

Eligibility for ACOSOG Z0011 Trial and Results on a Cohort of 3546 Breast Cancer Patients with Micro or Macro Metastases Sentinel Nodes

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2. Keywords

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1. Abstract

1.1. Purpose: Since results of ACOSOG-Z0011 and IBCSG-23-01 trials, complementary Axillary Lymph Node Dissection (cALND) was questioned for Breast Cancer (BC) with involved Sentinel Node (SN). We examine eligibility rate to Z0011-trial criteria and results among patients with SN micro or macro-metastases.

1.2. Methods: A large cohort of BC with SN micro or macro-metastases, has been analyzed to determined: eligibility rate to Z0011-trial, Non-Sentinel-Node (NSN) involvement rate at cALND, Overall (OS) and Disease-Free Survival (DFS) prognostic factors, Axillary Recurrence (AR) rate, analysis of specific sub-groups of patients and the possible effect of avoiding cALND.

1.3. Results: Among 3546 patients, 81.9% met Z0011 criteria. All factors analyzed were significantly different between patients eligible and non-eligible to Z0011, except cALND rate.

NSN-involvement rate was higher for patient's non-eligible to Z0011-trial and for SN macro-metastases (11.8% for SN-micro-metastases vs 37.7%), tumor size >20mm, lobular and mixt tumors, with lympho-vascular-invasion, with >2 involved-SN. We observed a significant decrease of NSN-involvement rate according to cALND performed after versus before adjuvant chemotherapy.

OS and DFS in case of cALND omission were not significantly different in comparison with cALND for all patients, but for patients with SN micro-metastases OS and DFS were higher when cALND was performed (HR: 2.04; p=0.042). Grade 3, mixt tumors and negative endocrine-receptors were associated with higher axillary recurrence rate.

1.4. Conclusion: A high patient's proportion met Z0011 criteria. We observed a significant decrease of NSN-involvement rate when cALND was performed after chemotherapy. Therapeutic combined effect of chemotherapy, endocrine-therapy and radiotherapy can explain a low AR rate.

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3. Introduction

A decrease of Axillary Lymph Node Dissection (ALND) rate since validation of Sentinel Lymph Node Biopsy (SLNB) for early Breast Cancer (BC) with non-involved SN [1] has been reported. Since results of ACOSOG-Z0011 and IBCSG-23-01 trials [2, 3], complementary ALND (cALND) was questioned for involved-SN.

Results of Z0011-trial were the object of numerous discussions about the limits and biases of this study [4]. Omission of cALND was held in some teams and recommendations [5, 6], underlining the strict conditions for cALND omission. An evaluation in particular groups of patients considered at high-risk was reported [7].

The aim of this study was to examine eligibility rate to ACOSOG-Z0011-trial criteria, Non-Sentinel-Node (NSN) involvement rate, Axillary Recurrence (AR) rate and survival results, among a multi-institutional cohort of patients with involved-SN by micro or macro-metastases. To establish the possible effects of omitting cALND, we assessed the clinical characteristics and prognosis factors of patients with or without cALND.

4. Material - Methods

4.1. Population

We included patients treated between March 1999 and December 2012 in 15 centers with early BC and involved-SN by micro or macro-metastasis, \leq cT2-N0, without pre-operative treatment and conservative treatment or mastectomy. We excluded patients with pre-operative treatment or cN1 or T3-4 or involved-SN by Isolated Tumor Cells (ITC).

4.2. Criteria

Five tumor subtypes were defined according to Immune-Histochemical (IHC) analysis of Endocrine Receptors (ER) and Her2-status: Luminal-A (ER+Her2- Grade 1-2, Her2+ER-, Triple negative (ER-Her2-), Luminal-B Her2- Grade 3, Luminal-B Her2+ER+ [8, 9].

Four categories of SN-status were defined: negative-SN (pN0i-), isolated tumor cells (ITC) (pN0(i+): \leq 0.2mm), detected either by Hematoxylin-Eosin (HE) staining or by cytokeratin IHC, micro-metastases (pN1mi: $>$ 0.2 to \leq 2mm), and macro-metastases ($>$ 2mm) [9, 10]. SLNB was performed similarly in all centers using isotopic +/- colorimetric detection [11].

Criteria's eligibility for Z0011-trial were conservative treatment for patients cN0 with 1 or 2 SN micro or macro-metastases, without pre-operative treatment and without capsular rupture. Three periods were analyzed in order to determined therapeutic modifications: before 2006, between 2006-2009 and after 2009.

4.3. Evaluation

We have analyzed eligibility rate to ACOSOG-Z0011-trial criteria, NSN-involvement rate at cALND, predictive factors of NSN-in-

volvement, AR rate, Overall and Disease-Free Survival (OS, DFS) according to Z0011-eligibility and cALND. Sub-groups of patients were also studied corresponding to SN micro-metastases, mastectomy, and patients considered as high-risk i.e. tumors Her2-positive or triple-negative and or $<$ 50-years old. We have compared our cohort with population of Z0011-trial.

4.4. Statistics

We used standard descriptive statistics (mean, standard deviation, median and range for quantitative variables, count and frequency for categorical variables) to describe patients and tumors characteristics. Univariate analyses were performed using Chi-Square and multivariate analyses using binary logistic regression. Survival analyses were performed using log-Rank test and Cox-model. All tests were two-sided. The level of statistical significance was set at a p-value of 0.05. We used SPSS-16.0.

5. Results

5.1. Population

Among 3546 patients, 2903 (81.9%) met Z0011 criteria and 643 had one or several factors of non-eligibility: 509 mastectomies, 130 patients with $>$ 2 involved-SN, 58 with SN capsular rupture. Population of patients according to ACOSOG-Z0011 eligibility and cALND or not are reported in Table 1. All factors analyzed were significantly different between patients eligible and non-eligible to ACOSOG-Z0011, except cALND rate, with cALND omission for 342 patients (9.6%).

We observed a significant association between lower rate of cALND and patients $>$ 75-years old, SN micro-metastasis, patients with $>$ 3 SN removed and during the last period (Table 2).

5.2. Patient's Characteristics According to NSN Status and to ACOSOG-Z0011 Eligibility (n=2467)

In univariate analysis, a higher NSN-involvement rate was observed for patient's non eligible to Z0011-trial, for Grade 2-3 tumors, with LVI, for lobular and mixt tumors, for tumor size $>$ 10mm, for SN macro-metastases and $>$ 2 involved-SN, for tumors others than Luminal-A and for patients with cALND performed before adjuvant chemotherapy (AC) (Table 3).

In multivariable analysis, higher NSN-involvement rates were significantly associated with SN macro-metastases, tumor size $>$ 20mm, with LVI, for lobular and mixt tumors, with $>$ 2 involved-SN and lower NSN-involvement rates when $>$ 3 SN were harvested and for patients without AC (Table 4).

For patients treated with AC, we observed a significant decrease of NSN-involvement rate according to cALND performed after or before AC, with a 56% (14 vs 31,8%) down staging for all SN-metastases sizes: respectively, a 26.6% down staging for SN-micro-metastasis (12.7 vs 17.3%) and 60.9% for SN-macro-metastases (15.8 vs 40.4%).

In binary logistic regression to predict the risk of 2 or more involved-NSN versus no involved-NSN or only one, significant factors were lobular tumor, grade 3, with LVI, SN macro-metastases, >2 involved-SN and only one SN harvested (Table 4) (univariate analysis: Supplementary-Table- 5).

Table 1: Patient’s characteristics according to ACOSOG Z0011 eligibility and according to ALND or not.

		eligible ACOSOG Z0011				p	ALND				
		Yes Nb	%	No Nb	%		Yes Nb	%	No Nb	%	p
ALND	yes	2616	90.1	588	91.4	0.168	3204				
	no	287	9.9	55	8.6				342		
age	<= 40	193	6.7	55	8.6	<0.0001	235	7.3	13	3.8	<0.0001
	40.1 - 50	713	24.6	193	30		841	26.3	65	19	
	50.1 - 74.9	1842	63.5	342	53.2		1985	62	199	58.2	
	>= 75	153	5.3	53	8.2		141	4.4	65	19	
Grade	1	920	31.7	145	22.6	<0.0001	957	29.9	108	31.6	0.083
	2	1416	48.8	334	51.9		1588	49.6	162	47.4	
	3	534	18.4	153	23.8		624	19.5	63	18.4	
	undetermined	33	1.1	11	1.7		35	1.1	9	2.6	
LVI	no	1720	67.5	314	55.6	<0.0001	1808	64.6	226	71.5	0.008
	yes	828	32.5	251	44.4		989	35.4	90	28.5	
Histology	Ductal	2406	82.9	477	74.2	<0.0001	2608	81.4	275	80.4	0.024
	Lobular	301	10.4	111	17.3		377	11.8	35	10.2	
	Mixt	69	2.4	21	3.3		84	2.6	6	1.8	
	Others	127	4.4	34	5.3		135	4.2	26	7.6	
ER	negative	245	8.5	81	12.8	0.001	301	9.5	25	7.5	0.137
	positive	2633	91.5	554	87.2		2878	90.5	309	92.5	
tumor size	<= 5 mm	78	2.7	32	5	<0.0001	95	3	15	4.4	0.236
	6-10 mm	547	19	73	11.4		552	17.4	68	20.1	
	11-20 mm	1616	56.1	263	41.2		1704	53.6	175	51.8	
	> 20 mm	638	22.2	271	42.4		829	26.1	80	23.7	
SN metastases	micro metastases	1446	49.8	229	35.6	<0.0001	1428	44.6	247	72.2	<0.0001
	macro metastases	1457	50.2	414	64.4		1776	55.4	95	27.8	
tumor subtypes	Luminal A	1478	74.1	296	63.5	<0.0001	1579	71.8	195	74.7	0.317
	Her 2	65	3.3	38	8.2		97	4.4	6	2.3	
	Triple negative	133	6.7	29	6.2		147	6.7	15	5.7	
	Lum B Her2- HR+ G3	225	11.3	58	12.4		249	11.3	34	13	
	Lum B Her2+ HR+	94	4.7	45	9.7		128	5.8	11	4.2	
surgery	conservative	2891	100	131	20.5	<0.0001	2735	85.7	287	84.7	0.33
	mastectomy	0		509	79.5		457	14.3	52	15.3	
chemotherapy	No	963	33.2	118	18.4	<0.0001	897	28	184	53.8	<0.0001
	Yes	1899	65.4	491	76.4		2232	69.7	158	46.2	
	unknown	41	1.4	34	5.3		75	2.3	0		
hormonotherapy	No	326	11.4	99	16.2	0.001	379	12.1	46	13.5	0.26
	Yes	2536	88.6	512	83.8		2752	87.9	296	86.5	
trastuzumab	No	2799	96.4	578	89.9	<0.0001	3051	95.2	326	95.3	0.534
	Yes	104	3.6	65	10.1		153	4.8	16	4.7	
radiotherapy	No	76	2.7	79	15	<0.0001	127	4.2	28	8.4	<0.0001
	Yes	2603	91.4	444	84.3		2750	90.4	297	89.5	
	unknown	168	5.9	4	0.8		165	5.4	7	2.1	
SN number	1 or 2	1879	64.9	279	47.1	<0.0001	1972	62.7	186	54.4	<0.0001
	3	575	19.9	170	28.7		677	21.5	68	19.9	
	≥ 4	441	15.2	143	24.2		496	15.8	88	25.7	
SN positive	<= 2	2894	100	461	78	<0.0001	3020	96.1	335	98.2	0.023
	> 2	0		130	22		124	3.9	6	1.8	
chemotherapy	No	536	26.8	71	16.5	<0.0001	607	25.2			
	before ALND	79	3.9	16	3.7		95	3.9			
	after ALND	1331	66.5	311	72.2		1617	67.1			
	undetermined	57	2.8	33	7.7		90	3.7			
NSN	negative	1590	76.2	302	63.4	<0.0001					
	positive	497	23.8	174	36.6						
eligible Z0011	yes						2616	81.6	287	83.9	0.168
	no						588	18.4	55	16.1	
periods	1999-2003						1070	33.4	86	25.2	<0.0001
	2004-2006						1053	32.9	76	22.3	
	> 2006						1081	33.7	179	52.5	

ALND: axillary lymph node dissection, LVI: lympho vascular invasion, ER: endocrine receptors, SN: sentinel node, NSN: non sentinel node.

Table 2: Factors correlated to ALND or not.

Predictive factors for ALND		OR	CI 95	p
age	<= 40	1		
	40.1 - 50	0.643	0.32-1.30	0.219
	50.1 - 74.9	0.488	0.25-0.96	0.037
	>= 75	0.083	0.04-0.17	<0.0001
LVI	no	1		
	yes	1.225	0.93-1.62	0.155
Histology	Ductal	1		
	Lobular	1.108	0.73-1.68	0.628
	Mixt	1.305	0.53-3.19	0.559
	Others	0.675	0.41-1.11	0.121
SN metastases	micro metastases	1		
	macro metstases	3.24	2.46-4.27	<0.0001
SN number	1 or 2	1		
	3	0.854	0.62-1.18	0.338
	≥ 4	0.416	0.30-0.57	<0.0001
SN positive	<= 2	1		
	> 2	1.69	0.64-4.43	0.288
periods	1999-2003	1		
	2004-2006	1.57	1.09-2.24	0.014
	> 2006	0.57	0.43-0.77	<0.0001

ALND: axillary lymph node dissection, LVI: lympho vascular invasion, SN: sentinel node.

Table 3: NSN status according to ACOSOG Z0011 eligibility.

eligible ACOSOG Z0011		YES			NO		
		NSN + rate		Chi2	NSN + rate		Chi2
		Nb	%	p	Nb	%	p
	Number	497	24.8		174	37.7	<0.0001
age	<= 40	40	26.7	0.34	15	36.6	0.564
	40.1 - 50	134	25.4		61	42.4	
	50.1 - 74.9	298	23.8		85	35.1	
	>= 75	24	32.4		13	38.2	
Grade	1	121	19.3	<0.0001	28	24.8	0.001
	2	260	25.9		94	40	
	3	113	32.1		51	48.6	
	undetermined	3	12.5		1	12.5	
LVI	no	256	22	<0.0001	65	28.6	<0.0001
	yes	168	31.3		84	50.3	
Histology	Ductal	383	23.4	<0.0001	127	37.2	0.588
	Lobular	68	32.7		31	41.9	
	Mixt	28	42.4		8	44.4	
	Others	18	18.8		8	28.6	
ER	negative	60	33.7	0.004	25	39.7	0.436
	positive	436	24.1		148	37.8	
tumor size	<= 5 mm	8	14.5	<0.0001	3	13	<0.0001
	6-10 mm	45	12		11	23.4	
	11-20 mm	258	23.6		61	32.1	
	> 20 mm	185	38.9		99	49.7	
SN metastases	micro metastases	118	11.8	<0.0001	21	12.1	<0.0001
	macro metastases	379	37.7		153	53.3	
tumor subtypes	Luminal A	230	24.4	0.006	73	38.6	0.478
	Her 2	18	40.9		12	52.2	
	Triple negative	33	36.3		12	42.9	
	Lum B Her2- HR+ G3	39	33.1		17	53.1	
	Lum B Her2+ HR+	20	31.2		13	41.9	
surgery	conservative	496	24.8		54	48.6	0.005
	mastectomy	0			119	34.3	
chemotherapy	No	73	13.8	<0.0001	14	20.3	<0.0001
	Yes	417	29		156	43.6	
	unknown	7	17.1		4	11.8	
hormonotherapy	No	58	29.7	0.065	27	38.6	0.46
	Yes	433	24.5		144	40.1	
trastuzumab	No	473	24.3	0.012	152	36.4	0.056
	Yes	24	38.1		22	50	
radiotherapy	No	6	14	<0.0001	6	12.8	<0.0001
	Yes	378	21.6		131	43.7	
	unknown	91	56.2		3	100	
SN number	1 or 2	361	27	0.004	66	33.5	0.092
	3	83	21.4		48	38.4	
	≥ 4	26	29.5		26	29.5	
SN positive	<= 2	496	24.8		93	29.9	0.002
	> 2				46	46.9	
chemotherapy	No	76	14.3	<0.0001	15	21.1	<0.0001
	before ALND	12	15.6		1	6.2	
	after ALND	387	29.7		125	40.5	
	undetermined	18	31.6		30	90.9	

ALND: axillary lymph node dissection, LVI: lympho vascular invasion, ER: endocrine receptors, SN: sentinel node, NSN: non sentinel node.

Table 4: Predictive factors of NSN involvement for all patients (ACOSOG Z0011 eligible or not) and predictive factors of 2 or more involved NSN.

		NSN involved predictive factors			≥ 2 involved NSN		
		OR	CI 95%	p	OR	CI 95%	p
SN metastases	micro metastases	1			1		
	macro metastases	4.514	3.53-5.78	<0.0001	4.743	3.29-6.83	<0.0001
tumor size	<= 5 mm	1			1		
	6-10 mm	0.766	0.33-1.80	0.542	0.766	0.21-2.80	0.687
	11-20 mm	1.511	0.67-3.40	0.319	1.35	0.40-4.55	0.629
	> 20 mm	2.337	1.04-5.27	0.041	2.438	0.72-8.25	0.152
Grade	1	1			1		
	2	1.186	0.90-1.56	0.223	1.399	0.94-2.09	0.1
	3	1.346	0.94-1.93	0.105	2.268	1.41-3.63	0.001
	undetermined	0.516	0.10-2.65	0.428	1.08	0.12-9.39	0.944
LVI	no	1			1		
	yes	1.37	1.07-1.75	0.011	1.956	1.42-2.69	<0.0001
Histology	Ductal	1			1		
	Lobular	1.464	1.03-2.09	0.035	1.738	1.11-2.73	0.016
	Mixt	2.28	1.27-4.07	0.005	0.94	0.41-2.13	0.881
	Others	1.031	0.60-1.78	0.913	1.523	0.76-3.07	0.239
ER	positive	1			1		
	negative	1.001	0.68-1.47	0.995	0.768	0.47-1.24	0.284
surgery	conservative	1			1		
	mastectomy	1.046	0.75-1.45	0.786	1.354	0.92-1.99	0.126
SN number	1 or 2	1			1.478*	1.08-2.01	0.013
	3	0.653	0.49-0.87	0.004	1**		
	≥ 4	0.562	0.39-0.81	0.002			
SN positive	<= 2	1			1		
	> 2	2.184	1.20-3.96	0.01	2.693	1.45-5.00	0.002
chemotherapy	after ALND	1					
	before ALND	0.621	0.33-1.19	0.149			
	No	0.741	0.55-0.99	0.049			
	undetermined	0.684	0.36-1.31	0.253			

LVI: lympho vascular invasion, ER: endocrine receptors, SN: sentinel node, NSN: non sentinel node. Supplementary.

Table 5: Characteristics of patients with one versus two or more involved NSN.

		1 NSN+		≥ 2 NSN+		p
		Nb	%	Nb	%	
ACOSOG Z0011	Number	352	52.5	319	47.5	
	eligible	287	81.5	210	65.8	<0.0001
	non eligible	65	18.5	109	34.2	
SN metastases	micro metastases	94	26.7	45	14.1	<0.0001
	macro metastases	258	73.3	274	85.9	
tumor size	<= 5 mm	6	1.7	5	1.6	<0.0001
	6-10 mm	34	9.7	22	6.9	
	11-20 mm	192	54.7	127	39.8	
	> 20 mm	119	33.9	165	51.7	
Grade	1	97	27.6	52	16.3	<0.0001
	2	191	54.3	163	51.1	
	3	63	17.9	101	31.7	
	undetermined	1	0.3	3	0.9	
LVI	no	198	64.1	123	46.6	<0.0001
	yes	111	35.9	141	53.4	
Histology	Ductal	272	77.3	238	74.6	0.088
	Lobular	46	13.1	53	16.6	
	Mixt	24	6.8	12	3.8	
	Others	10	2.8	16	5	
ER	negative	39	11.1	46	14.5	0.203
	positive	312	88.9	272	85.5	
tumor subtypes	Luminal A	175	72	128	57.1	0.016
	Her 2	14	5.8	16	7.1	
	Triple negative	20	8.2	25	11.2	
	Lum B Her2- HR+ G3	21	8.6	35	15.6	
	Lum B Her2+ HR+	13	5.3	20	8.9	
surgery	conservative	304	86.4	246	77.6	0.002
	mastectomy	48	13.6	71	22.4	
SN positive	<= 2	326	94.8	263	90.4	0.024
	> 2	18	5.2	28	9.6	
chemotherapy	No	71	20.3	20	6.3	<0.0001
	before ALND	5	1.4	8	2.5	
	after ALND	261	74.8	251	79.7	
	undetermined	12	3.4	36	11.4	
SN number	1 or 2	229	66.4	198	68	0.669
	3	70	20.3	61	21	
	≥ 4	46	13.3	32	11	
age	<= 40	30	8.5	25	7.9	0.668
	40.1 - 50	101	28.7	94	29.6	
	50.1 - 74.9	205	58.2	178	56	
	>= 75	16	4.5	21	6.6	

LVI: lympho vascular invasion, ER: endocrine receptors, SN: sentinel node, NSN: non sentinel node.

5.3. Survival Results

Median follow-up was 57.64 months (95%CI: 59.86-62.3). We observed 170 deaths, 275 recurrences and 128 BC related deaths.

Higher OS and DFS rates were observed for patients eligible to Z0011 in comparison with patient's non-eligible (Table 6). OS and DFS were not significantly different between SLNB alone and

cALND for all patients, but were higher for patients with SN micro-metastases when cALND were performed.

For OS and DFS, significant prognostic factors were grade 3, LVI, ER-negative, SN macro-metastases. Moreover, age >75-years was a significant prognostic factor for OS and <3 SN harvested was also significant for DFS (Supplementary-Table-7, Table 8).

Table 6: Five and 7-years overall survival (OS) and disease-free survival (DFS).

		Overall survival								Disease Free Survival							
		Nb	5-years	SD	at risk	7-years	SD	atrisk	p	Nb	5-years	SD	at risk	7-years	SD	at risk	p
eligible Z0011	yes	2816	95.6	0.5	1384	92.3	0.7	685	0.05	2863	92.2	0.6	1356	88	0.8	666	0.018
	no	593	92.3	1.5	198	88.1	2.1	105		617	86.9	1.8	199	82.4	2.4	106	
ALND	yes	3074	95.2	0.5	1486	92	0.7	752	0.099	3140	91.5	0.6	1462	87.4	0.8	735	0.198
	no	335	93.9	2	96	87.5	3.5	38		340	90.3	2.3	93	80.2	4.6	35	
SN metastases	micro	1581	96.5	0.6	728	94.5	0.8	351	<0.0001	1610	93.6	0.7	718	90	1.1	337	<0.0001
	macro	1828	94	0.7	854	89.4	1	439		1870	89.7	0.8	837	84.6	1.2	433	
pN1 mi	ALND	1339	96.7	0.6	654	95.2	0.8	327	0.019	1365	93.9	0.7	650	90.8	1.1	318	0.045
	no ALND	242	94.6	2.4	74	87.1	4.5	24		245	90.4	2.7	69	80.8	5.5	20	
pN1 macro	ALND	1735	94.1	0.7	832	89.5	0.1	425	0.287	1775	89.7	0.8	811	84.8	1.2	418	0.587
	no ALND	93	93.7	2.7	23	89.3	5.1	15		95	90.7	3.9	25	80.6	7.6	15	
pN1 mi eligible Z11	ALND	1173	96.9	0.6	591	95.4	0.8	291	0.007	1192	94.4	0.7	585	91.1	1.1	281	0.051
	no ALND	213	94.2	2.6	70	86.4	4.7	23		214	90.1	2.9	64	84	4.5	19	
pN1 mi not eligible Z11	ALND	166	95.6	2	64				0.416	173	89.6	3.1	65	87.8	3.5	37	0.599
	no ALND	29	100		4					31	95	4.9	5				

Supplementary Table 7: OS and DFS results: univariate analysis.

		Univariate analysis					
		Overall survival			Disease Free Survival		
		HR	CI 95%	p	HR	CI 95%	p
eligible Z0011	yes	1			1		
	no	1.4	0.99-1.96	0.051	1.37	1.05-1.79	0.019
ALND	yes	1			1		
	no	1.48	0.93-2.38	0.101	1.29	0.87-1.90	0.199
age	<= 40	1			1		
	40.1 - 50	0.921	0.52-1.63	0.777	0.62	0.43-0.90	0.013
	50.1 - 74.9	1.159	0.69-1.95	0.578	0.59	0.42-0.83	0.003
	>= 75	3.223	1.69-6.16	<0.0001	1.08	0.64-1.82	0.77
Grade	1	1			1		
	2	1.749	1.17-2.60	0.006	2.3	1.66-3.19	<0.0001
	3	4.844	3.25-7.22	<0.0001	5.02	3.59-7.04	<0.0001
	undetermined	1.165	0.28-4.86	0.834	1.71	0.61-4.79	0.306
LVI	no	1			1		
	yes	1.96	1.45-2.64	<0.0001	1.88	1.49-2.38	<0.0001
Histology	Ductal	1			1		
	Lobular	1.255	0.86-1.83	0.239	1.16	0.85-1.58	0.351
	Mixt	0.859	0.38-1.94	0.716	1.14	0.67-1.96	0.629
	Others	0.942	0.51-1.73	0.848	0.56	0.30-1.06	0.075
ER	positive	1			1		
	negative	3.456	2.52-4.73	<0.0001	3.1	2.39-4.03	<0.0001
tumor size	<= 5 mm	1			1		
	6-10 mm	0.731	0.25-2.14	0.568	0.77	0.32-1.84	0.552
	11-20 mm	1.111	0.41-3.02	0.837	1.26	0.56-2.85	0.576
	> 20 mm	1.933	0.71-5.26	0.197	2.3	1.02-5.21	0.046
SN metastases	micro metastases	1			1		
	macro metastases	1.871	1.40-2.49	<0.0001	1.53	1.23-1.91	<0.0001
tumor subtypes	Luminal A	1			1		
	Her 2	4.051	2.31-7.09	<0.0001	4.28	2.75-6.66	<0.0001
	Triple negative	4.116	2.60-6.52	<0.0001	3.58	2.43-5.28	<0.0001
	Lum B Her2- HR+ G3	3.287	2.12-5.09	<0.0001	2.96	2.09-4.18	<0.0001
	Lum B Her2+ HR+	1.316		0.49	1.51	0.86-2.63	0.147
surgery	conservative	1			1		
	mastectomy	1.255	0.85-1.85	0.249	1.39	1.05-1.86	0.024
chemotherapy	No	1			1		
	Yes	1.13	0.83-1.55	0.447	1.42	1.09-1.85	0.008
	unknown	1.52	0.77-3.01	0.224	1.8	0.99-3.26	0.052
hormonotherapy	yes	1			1		
	no	3.376	2.50-4.56	<0.0001	2.85	2.21-3.66	<0.0001
trastuzumab	No	1			1		
	Yes	1.531	0.81-2.89	0.19	1.75	1.11-2.75	0.016
radiotherapy	No	1			1		
	Yes	0.401	0.24-0.67	0.001	0.41	0.27-0.63	<0.0001
	unknown						
SN number	1 or 2	1			1		
	3	0.74	0.52-1.06	0.102	0.62	0.46-0.84	0.002
	>= 4	1.037	0.71-1.51	0.851	1.09	0.82-1.45	0.548
SN positive	<= 2	1			1		
	> 2	2.506	1.56-4.02	<0.0001	1.64	1.04-2.57	0.033

chemotherapy	No	0.946	0.64-1.39	0.775	0.72	0.53-0.99	0.045
	before ALND	1.03	0.42-2.54	0.944	0.54	0.22-1.30	0.17
	after ALND	1			1		
	undetermined	2.49	1.43-4.33	0.001	1.29	0.72-2.31	0.392
NSN	negative	1			1		
	positive	2.122	1.57-2.86	<0.0001	1.96	1.55-2.48	<0.0001

ALND: axillary lymph node dissection, LVI: lympho vascular invasion, ER: endocrine receptors, SN: sentinel node, NSN: non sentinel node, HR: Hazard ratio.

Table 8: OS and DFS results: multivariate analysis.

		Multivariate analysis			Disease Free Survival		
		HR	CI 95%	p	HR	CI 95%	p
age	<= 40	1		1			
	40.1 - 50	1.47	0.75-2.86	0.26	0.768	0.50-1.17	0.216
	50.1 - 74.9	1.83	0.98-3.44	0.058	0.776	0.53-1.14	0.2
	>= 75	5.84	2.69-12.6	<0.0001	1.24	0.68-2.26	0.48
Grade	1	1		1			
	2	1.29	0.83-2.02	0.261	1.72	1.19-2.49	0.004
	3	3.54	2.20-5.69	<0.0001	3.47	2.32-5.19	<0.0001
	undetermined	1.33	0.17-9.94	0.78	1.15	0.15-8.51	0.894
LVI	no	1		1			
	yes	1.56	1.14-2.14	0.006	1.36	1.06-1.74	0.016
ER	positive	1		1			
	negative	1.81	1.21-2.70	0.004	0.57	0.41-0.79	0.001
tumor size	<= 5 mm				1		
	6-10 mm				1.36	0.41-4.54	
	11-20 mm				1.53	0.48-4.87	
	> 20 mm				2.37	0.74-7.62	
SN metastases	micro metastases	1		1			
	macro metastases	1.39	1.005-1.91	0.046	1.06	0.83-1.36	0.647
SN number	1 or 2				1		
	3				0.597	0.42-0.85	0.004
SN positive	<= 2	1		1			
	> 2	1.16	0.60-2.23	0.656	1.07	0.53-2.16	0.859

LVI: lympho vascular invasion, ER: endocrine receptors, SN: sentinel node, HR: Hazard ratio.

5.4. Axillary Recurrence Rate

In univariate analysis there was no significant AR rate difference between eligibility or not to Z0011-trial. In binary logistic regression analysis, grade 3, mixt tumors and ER-negative tumors were associated with higher AR rate. (Supplementary-Table-9, Supplementary-Table-10).

5.5. Comparison of our Cohort and ACOSOG-Z0011-Trial

We observed 5-years OS and DFS differences between our cohort and Z0011-trial population according to ALND groups with several criteria's differences between these two populations (Supplementary-Table 11).

5.6. Invasive Lobular Cancer (ILC)

Among 412 patients with ILC, 73% (301 patients) met Z0011 criteria and involved-NSN rate at cALND was 35.1% (99/282), respectively 32.7 (68/208) and 41.9% (31/74) for ILCs that met Z0011 criteria versus those ILCs that did not (non-significant). Involved-NSN rate was higher for ILC versus Invasive Ductal Carcinoma (IDC) (OR: 1.46; p=0.035) (Table 4).

5.7. SN Micro-Metastases

SN micro-metastases was detected by SLNB in 1675 patients, with cALND in 85.2% (1428 patients) of cases and 216 patients who met Z0011 criteria had no cALND. Involved-NSN rate was reported for 11.8% of patients with cALND (139/1175) and 45 patients (32.4%) had >2 involved-NSN. AR rate was 0.068% (11/1616).

In univariate and multivariate analysis, OS and DFS were significantly higher for patients with cALND (Table 6). For OS, unfac-

orable significant prognostic factors were no cALND (HR 2.04, 95%CI: 1.025-4.057, p=0.042) and SBR grade 3 (HR: 4.00, 95%CI: 1.83-8.73, p<0.0001).

Supplementary Table 9: Factors correlated with Axillary Recurrence (AR) rate.

Axillary recurrence	No	%	Yes	%	Chi 2	
	Nb		Nb		p	
	Number	3458	99.2	28	0.8	
ACOSOG Z11	yes	2847	82.3	22	78.6	0.375
	no	611	17.7	6	21.4	
ALND	yes	3121	90.3	23	82.1	0.133
	no	337	9.7	5	17.9	
age	<= 40	238	6.9	4	14.3	0.094
	40.1 - 50	879	25.4	6	21.4	
	50.1 - 74.9	2138	61.9	14	50	
	>= 75	201	5.8	4	14.3	
Grade	1	1045	30.2	2	7.1	<0.0001
	2	1706	49.3	12	42.9	
	3	663	19.2	14	50	
	undetermined	44	1.3	0	0	
LVI	no	1987	65.4	10	38.5	0.005
	yes	1049	34.6	16	61.5	
Histology	Ductal	2815	81.4	21	75	0.052
	Lobular	398	11.5	3	10.7	
	Mixt	85	2.5	3	10.7	
	Others	160	4.6	1	3.6	
ER	negative	311	9.1	9	32.1	0.001
	positive	3123	90.9	19	67.9	
tumor size	<= 5 mm	108	3.1	0	0	0.681
	6-10 mm	608	17.7	4	14.3	
	11-20 mm	1830	53.4	15	53.6	
	> 20 mm	884	25.8	9	32.1	
SN metastases	micro metastases	1605	46.4	11	39.3	0.288
	macro metastases	1853	53.6	17	60.7	
tumor subtypes	Luminal A	1768	72.4	6	0.3	<0.0001
	HR- Her 2+	97	4	6	31.6	
	Triple negative	159	6.5	3	15.8	
	Lum B Her2- HR+ G3	279	11.4	4	21.1	
surgery	Lum B Her2+ HR+	139	5.7	0	0	
	conservative	2963	86.1	23	0.8	0.352
mastectomy	No	480	13.9	5	17.9	
	Yes	1047	30.3	6	21.4	0.401
chemotherapy	Yes	2336	67.6	22	78.6	
	unknown	75	2.2	0	0	
	No	146	4.4	3	12	0.189
radiotherapy	Yes	2972	90.4	21	84	
	unknown	171	5.2	1	4	
	1 or 2	2127	62.1	16	57.1	0.854
SN number	3	729	21.3	7	1	
	>= 4	570	16.6	5	17.9	
SN positive	<= 2	3297	96.3	27	96.4	0.721
	> 2	127	3.7	1	3.6	

ALND: axillary lymph node dissection, LVI: lympho vascular invasion, ER: endocrine receptors, SN: sentinel node.

Supplementary Table 10: Predictive factors of axillary recurrence.

predictive factors of AR	OR	CI 95%	p	
Grade	1	1		
	2	2.396	0.51-11.26	0.269
	3	5.4	1.09-26.67	0.039
LVI	no	1		
	yes	2.154	0.93-4.97	0.072
Histology	Ductal	1		
	Lobular	0.634	0.08-5.02	0.666
	Mixt	6.962	1.93-25.14	0.003
	Others	1.013	0.13-7.78	0.99
ER	positive	1		
	negative	2.818	1.11-7.18	0.03

Legends: LVI: lympho vascular invasion, ER: endocrine receptors, OR: Odd ratio.

Supplementary Table 11: Comparison of our cohort and Z00011 trial population according to ALND groups.

patients eligible for Z0011 trial		ALND				No ALND					
		Z0011	our cohort		Chi2	Z0011	our cohort		Chi2		
		Nb	%	Nb	%	p	Nb	%	p		
	Number	420		2616			436		287		
	median	56		56			54		60.56		
age											
Clinical stage	<= T1	284	67.6	2169	82.9	<0.0001	303	70.6	218	76.5	N.S.
	T2	134	31.9	446	17.1		126	29.4	67	23.5	
	unknown	2		1			7		2		
Tumor size (mm)	median	17		15			16		15		
ER status	positive	320	83.5	2372	91.3	<0.0001	328	83.7	261	92.9	<0.001
	negative	63	16.5	225	8.7		64	16.3	20	7.1	
	unknown	37		19			44		6		
LVI	yes	129	40.6	759	33.3	0.01	113	35.2	69	25.8	<0.02
	no	189	59.4	1522	66.7		208	64.8	198	74.2	
	unknown	102		335			115		20		
Grade	1	71	22	821	31.4	<0.0001	81	25.6	99	34.5	<0.001
	2	158	48.9	1280	48.9		148	46.8	136	47.4	
	3	94	29.1	488	18.7		87	27.5	46	16	
	unknown	97		27	1		120		6	2.1	
Histology	ductal	344	81.9	2174	83.1	<0.0001	356	84	232	80.8	N.S.
	lobular	27	6.4	271	10.4		36	8.5	30	10.5	
	other	45	10.7	171	6.5		32	7.5	25	8.7	
	unknown	4					12				
SN status	micro	137	37.5	1230	47	<0.001	164	44.8	216	75.3	<0.0001
	macro	228	62.5	1386	53		202	55.2	71	24.7	
	unknown	55					70				
NSN status	positive	97	27.3	497	24.8	N.S.					
	negative	258	69	1509	75.2						
	unknown	33		610							
Axillary recurrence	yes	2	0.5	17	0.7*	N.S.	4	0.9	5	1.7*	N.S.
	no			2565	99.3				282	98.3	
5-year OS		91.8		95.8			92.5		93.7		
5-year DFS		82.2		92.3			83.9		91.1		
Adjuvant therapy	yes	403	96	2514	92.8	<0.05	423	97	271	90.1	N.S.
	no	263	88.9	2339	97.3	<0.0001	277	89.6	264	93.6	<0.01
Radiotherapy	yes	33	11.1	64	2.7		32	10.4	12	4.3	
	unknown	124		213			127		11		

*p<0.05 In our cohort ALND vs non

Legends: ALND : axillary lymph node dissection, LVI: lympho vascular invasion, ER: endocrine receptors, SN: sentinel node, NSN: non sentinel node.

5.8. Mastectomy

Among 509 patients, cALND were performed in 457 cases respectively for 181 SN-micro-metastases (39.6%) and for 276 SN-macro-metastases (60.4%). (No cALND for 31 SN-micro-metastases and 21 SN-macro-metastases p=0.005). Patients had been treated by radiotherapy in 66% (31/47) of cases without cALND and in 83.7% (293/350) with cALND (p=0.005). We observed no-significant difference according to cALND or not for harvested SN-number, involved-SN number (<=2 versus >2), ER-status, tumor size, LVI, SBR-grade, histologic type and AR rate. More patients >75-years old had no cALND (28.8% versus 6.6%: 15/52 vs 30/457). In univariate and multivariate analysis, there was no significant impact on OS of cALND or not (HR: 1.25, 95%CI: 0.12-12.8, p=0.851). Significant factors on OS were SBR-grade 3 (HR: 9.91, 95%CI: 1.15-85.7, p=0.037), SN-macro-metastases (HR: 6.25, 95%CI: 1.05-37.1, p=0.044) and no radiotherapy (HR: 5.45, 95%CI: 1.81-16.4, p=0.003). There was also no significant impact on DFS of cALND or not (HR: 2.60, 95%CI: 0.87-7.76, p=0.087).

5.9. Patients Her2+ or Triple Negative or <50-Years

We have analyzed this population considered at high-risk [7, 12] versus others considered at low-risk (>50-years old and Her2-ER+ or Luminal-A or Luminal-B Her2-G3) for applicability of

Z0011-trial, AR rate, NSN-involvement rate and DFS. Among 1374 patients considered at high-risk, 77.9% were eligible to Z0011 trial (1071/1374) versus 85.2% (1064/1249) for low-risk (p<0.0001).

Involved-NSN rate at cALND were observed in 30.6% (316/1031) for high-risk group versus 29.2% (220/753) for low-risk group (p=0.275). Involved-NSN number >2 were observed in 50.6% in high-risk group (160/316) and 44.5% in low-risk group (98/220) (non-significant).

AR rates were 1.2% (16/1348) for high-risk group versus 0.5% (6/1249) for low-risk group (p=0.038). AR rates according to Z0011-eligibility were 1.2% (13/1054) and 0.6% (6/1064) respectively for high and low-risk groups (non-significant).

A cALND was performed more often for high-risk patients (53.4%: 1279/1375 versus 46.6%: 1114/1249, p<0.001). DFS were not significantly different for high-risk and for low-risk patients according to cALND or not.

6. Discussion

We found a high proportion of patients (81.9%) who met Z0011 criteria. Few authors have reported the proportion of patients eligible to Z0011-trial criteria on a large cohort: 12.1% (47/389) [13], 60.9% (558/916) [18], 69% (87/125) [14], 75% [15], 80% (2637/3312 of patients >66-years old) [17] and 93.3% (4482/4803) [16]. Higher OS and DFS survival rates were observed for patients eligible to Z0011 in comparison with patient's non-eligible in our study and in Delpech et al study [14].

6.1. NSN-Involvement Rate

Greater NSN-involvement rates were reported for patients non-eligible to Z0011-trial in comparison with eligible patients: respectively, 37.7% (174/461) in our study and 38.9% (14/36) in Delpech study [14] versus 25.7% (CI95%: 24.1-27.3, 757/2940) in literature (29.7% (25/84) [14], 24% (87/363) [15], 39% (51/132) [19], 27.3% (97/355) [2] and 24.8% (497/2006) in our study). For patients eligible to Z0011-trial, NSN-involvement rates were 36.3% (CI95%: 34.0-38.6, 593/1633) for SN-macro-metastasis (20%: 7/35 [13], 39.6%: 42/106 [19], 36.4%: 83/228 [2], 31.7%: 82/259 [15], 37.7%: 379/1005 in our study) and 12.06% (CI95%: 10.5-13.6, 205/1699) for SN-micro-metastases (5.7%: 5/88 [15], 10%: 14/137 [2], 34.6%: 9/26 [19], 13%: 59/447 SN-micro-metastases and ITC [3], 11.8%: 118/1001 in our study).

Few authors have reported involved-NSN number for patients eligible to Z0011 criteria, with only one involved-NSN in 71.4% (5/7) [13], 50.8% (26/51) [19], 62.7% (37/59) [3] and 57.7% (287/497) in our study (>1 involved-NSN in 42.2%, CI95%: 38.3-46.1, 259/614 of patients with involved-NSN), and with only one involved-NSN for SN-micro-metastases in 62.7% (37/59) [3] and 67.6% (94/139) in our study (>1 involved-NSN in 33.8%, CI95%: 27.2-40.4, 67/198). Higher rates of >1 involved-NSN for patient's non-eligible to Z0011 were observed, respectively 62.6% (109/174)

of patients with involved-SN in our study, and 78.6% (11/14) [14]. However, AR rate were not significantly different between eligible and non-eligible patients to Z0011 in our study, respectively 0.77% (22/2869) and 0.97% (6/617) but more non-eligible patients had received chemotherapy in comparison with eligible patients (76.4% versus 65.4%).

6.2. AR and Residual Axillary Nodal Burden (RNB) According to Adjuvant Therapies

RNB can be controlled by systemic therapies as AC, trastuzumab, endocrine therapy and tangential radiotherapy fields. More than 1 involved-NSN is in this perspective an important criterion. RNB was lesser when AC was realized before cALND (13/93: 14% versus 512/1612: 31.7%; $p < 0.001$) with > 2 NSN-involvement in 8 patients (8/93: 8.6%) versus 251 patients (251/1612: 15.6%) when AC was delivered after cALND (non-significant).

In trials with cALND randomization for women with non-involved SN, the false negative rates were 8.8% [20] and 9.8% [1] with respectively only 0.8% and 0.5% regional recurrences. In a previous study we reported that 14,095 patients who underwent SLNB for cN0 previously untreated BC experienced a 0.51% AR rate [21]. In Z0011-trial, the 10-years cumulative incidence of nodal recurrences were 0.5% in the cALND arm and 1.5% in the SLND arm ($p = 0.28$) [22]. In the present study, we could observe impact of ER-status and endocrine-therapy on AR rates with a significant difference ($p < 0.001$) between ER-positive and ER-negative tumors, respectively 0.6% (19/3142) and 2.8% (9/320) (OR: 2.82). AR rates were not significantly different between patients without PMRT in comparison with patients with breast or chest-wall radiotherapy (3/149: 2% versus 21/2993: 0.7%, $p = 0.102$).

6.3. Specific Patient's Populations

In our study, 77.9% (1071/1375) of high-risk patients met Z0011 criteria in comparison with 67% (125/186) [7] and 85% (205/242) [12] in others studies. In Giuliano et al. study [7], HER2-positivity was associated with the lowest rate of ineligibility compared with triple-negative BC and young age (< 50 -years) (16 vs 53 and 31 % respectively, $p = 0.01$). However, we observed different results (37 vs 32 and 21% respectively). In high-risk BC patients, NSN-involvement rates were 62% (23/37) [12], 38% (48/125) among patients who met Z0011 criteria [7] and 30.6% (316/1031) in our study.

In this specific population, with median follow-up of 5.5 years, there was no survival difference between patients with and without cALND [7], but when patients had 3 metastatic lymph nodes, the 5-year specific survival was significantly higher for patients with cALND compared with SLNB-alone: 91.5% and 85.1% ($p = 0.02$) [23].

6.4. Mastectomy and Positive SN

Mastectomy was done for 86 patients (9.2%) in IBCSG-23-01-trial [3] and 18 patients (7.7%) in AATRM-trial [24] without PMRT for

the majority of patients. No data was reported about mastectomy with SN-macro-metastases in previous randomized studies. Two trials explored omission of cALND for patients treated by mastectomy with involved-SN. BOOG-2013-07-trial [25] (closed for insufficient inclusions) and randomized SERC-trial [26] which is designed to investigate whether cALND can be safely omitted in SN-positive BC patients treated with mastectomy or conservative surgery.

6.5. Invasive Lobular Cancer

In Roberts et al. study [27], NSN-involvement rate was 40% (24/60) and was lower for ILCs that met Z0011 criteria versus those ILCs that did not (17 vs 56%; $p = 0.003$). In AMAROS-trial [28], NSN-involvement rate for ILCs was 43% (41/96). In our study, 73% (301/412) met Z0011 criteria and NSN-involvement rate was higher for ILC in comparison with IDC (OR: 1.46; $p = 0.035$) (99/282: 35.1% for ILC versus 510/1977: 25.8% for IDC).

7. Conclusion

A high patient's proportion (81.9%) met Z0011 criteria and a progressive significant decrease of cALND was reported. We observed a significant decrease of NSN-involvement rate when cALND was performed after AC. This therapeutic effect combined with therapeutic effect of tangential radiotherapy fields and endocrine-therapy could explain the low AR rate observed without cALND and absence of significant DFS difference between cALND and SLNB alone, except for SN micro-metastases.

Inclusion of patients in next trials which compared cALND or SLNB alone seems contributive for patients with SN-involvement, particularly for patients treated with mastectomy or for ILC, Her2+ and triple-negative tumors or patients < 50 -years (ie. SERC trial) [26].

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