



Is Sentinel Lymph Node Biopsy Alone Accurate for Breast Cancer Mastectomy? Results of a Cohort Study of 2,423 Patients

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Abstract

Background: Few patients with mastectomy and pN0(i+) or pN1mi Sentinel Node (SN) were included in randomized trial. To demonstrate SN biopsy accuracy for mastectomy.

Methods: We examined results of SN among a multi-institutional cohort of patients, <=cT2-N0, who required total mastectomy, according to SN-status and complementary Axillary-Lymph-Node-Dissection (cALND) or not. We have analyzed involved Non-Sentinel-Node (NSN) rate at cALND, overall (OS) and Disease-Free Survival (DFS).

Results: Among 2,423 patients we reported 1307 pN0(i-)SN, 120 pN0(i+)SN, 273 pN1mi SN and 723 pN1-macro-metastases-SN with cALND respectively in 24.5%, 73.3%, 82.4% and 93.1%. Median follow-up was 42.72 months.

Among 320 patients with pN0(i-)SN we observed 35 NSN-macro-metastases (10.9%) and among 723 patients with SN-macro-metastases, cALND was omitted in 50 patients (6.9%): In multivariate analysis, OS and DFS were not significantly different according to cALND or not.

Among 120 patients with pN0(i+)SN and 273 with pN1miSN, cALND were respectively omitted in 32 and 48 patients: Age, pT-size and SN-status were predictive of NSN-involvement. In multivariate analysis, post-mastectomy radiotherapy, regional nodal irradiation and adjuvant chemotherapy were significantly correlated to cALND and a significant lesser DFS rate was reported for patients without cALND (HR: 3.351, p: 0.004).

Conclusion: SN biopsy appeared as an accurate procedure for axillary staging of breast cancer mastectomy for pN0-SN status. For pN1-macro-metastases it is not possible to propose to avoid cALND. When SN was involved by pN0(i+) or micro-metastases, omission of cALND is still controversial and should have a negative prognosis impact in relation with a down staging and under treatment.

Keywords: Sentinel Node; Breast Cancer; Mastectomy

Background

A decrease of Axillary Lymph Node Dissection (ALND) rate since the development and validation of Sentinel Lymph Node Biopsy (SLNB) for non-involved Sentinel Node (SN) has been observed. More recently, since results of ACOSOG Z0011, IBCSG 23-01 and AATRM trials complementary ALND (cALND) was questioned in some situations for involved-SN. However, few studies were reported about SLNB accuracy for patients who need total mastectomy [1-4].

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Received Date: 11 Mar 2020

Accepted Date: 01 Apr 2020

Published Date: 03 Apr 2020

Citation:

Houvenaeghel G, Classe JM, Blache G, Mazouni C, Reyal F, Gimbergues P, et al. Is Sentinel Lymph Node Biopsy Alone Accurate for Breast Cancer Mastectomy? Results of a Cohort Study of 2,423 Patients. *Clin Oncol.* 2020; 5: 1689.

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Table 1: Characteristics of patients according to pN status.

	pN final status	pN0		pN0(i+)		pN1mi		pN1 macro		Total		Chi 2
		Nb	%	Nb	%	Nb	%	Nb	%	Nb	%	P
Total		1272	52.5	114	4.7	243	10	794	32.8	2423		
SN alone		987	88.4	32	2.9	48	4.3	50	4.5	1117		
SN+ALND	pN0(i-) sn	285	89.1	0		0		35	10.9	320	24.5	
	pN0(i+) sn	0		82	93.2	0		6	6.8	88	6.7	
	pN1 mi sn	0		0		195	86.7	30	13.3	225	17.2	
	pN1 macro sn	0		0		0		673	100	673	51.5	
age	≤40	101	7.9	23	20.2	32	13.2	82	10.3	238	9.8	<0.001
	40.1-50	317	24.9	29	25.4	60	24.7	262	33	668	27.6	
	50.1-74.9	718	56.4	56	49.1	125	51.4	393	49.5	1292	53.3	
	≥75	136	10.7	6	5.3	26	10.7	57	7.2	225	9.3	
pT mm	0-5	176	14.3	9	8	18	7.5	33	4.3	236	10	<0.001
	>5-10	260	21.2	19	17	30	12.4	53	6.8	362	15.4	
	>10-20	387	31.5	27	24.1	79	32.8	159	20.5	652	27.7	
	21-50	344	28	43	38.4	80	33.2	401	51.7	868	36.8	
	>50	61	5	14	12.5	34	14.1	130	16.8	239	10.1	
Grade	1	351	27.6	20	17.5	70	28.8	147	18.5	588	24.3	<0.001
	2	618	48.6	65	57	116	47.7	427	53.8	1226	50.6	
	3	246	19.3	24	21.1	51	21	213	26.8	534	22	
	Unknown	57	4.5	5	4.4	6	2.4	7	0.9	75	3.1	
LVI	No	950	86.8	69	63.9	135	63.7	350	51.3	1504	71.8	<0.001
	Yes	144	13.2	39	36.1	77	36.3	332	48.7	592	28.2	
	Unknown									327		
ER	Positive	1072	84.3	102	89.5	225	92.6	677	85.3	2076	85.7	<0.001
	Negative	171	13.4	9	7.9	16	6.5	114	14.4	310	12.8	
	Unknown	29	2.3	3	2.6	2	0.8	3	0.4	37	1.5	
Her2	Positive	160	13.7	17	17.5	26	12.7	130	17.8	333	15.1	0.003
	Negative	955	81.8	71	73.2	171	83.8	584	79.9	1781	81	
	Unknown	52	4.5	9	9.3	7	3.4	17	2.3	85	3.9	
Histology	Ductal	925	72.7	76	66.7	176	72.4	576	72.5	1753	72.3	0.001
	Lobular	225	17.7	26	22.8	38	15.6	161	20.3	450	18.6	
	Mixt	26	2	6	5.3	7	2.9	30	3.8	69	2.8	
	Others	96	7.5	6	5.3	22	9.1	27	3.4	151	6.2	
T subtypes	Lum A	775	69.8	54	61.4	134	68	436	61.2	1399	66.3	<0.001
	Lum B HER-	96	8.6	15	17	31	15.7	101	14.2	243	11.5	
	Lum B HER+	90	8.1	10	11.4	18	9.1	69	9.7	187	8.9	
	HER2	70	6.3	7	8	8	4.1	61	8.6	146	6.9	
	TN	80	7.2	2	2.3	6	3	46	6.5	134	6.4	
Chemotherapy	No	762	59.9	49	43	65	26.7	64	8.1	940	38.8	<0.001
	Yes adjuvant	493	38.8	63	55.3	167	68.7	663	83.5	1386	57.2	
	Yes Neoadjuvant	12	0.9	2	1.8	10	4.1	66	8.3	90	3.7	
	Unknown	5	0.4	0		1	0.4	1	0.1	7	0.3	
Endocrine Therapy	No	281	22.2	18	15.8	26	10.8	135	17.1	460	19.1	<0.001
	Yes	985	77.8	95	84.2	214	89.2	654	82.9	1949	80.9	
	Unknown									14		

Trastuzumab	No	1048	90.1	101	88.6	219	90.1	680	86.6	2048	88.9	0.102
	Yes	115	9.9	13	11.4	24	9.9	105	13.4	257	11.1	
	Unknown											
PMRT	No	754	59.4	39	34.2	58	23.9	42	5.3	893	36.9	<0.001
	Yes	514	40.5	75	65.8	185	76.1	752	94.7	1526	63.1	
	Unknown	1	0.1	0		0		0		1		
RNI	No	1000	84.8	57	58.8	104	48.8	77	11.2	1238	56.9	<0.001
	Yes	179	15.2	40	4.3	109	51.2	611	88.8	939	43.1	
	Unknown									246		

Abbreviations: SN: Sntinelnode; ALND: Axillary Lymphnode Dissectio; ER: Endocrine Receptor; LVI: Lymphovascular Invasion; PMRT: Post-Mastectomy Radio Therapy; RNI: Regional Nodal Irradiation

In Z0011 trial [2] patients undergoing up front conservative surgery followed by systemic adjuvant therapy for unifocal Breast Cancer (BC) with 1 or 2 SN involved by micro or macro-metastases, without capsular rupture, were included. Results were discussed concerning the limits and the biases of this study [5,6]. Omission of cALND was held in some teams and recommendations underlining the strict conditions of possible omission of cALND [7,8]. An evaluation in selected patients considered at high-risk was reported [9]. But some points remain unclear, particularly for patients who required total mastectomy. The possibility of cALND avoidance for patients who required total mastectomy is a timely topic. Very few patients with mastectomy were included in randomized trial and only for patients with pN0(i+) or pN1mi SN (86 patients in IBCSG 23-01 trial and 18 in AATRM trial) [3,4]. For this reason we designed the SERC trial to compare outcomes in patients with SN-involvement treated with cALND or no further treatment to the axilla with larger inclusion criteria [10,11].

The primary aim was to examine survival according to SN status and secondary aims were involved Non-Sentinel Node (NSN) rate, Axillary Recurrence (AR) rate among a multi-institutional cohort of patients who required total mastectomy.

Methods

We conducted a retrospective analysis of 2,423 consecutive patients managed between March 1999 and December 2012 in 9 specialized breast centers, referred for mastectomy and SLNB (not included in SERC trial) among a breast cancer data base of 23,145 patients. Total mastectomy was usually proposed to manage multi focal tumors, small invasive BC with a large in situ component, patients with a very small breast volume and patient's choice for total mastectomy.

All patients included in this study have been managed for early BC \leq cT2-N0, without pre-operative treatment before SLNB and total mastectomy. We excluded patients with axillary cN1 or T3-4. SLNB was performed using combined isotopic and colorimetric detection or isotopic detection alone with peri-tumoral and/or sub areolar injection [11]. Although the methods used for SN histological examination were not standardized in the protocol, all sites proceeded similarly: Serial sections were performed every 200 microns and stained with standard HE. The number of sections was six to ten, or pursued until node exhaustion in case of large SN. Additional IHC analysis was done in case of negative results at standard examination. For Lymph Nodes (LN) identified by cALND, routine HE analysis was performed [10,11].

For data analysis, we used:

Five tumor subtypes were defined according to Immunohistochemistry (IHC) analysis of Endocrine Receptors (ER) and Her2: Luminal-A (ER+ Her2- Grade 1-2, Her2 (Her2+ ER-), Triple negative (ER- Her2--: Negative estrogen and progesterone receptors), Luminal-B Her2- Grade 3, Luminal-B Her2+ ER+ 8, 9. ERs (Estrogen receptor and/or progesterone receptor expression) were considered as positive if they were expressed in at least 10% of the tumor specimen. HER2 status was determined according to French guidelines by IHC +/- fluorescent *in situ* hybridization.

Statistical analysis

Four categories of SN-status were defined: negative-SN (pN0(i-)), isolated tumor cells (ITC: pN0(i+) \leq 0.2 mm), detected either by Hematoxylin and Eosin (HE) staining or by cytokeratin IHC, micro-metastases (pN1mi $>$ 0.2 mm and \leq 2 mm), and macro-metastases ($>$ 2 mm) [10,12].

We have analyzed involved Non-Sentinel Node (NSN) rate at cALND and predictive factors of NSN involvement. Then we have evaluated Axillary Recurrence (AR) rate, Overall Survival (OS) and Disease-Free Survival (DFS) according to cALND or not. We used standard descriptive statistics (mean, Standard Deviation (SD), median and range for quantitative variables, count and frequency for categorical variables) to describe patients and tumors characteristics. In univariate analyses, comparisons were performed using Chi Square. Multivariable analysis was performed using binary logistic regression. Survival analysis was performed using log rank test for univariate analysis and Cox model for multivariate analysis. Overall survival was defined as the time elapsed between surgery and death from any cause. Disease-free survival was calculated from the date of surgery to the first date of loco-regional recurrence, distant recurrence or death from any cause, whichever occurred first.

All statistical analyses were conducted using SPSS 16.0. All statistical tests were two-sided. The level of statistical significance was set at a p value of 0.05.

All procedures performed in this study involving human participants were done in accordance with the French ethical standards and with the 2008 Helsinki declaration. This work was approved by our institutional review board (IPC-GSPC).

Results

Population

Among 2,423 patients with SLNB for BC mastectomy we reported 1,307 pN0(i-)SN, 120 pN0(i+)SN, 273 pN1miSN and 723 pN1

Table 2: Characteristics of patients according to sentinel node status and cALND or not.

	SN Status	pN0			pN0(i+)			pN1mi			pN1macro		
		SN+ALND	SN	Chi2	SN+ALND	SN	Chi2	SN+ALND	SN	Chi2	SN+ALND	SN	Chi2
		Nb	Nb	p	Nb	Nb	P	Nb	Nb	P	Nb	Nb	p
pN final	pN0	285	987										
	pN0(i+)				82	32							
	pN1mi							195	48				
	pN1macro	35	0		6	0		30	0				
age	<= 40	20	82	0.218	16	8	0.546	33	5	<0.0001	71	3	<0.0001
	40.1-50	89	239		22	8		62	7		231	10	
	50.1-74.9	184	555		46	13		118	22		328	26	
	>= 75	27	111		4	3		12	14		43	11	
T size	<=5 mm	25	154	<0.0001	7	3	0.238	15	4	0.93	24	4	0.418
	5.1-10	43	219		11	8		27	5		45	4	
	10.1-19.9	87	309		20	7		69	17		135	8	
	20-50	122	239		35	12		81	17		334	28	
	>50 mm	36	29		14	1		31	5		117	6	
Grade	1	66	287	0.001	18	3	0.325	63	10	0.103	131	10	0.935
	2	179	460		47	22		115	23		352	28	
	3	69	189		20	5		43	13		183	12	
	Unknown	6	18		3	2		4	2		7	0	
LVI	No	185	781	<0.0001	48	26	0.017	123	24	0.305	289	28	0.187
	Yes	55	103		34	6		73	18		283	20	
Endocrine	Yes	56	233	0.013	12	6	0.334	23	5	0.581	117	8	0.537
Therapy	No	262	750		76	26		199	43		553	40	
Her2/ER	ER+ Her2-	215	676	0.941	53	21	0.701	148	35	0.436	456	38	0.904
	ER- Her2-	20	63		2	0		6	1		40	2	
	ER- Her2+	16	57		5	2		10	0		52	4	
	ER+ Her2+	21	75		6	4		19	3		54	5	
Chemotherapy	No	140	623	<0.0001	30	19	0.034	48	19	0.025	51	10	0.006
	Yes adjuvant	160	354		55	13		162	29		573	40	
	Neo adjuvant	19	6		3	0		14	0		48	0	
	Unknown	1	4					1	0		0	0	
PMRT	No	95	660	<0.0001	25	15	0.048	42	16	0.023	34	6	0.05
	Yes	225	323		63	17		183	32		639	44	
RNI	No	211	794	<0.0001	41	18	0.128	79	28	0.001	61	6	0.132
	Yes	101	107		35	8		118	14		529	27	

macroSN. cALND has been performed for 1306 patients (53.9%), in 24.5, 73.3, 82.4 and 93.1% for SN pN0(i-), pN0(i+), pN1mi and pN1macro, respectively. Factors associated with pN final status with or without cALND are reported in (Table 1).

Median follow-up was 57.13 months (mean: 59.88%, CI: 95% 58.2 to 61.5% range: 0.26% to 226%). We reported 135 death and 232 recurrences including 164metastases, 26 axillary recurrences, 23 local recurrences and unknown site of recurrence, as first event [19].

pN0(i-) SN status

Among 1307 patients with pN0(i-)SN, 320 underwent an additional ALND, mainly before publication of NSABP B-32 trial results [1]. We observed 35 LN macro metastases at cALND (10.9%)

and false negative rate (FNR) was 3.63% among 964 patients with LN involvement (35/964) at cALND with pathologic results known or at SN.

In binary logistic regression, cALND was significantly associated with grade, LVI, ER, tumor size and periods of treatment. Adjuvant Chemotherapy (AC), Post-Mastectomy Radiotherapy (PMRT) and Regional Nodal Irradiation (RNI) were delivered more frequently for patients with cALND, including 95.4% (21/22) of AC and 97.1% (34/35) of PMRT for patients with involved NSN at cALND (Table 2).

In Cox regression analysis, OS and DFS were not significantly different according to cALND or not (Table 3, 4). AR rates were 1.5% for patients without cALND (14/917) and 0.3% with cALND

Table 3: Overall survival according to sentinel node status: Multivariable analysis.

Overall Survival		pN0 SN			pN0(i+) & pN1mi SN			pN1 macro SN		
		HR	CI 95%	p	HR	CI 95%	P	HR	CI 95%	P
ALND	Yes	1			1			1		
	No	1.007	0.468-2.167	0.987	2.485	0.777-7.947	0.125	0.904	0.325-2.517	0.847
Grade	1	1						1		
	2	0.711	0.305-1.661	0.431				5.128	1.578-16.66	0.007
	3	1.999	0.858-4.655	0.108				8.072	2.372-27.47	0.001
LVI	No	1			1					
	Yes	1.536	0.715-3.301	0.271	1.76	0.664-4.669	0.256			
Endocrine	Yes	1			1			1		
Therapy	No	2.246	1.148-4.395	0.018	3.762	1.214-11.66	0.022	1.378	0.772-2.459	0.278
Age	<= 40	1			1			1		
	40.1-50	0.795	0.217-2.918	0.73	0.894	0.193-4.143	0.886	0.589	0.254-1.363	0.589
	50.1-74.9	1.245	0.421-3.678	0.374	0.887	0.227-3.471	0.864	1.415	0.699-2.863	0.334
	>= 75	4.005	1.144-14.02	0.03	0.957	0.144-6.373	0.964	4.45	1.439-13.76	0.01
pN final	pN0	1								
	pN1macro	5.075	1.567-16.43	0.007						
Chemotherapy	No				1			1		
	Yes				2.637	0.442-15.73	0.287	1.284	0.464-3.553	0.631
	NAC							1.799	0.464-6.971	0.396
PMRT	No				1					
	Yes				0.177	0.029-1.089	0.062			
RNI	No				1					
	Yes				4.511	0.681-29.90	0.118			

Legend: Significant univariate variables were included in each model

Abbreviations: HR: Hazard Ratio; ALND: Axillary Lymph Node Dissection; LVI: Lympho Vascular Invasion; PMRT: Post-Mastectomy Radiotherapy; RNI: Regional Nodal Irradiation

(1/316) (p: 0.071): 2.9% (9/312) and 0.8% (5/602) for patients without cALND respectively with and without PMRT, 0.5% (1/222) and 0% (0/94) for patients with cALND respectively with and without PMRT (p: 0.036: cALND or not for patients with PMRT, 0.5% (1/222) vs. 2.9% (9/312)).

pN1 macro metastases SN status

Among 723 patients with SN macro-metastases, cALND was omitted in only 50 patients (6.9%). Among patients with involved-SN number known, only one SN macro-metastases was observed in 372 patients and more than one in 257 patients: 124 patients with only one SN macro-metastases had one or more NSN-involved at cALND (124/332: 37.3%). AC and PMRT were delivered more frequently for patients with cALND (Table 2). In Cox regression analysis, OS and DFS were not significantly different according to cALND or not (Table 3 and 4). AR rates were 1.1 and 0% respectively for patients with and without cALND (7/661 vs. 0/47), 0.9% and 2.5% respectively for patients with and without PMRT (6/668 vs. 1/40: p=0.330).

pN0(i+) and pN1mi SN status

Among 120 patients with pN0(i+) SN and 273 patients with pN1mi SN, cALND were respectively omitted in 32 patients (26.7%) and 48 patients (17.6%) (Table 2).

One or several macro-metastases in NSN at cALND was observed in 6 patients with pN0(i+) SN (6/88: 6.8%, 1 NSN positive for 4 patients, 2 and 6 NSN positive for 2 others) and 30 patients with pN1mi (30/225: 13.3%, 1 NSN positive for 21 patients, 2 NSN positive

for 7 patients, 3 and 6 NSN positive for 2 others).

In univariate analysis, age, pT size and SN status were significantly predictive of NSN involvement among patients with pN0(i+) or pN1mi SN and cALND (Table 5). These factors remained significant in binary logistic regression (Table 5).

Four groups were determined according to pT tumor size < or >= 20 mm and age > or <= 40 years-old with NSN involvement rate for pN0(i+) and pN1mi from 0 to 65%. In binary logistic regression cALND was not significantly associated to these 4 sub-groups and SN status.

For pN0(i+) and for pN1mi, AC and PMRT was delivered more frequently for patients with cALND, including for patients with involved NSN at cALND 100% (5/5) and 92.3% (24/26) of AC, 83.3% (5/6) and 100% (30/30) of PMRT for pN0(i+) and pN1mi respectively (Table 2).

In binary logistic regression, PMRT, RNI and AC were significantly associated with cALND but also to SN status and pT/age sub-groups (Table 6).

In univariate analysis (Log Rank), OS and DFS was lesser and significantly different for patients with pN0(i+) SN without cALND (respectively, p<0.0001 and <0.0001), but without difference for pN1mi SN (respectively, p: 0.699 and 0.222). In Cox regression analysis (Table 3 and 4), OS were not significantly different according to cALND or not for patients with pN0(i+) or pN1mi (HR: 2.485, CI:

Table 4: Disease Free Survival according to sentinel node status: Multivariable analysis.

DFS		pN0 SN			pN0(i+) & pN1mi SN			pN1 macro SN		
		HR	CI 95%	P	HR	CI 95%	P	HR	CI 95%	P
ALND	Yes	1			1			1		
	No	1.417	0.756-2.657	0.277	3.351	1.457-7.711	0.004	1.324	0.659-2.661	0.431
Grade	1	1								
	2	0.862	0.467-1.592	0.636						
	3	1.719	0.829-3.565	0.146						
LVI	No	1			1					
	Yes	2.32	1.285-4.188	0.005	1.262	0.587-2.713	0.551			
Endocrine therapy	Yes	1			1			1		
	No	2.608	1.526-4.458	<0.0001	3.449	1.329-8.948	0.011	2.384	1.562-3.638	<0.0001
SN status	pN0(i-)									
	pN0(i+)				1					
	pN1mi				0.37	0.078-1.751	0.21			
	pN1 macro									
T size	<=5mm	1						1		
	5.1-10	2.089	0.775-5.629	0.145				1.55	0.394-6.102	0.531
	10.1-19.9	2.488	0.945-6.549	0.065				0.832	0.231-2.997	0.779
	20-50	2.807	1.024-7.697	0.045				1.851	0.577-5.938	0.3
	>50 mm	4.161	1.263-13.71	0.019				3.651	1.118-11.92	0.032
Age	<= 40	1			1			1		
	40.1-50	0.853	0.325-2.237	0.746	0.634	0.206-1.956	0.425	0.794	0.429-1.468	0.462
	50.1-74.9	0.961	0.417-2.219	0.95	0.668	0.248-1.799	0.489	1.102	0.632-1.921	0.732
	>= 75	1.721	0.601-4.927	0.311	0.639	0.148-2.755	0.548	1.697	0.705-4.086	0.238
Chemotherapy	No	1			1			1		
	Yes	0.504	0.262-0.968	0.04	1.298	0.472-3.569	0.613	1.022	0.483-2.165	0.954
	NAC				1.037	0.099-10.81	0.976	1.572	0.598-4.133	0.359
PMRT	No				1			1		
	Yes				0.422	0.137-1.295	0.132	0.423	0.215-0.834	0.013
RNI	No				1					
	Yes				1.411	0.491-4.057	0.523			

Legend: Significant univariate variables were included in each model

Abbreviations: DFS: Disease Free Survival; HR: Hazard Ratio SN: Sentinel Node; ALND: Axillary Lymph Node Dissection; LVI: Lympho Vascular Invasion; PMRT: Post-Mastectomy Radiotherapy; RNI: Regional Nodal Irradiation

95%, 0.777 to 7.947, p: 0.125) and a significant lesser DFS rate was observed for patients without cALND (HR: 3.351, CI: 95%, 1.457 to 7.711, p: 0.004) and for patients without endocrine therapy, without other significant criteria (AC, LVI, age, SN status, PMRT and RNI) (Figure 1).

In Cox regression analysis adjusted on endocrine therapy (ET), SN status and pT/age (< or >= 20 mm/<= or >40 years-old), omission of cALND was negatively associated to DFS (HR: 3.855, CI: 95%, 1.801 to 8.252, p=0.001). Omission of cALND and no ET were negatively associated to RFS (respectively, HR: 2.787, CI: 95% 1.159 to 6.701, p: 0.022 and HR: 3.080, CI: 95%, 1.110 to 8.541, p: 0.031). On OS adjusted on ET, SN status, pT/age (< or >= 20 mm/<= or >40 years-old), LVI, only omission of cALND was negatively associated to OS (HR: 3.583, CI: 95%, 1.135 to 11.31, p: 0.030).

AR rates were no significantly different according to cALND or not and PMRT or not, 0% (0/46) and 0% (0/29) for patients without cALND, 1.2% (3/244) and 1.5% (1/66) for patients with cALND

respectively with and without PMRT.

Discussion

We reported from a large retrospective cohort of mastectomy, no OS and DFS significant difference between cALND or not for patients with pN0(i-) SN status and for patients with pN1 macro metastases SN status. However, few patients with pN1 macro metastases SN had no cALND. For patients with pN0(i+) or pN1mi SN, lesser DFS was reported for patients without cALND in comparison with patients with cALND in multivariable analysis (HR: 3.351, p: 0.004) but without significant difference for OS.

For patients with pN0(i-) SN, we reported analysis of 1307 patients without cALND in 75.5% of patients. In Veronesi et al. trial, randomization of cALND was proposed for patients cN0 with tumor diameter <=2 cm and breast conserving surgery: 8 positive NSN at cALND were reported (8/257: 3.1%) with 8.8% FNR (8/91) [13]. In NSABP-B32 trial1, randomization of cALND was proposed

Table 5: Binary logistic regression predictive of positive NSN.

		pN0(i+) & pN1mi with ALND			
		Univariate	Regression		
		P	OR	CI 95%	P
age	> 40	0.013	1		
	<= 40		2.306	1.078-4.932	0.031
pT size	< 20 mm	0.003	1		
	>= 20 mm		2.603	1.426-4.751	0.002
SN status	pN0(i+)	<0.0001	1		
	pN1mi		4.825	1.930-12.06	0.001
Grade	1 vs. 2 vs. 3	0.617			
LVI	No vs. Yes	0.43			
ER	No vs. Yes	0.34			
Periods	P1 vs. P2 vs. P3	0.17			
Her2/ER	ER+ Her2-	0.255			

Abbreviations: ALND: Axillary Lymph Node Dissection; SN: Sentinel Node; LVI: Lympho Vascular Invasion; ER: Endocrine Receptor; OR: Odds Ratio

for patients cN0 with unifocal tumor, mainly <=20 mm (83.8%: 3344/3989) with conservative treatment (87.5%) or mastectomy (n=499, 12.5%). In cALND arm, 75 patients (75/1975: 3.8%) had positive NSN with a FNR >8.3% (75 among 904 patients with SN positive or unknown). A lower FNR in our study (3.63%) should be attributed to more extensive SN pathologic analysis in our study with serial sections and IHC for negative HE analysis. After more extensive pathologic analysis, it was reported that 15.9% (CI: 95%, 14.7 to 17.1%) of SN (616/3884) presented occult metastases (69.8% among ITC: 430/616 and 27.9% among micro-metastases: 172/616) and in some cases macro-metastases (2.3% of macro-metastases: 14/616) [14]. It had been reported that SLNB was accurate for large tumors (1101 with tumors >20 mm and <30 mm and 748 tumors >=30 mm) and for multi-focal multi-centric tumors even if LN involvement rate was higher for these patients [15,16].

For patients who had a macro-metastases SN, the only reported trial with cALND randomization versus only SLNB2 had included macro and micro-metastases for conservative treatment. In AMAROS trial, with randomization between cALND versus axillary radiotherapy, patients with tumors up to 5 cm diameter, cN0, unifocal or multifocal and breast-conserving treatment or mastectomy were eligible: 19.4% of patients had tumors more than 2 cm (276/1425), 17.4% had mastectomy (248/1425), 60.4% had macro-metastases SN (861/1425), 28.8% had micro-metastases SN (410/1425) and 10.8%

Table 6: PMRT, RNI and AC realization for pN0(i+) and pN1mi SN status: binary logistic regression.

		PMRT			RNI			AC		
		OR	CI 95%	P	OR	CI 95%	p	OR	CI 95%	p
cALND or no	SN+cALND	1			1			1		
	SN	0.477	0.273-0.833	0.009	0.436	0.244-0.779	0.005	0.398	0.226-0.700	0.001
SN status	pN0(i+)	1			1			1		
	pN1mi	1.905	1.134-3.201	0.015	1.629	0.991-2.678	0.055	2.477	1.465-4.188	0.001
> 40 years	pT<20 mm	1			1			1		
	pT>=20 mm	3.019	1.774-5.137	<0.0001	2.155	1.322-3.513	0.002	4.098	2.421-6.937	<0.0001
<= 40 years	pT< 20 mm	2.168	0.885-5.312	0.09	1.222	0.541-2.761	0.63	5.402	1.970-14.81	0.001
	pT>=20 mm	17.82	2.330-136.3	0.006	4.545	1.692-12.21	0.003	28.89	3.681-226.7	0.001

Abbreviations: PMRT: Post-Mastectomy Radiotherapy; RNI: Regional Nodal Irradiation; AC: Adjuvant Chemotherapy; cALND: Complementary Axillary lymph Node Dissection; SN: Sentinel Node

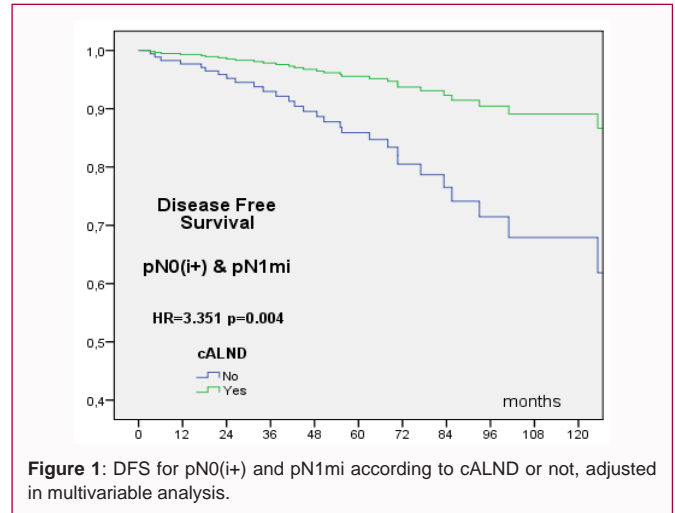


Figure 1: DFS for pN0(i+) and pN1mi according to cALND or not, adjusted in multivariable analysis.

had ITC SN (154/1425) [17]. In the cALND arm, involved NSN rate was 32.8% (220/671). In NSABP B-04 trial with randomization between ALND or no axillary surgery for patients with total mastectomy, no survival impact was observed with a long follow-up [18]. However, patients included in this trial had large tumors, which were very different with patients for whom SLNB is indicated, and any systemic treatment was administered with low survival rates in two arms. Omission of regional treatment with ALND had in consequence no survival impact.

In OTOASOR trial, with randomization between cALND versus axillary radiotherapy, patients with tumors up to 3 cm diameter, cN0, unifocal or multifocal and breast-conserving treatment or mastectomy were eligible: 48.7% of patients had tumors >2 cm (231/474) with 11.1% of multifocal tumors (53/474), 15.6% had mastectomy (74/474), 60.4% had macro-metastases SN (139/230), 33.5% had micro-metastases SN (77/230) and 6.1% had ITC SN (14/230) in the radiotherapy arm. In the cALND arm, involved NSN rate was 38.5% (94/244) [19].

Several trials are ongoing with randomization of cALND: INSEMA trial with only 1 or 2 SN macro-metastases and conservative treatment, POSNOC trial with only 1 or 2 SN macro-metastases and conservative treatment or mastectomy with cALND or radiotherapy versus no other axillary treatment SERC trial and BOOG 2013-07 trial for mastectomy (closed) and 1 to 3 involved SN by micro or macro-metastases with only mastectomies SENOMAC trial for patients with 1 or 2 SN macro-metastases including mastectomies [10,11,20-23].

In SERC trial 2,056 patients are actually included with randomization between cALND or no other treatment for involved SN by ITC or micro-metastases or macro-metastases with conservative treatment or mastectomy [10,11]. In the first 963 patients included in the first analysis (170 mastectomies and 793 conservative treatment), the overall rate of positive NSN was 19% (84/442) for patients with cALND, and crude rates of positive NSN according to SN status were 4.5% for patients with ITC (1/22), 9.5% for SN micro-metastases (13/137), 23.9% for SN macro-metastases (61/255).

For patients with pN0(i+) or pN1mi SN, two trials were reported with randomization of cALND, including 86 mastectomies in IBCSG 23-01 trial (86/931: 9.2%) and the rate of involved NSN in cALND arm was 13% [3-4]. In AATRM trial only 18 patients had had mastectomy [4]. In the study published by Tvedskov et al., these rates of involved NSN were 9.2% for ITC and 17.9% for Mic and in a previous study we had reported positive-NSN rates of 13.9% (40/287) for ITC and 14.1% (93/658) for pN1mi SN with a predictive nomogram based on tumor size, ratio of positive-SN/analyzed-SN, LVI, tumor histologic type [15,24,25].

In our study, lesser DFS rate for patients without cALND was observed. AC rate was not higher for patients without cALND for pN0(i+) and pN1mi in comparison with patients with ALND in our study, respectively 59.4% and 39.6% vs. 34.1% and 21.3%.

In the AMAROS trial, ALND realization had no impact on the decision of adjuvant treatment. In a study in 172 patients with pN1mi SN who underwent cALND, Mazouni et al. [17,26]. Showed the low impact of SN status in the therapeutic decision for AC, except in case of low grade or HER2-negative tumors. However, in the study by Aigner et al. [27] indication of AC was modified in 18.2% of cases. In the multicenter clinical trial AATRM4, 247 patients with Mic were randomized between cALND and no cALND and AC rate was higher in those who underwent cALND (40.2%) compared to those without cALND (36.8%). Finally, in the study by Savolt et al. with randomization between cALND and regional node RT, AC was more frequently administered in case of cALND (78 vs. 69%) [19]. In IBCSG trial AC was not different between cALND and no cALND: 32.1% (149/464) and 29.1% (136/467) [3]. Indications of AC depended of tumor phenotype and molecular tumor subtypes but also of presence or no of axillary lymph node macro-metastases. Under evaluation of axillary LN status with omission of cALND could result in AC under indication, particularly for Luminal-A or Luminal-B Her-negative tumors [2].

Endocrine therapy for luminal tumors and PMRT with tangential field's effect on axillary basin can explain a low AR rate for patients without cALND. PMRT rate was not lower in our study for pN0(i+) and pN1mi for patients with cALND vs. cALND (respectively, 34.1% and 21.3% vs. 59.4% and 39.6%). In IBCSG 23-01 trial, no PMRT was realized in all patients with mastectomy. The role of RT in the absence of cALND in patients with invaded SN has been extensively discussed [28]. In the ACOSOG Z0011 trial, adjuvant treatments associated with whole breast irradiation (WBI) using axillary tangential fields, likely contributed to the low rate of node recurrence (1% in the group without ALND). However, WBI with tangential fields and regional RT were specified in only one third of cases [29]. Most series evaluating the SN technique showed that tangential fields include the majority of levels I and II but others reported that standard tangential fields of breast RT include the axillary only to a limited extent [30,31].

AR is a rare event corresponding to a strong survival pejorative

factor [32]. In Gentilini et al. study, AR rates were significantly different between patients who received WBI or partial breast irradiation after conservative treatment [33]. At 10-years, AR rate were in IBCSG 23-01 trial 1.2% and 1.2% for 86 mastectomies respectively in arm with ALND (1/44) and without cALND (1/42) but AR rates for patients with conservative treatment with IORT without WBI were 0% (0/79) in arm with cALND and 6.25% (5/80) in arm without cALND. In our study, AR rates were no significantly different according to cALND or not and PMRT or not. PMRT is usually indicated for patients with lymph node macro-metastases [34]. Three trials explored omission of cALND for patients with positive-SN treated by mastectomy with determination of tangential fields: BOOG 2013-07, SENOMAC and SERC trials [10,11,22,23].

Conclusion

SLNB alone appeared as an accurate procedure for axillary staging of BC mastectomy for pN0 SN status. For pN1-macro-metastases, actually to avoid cALND could not be an option in case of BC mastectomy considering these results and literature results without trials including sufficient number of mastectomies. When SN was involved by ITC or micro-metastases, omission of cALND is still controversial and should have a negative prognosis impact in relation with under evaluation in 6.8% to 13.3% of patients with possible under treatment of radiotherapy and or AC.

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