

# Ductal Carcinoma In Situ: Review of the Role of Radiation Therapy and Current Controversies

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## Abstract

Despite a lack of randomized trials comparing breast-conserving therapy (BCT) and mastectomy, BCT represents a standard of care in the management of ductal carcinoma in situ (DCIS). Traditionally, BCT has consisted of breast-conserving surgery (BCS) followed by adjuvant radiotherapy (RT), with multiple randomized trials demonstrating an approximately 50% reduction in rates of local recurrence with adjuvant RT. However, over the past 2 decades, several trials have been performed to identify a low-risk cohort of patients for whom BCS alone would provide an acceptably low risk of local recurrence. Currently, patients who can forgo adjuvant RT without significantly increasing their chance of local recurrence have not been consistently identified. While future studies will look at tumor genetics to help identify low-risk cohorts, modern RT also allows for shortened courses of treatment to reduce the duration of adjuvant RT.

**Key words:** Breast cancer, radiation therapy, DCIS, breast-conserving therapy

## Introduction

Over the past several decades, the incidence of ductal carcinoma in situ (DCIS) has increased, coinciding with the increased utilization of screening mammography.<sup>1</sup> While no randomized trials comparing mastectomy and breast-conserving therapy (BCT) have been performed in patients with DCIS, BCT represents a standard of care in the treatment of DCIS, with long-term clinical outcomes and evidence-based guidelines supporting its utilization.<sup>2,3</sup> Initial randomized studies evaluating BCT in women with DCIS included breast-conserving surgery (BCS) followed by whole-breast irradiation (WBI), and this became the standard as the studies demonstrated a 50% reduction in local recurrence with adjuvant radiotherapy (RT).<sup>4,7</sup>

However, published studies demonstrate that women undergoing BCS do not always receive adjuvant RT due to factors including socioeconomic concerns, duration of treatment, and dis-

tance to treatment facilities.<sup>8,9</sup> In light of this, clinicians continue to study women with DCIS in order to identify cohorts based on patient, clinical, and pathologic criteria that may not require adjuvant RT, or those who may be treated with alternative RT techniques that can shorten the duration of treatment. The purpose of this review is to evaluate the role of RT in women with DCIS, as well as to evaluate current controversies that include omitting adjuvant RT and hypofractionation/accelerated partial-breast irradiation (APBI).

## Results of Randomized Trials

### *Role of Radiotherapy*

The role of RT in patients with DCIS was established with the publication of four randomized trials, which compared BCS with or without adjuvant RT, and consistently found a reduction in local recurrence with RT. NSABP B-17 randomized 813 women to adjuvant RT (50 Gy to the whole breast) or no further treatment following lumpectomy. Wapnir et al<sup>4</sup> have updated the results, and at 15 years, RT reduced the risk of all local recurrences (35% vs 19.8%), with a 52% reduction in invasive ipsilateral breast tumor recurrence (IBTR; 19.6% vs 10.7%;  $P < .001$ ) and a 47% reduction in DCIS IBTR (15.4% vs 9.0%;  $P < .001$ ).

Similarly, an update of the European Organisation for Research and Treatment of Cancer (EORTC) 10853 trial<sup>5</sup> confirmed the benefit of adjuvant RT. This randomized trial included 1010 women with the same randomization as NSABP B-17 (observation vs standard fractionation WBI). At 15 years, adjuvant RT was associated with a reduction in local recurrence (31% vs 18%;  $P < .001$ ), with similar findings noted for invasive recurrences (16% vs 10%;  $P = .007$ ) and DCIS recurrences (16% vs 8%;  $P = .003$ ), with all subgroups benefiting from RT.<sup>5</sup>

Similar findings were also noted from the SweDCIS trial,<sup>6</sup> which randomized 1046 individuals following BCS with negative margins, and found an increase in the rate of local recurrences when omitting RT (27% vs 12%), with similar reductions in invasive and DCIS recurrences noted, and no group based on stratification variables that had a low risk with excision alone. In order to address the role of RT in conjunction with endocrine therapy, randomized trials were performed evaluating the impact

**TABLE.** Treatment Options Following Breast-Conserving Surgery

Patients Age <50 Years
Standard Fractionation Whole-Breast Irradiation: Limited data on the omission of radiation (18.8%-20.5% of RTOG 9804, 20%-23.8% of ECOG 5194, 48% of DFCl) and current clinical guidelines do not support hypofractionated therapy (American Society for Radiology and Therapeutic Oncology [ASTRO]) or accelerated partial-breast irradiation (ASTRO/ABS). Standard fractionation treatment was utilized in multiple randomized phase III trials.
Patients Age >50 Years, Estrogen Receptor-Positive
Standard Fractionation Whole-Breast Irradiation
Hypofractionated Whole-Breast Irradiation: Clinical guidelines support the utilization of hypofractionated therapy in women over age 50 years. Retrospective data support the utilization of hypofractionated radiation in DCIS, with randomized data supporting its utilization in early-stage invasive disease.
Accelerated Partial-Breast Irradiation: Clinical guidelines support the utilization of APBI in this cohort of patients, with prospective and retrospective data supporting low rates of failure. Must meet other clinical characteristics as well as be eligible.
Endocrine Therapy: Randomized and prospective trials have demonstrated higher rates of local recurrence, with no difference in survival.
Patients Age >50 Years, Estrogen Receptor-Negative
Standard Fractionation Whole-Breast Irradiation
Hypofractionated Whole-Breast Irradiation
Accelerated Partial-Breast Irradiation

EORTC 10853, SweDCIS, UKCCCR) was performed, and found a significant reduction in IBTR with adjuvant RT at 10 years (28% vs 13%), with a benefit noted for young and older patients.<sup>11</sup> However, no survival benefit was noted. Importantly, even in women with small, low-grade tumors with negative margins, adjuvant RT reduced local recurrences. Recent series examining outcomes in women with DCIS treated with BCS and adjuvant RT with modern radiological, surgical, systemic, and RT techniques have confirmed excellent outcomes with surgery followed by adjuvant RT with endocrine therapy.<sup>12-14</sup>

*Omitting Radiation Therapy*

Multiple prospective studies have been performed evaluating the omission of RT for low-risk patients as defined by clinical and pathologic criteria. The ECOG 5194 trial<sup>15</sup> enrolled patients with low-/intermediate-grade DCIS (n=565) less than 2.5 cm or high-grade DCIS (n=105) less than 1 cm, with all patients having surgical margins greater than 3 mm following excision. Enrollment began in 1997 and was amended to allow for tamoxifen in 2000 (30% of patients). Initial data at 5 years demonstrated a 6.1% local recurrence rate in the low-/intermediate-grade cohort and a 15.3% recurrence rate in the high-grade cohort. However, with longer follow-up, the 12-year

of tamoxifen/endocrine therapy. The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) study<sup>7</sup> was a 4-arm trial that randomized 1701 women with DCIS following BCS to observation, adjuvant RT, tamoxifen, or both RT and tamoxifen. With a median follow-up of 12.7 years, adjuvant RT reduced the incidence of invasive IBTRs ( $P < .0001$ ) and DCIS IBTRs ( $P < .0001$ ) as well as all new breast events ( $P < .0001$ ). Tamoxifen was found to reduce all breast events ( $P = .002$ ) and DCIS IBTRs ( $P = .03$ ), but did not significantly reduce invasive IBTRs ( $P = .8$ ), and no synergy between RT and tamoxifen was noted.

NSABP B-24 was a randomized trial of 1799 patients with DCIS who were randomized to receive tamoxifen or placebo as a part of BCS (all underwent lumpectomy and adjuvant RT). The addition of tamoxifen was found to reduce invasive IBTRs by 32% ( $P = .025$ ), with a nonsignificant reduction in DCIS IBTRs.<sup>4</sup>

Recently, the role of aromatase inhibitors (AIs) as compared with tamoxifen was evaluated in NSABP B-35,<sup>10</sup> with results demonstrating an improvement in breast cancer-free interval at 10 years (93.5% vs 89.2%) when utilizing an AI in a randomized study of 3104 postmenopausal women with DCIS. The benefit of anastrozole was primarily noted in women less than age 60 years. Limited data are available at this time on the potential for synergism between AIs and RT.

A meta-analysis of the four randomized trials (NSABP B17,

rates of recurrence were 14.4% for the low-/intermediate-grade group and 24.6% for the high-grade cohort, with 7.5% and 13.4% respectively, being invasive.<sup>16</sup>

Similarly, a prospective study from the Dana-Farber Cancer Institute (DFCI) evaluated 158 patients with low-/intermediate-grade DCIS with margins greater than 1 cm and less than 2.5 cm of extent on mammogram.<sup>17</sup> Patients were treated with excision alone and did not receive endocrine therapy. With a median follow-up of 11 years, the 10-year local recurrence rate was 15.6% (75% in the original quadrant), with an annual rate of local recurrence of 1.9%, demonstrating a continuing risk of local recurrence with excision alone.

RTOG 9804<sup>18</sup> was a randomized trial evaluating the role of adjuvant RT; patients with low-risk disease (nonpalpable, size <2.5 cm, margins >3mm, grade I/II or III with necrosis in <1/3 ducts, clinically node-negative) were randomized to excision alone or adjuvant RT (standard or hypofractionated WBI), with tamoxifen utilized at physician discretion (62% of patients). At 5 years, RT reduced the risk of local recurrence 3.2% versus 0.4%, and at 7 years the rates were 6.7% versus 0.9%, with acute grade 3 or greater toxicity rates of 4% in both arms. Late radiation toxicity was minimal, with 4.6% of patients having grade 2 and 0.7% grade 3 toxicity.

It should be noted that these studies relied on clinical and

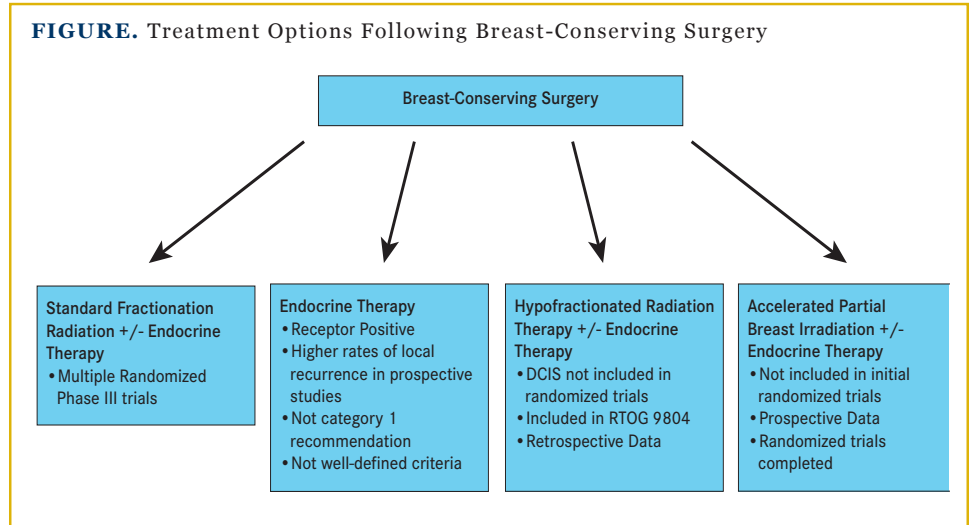
pathologic characteristics to define low-risk cohorts of patients. Similarly, the Van Nuys Prognostic Index (VNPI) was developed and has been updated to include size, margin, age, and histology, with recommendations ranging from excision alone for low scores (4-6) to mastectomy for higher scores (10-12).<sup>19,20</sup> However, external studies have failed to validate these findings, and further confirmatory studies are needed.<sup>21</sup> More recently, data have emerged on the role of multigene assays identifying low-risk cohorts of patients who may not require adjuvant RT

following BCS. Solin et al<sup>15</sup> evaluated a subset of patients from the ECOG 5194 trial (n = 327). They found that a prospectively defined scoring system using 12 genes (7 cancer-related, 5 reference) was associated with the risk of developing IBTR; however, in the low-score group, the 10-year rate of IBTR was 10.6%, with rates of 26.7% and 25.9% for the intermediate- and high-score groups. A similar study from Rakovitch et al<sup>22</sup> retrospectively evaluated 718 patients from a population-based cohort treated with excision alone. With a median follow-up of 9.6 years, the risk score was independently associated with any local recurrence, including invasive and DCIS recurrences. While these studies are promising, further data are required comparing outcomes with and without adjuvant RT based on risk score grouping to define the difference in local recurrence with and without adjuvant RT, while accounting for endocrine therapy by risk group. In the interim, guidelines do exist for the omission of RT based on data from the ECOG trial. However, the failure for recurrences to plateau in the ECOG study does raise concern about omitting RT, particularly for the high-grade cohort, which had a 24.6% IBTR rate at 12 years. It should be noted that no difference in survival has been found with this local recurrence increase; however, local recurrences are associated with potential for an invasive recurrence (50% of recurrences), a psychological impact, and additional cost associated with treatment of the recurrence. At this time, there is no standard as to what defines *acceptable local recurrence rates*, and some patients may accept a 10-year recurrence rate of 10%, as seen in the low-score DCIS groups presented by Solin et al. Informed discussion with patients is key to deciding whether to pursue adjuvant RT and which technique to employ.

### Alternative Options

Several alternatives to standard WBI exist to reduce the duration of adjuvant RT and improve compliance with BCT. One such alternative is hypofractionation, which delivers treatment to

**FIGURE.** Treatment Options Following Breast-Conserving Surgery



the whole breast while reducing treatment duration to 3 weeks. Whelan et al<sup>23</sup> evaluated the role of hypofractionation in a randomized study of 1234 women with T1-2N0 (no DCIS), with patients receiving either standard fractionated (50 Gy/25 fractions) or hypofractionated (42.5 Gy/16 fractions) WBI following BCS. At 10 years, no difference in outcomes or toxicity profiles was noted, and cosmesis was comparable. Similar results have been noted in trials from the UK, where the START A and B trials demonstrated equivalent local control and the potential for improved cosmetic outcomes with hypofractionation.<sup>24</sup>

While there are limited prospective data on hypofractionation in a pure DCIS cohort, Lalani et al<sup>25</sup> published a report of 1609 women with DCIS, with 40% (638) receiving hypofractionation and 60% (971) receiving standard fractionation; with a median follow-up of 9 years, local recurrence rates were similar between techniques. Similar results have been noted in several other studies, and have led to increased utilization of hypofractionation for DCIS in the United States.<sup>26,27</sup> Another alternative to standard fractionation WBI is APBI, which delivers treatment solely to the area surrounding the lumpectomy cavity in 1 week or less. Randomized trials comparing APBI with standard or hypofractionated WBI have been completed, with randomized data from Hungary demonstrating equivalent clinical outcomes using the interstitial/electron technique, although this was not a study of patients with DCIS.<sup>28</sup>

Increasing data are available on patients with DCIS treated with APBI. Vicini et al<sup>29</sup> published a series of 300 patients with DCIS treated with APBI. At 5 years, the rate of IBTR was 2.6% with comparable rates of IBTR as compared with invasive tumors. Similar findings have been noted from several institutional series as well as multi-institutional series, with The American Brachytherapy Society (ABS) APBI consensus statement including DCIS in the acceptable treatment category.<sup>30-34</sup>

### Future Directions

Recently, an observational Surveillance Epidemiology and End Results (SEER) study evaluated 10- and 20-year mortality in 108,196 patients following a diagnosis of DCIS. At 20-year follow-up, breast cancer mortality was 3.3%, with higher rates noted for women under age 35 years and African Americans. However, the risk of dying of breast cancer increased significantly with invasive IBTR (HR, 18.1;  $P < .001$ ). Radiotherapy following BCS reduced local recurrence with no difference in mortality. While provocative, these data are observational and face the limitations of such analyses. Future studies are required before the concept of surveillance represents an appropriate standard for women with DCIS; at this time, the standard of care remains surgery (mastectomy or BCS) with or without RT.<sup>2</sup>

### Discussion

Currently, RT remains a key component of BCT in women with DCIS. Even with improvements in surgical techniques and advancements in endocrine therapy, modern studies evaluating the role of RT have demonstrated a consistent reduction in local recurrence with RT that is reflected in current evidence-based guidelines.<sup>2</sup> Randomized and prospective studies have attempted to identify cohorts of low-risk patients who demonstrate minimal or no increase in local recurrence with the omission of RT, but traditional clinical and pathologic factors have failed to consistently identify such a group. Preliminary studies have been published, with further studies under way, evaluating the role of tumor genetics and multigene assays in identifying low-risk patients, and represent a potential tool for clinicians to utilize in the future. In the interim, alternative strategies include hypofractionated WBI and APBI to reduce the duration of adjuvant RT, allowing women to complete breast conservation and offering the ability to improve compliance following BCS. **Figure 1** provides a summary of treatment options for clinicians following BCS, with a synopsis of the data available for each treatment paradigm.

Clinical recommendations and treatment options are based on the available literature and evidence-based guidelines.

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