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## Multidisciplinary, Shared Decision-Making in the Management of Ductal Carcinoma in Situ of the Breast

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### Abstract

**Background**—Controversy continues regarding the use of adjuvant radiation therapy (RT) and hormonal therapy (HT) for patients undergoing breast conserving therapy (BCT) for ductal carcinoma in situ (DCIS).

**Methods**—A prospective database was queried to identify women 18 years of age treated for DCIS from 2002-2013.

**Results**—BCT was completed in 300 patients. Median age was 66 years and median size of DCIS was 0.7 cm (range 0.1 – 6.0 cm). Grade was 44% high, 37% intermediate, and 19% low. The closest margin was >3mm in 80% and >5mm in 63%. Adjuvant RT was administered to 183 (61%) patients with the RT status of 9 (3%) unknown. RT was associated with age, DCIS size, comedo necrosis, grade, and treatment in 2002-07 versus 2008-13. Adjuvant HT was administered to 86 (39%) estrogen receptor-positive patients with the HT status of 4 (2%) unknown. Median follow-up was 63 months (range 4-151). The 5-year overall local recurrence (LR) rate was 4% (95% CI 2.1% - 7.4%). For RT patients, the 5-year LR rate was 3.9% (95% CI 1.8% - 8.6%) and 4.1% (95% CI 1.6% - 10.7%) for patients not receiving RT. Ten of 13 LRs (77%) were DCIS, and three (23%) were invasive including one node-positive recurrence.

**Conclusions**—Multidisciplinary and joint decision-making in the treatment of DCIS results in a substantial, and increasing number of patients foregoing adjuvant RT and/or adjuvant HT. Reasonable 5-year LR rates suggest that such decision-making can appropriately allocate patients to adjuvant therapies.

### Introduction

Ductal carcinoma in-situ (DCIS) diagnoses have been increasing since the advent of mammographic screening[1] and the use of breast conserving therapy (BCT) for DCIS has also increased over time [2]. Despite this volume of experience, the application of adjuvant radiation therapy (RT) and adjuvant hormonal therapy (HT) to patients undergoing BCT for DCIS has not been standardized.

Randomized clinical trials have demonstrated that RT as a part of BCT for DCIS reduces the risk of local recurrence (LR) by approximately 50%, albeit with no survival advantage [2, 3], [4] [5] [6]. Similarly, randomized clinical trials have shown that adjuvant tamoxifen reduces the risk of all breast cancer events (ipsilateral plus contralateral) by approximately 30%, also with no clear survival advantage [7] [8] [5] [9]. Nonetheless, a substantial proportion of patients are treated with lumpectomy alone [10] [11]. Many patients and physicians seek to avoid adjuvant treatments due to potential adverse effects, time and travel demands, lack of demonstrable survival benefit, and costs. Despite the multiple randomized trials cited above, there is available evidence to argue both for and against the use of adjuvant RT. [12, 13]. Intergroup (Eastern Cooperative Oncology Group and North Central Cancer Treatment Group) trial E5194 enrolled patients with low- or intermediate-grade DCIS  $\leq 2.5$  cm (Group 1) or high-grade DCIS  $\leq 1$  cm (Group 2) with margin widths  $\geq 3$  mm into a prospective trial of no adjuvant RT and found that with a median follow-up of 6.2 years, the 5-year LR rate in Group 1 was 6.1%, suggested to be low enough to consider the omission of RT for such patients [14]. The recent Radiation Therapy Oncology Group (RTOG) 9804 study reported that at a median of 7 years, good-risk DCIS patients (unicentric, low/intermediate grade,  $<2.5$  cm) had a LR rate of 6.7% when randomized to no RT versus 0.9% with RT.[15] The National Comprehensive Cancer Network guidelines ([www.nccn.org](http://www.nccn.org)) include lumpectomy without RT as an alternative Category 2B recommendation “if the patient and physician view the individual risk as ‘low’...” and adjuvant HT with tamoxifen is recommended to be “considered” post-operatively but that “since a survival benefit has not been demonstrated, individual consideration of risks and benefits is important.”. Thus there is significant latitude in the decision-making for the application of adjuvant RT and HT to individual patients with DCIS.

At our institution, decisions regarding adjuvant RT and HT for patients undergoing BCT for DCIS are made by a multidisciplinary team in a shared way (i.e. with significant education of each patient allowing for considerable patient influence on these decisions). Such collaborative decision-making has the potential to provide the best outcomes by matching the available evidence to each patient's unique clinical circumstances and goals. However, the outcomes of such decision-making have not been well studied and are of interest to establish the effectiveness of such a model. This study was undertaken to examine the rates of adjuvant RT and HT with such decision-making and the outcomes of these patients.

## Methods

After obtaining institutional review board approval, a prospective breast database and institutional cancer registry were queried to identify women treated for DCIS with BCT between January 2002 and December 2013. Medical records were reviewed to supplement and verify the database information. Clinical records were examined to determine the physician team recommendations regarding each adjuvant therapy and the patient response. Margin status was characterized by the closest measurement from DCIS to an inked surface and categorized as positive, negative without measurement, negative but  $<1$  mm, 1-1.9 mm, 2-2.9 mm, 3-4.9 mm,  $\geq 5$  mm, or  $\geq 10$  mm. Not all margins were measured if larger than 5 mm, so some patients reported as having margins  $>5$  mm may have had margins  $>10$  mm.

Our institutional approach is to consider 2mm as adequate margins for DCIS, so patients with a margin <2mm routinely underwent a re-excision.

Demographic and clinical characteristics were summarized between those receiving and not receiving adjuvant RT. LR and overall survival rates were calculated at five years using the Kaplan-Meier method. Time to LR was calculated as time from diagnosis to first LR. Overall survival was calculated as time from diagnosis to death due to any cause. A patient was censored at last follow-up date if the specified event had not been observed. Univariable logistic regression was used to investigate variables associated with the receipt of RT. Variables that were significant at  $p < 0.05$  were included in a multivariable logistic regression model. This multivariable logistic regression model was used to obtain individual propensity scores. Propensity score was then included as a continuous variable in a Cox proportional hazards regression model of local recurrence rate to estimate the hazard ratio for adjuvant RT relative to no RT. SAS version 9.3 (Cary, NC) was used for analysis.

## Results

A total of 471 patients treated for DCIS were identified of which 313 (66%) underwent attempted BCT. Thirteen patients (4%) were subsequently converted to mastectomy due to extensive DCIS leaving 300 patients who completed BCT and are the focus of this study. The median age was 66 years (range 38-89) and 92% were Caucasian. The mean size of DCIS was 1 cm and the median size was 0.7 cm (range 0.1 – 6.0 cm). No size was recorded for 13 patients (4%). The grade of DCIS was 44% high, 37% intermediate, and 19% low. Thirty-nine patients (13%) had multifocal DCIS, 198 (66%) had comedo necrosis, and 82% of the patients for whom estrogen receptor (ER) status was determined were ER-positive (221/269). Preoperative breast MRI was obtained in 39 patients (13%). Final margins were pathologically negative for all patients. Twenty-six (9%) patients required re-excision of margins at a second operation. Final closest margin width among the 93% with a measured distance was 2mm in 98%, 5mm in 69%, and 10mm in at least 22%.

Of the 300 BCT patients, 183 (61%) underwent adjuvant RT with the RT status of nine (3%) unknown. The rate of adjuvant RT decreased from 70% during 2002-2007 to 57% during 2008-2013. The reasons for not receiving RT were: RT offered/recommended but declined in 74%, RT not recommended in 23%, and one patient each (1%) had prior radiation exposure, became too ill to receive RT, or had no identifiable target for surgery or RT after core biopsy. Among the patients not undergoing adjuvant RT, all had a modified Van Nuys Index [16] score of 5: 18% = 3, 55% = 4, and 28% = 5. Fifty-nine of these no-RT patients (55%) met the E5194 group 1 criteria and another 18 (17%) met the E5194 group 2 criteria. The characteristics of the patients who received adjuvant RT and those that did not are presented in Table 1. On univariable logistical regression analysis, receipt of RT was significantly associated with younger age, comedo necrosis, larger DCIS size, higher grade, and earlier time period (2002-2007 versus 2008-2013). Margin width, multifocal disease, use of MRI and re-excision of margins were not significantly associated with receiving RT. (Tables 2 and 3). Among all BCT patients, 99 (33%) underwent adjuvant HT with the HT status of six (2%) unknown. Of the 221 ER-positive BCT patients, 86 (39%) underwent

adjuvant HT with the HT status of four (2%) unknown. The treatment strategies employed for the patients in the cohort are summarized in Figure 2.

Median follow-up was 63 months (range 4-151), including 74 months for the RT patients, 48 months for the no-RT patients, and 58 months for the RT status unknown patients. The 5-year LR rate was 4% (events=13, 95% CI 2.1%-7.4%) overall. No regional or distant recurrences were observed. For RT patients, the 5-year LR rate was 3.9% (95% CI 1.8%-8.6%). For patients not receiving RT, the 5-year LR rate was 4.1% (95% CI 1.6%-10.7%, Figure 3). The risk of LR, after adjusting for patient and tumor factors (age, comedo necrosis, DCIS size, grade, hormone therapy and time period, Table 3), was not associated with receipt of RT, but the confidence intervals were wide (HR=0.59, 95% CI 0.15–2.31;p=0.45). The 5-year LR rate was 5.7% (95% CI 2.2%-14.6%) for those in whom RT was recommended/offered but the patient declined while no LRs were observed among 23 patients in whom RT was not recommended or among eight patients who had miscellaneous reasons RT was not given. The 5-year LR rate was 4.8% (95% CI 0.7%-29.3%) for patients who underwent a re-excision for <2 mm margins. The 5-year LR rate for the 274 patients who did not require re-excision of margins was 3.9% (95% CI 2.0%-7.5%).

Of the 13 LRs, 11 (85%) were in the same quadrant of the breast, 10 (77%) were recurrences of DCIS, and three (23%) were invasive recurrences including one (8%) node-positive recurrence. The recurrences were treated with repeat BCT in five (38%) patients (all of whom had not undergone adjuvant RT) and mastectomy in eight (62%) patients (all of whom had undergone adjuvant RT). The patient with a node-positive recurrence was the only patient treated with adjuvant cytotoxic chemotherapy. Overall survival at 5 years was 95% (95% CI 90.6% - 97.0%). No deaths were attributed to breast cancer.

## Discussion

Ideally, individualized medical care identifies the best evidence-based treatments as assessed by a multidisciplinary care team for their applicability to an individual patient, presents these in an understandable way to each patient, and applies the options aligned with the treatment goals and priorities of each patient. The treatment of DCIS presents several decision-points at which there are valid arguments for opposite sides of a given decision, especially regarding the “aggressiveness” of adjuvant treatment. Thus, if one applies multidisciplinary, shared decision-making in an individualized fashion for DCIS, one should expect some patients to choose adjuvant RT and/or adjuvant HT based on a higher perceived risk of recurrence and/or a prioritization of minimizing recurrence risk while others will decline such therapy based on a lower perceived risk of recurrence and/or a prioritization of avoiding additional therapies.

In the current cohort, with this model of decision-making, 61% of patients treated with BCT proceeded with adjuvant RT and 39% of the ER+ patients proceeded with adjuvant HT. The 61% rate of adjuvant RT is slightly higher than in previous reports of large groups of DCIS patients. [10] [11] The 39% rate of HT in the current study matches the rate reported in another cohort [17]. The rates of adjuvant RT declined during the time-period of this study,

which may suggest patients and/or providers are recognizing more clinical circumstances that suggest a low enough risk of recurrence to warrant forgoing RT and prioritizing simplified therapy. Additional resources for assessing the risk of recurrence and utility of RT for such patients include the DCIS Oncotype DX test[18] and a free, online nomogram. [19] We have only rarely used these tools when patients have a difficult time with their decision regarding adjuvant RT.

It is well established that adjuvant RT lowers the LR risk among patients treated for DCIS. The fact that the 5-year LR rates for the patients in this study were similar among those undergoing RT (3.9%) and not undergoing RT (4.1%) should not be taken to suggest otherwise. These rates, useful only as observations rather than for comparison, instead show that those allocated to no RT were of lower risk for LR. This is consistent with the findings on univariable logistical regression analysis showing that younger patients with large tumor size, higher grade, and presence of comedo necrosis (all known risks for LR) were more likely to receive RT. This assessment is further bolstered by the fact that no patient experienced a LR for whom the recommendation was to not undergo adjuvant RT. While margin width was not associated with receipt of RT, 80% of patients in the current study had a closest margin >3 mm (as called for in E5194) and 63% had a closest margin >5 mm. This large proportion of patients with relatively wide margins, therefore, may have obscured any statistical evidence of its consideration in RT decision-making. Overall, these LR rates suggest that multi-disciplinary, shared decision-making can be applied in an appropriate and safe manner for patients with DCIS.

The 5-year LR rates of approximately 4% in both the RT and no RT patients in this cohort is comparable to other studies. E5194 demonstrated a 5-year LR rate in Group 1 (low/intermediate grade stratum) of 6.1%,[14] and a retrospective analysis of patients treated with RT who met the E5194 criteria found a LR rate of 4.4% after seven years in the low-intermediate grade cohort and 2% in the high grade patient cohort [17]. It is worth remembering that even good-risk DCIS patients have their LR risk reduced by the addition of adjuvant RT [15]. Therefore, all patients with DCIS, regardless of estimated LR risk, should be educated about the option of RT and its ability to lower LR risk even further.

No deaths in the current cohort were attributed to disease, but this is of little value as an outcome measure over a median follow-up of only 63 months for DCIS patients. Among those that did experience a recurrence, only 23% were invasive recurrences and only 8% node-positive (n=1, 0.3% of entire cohort). Others have likewise reported a third or less of recurrences to be invasive disease.[20]

Some limitations of this study should be acknowledged. The multidisciplinary, shared decision-making for the patients in this cohort was performed at a highly integrated, National Cancer Institute-designated Comprehensive Cancer Center site so the applicability of this model to other types of practice settings cannot be determined. This study is also limited by a relatively small sample size that may obscure small but significant differences from the results presented here. A propensity score methodology was used to help compensate for a low number of events in this cohort, but with only 13 local recurrences observed our statistical power was limited to conduct multivariable analysis and adjust for

all the factors influencing LR. This study is useful to observe the practice patterns and 5-year LR rates with this method of decision-making, not to determine factors that influence LR which have been well documented in larger cohorts. Finally, the median follow-up time of 63 months is adequate to indicate reliable 5-year LR rates but whether these rates will rise significantly over time will need to be monitored and is too short to reliably determine disease-specific and overall survival for patients with DCIS.

## Conclusion

Shared, multidisciplinary decision-making in the treatment of DCIS patients results in two-thirds of patients undergoing breast conserving surgery of whom a substantial and increasing minority forego adjuvant RT and a majority forego adjuvant HT. Patients allocated to these treatment strategies have reasonable 5-year LR rates whether receiving RT or not. Thus shared, multidisciplinary decision-making for patients with DCIS is an effective strategy for individualized therapy.

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**Synopsis**

Shared, multidisciplinary decision-making in the treatment of DCIS patients results in 39% foregoing adjuvant radiation therapy and 67% foregoing adjuvant hormonal therapy. Patients allocated to these treatment strategies have reasonable 5-year LR rates whether receiving RT (3.9%) or not (4.1%).

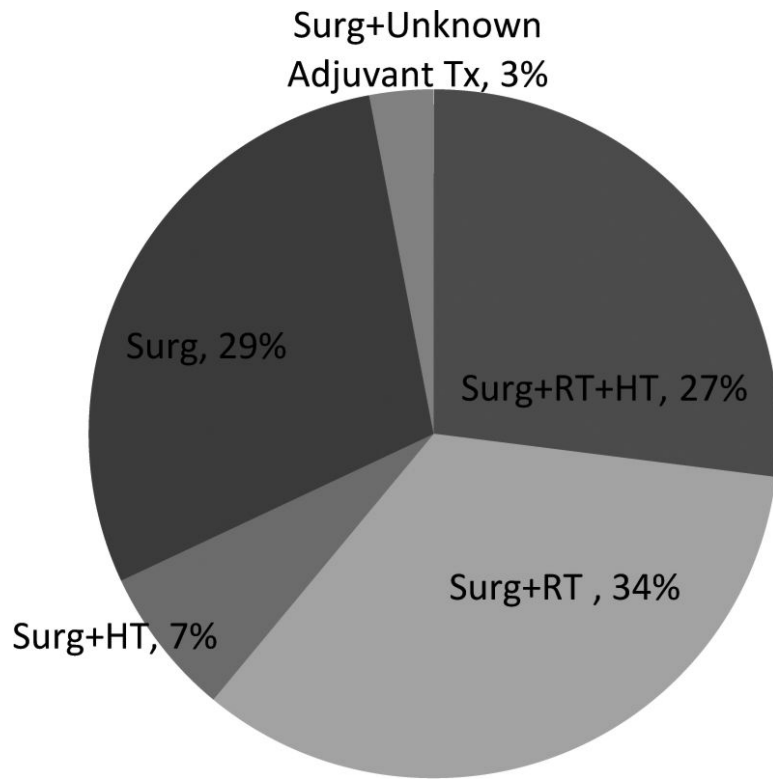
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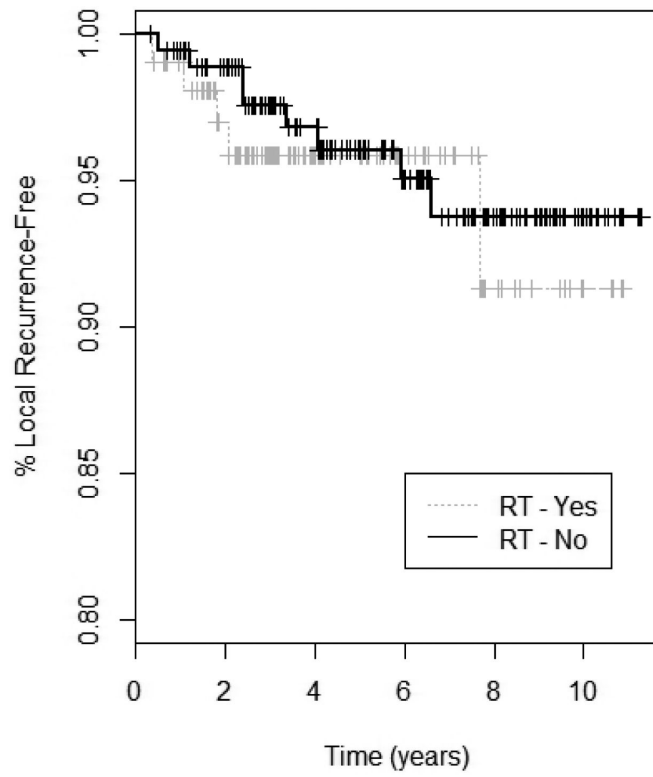
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**Figure 1.**  
Treatment Strategies  
Surg=Surgery, RT=Radiation Therapy, HT=Hormonal Therapy, Tx=Treatment



**Figure 2.**  
Local Recurrence-Free Rates  
RT = Radiation Therapy

**Table 1**

Characteristics of the BCT patients by receipt of Radiation Therapy (RT)

|                         | Adjuvant RT group (n=183) | No adjuvant RT group (n=108) | RT status unknown group (n=9) |
|-------------------------|---------------------------|------------------------------|-------------------------------|
| Median age              | 65 years                  | 68 years                     | 63 years                      |
| Median tumor size       | 0.8 cm                    | 0.6 cm                       | 1.2 cm                        |
| MRI performed           | 13%                       | 13%                          | 11%                           |
| Comedo necrosis         | 71%                       | 53%                          | 88%                           |
| Multifocal              | 14%                       | 12%                          | 11%                           |
| Closest Margin <2 mm    | 2%                        | 1%                           | 0                             |
| Margin re-excision      | 9%                        | 6%                           | 22%                           |
| High-grade DCIS         | 49%                       | 29%                          | 78%                           |
| Low-grade DCIS          | 15%                       | 25%                          | 0%                            |
| Adjuvant HT             | 43%                       | 18%                          | 33%                           |
| Median Follow-up        | 74 months                 | 48 months                    | 58 months                     |
| 5-year Local Recurrence | 3.9%                      | 4.1%                         | 0%                            |

**Table 2**

Univariable logistical regression analysis of characteristics' association with receipt of RT

| <b>Factor</b>                                 | <b>Odds Ratio (95% confidence interval)</b> | <b>p value</b> |
|---|---|----------------|
| Age (Per 1 year increase)                     | 0.97 (0.95, 0.99)                           | 0.004          |
| Comedo Necrosis (Reference: Not present)      | 2.15 (1.30, 3.56)                           | 0.003          |
| DCIS size (Per 1 cm increase)                 | 1.97 (1.30, 2.99)                           | 0.001          |
| DCIS Grade (Reference: 1)                     |   | 0.007          |
| 2   | 1.55 (0.79, 3.05)                           |                |
| 3   | 2.86 (1.44, 5.66)                           |                |
| Margin Width (Reference: Negative)            |   | 0.13           |
| 5 mm  | 2.60 (0.98, 6.89)                           |                |
| >5 mm   | 1.77 (0.71, 4.37)                           |                |
| Multifocal DCIS (Reference: Not present)      | 1.16 (0.57, 2.37)                           | 0.69           |
| MRI (Reference: Not done)                     | 1.01 (0.50, 2.06)                           | 0.97           |
| Re-excision (Reference: Not done)             | 1.48 (0.59, 3.69)                           | 0.40           |
| Time period of Surgery (Reference: 2002-2007) | 0.57 (0.35, 0.93)                           | 0.02           |

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**Table 3**

Multivariable logistical regression analysis of characteristics' association with receipt of RT

| <b>Factor</b>                                | <b>Odds Ratio (95% confidence interval)</b> | <b>p value</b> |
|--|---|----------------|
| Age (Per 1 year increase)                    | 0.96 (0.93, 0.99)                           | 0.002          |
| Comedo Necrosis (Reference: Not present)     | 2.18 (1.10, 4.31)                           | 0.03           |
| DCIS size (Per 1 cm increase)                | 1.63 (0.99, 2.70)                           | 0.06           |
| DCIS Grade (Reference: 1)                    |   | 0.12           |
| 2  | 1.03 (0.46, 2.33)                           |                |
| 3  | 2.04 (0.83, 5.01)                           |                |
| Time period of Surgery (Reference 2002-2007) | 0.52 (0.29, 0.96)                           | 0.04           |
| Hormone Therapy (Reference: No)              | 3.24 (1.67, 6.30)                           | <0.001         |

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