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ORIGINAL ARTICLE – BREAST ONCOLOGY

Women with Low-Risk DCIS Eligible for the LORIS Trial After Complete Surgical Excision: How Low Is Their Risk After Standard Therapy?

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ABSTRACT

Background. Identifying DCIS patients at low risk for disease progression could obviate need for standard therapy. The LORIS (surgery versus active monitoring for low-risk DCIS) trial is studying the safety of monitoring low-risk DCIS, although ipsilateral breast tumor recurrence (IBTR) rates in patients meeting enrollment criteria after complete surgical excision are unknown.

Methods. Women with pure DCIS treated with breast-conserving surgery (BCS) with/without radiation therapy (RT) from 1/1996–1/2011 were included from a prospectively maintained database. IBTR rates were compared between those who did and did not meet LORIS eligibility criteria (age $\geq$ 46 years, screen-detected calcifications, nipple discharge absence, minimal family history, non-high-grade DCIS) after complete surgical excision.

Results. A total of 2394 women were identified; 401 met LORIS criteria. Median follow-up was 5.9 years; 431 had $\geq$10 years follow-up. LORIS cohort median age was 61 years (range 46–86 years); 207 (52 %) underwent RT, 79 (20 %) received endocrine therapy. Of 401 patients, 24 experienced an IBTR. Overall 10-year IBTR rates were 10.3 % (LORIS) versus 15.4 % (non-LORIS) ($p = 0.08$); without RT, 12.1 versus 21.4 %, respectively ($p = 0.06$). The 10-year invasive-IBTR rates for women meeting LORIS criteria were: 5.3 % BCS overall, 6.0 % without RT.

Conclusions. Women meeting LORIS criteria (after complete surgical excision) are at somewhat lower risk for IBTR. Among such women undergoing excision without RT, the 10-year invasive-IBTR rate was 6 %. Given that approximately 20 % of women with core biopsy-proven non-high-grade DCIS have invasive cancer at excision, women managed without excision would be expected to incur higher invasive cancer rates. Additional criteria are needed to identify women not requiring intervention for DCIS.

Ductal carcinoma in situ (DCIS) is a noninvasive breast lesion with no theoretic metastatic potential and excellent survival.[1–3] With the increasing utilization of screening mammography, the incidence of DCIS has increased significantly and now accounts for approximately 20–25 % of all newly diagnosed breast cancers, with an estimated 60,290 cases of DCIS expected in the United States in 2015.[4,5] Although the natural history of untreated DCIS is not well studied, 2 older studies that examined outcomes for women who, retrospectively, were found to have undiagnosed low-grade DCIS in their excisional biopsy specimen found that 40–50 % will progress to invasive carcinoma after an average interval of 10–15 years.[6,7] The Nurses' Health Study also retrospectively detected DCIS in 13 women initially receiving a benign diagnosis, of whom 4 of 10 with low- or intermediate-grade DCIS developed ipsilateral invasive cancer.[8] While the lesions in these older studies may be different from the DCIS detected by modern breast screening, additional data regarding the risk of progression of DCIS in the modern era are lacking. However, it is well established that, following standard therapy for DCIS, approximately half of all recurrences are invasive at the time of detection.[9,10] The therapeutic goal for women with DCIS is the prevention of a potentially life-threatening invasive carcinoma.

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With the increasing incidence of this preinvasive lesion, there has been significant interest in identifying patients with DCIS who are at very low risk for the progression to invasive carcinoma to obviate the need for standard surgical and radiation therapies. While DCIS represents a heterogeneous lesion with a spectrum of risk, current literature fails to identify a subgroup of patients with DCIS who are not at risk for the progression to invasive carcinoma. While pathologic grade is often considered a surrogate for risk, long-term studies have often failed to show an association between grade of DCIS and risk of recurrence.[11,12] Furthermore, non-high-grade DCIS is associated with an approximately 20 % rate of upgrade to invasive carcinoma at the time of surgical excision.[13]

Two current European trials are comparing the safety of observation alone to standard surgical excision ± adjuvant therapies for women with low-risk DCIS diagnosed by vacuum-assisted core-needle biopsy.[14,15] They differ slightly in eligibility criteria. The LORIS (surgery versus active monitoring for low-risk ductal carcinoma in situ) trial defines the "low-risk" DCIS subset as women 46 years of age or older, without a significant family history of breast cancer, diagnosed with low- or "low-intermediate" grade DCIS diagnosed from screen-detected or incidental calcifications by vacuum-assisted needle biopsy.[15] The LORD (LOw Risk Dcis) study is similar in inclusion criteria, but is limited to low-grade DCIS alone and includes additional specifications regarding needle gauge, presence of microcalcifications in the biopsy specimen, and the number of required biopsies.

We sought to review our institution's long-term results of patients with DCIS who would or would not meet the "low-risk" criteria as defined by the LORIS trial. However, all of our patients were treated with standard surgical excision ± adjuvant radiation therapy. Thus, our "low-risk" population by design is at lower risk than those in the LORIS trial, because all of our patients underwent complete surgical excision of the index DCIS, and neither a high-grade nor an invasive component was identified.

METHODS

Following Memorial Sloan Kettering Cancer Center (MSKCC) institutional review board approval, women undergoing breast-conserving surgery for pure DCIS at MSKCC from 1/1996–1/2011, with or without radiation therapy, were identified from a prospectively maintained database. Clinicopathologic characteristics were analyzed, including age at diagnosis, menopausal status, family history of breast cancer, personal history of ovarian cancer, presentation, number of excisions, histologic architecture (micropapillary, papillary, cribriform, solid, and/or comedo component), presence of necrosis, nuclear grade, final margin status at excision (positive or close [≤2 mm], negative [>2 mm]), and the use of adjuvant whole breast radiation or endocrine therapy.

Women were identified who, after examination of all core biopsy and surgical excision tissue, met the following published "low-risk" registration eligibility criteria used in the LORIS trial: age 46 years or older at diagnosis, screen-detected calcifications, and non-high-grade DCIS diagnosed by needle biopsy (Fig. 1).[16] These women constituted the "LORIS cohort." Exclusion criteria for the LORIS study include a mass lesion on imaging, ipsilateral bloody nipple discharge, personal history of breast cancer, women at high risk for the development of breast cancer defined by the National Institute for Health and Care Excellence (United Kingdom) guidelines for familial breast cancer, or prior history of mantle radiation.[17] For our series, exclusion criteria for the "LORIS cohort" were high-grade DCIS, mass lesion on imaging, clinical presentation with palpable mass, nipple discharge or Paget's disease, ≥2 first- or second-degree relatives with breast cancer, and a personal history of either breast or ovarian cancer. These patients were defined as the "non-LORIS cohort." Women with ADH bordering on DCIS and any patient with invasion present at time of surgical excision were excluded from our database and are not in either cohort. IBTR rates were compared between the "LORIS" and "non-LORIS" cohorts.

Patient characteristics of the LORIS and non-LORIS cohorts were compared for those using the 2-sample t test for continuous variables and the χ^2 test for categorical variables. Time to IBTR was analyzed using the Kaplan–Meier method, and comparisons were made using the log-rank test. Cumulative incidence curves for DCIS versus invasive cancers were estimated using competing risk methods. A multivariable Cox proportional hazards model was fit to adjust for the effect of adjuvant therapy and margin status. All analyses were performed in SAS v9.4 or R version 3.1.1. Also, p values less than 0.05 were defined as significant.

RESULTS

Among 2394 women treated with breast-conserving surgery at MSKCC from 1/1996–1/2011, 401 (17 %) had clinicopathologic features following surgical excision of DCIS that met LORIS trial eligibility criteria; 1993 (83 %) did not. Table 1 compares clinicopathologic features of the 2 cohorts. Women meeting LORIS eligibility criteria were more likely to be postmenopausal (77 vs 64 %; $p < 0.0001$), less likely to have any family history of breast cancer (31 vs 41 %; $p = 0.0005$), underwent fewer

FIG. 1 Patient population meeting LORIS eligibility criteria (CONSORT diagram). The LORIS cohort consisted of those meeting eligibility criteria for the LORIS (surgery vs active monitoring for low-risk DCIS) trial after complete surgical excision and histologic examination of excision specimen. The non-LORIS cohort consisted of women with pure DCIS after undergoing complete surgical excision and histologic examination of the excision specimen, but not meeting all eligibility requirements. Any woman with invasion in excision specimen was excluded. *DCIS* ductal carcinoma in situ, *BCS* breast-conserving surgery, *US* ultrasound

excisions (29 vs 55 % with >1 excision; $p < 0.0001$), and more frequently had a micropapillary (35 vs 30 %; $p = 0.03$) or cribriform (86 vs 72 %; $p < 0.0001$) DCIS component. Significantly fewer women meeting LORIS criteria had positive/close margins on final excision (13 vs 20 %; $p = 0.0004$). Fewer women meeting LORIS eligibility criteria received adjuvant radiation therapy (52 vs 61 %; $p = 0.0003$); there was no difference in use of adjuvant endocrine therapy among the 2 groups (20 vs 24 %; $p = 0.08$).

Median follow-up for the entire population was 5.89 years (range 0–18 years); 431 women without recurrence were followed for at least 10 years. Rates of any IBTR at 5 and 10 years were numerically lower in the LORIS group compared with the non-LORIS group (5-year IBTR rates for LORIS compared with non-LORIS groups: 4.6 and 7.8 %, respectively; 10-year rates: 10.3 and 15.4 %, respectively; $p = 0.08$); however, there was no statistically significant difference in rates of IBTR between women who did and did not meet LORIS eligibility criteria regardless of receipt of radiation therapy (Table 2; Fig. 2a–c). The 5- and 10-year invasive and DCIS IBTR rates for the LORIS cohort are shown in Table 3, with nearly equal rates of DCIS and invasive recurrence at 10 years. Among

TABLE 1 Patient characteristics among women who did and did not meet LORIS trial eligibility criteria

Variable	Patients meeting LORIS criteria ($n = 401$)	Patients not meeting LORIS criteria ($n = 1993$)	p value
Age, years (mean, range)	61.4, 46.1–86.3	57.8, 25.6–92.6	<0.0001
Menopausal status			<0.0001
Premenopausal/perimenopausal	94 (23 %)	704 (35 %)	
Postmenopausal	307 (77 %)	1283 (64 %)	
Unknown	0	6 (0.3 %)	
Any family history of breast cancer[a]			0.0005
No	270 (67 %)	1161 (58 %)	
Yes	126 (31 %)	813 (41 %)	
Unknown	5 (1 %)	19 (1 %)	
Presentation			–
Radiologic	401 (100 %)	1754 (88 %)	
Clinical	0	239 (12 %)	
Unknown	0	0	
Number of excisions			<0.0001
1	286 (71 %)	896 (45 %)	
2	97 (24 %)	918 (46 %)	
≥3	18 (4 %)	178 (9 %)	
Unknown	0	1 (0.05 %)	
Histologic architecture			
Micropapillary component	140 (35 %)	590 (30 %)	0.03
Papillary component	48 (12 %)	259 (13 %)	0.6
Cribriform component	344 (86 %)	1430 (72 %)	<0.0001
Solid component	277 (69 %)	1389 (70 %)	0.9
Comedo component[b]	0	700 (35 %)	–
Unknown	3 (1 %)	8 (0.4 %)	
Necrosis present			0.9
Present	257 (64 %)	1272 (64 %)	
Unknown	2 (0.5 %)	29 (1 %)	
Nuclear grade			–
Low	81 (20 %)	317 (16 %)	
Intermediate	320 (80 %)	741 (37 %)	
High	0	826 (41 %)	
Unknown	0	109 (5 %)	
Invasive component	0	0	–
Margin status at excision			0.0004
Close/positive	53 (13 %)	404 (20 %)	
Negative	344 (86 %)	1509 (76 %)	
Unknown	4 (1 %)	80 (4 %)	
Adjuvant therapy			
Radiation ($n = 2516$)	207 (52 %)	1212 (61 %)	0.0003
Endocrine therapy ($n = 2507$)	79 (20 %)	474 (24 %)	0.08

LORIS cohort, meeting eligibility criteria for the LORIS (surgery vs active monitoring for low-risk DCIS) trial after complete surgical excision and histologic examination of excision specimen. Non-LORIS cohort, women with pure DCIS after undergoing complete surgical excision and histologic examination of the excision specimen, but not meeting all eligibility requirements. Any woman with invasion in excision specimen was excluded

DCIS ductal carcinoma in situ

[a] At least 1 first- or second-degree family member with breast cancer

[b] Total n for Comedo component = 2374

TABLE 2 The 5- and 10-year rates of any ipsilateral breast tumor recurrence

	No. of events	5-year IBTR		10-year IBTR		*p* value
		Percent	95 % CI	Percent	95 % CI	
Entire population						0.08
LORIS ($n = 401$)	24	4.6 %	2.8–7.5	10.3 %	6.4–16.3	
Non-LORIS ($n = 1993$)	220	7.8 %	6.6–9.2	15.4 %	13.3–17.7	
No RT						0.06
LORIS ($n = 193$)	16	6.9 %	3.9–12.3	12.1 %	7–20.3	
Non-LORIS ($n = 763$)	126	12 %	9.7–14.7	21.4 %	17.8–25.5	
RT						0.3
LORIS ($n = 207$)	8	2.3 %	0.9–6.1	8.8 %	3.8–20	
Non-LORIS ($n = 1212$)	94	5.2 %	3.9–6.7	11.4 %	9.1–14.2	

LORIS cohort, meeting eligibility criteria for the LORIS (surgery vs active monitoring for low-risk DCIS) trial after complete surgical excision and histologic examination of excision specimen. Non-LORIS cohort, women with pure DCIS after undergoing complete surgical excision and histologic examination of the excision specimen, but not meeting all eligibility requirements. Any woman with invasion in excision specimen was excluded

IBTR ipsilateral breast tumor recurrence, *95 % CI* 95 % confidence interval, *RT* radiation therapy

the entire LORIS cohort, 10-year rates of invasive cancer recurrence were 5.3 %; with invasive IBTR rates of 4.6 and 6.0 % for those treated with and without radiation therapy, respectively (Fig. 2d–f). The 5- and 10-year invasive IBTR rates for the non-LORIS cohort were 2.9 and 7.1 %, respectively.

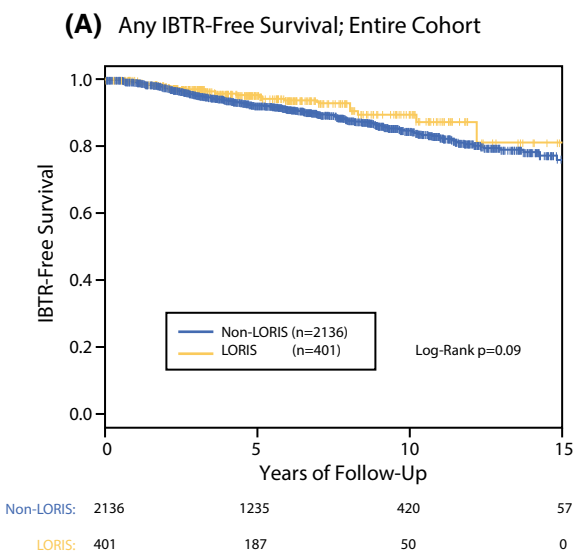
Due to the imbalance between the 2 cohorts in the proportion with close/positive margins and the use of adjuvant therapies (Table 1), a multivariable analysis was performed to determine the association of LORIS criteria and recurrence after controlling for radiation therapy, endocrine therapy, and margin status. The LORIS criteria were of borderline significance [hazard ratio (HR) non-LORIS criteria 0.65; $p = 0.051$]. Receipt of adjuvant radiation therapy and endocrine therapy were both strongly associated with a reduction in the risk of local recurrence (HR radiation 0.50; $p < 0.0001$; HR endocrine therapy 0.45; $p < 0.0001$). Close/positive margin status was associated with a nonsignificantly higher rate of local recurrence (HR close/positive margins 1.2; $p = 0.2$).

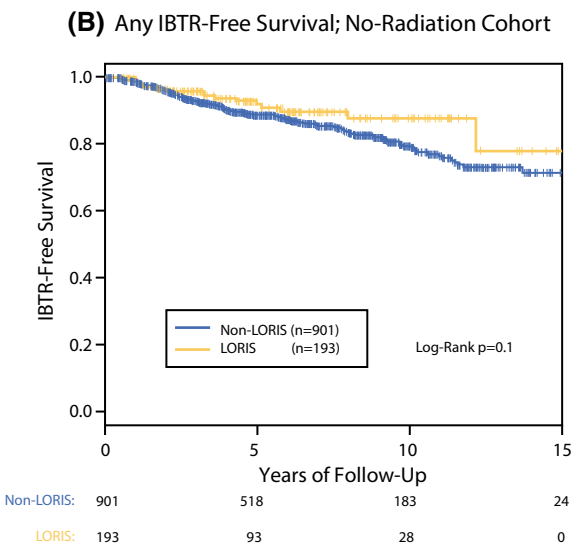
Ten patients from the low-risk LORIS cohort developed an invasive recurrence. Details on invasive tumor receptors and grade are missing for 1 and 2 patients, respectively. Of the invasive recurrences with details available, 100 % (9 of 9) were estrogen receptor positive, 1 of 9 was HER2-neu overexpressing, and 100 % (8 of 8) were moderately or poorly differentiated. Of these 10 patients, 2 (20 %) developed metastatic disease; 1 was diagnosed with simultaneous IBTR and metastatic disease, while 1 developed metastatic disease subsequent to their invasive recurrence. Of the 10 women who developed invasive recurrences, 3 occurred in patients who initially presented with low-grade DCIS.

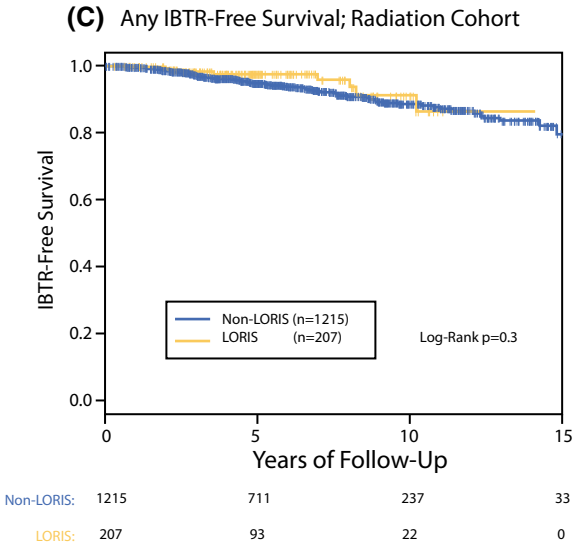
DISCUSSION

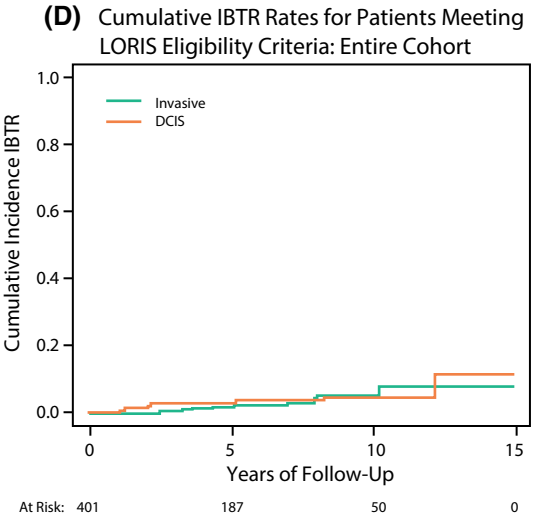
DCIS is a heterogeneous lesion representing a spectrum of risk for progression to invasive carcinoma. There is wide variation in current treatment recommendations for DCIS, from increasingly aggressive surgical management as represented by increasing mastectomy rates for DCIS in recent years to the investigation of observation after core biopsy alone.[14,15,18,19] With concerns for overtreatment of this preinvasive lesion, considerable interest exists in identifying women at very low risk for progression to invasive carcinoma who can be spared standard therapy and the potential morbidities.[20] We identified a population of women considered very low risk, defined as those meeting published LORIS trial registration eligibility criteria even after surgical excision, and report a 12 % 10-year risk of any ipsilateral IBTR and a 6 % risk of invasive carcinoma development following standard breast-conserving surgery. Among this large cohort of women with pure DCIS treated with breast conservation, the LORIS criteria identified a subgroup at slightly lower risk for IBTR compared with women who did not meet LORIS criteria; however, this difference was not statistically significant.

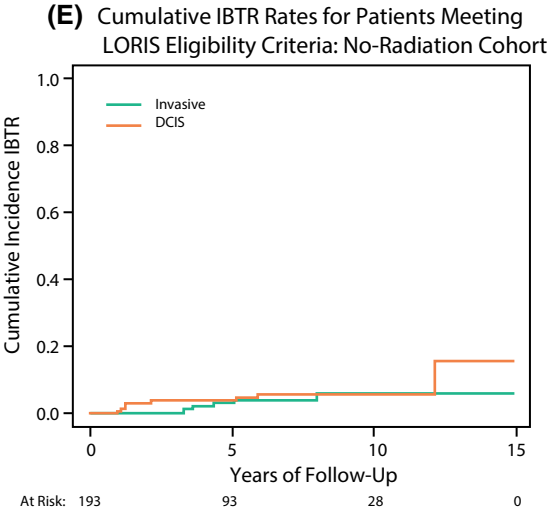
Importantly, by its very nature, our study population consists of women at lower risk than those meeting registration eligibility criteria for the LORIS trial, because our patients continued to fulfill all inclusion criteria even after surgical excision. The LORIS exclusion criteria (for example, a mass lesion on imaging) attempt to minimize the potential risk of an undiagnosed synchronous invasive carcinoma. Here, in our population, all patients have already undergone complete surgical excision, and, therefore, there are no undiagnosed invasive carcinomas and

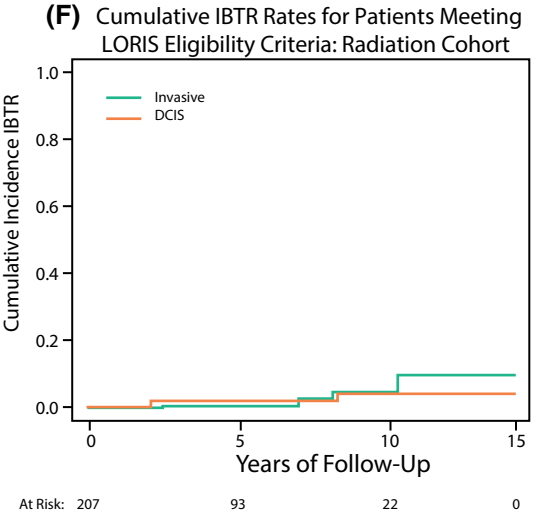

(A) Any IBTR-Free Survival; Entire Cohort
IBTR-Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Non-LORIS (n=2136)
LORIS (n=401)
Log-Rank p=0.09
0
5
10
15
Years of Follow-Up
Non-LORIS: 2136 1235 420 57
LORIS: 401 187 50 0


(B) Any IBTR-Free Survival; No-Radiation Cohort
IBTR-Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Non-LORIS (n=901)
LORIS (n=193)
Log-Rank p=0.1
0
5
10
15
Years of Follow-Up
Non-LORIS: 901 518 183 24
LORIS: 193 93 28 0


(C) Any IBTR-Free Survival; Radiation Cohort
IBTR-Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Non-LORIS (n=1215)
LORIS (n=207)
Log-Rank p=0.3
0
5
10
15
Years of Follow-Up
Non-LORIS: 1215 711 237 33
LORIS: 207 93 22 0


(D) Cumulative IBTR Rates for Patients Meeting LORIS Eligibility Criteria: Entire Cohort
Cumulative Incidence IBTR
1.0
0.8
0.6
0.4
0.2
0.0
Invasive
DCIS
0
5
10
15
Years of Follow-Up
At Risk: 401 187 50 0


(E) Cumulative IBTR Rates for Patients Meeting LORIS Eligibility Criteria: No-Radiation Cohort
Cumulative Incidence IBTR
1.0
0.8
0.6
0.4
0.2
0.0
Invasive
DCIS
0
5
10
15
Years of Follow-Up
At Risk: 193 93 28 0


(F) Cumulative IBTR Rates for Patients Meeting LORIS Eligibility Criteria: Radiation Cohort
Cumulative Incidence IBTR
1.0
0.8
0.6
0.4
0.2
0.0
Invasive
DCIS
0
5
10
15
Years of Follow-Up
At Risk: 207 93 22 0

◀**FIG. 2** IBTR rates. **a** IBTR-free survival; entire population ($n = 2394$). **b** IBTR-free survival; no-radiation ($n = 954$). **c** IBTR-free survival; radiation ($n = 1419$). **d** Cumulative IBTR rates for patients meeting LORIS eligibility criteria ($n = 401$). **e** Cumulative IBTR rates for patients meeting LORIS eligibility criteria; no-radiation ($n = 193$). **f** Cumulative IBTR rates for patients meeting LORIS eligibility criteria; radiation ($n = 207$). *IBTR* ipsilateral breast tumor recurrence, *LORIS* meeting eligibility criteria for the LORIS (surgery vs active monitoring for low-risk DCIS) Trial, *DCIS* ductal carcinoma in situ

none of the "low-risk" patients in this series had undiagnosed high-grade DCIS. Furthermore, it is well known that DCIS excised with positive margins has a higher recurrence rate than that excised with negative margins.[9,21] Therefore, one can deduce that those not undergoing excision at all must have a higher risk of recurrence than those undergoing upfront excision.

For women with DCIS diagnosed only on core biopsy who are managed with observation alone, one would postulate that the overall rate of subsequent invasive carcinoma would be higher, both due to potential progression of unresected DCIS and the possibility of unrecognized synchronous invasion. Although one small study by Soumian et al. reported zero upgrades to invasive carcinoma among a cohort of 19 women with low-grade DCIS who met all LORIS criteria, a meta-analysis of 52 studies including 7350 patients reported an overall underestimation rate of 26 %.[22] They found that among women with non-high-grade DCIS diagnosed by core biopsy, 21 % were upgraded to invasive carcinoma at the time of surgical excision.[13] We also recently assessed rates of invasive upgrade at the time of surgical excision for women meeting LORIS trial registration eligibility on core needle biopsy and found nearly identical results. Among 296 women, 59 (20 %) were upgraded to invasive carcinoma on final pathology.[23] Given this significant upgrade rate of 20 % of women with non-high-grade DCIS having invasive cancer found at excision, women meeting the LORIS criteria and managed with observation alone would be expected to incur significantly higher 10-year rates of invasive cancer development than the 6 % rate of recurrence reported in this study. The actual rates of clinically detectable invasive cancers identified in the LORIS study will provide vital information which will help direct clinical practice in the future.

The primary endpoint of the LORIS trial is the ipsilateral invasive breast cancer-free survival rate at 5 years. Our results suggest that longer follow-up is necessary in determining the safety of observation alone for non-high-grade DCIS, as the 10-year rates of invasive recurrence reported are more than double the 5-year rates, suggesting a slow disease evolution for this specific population.

The acceptable level of risk for subsequent invasive carcinoma is both controversial and debatable.[24] The clinical utility of different management strategies hinges on both the subsequent rate of progression to invasive disease and the potential morbidity of the therapeutic options. Rates of short-term complications following breast-conserving surgery are very low, reported at <2 % among more than 6600 women reported to the American College of Surgeons NSQIP database who underwent breast-conserving surgery with a sentinel lymph node biopsy, and, therefore, one could surmise that the complication rate following excision alone may be even lower.[25]

A recently published randomized trial of women with low-risk DCIS has shown that adjuvant radiation provides additional improvement in local control at 7 years for low-risk DCIS patients treated with breast-conserving surgery (7 % IBTR with surgery alone vs 1 % IBTR with radiation;

TABLE 3 The 5- and 10-year rates of invasive and in situ recurrence for patients meeting LORIS eligibility criteria

	No. of events	5-year IBTR (%)	10-year IBTR (%)
Entire LORIS cohort ($n = 401$)			
Invasive cancer	10	1.8	5.3
DCIS	14	2.8	5.0
No RT LORIS cohort ($n = 193$)			
Invasive cancer	6	3.0	6.0
DCIS	10	3.9	6.0
RT LORIS cohort ($n = 207$)			
Invasive cancer	4	0.6	4.6
DCIS	4	1.8	4.2

LORIS cohort, meeting eligibility criteria for the LORIS (surgery vs active monitoring for low-risk DCIS) trial after complete surgical excision and histologic examination of excision specimen. Non-LORIS cohort, women with pure DCIS after undergoing complete surgical excision and histologic examination of the excision specimen, but not meeting all eligibility requirements. Any woman with invasion in excision specimen was excluded

IBTR ipsilateral breast tumor recurrence, *DCIS* ductal carcinoma in situ, *RT* radiation therapy

$p < 0.001$), although the improvement in local control is coupled with an increased rate of complications in the radiation cohort.[26] Similarly, while the addition of postoperative endocrine therapy for DCIS reduces the risk of local recurrence, tamoxifen increases the risk of uterine cancer and thromboembolic events, and anastrozole is associated with increased musculoskeletal complaints and fractures.[27,28] Patient-reported data show that more than 20 % of women on tamoxifen report fatigue, depression, insomnia, hot flashes, and vaginal dryness.[29] While historical uptake of endocrine therapy for DCIS has been low, there is also growing interest in studying the use of endocrine therapy alone as a nonoperative DCIS management strategy, although to date there are limited data on this subject. One small study of 14 patients treated nonoperatively on endocrine therapy and active surveillance reported that 8 women required surgical intervention at a median follow-up of 28 months, with 5 women progressing to invasive carcinoma. This study is limited by the small sample size and also the heterogeneity of the patient population, as the study group includes a mix of patient age, DCIS grade, and extent of disease.[30] A computational risk analysis reported only small numeric differences in disease-specific cumulative mortality among women with DCIS modeled to undergo usual care or active surveillance.[31] Prospective patient data will emerge from the upcoming COMET trial, comparing operative to medical endocrine therapy for low-risk DCIS.[32] The COMET trial is similar to the LORIS study in that the trial will be limited to a select DCIS cohort.

For a noninvasive lesion with potential for progression to invasive carcinoma, the challenge remains balancing appropriate risk reduction with minimal harm. A nomogram that estimates risk of recurrence for women with DCIS has been developed and validated in several independent populations.[33–36] The nomogram provides numerical 5- and 10-year recurrence risk estimates based on 10 clinical and pathological variables. However, even with an individualized risk estimate, perceptions of acceptable levels of risk vary by individual. As posed in a published case presentation highlighting the DCIS dilemma, "When is good enough really good enough?"[37] For DCIS, there is no one-size-fits-all answer, as physician and patient preferences, and level of risk aversion to both treatment side effects and subsequent IBTR all clearly affect decision making. Importantly, as a secondary outcome, the LORIS trial will also assess the psychological impact of the studied treatment arms.

Our study is limited by its retrospective nature and lack of central pathology review; however, the information was obtained from a robust, prospectively maintained database, including both clinical and patient-reported data allowing for detailed clinicopathologic data, including factors such as family history and presence of bloody nipple discharge, making it possible to assess eligibility for the LORIS trial. Among a cohort of more than 2500 patients, only 17 % met all eligibility criteria, yet there remained a clinically meaningful rate of progression to invasive carcinoma following surgical excision.

In conclusion, while the LORIS criteria identify women at somewhat lower risk of IBTR, the 10-year rate of invasive recurrence after complete excision remains 6 %. Assuming the rate of subsequent progression to invasive disease would be higher with observation alone, both because of missed invasive cancer and progression of unexcised DCIS, surgical excision (with or without additional adjuvant therapy) is warranted outside of a clinical trial. The results of the randomized controlled trials, including the LORIS study, will provide important data regarding rates of clinically detectable invasive breast cancer development among this select group of patients and will help shape the future care of women with DCIS. Additional research is paramount to identify DCIS subsets lacking capacity for disease progression to allow evidence-based personalized treatment recommendations.

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