A Decision Analysis of the Effect of Avoiding Axillary Lymph Node Dissection in Low Risk Women with Invasive Breast Carcinoma

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BACKGROUND. Evidence that avoiding axillary lymph node dissection (AxD) strikes an appropriate balance between morbidity and recurrence risk in patients with invasive breast carcinoma generally is anecdotal and without a formally quantified basis. The current study presents a decision analysis of the difference in 5-year disease free survival (DFS) rate between treatment scenarios with and without routine AxD.

METHODS. To derive quantitative estimates of the effect of avoiding AxD on 5-year DFS, the authors examined outcomes for women undergoing 2 treatment scenarios: AxD or no AxD with adjuvant therapy decisions based on risk factors in the primary tumor. Eligible patients belonged to 2 lymph node metastases risk groups: low (patients without palpable lymph nodes and lymphatic or vascular invasion [LVI] negative tumors $\leq$ 0.5 cm in greatest dimension) and moderate (patients with mammographically detected, LVI negative tumors, between 0.6-2.0 cm in greatest dimension or patients with palpable LVI negative tumors between 0.6-1.0 cm in greatest dimension with nonpalpable lymph nodes). Along with observed data regarding treatment and recurrence, the authors employed estimates of the efficacy of chemotherapy, tamoxifen, and regional radiation therapy derived from published randomized trials to estimate the 5-year DFS rate for treatment scenarios with and without AxD.

RESULTS. Patients in the low risk group had a 5% risk of lymph node metastases. In these women, eliminating AxD and treating no patients with chemotherapy and/or tamoxifen resulted in a $<$ 1% decrease in the 5-year DFS rate. Patients in the moderate risk group had a 10% risk of lymph node metastases. Eliminating AxD and treating only those women with Grade 3 tumors $>$ 1 cm in greatest dimension with chemotherapy and/or tamoxifen resulted in a 1.8% decrease in the 5-year DFS rate. However, if all patients in this group were treated with chemotherapy and/or tamoxifen and no AxD, the 5-year DFS rate increased by 2.7%.

CONCLUSIONS. In patients with a low risk of lymph node metastases, it was estimated that eliminating AxD may result in only minimal changes in the estimated 5-year DFS rate. ***Cancer* 2000;88:1852–62.**

KEYWORDS: breast carcinoma, axillary dissection, lymph node metastasis, decision analysis.

Numerous prognostic techniques have been investigated in the hope that axillary lymph node status can be determined without the morbidity of axillary dissection. Axillary sampling,[1] immunoscintigraphy,[2] positron emission tomography,[3] ultrasound,[4] and prognostic mathematic modeling[5–13] all have been suggested as possible alternatives to axillary dissection. Although many of these techniques

have been shown to produce low false-negative rates in some populations, the probability of lymph node metastasis remains above 10% in the majority of women with invasive breast carcinoma. Axillary lymph node status traditionally has played an important role in staging and treatment selection and substantially reduces the risk of axillary relapse. However, recent increases in the number of mammographically detected tumors of lower risk, and the trend toward the use of systemic therapy for lymph node negative disease, have led physicians to question the value of axillary lymph node dissection (AxD) in some subgroups of patients.[1,14–18] In an extensive review of the issue, Recht and Houlihan argued that effective axillary lymph node therapy had some curative potential but noted that the benefit may be so small that some patients would not find the morbidity justifiable.[19]

Unfortunately, evidence that avoiding AxD strikes an appropriate balance between morbidity and survival in patients with invasive breast carcinoma is generally anecdotal and without a formally quantified basis. This report presents a decision analysis of the survival implications of treatment recommendations with and without routine AxD. In particular, previously published analyses of the probability of lymph node involvement,[20] treatment effectiveness estimates from published clinical trials data,[21–27] and Cox estimated relapse rates are used to estimate the 5-year disease free survival (DFS) rate for low risk patients undergoing treatment scenarios including and not including AxD.

METHODS

Subjects

Eligible cases were identified from the Breast Cancer Outcomes Database (BCOD) which is maintained by the British Columbia Cancer Agency (BCCA) in Vancouver, Canada. The BCOD contains detailed demographic, staging, treatment, and outcome information for all women referred to the BCCA since January 1, 1989. Eligible patients were diagnosed between January 1, 1989 and December 31, 1992, were 90 years of age or younger at the time of diagnosis, had survived at least 30 days from the time of diagnosis, had at least 1 lymph node examined pathologically, were not clinically or pathologically T4, N2, or M1, did not have pathologically pure in situ disease, and did not receive systemic antineoplastic therapy or regional radiotherapy before AxD. Because the decision to avoid AxD was based on tumor size, lymphatic or vascular invasion (LVI) and the palpability of the primary tumor and/or axillary lymph nodes, cases with missing values for any of these variables were excluded.

Data

Clinical factors abstracted for each patient were age at diagnosis and palpability of the malignant tumor (not palpable, palpable primary with negative axilla, palpable axillary lymph nodes). Pathologic factors assessed were number of positive axillary lymph nodes (0, 1–3, > 3), tumor grade (nuclear grade or histologic grade using the modified Scarff–Bloom–Richardson system[28]), size of the primary tumor (maximum histologic or macroscopic pathology size in mm or the clinical size from a preoperative mammogram or notes of the referring surgeon), estrogen receptor (ER) status (negative = ER $<$ 10 fmol/mg cytosol protein or no uptake on immunohistochemical staining; positive = 10 or more fmol/mg cytosol protein or positive immunohistochemical staining for ER, or unknown), and lymphatic or vascular space invasion (LVI) in the tumor (absent, present, unknown). The use of adjuvant systemic cytotoxic therapy, tamoxifen, and/or regional radiation therapy (RT) was recorded if given before the diagnosis or suspicion of recurrent or metastatic disease.

Analyses and Assumptions

The analyses were designed to generate the estimated 5-year DFS rate for treatment plans with or without AxD. Disease free survival was defined as any local, regional, or distant relapse or death from breast carcinoma. Patients without a known date of relapse or death were considered lost to follow-up if no information was available within 18 months of the analysis date. The selection of patients in which one might consider avoiding AxD was based on a previously reported risk of lymph node metastasis stratification system.[20] This stratification system was based on a multivariate analysis of prognostic risk factors in 4312 cases and outlines 4 risk groups of patients, 2 of which have a sufficiently low risk of lymph node metastases that one might consider avoiding AxD. The lowest risk group has a 5% chance of lymph node metastases and consists of patients with LVI negative tumors ≤ 0.5 cm in diameter, without palpable lymph nodes. In the current analysis, this group is referred to as the ''low risk'' group. The second lowest risk group has an approximately 12% chance of lymph metastases and consists of patients with mammographically detected, LVI negative tumors between 0.6 and 2.0 cm in diameter, without palpable lymph nodes or palpable, LVI negative tumors between 0.6 and 1.0 cm in diameter, with nonpalpable lymph nodes.[20] This group is referred to as the ''moderate'' risk group.

Overview of analyses

The analyses were conducted in four phases. In the first phase, we used Cox regression analysis to estimate the 5-year DFS rate for each low and moderate risk group woman in the sample if she did not receive any form of chemotherapy, tamoxifen, or regional RT. This Cox estimate is referred to as the estimated ''untreated'' 5-year DFS rate. Because all women in this sample received an AxD, the Cox untreated estimates are only valid for women treated with AxD and not receiving any form of chemotherapy, tamoxifen, or regional RT. In the second phase, we applied the AxD odds reductions given in Table 1 to the Cox untreated 5-year DFS estimates to determine the untreated 5-year DFS rate for each woman in the sample if no AxD was given. In the third phase, the chemotherapy, tamoxifen, and regional RT odds reductions given in Table 1 were applied to the estimated untreated 5-year DFS estimates to obtain ''treated'' 5-year DFS estimates for each woman in the sample under treatment scenarios including and not including AxD. Finally, to estimate the effectiveness of treatment scenarios including and not including AxD, the mean treated 5-year DFS rate was calculated for treatment scenarios including and not including AxD. The difference between the AxD and no AxD means represents the estimated absolute benefit of AxD. In the following sections, a detailed description of each phase of the analysis is given.

Estimating untreated 5-year DFS rate

To estimate the untreated 5-year DFS rate, a Cox regression model was constructed for all women in the sample. Treatment and prognostic variables eligible for entry into the model were risk group (low, moderate, other), lymph node status (negative, positive), age (< 50, 50–69, and > 69), ER status (negative, positive, unknown), a dummy variable with a value of 1 if tumor grade was 3 and size was > 1 cm and 0 otherwise, a dummy variable with a value of 0 if the patient received no chemotherapy or tamoxifen and 1 otherwise, and a dummy variable with a value of 1 if the patient received regional RT and 0 otherwise. Variables were retained in the model if they significantly ($P < 0.05$) improved the fit of the model. Using the resulting Cox model, we estimated the untreated 5-year DFS rate for each patient type in the low and moderate risk groups. Table 3 contains these estimates, rounded to the nearest whole number, for cases in the low and moderate risk groups. The Cox estimated untreated relapse rates subsequently were employed to determine estimates of the treated 5-year DFS rate for each risk group and treatment option.

TABLE 1
Assumed ORs in 5-Year DFS for Axillary Dissection, Chemotherapy, Tamoxifen, and Regional RT in Patient Groups Defined by Lymph Node Status, Age, and ER Status

Lymph node status	Age (yrs)	ER	OR			
			AxD	Chemo	Tam[a]	RT
Negative	<50	NEG	0	30	10	20
Negative	<50	POS	0	30	40	20
Negative	50–69	NEG	0	20	10	20
Negative	50–69	POS	0	20	40	20
Negative	>69	NEG	0	10	10	20
Negative	>69	POS	0	10	40	20
Positive	<50	NEG	30	30	10	30
Positive	<50	POS	30	30	40	30
Positive	50–69	NEG	30	20	10	30
Positive	50–69	POS	30	20	40	30
Positive	>69	NEG	30	10	10	30
Positive	>69	POS	30	10	40	30

OR: odds reduction; DFS: disease free survival; RT: radiation therapy; ER: estrogen receptors; AxD: axillary dissection; Chemo: chemotherapy; Tam: tamoxifen; NEG: negative; POS: positive.
[a] OR for tamoxifen in cases with ER unknown is 35% for all cases regardless of age or lymph node status.

This was done by applying the odds reduction of a given treatment (i.e., chemotherapy, tamoxifen, regional RT) to the untreated odds of relapse.

Treatment odds reductions

Table 1 gives the odds reductions that were used broken down by lymph node status, age, and ER status. Odds reductions for chemotherapy and tamoxifen were derived from meta-analyses published by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[21,22] For tamoxifen,[21] the EBCTCG report that, for all patients, 5 years of tamoxifen reduced the odds of recurrence by 43%. For 5 years of tamoxifen, this effect was similar, irrespective of lymph node status and/or age at diagnosis. However, in women with ER poor tumors, irrespective of the duration of tamoxifen, the proportional recurrence reduction was only 10%. In women with ER positive tumors, the proportional recurrence reduction was 50% and in ER unknown tumors the proportional recurrence reduction was 37%. Based on these figures, we have used an odds reduction for tamoxifen of 50% in ER positive, 35% in ER unknown, and 10% in ER negative tumors. These odds reductions were not adjusted for age or lymph node status.

For chemotherapy,[22] the EBCTCG reported that proportional reductions in recurrence risk were similar irrespective of lymph node status, ER status, or the type and/or duration of polychemotherapy regimen used. However, the effectiveness of chemotherapy did decrease statistically significantly with age at diagno-

sis. In women younger than 50 years, the overall proportional recurrence reduction was 35% and in women ages 50–69 years, the recurrence reduction was 20%. Limited data were available for women older than 69 years. We used, based on these figures, an odds reduction for chemotherapy of 35% for women $<$ 50 years of age, 20% for women ages 50–69 years, and 10% for women older than 69 years of age. To estimate the cumulative effect of combined chemoendocrine therapy, we reduced the odds reduction associated with a second systemic maneuver (chemotherapy after tamoxifen or tamoxifen after chemotherapy) by 50% as compared with the odds reduction used if the maneuver was given on its own.

Estimates of the effectiveness of regional RT were based on four recent randomized trials.[24–27] These studies show consistently that regional RT increases the odds of DFS by approximately 30% in women with lymph node positive disease. However, the data on lymph node negative disease are limited and usually are confined to women with high risk primary tumors. Despite the limited data, the three studies in which some lymph node negative cases were studied all showed a benefit for regional RT.[24,26,27] This benefit ranged between an odds reduction of approximately 10% and 35%. Although the data are limited and not entirely consistent, we decided to set the odds reduction for regional RT in lymph node negative cases at 20%, irrespective of age or ER status.

Estimates of the effectiveness of AxD were based on data from NSABP B-04.[23] For clinically lymph node negative women, this trial shows an absolute 4% difference in 5-year DFS between the radical mastectomy and mastectomy arms. Trial data showed that of these women approximately 40% would be expected to have pathologically positive axillary lymph nodes at the time of surgery. Assuming that axillary clearance has no benefit in women with pathologically negative axillary lymph nodes, it follows that the estimated absolute benefit of AxD in pathologically lymph node positive women should be approximately 10%. This absolute benefit translates to an approximate 25% odds reduction. Because some women in the mastectomy arm of the study received accidental limited AxD, we increased our estimate of the effectiveness of AxD in lymph node positive women to 30%.

Adjuvant therapy treatment plans

Treatment plans for patients in which axillary status is known were based on national, evidence-based clinical practice guidelines.[29,30] Tables 3 and 4 contain detailed descriptions of the treatment plans that were used for treatment scenarios including AxD, broken down by lymph node status, age, and ER status. Treatment plans that did not include AxD also are shown in Tables 3 and 4. For women in the low risk group, a single treatment plan was considered in which women were not given chemotherapy, tamoxifen, or regional RT. For women in the moderate risk group, two treatment plans were considered. Under treatment plan A, chemotherapy and/or tamoxifen were given only if the primary tumor was $>$ 1 cm in greatest dimension and Grade 3. Under treatment option B, chemotherapy and/or tamoxifen were given irrespective of the size or grade of the primary tumor. Regional RT was not given for low or moderate risk group women not receiving an AxD, irrespective of the pathologic features of the primary tumor.

Sensitivity analyses

To assess the stability of the difference in the 5-year DFS rate between AxD and no AxD treatment scenarios, sensitivity analyses were conducted in which we generated estimates of 5-year DFS for relatively low and high AxD, chemotherapy, tamoxifen, and regional RT odds reductions. To obtain estimates of the difference between AxD and no AxD treatment scenarios for low treatment odds reductions, we reduced the treatment effectiveness odds reductions given in Table 1 by 50%. To obtain estimates of the difference between AxD and no AxD treatment scenarios under high treatment odds reductions, we increased the odds reductions given in Table 1 by 50%. Figures 1, 2, and 3 show how the estimated difference in the 5-year DFS rate between AxD and no AxD treatment scenarios changed with 50% increases and decreases in the effectiveness of AxD, chemotherapy, tamoxifen, and regional RT.

RESULTS

Of 8103 cases of newly diagnosed breast carcinoma referred to the BCCA between January 1, 1989 and December 31, 1992, 3108 met eligibility criteria, and of those, 1075 (34.6%) had at least 1 positive axillary lymph node. The median number of lymph nodes examined was 10 (standard deviation = 5.82) with a range of 1–59. Median follow-up was 5.10 years with 7.2% of cases lost to follow-up.

Table 2 shows distributions of the abstracted prognostic and treatment variables and the proportion of cases with at least one involved axillary lymph node within each category of the prognostic/treatment factors. The strong relations between lymph node involvement and LVI status, tumor size and palpability, are consistent with results reported previously.[20] In further support of the low and moderate risk group classification scheme, cross-validation analyses indicated that the probabilities of lymph

TABLE 2
Percentage of Cases and Percentage of Cases with Positive Lymph Nodes in Each Category of the Prognostic and Treatment Variables

Variable and description	n	%	Positive lymph nodes (%)
Palpability ($P < 0.001$)[a]			
No palpable disease	454	14.6	18.9
Palp primary, nonpalpable lymph nodes	2385	76.7	31.7
Palpable axillary lymph nodes	269	8.7	86.6
Grade ($P < 0.001$)			
1	319	10.3	16.3
2	1332	42.9	33.4
3	1221	39.3	41.1
Unknown/missing	236	7.6	32.2
Size (cm) ($P < 0.001$)			
0.00–0.5	196	6.3	13.3
0.51–1.0	535	17.2	19.4
1.10–1.5	656	21.1	26.5
1.51–2.0	629	20.2	32.8
2.01–3.0	657	21.1	47.0
2.01–5.0	325	10.5	54.8
≥5.01	110	3.5	70.9
LVI ($P < 0.001$)			
Negative	1899	61.1	17.3
Positive	1209	38.9	61.7
Age (yrs) ($P < 0.001$)			
0–35	109	3.5	45.9
36–50	817	26.3	39.8
51–70	1471	27.3	32.8
71–89	711	22.9	30.7
ER status ($P = 0.581$)			
Negative	752	24.2	37.0
Positive	1778	57.2	38.1
Unknown	578	18.6	20.6
Systemic therapy ($P = 0.000$)			
None	1453	46.8	5.2
Some	1644	52.9	60.8
Unknown	11	0.4	0.0
Regional RT ($P = 0.000$)			
No	2562	82.4	24.1
Yes	546	17.6	83.7
Number of positive lymph nodes			
0	2033	65.4	—
1–3	643	20.7	—
> 3	432	13.9	—

LVI: lymphatic or vascular invasion; ER: estrogen receptor; RT: radiation therapy.
[a] *P* is the Pearson chi-square probability for the equality of the distribution of lymph node status over levels of each prognostic factor, not including missing values.

node metastases in the low and moderate risks groups in the current cohort were not significantly different from the probabilities observed by Olivotto et al.[20] In particular, in the current cohort of patients, 5.2% of cases in the low risk group and 10.1% of cases in the moderate risk group were lymph node positive, compared with 4.8% (for 5.2% vs. 4.8%, $P = 0.87$) and 12.4% (for 10.1% vs. 12.4%, $P = 0.27$) observed by Olivotto et al.[22] The similar rates of lymph node metastases in the two cohorts of women indicate that palpability, LVI, and tumor size can be used to reliably identify patients with a low (approximately 5%) and moderate (approximately 10–12%) risk of lymph node metastases.

Tables 3 and 4 contain Cox untreated 5-year DFS estimates for women in the low and moderate risk groups. Of the variables eligible for entry into the Cox model, risk group ($P < 0.001$), axillary lymph node status ($P = 0.009$), presence of Grade 3 tumor > 1 cm ($P < 0.001$), systemic therapy ($P = 0.017$), and regional RT ($P < 0.001$) had statistically significant multivariate relations with DFS. The Cox untreated 5-year DFS estimates for low risk women with AxD not receiving chemotherapy, tamoxifen, or regional RT were 93.0% for lymph node negative and 86.0% for lymph node positive women. The Cox untreated 5-year DFS estimates for women not receiving chemotherapy, tamoxifen, or regional RT in the moderate risk group were 87.0% if the women had negative lymph nodes but did not have a Grade 3 tumor > 1 cm in greatest dimension, 78.0% if they had negative lymph nodes and a Grade 3 tumor >1 cm in greatest dimension, and 77.0% if they had positive lymph nodes.

Tables 3 and 4 also contain untreated 5-year DFS estimates for treatment scenarios not including AxD. Table 3 shows that if all low risk group women did not receive an AxD, their estimated 5-year DFS rate would be 92.3%. This is only marginally lower than the estimated untreated 5-year DFS rate for low risk group, lymph node negative women receiving an AxD because the odds reduction for AxD applied only to the very few low risk women that had positive lymph nodes. Table 4 shows that if moderate risk group women without Grade 3 primary tumors not >1 cm were not given AxD, their estimated untreated 5-year DFS rate was 85.3%. If moderate risk group women with Grade 3 tumors > 1 cm in greatest dimension did not receive an AxD, the estimated untreated 5-year DFS rate was 78.0% in all but one prognostic category (i.e., age 50–69, ER negative). Because the estimated untreated 5-year DFS rate for moderate risk, the lymph node negative women with Grade 3 tumors > 1 cm in greatest dimension was also 78.0%, it follows that, with the exception of 50–69-year-old women with ER negative tumors, all of these women had negative lymph nodes.

The treated 5-year DFS rate estimates contained in Tables 3 and 4 are estimates of 5-year DFS for patients in a given risk group and prognostic category who received adjuvant therapy as indicated in the

TABLE 3
Estimated 5-Year DFS for Low Risk Women with Indicated Prognostic Characteristics, Adjuvant Therapy, and Surgery

Prognostic characteristics				Adjuvant therapy			
Lymph node status	Age (yrs)	ER status	Estimated 5-year DFS if no adjuvant therapy received[a]	Chem	Tam	RT	Estimated 5-year DFS if indicated adjuvant therapy received[b]
Axillary lymph node dissection performed							
Negative	Any	Any	93.0				93.0
Positive	< 50	Any	86.0	Yes		Yes	92.6
Positive	50–69	Positive	86.0	Yes	Yes	Yes	94.5
Positive	50–69	Negative	86.0	Yes		Yes	91.6
Positive	> 69	Any	86.0		Yes	Yes	91.7
Axillary lymph node dissection not performed							
Unknown	Any	Any	92.3				92.3

DFS: disease free survival; ER: estrogen receptor; Chem: chemotherapy; Tam: tamoxifen; RT: regional radiation therapy; Yes: treatment received.
[a] Mean Cox model estimated 5-year DFS if patients in the given prognostic group had indicated surgery (i.e., axillary lymph node dissection (AxD) or no AxD) but no chemotherapy, tamoxifen or regional RT.
[b] Mean estimated 5-year DFS if patients in the given prognostic group had surgery, chemotherapy, tamoxifen, and regional RT as defined in this table.

TABLE 4
Estimated 5-Year DFS for Moderate Risk Women with Indicated Prognostic Characteristics, Adjuvant Therapy, and Surgery

Prognostic characteristics					Adjuvant therapy			
Lymph node status	Age (yrs)	ER status	> 1-cm Grade 3	Estimated 5-year DFS if no adjuvant therapy received[a]	Chem	Tam	RT	Estimated 5-year DFS if indicated adjuvant therapy received[b]
Axillary lymph node dissection performed								
Negative	Any	Any	No	87.0				87.0
Negative	< 50	Any	Yes	78.0	Yes			83.5
Negative	50–69	Pos	Yes	78.0	Yes	Yes		87.4
Negative	50–69	Neg	Yes	78.0	Yes			81.6
Negative	> 69	Any	Yes	78.0		Yes		85.5
Positive	< 50	Any	Any	77.0	Yes		Yes	87.2
Positive	50–69	Pos	Any	77.0	Yes	Yes	Yes	91.4
Positive	50–69	Neg	Any	77.0	Yes		Yes	85.7
Positive	> 69	Any	Any	77.0		Yes	Yes	87.9
Axillary lymph node dissection not performed: adjuvant therapy option A								
Unknown	Any	Any	No	85.3				85.3
Unknown	< 50	Pos	Yes	NA[c]		Yes		NA
Unknown	< 50	Neg	Yes	78.0	Yes			83.5
Unknown	50–69	Pos	Yes	78.0	Yes	Yes		87.4
Unknown	50–69	Neg	Yes	75.4	Yes			79.3
Unknown	> 69	Any	Yes	78.0		Yes		85.5
Axillary dissection not performed: adjuvant therapy option B								
Unknown	< 50	Pos	Any	86.7		Yes		91.3
Unknown	< 50	Neg	Any	86.5	Yes			91.2
Unknown	50–69	Pos	Any	85.2		Yes		91.5
Unknown	50–69	Neg	Any	82.7	Yes			85.8
Unknown	> 69	Any	Any	85.3		Yes		91.1

DFS: disease free survival; ER: estrogen receptor; Chem: chemotherapy; Tam: tamoxifen; RT: radiation therapy; Pos: positive; Neg: negative; Yes: treatment received.
[a] Mean Cox model estimated 5-year DFS if patients in the given prognostic group had indicated surgery (i.e., axillary lymph node dissection (AxD) or no AxD) but no chemotherapy, tamoxifen, or regional RT.
[b] Mean estimated 5-year DFS if patients in the given prognostic group had surgery, chemotherapy, tamoxifen, and regional RT as defined in this table.
[c] No moderate risk group women in this sample with Grade 3 tumors > 1 cm in greatest dimension that were also < 50 years of age and ER positive.

table. Hence, if no adjuvant therapy is indicated (e.g., low risk, lymph node negative or low risk, no AxD) the untreated and treated 5-year DFS estimates are identical. In cases in which adjuvant therapy was given, depending upon the type of adjuvant therapy received and the odds reduction associated with a given therapy, the treated 5-year DFS rate was always higher than the untreated 5-year DFS rate.

Using estimated treated relapse risks shown in Tables 3 and 4, we estimated the mean difference between the 5-year DFS rate for AxD and no AxD treatment scenarios. Table 5 shows that, in the low risk group, the best estimate of the mean difference in DFS between AxD and no AxD treatment scenarios is $< 1\%$. For the moderate risk group, avoiding AxD and using chemotherapy and tamoxifen in women with Grade 3 tumors > 1 cm in greatest dimension (treatment option A) decreased the mean 5-year DFS rate by approximately 1.8%. However, if chemotherapy and/or tamoxifen was given to all moderate risk cases not receiving an AxD (treatment option B), an estimated 2.7 % fewer cases would experience a relapse within 5 years compared with a treatment scenario in which AxD was performed.

Figures 1 to 3 illustrate how varying the assumed effectiveness of chemotherapy, tamoxifen, regional RT, and AxD influenced 5-year DFS estimates in the low (Fig. 1) and moderate risk groups (Figs. 2 and 3), respectively. For low risk cases, changes in the odds reduction for AxD had the largest effect on estimates of the difference between AxD and no AxD treatment scenarios. However, even when the odds reduction for AxD in lymph node positive women was set at 45% (i.e., 15% + 30%), the estimated absolute difference in the 5-year DFS rate between AxD and no AxD treatment scenarios was $< 1\%$. For moderate risk women undergoing treatment option A, changes in the effectiveness of AxD also had the largest effect on the estimated difference between AxD and no AxD treatment scenarios. In particular, when the odds reduction for AxD in lymph node positive women was set at 45%, the estimated absolute 5-year DFS benefit of performing AxD was 2.36%. For moderate risk women undergoing treatment option B, changes in the effectiveness of tamoxifen had a significant impact on the estimated difference in the 5-year DFS rate. This was due to the large number of women eligible for tamoxifen under treatment option B and the relatively high efficacy of tamoxifen in both lymph node negative and positive women. However, even when the effectiveness of tamoxifen was reduced by 50% (i.e., 5% for ER negative, 17.5% for ER unknown, and 20% for ER positive), the treatment scenario with no AxD but liberal use of tamoxifen remained more beneficial than the treatment scenario with AxD. Overall, the results of the sensitivity analyses showed that, with the exception of tamoxifen for women in the moderate risk group undergoing treatment option B, changes of $\pm 50\%$ in treatment effectiveness estimates given in Table 1 resulted in a $< 0.5\%$ change in the estimated mean difference between treatment plans with and without AxD. It follows from these results that our estimates of the mean difference in the 5-year DFS rate between treatment plans with and without AxD are relatively stable across large variations in treatment effectiveness estimates.

DISCUSSION

In patients with clinically lymph node negative T1a tumors without lymphatic or vascular invasion, we estimate that a policy of avoiding AxD and not using chemotherapy, tamoxifen, or regional RT in any cases would decrease the 5-year DFS rate by less than 1% compared with a policy including routine axillary dissection. If this modeling is correct, the difference may be too small to be of clinical significance or warrant the morbidity associated with axillary dissection. Consistent with previous studies,[10,14,16] we therefore recommend that the value of ''routine'' axillary dissection in these cases should be reconsidered.

Estimated 5-year DFS decreased by approximately 1.8% for women in the moderate risk group when they received no AxD or regional RT and chemotherapy and/or tamoxifen was restricted to patients with Grade 3 tumors > 1 cm in greatest dimension. However, for the same patients, when chemotherapy and/or tamoxifen was used in all cases, the 5-year DFS rate increased by 2.7% compared with a treatment scenario in which therapy decisions were based on the AxD pathology. As an indication of the magnitude of these differences, a randomized clinical trial would require more than 3000 cases in each arm of the study to show such differences with a power of 0.9 and alpha of 0.05. Based on the number of cases normally assigned to clinical trials, these differences are, for practical purposes, too small to be detected in the majority of current clinical trials.

We acknowledge that estimates of treatment effectiveness are only approximations. One purpose of the sensitivity analyses was to assess the extent to which the stability of these results rests on the accuracy of our treatment efficacy estimates. Results indicated that the estimated mean difference between AxD and no AxD was fairly stable in spite of large changes in estimated treatment efficacy. However, errors in estimated treatment odds reductions are not the only potential source of instability in our estimates. In particular, our estimate of 5-year DFS for lymph node positive cases not receiving adjuvant therapy is a direct function of the number of positive lymph nodes involved. In situations in which lymph node positive cases have a higher number of lymph nodes involved than women in this series, axillary dissection is likely to provide more benefit than we have estimated. This is particularly true in light of recent data that indicate a survival benefit of locore-

TABLE 5
Estimated Mean Difference in 5-Year Disease Free Survival between Patients with and without Axillary Dissection

Risk group	Treatment option	Mean 5-year DFS (%)
Low	Axillary lymph node dissection	92.99
	No axillary lymph node dissection	92.28
	Decrease in DFS	0.71
Moderate, option A[a]	Axillary lymph node dissection	87.09
	No axillary lymph node dissection	85.27
	Decrease in DFS	1.82
Moderate, option B[b]	Axillary lymph node dissection	87.09
	No axillary lymph node dissection	89.84
	Increase in DFS	2.75

[a] Chemotherapy and/or tamoxifen used only for patients with Grade 3 tumors > 1 cm diameter.
[b] Chemotherapy and/or tamoxifen used in all cases.

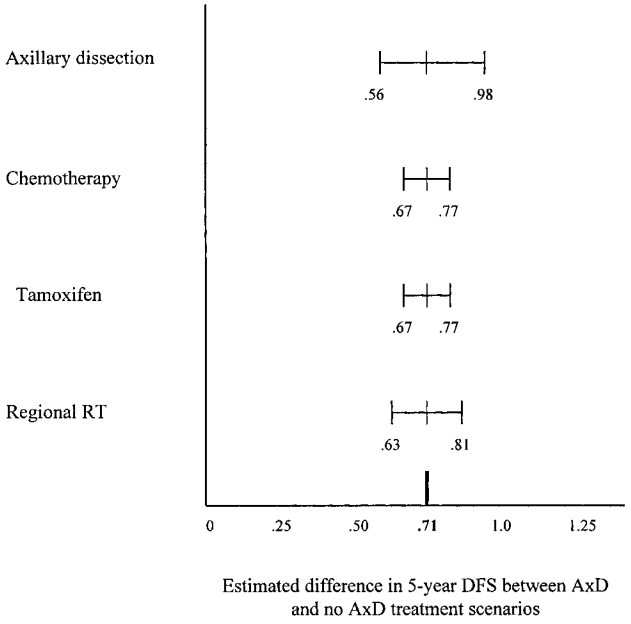

FIGURE 1. Effect of varying the effectiveness of chemotherapy, tamoxifen, regional radiation therapy (RT), and axillary lymph node dissection (AxD) by ±50% on the estimated difference in 5-year disease-free survival (DFS) between AxD and no AxD treatment scenarios for women in the low risk group is shown.

gional RT in lymph node positive women.[25,26,31–3] If the decision to treat with lymph node RT or the type of adjuvant chemotherapy depends on the extent of lymph node involvement, it may be best to confirm lymph node status with AxD.

The short 5-year duration of follow-up in this decision analysis also might be viewed as a potential source of uncertainty in the estimated benefit of AxD. However, in all meta-analyses and individual trials upon which treatment effectiveness estimates were based, the benefit of treatment upon DFS was largely observed in the first 5 years of follow-up. Although, in some cases, treatment did statistically significantly improve DFS in the second 5 years of follow-up; the additive benefits were consistently small and often confined to restricted subgroups of women. However, in all the trials we reviewed, a significant number of events were consistently observed in the second 5 years of follow-up. Because, for relatively low risk women, the absolute benefit associated with a given treatment odds reduction increases as the risk of relapse increases, the absolute benefit of treatment at 10 years should be larger than the benefit observed at 5 years. Hence, at 10 years of follow-up, the absolute benefit of AxD is likely to be larger than the absolute benefit observed at 5 years. Because women in the low and moderate risk groups have a very low risk of relapse in the second 5 years of follow-up, the benefit of AxD at 10 years is likely to be only slightly larger than the 5-year results reported here.

Although patients not receiving AxD are spared the morbidity of initial axillary surgery, some are at significantly higher risk of failure in the axilla. For clinically lymph node negative patients receiving no axillary dissection or RT, data from NSABP B-04 indicate that only approximately 50% of the cases with pathologically involved axillae will experience clinical relapse in the axilla.[23] In addition, NSABP B-04 and other series[34–38] indicate that axillary RT and AxD are of similar efficacy in preventing axillary relapse. Because we do not recommend axillary RT for the low or moderate risk cases, we should expect that approximately 50% of those with positive lymph nodes without AxD will relapse in the axilla. Based on the proportion of lymph node positive cases observed in this series, without AxD, approximately 5% of the moderate risk cases and 2–3% of the low risk cases might experience an axillary relapse and require delayed axillary dissection or RT. Although the extent to which tamoxifen or chemotherapy might reduce this risk is not well known, the NSABP B18 study of preoperative doxorubicin–cyclophosphamide chemotherapy showed that axillary positivity was reduced by 37%.[39] It therefore is reasonable to expect that moderate risk cases receiving systemic treatment and no AxD would have an axillary relapse rate of $< 5\%$.

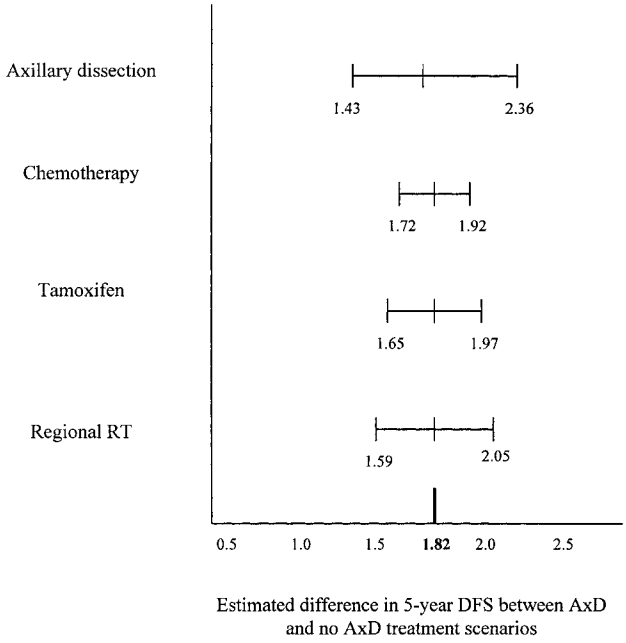

FIGURE 2. Effect of varying the effectiveness of chemotherapy, tamoxifen, regional radiation therapy (RT), and axillary lymph node dissection (AxD) by ±50% on the estimated difference in 5-year disease free survival (DFS) between AxD and no AxD treatment scenarios for women with a moderate risk of lymph node metastases (treatment option A) is shown.

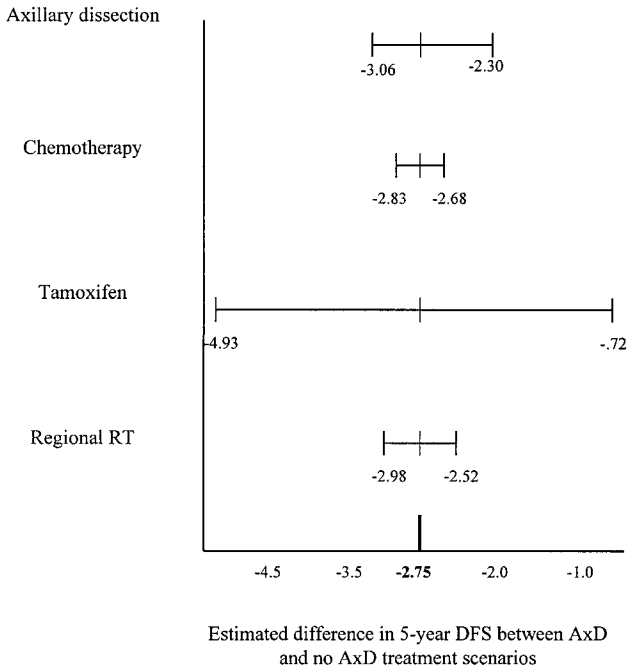

FIGURE 3. Effect of varying the effectiveness of chemotherapy, tamoxifen, regional radiation therapy (RT), and axillary lymph node dissection (AxD) by ±50% on the estimated difference in 5-year disease free survival (DFS) between AxD and no AxD treatment scenarios for women with a moderate risk of lymph node metastases (treatment option B) is shown.

Sentinel lymph node biopsy is currently attracting considerable attention as one possible method to avoid the morbidity of AxD.[40,41] Because, all other things being equal, the probability of positive lymph nodes is lower in women with a known negative sentinel lymph node than women in which pathologic lymph node status is not known, sentinel lymph node biopsy could be used to further reduce the estimated differences between AxD and no AxD treatment scenarios. The extent of reduction would depend upon the proportion of cases in which a sentinel lymph node could be identified and the proportion of low and moderate risk group women with a negative sentinel lymph node but positive axillary lymph nodes (i.e., the false-negative rate). Recent studies of sentinel lymph node biopsy have yielded 80–100% detection rates and 0–17 % false-negative rates.[41–45] If such rates held in low and moderate risk groups of women, our preliminary decision analysis (data not shown) suggests that the difference in 5-year DFS between complete AxD and no AxD with treatment decisions based on the sentinel lymph node pathology would not exceed 1% for any reasonable combination of treatment strategy and treatment effectiveness estimates.

The controversy over the efficacy of AxD is one indication that much is still not known about the natural history of invasive breast carcinoma. In part, our results indicate that if the true efficacy of AxD is as small as we have estimated, it will be necessary to conduct randomized trials of AxD or sentinel lymph node dissection with many thousands of patients in each arm of the study. Furthermore, because the efficacy of AxD is always in relation to some other form of axillary treatment, numerous such trials involving various different treatment arms will be required to determine whether other forms of treatment with lower morbidity can replace AxD. Until then, quantitative analyses of the kind conducted here offer a viable option to assess the efficacy of AxD in reducing recurrence and, ultimately, death as a result of breast carcinoma.

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