

CLINICAL INVESTIGATION

Breast

IS RADIATION ALONE ADEQUATE TREATMENT TO THE AXILLA FOR PATIENTS WITH LIMITED AXILLARY SURGERY? IMPLICATIONS FOR TREATMENT AFTER A POSITIVE SENTINEL NODE BIOPSY

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Purpose: To estimate the possible efficacy of axillary radiation therapy (AXRT) following a positive sentinel node biopsy (SNB), we evaluated the risk of regional nodal failure (RNF) for patients with clinical Stage I or II, clinically node-negative invasive breast cancer treated with either no dissection or a limited dissection (LD) defined as removal of 5 nodes or less followed by AXRT.

Materials and Methods: From 1978 to 1987, 292 patients underwent AXRT in the absence of axillary dissection; 126 underwent AXRT following LD. The median dose to the axilla was 46 Gy. The median dose to the supraclavicular fossa was 45 Gy. Among patients found to have positive nodes on LD, adjuvant chemotherapy and tamoxifen were administered to 81% and 7% of subjects, respectively. All patients had potential 8-year follow-up.

Results: Six of the 418 patients (1.4%) developed RNF as a first site of failure within 8 years. Among these 6 patients (1.4%) with RNF as the first site of failure, 4 had simultaneous distant and regional recurrences; and 2 had isolated axillary failures. Three of the 292 patients (1%) with no axillary dissection, none of 84 patients with pathologically negative nodes and 3 of 42 patients (7%) with pathologically involved nodes had RNF as a first site of failure. Radiation pneumonitis developed in 5 patients (1.2%), brachial plexopathy in 5 (1.2%) and arm edema in 4 (1.2%). In all cases, radiation pneumonitis and brachial plexopathy were transient.

Conclusion: These results imply that AXRT may be an effective and safe alternative to completion dissection for treatment of the axilla following a positive SNB. Further studies comparing these two options in specific patient subgroups are needed. © 2000 Elsevier Science Inc.

Axillary radiation therapy, Sentinel node biopsy.

INTRODUCTION

There is increasing interest in the use of sentinel node biopsy in the management of early-stage breast cancer. Sentinel node biopsy can provide accurate information regarding nodal status (1–5) and may carry a lower risk of arm morbidity than traditional Level I/II axillary dissection (although no firm data on this issue have been published). The introduction of sentinel node biopsy to the treatment of breast cancer has raised several new clinical questions, including the appropriate management of the axilla following a positive sentinel node biopsy. In series from the United States and Europe, between 33% and 66% of patients with a positive sentinel node biopsy have been found

to have residual axillary disease (1–6). Presumably, such patients require additional treatment to the axilla to prevent subsequent regional nodal failure. In addition, recently published randomized trials have shown that effective local regional treatment may improve survival (7–9).

Axillary radiation (AXRT) is an alternative to axillary dissection and might have a lower risk of morbidity. However, given the recent introduction of this approach, there are no data regarding the efficacy of AXRT following a positive sentinel node biopsy. Therefore, information regarding the possible efficacy of axillary radiation following a positive sentinel node biopsy can only be inferred from older treatment approaches.

We evaluated the risk of regional nodal failure in patients

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with clinically node-negative breast cancer treated with AXRT following either (1) no axillary dissection; or (2) a limited dissection (LD), defined as removal of less than or equal to 5 lymph nodes. Our analysis focused on three patient populations: (1) those who underwent no dissection, (2) those who underwent LD with pathologically negative nodes, and (3) those who underwent LD with pathologically positive nodes.

MATERIALS AND METHODS

From July, 1968 to December, 1987, 2140 patients without a history of prior malignancy (except non-melanoma skin cancer or *in situ* carcinoma of the cervix) were treated at the Joint Center for Radiation Therapy (JCRT) for unilateral Stage I or II invasive breast carcinoma. For patients who later developed a contralateral tumor, only the first side treated was considered in the analysis of site of first failure.

To reflect current standards of practice and ensure adequate follow-up, the study population was limited to 418 patients who met certain eligibility criteria. Patients had clinically node-negative breast cancer treated either with no axillary dissection or LD. All patients received tangential radiation to the breast, with a separate en-face third field directed at the full axilla and supraclavicular fossa. All patients had a minimum potential follow-up time of 8 years (i.e., the patient was treated at least 8 years ago and had a recurrence or died within 8 years of the start of radiotherapy, or was followed for a minimum of 8 years without recurrence, death due to other causes, or being lost to follow-up). All patients in the study population were treated between 1978 and 1987, reflecting the fact that limited dissection was not commonly performed before that time.

Patient characteristics are listed in Table 1. Patients with an unknown value for a given characteristic were not included when calculating percents. There were 292 patients who underwent no dissection, 84 patients who underwent LD with pathologically negative nodes, and 42 patients who underwent LD with pathologically positive nodes. The median ages at diagnosis were different among these three groups (66, 51, and 52, respectively, $p = 0.001$). There was a statistically significant relationship between tumor stage and use of axillary surgery. Patients who did not undergo axillary dissection were more likely to have T1 tumors (68%) compared to patients who underwent LD with pathologically negative nodes (50%) and patients who underwent LD with pathologically positive nodes (45%, $p = 0.0319$).

Necrosis was significantly more likely to be absent among patients who did not undergo dissection than among patients who underwent LD (52% for patients who did not undergo dissection vs. 35% and 27% for patients who underwent LD with either pathologically negative or positive nodes, $p = 0.0021$). Patients who underwent LD were significantly more likely to have an extensive intraductal component (EIC) (34% and 27% for patients who underwent LD with pathologically negative and positive nodes, respectively, vs. 19% for those who did not undergo nodal

dissection, $p = 0.0522$). Patients who underwent no dissection or LD with pathologically positive nodes were significantly more likely to have estrogen receptor positive tumors (72% and 66% for patients who did not undergo LD and those who underwent LD with pathologically positive nodes, respectively vs. 40% for patients who underwent LD with pathologically negative nodes, $p = 0.002$). Size and location of the primary, tumor histology, histologic grade, the presence of lymphatic vessel invasion, and margin status did not differ significantly among the three patient groups.

Surgery for the primary tumor consisted of gross total excision in all patients, without regard to microscopic resection margins. Decisions regarding who should receive an axillary dissection and the extent of dissection were at the discretion of the surgeon. We did not attempt to review operative reports to assess which axillary levels were dissected. For all patients who underwent LD, the median number of nodes removed was 4 (range, 1–5). For those who underwent LD with pathologically positive nodes, the median number of positive nodes was 1 (range, 1–4).

The dose to the entire breast was usually 45–46 Gy (median, 45 Gy; range, 41.4–51.3 Gy), delivered at 1.8–2.0 Gy per fraction, given 5 times weekly, typically prescribed to a point 1.5 cm from the posterior field edge. The median total dose to the primary tumor site (including the boost) was 65.94 Gy (range, 60–84 Gy), with 90% of patients receiving between 60 and 70 Gy. The median dose to the primary site was significantly higher for patients who underwent LD (68 Gy for patients with pathologically negative nodes and 67.55 Gy for patients with pathologically positive nodes) than for those who did not undergo dissection (64.30 Gy) ($p = 0.0001$).

All patients received a separate, third, slightly-angled, anterior field directed to the full axilla and supraclavicular fossa. The “hanging block” or “corner block” technique was usually used. The details of treatment technique and patient set-up have previously been described (10–12). The dose was prescribed to a depth of 5 cm. The lateral border of the third field extended two-thirds of the medial-to-lateral distance of the humeral head. The median total doses of radiation to the axilla for patients who underwent no dissection, limited dissection with pathologically negative nodes and limited dissection with pathologically positive nodes were 46, 46, and 50 Gy, respectively, ($p = 0.004$). Thirty percent of patients received an additional boost to the axilla with a posterior or en face photon or electron field. The median dose delivered with the boost was 6 Gy. The median doses to the supraclavicular fossa for patients who did not undergo dissection, and those who underwent LD with pathologically negative or positive nodes were 45, 46, and 45 Gy, respectively ($p = 0.25$).

Adjuvant chemotherapy was given to 2% of patients who did not undergo dissection and 6% of those who underwent LD with pathologically negative nodes. Eighty-one percent of women who underwent LD with pathologically involved nodes received adjuvant chemotherapy ($p < 0.001$). The chemotherapy regimens varied with regard to drugs, num-

Table 1. Patient characteristics by type and result of dissection

	Total <i>n</i> (%)	No dissection <i>n</i> (%)	No positive nodes <i>n</i> (%)	At least 1 positive node(s) <i>n</i> (%)	<i>p</i> value
Age at diagnosis (years)					0.0001
Mean	61	65	51	51	
Median	63	66	51	52	
Range	28–88	29–88	28–76	31–82	
<50	81 (19)	23	38	20	
50–59	97 (23)	59 (20)	27 (32)	11 (26)	
60–69	11 (27)	90 (31)	13 (16)	10 (24)	
≥70	12 (30)	120 (41)	6 (7)	1 (2)	
Year of diagnosis					<0.001
1970–1979	13 (32)	94 (32)	32 (38)	6 (14)	
1980–1981	96 (23)	44 (15)	40 (48)	12 (29)	
1982–1983	86 (21)	66 (23)	6 (7)	12 (29)	
1984–1987	10 (25)	88 (30)	6 (7)	14 (33)	
Size of primary tumor (cm)					0.184
Mean	2.24	2.18	2.31	2.50	
Median	2.0	2.0	2.2	2.5	
Range	0–5.0	0–5.0	0.7–4.5	0.5–5.0	
≤1	10 (26)	51 (20)	13 (16)	6 (15)	
1.1–2	14 (34)	105 (40)	27 (33)	10 (26)	
2.1–3	11 (28)	73 (28)	28 (34)	14 (36)	
3.1–4	38 (9)	20 (8)	13 (16)	5 (13)	
4.1–5	16 (4)	11 (4)	1 (1)	4 (10)	
Unknown	37	32	2	3	
Location of primary tumor					0.0742
Lower inner quadrant	19 (5)	11 (4)	4 (5)	4 (10)	
Lower outer quadrant	54 (12)	35 (12)	14 (17)	5 (12)	
Upper inner quadrant	112 (26)	76 (26)	30 (36)	6 (14)	
Upper outer quadrant	165 (40)	115 (40)	28 (33)	22 (52)	
Center	41 (10)	31 (11)	7 (8)	3 (7)	
Other	26 (6)	23 (8)	1 (1)	2 (5)	
Unknown	1	1	0	0	
Tumor stage					0.0319
1	242 (58)	181 (62)	42 (50)	19 (45)	
2	176 (42)	111 (38)	42 (50)	23 (54)	
Number of nodes sampled					
Median	0	0	4	4	
Range	0–5	0–0	1–5	1–5	
Number of positive nodes (among those with some diss)					
0	84 (67)		84 (100)	0	
1	24 (19)		0	24 (57)	
2	14 (11)		0	14 (33)	
3	3 (2)		0	3 (7)	
4	1 (1)		0	1 (2)	
Most aggressive histology					0.2377
Ductal	285 (80)	186 (77)	65 (86)	34 (92)	
Lobular	34 (10)	29 (12)	4 (5)	1 (3)	
Mixed ductal/lobular	19 (5)	16 (7)	2 (3)	1 (3)	
Others	17 (5)	11 (5)	5 (7)	1 (3)	
Unknown	63	50	8	5	
Histologic grade (of 285 subjects with ductal histology)					0.0660
1	62 (22)	42 (23)	14 (22)	6 (18)	
2	147 (52)	104 (57)	29 (45)	14 (41)	
3	74 (26)	38 (21)	22 (34)	14 (41)	
Unknown	2	2	0	0	
Necrosis					0.0021
Absent	163 (46)	126 (52)	27 (36)	10 (27)	
Scant	123 (35)	81 (34)	25 (33)	17 (46)	
Moderate	39 (11)	22 (9)	12 (16)	5 (14)	

Table 1. *Continued*

	Total <i>n</i> (%)	No dissection <i>n</i> (%)	No positive nodes <i>n</i> (%)	At least 1 positive node(s) <i>n</i> (%)	<i>p</i> value
Marked	29 (8)	12 (5)	12 (16)	5 (14)	
Unknown	64	51	8	5	
Extensive intraductal component					0.0522
Yes	66 (24)	35 (19)	22 (34)	9 (27)	
No	212 (76)	145 (81)	42 (66)	25 (74)	
Unknown	140	112	20	8	
Lymphatic vessel invasion					0.1892
Present	79 (22)	56 (23)	13 (17)	10 (27)	
Absent	219 (62)	154 (64)	45 (59)	20 (54)	
Indeterminate	57 (16)	32 (13)	18 (24)	7 (19)	
Unknown	63	50	8	5	
Estrogen receptor status					0.0002
Positive	148 (63)	106 (72)	23 (40)	19 (66)	
Negative	86 (37)	42 (28)	34 (60)	10 (35)	
Unknown	184	144	27	13	
Margins					0.6113
Negative > 1 mm	18 (25)	15 (25)	3 (60)	0	
Close	15 (21)	12 (20)	1 (20)	2 (22)	
Focally positive	19 (26)	15 (25)	1 (20)	3 (33)	
>Focal positive	11 (15)	9 (15)	0	2 (22)	
Any negative	8 (11)	6 (10)	0	2 (22)	
Any positive	2 (3)	2 (3)	0	0	
Unknown	345	233	79	33	
Total dose to primary (Gy)					0.0001
Mean	65.70	65.01	67.49	66.82	
Median	65.70	64.30	68.00	67.55	
Range	60–84	60–84	61–74	61–76	
Number receiving dose	418 (100)	292 (100)	84 (100)	42 (100)	
Dose to the axilla (cGy)					0.0041
Mean	46.81	46.66	46.69	48.16	
Median	46	46	46	50	
Range	15–60	15–60	44–59	24–59	
Number receiving dose	418 (100)	292 (100)	84 (100)	42 (100)	
Dose to the supraclavicular fossa (Gy)					0.2593
Mean	45.03	45.02	45.22	44.77	
Median	45	45	46	45	
Range	34–55	34–55	40–55	40–50	
Number receiving dose	417 (100)	291 (100)	84 (100)	42 (100)	
Adjuvant chemotherapy					<0.0001
Yes	45 (11)	6 (2)	5 (6)	34 (81)	
No	373 (89)	286 (98)	79 (94)	8 (19)	
Adjuvant tamoxifen					0.3350
Yes	8 (2)	5 (2)	1 (1)	2 (7)	
No	410 (98)	287 (98)	83 (99)	40 (95)	

ber of cycles and sequencing with radiotherapy, but cyclophosphamide, methotrexate, and fluorouracil (CMF)-based or doxorubicin-containing regimens were given to 92% of patients who received chemotherapy. Tamoxifen was given to 2% of the entire cohort. The use of tamoxifen did not vary significantly among the 3 groups of patients ($p = 0.3350$).

RNF was defined as the appearance of tumor in the ipsilateral supraclavicular, axillary, infraclavicular or internal mammary lymph nodes before or simultaneously with the development of distant metastases and before local recurrence or opposite breast cancer diagnosis. In estimating the incidence of failure at specific nodal sites, all failures at

that site were counted, whether or not other nodal or distant sites were also diagnosed simultaneously. RNF was usually, but not always, confirmed surgically. Patients who did not undergo biopsy were considered to have evidence of RNF based on physical examination, radiologic studies, and/or symptoms.

Patients who had a failure in the breast with clinical signs of axillary recurrence or pathologic axillary failure determined at salvage mastectomy were not scored as having RNF. Patients suffering recurrence in the breast who developed clinical RNF subsequently were also not scored as having RNF.

Table 2. First site of failure according to type of dissection

	Total	Regional	Local	Distant/ opposite breast	Dead without recurrence	NED
All patients	418	6 (1.4%)	40 (9.6%)	98 (23.4%)	86 (20.6%)	188 (45.0%)
No dissection	292	3 (1.0%)	24 (8.2%)	68 (23.3%)	78 (26.7%)	119 (40.8%)
Limited dissection: N-	84	0	13 (15.5%)	19 (22.6%)	5 (6.0%)	47 (56.0%)
Limited dissection: N+	42	3 (7.1%)	3 (7.1%)	11 (26.3%)	3 (7.1%)	22 (52.4%)

$p < 0.0001$ indicates overall distribution of failure sites varies significantly among the 3 subgroups. Note that it does not specifically deal with RNF alone.

Patients were censored from observation for RNF at the time of development of breast failure, opposite breast cancer or distant failure because further dissemination from these sites or systemic therapy may have altered the progression of disease. Also, recording of subsequent sites of failure in such patients is likely to have been incomplete.

Follow-up time and time to failure were calculated from the start of radiotherapy. Only patients with 8 years of potential follow-up (either without evidence of disease and actual follow up greater than 8 years, or start of radiotherapy at least 8 years before the date that 90% of surviving patients had follow-up) were included in the analysis. The median follow-up time was 15.1 years for surviving patients (range, 8.3–24.8 years).

All rates given are the crude rates of first sites of failure within the first 8 years after treatment. Confidence intervals for percents are based on the Poisson distribution.

RESULTS

By 8 years of follow up, 40 patients (9.4%) had a local recurrence as the first site of failure, 98 (23.4%) had a distant or opposite breast recurrence, 86 (20.6%) died without recurrence, and 188 (45%) had no evidence of disease. RNF was the first site of failure within 8 years for 6 patients (1.4%). Regional nodal failure occurred as the site of first failure in 3 of 292 patients (1%) who underwent no dissection, in none of the 84 patients who underwent LD with pathologically negative nodes, and in 3 (7%) of the 42 patients who underwent LD with pathologically positive nodes (Table 2). Local failure occurred in 8% of those who underwent no dissection, in 16% of those who underwent LD with pathologically negative nodes, and in 7% of those who underwent LD with pathologically positive nodes. The corresponding rates of distant or opposite breast recurrence were 23%, 23%, and 26%, respectively. Twenty-seven percent of patients who underwent no dissection died without any recurrence, compared to 6% and 7% for those who underwent LD with pathologically negative and positive nodes, respectively. Among those who did not undergo dissection, 41% were alive without evidence of disease at 8 years. For patients who underwent LD, 56% of those with pathologically negative nodes and 52% of those with pathologically positive nodes were alive without evidence of disease. The overall distribution of sites of first failure among the 3 patient groups was significantly different ($p < 0.001$).

RNF occurred in 3 of the 292 patients who underwent no dissection, (1%; 95% confidence interval, 0.2–3%): one in the supraclavicular fossa and 2 in the axilla. Among the 84 patients who underwent limited dissection with pathologically negative nodes, there were no RNFs (0%; 95% confidence interval, 0–4%). Among the 42 patients who underwent LD with pathologically positive nodes, there were 3 RNFs (7%; 95% confidence interval, 1–19%): one in the infraclavicular fossa and 2 in the axilla. As indicated by the overlapping confidence intervals, these differences in the incidence of RNF were not statistically significant.

We reviewed the clinical and pathological characteristics of the 3 patients who underwent LD with pathologically positive nodes and had a subsequent RNF. The patient who developed an infraclavicular failure presented with a T2 LVI-positive tumor. LD yielded 4 nodes, 1 of which was found to contain tumor. The patient received adjuvant chemotherapy, and the total dose to the axilla was 50 Gy. Of the patients who developed an axillary recurrence, 1 had a T1 LVI-positive tumor with 3 nodes removed at LD, of which 2 were found to contain tumor. The total dose to the axilla for this patient was also 50 Gy. The second patient who developed an axillary recurrence had a T2 LVI-negative tumor also with 3 nodes removed at axillary dissection, of which 2 were involved with tumor. The total dose to the axilla for this third patient was 45 Gy. The second and third patients did not receive adjuvant chemotherapy.

Table 3 shows the impact of the number of positive nodes and the number of nodes removed on the incidence of regional nodal failure. One might have expected RNF to occur among patients with the least number of nodes sampled and the greatest number of positive nodes. Surprisingly, RNF occurred in patients with 3 or 4 nodes sampled and 1 or 2 positive nodes. Given the small number of patients within each subgroup, it is difficult to draw conclusions regarding the impact of the number of nodes sampled and number of positive nodes on RNF in our series.

We assessed the toxicities of axillary/supraclavicular radiation. Five patients (1%) developed symptomatic radiation pneumonitis. Two of these patients underwent no dissection and 3 underwent limited dissection with pathologically positive nodes. The median dose to the axilla for these 5 patients was 50 Gy (range, 45–50 Gy). Three of these 5 patients received chemotherapy. No patient had persistent pulmonary symptoms, and none required hospitalization. Brachial plex-

Table 3. RNF as the first site of failure by the number of nodes sampled and number of positive nodes

No. nodes sampled	Number of positive nodes					Total
	0	1	2	3	4	
1	0/9	0/2	—	—	—	0/11
2	0/16	0/1	0/3	—	—	0/20
3	0/13	0/5	2/4 (50%)	—	—	2/22 (9%)
4	0/19	1/11 (9%)	—	0/3	0/1	1/34 (3%)
5	0/27	0/5	0/7	—	—	0/39
Total	0/84	1/24 (4%)	2/14(14%)	0/3	0/1	3/126(2%)

RNF = regional nodal failure.

opathy occurred in 5 patients (1%). Four of these patients underwent no dissection, and 1 underwent LD with 4 nodes removed, 1 of which contained tumor. The median dose to the axilla for patients developing plexopathy was 50 Gy (range, 46–52 Gy). Of these 5 patients, 3 received chemotherapy, which was delivered prior to radiation. Plexopathy was transient in all and resolved without intervention. Persistent, moderate-to-severe arm edema was noted in 5 patients (1%), of which 4 underwent no dissection, and 1 underwent LD with removal of 5 pathologically negative nodes. Arm edema resolved in 1 patient at 25 months but persisted for the remaining 4 patients.

DISCUSSION

This study reports the 8-year crude incidence of sites of treatment failure, including RNF, among patients with early-stage, clinically node-negative breast cancer treated with axillary irradiation after either no dissection or limited dissection. RNF occurred in 1.4% of our total cohort, and the toxicity of such treatment was minimal. Patients who underwent LD with pathologically positive nodes had a somewhat higher rate of regional nodal failure, 7% in this series.

The results of the current series are consistent with those of several other series which report the incidence of RNF among clinically node-negative patients treated with AXRT and either no dissection (13–16) or a LD (17–19). Among 785 clinically node-negative women treated at Yale–New Haven Hospital with axillary irradiation alone without any axillary surgery, regional nodal failure occurred in 3% of patients followed for a median of 10 years (13). Similarly, Wazer *et al.* reported 1 regional nodal failure among 73 clinically node-negative patients treated with axillary irradiation in the absence of axillary dissection (14). Halverson *et al.* noted 2 axillary recurrences among 75 patients treated with axillary radiation in the absence of axillary dissection at a median follow-up time of 55 months (15). Finally, in an earlier analysis of this data set, 116 patients with either no dissection or inadequate axillary dissection were treated with tangential and axillary irradiation. With a median follow-up time of 77 months, 1 patient (0.8%) experienced an axillary failure (16). Data regarding the long-term efficacy of axillary irradiation following axillary sampling or inad-

equate axillary dissection also show RNF rates comparable to those of the current series. In a series from Nottingham, England, patients with Grade 3 tumors who had a positive axillary sampling were randomized to either axillary radiation or no further axillary treatment (17). The number of nodes sampled, number of positive nodes, use of adjuvant chemotherapy, and the details of radiation were not specified. The incidence of RNF at 5 years among those who received axillary radiation was 11%, compared to 46% among those who received no further axillary treatment. The rate of axillary failure following axillary radiation in patients with positive nodes obtained through a limited dissection, has been reported to be lower in 2 other series from the United Kingdom. In a trial from Yorkshire, the incidence of axillary failure at 5 years in patients who had a positive axillary sampling and underwent subsequent axillary radiation was 4% (18–19). Adjuvant chemotherapy was administered to 28% of this cohort. The number of nodes sampled and the number of positive nodes, however, were not described. Similarly, in a series from Edinburgh, RNF occurred in 6 of 88 patients (7%) who underwent axillary radiation for positive nodes on axillary sampling defined as removal of 4 nodes (20). The median follow-up was 11 years, and all patients received systemic therapy. The number of positive nodes, however, was not specified.

Are there subsets of patients with a positive sentinel node biopsy who require no further axillary treatment? There are no long-term data regarding the incidence of regional nodal failure among patients with a positive sentinel node biopsy who receive no further axillary treatment. Data from Milan indicate that breast cancer patients with a positive sentinel node have a 28% risk of nodal involvement in Level II or III (21). These additional positive nodes may be outside the standard breast tangential fields in a significant proportion of patients. The current series was not designed to identify a subgroup of women in whom further axillary treatment could safely be omitted. In a review of patients treated on several ECOG protocols with chemotherapy following removal of 2–5 axillary nodes, regional nodal failure occurred in 7% of patients with 1–3 positive nodes in the absence of axillary radiation (22). Chu *et al.* identified factors associated with a low risk of residual axillary disease at complete dissection following a positive sentinel node biopsy (23). Of

157 women found to have a positive sentinel node, none of the patients (0/33) with a positive sentinel node by immunohistochemistry alone were found to have residual axillary disease at completion dissection. In addition, among patients with T1a tumors and either micro- or macroscopic involvement of the sentinel node and those with T1b tumors and microscopic involvement of the sentinel node, no patient had nodal involvement at completion dissection (0/4, 0/1, and 0/10, respectively). The ongoing American College of Surgeons Z-11 trial, which randomizes patients with a positive sentinel node biopsy to breast radiation alone without further axillary therapy or to breast irradiation plus axillary dissection, will determine the efficacy of tangential radiation alone following a positive sentinel node biopsy, and will identify subgroups of patients who may require additional axillary therapy.

Given the 7% risk of RNF among patients with a positive axillary node in the current series, one might also ask if axillary radiation is effective treatment to the axilla. Do such patients require axillary dissection? Our surgeons did not perform a directed surgery such as sentinel node biopsy. It is possible that a directed surgery is associated with a higher likelihood of removing any involved nodes. Alternatively, in the current series, the median number of recovered nodes among patients who underwent LD was 4, higher than the median number of nodes typically removed at SNB (5). Thus, the current series may either overestimate or underestimate the risk of RNF with axillary radiation following a positive sentinel node biopsy. Nevertheless, there may in fact be subgroups of patients with a positive sentinel node biopsy in whom the residual tumor burden in the axilla is high, and, thus, radiation may not be adequate treatment. For example, Chu *et al.* have found that on univariate analysis, size of the sentinel node metastasis, size of the primary tumor, number of tumor-positive sentinel nodes and lymphatic vessel involvement were associated with a high likelihood of residual axillary disease following a positive sentinel node (24). On multivariate analysis, patients with macroscopic involvement of the sentinel node and larger primary tumors were at significantly greater risk of nonsentinel node involvement. Presumably, the number of tumor-positive sentinel nodes and lymphatic vessel involvement dropped out on multivariate analysis, because of their significant correlation with primary tumor size and size of sentinel node metastasis. Thus, it is possible that patients with more than one involved sentinel node have a high likelihood of harboring residual axillary disease with a large tumor burden that cannot be adequately controlled with axillary radiation. However, because the number of patients in the current series with more than one involved node on LD is small and the number of regional nodal failures is few, it is not possible to determine whether AXRT is effective at preventing RNF among such patients. Ongoing studies at our institutions are designed to determine the efficacy of axillary radiation following a positive sentinel node biopsy and identify subgroups of patients for whom axillary dissection might more effectively prevent regional nodal failure.

Potential toxicities of axillary radiation following a pos-

itive sentinel node biopsy would include an increased risk of radiation pneumonitis, brachial plexopathy and arm edema. The results of the current series and others suggest that the incidence of such toxicities following axillary radiation after either no dissection (13–15, 25–27) or LD (25–27) is low. Ongoing studies will provide definitive information regarding the toxicity of axillary radiation following a positive sentinel node biopsy.

We would like to acknowledge the limitations of our study. First, this is a retrospective series and may be influenced by selection bias. For example, subjects who had no dissection were significantly older than those who underwent LD. The decision to omit an axillary dissection in these patients presumably reflected more extensive underlying comorbidities which may have placed this cohort at increased risk of death from other causes. Similarly, it is not clear why surgeons elected to perform less extensive dissection among the LD cohort. Second, the small number of patients in our cohort undergoing limited dissection with pathologically positive nodes and the small number of regional nodal failures among all 3 cohorts prevent confident identification of subsets of patients who may be at increased risk of regional nodal failure with AXRT following either no or limited dissection. Third, we did not perform formal pathologic assessment of the lymph node metastasis. Fourth, in our series, the extent of dissection was determined by the number of lymph nodes identified by the pathologist and not by review of the operative note or size of the axillary contents. It is possible that some patients in our series may have undergone formal Level I/II dissections with incomplete pathologic review of the axillary dissection specimen. Finally, LD may be an inexact model for sentinel node biopsy, and hence, comparisons between these 2 surgical interventions may not be accurate. Patients in the current series who underwent limited dissection with pathologically positive nodes may have had larger amounts of residual nodal disease than patients undergoing sentinel node biopsy. The current series may either underestimate or overestimate the risk of regional nodal failure with AXRT following a positive sentinel node biopsy.

Currently, we treat patients with a negative SNB with tangential radiation alone. Following a positive sentinel node biopsy at our institutions, when additional information from axillary dissection would not alter recommendations for adjuvant therapy, we offer patients axillary radiation consisting of a single anterior field directed to the full axilla and supraclavicular fossa usually prescribed to a depth of 5 centimeters given to a dose of 45 Gy. At the discretion of the radiation oncologist, this can sometimes be followed by a boost of an additional 4 Gy delivered with either a posterior or en face axillary boost. We are currently conducting a prospective trial to assess the long-term efficacy and toxicities of AXRT following a positive sentinel node biopsy. Additional studies may identify subgroups of patients with a positive sentinel node biopsy for whom tangential radiation alone provides

effective treatment to the axilla. Alternatively, such studies may also identify patients with a positive sentinel node biopsy at substantial risk of regional nodal failure for whom AXRT may not be sufficient treatment, in

whom axillary dissection is indicated. We believe at present that, outside of a formal protocol, all patients with a positive sentinel node biopsy should routinely receive some form of specific axillary treatment.

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