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Axillary Dissection *vs*. no Axillary Dissection in Breast Cancer Patients With Positive Sentinel Lymph Node: A Single Institution Experience

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Abstract. *Background/Aim: Axillary surgery of breast cancer patients is undergoing a paradigm shift, as axillary lymph node dissection's (ALND) usefulness is being questioned in the treatment of patients with tumor-positive sentinel lymph node biopsy (SLNB). The aim of this study was to investigate the overall survival (OS) and relapse-free survival (RFS) of patients with positive SLNB treated with ALND or not. Patients and Methods: We investigated 617 consecutive patients with cN0 operable breast cancer with positive SLNB undergoing mastectomy or conservative surgery. A total of 406 patients underwent ALND and 211 were managed expectantly. Results: No significant difference in OS and RFS was found between the two groups. The incidence of loco-regional recurrence in the SLNB-only group and the ALND group was low and not significant. Conclusion: The type of breast cancer surgery and the omission of ALND does not improve OS or RSF rate in cases with metastatic SLN.*

Sentinel lymph node biopsy (SLNB) is the standard technique used for nodal staging in all patients with invasive breast cancer and clinically-negative axillary lymph nodes. Nowadays, SLNB has replaced conventional axillary lymph node dissection (ALND) as a standard procedure (1-4). For years, axillary dissection was considered the standard procedure in cases with positive SLNB for macrometastasis (>2 mm) (5-6).

The rationale behind this procedure is the control of local recurrence and the increase of overall survival (OS). However, several authors have questioned the actual role of ALND in cases with positive SLNB. This procedure can lead to severe side effects such as lymphedema and reduction of limb and/or shoulder function in 5-39% of cases (7-9).

The American College of Surgeons Oncology Groups (ACOSOG) Z0011 Study showed that there was no statistically significant difference in local recurrence-free survival patients undergoing breast-conserving surgery and avoiding ALND at 6.3 years and at 9.25 years of follow-up compared with patients treated with ALND (10-12). Similar results were observed in the AMAROS trial (13) and in the IBCSG 23-01 trial (14). A recent meta-analysis that included the above-mentioned trials (ACOSOG Z011, IBCSG 23-01, AMAROS) and two other studies (OTOSAOR and AATRM-048-13-2000) did not show differences in survival or recurrence between ALND, SLNB or axillary RT, observing more local complications in patients treated with ALND (15). Bilimoira *et al*. (16) reviewed 20,075 SLNB-positive breast cancer patients from the National Cancer Database and Yi *et al*. (17) reviewed 26,986 SLNB-positive breast cancer patients from the surveillance, epidemiology and end results (SEER) database: both Authors did not show any significant differences in OS rates between patients treated with SLNB only and SLNB plus ALND. However,

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Key Words: Axillary surgery, breast cancer, sentinel lymph node biopsy, mastectomy, breast conservative surgery, local recurrence.

Table I. *Characteristics of 617 patients with operable breast cancer and positive sentinel lymph node positive divided into axillary dissection (ALND) and sentinel lymph node biopsy (SLNB) only.*

Characteristic	SLNB only (n=211)	ALND (N=406)	*p*-Value
Age, year, median (standard deviation)	57 (±11.5)	54 (±11.5)	0.09
Tumor size, mm, median (standard deviation)	19 (±7.9)	22 (±10.2)	0.07
Pathologic T stage			0.08
T1	118 (56%)	211 (52%)	
T2	82 (43%)	189 (46%)	
T3	1 (1%)	6 (2%)	
SLN metastasis			0.01
Micrometastasis (<2 mm)	115 (54.5%)	84 (20.6%)	
Macrometastasis (>2 mm)	95 (45.5%)	322 (79.4%)	
SLN metastasis size, mm median (standard deviation)	2.2 (±2.6)	4.3 (±5.4)	<0.001
Number of positive lymph nodes in axillary dissection			
0	N.A.	217 (53%)	
1-3	N.A.	134 (33%)	
>4	N.A.	55 (14%)	
Histology			0.269
Ductal	161 (76%)	287 (71%)	
Lobular	30 (15%)	82 (20%)	
Special type	20 (9%)	37 (9%)	
Grade			0.01
G1	60 (29%)	42 (20%)	
G2	104 (49%)	205 (51%)	
G3	47 (22%)	159 (39%)	
LVI			<0.001
Yes	94 (55%)	292 (72%)	
No	117 (45%)	114 (28%)	
ER			0.446
Positive	190 (90%)	352 (87%)	
Negative	21 (10%)	54 (13%)	
PgR			0.769
Positive	175 (83%)	352 (87%)	
Negative	36 (10%)	54 (13%)	
HER2-neu			0.01
Positive	26 (12%)	72 (26%)	
Negative	154 (73%)	235 (58%)	
Unknown	31 (15%)	99 (16%)	
Adjuvant chemotherapy			<0.001
Yes	85 (40%)	321 (78%)	
No	126 (60%)	85 (12%)	
Adjuvant hormonotherapy			0.487
Yes	187 (87%)	346 (84%)	
No	24 (13%)	60 (16%)	
Adjuvant radiotherapy			0.461
Yes	169 (80%)	335 (81%)	
No	42 (20%)	71 (19%)	
Surgery			0.763
Conservative	176 (83%)	337 (83%)	
Mastectomy	35 (17%)	69 (17%)	

ER: Estrogen receptor; PgR: progesterone receptor. LVI: lymphovascular invasion; N.A.: not available.

proposing ALND only in selected cases is still a matter of debate. The purpose of this retrospective study was to evaluate the overall survival (OS) and relapse free-survival (RFS) of patients with positive SLNB treated with ALND or not, and the impact of the type of breast surgery (mastectomy or conservative surgery).

Patients and Methods

From our institutional database, 2,329 consecutive women with invasive breast cancer treated with conservative surgery or mastectomy and SLNB from December 2004 to October 2014 were retrospectively identified. Patients who had neoadjuvant treatment

or previous axillary surgery were excluded. In 629 cases SLN was metastatic. Twelve patients lost to follow-up were excluded, leaving 617 cases. ALND was performed in 406 patients (ALND group) and 211 were managed expectantly (SLNB only group).

Primary tumor specific variables included: pathological tumor size, histological and nuclear grade, histological type (ductal, lobular, special type), estrogen and progesterone receptor status (ER, PgR), human epidermal growth factor receptor 2 (HER-2) status, presence of lymphovascular invasion (LVI) and SLN metastasis size. We also considered the type of breast surgery (conservative surgery or mastectomy) and adjuvant treatments (hormone therapy, chemotherapy and/or radiotherapy).

In the ALND group, 69 mastectomies and 337 conservative breast surgery interventions were performed, while in the SLNB only group 35 patients underwent mastectomy and 176 conservative breast surgery. In this cohort of patients, SLN was identified with lymphoscintigraphy (using 99mTc-labeled sulphide colloid); in the case of failure, SLN was identified with a peritumoral or periareolar injection of 2 to 5 ml vital dye (Patent blue V). In cases with negative SLN on frozen section, the SLN was examined on multiple sections stained with hematoxylin eosin and analysed by immunohistochemistry with anti-cytokeratin AE1/3 antibodies. A dedicated breast pathologist (AR) analyzed all cases (tumors histology and SLN).

For the first 5-year follow-up period, outpatient visits took place every 6 months, while from the 6th to the 10th year annually. A mammography and ultrasound breast examination were performed annually and, in case of suspicion of recurrence, further diagnostic tests were performed (abdominal/chest computed tomography, bone scan and/or positron emission tomography as appropriate). Disease status or cause of death was ascertained from clinical findings, phone follow-up or using Cancer Registry data of our Region (Piedmont Cancer Registry, Centre for Epidemiology and Prevention in Oncology in Piedmont, Turin, Italy). Overall the median follow-up was 84.4 months, for the ALND group was 90 months and for the SLNB only group was 74 months.

Statistical analysis. IBM® SPSS® v.23 (SPSS Inc. Chicago, IL, USA) software was used to conduct the statistical analyses. We analyzed the differences between ALND Group and SLNB only Group using Pearson's chi square test or Fisher's exact test for categorical variables; while numerical variables were compared with variance analysis (ANOVA). Survival and cumulative risk of recurrence for each of these groups were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression was used for multivariate analysis. Variables included in the multivariate analysis were those found to be statistically significant in the univariate analyses. All reported values are two sided, and $p<0.05$ was considered statistically significant.

Results

Patient and disease characteristics and postoperative treatments of both groups are summarized in Table I. The ALND group, compared with the SLNB only group, had more macrometastasis (79.9% *vs*. 45.5%, $p<0.01$), larger SLN metastasis size (4.3 mm *vs*. 2.2 mm, $p<0.001$), more positive LVI (72% *vs*. 55%, $p<0.001$), higher histological grade (G3) (39% *vs*. 22%, $p<0.01$) and more HER2-neu overexpression (26% *vs*. 12%, $p<0.001$). However, no significant differences between the two groups in median age, media tumor size, pathologic T stage, histotype and hormonal receptor status were seen. The distribution of the type of breast surgery (mastectomy or conservative surgery) does not differ statistically between the two groups. More patients in the ALND group received chemotherapy (78% *vs*. 37%, $p<0.001$), whereas there were no differences in the use of adjuvant hormone therapy and radiotherapy. Furthermore, we did not observe significant differences in loco-regional recurrences, onset of contralateral breast disease and cancer related deaths, while there were more distant metastases in the ALND group (Table II). In 217 cases of the ALND group (53.4%) SLN was the only node involving metastasis. The median follow-up was 84.4 months. OS was 87.8% in the ALND group and 94.8% in the SLNB only group (with a non-significant difference, log rank $p=0.07$; Figure 1A).

Table II. *Events in 617 patients with operable breast cancer and positive SLNB*.

Events	SLNB only (n=211)	ALND (N=406)	*p*-Value
Ipsilateral breast tumor recurrence	9 (4.2%)	8 (1.9%)	0.08
Ipsilateral axillary disease	3 (1.4%)	1 (0.2%)	0.12
Contralateral breast cancer	3 (1.4%)	6 (1.5%)	0.84
Distant metastasis	19 (9.0%)	62 (15.2%)	0.03
Died for disease	11 (5.2%)	50 (12.3%)	0.07
Died for other causes	4 (1.9%)	7 (1.7%)	0.09

The univariate analysis (Table III) showed that tumor size, SLN metastasis size, LVI, negative PgR and ER, positive HER2-neu, high grade (G3), lobular histotype compared with ductal histotype and the omission of hormonal therapy are related to worse OS, while in the multivariate analysis LVI, negative PgR and histology were not related with OS.

The relapse-free survival rate (RFS) (loco-regional and distant combined) was 82.3% in the ALND group and 87.1% in the SLNB only group (not significant, log rank $p=0.51$) (Figure 1B).

By analysing only distant metastasis, we obtained an 84.7% RFS rate in the ALND group and 90.9% RFS rate in the SLNB only group (log rank $p=0.14$). No difference was found in loco-regional RFS rate between the ALND group and the SLNB only group (respectively 98% and 95.7%, log rank $p=0.06$).

Using Cox regression model, tumor size, SLN metastasis size, LVI, negative PgR and ER, positive HER2-neu, high grade (G3), ductal histotype *vs*. lobular and special types were able to predict recurrence of breast cancer. The multivariate analysis confirmed all predictors except histotype

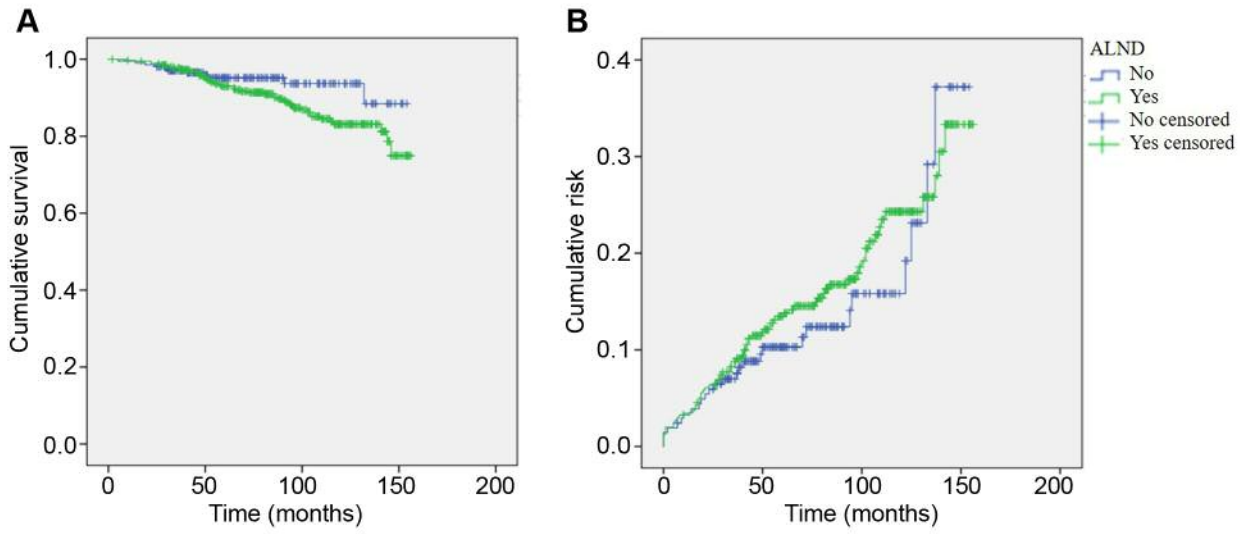

Figure 1. *Overall survival and cumulative risk of recurrence of pN1 patients with ALND versus patients with no ALND. A) Breast cancer survival (p=0.07). B) Cumulative risk of recurrence (p=0.43). ALND: Axillary lymph node dissection.*

and negative PgR. The same predictors at multivariate analysis could be observed for OS except for SLN metastasis size and LVI.

Discussion

The main goal of this study was to compare the OS and RSF of patients with positive SLNB treated with ALND compared to patients treated with SLNB only. This is a retrospective study subject to selection bias: in 211 patients (SLNB only group) axillary dissection was omitted because they had less tumor burden in SLN and were less likely to receive chemotherapy than ALND group. However, differences in the biological characteristics of tumors between the two groups are present in some previous non randomized clinical trials studies (18-20), which analyzed the differences in OS and recurrence between patients with positive SLNB who underwent axillary dissection or not. Despite the retrospective nature of this study, the axillary recurrence rate of 1.4% (3 cases) in our series, is comparable to the one reported in RCTs (10-14) in patients without palpable axillary lymph nodes and positive SLNB that did not undergo ALND. Moreover, we did not find any statistical differences between the two groups concerning the ipsilateral breast recurrence (1.9% in AND group *vs*. 4.2% in SLNB only group) in support of the limited therapeutic efficacy of axillary dissection on the loco-regional control. We found more distant metastasis in the ALND group compared to the SLNB only group, but without having a significant impact on RFS (log rank p=0.14); the higher number of events can be explained by a selection bias in the ALND group (more patients with worst biological prognostic factors than in the SNB only group). In the ALND group, SLN was the only metastatic lymph node in over half of cases. A similar trend was reported in the meta-analysis of Kim (21), where 47% of cases with ALND had no further metastases in the lymph nodes removed. Therefore, about 50% of patients received a useless procedure. We also investigated the potential impact of the type of breast surgery on OS and RFS. Currently, OS and RFS data on mastectomies are derived from retrospective studies: Fu *et al*. (22) compared 214 patients pN1 treated by mastectomy with SLNB plus RT *versus* ALND and did not observe any significant differences in terms of OS and RFS; similar findings were observed in a study by Snow et al (23) with no significant differences in OS and RFS after 10-years of follow-up. Furthermore, similar results were obtained by Fitz Sullivan *et al*. (24) in a retrospective study of 525 patients with invasive breast cancer and positive SLNB treated with mastectomy. Our results confirmed this trend. In April 2014, Roozendaal *et al*. (25) registered a non-inferiority randomized controlled trial (BOOG 2013-7) to study and clarify the impact of ALND on OS and RFS in patients with T1-2 N0 breast cancer treated with mastectomy, who also had a maximum of three SLNs containing micro and/or macrometastases. The only adjuvant therapy playing a significant role on OS and RFS is hormone therapy, probably due to the worse prognosis of tumors with negative hormone receptors. At multivariate analysis, the biological features were significant independent predictors of poorer OS and RFS, suggesting that tumor biology, rather than type of axillary and breast surgery, is predictive for the prognosis. In conclusion, our results support the omission of ALND in patients with positive SLNB, as no significant benefit in terms of OS and

Table III. *Cox regression analysis of treatments and biological tumor characteristics on recurrence and breast cancer death.*

Characteristic	Any Recurrence				Breast cancer death			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (per year)	0.99 (0.97-1.00)	0.13			0.98 (0.95-1.04)	0.12		
Tumor size	1.05 (1.03-1.06)	<0.001*	1.03 (1.01-1.05)	<0.001*	1.01 (1.02-1.05)	<0.001*	1.04 (1.02-1.06)	<0.001*
SLN metastasis size	1.07 (1.04-1.11)	<0.001*	1.04 (1.01-1.07)	0.001*	1.08 (0.96-1.20)	0.36		
Axillary dissection								
Yes	1.00				1.00			
No	0.86 (0.55-1.34)	0.51			0.55 (0.29-1.06)	0.07		
Adjuvant chemotherapy								
Yes	1.00				1.00			
No	1.25 (0.80-1.96)	0.33			1.48 (0.79-2.66)	0.22		
Adjuvant radiotherapy								
Yes	1.00				1.00			
No	1.59 (0.91-2.50)	0.10			0.97 (0.46-2.05)	0.94		
Adjuvant hormonotherapy								
Yes	1.00		1.00		1.00		1.00	
No	2.92 (1.36-4.32)	0.003*	6.62 (2.36-18.50)	<0.001*	2.19 (1.35-3.56)	0.002*	7.31 (1.82-28.36)	<0.05*
Breast surgery								
Mastectomy	1.00				1.00			
Conservative	1.82 (0.92-2.94)	0.06			1.64 (0.87-3.11)	0.13		
ER								
Positive	1.00		1.00		1.00		1.00	
Negative	2.02 (1.36-3.02)	<0.001*	5.05 (1.95-13.1)	<0.001*	2.02 (1.36-3.02)	0.01*	3.78 (1.07-13.4)	0.03*
PgR								
Positive	1.00		1.00		1.00		1.00	
Negative	1.96 (1.30-2.80)	<0.001*	1.63 (0.83-3.20)	0.15	1.90 (1.35-3.18)	0.01*	1.51 (0.69-13.4)	0.563
HER2-neu								
Negative	1.00		1.00		1.00		1.00	
Positive	2.02 (1.36-3.02)	<0.03*	1.19 (1.30-2.91)	0.02*	3.94 (1.78-8.75)	<0.001*	3.60 (1.72-7.79)	<0.001*
LVI								
No	1.00		1.00		1.00		1.00	
Yes	2.54 (1.37-4.72)	<0.001*	2.67 (1.25-5.70)	0.01*	3.87 (1.84-8.15)	<0.001*	1.79 (0.74-4.32)	0.19
Grade								
G1	1.00		1.00		1.00		1.00	
G2	2.04 (0.85-4.76)	0.10			1.47 (0.50-4.42)	0.46		
G3	5.34 (2.30-12.4)	<0.001*	4.9 (2.19-11.3)	<0.001*	5.34 (2.30-12.4)	<0.001*	5.31 (2.35-12.4)	<0.001*
Histology								
Ductal	1.00		1.00		1.00		1.00	
Lobular	0.43 (0.23-0.80)	0.02*	0.23 (0.65-1.46)	0.34	0.50 (0.25-1.01)	0.18	1.20 (0.22-3.52)	0.20
Special type	0.45 (0.26-0.79)	0.02*	1.03 (0.56-1.89)	0.73	0.46 (0.38-0.79)	0.03*	1.49 (0.50-4.40)	0.47

HR: Hazard ratio; CI: confidence interval; ER: estrogen receptor; PgR: progesterone receptor; LVI: lymphovascular invasion. *Statistically significant.

RFS was found, especially for loco-regional control of the disease. This procedure should be reserved for high-risk patients or in case of clinical metastatic axillary sentinel lymph node (higher tumor burden in SLN is related to worst prognosis) (24). Results from this study confirm what has been previously reported by several other studies (including RCTs), suggesting that most patients with invasive breast cancer and metastatic SLN do not benefit from ALND. Indeed, biological prognostic factors and adequate systemic therapy are probably more important than the type of breast and axillary surgery to reduce disease mortality and the recurrence rate. Further studies are required to identify positive SLNB patients who can benefit from ALND, in order to reduce the number of patients undergoing axillary surgery, a procedure with serious comorbidities that increase operative times and health system costs.

Conflicts of Interest

The Authors indicate no potential conflict of interest regarding this study.

Authors' Contributions

Study conceptions and design: RA, FB, CB, DK. Acquisition of data: RB, MP, AD, MB, CD, SD. Analysis and interpretation of data: RA, FB, RB, MP, AD, MB, CD, SD. Drafting of manuscript: RA, FB, DK. Critical revision: all Authors.

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