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

Treatment of Ductal Carcinoma In Situ: Considerations for Tailoring Therapy in the Contemporary Era

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Abstract

Purpose of Review Standard options for the treatment of ductal carcinoma in situ (DCIS) include breast-conserving surgery (BCS) alone; BCS with radiotherapy or endocrine therapy, or both; and mastectomy. Survival is excellent with all options, but rates of local recurrence (LR) vary, as do quality-of-life measures. Here, we discuss treatment outcomes, risk factors for LR, and tools for risk estimation.

Recent Findings After BCS, radiotherapy reduces the risk of LR by half, and endocrine therapy reduces the risk by a third. Young age, inadequate margins, and greater volume of disease are associated with higher risk of LR after BCS, while young age, high grade, and microinvasion are associated with higher risk of locoregional recurrence after mastectomy. Clinical tools, including the Memorial Sloan Kettering Cancer Center (MSKCC) DCIS nomogram, provide LR risk estimates after BCS that appear more accurate than current genomic assays. The safety of active surveillance for seemingly low-risk patients remains uncertain.

Summary Estimation of LR risk, utilizing a multitude of clinicopathologic and treatment factors, can help a woman balance that risk with her values and priorities, and allow her to choose the optimal treatment option for her.

Keywords Ductal carcinoma in situ · Breast-conserving surgery · Mastectomy · Local recurrence · Risk estimation · Nomograms

Introduction

Ductal carcinoma in situ (DCIS) is a non-invasive malignancy comprising approximately 20% of all newly diagnosed breast cancers [1]. Distinguished by a malignant proliferation of ductal epithelial cells that are confined to the milk ducts, this "stage 0" entity has been increasingly detected with the widespread adoption of screening mammography. Standard treatment options include breast-conserving surgery (BCS); BCS with adjuvant irradiation or endocrine therapy, or both; and mastectomy. Survival is excellent with all surgical options, with 20-year breast cancer-specific mortality rates of 3–4% [2•, 3], and no added survival benefit conferred by either adjuvant irradiation or endocrine therapy [3–6, 7•]. However, rates of local recurrence (LR) vary widely. When a limited extent of disease allows for oncologically safe utilization of various options, decision making may become paradoxically complex, requiring consideration of both risk of LR and quality-of-life factors. The optimal approach for each patient is best determined by thorough discussion grounded in evidence-based risk estimation, and a clear understanding of the patient's individual priorities.

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Standard Treatment Options

The fundamental goals of treating DCIS are to eradicate disease in the breast and prevent future development of invasive recurrence. This may be accomplished with mastectomy or BCS with or without adjuvant irradiation, and/or endocrine therapy.

Mastectomy

Once the gold standard for treatment of all DCIS, mastectomy is now considered necessary only for extensive or multicentric DCIS. However, rates of mastectomy for DCIS are increasing in the contemporary era, especially among young women [8,

9], with decision making influenced by concerns about disease recurrence [10]. Overall rates of LR after mastectomy for DCIS are low, with a meta-analysis of eight studies demonstrating a 10-year adjusted LR rate of 2.6% (95% confidence interval [CI] 0.8–4.5%) [11]. In comparison with BCS, mastectomy carries an increased risk of surgical morbidity [12] and potential long-term impacts on body image and sexual well-being [13]—risks that should be discussed with women who are considering mastectomy but are candidates for BCS.

Breast-Conserving Surgery With or Without Adjuvant Radiotherapy

While there have been no randomized trials directly comparing LR and survival between BCS and mastectomy in patients with localized DCIS, the safety of BCS for these patients was extrapolated from randomized trials showing equivalent outcomes in early-stage invasive cancers [14–17].

The role of adjuvant radiotherapy (RT) after BCS for DCIS has been studied in four prospective randomized trials (Table 1). With mature follow-up of 13 to 17 years, LR rates were 20–35% with BCS alone, with a relative risk reduction of approximately 50% with the addition of RT [3–6, 7•]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) individual patient-level meta-analysis cumulatively analyzed data from 3729 patients in these trials, finding an absolute 15% reduction in 10-year LR with adjuvant RT (28.1% no RT versus 12.9% RT, $p < 0.0001$), with a benefit conferred in all subsets of age, method of detection, margin status, extent of BCS, and pathologic characteristics (focality, grade, size, and comedonecrosis). Importantly, there was no survival benefit; 10-year rates of breast cancer mortality (3.5% no RT versus 4.1% RT, p = not significant [NS]) and overall mortality (8.2% no RT versus 8.4%, p = NS) were similar in both groups [7•].

However, subsequent studies have demonstrated that recurrence rates have decreased for women treated without adjuvant RT [18•]. Three prospective studies of patients with selected low-risk DCIS treated with BCS alone, albeit with varying rates of tamoxifen use (0–62%), reported LR rates ranging from 11.4% to 15.6% at 10–12 years of follow-up [19–21, 22••]. These lower rates suggest a smaller absolute benefit of radiation among low-risk DCIS patients in the modern era. Therefore, the risk reduction associated with RT must be weighed against the known rare but potentially serious risks of cardiovascular/pulmonary disease and radiation-induced malignancies after irradiation for breast cancer for the individual woman [23, 24].

Adjuvant Endocrine Therapy

Randomized trials showed a 25–30% reduction in LR with the addition of endocrine therapy for estrogen receptor (ER)–positive DCIS following BCS with or without RT, but have found no impact on survival [4, 6, 25]. Among 1804 women with DCIS treated with BCS and RT in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial, the 15-year ipsilateral recurrence was reduced from 18.3% to 16.0% with the addition of 5 years of tamoxifen, with no reduction in breast cancer-specific or overall mortality [6]. Interestingly, among 1576 women randomized in the UK, Australia, and New Zealand (UK/ANZ) trial, of whom 67% received RT and 33% did not, a significant reduction in LR was observed only among those treated without RT, declining from 26.4% to 20.9% at median 12.7 years of follow-up (p = 0.04) [4]. While the magnitude of risk reduction of breast events was similar in both trials, neither found any improvement in survival with adjuvant tamoxifen, with breast cancer mortality of ≤ 4% in all groups [4, 6].

More recently, the benefit of anastrozole was compared with tamoxifen among postmenopausal women with ER-

Table 1 Randomized trials examining local recurrence and breast cancer mortality with and without adjuvant radiotherapy following breast-conserving surgery for ductal carcinoma in situ, among patients who did not receive endocrine therapy

Study	*n*	Follow-up (years)	Local recurrence			Breast cancer mortality	
			No RT	RT	Relative risk reduction	No RT	RT
NSABP B-17 [6] 1985–1990	813	15	35%	18%	50%	3.1%	4.7%
EORTC 10853 [5] 1986–1996	1010	15	31%	18%	48%	5%	4%
SweDCIS [3] 1987–1999	1046	20	32%	20%	38%	4.2%	4.1%
UK/ANZ DCIS [4]* 1990–1998	475	12.7	25%	9%	69%	2.0%	1.5%
EBCTCG Meta-analysis [7•]** 1985–1999	3729	10	28.1%	12.9%	54%	3.7%	4.1%

RT radiotherapy, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *EORTC* European Organisation for Research and Treatment of Cancer, *SweDCIS* Swedish Ductal Carcinoma In Situ, *UK/ANZ* United Kingdom, Australia, and New Zealand, *EBCTCG*, Early Breast Cancer Trialists' Collaborative Group

*Among patients not receiving tamoxifen

**10-year results obtained from patient-level meta-analysis of the four randomized trials listed above

positive DCIS treated with BCS in the NSABP B-35 and International Breast Cancer Intervention Studies (IBIS)-II trials [26, 27]. All 3104 patients enrolled in the NSABP B-35 trial and 2091 of 2890 (71%) women in the IBIS-II trial received RT. While results of B-35 indicated a lower 10-year breast cancer event rate with anastrozole (6.9% anastrozole versus 10.9% tamoxifen, $p = 0.02$), results of IBIS-II suggested non-inferiority of anastrozole, with both agents conferring a 5% breast cancer event rate [26, 27].

The rate of uptake of adjuvant endocrine therapy among DCIS patients is reported to range from 20% to 48% [28, 29], and is likely affected by the broad profile of side effects, including arthralgias and osteoporosis with aromatase inhibitors, risk of thromboembolic/cardiovascular events and endometrial cancer with tamoxifen, and menopausal symptoms with both types of endocrine therapy [26, 27]. These not-insignificant risks must be carefully considered, particularly given the lack of added survival benefit after adequate local therapy for DCIS.

Breast Conservation: Risk Factors for Locoregional Recurrence

While early trials provided a foundation for understanding the risk of LR after treatment of DCIS, modern data—largely examining patients who underwent BCS—suggest a substantial influence of several clinicopathologic features on risk of LR (Table 2). Recent and continued investigations of the interplay of these risk factors allow for more precise risk stratification, and appropriate tailoring of local and adjuvant therapies.

Table 2 Ten-year rates of local recurrence following breast-conserving surgery for ductal carcinoma in situ, stratified by risk factors and receipt of adjuvant radiotherapy. *RT* radiotherapy

Risk factor		No RT	RT
Time period [18•]	1978–1998	26%	13%
	1999–2010	19%	11%
Margin status [30•]	Tumor on ink	41%	23%
	≤ 2 mm	27%	12%
	> 2–10 mm	23%	13%
	≥ 10 mm	16%	10%
Age [31••]	< 40 years	37.5%	20%
	40–49 years	22%	17%
	50–59 years	17%	9%
	60–69 years	24%	7%
	70–79 years	17.5%	8%
	≥ 80 years	9%	0%
Volume [7•, 32]	Minimal (core biopsy only)	14.5%	6%
	1–20 mm	29%	13%
	20–50 mm	39%	13%

Treatment Period

Rates of LR after BCS for DCIS have declined over time, with contemporary rates evidently lower than those observed in the aforementioned early randomized trials. Subhedar et al. [18•] examined trends in LR rates in a retrospective analysis of 2996 patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) over a 32-year period, finding that 10-year recurrence rates declined significantly, from 20% among those treated from 1978 to 1998, to 14% among those treated from 1999 to 2010 ($p < 0.0001$). Treatment in the later period was independently associated with LR (hazard ratio [HR] 0.74, $p = 0.02$) even after controlling for multiple other factors, including age, family history, mode of detection, nuclear grade, necrosis, margin status, and receipt of RT and/or endocrine therapy. This association was predominantly due to reduction in LR among patients who did not receive RT, suggesting that the observed decline in LR rates over time is not attributable to improved radiation techniques.

Age

Evidence for an association of young age with increased risk of LR after treatment of DCIS with BCS with or without RT was first noted in a small series from 1999 [33], and later supported by the early randomized trials. In the joint analysis of the NSABP B-17 and B-24 trials, young women had higher risk of LR, both invasive (with age ≥ 65 years as reference: HR 2.1 among those age < 45 years, HR 1.8 among those age 45–54 years, and HR 1.5 among those age 55–64 years, $p = 0.003$) and DCIS (HR 2.9 among those age < 45 years, HR 1.8 among those age 45–54 years, and HR 1.7 among those age 55–64 years, $p < 0.001$) [6]. Similarly, in the European Organisation for Research and Treatment of Cancer (EORTC) 10853 randomized trial, women age ≤ 40 years had a higher risk of LR compared with those > age 40 years (HR 1.94, $p = 0.009$) at 15.7 years of follow-up [5]. Summative results from the EBCTCG meta-analysis showed a 10-year absolute risk of ipsilateral breast cancer events after BCS followed by RT of 18.5% among women age < 50 years, compared with 10.8% among women age ≥ 50 years. Interestingly, younger women also achieved a lesser proportional risk reduction from RT (HR 0.69 if age < 50 years versus HR 0.38 if age ≥ 50 years, $p = 0.0004$) [7•].

In a contemporary analysis across the full spectrum of age among nearly 3000 patients with DCIS treated with BCS, Cronin et al. demonstrated that risk of recurrence decreased with age, with the highest 10-year rates of LR of 27.3% observed among women age < 40 years, and the lowest rates of 7.5% among those age ≥ 80 years ($p < 0.0001$). An association

was seen by decade of age, even after adjustment for eight clinicopathologic and treatment variables (HRs with age < 40 years as reference: [0.82, $p = 0.36$], 50–59 [0.46, $p = 0.0005$], 60–69 [0.50, $p = 0.003$], 70–79 [0.56, $p = 0.02$], and ≥ 80 years [0.21, $p = 0.0015$]). Women age < 40 years also had a markedly higher risk of invasive recurrence, with a 10-year rate of 15.8% among those age < 40 years as compared with 6.5% among those age ≥ 40 years [31••].

Margin Status

The early randomized trials of RT showed an association of positive margins with a higher risk of LR after BCS for DCIS [3, 5, 6, 7•]. In the NSABP B-24 trial of tamoxifen versus placebo in DCIS patients undergoing BCS and RT, among those with positive margins, there was a significant increase in invasive recurrence as compared to those with negative margins (HR 2.61, 95% CI 1.68–4.05, $p < 0.0001$) [6]. Most of the early trials did not quantify the width of negative margins, limiting ability to study the ideal margin width required.

In a large population of almost 3000 DCIS patients who underwent BCS with or without RT over a 32-year period, Van Zee et al. demonstrated lower risk with wider margins: the 10-year rate of LR was 31% among those with positive margins versus 13% among those with margins > 10 mm. This association persisted among those who did not receive RT ($n = 1225$) on multivariable analysis that controlled for relevant clinicopathologic and treatment factors (with positive margins as reference: HR 0.75 for close ≤ 2 mm margins, HR 0.58 for 2–10 mm margins, HR 0.31 for > 10 mm margins, $p < 0.0001$). There was no clear association among those who did receive RT ($p = 0.95$) [30•].

In 2016, a consensus statement was established by the Society of Surgical Oncology, the American Society for Radiation Oncology, and the American Society of Clinical Oncology [34••] based upon findings from a study-level meta-analysis of the literature including 7883 women from 20 studies [35••]. It stated that among women undergoing BCS and RT, a negative margin definition of ≥ 2 mm minimized risk of LR as compared with a more narrow threshold (odds ratio [OR] 0.51, 95% CI 0.31–0.85), while a negative margin definition of > 2 mm offered no greater benefit among those receiving RT (OR 0.99, 95% CI 0.61–1.64) [35••].

Volume of Disease

The quantification of volume of DCIS has been fraught with limitations due to variable reporting of size and extent, and difficulty measuring the total extent of a lesion that extends to multiple pathologic sections. Among patients treated with BCS and RT, 10-year LR rates in the EBCTCG meta-analysis were similar among those with smaller tumors (measuring 13.1–20 mm, 13.1%) and those with larger tumors (measuring 20–50 mm, 13.0%) [7•]. In contrast, among women not receiving RT, larger size of DCIS was associated with higher 10-year LR rates (36.4% vs. 26.3%). Recent data lend further support for this association between increasing tumor size and LR among those not receiving RT. In the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) E5194 prospective study, among 665 patients with low-risk DCIS who underwent BCS alone, there was a significant association of increasing tumor size with higher risk of LR (with 5 mm size as reference: 6–10 mm [HR 1.42], > 10 mm [HR 2.11], $p = 0.03$) [20].

However, even women with very low volume of disease are not at negligible risk of LR. In a study of women treated from 1990 to 2011 for minimal-volume DCIS, defined as DCIS diagnosed on core biopsy with no residual disease identified at excision, the 10-year rate of LR was 14.5% among those who underwent BCS without RT ($n = 207$). This rate was significantly higher than contralateral breast event rates, and was much higher than in those who received RT (6%) [32]. These findings emphasize the rationale for considering adjuvant therapy for other concomitant risk factors, even among those with a minimal volume of disease.

Mastectomy: Risk Factors for Locoregional Recurrence

While the aforementioned factors are known to confer higher risk of LR after BCS, widely variable results have been reported on their association with locoregional recurrence after mastectomy, with past studies being limited by retrospective nature and small populations [36–39]. In a recent study of a consecutive cohort of over 3000 women treated with mastectomy without adjuvant RT for DCIS over two decades at two cancer centers, Mamtani et al. found a low overall cumulative 10-year incidence of locoregional recurrence of 1.4%, with young age < 50 years being independently associated with locoregional recurrence (HR 14.7, 95% CI 3.5–61.5, $p < 0.001$), along with microinvasion (HR 2.88, 95% CI 1.4–5.92, $p = 0.004$) and high nuclear grade (HR 3.09, 95% CI 1.38–6.94, $p = 0.006$); margin status was not significantly associated ($p = 0.14$) [40••]. Overall, the cumulative 10-year incidence of locoregional recurrence was 4.2% among women age < 40 years, 2.0% among women age 40–49 years, and 0.2% among women age ≥ 50 years ($p < 0.0001$), with the majority of excess risk harbored by women with all three risk factors of young age, high grade, and microinvasion [40••]. For those age ≥ 50 years, locoregional recurrence was ≤ 2% in all subsets, regardless of grade or presence of microinvasion. These results provide contemporary data for evidence-based risk estimation and appropriate preoperative counseling for patients with DCIS considering mastectomy.

Risk Estimation

A key aspect of decision making for many patients is an understanding of their individual risk of LR. Given the complex interplay of various factors, it is difficult to estimate LR risk without a predictive model that can appropriately integrate the multitude of clinicopathologic characteristics and treatment factors that influence risk of recurrence.

DCIS Nomogram

Rudloff et al. [41•] developed a DCIS nomogram to estimate 5- and 10-year risks of LR after BCS, inclusive of 10 known clinicopathologic and treatment variables. This model was based upon a consecutive population of 1681 patients treated with BCS from 1991 to 2006. The variables included were patient age, family history, year of surgery, presentation, nuclear grade, presence of necrosis, margin status, number of re-excisions, and receipt of RT and/or endocrine therapy. The DCIS nomogram was internally validated with good discrimination (C-index 0.704, bootstrap corrected 0.688) [41•] and has since been externally validated in multiple independent populations (C-index 0.63–0.92) [42–46]. This free-of-charge online tool (www.nomograms.org) allows patients and physicians to both estimate individual risk, and to more objectively consider the benefit of various treatment choices.

Oncotype DX DCIS Score

In recent years, genomic assays have been increasingly studied for application in clinical care. The Oncotype DX (Genomic Health, Redwood City, CA) DCIS score was developed to estimate LR risk in DCIS patients treated with BCS using a 12-gene assay. This DCIS score was applied to a subset of 327 patients in the ECOG-ACRIN E5194 study and was found to be associated with development of both any LR (HR 2.31) and invasive recurrence (HR 3.68). However, an "intermediate" score was associated with a greater rate of recurrence than a "high" score was, with 10-year risks of LR of 26.7% and 25.9%, respectively [47]. Furthermore, examination of this score in a population of 571 patients with DCIS in Ontario treated with BCS alone suggested that while a 50-point increase in the DCIS score was associated with LR (HR 1.68, $p = 0.02$), a number of other clinicopathologic features had a larger effect on risk [48], emphasizing the importance of incorporating all factors into risk estimation. As a result, a Refined Oncotype DX DCIS Score (RDS) was created with inclusion of age, extent, and year of surgery [49].

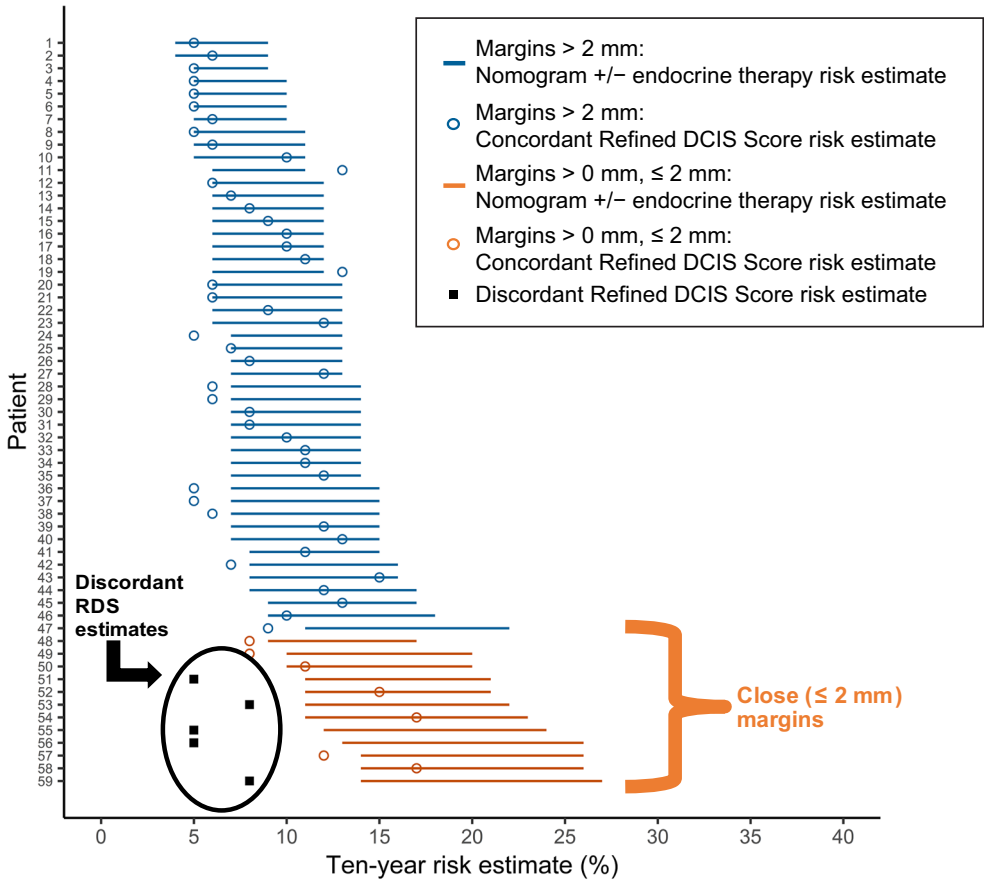

Fig. 1 Comparison of 10-year risk estimates of Refined Oncotype DX (Genomic Health, Redwood City, CA) Breast DCIS Score and Memorial Sloan Kettering Cancer Center (MSKCC) Nomogram. In 92% of patients, the estimates are concordant, but the RDS appears to underestimate risk for most patients with close margins. Abbreviations: DCIS, ductal carcinoma in situ; RDS, Refined Oncotype DX Breast DCIS Score

However, all novel tools should be validated in independent populations and evaluated using standard metrics (calibration and measures of discrimination) to determine if there is added value beyond available tools, before acceptance into practice. In a recent study comparing the RDS with the MSKCC DCIS Nomogram in a cohort of patients 50 years of age or older with DCIS size 2.5 cm or smaller, the 10-year LR estimates were concordant in 92% of patients, while the RDS underestimated LR risk in the remaining 8% of discordant cases (Fig. 1). These data (Fig. 1) suggest that among women age ≥ 50 years with limited DCIS, routine use of the Refined Oncotype DX DCIS Score is not warranted at this time, particularly given its high cost (> $4600) [50••].

Present Relevance and Controversies

As a non-invasive entity with numerous treatment options, the optimal course of action for a patient with DCIS remains a subject of controversy, with concerns regarding both overtreatment and undertreatment.

Given the excellent survival with multiple treatment options, some have raised concerns for possible overtreatment of DCIS, with interest in examining active surveillance for low-risk DCIS instead of surgery. Three ongoing trials are examining rates of ipsilateral invasive breast cancer-free survival among selected patients: the LORIS (*Surgery* versus *Active Monitoring for Low-Risk DCIS*) trial [51], the LORD (*Low-Risk DCIS*) trial [52], and the COMET (*Comparison of Operating to Monitoring with or without Endocrine Therapy*) trial [53]. A concern regarding these trials is whether the specified "low-risk" criteria indeed represent a group at acceptably low risk for development of invasive cancer. In a study of 296 patients meeting LORIS criteria after core biopsy (age ≥ 46 years with screen-detected, non-high-grade DCIS without comedonecrosis), 20% were found to have invasive carcinoma at surgical excision, demonstrating a considerable upgrade rate even among supposedly "low-risk" patients [54]. Even after exclusion of those with invasion or any high-grade DCIS on excision, in the remaining patients who were "LORIS eligible," there was a 12% rate of LR at 10 years, and a 6% rate of invasive LR [55]. Furthermore, a recent study from the National Cancer Database, including 140,615 patients with DCIS, demonstrated incremental delay to surgery to be independently predictive of invasive breast cancer, which raises further concern regarding observation alone [56]. With results from the trials of observation yet forthcoming, surgical excision remains a standard component of therapy for all patients with DCIS.

On the other end of the spectrum is the potential for undertreatment. Prospective studies have demonstrated that even among selected patients with "low-risk" DCIS, LR rates ranged from 11.4% to 15.6% at 10 to 12 years of follow-up among patients treated with BCS alone, without RT [19–21, 22••]. And, in a Surveillance, Epidemiology and End Results (SEER) database analysis of over 32,000 patients with DCIS treated between 1988 and 2007, Sagara et al. found lower breast cancer mortality associated with use of RT among patients with high-risk factors of high nuclear grade, young age, and larger tumor size. Yet, they found that approximately 38% of such "high-risk" patients did not receive RT [57]. These findings reiterate the importance of taking all relevant risk factors into account when estimating individual LR risk.

Conclusions

In the contemporary era, there are a variety of treatment options for DCIS, a non-invasive precursor to breast cancer. Complete removal of DCIS remains crucial in order to minimize risk of LR, particularly invasive recurrence. Adjuvant RT decreases LR risk after BCS by approximately 50%. Individual risk of LR after surgery is variable, and modified by a complex interplay of multiple risk factors. As RT and endocrine therapy have no proven impact on breast cancer–specific survival, risks and benefits of these treatments must be carefully considered in the context of possible side effects, impact on quality of life, and expected benefit in reducing LR. Accurate and evidence-based risk estimation is a critical component of tailoring therapy. Integrating this information with an understanding of individual priorities is essential when counseling a woman with DCIS, to equip her to select the best treatment option for her.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest. The preparation of this article was supported in part by NIH/NCI Cancer Center Support Grant No. P30CA008748 to Memorial Sloan Kettering Cancer Center.

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