Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 1, pp. 59–65, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.12.017

CLINICAL INVESTIGATION **Breast**

THE RATIO OF POSITIVE TO EXCISED NODES IDENTIFIES HIGH-RISK SUBSETS AND REDUCES INTER-INSTITUTIONAL DIFFERENCES IN LOCOREGIONAL RECURRENCE RISK ESTIMATES IN BREAST CANCER PATIENTS WITH 1–3 POSITIVE NODES: AN ANALYSIS OF PROSPECTIVE DATA FROM BRITISH COLUMBIA AND THE M. D. ANDERSON CANCER CENTER

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Purpose: To examine the power of the nodal ratio (NR) of positive/excised nodes in predicting postmastectomy locoregional recurrence (LRR) in patients with 1–3 positive nodes (*N*+) and in identifying cohorts at similar risk across independent data sets.

Methods and Materials: Data from 82 patients with 1–3 *N*+ treated without postmastectomy radiotherapy (PMRT) in the British Columbia (BC) randomized trial were compared with data from 462 patients treated without PMRT in prospective chemotherapy trials at the M. D. Anderson Cancer Center (MDACC). Kaplan-Meier LRR curves were compared between centers using the absolute number of *N*+ and nodal ratios.

Results: The median number of excised nodes was 10 in BC and 16 in MDACC ($p < 0.001$). Examining LRR by number of *N*+, the 10-year LRR rate for patients with 1–3 *N*+ was higher in BC compared with MDACC (21.5% vs. 12.6%; $p = 0.02$). However, when examining LRR using NR, no differences were found between institutions. In patients with NR ≤ 0.20, the 10-year LRR rate was 17.7% BC vs. 10.9% MDACC ($p = 0.27$). In patients with NR ≥ 0.20, the 10-year LRR rate was 28.7% BC vs. 22.7% MDACC ($p = 0.32$). On Cox regression analysis, NR was a stronger prognostic factor compared with number of *N* +.

Conclusions: In patients with 1–3 *N*+, evaluating nodal positivity using NR reduced inter-institutional differences in LRR estimates that may exist due to variations in numbers of nodes excised. Nodal ratio >0.20 was associated with LRR >20%, warranting PMRT consideration. Nodal ratio may be useful for extrapolating data from prospective trials to clinical practices in which axillary staging extent vary. © 2007 Elsevier Inc.

Breast cancer, Nodal ratio, Locoregional recurrence, Mastectomy, Axillary dissection.

INTRODUCTION

Randomized trials from the British Columbia (BC) Cancer Agency (1, 2) and the Danish Breast Cancer Cooperative Group have demonstrated that for patients with Stage II–III breast cancer, the use of postmastectomy radiotherapy (PMRT) in women receiving systemic therapy was associated with reduced locoregional recurrence (LRR) and improved survival (3–6). However, the LRR rates in patients randomized to receive no PMRT in these trials were higher compared with LRR rates reported in patients enrolled in systemic trials without RT in a number of U.S. groups (7–10).

Variations in the extent of axillary staging surgery yielding different numbers of excised nodes may contribute to the higher LRR rates noted in the BC and Danish Breast Cancer Cooperative Group trials relative to those in the U.S. pattern-of-failure series. For example, the median number of excised nodes was 7 in the Danish studies, 11 in the BC study, and 15 or greater in the U.S. series (1–10). Axillary

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Presented in part at the 48th Annual Meeting of the American Society of Therapeutic Radiology and Oncology (ASTRO), November 5–9, 2006, Philadelphia, PA.

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Conflict of interest: none.

Received Oct 23, 2006. Accepted for publication Dec 1, 2006.

surgery that removes few nodes may underestimate the true number of involved nodes. For example, a patient undergoing limited axillary surgery yielding 2 positive nodes out of 5 removed nodes may have had 4 or more positive nodes if more than 10 nodes were excised. Such understaging not only limits prognostic accuracy but may also compromise locoregional disease control.

Decisions to use PMRT have been primarily based on tumor stage and the absolute number of positive nodes (11, 12). Although data from the BC and Danish trials would suggest that patients with 1–3 positive nodes may benefit from PMRT, because of the discrepancies in reported baseline LRR risks, the use of PMRT in this patient subset remains controversial (11, 12). Accordingly, alternative methods of evaluating axillary disease extent that take into account the number of nodes excised may be of significant clinical value in appraising LRR risks in these patients. One method for potentially accomplishing this is to examine the nodal ratio, defined as the number of positive/excised nodes. Previously, investigators at the University of Texas M. D. Anderson Cancer Center (MDACC) used recursive partitioning analysis to demonstrate that a nodal ratio >0.20 was the most powerful discriminator of LRR in patients treated with mastectomy and chemotherapy (7). Investigators at the University of British Columbia BC Cancer Agency also found that nodal ratio was a significant prognostic factor for LRR, distant recurrence, and overall survival in a retrospective, population-based analysis of women with T1–2 breast cancer with 1–3 positive nodes (13). Examining nodal ratios thus has the potential to account for differences in the extent of axillary surgery and differences in the pathologic processing of axillary specimens.

The present report is a collaborative analysis of prospective data from women with 1–3 positive nodes enrolled in the control arm of the BC PMRT randomized trial and in the MDACC prospective trials of chemotherapy without PMRT. In this study, we evaluated the use of the nodal ratio as a discriminator of postmastectomy LRR and tested the hypothesis that nodal ratio is a prognostic indicator that may be applied across independent data sets to identify cohorts of similar LRR risks.

METHODS AND MATERIALS

Data from patients with 1–3 positive nodes treated without PMRT on the BC randomized trial were compared with data from patients with 1–3 positive nodes treated without PMRT on prospective chemotherapy trials at the MDACC.

BC data set

From 1979 to 1986, 318 premenopausal women with Stage II and III breast cancer who were referred to the BC Cancer Agency after modified radical mastectomy and axillary dissection were randomly assigned to PMRT or no additional treatment (1, 2). All patients received cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy (1, 2). Of the 154 patients randomized to the control arm, 8 had PMRT at their own request after randomization. These 8 patients were excluded from the current analysis. Patients with unknown number of positive nodes ($n = 8$) and unknown number of excised nodes ($n = 16$) were also excluded. Among 122 remaining patients, 82 had 1–3 positive nodes and formed the BC cohort in this analysis.

MDACC data set

From 1975 to 1994, 1,031 patients with Stage II and III breast cancer treated with mastectomy without RT were enrolled in five prospective trials of doxorubicin-based chemotherapy at the MDACC (7, 8). The current analysis excluded patients with node-negative disease ($n = 141$), unknown number of positive nodes ($n = 5$), and unknown number of excised nodes ($n = 13$). Of the remaining patients, 462 had 1–3 positive nodes and formed the MDACC cohort in this analysis.

Locoregional recurrence

Locoregional recurrences were recoded in the MDACC data set to be consistent with BC definitions. Locoregional recurrence was defined in both data sets as the first site of recurrence involving the chest wall (local) and/or axillary, supra- or infraclavicular, and internal mammary nodes (regional). Patients with LRR that occurred simultaneously with distant recurrence were scored as having had an LRR event. Patients who had LRR events that occurred more than 1 month after distant recurrence were censored at the time of distant recurrence.

Statistical analysis

Patient and tumor characteristics were compared between the two data sets using chi-square and Fisher's exact tests. The tumor factors analyzed were histology, primary tumor size, pathologic T stage, nuclear grade, lymphovascular invasion, estrogen receptor status, number of positive nodes, number of excised nodes, and nodal ratios. Kaplan-Meier LRR curves were compared between the two centers, according to the absolute number of positive nodes and according to nodal ratios. The statistical significance of LRR differences was determined using log–rank tests. To examine the effect of progressively increased nodal ratios on LRR, nodal ratios ≤ 0.10, 0.11–0.20, 0.21–0.29, and ≥ 0.30 were examined. The nodal ratio cut point of 0.20, previously identified using regression tree analysis in the MDACC data set (7), was also tested in the BC data set. Cox regression analysis was performed with treatment center, number of positive nodes, and nodal ratio as covariates. Statistical analyses were performed with SPSS software (version 12.0; SPSS, Chicago, IL).

RESULTS

Median follow-up time was 18.7 years (range, 1.13–25.8 years) for the BC cohort and 10.1 years (range, 0.25–21.8 years) for the MDACC cohort.

Patient and tumor characteristics

Table 1 summarizes the patient and tumor characteristics in the two data sets. The median age of patients in the BC cohort was 43 years, compared with 48 years in the MDACC cohort ($p < 0.001$). Patients in the BC cohort had fewer nodes excised compared with the MDACC cohort (median 10 vs. 16; $p < 0.001$). Forty-six percent of patients in the BC cohort and 82% of patients in the MDACC cohort had more than 10 nodes excised ($p < 0.001$). Higher

Table 1. Comparisons of patient and tumor characteristics between centers

	BCCA (n = 82)	MDACC (n = 462)	p*
Age (y)			
Median (range)	43 (29–55)	48 (23–76)	<0.001
≤45	45 (55)	153 (33)	<0.001
45–55	37 (45)	189 (41)	
55–65	0	86 (19)	
≥65	0	34 (7)	
Histology			0.11
Ductal	70 (85)	398 (86)	
Lobular	10 (12)	25 (5)	
Mixed	2 (3)	19 (4)	
Other	0	15 (4)	
Unknown	0	5 (1)	
T size (cm), median (range)	3 (0–10)	2.5 (0.4–15)	0.61
Pathologic T stage			0.32
T1	30 (37)	143 (31)	
T2	40 (59)	231 (50)	
T3	4 (5)	43 (9)	
Unknown	8 (10)	45 (10)	
Nuclear grade			0.19
I/II	40 (49)	215 (47)	
III	20 (24)	154 (33)	
Unknown	22 (27)	93 (20)	
Lymphovascular invasion			<0.001
Negative	20 (24)	303 (66)	
Positive	43 (52)	153 (33)	
Unknown	19 (23)	6 (1)	
Estrogen receptor status			<0.001
Negative	19 (23)	153 (33)	
Positive	63 (77)	234 (51)	
Unknown	0	75 (16)	
No. of excised nodes			
Median (range)	10 (1–41)	16 (1–43)	<0.001
≤10	44 (54)	81 (18)	<0.001
>10	38 (46)	381 (82)	

Abbreviations: BCCA = British Columbia Cancer Agency; MDACC = M. D. Anderson Cancer Center.

Data are presented as number (percentage), unless otherwise specified.

* Test statistics applied to known values only

proportions of lymphovascular invasion–positive and estrogen receptor–positive disease were observed in the BC cohort (both $p < 0.001$). Distributions of pathologic T stage, histologic subtypes, and nuclear grade were similar in the two groups.

Locoregional recurrence comparisons

Comparisons of 10-year Kaplan-Meier LRR between centers according to absolute number of positive nodes and nodal ratios are presented in Table 2. Examining LRR by absolute number of positive nodes, the 10-year Kaplan-Meier LRR risk for patients with 1–3 positive nodes was significantly higher in BC patients compared with MDACC patients (21.5% vs. 12.6%; $p = 0.02$) (Fig. 1).

When LRR was assessed using nodal ratios, no statistically significant differences were observed between the two centers (Fig. 2). In patients with 1–3 positive nodes, nodal ratios of ≤0.10 and 0.11–0.19 were associated with modest 10-year LRR risks of less than 20% in both data sets (Figs. 2a and 2b). The risk of LRR increased with increasing nodal ratios (Table 2, Figs. 2c and 2d). In patients with nodal ratios >0.20, the 10-year LRR risk was 28.7% in the BC cohort and 22.7% in the MDACC cohort ($p = 0.32$).

Cox regression analysis

In the Cox regression model, nodal ratio was a stronger prognostic factor for LRR compared with absolute number of positive nodes (Table 3). Treatment center was not a significant factor for LRR in the multivariate analysis.

DISCUSSION

The Early Breast Cancer Trialists' Collaborative Group overview of more than 30 randomized trials clearly demonstrated that adjuvant RT confers a consistent relative reduction in LRR of approximately two thirds, independent of tumor or nodal characteristics (14). The overview also suggested that absolute reductions in LRR of 20% corresponded to absolute reductions in breast cancer–specific mortality of approximately 5% (14). Currently, adjuvant RT decisions are primarily based on LRR risk estimates associated with the absolute number of positive nodes (11, 12). For patients with 1–3 positive nodes, the baseline LRR risk without RT is controversial. The 10-year LRR rate without PMRT was approximately 30% in the Danish trials (3, 4) and approximately 20% in the BC trial (1, 2). These LRR estimates were higher compared with those reported in pattern-of-failure studies of patients enrolled in adjuvant systemic therapy trials without radiation (LRR, 12–20% at 10 years) (7–10). Variations in the extent of surgical staging and axillary clearance have been implicated as the source of discrepancy in these reported LRR risks. The nodal ratio of positive/excised nodes may be a more comprehensive approach to estimating LRR because it takes into account the number of excised nodes and may accordingly adjust for differences in axillary surgical staging. The current analysis has confirmed that when only the absolute number of positive nodes was used, LRR among patients with 1–3 positive nodes in the BC cohort was significantly higher compared with the MDACC cohort. However, when LRR was examined using nodal ratios, differences between institutions were no longer significant. These observations support the hypothesis that using the nodal ratio rather than the absolute number of positive nodes reduced inter-institutional differences in LRR risk estimates that may exist because of variations in the number of nodes excised.

The American Joint Committee on Cancer staging system was recently revised, grouping patients according to absolute number of positive nodes (0 vs. 1–3 vs. ≥4 positive nodes) (15). This classification improved stratification in overall survival (16), but the confounding effect that the number of excised nodes may have on the yield of positive nodes and its impact on LRR prognostic accuracy and

Table 2. Comparisons of crude LRR and 10-year Kaplan-Meier LRR according to number of positive nodes and nodal ratios

	BCCA		MDACC		
	Crude LRR rate	10-year KM LRR (%)	Crude LRR rate	10-year KM LRR (%)	Log–rank *p*
No. of positive nodes	17/82	21.5	53/462	12.6	0.02
Nodal ratio					
≤0.10	3/24	14.4	23/244	10.3	0.64
0.11–0.19	5/28	20.4	16/145	11.8	0.38
0.20–0.29	3/16	15.4	8/51	19.3	0.80
≥0.30	6/14	43.4	6/22	31.0	0.58
<0.20	8/52	17.7	39/389	10.9	0.27
≥0.20	9/30	28.7	14/73	22.7	0.32

Abbreviations: BCCA = British Columbia Cancer Agency; MDACC = M. D. Anderson Cancer Center; LRR = locoregional recurrence; KM = Kaplan-Meier.

therapeutic decisions remain unresolved with the current staging system. Consensus has been reached that PMRT is indicated for patients with ≥4 positive nodes (11, 12). In the present analysis, we focused on patients with 1–3 positive nodes because this is the patient subset in whom adjuvant RT use is most often debated and in whom the application of the nodal ratio may be of most clinical value in locoregional therapy decision making. In both data sets analyzed, a nodal ratio >0.20 was associated with LRR risks in excess of 20%. Because optimal locoregional control may favorably impact survival (1–6, 14), PMRT should be considered and discussed with patients with this risk magnitude.

The growing body of literature supporting the use of nodal ratios in conjunction with absolute number of positive nodes to prognosticate recurrence and survival outcomes was summarized in a review article by Woodward *et al.* (17). Mathematical modeling studies using large samples of patients registered in the Surveillance, Epidemiology, and End Results (SEER) program have evaluated the potential advantages of nodal ratios over absolute number of positive nodes in predicting breast cancer prognosis (18, 19). Vinh-Hung *et al.* (18) used Cox models to examine hazard ratios for breast cancer–specific and overall mortality associated with escalating numbers of positive nodes in 4,387 patients with T1–2, node-positive breast cancer treated with mastectomy without RT. The plot of hazard ratios as a function of number of positive nodes showed a continuous increasing risk with each positive node without any identifiable cut points (18). In another analysis using SEER data of 83,686 women with nonmetastatic T1–2 breast cancer staged by axillary dissection, these investigators examined multiple Cox models for breast cancer–specific mortality based on different expressions of nodal involvement. Comparisons of these models suggested that the ratio of positive/excised nodes provided at least the same prognostic value as the traditional staging using absolute number of positive nodes but had the added advantage of standardization to the number of excised nodes (19).

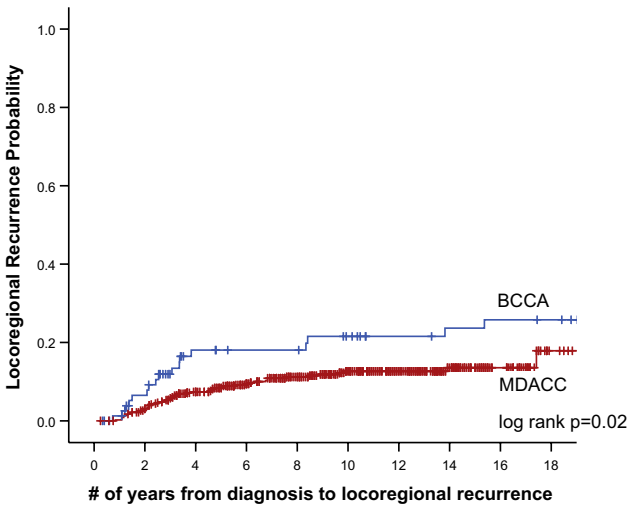

Fig. 1. Comparison of locoregional recurrence between centers according to absolute number of positive nodes. BCCA = British Columbia Cancer Agency; MDACC = M. D. Anderson Cancer Center.

Among clinical studies that examined nodal ratios in breast cancer management, various thresholds have been reported to be significant predictors of LRR and survival outcomes. These studies span various breast cancer stages and used diverse treatment approaches (7, 13, 20–26). Investigators at the MDACC were among the first to demonstrate that a nodal ratio of >0.20 was a strong predictor for postmastectomy LRR risk (7). A population-based analysis from British Columbia of 821 women with T1–2 breast cancer with 1–3 positive nodes reported that nodal ratio >0.25, age <45 years, medial tumor location, and estrogen receptor–negative status were individual factors associated with postmastectomy LRR risk >20% and that combinations of these factors were associated with even greater LRR risks (20). A subsequent analysis examining additional outcomes of distant recurrence and overall survival demonstrated that whereas the absolute number of positive nodes and the nodal ratio were both significant on univariate analysis, on multivariate analysis, the nodal ratio superseded the number of positive nodes in significance for all endpoints (13).

The current study compared two independent, prospective data sets of patients enrolled in clinical trials and treated

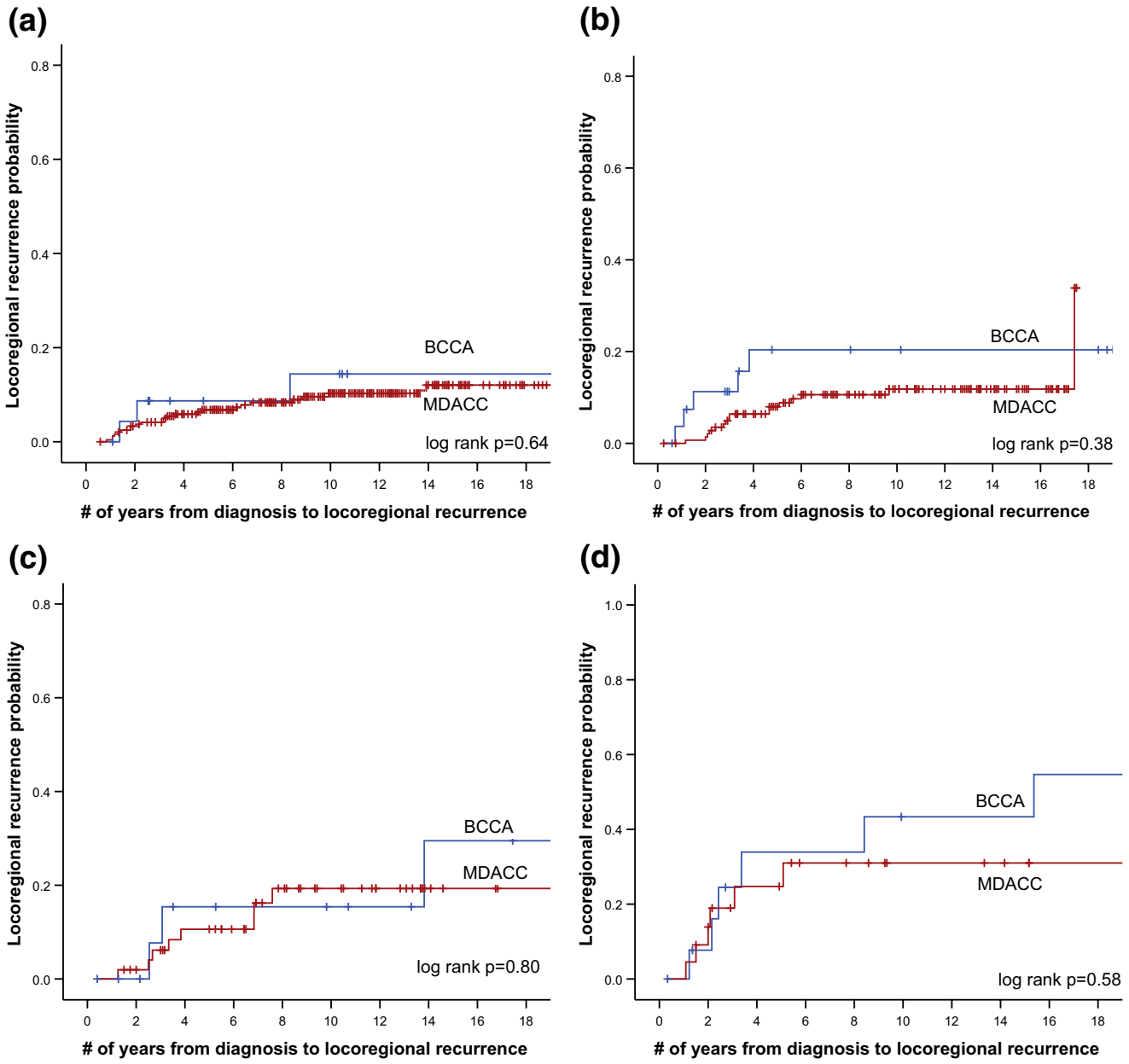

Fig. 2. Comparison of locoregional recurrence between centers according to nodal ratios. (a) ≤0.10; (b) 0.11–0.19; (c) 0.20–0.29; (d) ≥0.30. BCCA = British Columbia Cancer Agency; MDACC = M. D. Anderson Cancer Center.

without PMRT at centers where surgical staging varied, yielding different numbers of median nodes excised. The observation that the nodal ratio reduced inter-institutional differences in LRR estimates suggests that the nodal ratio may be a useful method for extrapolating data from prospective trials to clinical practices and adjusting for variations in axillary surgery. The finding in the current analysis that the nodal ratio was a stronger prognostic factor compared with the absolute number of positive nodes is consistent with results from other outcomes analyses (21–23). A study from The Netherlands, with 453 patients with Stage I–II breast cancer treated with mastectomy or breast-conserving therapy, reported that a nodal ratio of 0.20 was a significant predictor of survival that superseded the number of positive nodes (21). Similarly, a study from Belgium with 741 patients with node-positive breast cancer examining nodal ratios using different cutoff points (≤0.10, 0.11–0.50) reported that the nodal ratio was the most significant predictor of overall survival and that the number of positive nodes lost significance when the nodal ratio was included in

Table 3. Cox regression analysis of locoregional recurrence

Variable	Hazard ratio	*p*	95% confidence interval
Center	0.61	0.10	0.34–1.09
No. of positive nodes	1.26	0.14	0.93–1.73
Nodal ratio	3.69	0.06	0.93–14.60

multivariate analysis (22). Finally, investigators from Quebec analyzing 1,372 women with T1–2, node-positive breast cancer demonstrated that the nodal ratio was a significant prognostic factor for LRR that may be used to identify patients who can benefit from regional RT after breast-conserving surgery (23). Taken together, the data from these studies and the present analysis support the contention that the nodal ratio is a useful prognostic indicator that may be used in locoregional management decisions.

We acknowledge several limitations to the current study. Although our objective was to evaluate nodal ratios using available independent prospective data sets to reduce treatment selection bias, the sample size of the cohort with 1–3 positive nodes randomized to the control arm of the BC randomized trial was small and may have limited statistical power. The subjects enrolled in trials in BC and MDACC were relatively young (median age <50 years) and may have inherently different characteristics compared with older breast cancer populations. We examined different nodal ratio cutoff points and tested the cut point of 0.20 identified by recursive partitioning by MDACC investigators against the BC data set. Although this cut point was found to be associated with LRR in excess of 20% in both data sets and supported the suggestion that the use of nodal ratios can reduce inter-institutional differences in LRR estimates, definitions of appropriate nodal ratio thresholds to group patients according to different risk groups require additional prospective evaluation using larger samples with long-term follow-up data and adequate statistical power.

Finally, the application of nodal ratios to guide treatment decisions for breast cancer patients in contemporary practice must be considered in the context of evolving staging strategies. Sentinel node biopsy has emerged as an accurate staging modality associated with fewer surgical morbidities compared with axillary dissection (27). Its role as a stand-alone procedure without axillary dissection is being investigated by prospective, randomized trials (28). Because sentinel node surgery generally yields fewer numbers of nodes compared with axillary dissection, the mathematical ratio possibilities are correspondingly fewer, raising the suggestion that nodal ratios after sentinel node biopsy alone may be a less sensitive discriminator of outcome (17). Despite this caveat, recent studies have emerged reporting that the ratio of positive to excised sentinel nodes is an indicator of regional disease burden and an independent predictor of non-sentinel node involvement (29, 30).

CONCLUSION

In patients with 1–3 positive nodes, evaluating nodal positivity using the nodal ratio reduced inter-institutional differences in LRR risk estimates that may exist owing to variations in numbers of nodes excised. Nodal ratio >0.20 identified patient subsets with baseline LRR risks in excess of 20%, a risk magnitude that warrants consideration of PMRT. The nodal ratio should be considered in appraising LRR risks for patients with 1–3 positive nodes and may be a useful method for extrapolating data from prospective trials to clinical practices in which the extent of axillary staging varies.

REFERENCES

1. Ragaz J, Jackson SM, Le N, *et al.* Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997;337:956–962.
2. Ragaz J, Olivotto IA, Spinelli JJ, *et al.* Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005;97:116–126.
3. Overgaard M, Hansen PS, Overgaard J, *et al.* Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy: Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997;337:949–955.
4. Overgaard M, Jensen MB, Overgaard J, *et al.* Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group 82c randomized trial. *Lancet* 1999;353:1641–1648.
5. Nielsen HM, Overgaard M, Grau C, *et al.* Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: Long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol* 2006;24:2268–2275.
6. Nielsen HM, Overgaard M, Grau C, *et al.* Loco-regional recurrence after mastectomy in high-risk breast cancer—risk and prognosis. An analysis of patients from the DBCG 82 b and c randomization trials. *Radiother Oncol* 2006;79:147–155.
7. Katz A, Buchholz TA, Thames H, *et al.* Recursive partitioning analysis of locoregional recurrence patterns following mastectomy: Implications for adjuvant irradiation. *Int J Radiat Oncol Biol Phys* 2001;50:397–403.
8. Katz A, Strom EA, Buchholz TA, *et al.* The influence of pathologic tumor characteristics on locoregional recurrence rates following mastectomy. *Int J Radiat Oncol Biol Phys* 2001;50:735–742.
9. Recht A, Gray R, Davidson NE, *et al.* Locoregional failure ten years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: Experience of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999;17:1689–1700.
10. Taghian AG, Jeong JH, Mamounas E, *et al.* Pattern of locoregional and distant failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: Results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. *J Clin Oncol* 2004;22:4247–4254.
11. Recht A, Edge SB, Solin LJ, *et al.* Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1539–1569.
12. Harris JR, Halpin-Murphy P, McNeese M, *et al.* Consensus statement on postmastectomy radiation therapy. *Int J Radiat Oncol Biol Phys* 1999;44:989–990.
13. Truong PT, Berthelet E, Lee J, *et al.* The prognostic significance of the percentage of positive/dissected axillary lymph

nodes in breast cancer recurrence and survival in patients with one to three positive axillary lymph nodes. *Cancer* 2005;103: 2006–2014.
14. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomized trials. *Lancet* 2000;355:1757–1770.
15. Singletary SE, Allred C, Ashley P, *et al.* Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol* 2002;20:3628–3636.
16. Woodward WA, Strom EA, Tucker SL, *et al.* Changes in the 2003 American Joint Committee on Cancer staging for breast cancer dramatically affect stage-specific survival. *J Clin Oncol* 2003;21:3244–3248.
17. Woodward WA, Vinh-Hung V, Ueno NT, *et al.* Prognostic value of nodal ratios in node-positive breast cancer. *J Clin Oncol* 2006;24:2910–2916.
18. Vinh-Hung V, Storme G. No nodal cutoff in node-positive breast cancer women treated with mastectomy. *Breast Cancer Res Treat* 2006;98:1273–1278.
19. Vinh-Hung V, Verschraegen C, Promish DI, *et al.* Ratios of involved nodes in early breast cancer. *Breast Cancer Res* 2004;6:R680–R688.
20. Truong PT, Olivotto IA, Kader HA, *et al.* Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;61:1337–1347.
21. van der Wal BC, Butzelaar RM, van der Meij S, *et al.* Axillary lymph node ratio and total number of removed lymph nodes: Predictors of survival in stage I and II breast cancer. *Eur J Surg Oncol* 2002;28:481–489.
22. Voordeckers M, Vinh-Hung V, Van de Steene J, *et al.* The lymph node ratio as prognostic factor in node-positive breast cancer. *Radiother Oncol* 2004;70:225–230.
23. Fortin A, Dagnault A, Blondeau L, *et al.* The impact of the number of excised axillary nodes and of the percentage of involved nodes on regional nodal failure in patients treated by breast-conserving surgery with or without regional irradiation. *Int J Radiat Oncol Biol Phys* 2006;65:33–39.
24. Nieto Y, Nawaz S, Jones RB, *et al.* Prognostic model for relapse after high-dose chemotherapy with autologous stem-cell transplantation for stage IV oligometastatic breast cancer. *J Clin Oncol* 2002;20:707–718.
25. Bolwell B, Andresen S, Pohlman B, *et al.* Prognostic importance of the axillary lymph node ratio in autologous transplantation for high-risk stage II/III breast cancer. *Bone Marrow Transplant* 2001;27:843–846.
26. Grills IS, Kestin LL, Goldstein N, *et al.* Risk factors for regional nodal failure after breast-conserving therapy: Regional nodal irradiation reduces rate of axillary failure in patients with four or more positive lymph nodes. *Int J Radiat Oncol Biol Phys* 2003;56:658–670.
27. Veronesi U, Paganelli G, Viale G, *et al.* A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003;349:546–553.
28. White RL Jr, Wilke LG. Update on the NSABP and ACOSOG breast cancer sentinel node trials. *Am Surg* 2004;70:420–424.
29. Tan YY, Fan YG, Lu Y, *et al.* Ratio of positive to total number of sentinel nodes predicts nonsentinel node status in breast cancer patients. *Breast J* 2005;11:248–253.
30. Barranger E, Coutant C, Flahault A, *et al.* An axilla scoring system to predict non-sentinel lymph node status in breast cancer patients with sentinel lymph node involvement. *Breast Cancer Res Treat* 2005;91:113–119.