Original Article

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Axillary Surgical Attitude Changing with Retrospective Application of *ACOSOG Z0011* Eligible Criteria: An Institutional Evaluation

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ABSTRACT

Objective: Sentinel lymph node biopsy (SLNB) represents the gold standard for axillary surgical staging. The aim of this study was to assess the proportion of axillary lymph node dissection (ALND) that could be avoided after retrospective application of the *ACOSOG Z0011* criteria and to evaluate the short-term complications associated with axillary surgery.

Materials and Methods: We reviewed breast cancer (BC) patients treated by primary breast-conserving surgery from 2012 to 2015. The percentage of SLNB vs ALND performed before and after the application of the *ACOSOG Z0011* criteria was calculated. Complications were analyzed using crosstabs, with $p<0.05$ considered significant.

Results: Two hundred fifty one patients with a median age of 59.3 years were included. BC tumors had a median size of 13 mm and were mostly unifocal (83.9%). There were 30.3% with 1-2 metastatic lymph nodes (MLN). ALND was performed in 44.2%. The patients with 1-2 MLN, had only SLNB in 14.5% of cases. By applying the *ACOSOG Z0011* criteria, ALND would have been avoided in 40.2% of patients. At least one postoperative complication was reported after SLNB or ALND for 45.7% and 74.7% of patients respectively. Seroma was the most frequent complication, and occurred in 29.3% of cases after SLNB and in 59.5% after ALND.

Conclusion: SNLB is the most commonly used axillary surgical staging procedure in this series (55.8%). With a retrospective application of the *ACOSOG Z0011* criteria in our population, ALND could have been avoided for 40.2% patients. Post-operative complications rate was higher after ALND, with a seroma rate at 59.5%.

Keywords: Breast-conserving surgery; sentinel lymph node biopsy; axillary surgery; axillary lymph node dissection; seroma

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Key Points

- The *ACOSOG Z0011* trial results have set a new standard for surgical management of the axilla.
- The results of Z0011 trial were received with some reluctance in the daily practice.
- By applying the Z0011 criteria, axillary lymph node dissection would have been avoided in 40.2% of patients.
- In our opinion surgical teams should not look with so much reluctance at the results of trials that may led to a change in surgical practice.

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women (1). Its management is complex and can involve a combination of different modalities such as surgery, radiotherapy, and various systemic treatments (2).

Surgical excision of the tumor remains an essential step in the therapeutic scheme for the treatment of BC. Surgical staging of the axilla is necessary for optimal treatment planning.

Until the early 2000s, axillary lymph node dissection (ALND) was the standard procedure used for the treatment and staging of axillary lymph nodes (ALN) (3-5). Nearly thirty years ago, the sentinel lymph

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node (LN) biopsy (SLNB) technique opened new perspectives in the management of patients with early BC (6). Since then, there has been an evident de-escalation of axillary surgical staging, giving way to the SLNB technique, which has become the gold standard in the management of BC at the early stage cT1-2N0 (7-9).

The short- and long-term side effects associated with ALND (seroma, wound healing problems, infection, neuropathy and especially lymphedema of the arm) have always been a concern. Comparative studies of morbidity with different types of axillary surgery (AS), such as that of Giuliano et al. (11), have shown that SLNB leads to fewer side effects than ALND, with an overall complication rate of 3% after SLNB compared to 35% after ALND (10, 11).

The pathological stage of the ALN represents a major prognostic factor for BC, but it is less commonly used for deciding adjuvant treatment (12). In this context and given the high morbidity rate of ALND, management strategies for micro- or macro-metastatic ALN have evolved considerably over time (3).

In 2011, the publication of the results of the *ACOSOG Z0011* trial led to a change in the axillary management of early-stage BC (7). They demonstrated that completion ALND (cALND) in patients with clinical T1-2 N0 tumors treated with breast-conserving surgery (BCS) and external radiotherapy (ER), with a maximum of two micro- or macro-metastatic SLN's, did not provide benefit in terms of overall survival (OS) or disease-free survival (DFS), especially in the case of adjuvant treatment with chemotherapy (CT) and/or endocrine therapy (ET) (9, 13, 14).

Following the publication of these results, some teams (mainly in the United States) quickly changed their clinical practices and decided to no longer perform cALND in this specific situation (15). On the other hand, in Europe, and at our institution, Institute Jules Bordet (IJB) in particular, the results of this study were received with some reluctance and raised many questions about the export of the *ACOSOG Z0011* criteria in the daily clinical situations and the risk of under-treatment linked to ignorance of complete ALN status (16, 17). Currently, the *ACOSOG Z0011* trial results have set the standard for surgical management of the axilla in patients meeting the trials inclusion criteria, included in all international and national recommendations (5, 15, 18, 19).

The aim of this study was to evaluate the possible modifications in the surgical attitude of the axilla by retrospective application of the *ACOSOG Z0011* trial criteria in a cohort of patients with early-stage invasive BC treated with BCS and adjuvant ER at the IJB. We also sought to compare the OS and DFS of these patients according to the degree of ALN invasion and to evaluate the rate of short-term post-operative complications according to the type of axillary surgery.

Materials and Methods

Study Population and Design

This was a retrospective, exploratory, monocentric study of patients with early-stage invasive BC, treated by BCS (and adjuvant ER) at the IJB over a period of 4 years (January 2012-December 2015). The study was approved by the IJB Ethics Committee under approval number CE3446.

Inclusion and exclusion criteria

We only included patients over 18 years of age with invasive BC clinically classified as cT1-2N0M0, treated with BCS, whole breast radiotherapy and adjuvant systemic treatment (CT and/or HT). Patients with invasive BC treated by mastectomy or BCS and intraoperative radiotherapy, as well as patients with metastatic or in situ BC were excluded.

Clinical Data and Procedures

All clinical data were extracted from patients computerized medical records and stored in a prepared database on REDCap (Research Electronic Data Capture). For each patient, the following information was collected: Demographic data, imaging characteristics of the tumor, clinical nodal status; tumor pathology data, pathological data of ALNs (number of invaded LNs, presence of micro- or macro-metastasis); data on therapeutic management including the type of axillary surgery (SLNB, SLNB and cALND or ALND) and adjuvant treatment; the follow-up data of recurrence (local or distant) and/or death; and data on post-operative complications.

Patients were divided into two groups: One group had only SLNB and the other group had an ALND (either SLNB plus cALND or ALND alone).

Study Evaluation Criteria

The primary endpoint measures were: The percentage of ALND that could have been avoided (number of ALNDs performed when only 1-2 SLNs were positive) and the percentage of types of axillary surgery performed (SLNB vs ALND) before and after application of the *ACOSOG Z0011* criteria.

The secondary endpoint measures were OS, DFS and percentage of short-term post-operative complications. OS was defined as the time interval between the date of diagnosis and the date of last follow-up or death (related to BC or death from any cause). DFS was defined as the time interval from the date of diagnosis to the date of first recurrence or last follow-up or death, whichever occurred first. Recurrence was regarded as any local, regional, or distant tumor recurrence. Patients alive at last follow-up or lost to follow-up were censored. Data on follow-up were collected until March 31, 2022.

The post-operative complications assessed were: Wound dehiscence, hematoma (breast and/or axillary), (local) infection at the axillary surgery site divided into superficial (presence of inflammatory signs) or deep (microbial fluid culture positive), and seroma (serous and/or lymphatic collection at the axillary surgical site, clinically detected and requiring at least 1 puncture). Short-term post-operative complications were considered complications that occurred less than 3 months postoperatively. Due to the lack of systematic registration of late complications, such as lymphedema or shoulder neuropathy, their incidence could not be assessed.

Statistical Analysis

The statistical analysis was conducted using SAS software version 9.4. Descriptive statistics were employed to summarize the patient cohort and tumor characteristics, including nominal and categorical variables reported as frequencies and proportions, and continuous variables reported as means and standard deviations or medians and interquartile ranges.

Cross-tabulation was used to examine the relationship between nodal status and type of surgery. Survival rates were analyzed using Kaplan-Meier curves, and compared between patients without LN metastasis, those with 1-2 LN metastases (per *ACOSOG Z0011* criteria), and

those with ≥3 LN metastases. Time to death and time to event were calculated using the diagnosis date as a reference point, and both OS and DFS were reported at five years.

Short-term complications were analyzed based on the type of axillary surgery (SLNB vs. ALND) through cross-tabulation and statistical tests such as the chi-squared test or Fisher's Exact test. A *p*-value of less than 0.05 was considered statistically significant for all analysis.

Results

Characteristics of the study population

During the study period, 251 patients with invasive BC (cT1-2N0M0) were treated at the IJB by BCS followed by external whole breast radiotherapy and were included in the study. The clinical and pathological characteristics of the population studied are shown in Table 1. Women had a median age of 59.3 years and a median body mass index of 24.09 kg/m², 67.8% were post-menopausal. The median tumor size was 13 mm (1.00-45.00 mm), tumors were mostly unifocal (83.9%) and of the infiltrating ductal carcinoma type (70.1%). Most of the tumors were luminal A molecular subtype (66.4%). Regarding hormone receptor status, 90.8% were positive for estrogen receptor (ER) and 82% for progesterone receptor. As adjuvant systemic treatment, 45.4% of patients received CT and 92.4% ET.

Type of axillary surgery and LN status

One hundred forty (55.8%) had only a SLNB and 111/251 patients (44.2%) underwent an ALND. Among the patients with ALND, 87/111 patients had a cALND after SLNB. In our cohort, 165 patients did not present with ALN involvement. Among patients with ALN involvement, 76 patients (30.3%) had only 1-2 metastatic ALNs. The median number of SLNs removed was 2 (1-7) and the median number of LNs in the ALND specimen was 14 (2-34), with a median number of invaded ALNs of 1 (1-20, for cN0). The characteristics of removed ALNs are listed in Table 2. Among the 78 patients treated with SLNB followed by cALND because of metastasis of the SLN, 25.6% of patients had at least one positive complementary LN node in the cALND specimen.

Axillary surgical procedure and axillary LN status

Among the 165 patients whose pathologic ALN status was negative (pN0), 77.6% patients were treated with SLNB alone. Among the 76 patients with only 1-2 metastatic LNs (and thus meet the *ACOSOG Z0011* criteria), only 14.5% of patients underwent SLNB alone, while 65 of them, representing 85.5% of patients, were treated by radical axillary surgery (ALND) in IJB. The distribution of the type of axillary surgery according to axillary LN status is presented in Table 3. By applying the *ACOSOG Z0011* criteria to our entire population, only 10/251 patients (3.9%) should have had an cALND, so we could have avoided cALND in 101/251 patients (40.2%) (Figure 1).

OS and DFS

The median follow-up of patients was 7 years. At the time of analysis, 16 (6.4%) patients had died. The 5-year OS was 96.9%: 95.7% in patients without metastasis of the LNs, 98.5% in patients with metastasis of only 1-2 LNs (*ACOSOG Z0011* criteria) and 100% for in patients with metastasis of ≥3 SLNs ($p = 0.101$). In total, 18 (7.2%) patients experienced recurrence: One patient with a loco-regional relapse and 17 patients with a distant relapse. The 5-year DFS was 96% overall: 94.4% in patients without metastasis of the LNs, 98.6% in patients with metastasis of 1-2 LNs (meeting the *ACOSOG Z0011* criteria) and 100% in patients with metastasis of ≥3 SLNs ($p = 0.146$).

Table 1. Clinical, pathological and treatment characteristics of the study population

Characteristics	Entire cohort	
	n	%
Patients	251	100
Age		
Median	59.3	
Mean (range)	58.6 (26.8-85.8)	
BMI		
Median	24.09	
Mean (range)	25.01 (16.49-48.44)	
<25	152	60.56
25 - <30	64	25.50
≥30	35	13.94
Pre-menopause	79	32.11
Post-menopause	167	67.89
Pathological tumor size (mm)		
Median	13	
Mean (range)	14.24 (1.00-45.00)	
<10 mm	51	20.32
10-20 mm	168	66.93
>20 mm	32	12.75
Histological type		
IDC	176	70.10
ILC	70	27.90
Others	5	2.00
Tumor grade		
G1	78	31.08
G2	107	42.63
G3	66	26.29
Ki-67 status		
Median	10	
Mean (range)	19.34 (2.00 – 95.00)	
Molecular subtype		
Luminal A	166	66.40
Luminal B	62	24.80
HER2-enriched	5	2.06
Triple-negative	17	7.00
Type of axillary surgery		
SLNB	140	55.77
SLNB + cALND	87	34.66
ALND	24	9.57
Chemotherapy		
Yes	114	45.42
No	137	54.58
Endocrine therapy		
Yes	232	92.43
No	19	7.57

BMI: body mass index; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; HER2: human epidermal growth factor receptor 2; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection

Postoperative complications

In our cohort, 58.5% of patients experienced at least one short-term postoperative complication, 64/140 patients (45.7%) for the SLNB-only group and 83/111 (74.7%) in the ALND group. Axillary seroma was the most common complication, 29.3% in the SLNB-only group and 59.4% in the ALND group. The difference for other complications such as hematoma, wound dehiscence, and infections between the 2 groups (SLNB-only vs ALND) was not significant. Regarding infectious problems, the most common infectious agent identified was *Staphylococcus epidermidis*. A summary of complications is presented in Table 4.

Table 2. The characteristics of removed axillary lymph nodes

Characteristics	n	%
Number of SLNs		
Median (SQR)	2	(2-3)
Mean (range)	2.3	(1-7)
SLN		
Negative	141	62.11
Positive	86	37.89
Number of ALND nodes		
Median	14	
Mean (range)	13.9	(2-34)
ALND nodes		
Negative	37	33.33
Positive	74	66.67
Lymph node status		
Negative	16	65.74
1-2 positive	76	30.28
≥3 positive	10	23.74
LNs status in involved SLN and cALND		
Complementary positive LN	20	25.64
Complementary negative LN	58	74.36

SLN: sentinel lymph node; ALND: axillary lymph node dissection; LN: lymph node; cALND: completion axillary lymph node dissection

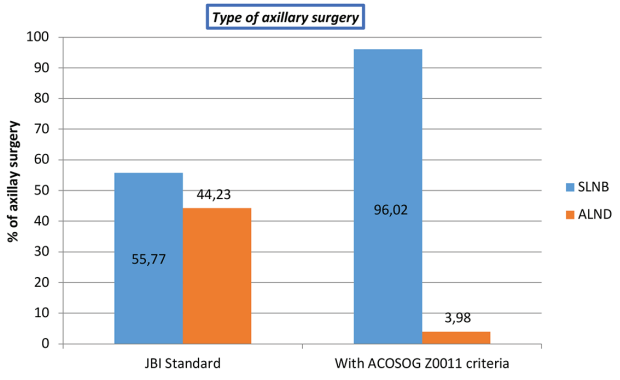

Figure 1. Comparison between the type of standard axillary surgery at IJB and according to the *ACOSOG Z001* criteria for cT1-2N0M0 patients. Figure 1 shows the comparison of the type of axillary surgery according to the standard procedure at the JBI during the study period and the possible effect of application of the *ACOSOG Z0011* criteria. The blue colons represent the patients with a sentinel lymph node biopsy and the orange colons those with axillary lymph node dissection

Discussion and Conclusion

As part of the de-escalation of BC surgical treatment, axillary surgery has undergone major changes over the past 3 decades. Our study was able to show that 40.2% of the patients in our cohort could have been spared more aggressive axillary surgery like ALND if the patient selection criteria of the *ACOSOG Z0011* study were applied. More particularly for the group of patients with 1-2 metastatic SLNs, ALND could have been avoided in almost 9 out of 10 patients (65/76 patients). This change in the axillary surgical attitude seems to be in agreement with other studies published after the adoption of the *ACOSOG Z0011* criteria in the USA and Europe (20, 21-23). Morrow and colleagues, in a prospective study that evaluated the rates of ALND in patients eligible for *ACOSOG Z0011*, showed that 84% of ALNDs were prevented in their cohort (21). Similarly, Hennigs and colleagues, in a retrospective study evaluating the impact of the *ACOSOG Z0011* criteria on the axillary management of patients with BC, reported that nearly one in two patients still had ALND in situations where it could have been avoided (22). The main argument put forward for performing an ALND when it was not recommended was the fear of under-treatment which could impact the survival of the patient. This was emphasized by the fact that he indication for adjuvant CT sometimes depended on the number of metastatic ALN, which is not actually known when an ALND is not performed (5, 23). However, this fear of under treatment led to the realization of an ALND in 37/165 patients (22.4%) who had a negative SLN status. The reasons given for the completion of the ALND in our series were either the presence of isolated tumor cells (pN0, i+) in the SLN, or a tumor size >3 cm, or the presence of a multifocal tumor.

In our cohort, among the 72 patients who had 1-2 metastatic SLNs, only 21.7% of patients had at least one additional positive LN after cALND. These results are in concordance with the data of the *ACOSOG Z0011* trial that reports in the ALND arm, a complementary positive LN rate of 27.3%, and close to that reported by Galimberti et al. (23), in which the rate was 13% (4, 13). Some studies have also demonstrated that after an additional ALND, the information obtained did not have a significant impact on survival and on the indication of systemic adjuvant treatment (CT and/or HT) (9, 13, 14). The AMAROS trial compared in patients with T1-2N0 BC, ALND to axillary radiotherapy in case of positive SLNs (1 to 2 or even 3-4), showed that the additional cALND had no impact on adjuvant treatment, and that other factors such as age, tumor grade, size of metastasis in the SLN and multifocal tumors were significantly related

Table 3. Distribution of type of axillary surgeries performed in our cohort according to pathological lymph node status

Pathological nodal status	Axillary surgical procedure			
	SLNB		ALND	
	n	%	n	%
Negative	128	77.57	37	22.43
Positive: 1-2 lymph nodes	11	14.47	65	85.53
Positive: >2 lymph nodes	1	10.00	09	90.00

SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection

Table 4. Short-term post-operative complications (<3 months) according to different type of axillary surgeries

Complication type	SLNB		ALND		*p*-value
	n	%	n	%	
Hematoma	6	4.29	9	8.11	0.2550
Axillary seroma	41	29.29	66	59.46	**<0.0001**
Wound dehiscence	6	4.29	6	5.41	0.7650
Infections - Superficial	15	10.71	20	18.02	0.1470
- Deep	2	1.43	7	6.31	0.4650
At least one complication	64	45.71	83	74.77	**<0.0001**

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

to the prescription of CT and not the number of complementary positive LNs (4, 9, 13, 14, 24).

Currently, ALND has been effectively replaced by the SLNB technique, in almost all cases of primary surgery. Even if axillary LN involvement represents one of the major prognostic factors in BC, the adoption of a more conservative axillary surgery, like SLNB is a safe attitude with respect to survival of patients (5, 11, 25).

In the current study, there was no difference in OS and DFS between patients without metastatic invasion of the LNs compared to patients with metastatic invasion of only 1-2 LNs (*ACOSOG Z0011* criteria) or with metastatic invasion of ≥3 SLNs ($p = 0.101$ and $p = 0.146$). These results are more likely the reflection of breast tumor characteristics (size, grade, molecular subtype, etc.) and probably the effect of the adjuvant treatments (used to treat our patients), than a reflection of the surgical aggressiveness.

These findings are in accordance with the *ACOSOG Z0011* trial that was able to demonstrate that removing "all" positive ALN does not improve long-term patient survival, in cases where the axillary tumor burden is low. The results updated in 2017 (10 years of follow-up) confirmed the absence of significant difference in terms of OS (83.6% for the ALND group versus 86.3% for the SLNB group, $p = 0.72$), DFS (78.2% for the ALND group versus 80.2% for the SLNB group, $p = 0.44$) and axillary recurrence (0.5% in the ALND group versus 1.5% in the SLNB group) (13, 20).

As several studies have already shown, patients treated with SLNB alone have fewer immediate and especially long-term postoperative complications compared to patients who have undergone ALND (6, 10, 11, 24, 25). In our study, we were also able to show a significant reduction ($p<0.0001$) in the rate of complications between these 2 groups. As expected, following ALND, axillary seroma was the most common complication in 59.5% of patients.

Information on short-term complications such as seromas, hematoma, wound dehiscence, and infection, is rarely reported in the literature. Nevertheless, Purushotham et al. (10) showed a significant reduction in physical arm morbidity over one year of follow-up in patients who underwent SNLB only compared to patients who underwent ALND. Numbness, paresthesia, and loss of sensitivity were also significantly reduced (10). The Milan group who compared the 2 types of axillary surgery over a period of 6 months, also showed that patients in the SLNB group had less pain and numbness and had better arm mobility than those who underwent ALND (6). Warmuth et al. (26) showed that inflammatory problems and/or infection of the arm or breast are common in patients treated with BCS and ALND. Abass et al. (27) published the results of a prospective study of patients who underwent ALND, which confirmed that more than 40% of patients experienced adverse events, primarily seroma formation and paresthesia.

Long-term complications are widely reported in the literature and that these can have a greater negative influence on the quality of life of patients, but the short time complications must not be neglected (24). Our retrospective analysis shows that complications such as chronic pain, impaired arm mobility, paresthesia or even arm lymphedema are less well documented in the follow-up of patients in everyday practice. In the future, we, like other care givers, should provide a standard evaluation of these short and long-term complications after BC and axillary surgery in order to have more precise information on their incidence, and be able to better treat or prevent them.

In an era of accelerated innovation in medicine, with new and rapidly changing clinical practices, the new surgical practice to align with evidence-based guidelines has not consistently been adopted promptly, in all surgical disciplines (28). Randomized controlled trials comparing different surgical procedures are relatively rare, due principally to methodological difficulties. Moreover, they are also most often received with scepticism and reluctance, and often criticized. This was also the situation for *ACOSOG Z0011* trial (16, 17, 28). This delay in adopting changes in surgery can have consequences especially on patients, but also on health systems. A recent retrospective evaluation of nearly 14.000 patients with *ACOSOG Z0011* criteria from 179 German breast cancer units, showed that the implementation of *ACOSOG Z0011*, resulted in gain of 335 quality-adjusted life-years and substantial cost savings for the society (1,924 EUR per patient). The authors concluded that this gain would have been more than double if all of the patients had been treated according to ACOSOG Z0011 trial recommendations (29).

Study Limitations

This study has several limitations. First, the exploratory retrospective nature of the study, second, the limited number of patients analyzed. Also, with this study design, we could not account for all the different reasons why a certain patient underwent ALND and not SLNB and vice versa. And not last, the fact that there has not been the possibility

of studying the adoption of the *ACOSOG Z0011* criteria on the change in axillary surgical attitude within our study cohort, by the absence of a real control group. Moreover, this cohort represents the real-world experience. Furthermore, we would like to highlight our opinion that surgical teams should not look with so much reluctance at the results of trials that may led to a change in surgical practice.

The SLNB was the most used axillary surgical procedure (55.8%) in our series of patients with early-stage invasive BC, and an axillary LN involvement was observed in 34.2% of patients. With the retrospective application of the ACOSOG Z0011 criteria to our study population, 40.2% of ALNDs could have been avoided in our patients. Short-term post-operative complications are higher after ALND, with an estimated seroma rate of 59.5%. Standard evaluation of these short- and long-term postoperative complications should be performed regularly for our patients in order to have more precise information on their incidence and to be able to subsequently improve the quality of life of our patients.

Ethics Committee Approval: The study was approved by the IJB Ethics Committee under approval number CE3446.

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.F.P., M.R., D.L., I.V., F.D.N.; Concept: C.F.P., L.D.N., I.V., F.D.N.; Design: C.F.P., L.D.N., M.M., F.D.N.; Data Collection or Processing: C.F.P., L.D.N., E.E.H., M.M.; Analysis or Interpretation: C.F.P., L.D.N., M.M., I.V., F.D.N.; Literature Search: C.F.P., L.D.N., E.E.H.; Writing: C.F.P., L.D.N., E.E.H., M.M., M.R., D.L., I.V., F.D.N.

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