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The current application of ACOSOG Z0011 trial results: Is further implementation of sentinel lymph node intra-operative histopathological examination mandatory in breast cancer patients – a single-center analysis

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The main objective of the ACOSOG Z0011 trial was to determine the impact of abandoning complete axillary lymph node dissection (ALND) on survival of breast cancer patients with sentinel node lymph (SLN) metastasis in whom breast conserving therapy (BCT) had been performed. The aim of our study was to assess the clinical value of intra-operative histopathological examination of SLN. Our study comprised 1284 invasive breast cancer patients in whom sentinel lymph node biopsy (SLNB) was carried out. SLN intra-operative histopathological assessment was routinely performed in patients treated within the first period (07.2013–06.2014). However, the decision regarding intra-operative assessment was made by the surgeon for the patients who underwent this evaluation in the later period 07.2014–06.2015 and were submitted for BCT. BCT was performed in 72.4% of patients. In total, 316 patients (24.6%) developed SLN-metastasis. Within the period 07.2014–06.2015, SLN intra-operative microscopic evaluation was performed in 20.8% of patients submitted for BCT. ALND was omitted in 27.5% of patients demonstrating SLN metastasis, in comparison with 15.5% of the group from the previous period (p=0.0094). The proportion of patients demonstrating macrometastasis in SLN who received conservative treatment to the axilla increased from 5.4% to 23.1% (p=0.0007). The choice of SLN final histopathological assessment may allow for deferral of decision on more extensive surgery of the axilla in patients submitted for SLNB. The omission of routinely-performed SLN intra-operative histopathological evaluation has led to a statistically significant increase in the proportion of patients in whom complete ALND was avoided.

Key words: breast cancer, ACOSOG Z0011, sentinel lymph node biopsy, macrometastasis

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was performed to determine the impact of omitting complete axillary lymph node dissection (ALND) on the survival of breast cancer patients with sentinel lymph node (SLN) macrometastasis [1]. In each patient, sentinel lymph node biopsy (SLNB) and breast conserving therapy (BCT) including post-operative standard tangential field radiation was performed. The SLN-positive patients were randomized into two arms: one receiving complete ALND, and the receiving no radical treatment. Neither five-year overall survival (OS) nor disease-free survival (DFS) differed significantly between the two groups. These observations have led to the creation of a new therapeutic option for patients who underwent SLNB and developed macrometastasis in no more than two lymph nodes.

In current diagnostic and therapeutic guidelines on the management of early breast cancer patients, SLNB remains the gold standard [2, 3]. Dissected SLNs require pathological examination, which is either intra-operative or final, depending on the cancer center.

The American Joint Committee on Cancer classification classifies metastasis as isolated tumor cells (ITC), where the lesions are smaller than 0.2 mm, micrometastasis (0.2–2.0 mm) and macrometastasis (greater than 2.0 mm)

[4]. The detection of ITC or micrometastasis in SLN does not require radical surgery, i.e. complete ALND [2, 3, 5]. The findings of the ACOSOG Z0011 trial indicate that ALND may be omitted in patients presenting SLN macrometastasis.

The Z0011 also examined other clinical issues concerning the studied group of patients. The aim of the present study was to assess the necessity of conducting SLN intra-operative histopathological examination in breast cancer patients. Possibility of choosing to perform conservative treatment in the case of SLN macrometastasis significantly decreases the legitimacy of intra-operative SLN histopathological examination.

Patients and methods

The examined group of patients. A total number of 1284 early stage invasive breast cancer patients, clinically node negative, were enrolled into the trial. The prospective study was conducted from 07.2013 to 06.2015. Enrolled patients underwent full surgical treatment for breast cancer in our hospital. SNLB was performed in all analyzed cases. During the first part of the study (07.2013–06.2014), SLN intra-operative histopathological examination (using frozen section analysis – FSA) was routinely performed during the SLNB procedure. If macrometastasis was discovered, ALND was immediately conducted. Management was performed according to the standards of invasive carcinoma treatment valid in our hospital.

In the successive period (07.2014–06.2015), routine SLN intra-operative evaluation was withdrawn for patients who underwent BCT. The decision to perform intra-operative pathological assessment was made by the operating surgeon. Patients requiring mastectomy still underwent SLN intra-operative pathological examination (by FSA) – Figure 1.

Follow up was carried out until the end of December 2016.

Clinical features. In the analyzed group of patients, the following clinical features were evaluated: age, size of primary tumor – clinical (cT) and pathological (pT) assessment, histopathological type and grade, multifocality and vascular invasion, involvement of axillary lymph nodes – histopathological evaluation, presence of estrogen (ER) and progesterone (PR) receptors, HER2 receptor expression [6], surrogate of intrinsic subtype of breast cancer [7, 8], number of dissected SLNs. Clinical consequences resulting from withdrawal of routinely performed SLN intra-operative histopathological examination within the first period were evaluated. For this purpose, the proportion of cases requiring radicalization of surgical approach, e.g. ALND or conservative treatment, was assessed in the group of patients presenting metastasis in SLN. The observation period was on average 29.7 months (ranging from 18 to 42 months).

Statistical analysis. Because the analyzed variables were not normally distributed within the studied patient groups, the Mann-Whitney U-test was used for comparisons of continuous variables between these groups. The independence of nominal variables between the studied groups was analyzed in two steps. For initial calculations, the goodness-of-fit test (i.e. the G-test) was used. If the level of statistical significance of this test was below the accepted threshold (alpha=0.05), the independence of each level of nominal variables was analyzed with the use of the Pearson's chi-squared test. This analysis did not address any differences in data missing between the periods, nor was missing data included in the analysis. The statistical analysis was performed using Microsoft Excel, STATISTICA v.12 (StatSoft) and DescTools software, written in R.

Results

No statistically significant differences were observed between the two periods with regard to the majority of clinical characteristics (Table 1). In total, 929 patients (72.4%) underwent BCT, with mastectomy performed in the

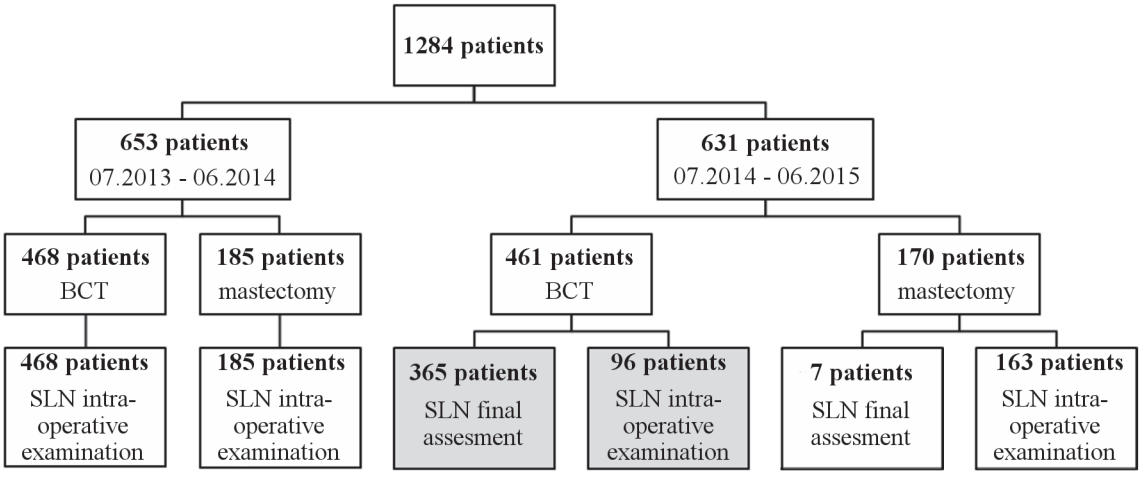

Figure 1. Patients submitted to the procedure – type of SLN histopathological examination.

remaining 355 cases (27.6%). The proportions of these surgical procedures did not differ significantly between the two periods (p=0.5779). The presence of metastasis in the SLN was detected in 316 cases (24.6%): in 26.6% of patients (174/653) during the first period, and in 22.5% (142/631) during the successive period (p=0.0849).

Most SLN metastasis was macrometastasis: 276 patients (87.3% of cases). Micrometastasis was diagnosed in 40 cases (12.7%). No statistically significant differences were observed between the two analyzed periods regarding the distribution of SLN metastasis (p=0.5018). ALND was omitted in 27.5% of patients (39/142) with SLN metastasis treated within the second period compared to 15.5% (27/174) from the previous period (p=0.0094) – Table 2. In the second period, SLN intra-operative examination was not performed in 79.2% of patients who underwent BCT (365/461). In group of 78 patients with SLN macrometastasis, ALND was not performed in 23.1% of cases, compared to 5.4% in BCT patients treated in the first period (p=0.0007). In patients requiring mastectomy, conservative treatment of the axilla was the method of choice in 16.7% of cases compared to 3.5% in those treated from 07.2013 to 06.2014 (p=0.0221) – Table 2.

SLN intra-operative evaluation was performed in 96 patients who underwent BCT in the period 07.2014–06.2015. The most frequent reason for not abandoning intra-operative examination in the second period was intra-operative suspicion of SLN metastasis (90/96) based on macroscopic assessment by the surgeon. Metastatic lesions were detected in 72 patients from the deferred group (19.7%) and in 18 patients from the intra-operative group (18.8%) – Table 3.

Within the period preceding the changes of SLN evaluation, 19 patients submitted to BCT (4.1% of all treated patients) required deferred ALND. The most common reason for this course of action was a false negative result of SLN intra-operative histopathological examination with presence of metastasis (18 patients – 94.7%) exceeding 2 mm detected by SLN final assessment. In one case it was the preference of the patient.

Table 1. Study patients – clinical and pathological features.

Clinical and pathological features	Time frame 07.2013–06.2014 n=653 (%)	Time frame 07.2014–06.2015 n=631 (%)	p-value
Mean age [years]	58.7	58.8	0.8471
Mean tumor size cT [mm]	22.3	21.7	0.4293
Tumor size (cT):			
CT1	356 (54.5)	370 (58.6)	
CT2	283 (43.3)	241 (38.2)	0.1047
CT3	13 (2.0)	20 (3.2)	
CT4	1 (0.2)	0 (0.0)	
Histopathological type of cancer:			
invasive ductal	552 (84.5)	555 (88.0)	0.0847
invasive lobular	65 (10.0)	56 (8.9)	
invasive – other types	36 (5.5)	20 (3.2)	
Histopathological grade:			
G1	39 (6.0)	26 (4.1)	
G2	479 (73.4)	466 (73.9)	0.2314
G3	111 (17.0)	105 (16.6)	
missing	24 (3.6)	34 (5.4)	
Tumor size (pT) [mm]	21.0	20.9	0.8459
Tumor size (pT):			
pT1	378 (57.9)	354 (56.1)	
pT2	261 (40.0)	262 (41.5)	0.9777
pT3	11 (1.7)	12 (1.9)	
pT4	1 (0.2)	1 (0.2)	
pTx	2 (0.3)	2 (0.3)	
Axillary lymph nodes involvement (pN)			
pN0	485 (74.3)	491 (77.8)	
pN1	123 (18.8)	112 (17.7)	0.0422
pN2	38 (5.8)	18 (2.9)	
pN3	7 (1.1)	10 (1.6)	
Tumor multifocality	81 (12.4)	84 (13.3)	0.6270
Vascular invasion	21 (3.2)	17 (2.7)	0.5812
ER(+)	546 (83.6)	516 (81.8)	
ER(-)	107 (16.4)	114 (18.1)	0.4290
missing	0 (0.0)	1 (0.1)	
PgR(+)	491 (75.2)	436 (69.1)	
PgR(-)	162 (24.8)	194 (30.7)	0.0340
missing	0 (0.0)	1 (0.2)	
HER2(+)	97 (14.9)	81 (12.8)	
HER2(-)	556 (85.1)	547 (86.7)	0.1264
missing	0 (0.0)	3 (0.5)	
Molecular type of the breast cancer:			
luminal A	189 (28.9)	188 (29.8)	
luminal B HER2(-)	253 (38.7)	274 (43.4)	
luminal B HER2(+)	66 (10.1)	52 (8.2)	0.5657
non-luminal HER2(+)	31 (4.7)	29 (4.6)	
triple negative	73 (11.2)	82 (13.0)	
missing	41 (6.3)	6 (1.0)	
Number of dissected SLNs:			
mastectomy	2.5±1.2	2.7±1.3	0.0647
BCT+SLN intra-operative examination	2.4±1.1	2.2±1.0	0.0619
BCT+SLN final assessment	–	2.3±1.0	–

Table 2. Study group – size of metastasis in SLN and type of treatment.

Size of metastasis	Time frame 07.2013–06.2014 n=174 (%)		Time frame 07.2014–06.2015 n=142 (%)	
	ALND n (%)	SLNB only n (%)	ALND n (%)	SLNB only n (%)
Macrometastasis:				
BCT	88 (94.6)	5 (5.4)	60 (76.9)	18 (23.1)
mastectomy	55 (96.5)	2 (3.5)	40 (83.3)	8 (16.7)
Micrometastasis:				
BCT	4 (20.0)	16 (80.0)	1 (8.3)	11 (91.7)
mastectomy	–	4 (100.0)	2 (40.0)	2 (50.0)
Total	147	27	103	39

Table 3. Characteristics of patients recommended for BCT between 07.2014-06.2015 – a comparison of the type of metastatic lesions revealed in SLN and selected treatment.

Type of SLN histopathological evaluation	Type of metastatic lesions		
	Total n (%)	Macro-metastasis n (%)	Micro-metastasis n (%)
Intra-operative examination (n=96)	18 (18.8)	17 (94.4)	1 (5.6)
ALND	13 (72.2)	13 (76.5)	–
SLNB only	5 (27.8)	4 (23.5)	1 (100.0)
Final assessment (n=365)	72 (19.7)	61 (84.7)	11 (15.3)
ALND	48 (66.7)	47 (77.0)	1 (9.1)
SLNB only	24 (33.3)	14 (23.0)	10 (90.9)
Total	90	78	12

Within the second analyzed period, ALND was applied in 51 cases following BCT (11.1%; p=0.0001). Most of these cases were patients in whom SLN intra-operative histopathological evaluation was not performed, and therefore metastasis was detected during the final assessment (48/51). In two cases, the reason for ALND deferral was a false negative result for the SLN intra-operative examination, one case was deferred at the request of the patient.

Among our study group, 1260 patients (98.1%) have follow-up information. In those being operated within the first period, 32 deaths were recorded. 15 cases resulted in progression of breast cancer (metastatic spread), remaining 17 were caused by other factors (comorbidities). Following second period, death occurred in 16 patients; 14 due to the spread of the disease, 2 from comorbidities.

Discussion

Although this study does not attempt to replicate the Z0011 trial, it does concern previously established goals and conclusions. Its aim was to determine the clinical consequences ensuing from the omission of routinely performed SLN intra-operative histopathological examination.

Morrow et al. reports that 292,130 new cases of breast cancer were recorded in the US alone in 2015 [9]. Data from the same period from Great Britain [10] and the Netherlands [11] also confirms a high prevalence of breast cancer in these countries. In early breast cancer, the use of limited surgery is feasible in the majority of cases. In the light of the results of the Z0011 trial, the clinical goals considered in our analysis may apply to the treatment of thousands of early-stage breast cancer patients.

The results of the Z0011 trial raised the question of whether SLN intra-operative histopathological examination should be performed in breast cancer patients submitted for SLNB. Application of the method of treatment proposed by the authors allows for deferral of the decision on whether to radicalize the surgical approach until SLN final assessment is obtained. In the present analysis, conservative treatment without supplementary ALND was performed in one third of patients diagnosed with SLN macrometastasis submitted for BCT. The restriction of ALND allowed the risk of adverse effects resulting from surgical treatment to be reduced [12, 13].

By omitting SLN intra-operative histopathological examination, the patient is relieved of any need to give pre-operative consent for ALND, which is often an emotional decision. In the event of macrometastasis detection in SLN, the data in the final pathology report allows the most efficient conservative treatment to be chosen. Hence, the avoidance of complete ALND was greater in patients treated within the second period.

However, in some cases, especially when informed consent is lacking for conservative treatment following diagnosis of SLN metastasis or extracapsular invasion, the omission of SLN intra-operative histopathological examination hinders immediate radicalization of the surgical approach. These doubts were expressed in the present study by 20% of patients submitted for BCT and SLNB, who also underwent SLN intra-operative histopathological examination at the request of the surgeon.

A significant decrease in the use of such intra-operative examination was noticed by Caudle et al. [14]. The proportion undergoing examination fell from 69% in the first period to 26% within one year following publication of Z0011 trial results ($p<0.001$). Changing patterns in diagnostics and treatment in patients with SLN macrometastasis triggered a decrease in complete ALND (from 85% to 24% after Z0011; $p<0.001$) and length of surgery (from 92 to 79 minutes; $p<0.001$).

A multicenter trial by the Melbourne Breast Group examined the management of breast cancer in patients with metastasis in SLN. The percentage of patients undergoing ALND following macrometastasis detection fell from 83.1% in the years 2009–2010 (pre-Z0011 era) to 68.8% in the period 2011–2012 (post-Z0011 era). The authors describe it as a worldwide trend [15]. This finding has been also confirmed in different papers [16, 17].

The above statement refers only to BCT patients meeting the Z0011 criteria, intra-operative SLN verification is still indicated in the case that mastectomy is necessary. The detection of macrometastasis in the intra-operative examination requires a more extensive procedure and immediate ALND in mastectomy patients [18].

High risk breast cancer patients, i.e. those who are triple negative, HER2-positive, or have a young age at the onset of disease, and in whom SLN macrometastasis has been detected, may also benefit from conservative treatment [19]. Regardless of the type of performed treatment (SLNB or SLNB+ALND), no differences in the long-term outcomes of therapy were revealed (mean follow-up 5.5 years; p=0.94). These findings emphasize the decreasing importance of SLN intra-operative histopathological examination.

Similar results on the possible application of different approaches of disease management in patients with a high risk of breast cancer and the presence of metastasis in SLN were obtained by Mamtani et al. [20], with similar inclusion criteria as those used by Chung [19]. Within an average 31-month follow-up (moderate-risk breast cancer), no isolated regional recurrence in the axilla was found. In both groups, however, single cases of local recurrence in breasts and distant metastases were detected [18].

Since the publication of the Z0011 trial, the results have remained a subject of debate [16, 17, 21]. However, a subsequent study examines the outcome of patients following a post-operative follow-up period of over nine years [22]. No statistically significant differences were found between two compared groups with regard to locoregional recurrence-free survival (p=0.13), combined ratio of regional recurrence (0.5% – SLNB+ALND group vs 1.5% – SLNB-only group; p=0.28) and locoregional recurrence ratio analyzed within 10 years (6.2% – SLNB+ALND group vs 15.3 % – SLNB-only group; p=0.36).

The present study assesses the diagnostic value of macroscopic intra-operative assessment of dissected SLN by the operating surgeon. Macroscopic evaluation by the surgeon was of paramount importance when deciding to use intra-operative histopathological examination. However, no significant difference was found with regard to the percentage of identified metastatic SLNs between intra-operative (18.4%) or final (18.6%) examination. Macroscopic SLN assessment therefore appears to have significantly limited diagnostic value as a predictor of metastatic involvement.

The choice of SLN examination mode was not influenced by the primary tumor size nor by the prognostic or predictive factors (presence of ER receptor: p=0.4290; PR: p=0.0340; HER2 overexpression/amplification: p=0.1264; histopathological type of cancer: p=0.0847; histopathological grade: p=0.2314).

Is it reasonable to introduce SLNB and BCT as a standard of treatment in breast cancer patients with the omission of SLN intra-operative histopathological examination? Such guidelines have been already recommended in melanoma, and any deviation is considered malpractice [23]. However, as the treatment of early-stage breast cancer seems to be more complex, any decision will be determined by complete acceptance of conclusions from the ACOSOG Z0011 trial. It appears that avoiding SLN intra-operative histopathological examination is justified in patients who undergo BCT, with metastasis present in no more than two SLNs. The introduction of a different therapeutic option may result in a major increase in additional ALND procedures. Our findings indicate that supplementary ALND was needed twice as much in the second evaluated group of patients (11.1%) than in the first (4.1%).

In conclusion, histopathological verification of SLN as a final assessment allows for deferral of the decision for possible radicalization of surgical treatment of the axilla in patients subjected to SLNB. Following the omission of routinely-performed SLN intra-operative examination, a significantly greater rate of avoiding supplementary ALND was observed. The application of our findings requires further specification and implementation of guidelines concerning conservative treatment of the axilla in groups of patients with SLN macrometastasis fulfilling the Z0011 criteria. Longer follow-up and outcome monitoring is needed before a comprehensive assessment of clinical value of this undertaken diagnostic option will be possible.

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