Current Oncology Reports (2019) 21: 33
https://doi.org/10.1007/s11912-019-0777-3

BREAST CANCER (B OVERMOYER, SECTION EDITOR)

Management of Ductal Carcinoma In Situ (DCIS) of the Breast: Present Approaches and Future Directions

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Published online: 5 March 2019

Abstract

Purpose of Review Ductal carcinoma in situ (DCIS; intraductal carcinoma) of the breast is commonly found in an asymptomatic woman on routine screening mammography. The purpose of this review is to describe current approaches to the management of DCIS as well as areas for future investigation.

Recent Findings Randomized trials have demonstrated that adding radiation treatment after breast conservation surgery (lumpectomy; surgical excision) reduces the rate of ipsilateral local recurrence by about half, and that adding hormonal therapy reduces the rate of all breast cancer events (ipsilateral plus contralateral). Early clinical studies attempted to stratify the risk of recurrence using conventional clinical and pathologic features. More recent clinical studies have attempted to define prospectively patients with lower risk DCIS for whom omission of radiation treatment after lumpectomy is a reasonable option. Molecular profiling is a newer approach to define risk stratification for DCIS. Combining molecular profiling with clinical and pathologic features appears to be more accurate in defining and stratifying the risk of recurrence after lumpectomy.

Summary After lumpectomy for DCIS, risk stratification using clinical and pathologic characteristics, and more recently molecular profiling, can help guide clinical decision-making for the use of radiation treatment and hormonal therapy. Ongoing studies are evaluating the possibility of de-escalating therapy, and in some studies, even using core biopsy alone, without surgical excision.

Keywords Ductal carcinoma in situ · DCIS · Breast conservation surgery · Lumpectomy · Radiation treatment · Hormonal therapy

Introduction

Ductal carcinoma in situ (DCIS; intraductal carcinoma) is typically detected in an asymptomatic woman on routine screening mammography. DCIS is a common diagnosis in the USA, with over 50,000 estimated new cases of DCIS diagnosed yearly [1].

The management of DCIS typically includes various combinations of surgery, radiation treatment, and hormonal therapy. After breast conservation surgery (lumpectomy; surgical excision), adding radiation treatment and hormonal therapy reduces the risk of recurrence of disease, but has no impact on mortality. National guidelines allow for omission of radiation treatment after lumpectomy for patients with low-risk DCIS, although without specifying criteria to define low risk [2, 3]. Long-term outcomes after breast conservation surgery with radiation treatment show high rates of local control and survival [4–10].

Mortality from breast cancer after the treatment of DCIS is very low, regardless of the method of treatment. In an analysis of 108,196 women with DCIS from the SEER (Surveillance, Epidemiology, and End Results) database, the 20-year breast cancer-specific mortality was 3.3% [11•]. Adding radiation treatment after lumpectomy reduced the 10-year rate of an ipsilateral invasive recurrence (2.5% versus 4.9%, respectively; adjusted HR [hazard ratio] = 0.47; $p < 0.001$), but did not reduce the 10-year rate of breast cancer-specific mortality (0.8% versus 0.9%, respectively; adjusted HR = 0.86; $p = 0.22$).

As the large majority of women with mammographically detected DCIS are eligible for breast conservation surgery, these women face the difficult decision of whether or not to undergo additional treatment after surgical excision. Given

This article is part of the Topical Collection on *Breast Cancer*

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that variations in treatment have no significant impact on mortality, deciding on the best course of treatment involves complex judgments about the individual patient's tolerance for the potential risk of recurrence balanced against the patient's tolerance for the potential risk of complications associated with adding radiation treatment and hormonal therapy. After surgical excision, adding radiation treatment and hormonal therapy reduces the risk of recurrence of disease but exposes the patient to the small, but real, potential side effects of those treatments. In contrast, omitting radiation treatment and hormonal therapy leaves the patient at an increased risk of recurrence, but avoids the potential risk of side effects associated with adding those treatments.

Current Approaches

Clinically Evaluable Endpoints

Clinically evaluable endpoints for analyzing outcome studies of DCIS are limited. For studies of local treatment using breast conservation surgery with or without adding radiation treatment, evaluable endpoints include local recurrence in the treated breast (also referred to as an ipsilateral breast event [IBE] or an ipsilateral breast tumor recurrence [IBTR]). Local recurrence is often divided into the subsets of DCIS local recurrence and invasive local recurrence (with or without associated DCIS). In the majority of studies of local treatment, the most frequent type of event is a local recurrence. Therefore, most prospective studies evaluating local treatment use local recurrence as the statistical endpoint to determine study sample size, and are therefore underpowered for the endpoints of distant metastatic disease, death from breast cancer, and overall survival.

For studies of adjuvant hormonal therapy, evaluable endpoints include all new breast cancer events, which is the sum of ipsilateral breast events (DCIS or invasive carcinoma) plus contralateral breast events (DCIS or invasive carcinoma). Some studies of adjuvant hormonal therapy also separately report ipsilateral breast events and contralateral breast events.

Events such as distant metastatic disease or deaths from breast cancer are too infrequent to be useful in analyzing treatments for DCIS. However, side effects of local or systemic therapies are important clinical endpoints, given that therapies have no demonstrated effect on survival. Therefore, comparisons of different treatments must heavily weight the side effect profiles of the respective treatment options.

Randomized Clinical Trials

Multiple prospective, randomized clinical trials have convincingly and reproducibly demonstrated that adding radiation treatment to the whole breast after surgical excision reduces the risk of local recurrence in the ipsilateral breast, typically by about half [12–15, 16•, 17, 18•, 19, 20•]. In these randomized trials, the radiation treatment was delivered to the whole breast, generally without a radiation boost to the primary surgical site.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported a meta-analysis of 3729 women in four randomized trials of lumpectomy with versus without radiation treatment [20•]. Adding radiation treatment after lumpectomy reduced the 10-year rate of local recurrence in the ipsilateral breast from 28.1 to 12.9% ($p < 0.00001$) and reduced the 10-year rate of the subset of invasive local recurrence in the ipsilateral breast from 15.4 to 6.8% ($p < 0.001$). Notwithstanding these large differences in the rates of local recurrence, there were no differences in the 10-year rates of breast cancer mortality (3.7% versus 4.1%, respectively; $p > 0.1$) or mortality from all causes (8.2% versus 8.4%, respectively; $p > 0.1$).

After the report from the EBCTCG, McCormick et al. published the results from a randomized clinical trial for patients prospectively defined as having good-risk DCIS [18•, 19]. This study was conducted by NRG (NSABP [National Surgical Adjuvant Breast and Bowel Project], RTOG [Radiation Therapy Oncology Group], and GOG [Gynecologic Oncology Group]). In this study (NRG/RTOG 9804; formerly RTOG 9804), good-risk DCIS was defined as unicentric disease, tumor size $\leq$ 2.5 cm, low or intermediate nuclear grade, and negative surgical margins from the lumpectomy specimen of 3 mm or greater. Adding radiation treatment reduced the 12-year rates of local recurrence from 11.4 to 2.8% (HR = 0.26; $p = 0.0001$) and the subset of invasive local recurrence from 5.8 to 1.5% (HR = 0.34; $p = 0.016$). There was no difference between the two arms for overall survival or disease-free survival.

The value of adding hormonal treatment in the setting of breast conservation surgery has been evaluated in randomized clinical trials. In the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-24 study, adding tamoxifen after lumpectomy plus radiation treatment reduced the 10-year risk of any breast cancer event (ipsilateral plus contralateral; invasive carcinoma or DCIS) for estrogen receptor positive DCIS (HR = 0.49; $p < 0.001$), but not for estrogen receptor negative DCIS (HR = 0.84; $p = 0.59$) [21•]. The UK/ANZ (United Kingdom, Australia, and New Zealand) study used a 2 × 2 randomization design for radiation treatment and tamoxifen after lumpectomy [16•]. Adding tamoxifen reduced the incidence of all new breast events (HR = 0.71; $p = 0.002$). In subset analyses, adding tamoxifen reduced the incidence of all new breast events for the patients not receiving radiotherapy (HR = 0.71; $p = 0.001$), but not for the patients receiving radiotherapy (HR = 0.99; $p = 0.8$). In both studies, tamoxifen reduced the risk of developing a new contralateral breast cancer.

For postmenopausal women, randomized clinical trials have compared an aromatase inhibitor (anastrozole) to tamoxifen. In the NSABP B-35 study, the 10-year breast cancer-free interval was 93.1% for anastrozole and 89.1% for tamoxifen (HR = 0.73; $p = 0.0234$), with the benefit limited to postmenopausal women age < 60 years [22•]. In the IBIS-II (International Breast Cancer Intervention Study – II) study, there were no statistically significant differences between the two groups for overall recurrences (HR = 0.89; $p = 0.49$) or deaths (HR = 0.93; $p = 0.78$) [23•]. As expected, the toxicity profiles in both studies were different for the two hormonal therapies [22•, 23•, 24, 25].

Risk Stratification Using Clinical and Pathologic Characteristics

A major goal of risk stratification is to identify those individual patients for whom the risk of recurrence is sufficiently low based on conventional clinical and pathologic factors that treatment using lumpectomy alone (without radiation treatment) is reasonable. A number of studies have evaluated different methods of using clinical and pathologic characteristics for determining the risk of recurrence after surgical excision. However, no single method of risk stratification using clinical and pathologic characteristics has gained wide acceptance. Although many different characteristics have been reported as significant in various studies, the most reproducible characteristics among studies are as follows: (a) patient age, (b) surgical margins of resection, (c) tumor size, and (d) grade. The specific constellation of clinical and pathologic characteristics that is prognostic varies widely among studies, and virtually no two studies are in agreement. This lack of reproducibility and the lack of independent, external validation are major problems in clinical practice for determining individual treatment algorithms for individual patients, thereby limiting clinical utility and implementation.

Three studies have prospectively defined patients at lower risk for local recurrence using clinical and pathologic characteristics (Table 1) [18•, 19, 26, 27•, 28]. Two of these studies were prospective non-randomized registry studies, and one was a prospective randomized clinical trial. For the patients with grade 1–2 DCIS treated with surgical excision but without radiation treatment, the rate of developing a local recurrence in these three studies was similar at approximately 1–1.5% per year. In the NRG/RTOG 9804 randomized study, adding radiation treatment after surgical excision significantly decreased the 12-year rates of local recurrence and the subset of invasive local recurrence (Table 1; also see above).

The USC/VNPI (University of Southern California Van Nuys Prognostic Index; formerly VNPI) is a method of using clinical and pathologic variables to determine the risk of local recurrence after initial treatment of DCIS, and has undergone a number of iterations over time [29–33]. The current algorithm includes four clinical and pathologic variables: (a) patient age, (b) tumor size, (c) negative margin width, and (d) pathologic tumor characteristics. The USC/VNPI uses a point system combined with the measurement of negative margin width to determine the risk of local recurrence, and more recently, also to specify treatment recommendations for lumpectomy alone, lumpectomy plus radiation treatment, or mastectomy. Limitations of the USC/VNPI include the changing criteria over time for determining recurrence risk and treatment recommendations, as well as the lack of independent, external validation.

The Memorial Sloan Kettering Cancer Center (MSKCC) nomogram uses 10 clinical, pathologic, and treatment variables to estimate the 5-year and 10-year probabilities of local recurrence [34]. This nomogram uses a point system from these 10 variables to estimate the risk of local recurrence. The two most heavily weighted variables are the treatment variables of adding radiation treatment (versus not) and adding adjuvant endocrine therapy (versus not), thereby strongly weighting the nomogram in favor of adding these treatments. However, an independent attempt to validate the MSKCC nomogram by investigators from MD Anderson Cancer Center demonstrated only limited ability of the nomogram to predict local recurrence accurately [35].

Punglia et al. have developed a simplified clinical risk score using the three variables of patient age, comedo necrosis, and estrogen receptor status [36]. After surgical excision with negative margins but without adjuvant treatment, the 5-year predicted risks of local recurrence were 9%, 23%, and 51% for the low-, intermediate-, and high-risk groups, respectively. Limitations of this simplified clinical risk score include the limited follow-up of 5 years, the relatively large amount of missing information for grading (23%), and the limited number of cases in the intermediate- and high-risk groups (16% and 2%, respectively).

Risk Stratification Using Molecular Profiling

The 12-gene Oncotype DX DCIS Score (also referred to as the DCIS Score) is a molecular biomarker test that gives the predicted 10-year risks of local recurrence and the subset of invasive local recurrence for DCIS after surgical excision without radiation treatment [37•]. The DCIS Score includes seven cancer-related genes and five reference genes. The DCIS Score was developed and validated in accordance with the rigorous criteria for the development and clinical implementation of tumor biomarkers as defined by Simon et al., including validation in two independent studies [37•, 38, 39]. The first validation study for the DCIS Score was reported by Solin et al. from the ECOG-ACRIN (Eastern Cooperative Oncology Group American College of Radiology Imaging Network; formerly ECOG) E5194 study for patients prospectively selected as having low-risk DCIS (Table 1) [37•]. In the E5194 study, there were two non-randomized arms: (a) low- or intermediate-grade DCIS, size $\leq$ 2.5 cm ($n = 561$ patients);

Table 1 Summary of studies prospectively identifying low-risk DCIS for treatment using breast conservation surgery with or without radiation treatment (RT)

Study	Number of patients	Definition of low risk			Use of tamoxifen	Use of RT	Local recurrence	*p* value
		Tumor size (cm)	Negative margin width (mm)	Grade				
NRG/RTOG 9804 [18•, 19]								
Arm 1	298	≤ 2.5	≥ 3	1–2	65%	No	11.4% at 12 years	0.0001
Arm 2	287	≤ 2.5	≥ 3	1–2	58%	Yes	2.8% at 12 years	
Harvard study [26]	143	≤ 2.5	≥ 10	1–2	No	No	15.6% at 10 years	n/a
ECOG-ACRIN E5194 [27•, 28]								
Cohort 1	561	≤ 2.5	≥ 3	1–2	31%	No	14.4% at 12 years	0.003
Cohort 2	104	≤ 1.0	≥ 3	3	24%	No	24.6% at 12 years	

DCIS ductal carcinoma in situ, *RT* radiation treatment, *NRG NSABP* National Surgical Adjuvant Breast and Bowel Project, *RTOG* Radiation Therapy Oncology Group, and *GOG* Gynecologic Oncology Group, *n/a* not applicable, *ECOG-ACRIN* Eastern Cooperative Oncology Group American College of Radiology Imaging Network

or (b) high-grade DCIS, size ≤ 1 cm ($n = 104$ patients) [27•, 28]. Protocol specifications included surgical excision of the DCIS tumor with negative surgical margins of 3 mm or greater. During the later years of the study, adjuvant tamoxifen was allowed as optional.

Using patient information from the E5194 study, the DCIS Score was found to be strongly associated with local recurrence and the subset of invasive local recurrence [37•]. For the prespecified groups of low risk, intermediate risk, and high risk, the 10-year risks of local recurrence were 10.6%, 26.7%, and 25.9%, respectively ($p = 0.006$), and the 10-year risks of the subset of invasive local recurrence were 3.7%, 12.3%, and 19.2%, respectively ($p = 0.003$). On multivariable analysis, the DCIS Score, tumor size, and menopausal status were statistically significant for local recurrence (all $p \leq 0.02$).

A second, independent validation of the DCIS Score was performed using a population-based cohort of women with DCIS from Ontario, Canada, and showed results that were highly consistent with the results from the E5194 study (Table 2) [37•, 39]. Using population-based registry data, Rakovitch et al. identified patients with DCIS treated with breast conservation surgery but without radiation treatment, and DCIS Score testing was performed for 571 patients [39]. For the prespecified groups of low risk, intermediate risk, and high risk, the 10-year risks of local recurrence were 12.7%, 33.0%, and 27.8%, respectively ($p < 0.001$), and the 10-year risks of the subset of invasive local recurrence were 8.0%, 20.9%, and 15.5%, respectively ($p = 0.03$). On multivariable analysis, the DCIS Score, tumor size, patient age, multifocality, and tumor subtype were statistically significant for local recurrence (all $p \leq 0.04$).

To further refine the prognostic value of the DCIS Score, a combined analysis of the E5194 and Ontario cohorts was performed [40•]. By integrating the DCIS Score with the clinical and pathologic features of tumor size and patient age, risk stratification was improved (Table 3).

Rakovitch et al. have demonstrated that adding radiation treatment after lumpectomy reduced the 10-year risk of local recurrence by about half, regardless of the DCIS Score [41•]. Thus, the benefit of adding radiation treatment is smaller for a patient with a low-risk DCIS Score, and larger for a patient with an intermediate- or high-risk DCIS Score. Although not randomized, these data are consistent with the randomized trials demonstrating that adding radiation treatment after lumpectomy reduces the risk of local recurrence by about half (see above).

The Decision Score is a second molecularly based tool for determining the risk of local recurrence after the surgical excision of DCIS [42, 43]. The Decision Score is determined from seven genes combined with four clinical and pathologic factors (age, tumor size, margins, and palpability) into a single score. The Decision Score is then divided in a binary fashion into low risk versus elevated risk.

Using the Decision Score, outcomes with and without radiation treatment (RT) after lumpectomy have been reported. For the endpoint of any local recurrence (any ipsilateral breast event [IBE]) after breast conservation surgery, the 10-year risks were 8% without RT for a low-risk Decision Score, 7% with RT for a low-risk Decision Score, 23% without RT for an elevated-risk Decision Score, and 11% with RT for an elevated-risk Decision Score. For the subset of an invasive local recurrence, the 10-year risks were 4% without RT for a low-risk Decision Score, 3% with RT for a low-risk Decision Score, 15% without RT for an elevated-risk Decision Score, and 9% with RT for an elevated-risk Decision Score.

Multivariate analyses were performed for 10-year outcomes, with adjustments for excluding margin positive patients and for year of diagnosis. On multivariate analysis for any local recurrence (any ipsilateral breast event [IBE]), statistically significant variables were the Decision Score, the use of radiation treatment with an elevated Decision Score, and the year of diagnosis. On multivariate analysis for the subset

Table 2 Ten-year risks of local recurrence according to the 12-gene Oncotype DX DCIS Score after treatment using breast conserving surgery without radiation treatment

Study	DCIS Score risk group	Number (%) of patients	Local recurrence at 10 years (%)	*p* value	Subset of invasive local recurrence at 10 years (%)`	*p* value
ECOG-ACRIN	Low	230 (70)	10.6	0.006	3.7	0.003
E5194 [37•]	Intermediate	53 (16)	26.7		12.3	
	High	44 (13)	25.9		19.2	
Ontario, Canada	Low	355 (62)	12.7	< 0.001	8.0	0.03
population-based	Intermediate	95 (17)	33.0		20.9	
cohort [39]	High	121 (21)	27.8		15.5	

DCIS ductal carcinoma in situ, *ECOG-ACRIN* Eastern Cooperative Oncology Group American College of Radiology Imaging Network

of invasive local recurrence, statistically significant variables were the Decision Score and the use of radiation treatment with an elevated Decision Score.

Future Directions

De-escalating Therapy

The rationale for de-escalating therapy in the setting of newly diagnosed DCIS is based on a number of observations. First, although randomized clinical trials of adding radiation treatment and hormonal therapy after lumpectomy have demonstrated improvements in the risk of recurrence, no benefit has been shown for survival or freedom from distant metastases. Second, both radiation treatment and hormonal therapy each have a small, but real, risk of side effects. Third, clinical, pathologic, and molecular characteristics have been demonstrated to stratify the risk of recurrence. Given these observations, de-escalation of therapy at the time of initial diagnosis is a newer approach to management currently being evaluated in prospective randomized clinical trials [44–47]. Having de-escalation of therapy as a potential future therapeutic option would allow patients and their physicians to consider the potential trade-off of decreasing upfront therapy for all patients at the cost of increasing the future risk of diagnostic and therapeutic procedures some years after initial diagnosis, hopefully in only a small subset of patients. Increased future risks might include any number of issues, for example, an increased number of surgical biopsies, an increased number of imaging studies, increased cost, or reduced quality of life. In a subset of patients with DCIS treated with core biopsy only, untreated invasive carcinoma might be left in the ipsilateral breast. However, if these increased risks could be quantified, then patients and physicians would have another potential option for management at the time of initial diagnosis of DCIS based on core biopsy.

Three prospective randomized clinical trials in the USA and Europe are currently in progress to address de-escalating therapy for patients with newly diagnosed, low-risk DCIS. In these clinical trials, eligibility is based on clinical and pathologic characteristics alone. These clinical trials are ongoing and will not have outcome data for a number of years.

In the USA, the COMET (Comparison of Operative to Monitoring and Endocrine Therapy; ClinicalTrials.gov identifier NCT02926911) study for low-risk DCIS is currently open [44, 45]. The study randomizes patients to guideline concordant (standard) care versus active surveillance. In the guideline concordant care arm, the treatment is surgery

Table 3 Ten-year risks of local recurrence according to combinations of tumor size, patient age, and the 12-gene Oncotype DX DCIS Score risk group after treatment using breast conserving surgery without radiation treatment [40•]

Patient age	Tumor size (cm)	Local recurrence at 10 years (%)		
		Low DCIS Score	Intermediate DCIS Score	High DCIS Score
< 50 years	≤ 1.0	10.2	15.8	19.6
	1.1–2.5	14.5	18.9	23.2
	> 2.5	30.2	39.5	48.6
≥ 50 years	≤ 1.0	7.2	11.3	14.6
	1.1–2.5	10.1	13.9	19.5
	> 2.5	20.4	29.1	41.1

DCIS ductal carcinoma in situ

(lumpectomy or mastectomy) with or without radiation treatment. In the active surveillance arm, only core biopsy showing DCIS (or incomplete excision) is required. Hormonal therapy is optional in either study arm.

In Europe, the two open randomized clinical trials for low-risk DCIS are the LORD (Low Risk DCIS; ClinicalTrials.gov identifier NCT02492607) study and the LORIS (Low Risk DCIS; Cancer Research UK [United Kingdom]) study [46, 47]. Although the eligibility criteria for the two studies are different, both studies randomize patients to standard treatment (including surgery) versus active surveillance. In the standard treatment arm, treatment options are wide local excision (with or without radiation treatment) or mastectomy, and hormonal therapy is optional. In the active surveillance arm, only core biopsy showing DCIS is required.

These three randomized trials should provide important data for understanding the potential role of de-escalating therapy in the setting of newly diagnosed, low-risk DCIS. Quantifying potential risks and identifying appropriate subsets of patients for de-escalating therapy will help inform decision-making for potential treatment options in the future.

Molecular Profiling

The DCIS Score has been validated for clinical use in accordance with rigorous scientific methodology, and is strongly prognostic for the 10-year risks of local recurrence and the subset of invasive local recurrence. Integrating clinical and pathologic characteristics in combination with the DCIS Score further improves the prognostic information. The Decision Score is a second molecularly based tool that has been developed for DCIS to help guide local management.

Based on the existing foundations of molecular profiling for DCIS, a number of future developments can be envisioned with the potential for meaningful clinical use. Beyond the limited panels of genes included in the DCIS Score and the Decision Score, respectively, full gene sequencing might identify additional molecular approaches to refine further the risk of local recurrence and to guide local management. Another potentially important advance would be to identify those genes most closely associated with transformation from an initial DCIS to a subsequent invasive carcinoma.

Radiologic Imaging

As the large majority of DCIS lesions are detected in the asymptomatic patient on routine screening mammography, the incidence of DCIS in the USA has risen dramatically with the widespread use of screening mammography. Adding breast MRI (magnetic resonance imaging) to standard mammography has not been shown to improve local control in the setting of breast conservation treatment [48, 49]. However, the optimal approach to imaging for DCIS may become further refined, particularly with newer management approaches emphasizing de-escalation of therapy (see above). In addition, the role of MRI in combination with molecular assays is another area of active investigation with the potential for clinical application [50].

Conclusions

Ductal carcinoma in situ (DCIS) is most commonly detected in an asymptomatic woman on routine screening mammography and is typically eligible for breast conservation surgery as initial local treatment. Randomized clinical trials have demonstrated that adding definitive radiation treatment after local surgical excision reduces the risk of ipsilateral local recurrence by about half, and adding adjuvant hormonal therapy reduces the risk of all breast cancer events (ipsilateral plus contralateral), although without any impact on mortality. Those lower risk patients potentially eligible for treatment using surgical excision alone have not been reproducibly and reliably identified using conventional clinical and pathologic characteristics. Molecular profiling for stratifying risk has been developed and validated for clinical use in accordance with rigorous scientific methodology. Combining molecular profiling with clinical and pathologic features is more accurate in defining and stratifying risk of recurrence. De-escalation of therapy is a newer research approach that is under active investigation in ongoing randomized clinical trials.

Compliance with Ethical Standards

Conflict of Interest Lawrence J. Solin has received compensation from Genomic Health, Inc. for participating on speaker's bureaus and advisory boards.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the author have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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