Disease Recurrence in Sentinel Node-Positive Breast Cancer Patients Forgoing Axillary Lymph Node Dissection

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Abstract

Background—Clinically node-negative breast cancer patients usually undergo sentinel lymph node (SLN) biopsy. When metastasis is identified, completion axillary lymph node dissection (CALND) is recommended. Newer data suggest that CALND may be omitted in some women as it does not improve local control or survival.

Methods—Women with a positive SLN diagnosed between 1999 and 2010 were included in this review and were stratified according to whether they did or did not undergo CALND. Primary endpoints included recurrence and breast cancer-specific mortality. Differences between the groups and in time to recurrence were compared and summarized.

Results—Overall, 276 women were included: 206 (79 %) women who underwent CALND (group 1) and 70 (21 %) women in whom CALND was omitted (group 2). Group 1 patients were younger, had more SLN disease, and received more chemotherapy ($P < 0.05$ for each). The groups did not vary by tumor characteristics ($P > 0.05$ for each). Median follow-up was 69 (range 6–147) and 73 (range 15–134) months for groups 1 and 2, respectively. Five (2 %) women in group 1 and three (4 %) women in group 2 died of breast cancer ($P = 0.39$). Local–regional or distant recurrence occurred in 20 (10 %) group 1 patients and in 10 (14 %) group 2 patients ($P = 0.39$). On multivariate analysis, only estrogen receptor negativity and lymphovascular invasion predicted for recurrence.

Conclusions—Omission of CALND in women with SLN disease does not significantly impact in-breast, nodal, or distant recurrence or mortality. Longer-term follow-up is needed to verify that this remains true with time.

Sentinel lymph node (SLN) biopsy is the standard of care for axillary staging in clinically node-negative breast cancer patients. Since the adoption of this technique, the consensus in

the oncology community has been to proceed with completion axillary lymph node dissection (CALND) in the setting of a positive SLN, i.e., when tumor metastasis is found within the SLN.[1] However, only about half of patients with macrometastasis in the SLN will have positive non-SLNs, and that likelihood lessens as the amount of SLN disease decreases.[2–5] Recently, investigators have questioned whether patients with positive SLNs benefit from CALND, as axillary recurrence rates are low in these patients when CALND is omitted.[6–10]

To investigate the benefit of CALND following a positive SLN biopsy, the American College of Surgeons Oncology Group created a prospective trial, Z0011. This study randomized women with positive SLNs to CALND or to no further axillary surgery. The results were recently published, and no local control or survival advantage was seen with CALND.[11,12] This paper has been practice-changing, but it has been criticized for its limited follow-up and for its failure to meet its accrual goal.

The purpose of our study is to review our SLN-positive patients, comparing local, regional, and distant recurrence rates in those who underwent CALND with those who did not, and to see whether our retrospective cohort produced results similar to those of Z0011.

METHODS

Institutional review board approval was obtained prior to the commencement of this retrospective study. Clinical, demographic, and pathologic data from all breast cancer patients treated at our institution are prospectively recorded in a database. We reviewed this database and identified 1,797 patients with breast cancer who underwent SLN biopsy at our institution between January 1, 1999 and August 31, 2010. Of this cohort, 356 women had positive SLNs. No follow-up information was available for 23 patients, and they were excluded. Fifty-seven patients had only isolated tumor cells (ITCs) in their sentinel nodes, and these patients were also excluded. Altogether, 276 women were included in the analysis. Data recorded included age at diagnosis, race, tumor size, histology, grade, estrogen receptor (ER) status, progesterone receptor (PR) status, Her-2neu status, type of surgical therapy [mastectomy versus breast-conservation therapy (BCT)], use of neoadjuvant or adjuvant systemic therapy, use of axillary-specific radiation therapy (radiation fields specifically designed to include axillary nodes), and the size of the SLN metastasis (micrometastatic versus macrometastatic). For patients who received neoadjuvant systemic therapy, pretreatment clinical tumor size was used.

Patients were divided according to whether they underwent CALND (group 1) or had no further axillary surgery (group 2). Local, axillary, and distant recurrences were identified and recorded, as were deaths due to breast cancer and to non-breast cancer causes. Patients who underwent lumpectomy were followed by clinical examination and by mammography; routine axillary imaging surveillance was not performed. Computed tomography, positron emission tomography, and bone scans were performed at the discretion of the treating physicians. Differences between the two groups in demographic and clinical characteristics were compared using Fisher's exact test, two-sample *t* test, or Mann–Whitney rank-sum test as appropriate. Differences between the groups in time to recurrence were summarized using

Kaplan–Meier product limit method and compared by log-rank test. Univariate Cox proportional hazard models were used to assess the effects of patient demographic and clinical characteristics on time to recurrence. A multivariate Cox model was also developed via a backward selection procedure to identify factors independently predictive of recurrence. Due to relatively small number of recurrences, a preselection was performed first and only those factors showing $P < 0.30$ on univariate analysis were included to undergo backward selection procedure. All statistical analyses were performed using a statistical package SAS (SAS Institutes, Cary, NC). p value under 0.05 was taken to indicate significance, and all statistical tests were two-sided.

RESULTS

Of 276 patients with SLN disease, 206 (79 %) underwent CALND (group 1) and 70 (21 %) had no further axillary surgery (group 2). The median age of group 1 patients was 51 (range 20–89) years. This was significantly younger than 57 (range 31–86) years, the median age of group 2 patients ($P = 0.016$). There was a trend toward larger tumor size in group 1, but this latter variable did not reach statistical significance. The groups did not differ significantly in terms of patient race, histology, receptor status, tumor grade, or presence of lymphovascular invasion. Patients in group 1 were more likely to have had a mastectomy compared with patients in group 2 ($P < 0.001$), but there were no differences between the groups with respect to use of adjuvant endocrine therapy. Group 1 patients were significantly more likely to have received chemotherapy, including neoadjuvant chemotherapy ($P = 0.002$), and were more likely to have had macrometastatic SLN disease versus micrometastatic disease ($P = 0.001$). Patients in group 1 were less likely to have received axillary-specific radiation therapy, but this was not statistically significant. The characteristics of the two groups are summarized in Table 1.

The median follow-up for group 1 was 69 (range 6–147) months, and the median follow-up for group 2 was 73 (range 15–134) months. During the follow-up period for group 1, 20 women (10 %) experienced recurrence: there were 7 in-breast recurrences, 4 regional nodal recurrences, and 14 distant recurrences. Five women in group 1 (2 %) died of breast cancer and six women (3 %) died of non-breast cancer causes. The median time to a breast cancer-related event (recurrence or death) was 24 (range 2–83) months. During the follow-up period for group 2, 10 women (14 %) experienced recurrence: there were 3 in-breast recurrences, 0 regional nodal recurrences, and 9 distant recurrences. Three women (4 %) in group 1 died of their disease and three (4 %) died of other causes. The median time to a breast cancer-related event in group 2 was 38 (range 13–100) months. The number of breast cancer recurrences and deaths did not differ significantly between the two groups ($P > 0.05$ for each), and these follow-up data are summarized in Table 2. Figure 1 illustrates the disease-free survival curves of the two groups ($P = 0.387$).

Of the 20 women in group 1 who experienced any recurrence, 5 had axillary radiation, 5 did not, and data were unknown for 10. Of the four women in group 1 who had an axillary recurrence, two had axillary-specific radiation, one did not, and data were unknown for one. Ten (50 %) of the women who recurred were ER negative. Five of the women in group 1 who experienced a recurrence were Her-2neu-amplified (25 %). Receptor status was

unknown for one of the women who recurred. Of the 10 women in group 2 who experienced any recurrence, 4 had axillary-specific radiation, 2 did not, and data were unknown for 4. None of these recurrences were in axillary nodes. Five of these 10 women were ER negative (50 %). Two of the 10 were Her-2neu-amplified (20 %).

The effects of demographic and clinical factors on recurrence-free survival were also evaluated in the whole sample (Table 3). On univariate analysis, ER negativity, PR negativity, higher tumor grade, and lymphovascular invasion were associated with recurrence (*P* <0.05 for each). Patient age, race, tumor size, histology, Her-2neu status, and type of surgical therapy (mastectomy versus BCT) were not associated with recurrence (*P* >0.05 for each). Use of axillary-specific radiation therapy was included in this final analysis, but data were unknown for a significant number of patients in both groups and therefore no significant conclusion can be drawn regarding its effect on recurrence. After backward selection, ER negativity and lymphovascular invasion were included in multivariate analysis. Both remained predictors of recurrence; the effect of ER negativity was significant (*P* <0.0001), and the presence of lymphovascular invasion approached significance (*P* = 0.051). The between-group differences remained insignificant (*P* = 0.643) after adjusting for ER status and lymphovascular invasion; women in whom CALND was omitted were not likelier to experience recurrence.

DISCUSSION

SLN biopsy has supplanted CALND for axillary staging in clinically node-negative breast cancer patients. Current American Society of Clinical Oncology guidelines recommend proceeding with CALND when tumor deposits greater than 0.2 mm are identified within the SLN.[1] It has been assumed that CALND provides better disease control, and better local control has been shown to improve survival.[13–20] More recent studies, however, have questioned the disease control advantage of CALND, especially in the setting of effective systemic therapy.[6–10,21]

This past year, the American College of Surgeons Oncology Group published results of the Z0011 trial, and recommendations regarding use of CALND in this setting are changing as a result of this study.[22] The Z0011 trial was a prospective, randomized noninferiority trial that compared CALND with no CALND in women with positive SLNs. Eligible patients were women with early-stage disease (tumor size <5 cm, clinically node negative) who were found to have SLN disease. All patients were treated with lumpectomy, and all were expected to receive whole-breast radiation therapy. Women with three or more positive SLNs, with extranodal extension, with matted nodes, or who underwent neoadjuvant systemic therapy were excluded. Women were randomized to CALND or to no CALND and were stratified by age, tumor size, and ER status. Systemic therapy was determined by the treating physicians. The study was expected to accrue 1,900 patients but closed early to due poor enrollment and due to a very low number of deaths. Altogether, 891 patients were included in the analysis. Median follow-up was 6.3 years. Almost 90 % of the women in both cohorts did receive standard whole-breast radiation therapy. Of note, over 95 % of the women in Z0011 received adjuvant systemic therapy. Overall survival, disease-free survival, and local–regional recurrence rates did not differ significantly between the two groups.[11,12]

The authors did comment that their data apply specifically to women meeting the Z0011 inclusion criteria, and therefore should not be extrapolated to women treated with mastectomy or neoadjuvant systemic therapy, women in whom adjuvant radiation is omitted, and women undergoing partial-breast radiation.[12] National Comprehensive Cancer Network guidelines reflect these exclusions.[22] Our study included a significant number of women who would have been excluded from Z0011; for instance, a significant proportion of our patients underwent mastectomy (52 % of group 1 patients and 26 % of group 2 patients). As discussed above, the type of breast surgery (mastectomy versus BCT) did not significantly affect disease recurrence. Our study also included a significant minority of patients treated with neoadjuvant chemotherapy or endocrine therapy (18 % of group 1 patients and 9 % of group 2 patients). Women in both groups who recurred were more likely to have had adjuvant or neoadjuvant chemotherapy when compared with women who did not recur, likely reflecting more aggressive or advanced disease. Overall, however, only five patients in group 1 and two patients in group 2 treated with neoadjuvant chemotherapy recurred, and given these small numbers, no meaningful statistical analysis could be performed to evaluate the effect of neoadjuvant chemotherapy on recurrence. No recurrences were seen with neoadjuvant endocrine therapy in either group. Women in Z0011 were expected to receive whole-breast radiation, which typically includes the low axilla and which may therefore add local control benefit. In our study, women in group 2 were more likely to have received axillary-specific radiation, but this was not statistically significant, and no differences in axillary radiation rates were seen within the groups between women who did and did not recur. As discussed above, the large proportion of women with unknown axillary radiation status prohibited a strong conclusion regarding the effect of radiation on recurrence. In addition, because there were no axillary recurrences in group 2, it is impossible to comment on whether axillary radiation can substitute for CALND for regional disease control.

In our study, only ER negativity predicted for axillary recurrence on univariate and multivariate analysis. The proportion of our cohort with ER-negative disease was similar to that seen in Z0011, but ER negativity was only a predictor of recurrence in Z0011 on univariate, and not multivariate, analysis.[11] In other series reporting on outcomes for SLN-positive patients in whom CALND was omitted, recurrence events were infrequent and little comment could be made on the impact of ER status. Pepels et al. reported a significantly higher risk of regional recurrence with hormone receptor negativity, but the authors commented that the majority of their patients did not receive systemic therapy, and a significant proportion underwent mastectomy (and therefore did not have whole-breast radiation therapy).[23] When we controlled for ER status, no significant difference in recurrence was seen between our two groups; recurrence in ER-negative women seems more attributable to disease biology than to omission of surgical therapy.

Our study has several limitations. First, it is a retrospective review. We do not know why the 70 women in group 2 did not undergo CALND, but they were older, had less SLN disease, were more likely to have had BCT, and were less likely to have received chemotherapy. Although not statistically significant, they had smaller tumors. This suggests selection bias and that group 2 patients had more favorable prognosis compared with group 1. Second, we were unable to find documentation regarding the use of axillary-specific radiation for a

significant number of patients. Therefore, we cannot comment on whether nodal radiation had a significant effect on recurrence, specifically for women in group 2; axillary radiation is often used as a replacement therapy when CALND is omitted.[24–26] Third, our follow-up period is similar to Z0011. For the majority of women who are ER positive and who would have been prescribed antiestrogen therapy, many would have only recently completed that therapy; it is possible that longer-term follow-up may reveal higher recurrence rates.

Despite these limitations, our study demonstrates no axillary recurrences at a median follow-up of 73 months in women with a positive SLN who did not undergo CALND. Our findings are similar to those of other studies reporting low axillary recurrence rates when CALND is omitted despite the presence of SLN disease, as summarized in Table 4. These studies, and ours, support the idea that CALND is of limited value for local control. In fact, women in whom CALND was omitted were not significantly more likely to experience recurrence at any site and did not have higher disease-specific mortality. Increased recurrence risk is instead seen with higher grade, ER and PR negativity, and lymphovascular invasion, suggesting that tumor biology more than surgical therapy is a predictor of recurrence. Future studies should include women not meeting the inclusion criteria for Z0011; if biology and adequate systemic therapy are more important than surgical therapy for decreasing disease-related mortality, then CALND would likely provide little advantage to women undergoing mastectomy, partial-breast radiation, and neo-adjuvant therapy. Longer-term data are also needed to prove that these results are consistent with time, especially for women with ER-positive disease who are maintained on antiestrogen therapy for 5 years posttreatment.

Acknowledgments

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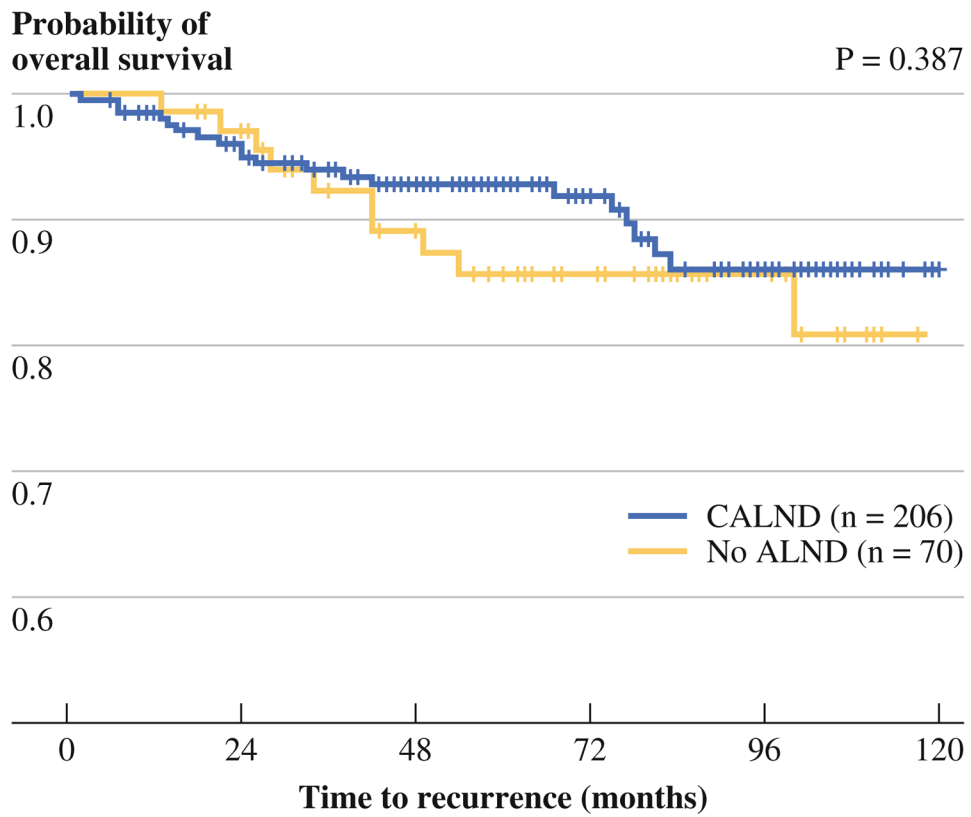
Probability of overall survival

P = 0.387

FIG. 1.

Kaplan–Meier curves of recurrence-free survival for women undergoing completion axillary lymph node dissection (CALND) compared with women in whom CALND was omitted. Vertical bars in each curve represent distribution of censored cases in the corresponding group. Curves are based on univariate analysis

TABLE 1

Patient and tumor characteristics for group 1 (CALND after SLN biopsy) and group 2 (no CALND after SLN biopsy)

Variable	Group 1 (*n* = 206), *n* (%)	Group 2 (*n* = 70), *n* (%)	*P* Value
Age			0.016
Range, years	20–89	31–86	
Median, years	51	57	
Mean, years	53.2	57.7	
Race			0.569
White	158 (77)	51 (73)	
Black	43 (21)	16 (23)	
Other	5 (2)	3 (4)	
Tumor size			0.062
Tis	1 (0)	1 (1)	
T1	122 (59)	50 (71)	
T2	73 (35)	19 (27)	
T3	9 (4)	0	
T4	1 (0)	0	
TX	0 (0)	0	
Tumor histology			0.483
Ductal	156 (76)	58 (83)	
Lobular	26 (13)	5 (7)	
Other/mixed	23 (11)	7 (10)	
Unknown	1 (0)	0	
ER status			0.856
Positive	169 (82)	57 (81)	
Negative	35 (17)	13 (19)	
Unknown	2 (1)	0	
PR status			0.656
Positive	139 (67)	45 (64)	
Negative	64 (31)	24 (34)	
Unknown	3 (1)	1 (1)	
Her-2neu status			0.497
Amplified	40 (19)	17 (24)	
Nonamplified	160 (78)	53 (76)	
Unknown	6 (3)	0	
Tumor grade			0.937
I	55 (27)	21 (30)	
II	89 (43)	30 (43)	
III	57 (28)	19 (27)	
Unknown	5 (2)	0	
Lymphovascular invasion			0.195

Variable	Group 1 ($n = 206$), n (%)	Group 2 ($n = 70$), n (%)	P Value
Present	45 (22)	21 (30)	
Absent/unknown	161 (78)	49 (70)	
Micrometastatic SLN			0.001
Yes	47 (23)	31 (44)	
No	159 (77)	39 (56)	
Surgical therapy			<0.001
Breast conservation	98 (48)	52 (74)	
Mastectomy	108 (52)	18 (26)	
Chemotherapy			0.002
Yes, adjuvant	134 (65)	47 (67)	
Yes, neoadjuvant	35 (17)	4 (6)	
No	22 (11)	18 (26)	
Unknown	15 (7)	1 (1)	
Endocrine therapy			0.207
Yes, adjuvant	150 (73)	50 (71)	
Yes, neoadjuvant	2 (1)	2 (3)	
No	7 (3)	0	
Unknown	18 (9)	5 (7)	
Not indicated (ER negative)[a]	29 (14)	13 (19)	
Axillary radiation therapy			0.151
Yes	50 (24)	27 (39)	
No	56 (27)	17 (24)	
Unknown	100 (49)	26 (37)	

CALND completion axillary lymph node dissection, *SLN* sentinel lymph node, *ER* estrogen receptor, *PR* progesterone receptor

[a] Some women with tumors categorized as ER− were sometimes considered weakly ER+ by the oncologists and were given endocrine therapy

TABLE 2

Subsequent events and follow-up of group 1 (CALND after SLN biopsy) and group 2 (no CALND after SLN biopsy)

	Group 1 (*n* = 206) *n* (%)	Group 2 (*n* = 70) *n* (%)	*P* Value
Follow-up period			0.349
Range in months	6–147	15–123	
Median in months	69	73	
Mean in months	69.9	73.5	
Breast cancer recurrence			
In-breast recurrence, number of events (events/*n*, %)	7 (4)	3 (4)	0.718
Regional nodal recurrence, number of events (events/*n*, %)	4 (2)	0	0.575
Distant recurrence, number of events (events/*n*, %)	14 (7)	9 (13)	0.133
All cancer recurrences together	20 (10)	10 (14)	0.276
Deaths			
Breast cancer-related deaths (deaths/*n*, %)	5 (2)	3 (4)	0.422
Breast cancer-related hospice or unknown living status (events/*n*, %)	0	2(3)	0.064
Non-breast cancer deaths (deaths/*n*, %)	6 (3)	3 (4)	0.697
Total deaths, all causes	10 (5)	6 (9)	0.248

Some patients had more than one subsequent event (breast/chest wall, nodal, or distant recurrence or death) and therefore count multiple times in this table

TABLE 3

Hazard ratios (HR) and 95 % confidence intervals (CI) for the effects of listed variables on recurrence-free survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Group				
No CALND vs. CALND	1.40 (0.65–2.99)	0.387	1.20 (0.55–2.62)	0.643
Age				
Per 1-year increase	0.97 (0.94–1.00)	0.089		
Race				
Black vs. White	1.23 (0.52–2.89)	0.639		
Other vs. White	2.47 (0.58–10.6)	0.221		
Tumor size				
T2–4 vs. T1	1.83 (0.89–3.74)	0.098		
Tumor histology				
Lobular vs. ductal	0.25 (0.03–1.86)	0.177		
Others vs. ductal	0.22 (0.03–1.63)	0.139		
ER status				
Positive vs. negative	0.19 (0.09–0.40)	<0.0001	0.20 (0.10–0.41)	<0.0001
PR status				
Positive vs. negative	0.26 (0.12–0.56)	0.0005		
Her-2neu status				
Amplified vs. not	1.34 (0.60–3.04)	0.478		
Tumor grade				
Grade II vs. grade I	7.85 (1.02–60.30)	0.048		
Grade III vs. grade I	19.70 (2.62–147.94)	0.004		
Lymphovascular invasion				
Present vs. absent	2.13 (1.02–4.42)	0.043	2.11 (1.00–4.47)	0.051
Micrometastatic SLN				
Micro- vs. macrometastatic	0.66 (0.27–1.60)	0.353		
Surgical therapy				
Mastectomy vs. BCT	1.49 (0.73–3.06)	0.276		
Axillary radiation therapy				
Yes vs. no	1.63 (0.59–4.47)	0.347		

CALND completion axillary lymph node dissection, *ER* estrogen receptor, *PR* progesterone receptor, *SLN* sentinel lymph node, *BCT* breast-conservation therapy

TABLE 4

Summary of studies reporting axillary recurrence rates when axillary lymph node dissection is omitted despite the presence of sentinel lymph node metastasis[6,8–11,21,23,27–30]

Author	Years	N	Micro- or macrometastatic sentinel node disease	Axillary recurrence rate (%)	Median follow-up (months)
Fant	2003	31	Both[a]	0	30
Hwang	2007	196	Both[a]	0	29.5
Jeruss	2005	73	Both	0	27.6
Naik	2004	210	Both[a]	1.4	31
Giuliano	2011	891	Both	0.9	75
Bilimoria	2009	20,217	Both	1	63
Yi	2010	2,185	Both	0.2[b]	50
Milgrom	2012	234	Both	1.5–2.5[c]	57.8
Pepels	2012	141	Micrometastatic	5.6	61
Rayhanabad	2010	33	Micrometastatic	1.6	70
Yegiyants	2010	47	Both	4.3	82

[a] Studies included sentinel node metastases identified with immunohistochemistry

[b] Axillary recurrence was inferred from "ipsilateral regional events," as described in the Surveillance, Epidemiology, and End Results (SEER) database

[c] Breast conservation was associated with a regional recurrence rate of 1.5 %; mastectomy was associated with a regional recurrence rate of 2.5 %