	1995–2006	83	53	1.1% (crude)
Southern California Permanente	1994–2002	80 (< 10 mm margin)	61	7.5% (5 years)
Netherlands Cancer Institute	1986–2005	294	79	0.9% (crude)
France Multi-Center	1985–1996	145	91	2.1% (crude)
University of California Los Angeles	1985–1992	88	99	4% (crude)
Louisiana State University	1982–1992	50	103	0%