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NON-INVASIVE BREAST CANCER DIAGNOSIS AND TREATMENT (ES HWANG, SECTION EDITOR)

DCIS: Radiation Considerations

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Abstract

Purpose of Review Ductal carcinoma in situ (DCIS) is commonly treated with radiotherapy as a part of breast-conserving therapy, though increasingly the use of routine radiation treatment is being questioned. The intent of this review is to summarize studies on the role of radiotherapy for DCIS, with an emphasis on more recent trials.

Recent Findings While older randomized clinical trials have established a local control benefit for adjuvant radiotherapy following breast-conserving surgery in all patients including those with low-risk DCIS, these and subsequent studies have failed to demonstrate any survival benefit. Given the risks associated with radiotherapy, studies have aspired to demonstrate that subgroups of DCIS patients who derive less benefit from treatment may safely avoid adjuvant radiotherapy. Nomograms based on retrospective analyses have been employed to help identify patients for omission of radiotherapy, and genomic assays as a proxy for tumor biology are being explored as strategies for patient selection. When patients do receive radiotherapy, radiation options such as hypofractionation, inclusion of a radiation boost to the resection cavity, and partial-breast irradiation are considerations to help individualize treatment. Finally, initial treatment for DCIS may have implications for subsequent therapy in the setting of salvage therapy for recurrent breast cancer.

Summary More recent studies on DCIS have aimed at identifying subgroups of DCIS patients who may safely omit radiotherapy and strategies to individualize radiation treatment of DCIS. Radiotherapy for DCIS should be a decision made after a careful discussion between physicians and patients, taking into account individual patient characteristics and preferences.

Keywords Ductal carcinoma in situ · DCIS · Non-invasive breast cancer · Radiation therapy · Radiation treatment · Radiotherapy

Introduction

Ductal carcinoma in situ (DCIS) has been increasingly frequently diagnosed in the last few decades due to the widespread adoption of screening mammography in the developed world [1]. Treatment options for DCIS have evolved. Historically, DCIS was routinely treated with mastectomy. Following the establishment of breast-conserving therapy paradigm for invasive breast cancer, the use of this paradigm was adopted for DCIS. Breast-conserving therapy, consisting of breast-conserving surgery followed by radiotherapy, is now considered a standard of care for DCIS [2].

More than 70% of DCIS cases are now treated with breast-conserving surgery, with more than 50% of these patients receiving adjuvant radiotherapy, though significant national-regional variation exists in its use [3]. With these treatments, patients with DCIS have been demonstrated to have excellent survival rates, with breast cancer-specific mortality rates of less than 5% [4, 5].

Benefit of Adjuvant Radiation Therapy

Four older randomized clinical trials comparing lumpectomy followed by radiotherapy to lumpectomy alone established a local control benefit for the inclusion of radiotherapy in treatment of patients with DCIS. National Surgery Adjuvant Breast and Bowel Project (NSABP) B-17 was a study of

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818 patients treated from 1985 to 1990 [6]. European Organization for Research and Treatment of Cancer (EORTC) 10,853 was a study of 1010 patients treated from 1986 to 1996 [7]. SweDCIS was a study of 1046 patients treated from 1987 to 1999 [8]. UK/ANZ, a 2 × 2 factorial trial of radiotherapy, tamoxifen, or both, included 1030 patients treated from 1990 to 1998 [9]. The treatment characteristics and most recently reported results of these trials are summarized in Table 1.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of the individual patient data for 3729 women from these four seminal trials showed that the addition of adjuvant radiotherapy reduced the 10-year risk of either recurrent DCIS or invasive cancer in the ipsilateral breast by 15% in all patients, regardless of age, margin status, use of tamoxifen, focality, grade, or tumor size. However, there was no improvement in breast cancer-specific mortality or all-cause mortality with radiotherapy [4].

Omission of Adjuvant Radiation Therapy

Improvements in surgery and systemic therapy in the last 20 years call into question the routine use of adjuvant radiotherapy with improved pathologic and imaging evaluation. A single institution study found that among 246 patients with DCIS treated with standard breast-conserving therapy, the rate of local recurrence was zero at almost 5 years [10]. Other studies also aimed to identify subgroups of patients with DCIS who might have inherently lower risk of recurrence and in whom adjuvant radiotherapy may be of particularly limited benefit.

Radiation Therapy Oncology Group (RTOG) 9804 was a randomized clinical trial of 636 patients with baseline low risk of recurrence, comparing adjuvant whole-breast radiotherapy with observation following breast-conserving surgery, conducted from 1999 to 2006. Patients that were enrolled had mammographically detected low- or intermediate-nuclear-grade DCIS, measuring less than 2.5 cm, with margins width of 3 mm or more. At a median follow-up of 12.4 years, adjuvant radiotherapy significantly reduced local recurrence of breast cancer, from 11.4% with observation to 2.8% with radiotherapy (HR, 0.26; 95% confidence interval [CI], 0.13 to 0.54; $p = 0.0001$), and cumulative incidence of invasive breast cancer, from 5.8% with lumpectomy alone to 1.5% with lumpectomy and adjuvant radiotherapy (HR, 0.34; 95% CI, 0.14 to 0.85; $p = 0.016$) [11, 12]. In fact, this is an even higher rate of risk reduction than that demonstrated by the EBCTCG meta-analysis of earlier trials. One limitation of this study is that it was closed early due to low accrual and had a lower than planned number of patients and events.

Eastern Cooperative Oncology Group (ECOG)-American College of Radiology Imaging Network (ACRIN) E5194 was a single-arm prospective trial of 665 patients with low-risk characteristics who were treated with lumpectomy alone, enrolled from 1997 to 2002. Eligible patients had margin width 3 mm or more and either low- or intermediate-grade DCIS ≤ 2 .5 cm in size or high-grade DCIS ≤ 1 cm in size. The study found 12-year rates of ipsilateral breast cancer to be 14.4% for patients with larger and lower grade tumors and 24.6% for patients with smaller and high-grade tumors. For patients with larger and lower grade tumors, 12-year rates of invasive ipsilateral breast cancer were 7.5% and 13.4% for patients with smaller and higher grade tumors [13].

Similar results were demonstrated by a single-arm single-institution study of 143 patients with tumors ≤ 2.5 cm that were low or intermediate grade and had margins ≥ 1 cm, enrolled from 1995 to 2002. The 10-year local recurrence rate was 15.6%, and an annual local recurrence rate of 1.9% per patient-year was predicted [14]. Of note, these studies preceded routine testing for estrogen receptor (ER) and use of endocrine therapy for DCIS for a majority of the patients in the cohort. Local recurrence rates are higher than would be seen in current practice given that multiple studies have demonstrated that adjuvant endocrine therapy reduces the risk of recurrence in patients with ER-positive DCIS, with or without adjuvant radiotherapy [9, 15, 16]. UK/ANZ showed that tamoxifen alone, without radiotherapy, reduces the risk of recurrence in patients with ER-positive DCIS, particularly in the

Table 1 Treatment characteristics and most recent results of historic trials comparing breast-conserving surgery (BCS) followed by radiotherapy to BCS alone

Trial name (year updated)	Number of patients	Follow-up time (years)	Margins	Radiation dose (gray/fraction)	Received a boost (%)	Locoregional recurrence	
						BCS (%)	BCS + RT (%)
NSABP B-17 (2011) [6]	818	17.2	13% involved or unknown	50/25	9	35	20
UK/ANZ (2011) [9]	1030	12.7	All negative	50/25	0	26	9
EORTC 10853 (2013) [7]	1010	10.5	16% involved or < 1 mm	50/25	5	26	15
SweDCIS (2014) [8]	1067	17.0	11% positive, 9% unknown	50/25 (80%), 48/20 (13%), 54/27 (7%)	0	32	20

contralateral breast. Endocrine therapy is sometimes considered as an alternative adjuvant monotherapy in patients who do not receive radiotherapy. However, it is notable that in the UK/ANZ study, tamoxifen alone was associated with HR 0.71 (95% CI, 0.57–0.87; $p = 0.001$) for all secondary breast events, either recurrence of DCIS or invasive breast cancer, while radiotherapy alone was associated with HR 0.41 (95% CI, 0.30–0.57; $p < 0.0001$) [9].

Patient Selection

While adjuvant radiotherapy has been consistently shown to improve local control in both older and more recent studies, and across all subgroups of patients, its absolute benefit is modest. As discussed, adjuvant radiotherapy does not affect rates of distant recurrence or survival. Moreover, radiotherapy is associated with risks, including skin toxicity with cosmetic implications, transient pulmonary toxicity, long-term cardiac toxicity, and risk of radiation-induced second malignancy. Financial toxicity of cancer treatments is another important consideration including time spent away from work, transportation, and patient co-pays [17]. In select patients, the local control benefit may be too small to justify the morbidity and burden of treatment. Nomograms and tumor biology defined by genomic assays may help with patient selection in these cases.

Multiple nomograms have been developed to help predict the risk of local recurrence after breast-conserving surgery for DCIS. The most-cited of these are the Memorial Sloan-Kettering Cancer Center (MSKCC) and the University of Texas MD Anderson Cancer Center (MDACC) nomograms. The MSKCC nomogram was based on a retrospective review of 1868 patients treated from 1991 through 2006 and incorporates age, margin status, number of excisions, treatment era, and receipt of endocrine therapy. The concordance index is reported to be 0.704 [18]. The MDACC nomogram was based on a retrospective review of 794 patients treated from 1997 through 2007 and incorporates tumor grade, prevalence of necrosis, initial presentation, margin status, and receipt of endocrine therapy and was based on a cohort that received more radiotherapy, had longer follow-up, and had a lower 10-year recurrence rate than the MSKCC cohort. The concordance index for the MDACC nomogram is reported to be 0.63 [19].

Genomic testing is increasingly used in lieu of or in addition to nomograms to assess tumor biology and estimate outcomes. The predictive and prognostic value of genomic assays has been well-established in early-stage invasive breast cancer and helps to provide guidance for inclusion of additional therapy. Oncotype Dx, a 21-gene assay, is routinely used to predict risk of distant recurrence in patients with estrogen receptor-positive, node-negative invasive breast cancer and helps to determine if chemotherapy should be given [20]. In DCIS, the key utility of such tests is to forecast the benefit of adjuvant radiotherapy.

The DCIS score, which includes a subset of genes from the Oncotype Dx test, has now been validated as a tool for patients with DCIS to help quantify the risk of an ipsilateral breast event in women who undergo breast-conserving surgical excision without adjuvant radiotherapy [21, 22]. Another biological signature, DCISionRT (PreludeDx), was developed for DCIS specifically, to help predict the risk of invasive breast cancer or any ipsilateral breast event, either DCIS or invasive breast cancer, after breast-conserving surgery followed by radiotherapy, and has been demonstrated to be prognostic for these endpoints [23]. These tests have not yet been incorporated into routine clinical practice but are likely to be increasingly adopted as costs decrease and testing sensitivity and specificity increase. Interestingly, a recent small study ($N = 59$ patients) demonstrated 92% concordance between traditional nomograms and Oncotype Dx, arguing against the routine use of an expensive test when nomograms are widely available online to the public, free of charge [24].

Indeed, an economic analysis of genetic testing for determining whether or not radiation should be used found that testing was not cost-effective [25]. Instead, relative patient utilities for being without disease after radiation therapy or observation (i.e., fear of side effects of treatment versus recurrence) drove the decision to select radiation, underscoring the need to incorporate individual patient preferences regarding the risks and benefits of treatment in the decision-making process. Online decision tools that inform women about their options and the effect of each treatment on their individual risk may lead to improved decision-making about DCIS treatment by helping women gain a more complete understanding of treatment risks and benefits. Such tools allow patients and physicians to view outcomes tailored to individual characteristics (e.g., age, grade, ER status) for each treatment option [26]. One important message conveyed by decision aids for DCIS is that survival outcomes are essentially the same with whichever treatment chosen. Armed with this information, patients may be able to better evaluate treatments based on their preferences, their tolerance for recurrence versus the inconvenience or side effects of treatment, and improve the quality of their DCIS treatment decisions. While such decision tools may be useful in enabling personalized decision-making, these tools will need to be adaptive in order to incorporate novel prognostic and predictive factors, including those based upon new generation genetic tests. Furthermore, novel methods for communicating risk and uncertainty will need to be evaluated for their accessibility to patients. A study of informed consent practices for radiation therapy found that most did not meet the readability standards recommended by the American Medical Association, highlighting an important gap that patient-facing tools should strive to fill [27].

Radiation Options: Hypofractionation and Boost

When adjuvant radiotherapy is selected or recommended, treatment can be tailored for patients. For example, the burden of daily radiotherapy may be reduced by hypofractionating treatment in patients who meet the dose constraints imposed by shorter course treatment. Conversely, dose escalation through a radiation boost to the resection cavity may be beneficial for patients with higher risk disease.

The non-inferiority of hypofractionation has been well-established for early-stage invasive breast cancer through multiple randomized clinical trials [28, 29]. The use of hypofractionated radiation for DCIS has been supported by extrapolation from that data and retrospective studies, but results from large randomized clinical trials of exclusively DCIS patients have not yet been published. A retrospective study of 1609 DCIS patients treated in Ontario utilized propensity score-adjustment to compare patients who received conventionally fractionated radiotherapy (50 Gy in 25 fractions) and hypofractionated radiotherapy (42.5 Gy in 16 fractions) and showed 10-year local recurrence rate for DCIS or invasive carcinoma to be 12.8% and 10%, respectively. There was no association between hypofractionation and risk of local recurrence on multivariate analysis (HR, 0.8; 95% CI, 0.5–1.2; $p = 0.34$) [30].

While the locoregional control benefit of a radiotherapy boost to the resection cavity has only been demonstrated for invasive breast cancer in a randomized clinical trial [31], a large multi-institutional pooled retrospective analysis of 4131 patients suggests a similar benefit for DCIS (HR, 0.73; 95% CI, 0.57–0.94; $p = 0.01$) which benefit persisted across all age groups [32]. A randomized clinical trial examining the optimal radiation dosing strategy for DCIS closed to accrual in 2014, and results have not yet been reported. Breast International Group (BIG) 3–07/Trans-Tasman Radiation Oncology Group (TROG) 07.01 (NCT 00470236) is a 2×2 factorial design randomized phase III trial of 1608 patients. Comparing conventional fractionation (50 Gy in 25 fractions) with hypofractionation (42.5 Gy in 16 fractions) and boost (16 Gy in 8 fractions after either initial course) with no boost using the endpoints of local recurrence, survival, toxicity, and quality of life, this study was also designed to identify and evaluate the use of molecular signatures to facilitate individualization of therapy.

The 2018 American Society for Radiation Oncology (ASTRO) consensus guidelines for whole-breast irradiation, based on literature review and expert opinion, support the use of hypofractionation for DCIS. It also recommends a boost to the tumor bed in DCIS patients with risk factors for recurrence, including age ≤ 50 years, high grade tumors, or margins < 2 mm [33].

Radiation Options: Partial-Breast Irradiation

Another strategy to de-escalate therapy for select patients with DCIS and potentially reduce the morbidity of treatment is partial-breast irradiation. A pooled analysis of 300 patients treated with accelerated partial-breast irradiation (APBI) reported an ipsilateral breast tumor recurrence rate of 2.6% at 5 years and no difference when compared with patients with invasive disease, who had an ipsilateral breast tumor recurrence rate of 3.1% at 5 years ($p = 0.9$) [34]. Based on this and other retrospective studies, the 2017 ASTRO consensus statement for APBI revised a prior recommendation against the use of APBI for DCIS. The updated guidelines suggest that patients with low-risk DCIS meeting RTOG 9804 criteria are suitable candidates for APBI [35].

Mammosite is the most well-studied method of APBI for DCIS, but this and other invasive techniques have become less popular in recent years, at least in part due to concern regarding long-term cosmetic outcomes. NRG B-39/RTOG 0413 is a randomized clinical trial comparing whole-breast and partial-breast irradiation and included and stratified patients with DCIS, who made up 24% of participants [36]. PBI methods allowed in the trial included multi-catheter brachytherapy, Mammosite, and 3D conformal external beam radiation. Cosmetic results presented at ASTRO 2019 suggested similar patient-rated global cosmetic score but worse physician-rated global cosmetic score for PBI [37]. In theory, any of these methods of PBI delivery can be used for patients with DCIS. In practice, 3D conformal external beam radiation may be the easiest for both patients and physicians.

The Future of Radiotherapy for DCIS

Active surveillance is being considered as an initial strategy following diagnosis of DCIS. Several population-based studies have evaluated the natural history of DCIS without treatment, most recently a SEER database analysis of 1286 patients captured in the database from 1992 to 2014, published in 2019. Among patients with tumor grades I/II and III, the 10-year net risk of ipsilateral invasive breast cancer was 12.2% (95% CI, 8.6 to 17.1%) and 17.6% (95% CI, 12.1 to 25.2%), respectively [38]. These low rates, comparable or even lower than those reported by ECOG-ACRIN E5194, suggest that many patients with DCIS may safely omit all locoregional treatment.

A US-based multi-institutional randomized clinical trial for low-risk DCIS, Comparison of Operation to Monitoring with or without Endocrine Therapy (COMET) (NCT02926911), will compare the strategy of active surveillance, which allows endocrine therapy as per physician choice, and "guideline concordant care," which consists of breast-conserving surgery ± adjuvant radiotherapy per physician choice ± endocrine

therapy per physician choice. The planned accrual goal is 1200 patients and will provide evidence regarding the oncologic and patient-reported outcomes associated with active surveillance for low-risk DCIS.

Internationally, the management of low-risk DCIS (LORD) study (NCT02492607)

in Europe and the trial of surgery versus active monitoring for low-risk DCIS (LORIS) (ISRCTN27544579) in the UK will similarly compare current standard treatments for DCIS with active surveillance. In Japan, a single-arm trial of endocrine therapy alone for DCIS, called LORETTA (UMIN000028298), is underway.

Treatment after Prior Radiotherapy

Salvage treatment for recurrent DCIS or invasive disease after prior treatment for DCIS poses unique challenges. In fact, the limitation of salvage treatment options can be an important consideration for some women who are deciding upon adjuvant radiotherapy for DCIS. In a study of 745 women treated for DCIS, "radiation would not be an option" for future treatment was the fourth most commonly cited reason, more common than the concern for toxicities, among women who did not receive adjuvant radiation after breast-conserving surgery [39].

The four randomized clinical trials comparing patients who received radiotherapy following lumpectomy to lumpectomy alone did not demonstrate any overall differences in mortality [4]. However, among the small number of patients who later developed invasive breast cancer following radiotherapy for DCIS in the ipsilateral breast, there was a trend toward higher breast cancer-specific mortality. A Surveillance, Epidemiology, and End Results (SEER) database analysis of 3407 patients supports the finding that radiotherapy for DCIS is associated with increased breast cancer-specific mortality in women who later developed an invasive second breast cancer, particularly among patients who developed invasive disease in the ipsilateral breast. The breast cancer-specific mortality was 8.0% for patients who received prior radiotherapy for DCIS, compared with 4.7% for patients who did not [40].

In the event of recurrent DCIS or invasive disease in patients who previously received adjuvant radiotherapy, salvage mastectomy is the standard approach. A second breast-conserving surgery for an ipsilateral breast event, either DCIS or invasive carcinoma, is another possibility in patients who previously received breast-conserving surgery alone for DCIS. A SEER and SEER-Medicare database analyses of 2679 patients with recurrent breast cancer who were previously treated for DCIS between 1990 and 2011 found that provider-related factors were associated with the decision for breast preservation at the time of ipsilateral breast event, such that providers in geographical areas with more radiotherapy use increased the likelihood of mastectomy use, even in patients who previously received breast-conserving surgery alone and may have been eligible for breast-conserving therapy at the time of the second breast event [41].

Re-irradiation with curative intent may be considered in select patients and has been reported in small series to be tolerated with significant cosmetic sequelae but no other significant toxicities [42, 43].

Conclusion

DCIS is a precursor of invasive breast cancer but not all women with DCIS will progress to develop invasive cancer. DCIS has been found incidentally in 8.9% of women postmortem [44], without ever impacting quality of life or mortality. Yet, DCIS is routinely treated similarly to invasive breast cancer, with surgery followed by radiotherapy and endocrine therapy, leading to concerns regarding overtreatment. Older randomized clinical trials on the addition of radiotherapy demonstrated local control but not survival benefits. More recent studies such as RTOG 9804 and ECOG-ACRIN E5194 have sought to identify women in which the omission of radiotherapy is associated with acceptably low rates recurrence. Evaluation of tumor biology with assays like Oncotype Dx and DCISionRT has emerged as another strategy by which patients may be selected for de-escalation of treatment.

In women who are recommended adjuvant radiotherapy, options exist that can help providers individualize treatment. These options include hypofractionation, delivery of a boost to the resection cavity, and partial-breast irradiation. BIG 3–07/ TROG 07.01 is a randomized clinical trial that will help clarify the role of hypofractionation and boost radiation. The future of radiotherapy for DCIS will be affected by the COMET study, investigating the safety of employing an active surveillance strategy for DCIS, similar to that used for low-risk prostate cancer. Endocrine therapy alone provides an alternative method of risk reduction for patients with DCIS.

The treatment paradigm for DCIS continues to evolve, trending toward de-escalation. Ultimately, we feel that the inclusion or omission of adjuvant radiotherapy and radiotherapy regimen chosen for DCIS should be a decision made after a careful discussion between a patient and her physician, taking into account individual patient characteristics and preferences. Communicating the benefits and risks of treatment options, as well as assessing the burden imposed by treatment for an individual patient, is critical in ensuring treatment is consonant with patient preferences.

Compliance with Ethical Standards

Conflict of Interest Puyao Li and Rinaa Punglia declare no conflict of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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