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ARTICLE

Modeling the Effectiveness of Initial Management Strategies for Ductal Carcinoma In Situ

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Background The prevalence of ductal carcinoma in situ (DCIS) and the marked variability in patterns of care highlight the need for comparative effectiveness research. We sought to quantify the tradeoffs among alternative management strategies for DCIS with respect to disease outcomes and breast preservation.

Methods We developed a disease simulation model integrating data from the published literature to simulate the clinical events after six treatments (lumpectomy alone, lumpectomy with radiation, lumpectomy with radiation and tamoxifen, lumpectomy with tamoxifen, and mastectomy with and without breast reconstruction) for women with newly diagnosed DCIS. Outcomes included disease-free, invasive disease-free, and overall survival and breast preservation.

Results For a cohort of 1 million simulated women aged 45 years at diagnosis, both mastectomy and lumpectomy with radiation and tamoxifen were associated with a 12-month improvement in overall survival relative to lumpectomy alone. Adding radiation therapy to lumpectomy resulted in a 6-month improvement in overall survival but decreased long-term breast-preservation outcomes (likelihood of lifetime breast preservation = 0.781 vs 0.843 for lumpectomy alone). This decrement with radiation therapy was mitigated by the addition of tamoxifen (likelihood of lifetime breast preservation = 0.846).

Conclusions Overall survival benefits of the six management strategies for DCIS are within 1 year, suggesting that treatment decisions can be informed by the patient's preference for breast preservation and disutility for recurrence. Our delineation of personalized outcomes for each strategy can help patients understand the implications of their treatment choice, so their decisions may reflect their own personal values and help improve the quality of care for patients with DCIS.

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The incidence of ductal carcinoma in situ (DCIS) has risen over the past 25 years (1,2). Despite the large number of women affected, the risk conferred by DCIS and the optimal treatment remain uncertain, leading to challenges in treatment decision-making for women and their physicians.

Although breast-conserving surgery (ie, lumpectomy) and mastectomy are both considered standard treatment options for DCIS, a randomized trial comparing these approaches has not been performed and is likely infeasible. In contrast, randomized clinical trials have assessed the benefit of radiation therapy for patients treated with lumpectomy (3–6). These trials demonstrated that radiation therapy reduces the risk of ipsilateral breast cancer recurrence by approximately 50% to 60%. Nevertheless, none of the trials found a statistically significant difference in overall survival. Two large trials have evaluated the utility of tamoxifen, a selective estrogen-receptor (ER) modulator, for secondary prevention. Both studies demonstrated that tamoxifen reduced the risk of ipsilateral breast cancer by approximately 30% and contralateral breast cancer by 50% (3,5,7–9).

Recent studies have begun to identify biomarkers, gene expression patterns, clinical traits, and histopathological factors that may help indicate which DCIS lesions carry an elevated risk of invasive breast cancer occurrence vs DCIS recurrence (10,11). Patients at elevated risk of invasive recurrence may derive more benefit from treatment. However, therapeutic decision-making must also incorporate the downstream consequences of treatment. For example, although radiation therapy decreases the risk of local recurrence, those who develop recurrence must undergo mastectomy. Therefore, some DCIS treatment strategies may improve short-term disease-related outcomes while compromising the likelihood of long-term breast preservation. The optimal treatment strategy for an individual patient may depend on her risk of recurrence and her preferences regarding the different outcomes involved.

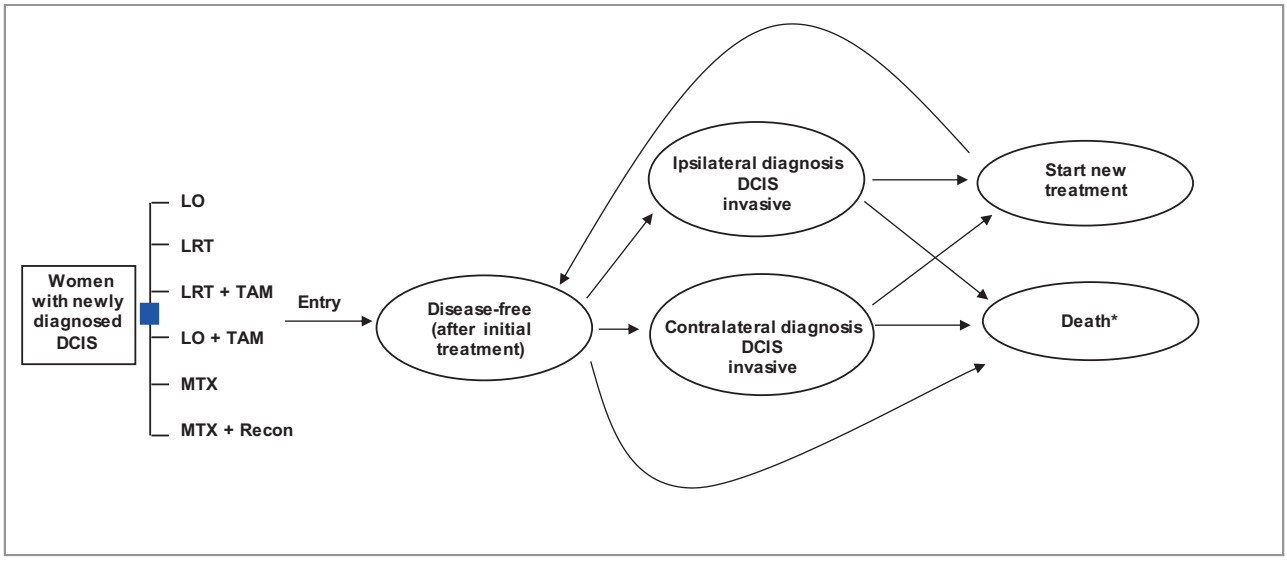

Figure 1. Discrete event simulation schematic. *Death can be from breast cancer or non–breast cancer causes. Only women with an invasive diagnosis can die from breast cancer. DCIS = ductal carcinoma in situ; LO = lumpectomy alone; LO + TAM = lumpectomy with tamoxifen; LRT = lumpectomy with radiation; LRT + TAM = lumpectomy with radiation and tamoxifen; MTX = mastectomy; MTX + Recon = mastectomy with reconstruction.

To fully assess the tradeoffs among DCIS management strategies, including any small benefit in survival, would require a randomized study of tens of thousands of patients with a long follow-up period. Furthermore, no randomized trial to date has had the power to fully delineate the limitations in treatment choices faced at time of recurrence after DCIS-imposed initial management strategy. To address these gaps in existing data, disease simulation models can provide a framework that synthesizes data from randomized trials and retrospective studies to evaluate the relative performance of health interventions. These models can also be used to tailor results to an individual set of clinical circumstances and can produce a range of outcomes relevant to an individual patient.

The objective of this study was to quantify the tradeoffs of six treatment scenarios for DCIS that are considered current standard practice with respect to long-term disease and breast-preservation outcomes.

Methods

Model

We developed a discrete-event simulation model that integrated empirical data from the published literature to estimate the impact of different treatment options on outcomes after newly diagnosed DCIS. The simulation approach allows for incorporation of details about patient-specific characteristics and individual variation in the disease process that cannot be achieved by other modeling approaches (12). Given a specific age at diagnosis of DCIS, the model simulates a patient's disease trajectory, including events such as recurrence or new primary breast cancer over the individual's lifetime. Model outcomes include survival measures as well as breast preservation. We investigated six treatment scenarios for DCIS: 1) lumpectomy alone; 2) lumpectomy with radiation; 3) lumpectomy with tamoxifen; 4) lumpectomy with radiation and tamoxifen; 5) mastectomy; and 6) mastectomy with breast reconstruction. The model was constructed in TreeAge Pro (version 2008; Williamstown, MA: TreeAge Software, Inc.).

All women entered the model in a disease-free state after initial treatment and were at risk of recurrence in the ipsilateral breast, development of a new primary cancer in the contralateral breast, and death from non–breast cancer causes (Figure 1). To model the disease course for a simulated woman, we established the temporal order and timing of discrete events. We randomly sampled times for each possible event, choosing the event with the earliest time to occur next and discarding the other times (13). At time of a new event, the time elapsed was noted, and the age of the woman was updated. This process was repeated after the occurrence of each new nonfatal event. With this approach, the sequence of events experienced by the women was randomly generated from the distributions assigned in the model. The simulation ended when a woman died from breast cancer or other causes or her age equaled or exceeded 100 years. To achieve convergence in model outcomes, a population of 1 million women of a given age at diagnosis was simulated for each treatment strategy, and the history of events for each individual was tracked over her lifetime and aggregated.

If a woman experienced a DCIS or a nonmetastatic invasive recurrence in the ipsilateral breast, she received a second treatment. If her first treatment included radiation, she was eligible for mastectomy with or without breast reconstruction. Otherwise, she also had the option of lumpectomy with radiation. If a woman experienced a new event in the contralateral breast, she was eligible for mastectomy with or without reconstruction or breast-conserving surgery with radiation. After a mastectomy, women had a small risk of chest wall or distant recurrence. After a chest wall recurrence, a patient might die of breast cancer or other causes. Women diagnosed with a metastatic disease were no longer eligible for future breast cancer diagnoses and were

at risk of death from either breast cancer or non–breast cancer causes.

Data and Assumptions

Treatment Efficacy. The risks of recurrence and new primary cancer over time were specified for each of the six initial treatment strategies. Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 and NSABP B-24 trials (8) were used to inform these parameters for lumpectomy alone, lumpectomy with radiation, and lumpectomy with radiation and tamoxifen. Because the NSABP trials did not include an arm treated with breast-conserving surgery with tamoxifen without radiation, we inferred the effects of tamoxifen from the UK, Australia, and New Zealand (ANZ) DCIS trial (9). Therefore, we adjusted the lumpectomy with radiation and tamoxifen data from the NSABP B-24 trial using the hazard ratios between the lumpectomy with radiation and tamoxifen arm relative to the lumpectomy with tamoxifen arm from the UK/ANZ DCIS trial. A time to recurrence for each treatment type was randomly drawn from time-to-event (ie, cumulative incidence) distributions based on trial data for each simulated individual. For mastectomy, women were assumed to no longer be at risk of a DCIS recurrence and to have a 1% recurrence risk of stage III or IV invasive disease over a 10-year period (14,15). Model input parameters are detailed in Table 1.

Stage Distribution and Treatment After Recurrence. If a woman developed an invasive breast cancer, the stage of cancer was determined using the stage distribution of women diagnosed with invasive cancer after DCIS between 1995 and 2005 in the Surveillance Epidemiology and End Results (SEER) limited use database (16). We assumed 33% of patients would receive mastectomy vs lumpectomy with radiation in a breast that had not been previously irradiated (17) and varied this parameter in sensitivity analyses. We used age-specific likelihood of reconstruction after mastectomy obtained from data collected as part of the National Initiative on Cancer Care Quality (18).

Breast Cancer and Non–Breast Cancer Mortality. We assumed that DCIS carried no direct risk of breast cancer mortality (19). Stage-specific invasive breast cancer survival distributions were obtained from an observational study of newly diagnosed patients treated in British Columbia, Canada (20). Each patient was subject to risk of mortality from non–breast cancer causes based on the 1960 birth cohort US life tables that had removed breast cancer as a cause of death (21). Varying the risk of other cause mortality was evaluated in sensitivity analyses.

Statistical Analysis

We compared the treatment strategies by calculating the average values of lifetime outcomes, including disease-free survival, invasive disease-free survival, overall survival, breast preservation, and death from breast cancer. We present results for three selected ages at DCIS detection to illustrate the influence of age on model outcomes.

To illustrate variation in treatment outcomes for different recurrence risk profiles, we used categories generated by the "DCIS score," an algorithm designed to predict recurrence using gene expression (11).

In supplementary analyses, we varied the risk of recurrence by age and the likelihood of mastectomy after a recurrence to understand the impact on survival outcomes and breast status. To vary risk of recurrence by age, we used age-specific rates of ipsilateral breast events for lumpectomy and lumpectomy with radiation therapy from a meta-analysis of randomized DCIS trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (22).

Results

Model Validation

The model was validated by comparing our model outputs to data not used in model development obtained from the European Organization for Research and Treatment of Cancer (EORTC) randomized trial 10853, which reported 10-year event-free local recurrence rates of 74% for lumpectomy alone and 85% for the lumpectomy with radiation arm (3). To replicate this trial, we simulated a population of women aged 53 years at diagnosis (median age of EORTC trial). Our model predicted 10-year percentages of no further local event in the ipsilateral breast of 71% for lumpectomy alone and 87% for lumpectomy with radiation. Although our model projections for the effects of radiation were larger than those found in the EORTC trial (16% vs 11% difference), the rank ordering of outcomes across treatment strategies was consistent. The difference between the baseline model and results from using the EORTC data could be expected given the different input parameters of these studies.

Model estimates of breast cancer–specific and overall survival were also compared with SEER data for three ages (ages = 45, 60, and 70 years) of US women diagnosed with DCIS from 1995 to 2008 (16). With respect to breast cancer–specific survival, our analysis showed very similar results to SEER for all age groups (Supplementary Figure 1, available online). For overall survival, our results showed similar trends for the 45- and 60-year-old age groups. However, SEER survival 10 years after diagnosis for 70-year-old women was approximately 8% lower than the model estimate, consistent with the use of general US data vs that of the SEER population.

Survival Outcomes

The model results indicated that for women aged 45 years at diagnosis, mastectomy provided the greatest number of disease-free years per patient and compared with lumpectomy alone yielded an additional 9.1 disease-free years (DCIS or invasive cancer) (Table 2). Both mastectomy and lumpectomy with radiation and tamoxifen yielded the greatest invasive disease-free survival, providing an additional 5 years without invasive breast cancer compared with lumpectomy alone. As expected, differences between treatment strategies were less pronounced with respect to overall survival. The use of lumpectomy with radiation and tamoxifen and mastectomy were associated with a 12-month improvement in overall survival relative to lumpectomy alone. Adding radiation therapy to lumpectomy increased survival by only 6 months.

Lumpectomy alone was associated with the highest likelihood of death from breast cancer, whereas the mastectomy and

Table 1. Model assumptions and input parameters*

Variable	Value at 10 years	Value at 10 years		
Risk of recurrence	**DCIS**	**Invasive**	**Type**	**Source**
Lumpectomy†				Wapnir et al. 2011 (8)
Ipsilateral	0.14	0.16		
Contralateral	0.02	0.06		
Lumpectomy with radiation†				
Ipsilateral	0.08	0.06		
Contralateral	0.03	0.05		
Lumpectomy with radiation and tamoxifen†				
Ipsilateral	0.06	0.05		
Contralateral	0.01	0.03		
Lumpectomy with tamoxifen				Cuzick et al. 2011 (9)
Ipsilateral	0.35	0.44	HR	
Contralateral	0.66	1.17	HR	
Mastectomy with or without reconstruction				
Ipsilateral	—	0.01		Boyages et al. 1999 (14), Lee et al. 2006 (15)
Stage distribution of invasive recurrence				NCI 2010 (16)
Stage I	0.61			
Stage II	0.27			
Stage III	0.07			
Stage IV	0.05			
Stage distribution of invasive new breast cancer				NCI 2010 (16)
Stage I	0.63			
Stage II	0.29			
Stage III	0.05			
Stage IV	0.03			
Probability of mastectomy after recurrence	0.33			Fong et al. 2011 (17)
Probability of reconstruction after mastectomy				Greenberg et al. 2008 (18)
Age, y				
25–34	1.00			
35–44	0.71			
45–54	0.58			
55–64	0.44			
65–74	0.22			
≥75	0.07			
Mortality				
Breast cancer–specific by stage				Olivotto et al. 2003 (20)
Stage I	0.08			
Stage II	0.27			
Stage III	0.52			
Stage IV	0.88			
Non–breast cancer causes	US life table			Rosenberg 2006 (21)
Sensitivity analyses				
Risk of recurrence				Solin et al. 2011 (11)
Low	0.49	0.31	Adjustment factors compared with base case	
Intermediate	1.11	0.54		
High	0.58	1.16		
Age-specific recurrence rates	LO	LO + RT		EBCTCG 2010 (22)
<50 years: 5 years after diagnosis	1.1	1.59	Risk ratios compared with base case	
10 years	1.04	1.43		
≥50 years: 5 years	0.97	0.82		
10 years	0.99	0.84		

* DCIS = ductal carcinoma in situ; EBCTCG = Early Breast Cancer Trialists' Collaborative Group; HR = hazard ratio; LO = lumpectomy; NCI = National Cancer Institute; RT = radiation.

† In this table we only report the 10-year cumulative incidence of events. However, in the model we use time-to-event distributions based on data from the National Surgical Adjuvant Breast and Bowel Project B-17 and B-24 trials [Wapnir 2011 (8)].

the lumpectomy with radiation and tamoxifen strategies were associated with the lowest likelihood (Figure 2). For example, the model projected between 1000 and 1500 additional deaths from breast cancer per 100 000 women at 10 years after their initial diagnosis for lumpectomy alone compared with other treatment arms.

Table 2. Estimated survival in years by ductal carcinoma in situ treatment for selected ages at detection

Treatment choices	45-year-old woman			60-year-old woman			70-year-old woman		
	Disease-free survival	Invasive disease-free survival	Overall survival	Disease-free survival	Invasive disease-free survival	Overall survival	Disease-free survival	Invasive disease-free survival	Overall survival
Lumpectomy	24.4	29.3	36.2	16.6	19.5	23.5	12.1	13.9	16.3
Lumpectomy with radiation	28.1	31.7	36.7	19.1	21.1	23.8	13.8	15.1	16.6
Lumpectomy with radiation and tamoxifen	31.5	34.2	37.2	20.9	22.4	24.1	14.8	15.7	16.7
Lumpectomy with tamoxifen	25.7	31.6	36.6	17.5	20.9	23.7	12.7	14.9	16.5
Mastectomy with or without reconstruction	33.5	34.3	37.2	22.1	22.6	24.1	15.6	15.9	16.7

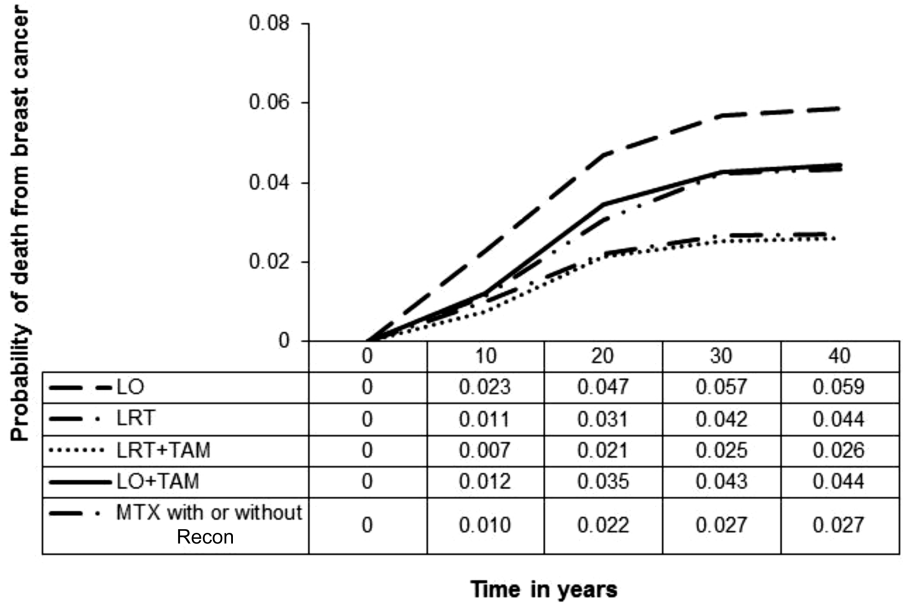

Figure 2. Death from breast cancer for the different treatment strategies over time. LO = lumpectomy alone; LO +TAM = lumpectomy with tamoxifen; LRT = lumpectomy with radiation; LRT +TAM = lumpectomy with radiation and tamoxifen; MTX = mastectomy; Recon = reconstruction.

Individualized Risk Groups. We explored the impact of alternative assumptions about recurrence risk on outcomes for the lumpectomy arms using a proposed DCIS score for three risk groups characterized as low, intermediate, and high (11). In this example, adding radiation therapy to lumpectomy alone improved survival for women aged 45 years by 1 months, 4 months, and 7 months for low-, intermediate-, and high-risk scores, respectively (Table 3).

Breast Preservation

Among women treated for DCIS at age 45 years, the likelihood of ipsilateral recurrence was minimized with mastectomy, and the likelihood of contralateral breast cancer was minimized with lumpectomy with radiation and tamoxifen (Table 4). The likelihood of long-term native breast preservation (the sum of the probability of having no further local event plus lumpectomy with radiation for a local event) was greatest among women whose initial treatment strategy included lumpectomy alone (0.843), lumpectomy with tamoxifen (0.845), or lumpectomy with radiation and tamoxifen (0.846) vs those who underwent upfront lumpectomy with radiation (0.781).

Age-Specific Recurrence Rates

The analysis was repeated using age-specific rates of ipsilateral breast events for lumpectomy and lumpectomy with radiation therapy as reported in the EBCTCG report. Using these rates, the estimated survival benefit with radiation was smaller relative to the base case in younger women (aged <50 years) and larger in older women (aged ≥50 years). However, for women aged 70 years the benefit from radiation therapy was similar to that reported in the base-case analysis. In this analysis using age-specific recurrence rates relative to lumpectomy alone, radiation improved survival by 4 months in the model simulating women aged 45 years and increased survival by 5 months in the women aged 60 years (Supplementary Table 1, available online).

Varying the Likelihood of Mastectomy After a Recurrence in an Unirradiated Breast

We also studied the impact of varying the likelihood of mastectomy at time of recurrence in an unirradiated breast on lifetime ipsilateral breast preservation (Figure 3). Radiation was associated with a decrement in lifetime breast preservation for a woman aged

Table 3. Survival results in years by proposed ductal carcinoma in situ risk score for an exemplar 45-year-old woman at detection

Treatment choices	Low*			Intermediate*			High*		
	(<39)			(39–54)			(≥55)		
	Disease-free survival	Invasive disease-free survival	Overall survival	Disease-free survival	Invasive disease-free survival	Overall survival	Disease-free survival	Invasive disease-free survival	Overall survival
Lumpectomy	29.9	33.0	37.0	26.2	31.9	36.7	25.1	28.2	36.0
Lumpectomy with radiation	31.5	33.7	37.1	29.2	33.2	37.0	28.7	31.1	36.6
Lumpectomy with radiation and tamoxifen	34.1	35.8	37.5	32.3	35.2	37.4	32.0	33.8	37.1
Lumpectomy with tamoxifen	31.3	34.9	37.3	27.0	33.7	37.0	27.1	30.8	36.5

* The categorization in low-, intermediate-, and high-risk groups of recurrence is based on a prespecified ductal carcinoma in situ score that was designed to predict recurrence using an optimized gene expression algorithm.

45 years unless the likelihood of mastectomy at time of recurrence or new diagnosis in an unirradiated breast exceeded 56.2%.

Discussion

Using a simulation model, we evaluated an extensive array of DCIS treatment choices. Consistent with the lower recurrence and new breast cancer risks associated with mastectomy, our findings showed that this approach was associated with longer disease-free time and a relatively smaller improvement in overall survival. Likewise, there was a similar improvement in overall survival with the addition of radiation therapy and tamoxifen relative to lumpectomy alone. Adding radiation to lumpectomy resulted in even smaller improvements in overall survival. The survival benefit with radiation was a consequence of the reduced risk of an invasive local recurrence and consistent with the effects of radiation on the subsequent development of invasive recurrence and of invasive recurrence on survival (23).

In this study, the magnitude of overall survival benefits of the strategies is within 1 year, a finding consistent with the lack of difference observed in the randomized trials of radiation for DCIS (22) and with prior DCIS modeling efforts (24). The magnitude of benefit is a critical factor in determining which treatment choice is appropriate for an individual patient. However, this should be weighed against the consequences of treatment in terms of breast-preservation outcomes. Our model demonstrated that adding radiation to lumpectomy reduces the likelihood of native breast preservation (no further local event or lumpectomy with radiation) and increases the likelihood of mastectomy; however, this decrement in breast preservation with radiation was mitigated by the addition of tamoxifen.

We used simulation methodology to evaluate the trade-offs in lifetime risks and benefits of management strategies for DCIS. The model was not designed to be used as a policy model but rather to produce output that can be used as input data for a decision aid to foster individual patient-centered decision-making. We intentionally omitted population-based utility values from the analyses because utilities may vary widely among individual patients (ie, the utility after mastectomy vs that of living with the risk of recurrence after breast preservation). Such differences create different optimal treatment choices for individual patients that would not be preserved if average measures of utility were used.

Several study limitations must be acknowledged. First, we made some simplifying assumptions about the natural history and treatment of disease to specify a finite number of clinical events. For example, we assumed that recurrence by stage had the same prognosis as de novo carcinomas by stage and for each treatment arm. It is possible that some breast cancers may be more aggressive, in which case we may have overestimated the effect of treatment. However, we used estimates derived from the literature or databases to inform our base-case analysis and allowed for flexibility of the model for additional refinement of personalized recurrence risks [eg, by incorporating data on low-risk patients forthcoming from the RTOG 9804 trial (25)]. Second, patients in the NSABP B-17 trial were accrued between 1985 and 1990 and the B-24 trial between 1991 and 1994. Since then, improved mammographic and pathologic evaluation and greater attention

Table 4. Lifetime risk of experiencing a second local event by ductal carcinoma in situ treatment for an exemplar 45-year-old woman at detection*

Initial treatment	Breast	No further local event†	Treatment for second event		
			LRT	MTX	MTX + Recon
Lumpectomy	Ipsilateral	0.618	0.225	0.086	0.069
	Contralateral	0.839	0.099	0.038	0.023
Lumpectomy with radiation	Ipsilateral	0.781	0	0.123	0.095
	Contralateral	0.840	0.099	0.038	0.023
Lumpectomy with radiation and tamoxifen	Ipsilateral	0.846	0	0.083	0.071
	Contralateral	0.916	0.052	0.019	0.013
Lumpectomy with tamoxifen	Ipsilateral	0.621	0.224	0.088	0.067
	Contralateral	0.894	0.066	0.025	0.015
Mastectomy with or without reconstruction	Ipsilateral	0.993	0	0	0
	Contralateral	0.849	0.094	0.035	0.022

* LRT = lumpectomy with radiation; MTX = mastectomy; MTX + Recon = mastectomy with reconstruction.

† The probabilities do not sum to one because women also had a small risk of chest wall or distant recurrence. This risk is subtracted from the "No further local event" probability.

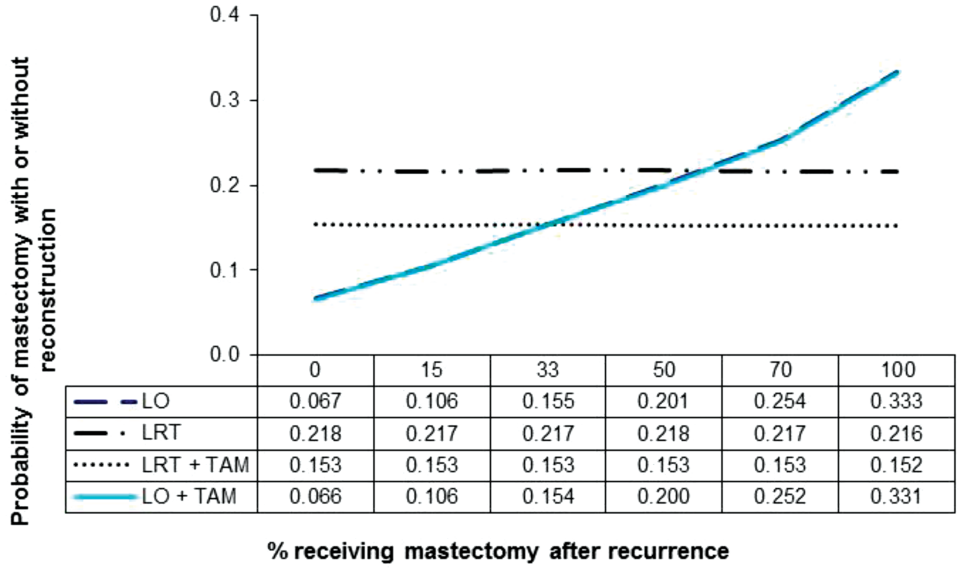

Figure 3. The impact of varying the likelihood of mastectomy after a recurrence in an unirradiated breast on lifetime ipsilateral breast preservation. The lumpectomy (LO) and lumpectomy with tamoxifen (LO + TAM) curves overlap in this figure. LRT = lumpectomy with radiation; LRT + TAM = lumpectomy with radiation and tamoxifen.

to achieving negative margins may result in a lower risk of local recurrence than observed in the trials (26). Using these older trials to inform treatment efficacy in our model could therefore imply an overestimation of the treatment effects if risk of recurrence after lumpectomy alone is now lower. Third, we did not stratify our patient population by hormone receptor status, largely because of a lack of available data. A recent study reveals that only DCIS that expresses ER may benefit from tamoxifen (27). Therefore, if only ER-positive DCIS patients are included in the model (76% of patients are ER-positive in the current model), the superiority of the tamoxifen arms may become more prominent. However, because the study only provides risk estimates by ER status for radiation with and without tamoxifen and not for the other treatment arms, we did not include the data in our analyses. We hypothesize that the results of the other treatment arms (eg, lumpectomy) may also change by ER status. Fourth, we did not explore the impact of uncertainty in model input parameters on results across multiple parameters simultaneously; instead we conducted several univariable sensitivity analyses on key input parameters. Therefore, the relatively small differences in outcomes between some of the treatment options may not be meaningful if overall joint uncertainty is considered.

In conclusion, overall survival benefits of the six management strategies for DCIS are within 1 year, suggesting that treatment decisions can be informed by the patient's preference for breast preservation and disutility for recurrence. Population-based analyses reveal large regional variation in treatment of DCIS (28–31). This type of variation as opposed to selection of treatment according to patient preference is a marker of poor quality of care (32). Our delineation of personalized outcomes for each strategy can

help patients understand the implications of their treatment choice, so their decisions may reflect their own personal values and help improve the quality of care for patients with DCIS.

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