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The effect of age in the outcome and treatment of older women with ductal carcinoma in situ

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ABSTRACT

The effect of increasing age on outcomes and type of treatment given to older women with ductal carcinoma in situ (DCIS) was assessed. 646 women ≥60 years old (654 cases) receiving surgery for DCIS at Memorial Sloan-Kettering Cancer Center between 2000 and 2007 (8 bilateral) had wide local excision (WLE; 37%), WLE plus radiotherapy (WLE + RT; 41%), or mastectomy (22%). 45%, 38%, and 16% of patients 60–69 years, 70–79 years, and ≥80 years, respectively, received WLE + RT ($P < 0.001$) and 25%, 20%, and 13%, received mastectomy, respectively ($P < 0.001$). Age ($P < 0.001$), grade ($P < 0.001$), and necrosis ($P < 0.01$) were highly associated with treatment. Four-year local recurrence was 3.6%. Overall local recurrence differed by treatment (mastectomy, 0%; WLE, 5%; WLE + RT, 4%; $P < 0.00001$) but not age. It is possible to identify older women with DCIS in whom the risk of recurrence is acceptably low after WLE alone. WLE alone may be a viable treatment option for select older women with DCIS.

1. Introduction

Many breast-cancer physicians in the 21st century would agree that the optimal treatment of ductal carcinoma in situ (DCIS) has yet to be defined. Despite the publication of several randomized studies[1–7] over the past decade, two prospective studies[8,9] and several large retrospective studies[10,11] documenting long-term outcomes data on DCIS patients after various treatments, controversy over the management still persists, as exemplified by the wide variation in practice patterns in DCIS in both Europe and the United States.[12–16]

Recent epidemiologic data reflect a dramatic increase in the number of elderly women with cancer in the United States.[17] The number of women ≥65 years old diagnosed with DCIS in 2010 is projected to be 25,000 and will increase by 56% to 39,000 by 2030.[18] These changes can be attributed to recent socioeconomic and public health trends, such as the enlarging pool of older women,[19,20] the prevalence of breast cancer in older women, and increased detection of DCIS secondary to greater availability and accessibility of mammographic screening.[21] Thus, the necessity of elucidating treatment options and better understanding of factors that impact treatment choices becomes even more important in treating older women with DCIS.

Several retrospective studies have suggested older women with DCIS experience lower rates of local recurrence (LR) than younger women.[10,11,22,23] In the 1999 Memorial Sloan-Kettering Cancer Center (MSKCC) analysis of women with DCIS treated with breast-conserving surgery, Van Zee et al. reported lower 6 year actuarial LR rates in older patients independent of histologic subtype, other pathologic parameters, and the use of postoperative radiotherapy.[11] In a study of long-term outcomes after breast-conserving surgery and radiation for mammographically detected DCIS, Solin et al. demonstrated that age >50 years was independently associated with a lower risk of failure.[10]

The paucity of outcomes and treatment data specific to older patients with DCIS, and the lack of uniform consensus among physicians on the benefit of radiation after breast-conserving surgery in all DCIS patients, makes it difficult to determine whether excision alone may suffice for elderly women with DCIS. With the exception of one recently published prospective trial of wide excision alone in which the median age of the patients was 60 years, women >60 years were under-represented in the randomized studies investigating WLE with or without radiation[1–5,24,25] and in another prospective trial of wide excision alone[8,9] in DCIS (Table 1).

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Table 1
Representation of women ≥60 Years of Age in Studies of DCIS.

Study	Study design	Age group (years)	Number of patients ≥60 years old	Total number of patients (all ages)
NSABP B-17[1–3]	RCT	≥60	294	818
EORTC[4,5]	RCT	NR	NR	1010
SweDCIS[6]	RCT	≥65	240	1067
		58–64	264	
UKCCR[7]	RCT	≥60–64	447	1701
		≥65	168	
Dana-Farber.[8]	Prospective	≥60	37	158
ECOG.[9]	Prospective	65–88	241	711
Solin et al.[10]	Retrospective	≥60	321	1003
Van Zee et al.[11]	Retrospective	40–69	103	171
		≥70	39	

ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; NR=not reported; National Surgical Adjuvant Breast and Bowel Project; RCT=Randomized controlled trial; SweDCIS=Swedish Ductal Carcinoma In Situ; UKCCR=United Kingdom Co-ordinating Committee on Cancer Research.

More importantly, outcomes were not analyzed with respect to older age in these studies.

In this study, we aimed to determine the impact of increasing age and other clinicopathologic features on treatment patterns and outcomes in older women with DCIS treated within a contemporary era of surgical and radiation treatments, modern breast imaging, and rigorous microscopic margin assessment at a single large academic center.

2. Materials and methods

Between January 2000 and December 2007, 779 women ≥60 years old underwent surgery for newly diagnosed pure DCIS at MSKCC. After excluding 103 patients with a history of invasive breast cancer, five with synchronous melanoma skin cancers, and 25 with a synchronous contralateral invasive breast cancer, 646 patients and 654 cases of DCIS remained.

WLE consisted of complete removal of known tumor. All slides were evaluated by a team of dedicated breast pathologists for histologic subtype, the presence of necrosis, nuclear grade, and involvement of margins by DCIS. Microscopic size of the DCIS lesion was not routinely evaluated. SLNB was generally performed in "high-risk" patients in whom there was clinical or radiological suspicion of invasion such as a palpable or mammographic mass, pathology suspicious but not diagnostic for invasion, or extensive disease requiring mastectomy. The most common reason for SLNB was multicentric disease requiring mastectomy. Post-excision mammograms were performed in patients presenting with suspicious calcifications and receiving WLE.

Nuclear grade was categorized as low, intermediate, or high, based on the Lagios nuclear grading system.[26] Necrosis was defined as the presence of a central zone of necrotic debris with karyorrhexis, and categorized as minimal, moderate, or extensive. ER receptor status was not routinely evaluated. Although microscopic margin evaluation was performed on every case, exact margin width and number of ducts involved by DCIS at the margin was not routinely measured. Margins were categorized as negative, close, or positive. Close margins were defined as the presence of duct(s) involved by DCIS ≤2 mm from the inked surface of the specimen.

Adjuvant radiation was delivered with two tangential beams. For the 127 patients who received radiation at an outside institution, treatment summaries documenting the dose and fraction size were obtained. A sequential boost to the lumpectomy cavity was delivered to 60% (159/264) of patients who received whole breast radiation. No patients received cytotoxic chemotherapy. 17% received hormonal therapy, consisting of mostly tamoxifen, although letrozole, anastrozole, and raloxifene were also utilized.

Follow-up consisted of annual mammograms, routine interval history, and physical examinations, commencing from the date of definitive surgery (excision or re-excision) for DCIS. LR was defined as the subsequent occurrence of biopsy-proven invasive or intraductal breast cancer in the treated breast and/or regional lymph nodes. Time to LR was calculated from the date of the definitive surgery to the date of histologically proven recurrence.

The chi-square test was used to examine differences between the distribution of characteristics among age and treatment groups. An ordinal logistic regression model was used for multivariate analysis of predictors of treatment received. We reported the odds ratios with their 95% confidence intervals. Kaplan–Meier methods were utilized to calculate time to local recurrence and overall survival. Univariate associations between clinicopathologic variables and recurrences were assessed using the log rank test. Multivariate analysis of recurrence could not be performed due to a small number of events.

3. Results

Table 2 details patient and tumor characteristics of the 646 patients. The median age at diagnosis was 67 years (range, 60–88 years). Eighty-seven percent of patients presented with mammographically detected disease without a palpable mass. Abnormal mammogram findings included suspicious calcifications in 73%, mass in 12%, and both in 3%. Intermediate- or high-grade DCIS together represented 83% of lesions. Necrosis was identified in 459 (70%) cases, 292 of which were moderate or extensive. Margins

Table 2
Patient and tumor characteristics.

	Number	%
Age (years)		
60–69	401	62.1
70–79	191	29.6
≥80	54	8.4
Ethnicity		
Caucasian	532	82.4
Hispanic	32	5.0
African-American	57	8.8
Other	25	3.9
Laterality at diagnosis		
Right	316	48.9
Left	322	49.8
Bilateral	8	1.2
Grade		
Low	109	16.7
Intermediate	312	47.7
High	229	35.0
Unknown	4	0.6
Necrosis		
None	142	21.7
Focal	167	25.5
Moderate	195	29.8
Extensive	97	14.8
Unknown	53	8.1
Margin status		
Negative	547	83.6
Positive	22	3.4
Close (<2 mm)	85	13.0
ER status		
Negative	25	3.8
Positive	66	10.1
Unknown	563	86.1

ER=estrogen receptor.

were negative in 84% of cases, within 2 mm in 13%, and positive in 3%. ER status was unknown in 86% of patients, as receptor testing was not routinely performed. Ten percent of patients were ER positive and 4% were ER negative.

Treatment characteristics are outlined in Table 3. Of 646 patients, 240 (37%) received WLE alone, 266 (41%) WLE with radiation, and 148 (22%) mastectomy. Eight patients had bilateral DCIS. Approximately one-third (32%) of patients underwent axillary lymph-node evaluation, either SLNB alone in 192 (29%), SLNB followed by axillary dissection in 16 (2%), or axillary dissection only in 2 (0.3%). Radiation was delivered to the whole breast in 265 (41%) patients after breast-conserving surgery. Sixty percent (159/265) of patients receiving whole breast radiation also received a boost to the lumpectomy cavity. The median dose and number of fractions of patients receiving whole breast radiation was 5500 cGy (range, 4240–6840 cGy) and 28 fractions, respectively. One patient received partial breast radiotherapy to a dose of 3400 cGy. The vast majority (83%) of patients did not receive hormonal therapy.

Table 4 represents the clinicopathologic characteristics of all 654 cases stratified by treatment type. A significantly higher proportion of patients who received mastectomy were 60–69 years old (70%), compared with those 70–79 and ≥80 years (26% and 5%, $P < 0.0001$). Similarly, a significantly higher proportion of patients who received radiation following WLE were 60–69 years (69%), compared with 70–79 and >80 years (27% and 3%, $P < 0.0001$). As the amount of necrosis increased, so did the proportion of patients receiving mastectomy or radiation in addition to WLE ($P < 0.0001$). Patients with high-grade tumors were also more likely to receive post-excision radiation or mastectomy ($P < 0.0001$). Other clinicopathologic variables stratified by age group are seen in Table 5. A significant trend was seen in the use of radiation and mastectomy in the 60–69 years age group (45% and 25%) and 70–79 years (38% and 20%) age group, compared with the ≥80 age group (16% and 13%, $P < 0.0001$). All other examined variables did not correlate significantly with age.

Table 3
Treatment characteristics.

	Number	%
Treatment type		
WLE	240	37%
WLE + RT	266	41%
Mastectomy	148	22%
Lymph-node evaluation		
Not evaluated	444	67.9%
SLNB only	192	29.4%
AD only	2	0.3%
SLNB + AD	16	2.4%
Hormones		
No	543	83.0%
Yes	111	17.0%
Radiation therapy		
No	388	59.3%
Yes	266	40.7%
Boost		
No	74	11.3%
Yes	159	24.3%
Unknown	33	5.0%
No RT	388	59.3%
Radiation volumes		
Partial breast	1	0.2%
Whole breast	265	40.5%
No RT	388	59.3%

AD=axillary dissection; RT=radiotherapy; SLNB=sentinel lymph node biopsy; WLE, wide lesion excision.

Table 4
Clinicopathologic and treatment characteristics by treatment type.

	WLE (n=240)		WLE + RT (n=266)		Mastectomy (n=148)		P value
	Number	%	Number	%	Number	%	
Age (years)							
60–69	120	50%	184	69%	103	70%	<0.0001
70–79	81	34%	73	27%	38	26%	
≥80	39	16%	9	3%	7	5%	
Ethnicity							
Caucasian	208	87%	220	83%	111	75%	0.12
Hispanic	8	3%	14	5%	10	7%	
African-American	16	7%	24	9%	17	11%	
Other	8	3%	8	3%	10	7%	
Grade							
Low	68	28%	28	11%	13	9%	<0.0001
Intermediate	120	50%	126	47%	66	45%	
High	50	21%	110	41%	69	47%	
Unknown	2	1%	2	1%	0	0%	
Necrosis							
None	82	34%	46	17%	14	9%	<0.0001
Focal	62	26%	53	20%	52	35%	
Moderate	52	22%	98	37%	45	30%	
Extensive	22	9%	51	19%	24	16%	
Unknown	22	9%	18	7%	13	9%	
Margin status							
Negative	195	81%	209	79%	142	96%	0.0001
Positive	10	4%	11	4%	1	1%	
Close (<2 mm)	35	15%	46	17%	4	3%	
Unknown	0	0%	0	0%	1	1%	

In an ordinal logistic regression model, age group ($P < 0.001$), grade of tumor ($P < 0.001$), and necrosis (P=0.01) were found to be statistically significant predictors of treatment type when comparing WLE, WLE + RT, and mastectomy (Table 6). Younger age was correlated to more aggressive treatment. Similarly, the higher

Table 5
Clinicopathologic and treatment characteristics by age group.

	60–69 Years (n=407)		70–79 Years (n=192)		≥80 Years (n=55)		P value
	Number	%	Number	%	Number	%	
Ethnicity							
Caucasian	328	81%	183	85%	48	87%	0.35
Hispanic	20	5%	8	4%	4	7%	
African-American	38	9%	16	8%	3	5%	
Other	21	5%	5	3%	0	0%	
Grade							
Low	58	14%	42	22%	9	16%	0.28
Intermediate	204	50%	84	44%	24	44%	
High	143	35%	64	33%	22	40%	
Unknown	2	0%	2	1%	0	0%	
Necrosis							
None	85	21%	45	23%	12	22%	0.39
Focal	95	23%	54	28%	18	33%	
Moderate	132	32%	52	27%	11	20%	
Extensive	61	15%	29	15%	7	13%	
Unknown	34	8%	12	6%	7	13%	
Margin status							
Negative	351	86%	154	80%	41	75%	0.2
Positive	12	3%	8	4%	2	4%	
Close (≤2 mm)	43	11%	30	16%	12	22%	
Unknown	1	0%	0	0%	0	0%	
Treatment type							
WLE	120	29%	81	42%	39	71%	<0.0001
WLE + RT	184	45%	73	38%	9	16%	
Mastectomy	103	25%	38	20%	7	13%	

RT=radiotherapy; WLE=wide local excision.

the grade of DCIS and greater the extent of necrosis, the more aggressive the treatment received. However, when comparing the WLE vs WLE + RT groups alone, only age and grade were associated with the receipt of radiation. The older the age group, the less likely postoperative radiation was received ($P < 0.0001$, Table 6). The use of postoperative radiation after WLE was also associated with intermediate- or high-grade tumors ($P < 0.0001$). Margin status and necrosis were not found to be statistically significant predictors of treatment received when only the WLE and WLE + RT groups were compared.

Median follow-up was 54 months (range, 6–112 months) for the 646 cases. Median follow-up for each treatment group was as follows: mastectomy, 53 months, WLE + RT, 52 months, WLE 49 months. Four-year overall survival for the entire group was 95.4% (Fig. 1a) and 4-year local control rate was 96.4% (Fig. 1b), with 31 local recurrences. Twenty-two of the local recurrences were DCIS and nine were invasive. Differences in 4-year recurrence rates by treatment type were statistically significant when all three treatment groups (mastectomy, WLE, and WLE + RT) were compared (P=0.005, Fig. 2a). However, there was no statistically significant differences between 4-year recurrence rates when only WLE vs WLE + RT were compared (95% and 96%, respectively; P=0.66, Fig. 2b).

Among the 240 patients who received WLE alone, 16 had local recurrences (10 DCIS, six invasive) (Fig. 3). Among the 266 patients who received WLE and radiation, there were 15 local recurrences (12 DCIS, three invasive). None of the 148 patients who received mastectomy experienced a recurrence at her last follow-up prior to data analysis. There were 20 LRs (15 DCIS, five invasive) among the 401 patients 60–69 years, six LRs (four DCIS, two invasive) among the 191 patients 70–79 years, and five LRs (three DCIS, two invasive) among the 54 patients ≥80. Four-year recurrence-free survival did not differ by age and was 97%, 98%, and 96%, respectively (P=0.07). Associations between margin status, necrosis, and grade and the risk of recurrence in patients who received WLE vs WLE + RT were not statistically significant.

Table 6
Multivariate model of predictors of treatment.

	Odds ratio (95% CI)	*P* value
All treatment groups		
Age (years)		
60–69	Reference	<0.0001
70–79	0.66 (0.47–0.91)	
≥80	0.17 (0.09–0.32)	
Grade		
Low	Reference	<0.0001
Intermediate	1.77 (1.08–2.88)	
High	3.41 (1.96–5.94)	
Unknown	0.80 (0.11–6.03)	
Necrosis		
None	Reference	0.01
Minimal/Focal	2.34 (1.45–3.78)	
Moderate	1.87 (1.15–3.05)	
Extensive	1.81 (1.01–3.24)	
Unknown	1.86 (0.98–3.55)	
Excluding mastectomy group		
Age (years)		
60–69	Reference	<0.0001
70-79	0.65 (0.43–0.99)	
≥80	0.12 (0.05–0.28)	
Grade		
Low	Reference	<0.0001
Intermediate	2.42 (1.43–4.10)	
High	5.32 (2.96–9.56)	
Unknown	1.17 (0.14–9.78)	

4. Discussion

Selecting the appropriate treatment for DCIS is a clinical quandary that has resulted in substantial variation in both the perception of risk and management of the disease among breast-cancer physicians.[27] Although treatments for DCIS do not impact survival, uncertainty in choosing among treatment options is magnified by competing comorbidities in older women. Data from multiple randomized trials[1–7] demonstrate a reduction in local recurrence with the addition of radiation after lumpectomy. However, without data that can reliably identify a group whose risk of recurrence is low enough to justify withholding radiation, many patients, including elderly women, are often overtreated to achieve the risk reduction seen when adding radiation.

Currently, little is known regarding the clinical, pathologic, and patient-driven factors that shape treatment decisions in older women with DCIS. The significance of the latter was recently highlighted in a large SEER-Medicare study of 1125 patients (including those >79 years) with DCIS and invasive breast cancer,[28] which aimed to determine the role of age and age-related factors in surgical decision-making for breast-cancer treatments. Older women with DCIS were found to choose mastectomy over breast-conserving treatment in DCIS equally compared with younger women, but used less knowledge to decide. Larger tumor size, lower education level, and number of surgeons consulted

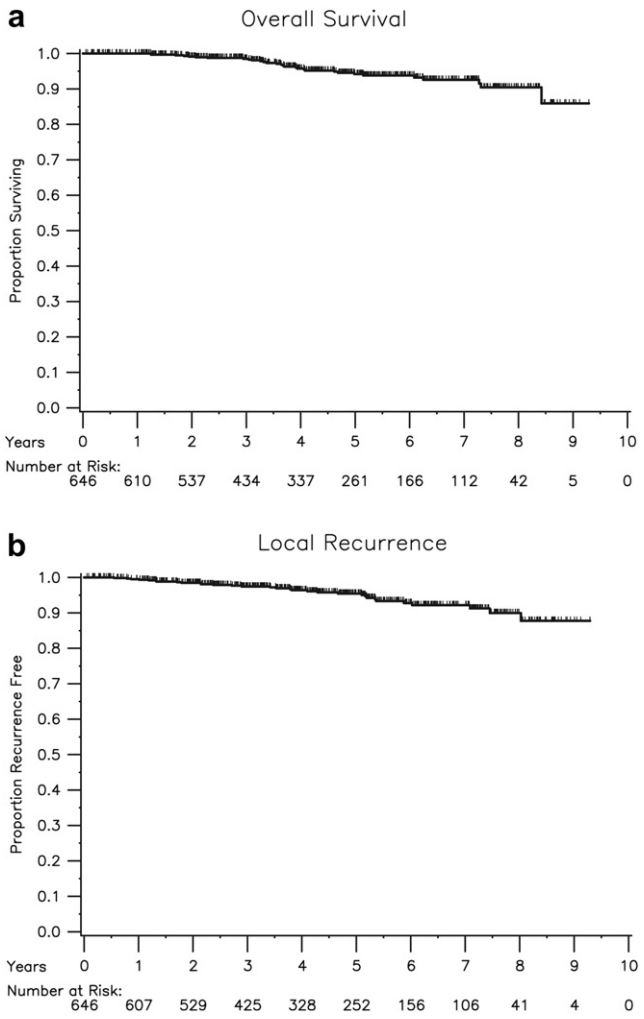

Fig. 1. Outcomes for entire cohort: 4-year overall survival=95.4%, cause-specific survival=100% and 4-year recurrence-free survival=96.4%.

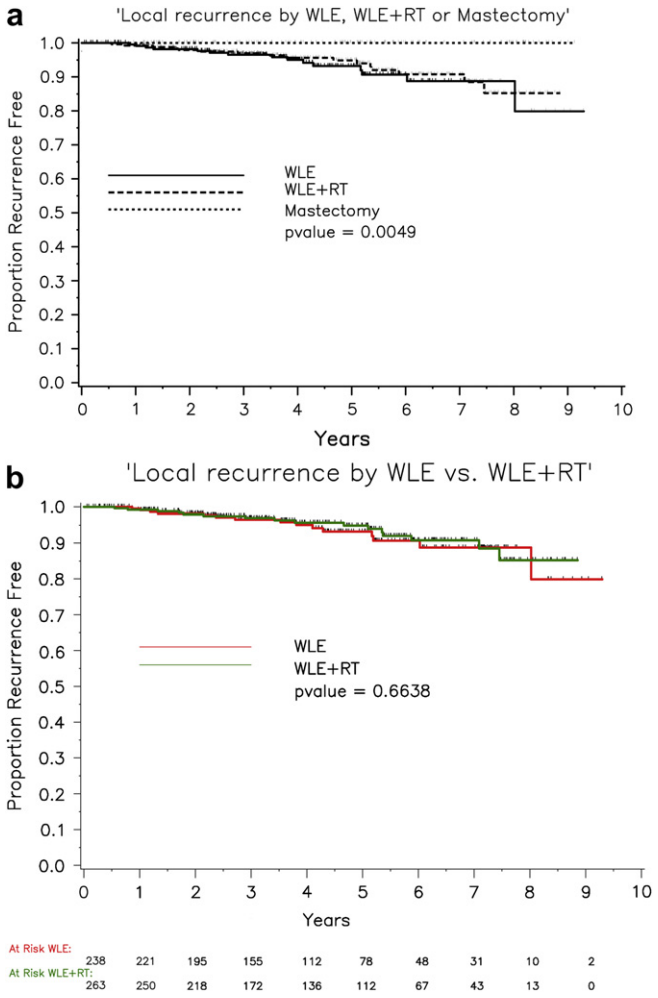

Fig. 2. a. Local recurrence by WLE±RT or mastectomy. Four-year recurrence-free survival: WLE, 95%; WLE + RT, 96%; mastectomy 100%. b. Local recurrence by WLE ± RT. Four-year recurrence-free survival: WLE, 95%; WLE + RT, 96%.

significantly predicted choosing mastectomy, whereas age, invasion, and comorbidities did not.

In our study, age was highly associated with aggressiveness of treatment. Also, increasing extent of necrosis and grade correlated with the addition of radiation to WLE and mastectomies, both of which were performed more frequently in patients 60–69 years old or with tumors with extensive necrosis or high-grade histology. However, unlike the above SEER registry study, we did not factor in the impact of comorbidities, in elderly patients, in whom morbidities from other co-existing illnesses may transcend the small risk of death due to DCIS and drive treatment choice.

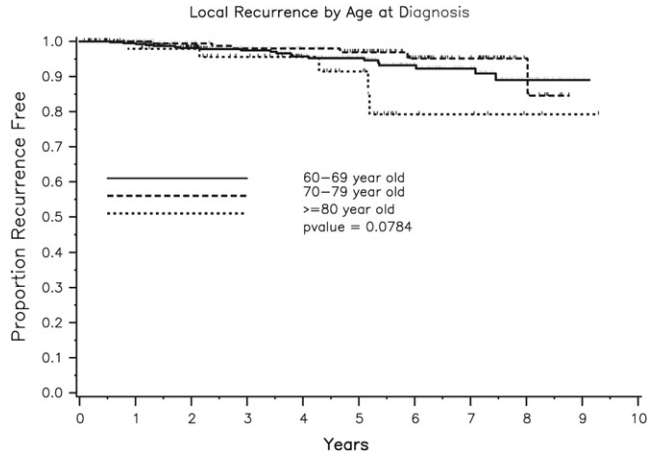

Fig. 3. Recurrence-free survival by age group. 4Y-RFS: 97% (60–69 years old), 98% (70–79 years old), 96% (>80 years old).

An LR rate of 3.6% at 4 years was reported for the entire population, comparable to 3%–6% 5-year recurrence rates reported in studies of breast-conserving surgery with radiation,[10,29] and lower than the 9%–16% 5-year recurrence rates seen with surgery alone.[22,29] There was no difference between recurrence rates by age group or by treatment received. Considering the high proportion (83%) of patients in the study who presented with either intermediate- or high-nuclear grade lesions, the low 4-year recurrence rate is encouraging, as higher-grade tumors are typically prognostic for early rather than late recurrence risk,[30] and we would therefore have expected the bulk of local recurrences from higher-grade tumors to manifest themselves within the median follow-up period of the study.

The benefit of radiation added to breast-conserving surgery has been clearly documented in a SEER-cohort based study of 3409 patients ≥66 years old with DCIS treated with breast-conserving surgery, with nearly half the patients receiving postoperative radiotherapy.[12] The primary outcome was a second breast-cancer event, including either salvage mastectomy or subsequent breast cancer. High-risk was defined as the presence of at least one of the following features: age 66–69 years, tumor size >2.5 cm, comedo histology, and/or high-grade. The addition of radiation to WLE was found to lower the 5-year risk of a second breast-cancer event in both the low risk (8% for WLE vs 1% for WLE + RT, $P < 0.001$) and high-risk (14% for WLE vs 4% for WLE + RT, $P < 0.001$) groups.

Several explanations may account for the observed differences between these population-based studies and our results. Among other well-described risk factors for local recurrence in DCIS such as histologic subtype, presence of necrosis, grade, and young age,[5,31,32] margin status has been described as the most important of them all.[33] Patient-specific data on margins and amount of necrosis were not reported in the SEER study, as this information was not readily available through Medicare claims data and was therefore not factored into the categorization of low- versus high-risk groups in the study. Moreover, population-based studies theoretically reflect the clinical practice patterns in a diverse community setting. It is possible that there may have been a wide variability in margin evaluation and status, subsequently biasing physicians towards recommending radiation in patients with involved margins and thereby overestimating the benefit of radiation.

In contrast, the patients in our study were subjected to the practice patterns of a single, large academic institution, where margin status was regularly evaluated by dedicated breast pathologists and patients were treated by one of a group of 11 breast surgeons who share relatively compatible treatment philosophies on the significance of obtaining clear margins in DCIS, as reflected by the few patients with positive (3%) or close (13%) margins in the study and the even distribution of positive or close margins among the WLE±RT groups (Table 2). The high percentage of patients with negative margins in our study may have reduced the observed potential benefits of radiation. An association between margin status and recurrence rates in patients treated with WLE±RT was not seen, likely due to the small sample size in each subgroup. Again, secondary to the low total number of events, this study with relatively short follow-up lacked the statistical power required to detect a significant benefit conferred by radiation.

Several shortcomings of the study deserve mention. We were unable to investigate whether re-excision rates influenced treatment received. The number of re-excisions performed per patient was not quantified, but it has been shown that multiple re-excisions

to obtain clear margins do not appear to negatively impact local recurrence in DCIS.[34] Although the number of re-excisions has been associated with the greater likelihood of mastectomy in young women,[35] the impact in the older population is largely unknown. In addition, neither pathologic size of the tumor nor the extent of calcifications correlating with the DCIS lesion on mammogram were routinely measured at our institution, because quantifying the pathologic size of the DCIS lesion is technically difficult and calcifications seen on mammogram can underestimate the true pathologic extent of the lesion. Tumor size may not predict LR in DCIS, as a linear relationship was not identified in either the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 or European Organization for Research and Treatment of Cancer (EORTC) randomized trials of WLE±RT for DCIS.[1,4] Although we would anticipate that large tumor size could be a surrogate for extensive disease requiring mastectomy, it would have been useful to assess whether tumor size impacted the receipt of radiation after WLE. Lastly, our median follow-up period is short, considering the long natural history of DCIS.

It is critical to interpret these results within the framework of the inherent biases that accompany this retrospective study. Well-established pathologic risk factors for recurrence such as extensive necrosis and high-grade tumors were more representative in patients in the WLE + RT and mastectomy groups than the WLE alone group, which could explain the similarity in short-term outcomes between the three treatment groups. Rather than concluding that postoperative radiation does not make a difference in this patient population, our study demonstrates that it is possible for clinicians to select older women with low risk features who do well in the short-term with WLE alone. Although the prospect of omitting radiation in this defined population is appealing, it clearly requires validation in a prospective setting and collection of long-term outcomes data prior to acceptance as routine practice.

5. Conclusions

Recent advancements in radiation have afforded more options to older patients with DCIS receiving radiation, including the omission of a boost, the use of hypofractionated radiation regimens, and partial breast irradiation, all of which can subsequently reduce the costs, time, and morbidity of adjuvant radiation. A deeper understanding of molecular features unique to older women with DCIS[36] that are predictive for the development of invasive disease, as well as tools that elucidate the decision-making process of older women with breast cancer, will aid us greatly in the further refinement of our treatment options for this unique population.

Conflict of Interest Statement

The authors have no conflicts of interest.

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