Current Breast Cancer Reports (2023) 15:58–68
https://doi.org/10.1007/s12609-023-00475-5

De-escalation in DCIS Care

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Accepted: 7 January 2023 / Published online: 15 March 2023

Abstract

Purpose of Review Standard DCIS management consists of surgery with consideration of adjuvant radiation and endocrine therapy. However, widespread recognition of the overdiagnosis and overtreatment burden in DCIS has led to a reevaluation of this standard. The purpose of this review is to summarize the foundational clinical trials in DCIS and to discuss ongoing efforts in treatment de-escalation.

Recent Findings Standard of care DCIS management is based on large high-quality randomized clinical trials. The results of those trials have been durable over more than a decade of follow-up. However, we now better appreciate that DCIS is a heterogeneous disease with variable risk of progression. Clinicopathologic and molecular tools are helping better define which patients with DCIS would benefit from de-escalation. Modern clinical trials have proven the safety of shorter and lower dose radiation regimens in low-risk patients, and results from active monitoring trials are highly anticipated. In addition, decision support tools, shared decision-making, and molecular testing promise to help guide patients through an increasingly complex decision-making process.

Summary Current treatment of DCIS has moved towards successful de-escalation of treatment for those patients with low risk of progression. Further incorporation of molecular tools will allow for personalized treatment based on individual risk and preferences.

Keywords De-escalation · Breast cancer · DCIS · Molecular testing · Active monitoring · Radiation

Introduction

Ductal carcinoma in situ (DCIS) was previously understood to be a precursor to invasive cancer and thus has been treated with surgery with or without adjuvant radiation. This approach has been very successful, and as a result, long-term breast cancer mortality following treatment for DCIS is very low, only 1.5−3% [1, 2]. But with improved understanding of disease pathogenesis, we now understand that this approach comes at the expense of overtreatment for some patients. It is likely that we detect and treat lesions that would not cause harm during a patient's lifetime. This contributes to rising healthcare costs, medical waste, and patient physical, financial, and psychological morbidity.

In concert with a refocusing of the healthcare system at large on value, it is only within the past 5−10 years that the concepts of overdiagnosis and overtreatment have gained traction in academic literature [3, 4]. Numerous studies support the now widely held principle that DCIS is a significant contributor to the overdiagnosis burden in breast cancer. Studies of clinically detected lesions treated with biopsy alone report invasive cancer rates of 39−53% with long-term follow-up [5–9]. If the ultimate goal of de-escalation is to treat only those lesions which have the potential to cause harm during a patient's lifetime, these data suggest that 47−61% of clinically detected DCIS is

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overdiagnosed. A study by Ryser et al., which used the Breast Cancer Surveillance Consortium to predict the natural course of screen-detected breast cancers, estimated an overdiagnosis rate of 15.4% [10]. Though estimates of overdiagnosis vary according to the methods used, these data have called into question the traditional understanding of breast cancer pathogenesis as progressing from DCIS to invasive cancer. Indeed, it is now better understood to be a non-obligate precursor. DCIS was rare prior to widespread breast cancer screening, but now represents 20−30% of screen-detected breast cancers [11]. Despite a notable rise in DCIS incidence, there has been no reduction in the diagnosis of late-stage breast cancer, suggesting that not all DCIS would have progressed [12]. Taken together these data suggest that a significant proportion of DCIS lesions are overdiagnosed.

Further, uniform application of standard therapies for DCIS results in overtreatment in many patients. Multiple studies have demonstrated that clinicopathologic criteria can stratify recurrence risk; it is generally accepted that patients with low-risk DCIS derive less absolute benefit from standard therapies than patients with high-risk DCIS [1, 13–21]. However, no consensus definition of low risk has yet emerged. Evidence in support of overdiagnosis and overtreatment in DCIS has reached critical mass and has been used to support broad-based de-escalation efforts. This review will summarize early clinical trials and will explore the state of the science in de-escalation across treatment modalities in DCIS care.

Early Randomized Trials of Adjuvant Therapy for DCIS

Adjuvant Radiation Therapy

The management of DCIS with adjuvant radiotherapy (RT) has been driven by high quality clinical trials. Four randomized clinical trials initiated in the 1980s and 1990s and two subsequent meta-analyses have evaluated the use of RT in patients with DCIS [1, 13, 18–20, 22, 23] These trials, which include NSABP B-17, EORTC 10853, SweDCIS, and UK/ANZ, enrolled nearly 4000 patients and form the basis of support for the benefit of adjuvant RT in reducing the risk of local recurrence following lumpectomy for DCIS [24]. They included all-risk DCIS and employed whole breast radiation (WBI), generally without a boost to the tumor bed. As summarized in the EBCTCG meta-analyses, adjuvant RT reproducibly reduces the risk of in situ and invasive ipsilateral breast tumor recurrence (IBTR) by 50% or more [20, 23]. While adjuvant RT has not been shown to reduce breast cancer mortality following lumpectomy for DCIS, it does reduce the risk of invasive IBTR, which has been shown to be associated with an increased risk of death [1].

Adjuvant Systemic Therapy

Three randomized trials have evaluated the use of tamoxifen in DCIS. IBIS-I, which published long-term follow-up data in 2015, reported that tamoxifen therapy reduced the risk of all new breast cancers by 29%, but had no effect on breast cancer-specific survival [21]. Similarly, NSABP B-24 reported that tamoxifen reduced the risk of invasive IBTR and contralateral breast cancer by 32% without an effect on mortality [1]. A subgroup analysis of patients enrolled in NSABP B-24 confirmed that endocrine therapy only benefitted patients with ER-positive DCIS [25]. The NSABP B-35 and ATAC trials supported the superiority of anastrozole to tamoxifen in postmenopausal women, primarily in those < 60 years of age [26, 27]. IBIS-II confirmed the non-inferiority of anastrozole in postmenopausal women, but failed to establish its superiority, likely due to a low event rate and shorter follow-up [28].

For patients with HER2-positive DCIS, the NSABP B-43 trial explored the use of adjuvant trastuzumab in conjunction with RT. The study enrolled over 2000 patients but did not meet its pre-specified event threshold. The trial reported a non-significant 19% reduction in IBTR events between the RT with trastuzumab and RT alone groups ($p = 0.26$) [29].

Importantly, adherence to endocrine therapy is variable. Studies conducted in different settings among various patient populations report adherence rates of 30−72% [30–32]. One potential option to improve adherence is dose reduction; DeCensi and colleagues conducted a multi-center trial of tamoxifen 5 mg daily for 3 years in women with high risk histologies, including DCIS, and found that dose-reduced tamoxifen decreased the risk of all events (HR of 0.48, 95% CI, 0.26 to 0.92; $P = 0.02$) and contralateral events (HR 0.25, 95% CI, 0.07 to 0.88; $P = 0.02$) [33]. Nevertheless, since side effects can be significant, while absolute benefit is small, the threshold to discontinue endocrine therapy in women with DCIS should be low.

De-escalation of Treatment Modalities

Radiation Therapy

Although adjuvant radiotherapy consistently reduces the risk of IBTR following lumpectomy for DCIS [20, 23], the absolute benefit of radiotherapy depends on baseline recurrence risk. For some women, the recurrence risk following lumpectomy alone may be low enough where observation is acceptable. An ipsilateral recurrence risk of < 10% at 10 years is generally considered an acceptable threshold at which to omit RT, though individual patients may assess risk differently. Three studies have prospectively defined low-risk DCIS using similar clinicopathologic criteria and have reported LR rates of 14.4−15.6% at 10−15 years without RT (Table 1)

[13, 34, 35]. RTOG 9804 defined low-risk DCIS as those lesions that were grade 1 or 2, ≤.5 cm, and were excised with margins ≥3 mm. Even in this low-risk group, where the median size of DCIS was only 0.5 cm, RT reduced the risk of LR by 64% (7.1% with RT vs 15.1% without RT) at 15 years [13]. The prospective cohort ECOG-ACRIN E5194 and DFCI studies similarly reported rates of LR of about 1% per year without plateau [34, 35]. As evidenced by these studies, clinicopathologic criteria have been unable to identify a population of patients who have a recurrence risk of < 10% without adjuvant RT. Investigation into the ability of refined clinicopathologic criteria and molecular testing to prospectively identify patients with lower rates of recurrence following lumpectomy alone for DCIS is ongoing (Table 2).

Table 1 Published phase III clinical trials in radiotherapy omission, hypofractionation, and APBI for DCIS

Study Name	Age	Study design	Pathologic inclusion criteria	Patients, n	Experimental arm	Comparator	Median follow up	Recurrence
RT omission								
DFCI	≥ 18	Prospective cohort	≤ 2.5cm, Grade 1-2, 1cm margins	158	Observation	None	10 years	Local recurrence rate: 15.5%
ECOG-ACRIN E5194	≥ 18	Double arm Non-randomized	≤ 2.5cm, Grade 1-2, 3mm margins	561	Observation	None	12 years	Local recurrence rate: 14.4%
	≥ 18		≤ 1cm, Grade 3, 3mm margins	104	Observation	None	12 years	Local recurrence rate: 24.6%
RTOG 9804	≥ 18	Double arm RCT	≤ 2.5cm, Grade 1-2, 3mm margins	585	Observation	50 Gy, 25 fr 50.4 Gy, 28 fr 42.5 Gy, 16 fr	6.6 years	Local recurrence risk difference: 0.41% (95% CI-.86 to 1.69)*
Hypofractionation								
DBCG-HYPO	> 40	Double arm RCT	Underwent breast conserving surgery	1,882	40 Gy, 15 fr	50 Gy, 25 fr	7.3 years	Locoregional recurrence: HR1.40 95% CI 0.49-4.05
BIG 3-07/RTOG 07.01	≥ 18	4-arm RCT	< 50: any ≥ 18 50: palpable, multifocal, size ≥ 1.5cm, grade 2-3, necrosis, comedo type,margin <1 cm	1,608	42.5 Gy, 16 fr 16 Gy, 8 fr boost	50 gy, 25 fr No boost	6.6 years	Boost: 5-year freedom from LR: HR 0.47; 95% CI 0.31 to 0.72 Hypofractionation: 5-year freedom from LR: HR 0.94; 95% CI 0.51 to 1.73
APBI								
NSABP B-39/ RTOG 0413	≥ 18	Double arm RCT	≤ 3cm No ink on tumor	4,216	Brachytherapy: 34 Gy, 10 fr 3DCRT: 38.5 Gy, 10 fr	WBRT 50 Gy, 25 fr Optional boost 10-16 Gy	10.2 years	IBTR: HR 1.01 (95% CI 0.61-1.68)
RAPID	≥ 40	Double arm RCT	≤ 3cm	2,135	3DCRT 38.5 Gy, 10 fr	WBRT 42.5 Gy, 16 fr Optional boost 10 Gy, 4-5 fr	8.6 years	IBTR: HR 1.27 [90% CI .84-1.91]*
2009-APBI	≥ 40	Double arm RCT	≤ 3cm ≥ 2mm margins	656	IMRT 38.5 Gy, 10 fr	3DCRT, 38.5 Gy, 10 fr	3 years	5-year disease free survival: 89% and 88% (NS)
APBI-IMRT-Florence	≥ 40	Double arm RCT	< 2.5cm > 5mm margins	520	IMRT 30 Gy in 5 fr	WBI 50 Gy in 25 frwith tumor bed boost	10.7 years	IBTR: HR 1.56 95% CI, 0.55-4.37, p=0.40]

Fr=fraction; Gy=gray; RCT=Randomized controlled trial;IMRT=Intensive modulated RT; 3DCRT=3-dimensional conformational RT; WBI=Whole breast radiation

*Includes entire study population

Table 2 Ongoing clinical trials in radiotherapy de-escalation and molecular testing for DCIS

Study	Study design	Primary outcome	Experimental Arm	Comparator	Age	Pathologic inclusion criteria
Hypofractionation						
ROMANCE NCT03878342	*Double arm RCT*	*5-year ipsilateral recurrence*	*50 Gy, 25 fr 40 Gy, 15 fr*	*Active monitoring*	*≥50*	*≤2.5cm, Grade 1-2, 2mm margins , ER/PR+*
NOVEMBER NCT03345420	*Single arm*	*Breast cosmesis at 24 months*	*9 fr**	*None*	*≥18*	
APBI						
OPAR NCT02637024	*Double arm RCT*	*Adverse cosmesis*	*3DCT or IMRT 27.5 Gy, 5 fr*	*3DCRT or IMRT 30 Gy, 5 fr*	*≥50*	*≤3cm, grade 1 or 2 No ink on tumor*
MD Anderson Cancer Center NCT01245712	*Prospective cohort*	*Cosmesis*	*Proton 10 fr**	*None*	*≥18*	*≤3cm No ink on tumor*
TRIUMPH-T NCT02526498	*Prospective cohort*	*Rate of toxicity > grade 2*	*Brachytherapy 22.5 Gy, 3 fr*	*None*	*≥45*	*≤3cm, ER/PR+ No ink on tumor*
Mayo NCT03391388	*Prospective cohort*	*% difference in adverse cosmesis*	*3DCRT, proton, brachytherapy*	*None*	*≥50*	*≤2.5cm No ink on tumor*
MAPBI NCT03936478	*Prospective cohort*	*Physician reported cosmesis*	*MRI-guided 8.2 Gy, 3 fr*	*None*	*≥40*	*≤2.5cm, grade 1-2 ≥3mm margins*
MSKCC NCT04084730	*Prospective cohort*	*Toxicity*	*External beam 24 Gy, 3 fr*	*None*	*≥45*	*<3cm, grade 1 or 2 No ink on tumor*

Fr=fraction; Gy=gray; IMRT=Intensity modulated RT; RCT=Randomized controlled trial; 3DCRT=3-dimensional conformational RT

*Dose not reported

For those who receive RT, there is now an array of options for appropriately selected patients that can dramatically reduce treatment time and toxicity. Randomized data support the use of hypofractionated WBI with or without a tumor bed boost [36, 37] or accelerated partial breast radiation (APBI) [38]. Several recently published results have contributed to these recommendations.

Hypofractionation reduces the duration of RT treatment from 6−7 weeks to 3 weeks or less while still treating the entire breast [39]. Recently published randomized data now support the safety of hypofractionation in DCIS patients. The DBCG-HYPO trial randomized 246 (13.3% of the overall cohort) patients with DCIS to receive the standard 50 Gy in 25 fractions or 40 Gy in 15 fractions and did not find a difference in LR based on fractionation [36]. More recently, the BIG 3-07/TROG 07.01 randomized study showed no difference in recurrence rates between the standard and hypofractionation arms for patients with DCIS [40]. The ongoing NOVEMBER trial is enrolling patients with all-risk DCIS lesions to be treated with 9 fractions over the course of 2 weeks (Table 2; NCT03345420).

APBI has the potential to reduce treatment duration even further, but risks leaving potentially untreated disease elsewhere in the breast and is therefore only recommended for patients with low-risk DCIS. Summarized in Tables 1 and 2, modes of APBI delivery are numerous, but the body of evidence supporting APBI use in DCIS is limited by the small number of patients included in trials. A Cochrane review of partial breast irradiation for early breast cancer published in 2021 reported slightly reduced local recurrence-free survival with the use of PBI/APBI compared to WBI (HR 1.21 [95% CI 1.03−1.42]) with similar overall survival and cause-specific survival [41]. However, only 6.3% of included patients had DCIS [41]. Nevertheless, the most recent ASTRO APBI consensus statement, published in 2017, expands the acceptability conditions to include DCIS patients meeting RTOG 9804 inclusion criteria based on the low recurrence rate in the observational arm of this trial (Table 1) [42].

The largest and most mature clinical trial of APBI in DCIS is NSABP B-39/RTOG 0413, which randomized 4216 patients, 24% of whom had DCIS, to WBI or APBI (Table 1) [38]. At 10 years of follow-up, there was no increased risk of IBTR in the DCIS patients who received APBI (HR 1.01 [CI.61−1.68], $P = 0.48$) [38]. The RAPID trial randomized patients to receive either twice daily external beam APBI or WBI with or without a boost. There was no difference in IBTR between study groups (Table 1; HR 1.27 [90% CI 0.84−1.91]), but there was increased late toxicity and adverse cosmesis in the APBI arm [43]. Boutrus et al. reported improved cosmetic outcomes with once daily versus twice daily fractions and similar recurrence rates, although median follow-up was only 74 months and only 8.8% of the patients had DCIS [44]. Twice daily regimens have since gone out of favor. There are several ongoing trials investigating the use

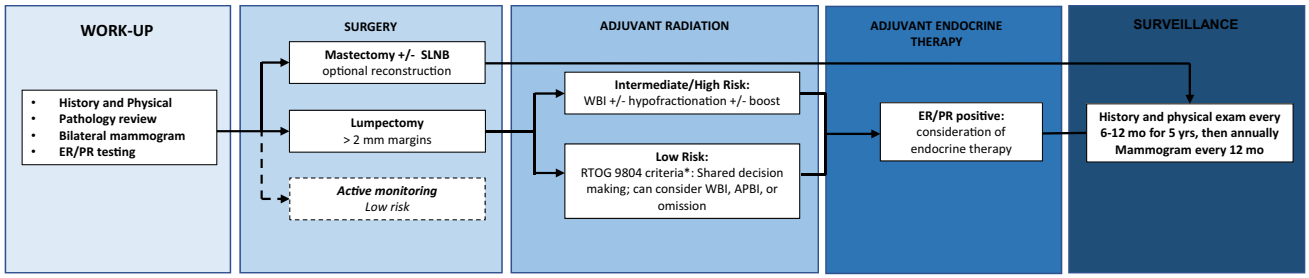

Fig. 1 Treatment guidelines for DCIS. Ongoing active surveillance trials may add observation as an option for primary treatment of DCIS (dashed lines). In addition, ongoing biomarker research may add molecular testing as part of the workup for some or all DCIS patients to determine benefit from adjuvant radiation

of APBI for DCIS patients (Table 2). Optimal de-escalation of RT will reduce total treatment duration without sacrificing recurrence risk or cosmesis (Fig. 1).

Surgery

De-escalation efforts in the surgical management of DCIS center around the safety of active monitoring (AM) for patients with low-risk disease. AM is currently not recommended outside of a clinical trial, as prospective data are lacking. However, multiple studies have predicted the safety of AM using both real-world and simulated datasets [45, 46]. In their analysis of the Surveillance, Epidemiology, and End Results (SEER) database, Byng et al. reported a 3% risk of ipsilateral invasive breast cancer at 10 years in a cohort of women with low-risk DCIS who did not receive local treatment [14, 47]. This is well within age-specific norms for women without a previous diagnosis of DCIS or invasive breast cancer [14, 47].

To fill the evidence gap, four phase III, international, randomized clinical trials have been initiated to determine the safety and effectiveness of AM: COMET (USA; NCT02926911), LORD (Europe; NCT02492607), LORIS (UK), and LORETTA (Japan) [48–51]. The LORD trial converted to a patient preference trial in 2020. The ability of these trials to accurately identify cases of DCIS at low risk of invasive progression will be critical to their success. As discussed previously, clinicopathologic criteria have been unable to sufficiently risk stratify patients considering adjuvant RT. Even so, all four of these trials use clinicopathologic criteria to define trial eligibility. Understandably, several studies have called this strategy into question. The upstage rate to invasive disease at surgery among patients eligible for active monitoring trials has been reported in various studies: 6−21.7% for COMET, 7−24% for LORIS, and 5−10% for LORD [52–54]. While a valid concern, eliminating any risk of upgrade is impossible, and a prospective study is the best setting in which to test the long-term safety of AM and its ability to appropriately identify and manage disease progression. Indeed, the cancer-specific survival of patients on AM in the prostate cancer literature is over 95% despite a known risk of progression, suggesting the potential for real world feasibility of AM in DCIS [55].

A key component of AM will also be its acceptability to patients. It is well understood that patients with DCIS dramatically overestimate their risk of invasive cancer, which contributes to psychological morbidity and could limit incorporation of AM into practice in the future [56–59]. And so, patient reported outcomes from ongoing trials will provide much needed insight into AM acceptability and associated psychosocial morbidity.

In the meantime, prostate cancer serves as a valid model for the tolerability of AM in cancer patients. Low-risk prostate cancer has a prolonged natural history and excellent survival, like DCIS. Furthermore, patients with prostate cancer cite many of the same factors as important in their treatment decision making as those reported by DCIS and breast cancer patients [57, 58, 60–62]. Evidence from prospective AM prostate cancer cohorts suggests that patients have generally favorable levels of anxiety and depression and that few patients opt for active treatment unless clinically indicated [63–65]. While an imperfect surrogate, these findings suggest that some DCIS patients may tolerate AM without undue psychosocial effects. The percentage of patients opting for AM of prostate cancer has increased dramatically since it was first recommended, lending credence to this conclusion [66]. Evaluation of patient-reported outcomes will be critical to understanding the role of surgical de-escalation for low-risk DCIS.

Prognostic and Predictive Tools

The holy grail of prognostic and predictive tools in DCIS care is a method to predict the risk of invasive recurrence or progression and the benefit from local and adjuvant

therapies. Multiple tools have been developed that use clinicopathologic characteristics to predict the local recurrence risk following surgical excision. The Van Nuys prognostic index (VNPI), originally published in 1995 and updated since, is one such example [67]. Silverstein et al. identified a population of patients with VNPI scores of 4−6 who did not have improved recurrence-free survival with adjuvant radiation [67]. However, subsequent studies have contradicted these findings [16, 68]. The Memorial Sloan Kettering Cancer Center (MSKCC) nomogram uses 10 variables to predict 5- and 10-year probability of IBTR [69]. Attempts at external validation of the nomogram have had variable results [15, 70, 71]. Yi et al. reported that the nomogram overestimated the observed risk of recurrence, especially among patients with the highest estimated risk [70]. These findings are supported by others [71]. Thus far, clinicopathologic variables have not been able to reliably predict local recurrence (LR).

In keeping with the rise in genomic testing in oncology more broadly, several molecular tests have been developed to identify low-risk subsets of DCIS patients. The Oncotype DX DCIS Score is a 12-gene assay that is predictive of LR risk following breast conserving surgery [72]. The assay has two major limitations. The first is that it does not predict adjuvant RT benefit [72]. The second is that clinicopathologic criteria remained significant predictors of LR independent of DCIS score, limiting the interpretability of the test. In a subsequent analysis, the authors explored the effects of these other variables on 10-year LR rates [73]. They provided further detail on LR risk within subgroups of tumor size, age, and DCIS score [73]. Multiple subgroups had a LR risk of less than 8% at 10 years, suggesting that these patients might reasonably consider omission of RT [73]. These additional clinical variables have now been incorporated into DCIS Score reporting, now called the Refined DCIS Score (RDS).

Two studies are investigating the use of the RDS in clinical practice. The ELISA study is prospective cohort study investigating outcomes following surgery alone in women with low-risk DCIS according to RDS and clinicopathologic criteria (NCT04797299). The DUCHESS study is evaluating the effect of RDS on treatment decisions and published initial results in 2021 (NCT02766881) [74]. They reported that the assay led to a change in treatment recommendation in 35.2% of cases and decreased the percentage of cases in which RT was recommended from 79% to 50%. Use of the assay was also associated with improved patient satisfaction and reduced decisional conflict [74].

Oncotype Dx, a 21-gene assay, itself widely used in early-stage luminal A invasive breast cancer, has also recently been shown by Rakovitch et al. to predict breast cancer-related mortality benefit from RT in 1362 patients in the Ontario DCIS cohort [24, 75]. Though retrospective in nature, this study was the first to report a population of DCIS patients who had improved cause-specific mortality with the addition of RT [75]. This study highlights the need for thoughtful consideration of valid endpoints in DCIS trials, which are almost always recurrence and not survival, but further studies are needed to clarify the role of Oncotype Dx in DCIS care.

The DCISionRT assay is the only molecular test in DCIS that has been shown to identify a subgroup of patients that do not benefit from RT [76]. Bremer and colleagues retrospectively analyzed archived tissue samples from 721 patients with DCIS treated with breast conserving surgery [76]. The authors incorporated molecular and clinicopathologic characteristics into a biological signature, called DCISionRT, that is expressed as a Decision Score (DS) on a scale of increasing LR risk from 0 to 10. Patients with a score or 3 or less had a 10-year invasive breast cancer (IBC) risk of 4% [76]. Among patients with DS≤3, adjuvant radiation also did not appear to significantly reduce the risk of IBC (HR 0.6 [95% CI 0.2−2.3]; $P = 0.49$) [76]. In comparison, patients with DS > 3 had a 70% reduction in IBC risk with adjuvant RT (HR 0.3 [95% CI 0.1−0.6]; $P = 0.003$). However, the confidence interval in the low-risk group was wide, and there were only 33 IBC events [76]. The PREDICT registry trial will prospectively evaluate the impact of DCISionRT on treatment decisions and monitor outcomes (NCT03448926).

Cost Effectiveness of Predictive Tools

The proliferation of expensive molecular testing has appropriately raised questions as to how these tests should be applied in clinical practice to promote high value care. Highlighting this, a comparison of the MSKCC Nomogram, which is available for free online, and RDS, reported that LR risk estimates were concordant in 92% of the 59 patients in the study [71]. Further analysis suggested that benefit from RDS may be restricted to patients at highest risk of recurrence according to clinicopathologic criteria. Kim et al. determined that DCISionRT testing is cost-effective compared to the current practice of using clinicopathologic characteristics to make RT treatment decisions, especially among patients with clinically high-risk DCIS [77]. Raldow and colleagues used a similar method to evaluate DCISionRT, but they did not incorporate clinicopathologic characteristics into their modeling and used higher cost estimates than other studies. Universal DCISionRT testing with RT for patients with elevated genomic risk became cost effective when the cost of testing was less than $4588 [78]. Overall, DCISionRT is likely to be cost-effective for use in clinical practice in some situations. As the cost of molecular testing comes down, barriers to more routine use will become less significant.

Only one study has evaluated the cost effectiveness of the Oncotype DCIS Score. The results, which showed that the DCIS Score is not cost effective, likely reflect the inability of this assay to predict benefit from RT [79]. Results varied significantly with only minor changes in treatment utility, emphasizing the importance of patient risk tolerance in DCIS treatment decision-making [79]. Taken together, the cost-effectiveness of molecular testing is dictated largely by the predictive power of the test, the clinical risk of the lesion, patient risk tolerance, and cost. As molecular tests improve and costs decrease, their clinical applications will likely expand. It is also important to note the value that patients place on personalized medicine, which will likely continue to drive the development and use of molecular assays [74].

Decision Aids and Shared Decision-Making

Decision aids are patient-facing tools designed to communicate diagnostic and prognostic information and help clarify patient values [80]. Shared decision-making (SDM) is the process of partnering with patients in health decisions. Together, the clinician and patient discuss reasonable options and patient preferences and collaborate to reach a decision [81]. The relative equivalence of standard treatment options and ongoing de-escalation efforts mean that DCIS treatment decision-making is highly sensitive to patient preferences and therefore well suited to SDM [82, 83]. An ongoing shift away from paternalistic practice creates even more space for values-based decision-making.

While this represents a positive step in healthcare delivery, we should also recognize that patients and clinicians are being asked to navigate an increasingly complex treatment landscape, and the factors that affect treatment decisions are widely varied and fluid [58, 84–87]. Time pressure in clinical encounters makes it challenging to effectively communicate diagnostic and prognostic information, discuss relevant treatment options and values and preferences, and come to a shared decision all within the time allotted. Recently, the information gathering and decision-making process has expanded outside of the clinical encounter in the form of decision aids [80, 88–90]. The quality of decision aids is variable, but some have been shown to increase knowledge, improve risk perception, and reduce decisional conflict [91, 92]. However, utilization of decision aids in routine practice is low [93–95]. Increased attention should be given to developing and sustainably implementing high quality decision aids, as this may facilitate quality decision making and improve patient-reported outcomes where treatments are preference sensitive.

The shift from a more paternalistic practice of medicine to one that actively engages patients in their own care is almost certainly here to stay. Therefore, SDM is now a foundational skill in clinical practice. However, as with decision aids, incorporation into clinical practice varies. While physicians generally support SDM in theory, this does not reflect actual behavior, where use of SDM is much lower [96, 97]. Clinician-cited barriers to SDM include challenges communicating treatment equipoise, the perceived difficulties of engaging patients with less formal education, a feeling that some patients might prefer a more paternalistic approach, and the constraints of time [81, 96]. Patients often describe physician communication as a barrier [97]. Thus, there is a need for innovative approaches to support and incentivize providers to authentically partner with their patients in the treatment planning process. In the end, de-escalation should be centered on patients: how best to prepare and safely guide them through DCIS treatment in a way that is most aligned with their values and preferences, and which promotes high value care delivery.

Conclusion

De-escalation aims to right-size therapies using high quality evidence to better balance the risks of a disease with the risks and benefits of its treatment. De-escalation is therefore hinged on accurate risk stratification, which determines eligibility for an increasingly complex array of treatment pathways. In the case of DCIS, clinicopathologic criteria have thus far been unable to stratify patients to the degree required to make treatment decisions, and so focus has shifted onto molecular assays, following a similar trend to that seen in invasive breast cancer. It is likely that molecular assays will become important tools in surgical and adjuvant decision making in DCIS. Risk assessments are then contextualized within a patient's own values and goals, with the help of the provider, to come up with a treatment plan. The complexity of this process requires a creative and multifaceted approach to preparing patients and providers for informed shared decision making that will extend beyond the bounds of the clinical encounter, to right-size treatment to both disease risk and patient preference.

Declarations

Conflict of Interest Authors ALN, SW, and SM declare no conflicts of interest. ESH has research support from R01 CA185138-01; U2C CA-17-035 Pre-Cancer Atlas (PCA) Research Centers; DOD BC132057; BCRF 19-074; PRECISION CRUK Grand Challenge (E.S.H.).

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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•• Of major importance

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