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AXILLARY LYMPH NODE DISSECTION COULD BE OMITTED IN THE BREAST CANCER PATIENTS WITH A LIMITED SENTINEL LYMPH NODE INVOLVEMENT FOLLOWING NEOADJUVANT SYSTEMIC TREATMENT

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Summary

Background: In modern breast cancer management, SLNB is a standard of care. For the patients with limited sentinel lymph node involvement in the upfront surgery setting, ALND can be safely omitted. However, for any sentinel node metastasis detected following neoadjuvant systemic treatment (NST), ALND is still considered a mandatory procedure.

Patients and methods: Present retrospective analysis has included all breast cancer patients submitted to surgery following NST in Clinical Hospital Centre (CHC) Rijeka in the period from 2017 till 2020.

Results: SLNB was performed in 151 of 222 consecutive patients, and sentinel node metastasis was detected in 49 cases. The risk of non-sentinel lymph node involvement in sentinel node-positive patients was 34.7%, but exclusively for cases with macro-metastatic disease detected in the sentinel node. In addition, for the patients diagnosed with clinically uninvolved axilla, the risk of ypN2-3 status was only 2.8%.

Conclusions: ALND following NST is overtreatment in 65.3% of sentinel node-positive patients. Axillary irradiation with the omission of ALND should be considered for the sentinel-positive patients with only micro-metastatic disease detected in the sentinel node following neoadjuvant chemotherapy, as well as for those with low volume macro-metastatic disease, diagnosed with the uninvolved axilla.

KEYWORDS: *breast cancer, neoadjuvant chemotherapy, sentinel lymph node biopsy*

INTRODUCTION

In modern breast cancer (BC) management, ALND is rarely performed procedure in the upfront surgery setting for the early-stage BC. SLNB is a standard of care for all patients presenting with clinically uninvolved axilla (cN0), although the false-negative rate (FNR) of axillary ultrasound (AUS) may be up to 30%. Due to Z0011 and AMAROS trial results(1-3), ALND can be safely omitted even in those cases with up to 2 sentinel lymph nodes (SLN) involved with macro-metastatic disease, although in higher-risk cases axillary irradiation (AxRT) is recommended instead.

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In both mentioned trials, as well as in several other ALND-omission trials(1-6), the calculated risk of additional nodal involvement in the SLN-positive population is 13-38.5% and is correlated with the size of metastatic disease in SLN as well as with the number of involved SLN. However, after follow up period of 10 years, this risk of metastatic involvement of non-sentinel lymph nodes left behind, did not translate into any clinical significance in terms of higher rates of regional recurrences or poorer disease control and survival i.e., the omission of ALND did not alter the oncological outcomes in SLN positive populations of early-stage BC patients.

Nowadays, however, many early-stage BC patients commence treatment with neoadjuvant systemic treatment (NST). According to several validation trials(7-10) and all relevant BC management guidelines(11,12), since 2017 SLNB is accepted as an option for axillary staging even after NST. However, the procedure is still not universally accepted as a standard of care. Moreover, ALND is still considered a mandatory procedure in all cases of metastatic disease detected in SLN, irrespective of its size and clinical nodal status (cN) at presentation. This results in a paradoxical situation in a substantial number of cases diagnosed as cN0, but with the metastatic disease eventually detected in SLN following NST, especially those patients with micrometastatic or low volume macro-metastatic disease.

As the basis for this recommendation is a single randomized controlled study with a relatively low sample size(13) and is discordant with the clinical practice in our institution, we have undertaken the present analysis. The main purpose was to calculate the overall risk of additional nodal involvement and the risk of massive, clinically significant nodal involvement of non-sentinel lymph nodes, defined as ypN2-3 i.e., the only reasonable indication for therapeutic ALND, in the case of SLN positive disease following NST. In addition, we have searched for correlations of both calculated risks with the nodal status at presentation, size of SLN metastasis, and the number of involved SLN, as well as with other elements of the standard histopathological report.

PATIENTS AND METHODS

All BC patients in stage T1-3 N0-2 M0, submitted to surgery in Clinical Hospital Centre (CHC) Rijeka following NST, in the period from 2017 till 2020, were included in the present analysis. Relevant data were extracted retrospectively from Integrated Hospital Informatics System (IBIS), analysed with Statistica 13.5 software, and interpreted at the level of statistical significance p=0.05. Pearson Chi-square test, Fisher exact one-tailed test and Mann-Whitney U test were used for testing the correlations between the elements of the histopathological report and calculated risk of non-sentinel lymph node involvement in SLN positive patients following NST.

The analysis was approved by the institutional ethics committee.

Before initiating NST, nodal status was determined by AUS (Logiq S8 and Logiq E9®, General Electric Healthcare, Chicago, USA) and dedicated breast MRI scanner (Magnetom Avanto and Aera®, 1.5 T, Siemens, Erlangen, Germany) All suspicious appearing lymph nodes with cortical thickening > 3 mm were sampled under US guidance and the presence of metastasis was cytologically or histologically proven. Although most of those proven metastatic lymph nodes were marked with the tissue marker (titanium clip), confirmation of their removal following NST was not mandatory.

All patients received the standard neoadjuvant systemic protocol; 4 cycles of anthracyclines and cyclophosphamides followed with 12 cycles of taxanes, with the addition of dual anti-HER2 blockage for HER2 positive patients.

Before surgery nodal status was re-evaluated with the MRI and SLNB was performed for all patients with unsuspicious post-treatment axillary lymph nodes, irrespective of the initial nodal status.

The lymphoscintigraphy with technetium labelled nano-colloid particles was the most frequently used method for SLN detection, although other tracers (Magtrace® and methylene blue dye) were also used. Dual mapping was applied as a surgeon's choice i.e., it was not mandatory. The median number of removed SLN was 3, range from 1 to 8. In 16 cases (11% of patients submitted to SLNB), more than 5 LN were removed during the procedure due to inadequate mapping or surgeons' choice to remove clinically suspicious lymph nodes in addition to true sentinel node(s).

All removed SLNs were intraoperative longitudinally transected on 3- 4 mm cuts and analyzed by imprint cytology. For all positive or suspected

cases, cuts are frozen and histologically examined for presence or absence of metastasis. Sentinel lymph nodes negative on imprint cytology were transected sequentially in two to three levels for hematoxylin-eosin and pan-cytokeratin staining, therefore, detection of every residual tumor in the lymph node, including Isolated Tumor Cells (ITC), was ensured.

The pathologic stage of the primary tumor and lymph node was determined according to the 4th edition of WHO TNM classification form 2012(14) and the appendix of AJCC manual for breast cancer staging(15).

The standardized pathological report was used for primary tumor description, including histological type according to 4th edition of WHO TNM classification and appendix of AJCC manual for breast cancer staging, Nottingham combined histologic grade, tumor bed size, size of largest residual focus of tumor, percentage of cellularity, and percentage of ductal in situ carcinoma, number of positive lymph nodes and size of metastases. According to Detailed Pathology Methods for Using Residual Cancer Burden provided on MD Anderson Internet pages, pathologic residual cancer burden (pRCB) was calculated. Tumor infiltrating lymphocytes (TILs) were determined according to recommendations made by an International TILs Working Group 2014(16). Standard prognostic and predictive biomarkers as estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor were determined in every residual tumor and the immunophenotype was determined according to the ASCO CAP guidelines for ER and PR from 2020(17) and for HER-2 from 2018(18). Lymphatic vascular invasion (LVI) was, in most cases, confirmed with immunohistochemical staining of endothelial cells.

In addition to SLNB, ALND was performed in all SLN positive cases, regardless of the initial nodal status, size of the metastasis detected in SLN, the number of positive SLN, and time of detection (intraoperative and final pathological report).

The main purpose of the present analysis was to determine the risk of additional positive axillary lymph nodes among SLN positive patients, which we have defined and calculated as a rate of ALND positive patients in the SLN positive group.

Similarly, we have calculated the risk of the clinically significant (massive) nodal involvement, which we have defined as more than 2 non-SLNs harboring a metastatic disease in addition to involved SLN(s). Besides, we have determined and compared values of both above-mentioned risks in specific subgroups of SLN positive patients; cN0 and cN1-2, micro and macro-metastatic SLN(+) disease, and SLN(+) disease with up to 2 and more than 2 SLNs involved.

Finally, we have checked if there are any correlations among the risk of metastatic disease in non-SLN and standard elements of the histopathological report in SLN positive patients following NST i.e., if any of the current standard pathological biomarkers may help us in the decision-making process of omitting or proceeding with ALND in SLN positive patients following NST.

RESULTS

Overall, 222 consecutive, post-NST, BC patients were included in the present analysis. The study results are displayed in table 1.

Table 1.

Study results

cN at presentation	**cN0** (107)	**cN1-2** (115)	Overall (222)
ALND performed without SLNB	11	65	**76**
Node-negative	11	19	30
Node-positive	0	46	46
SLNB (-)	65	32	**97**
SLNB (+)	31	18	**49**
Micrometastasis	8	3	11
Macrometastsis	23	15	38
ALND(-)	21	11	32
ALND(+); ≤ 2 additional LN(+)	7	1	8
ALND (+); >2 additional LN(+)	3	6	9

The axillary conversion rate in the cN1-2 group was 44.3% (51/115 patients). Due to the high overestimation rate (39.5%) of post-treatment MRI, used for the nodal status re-evaluation, SLNB procedure was performed for only 27.8% (32/115) patients diagnosed with axillary metastasis.

Although pre-treatment AUS is considered the most reliable method for lymph node evaluation, the underestimation rate calculated for the cN0 group in the present analysis was 29%. However, the risk of underestimation of ypN2-3 status in the same group was only 2.8%.

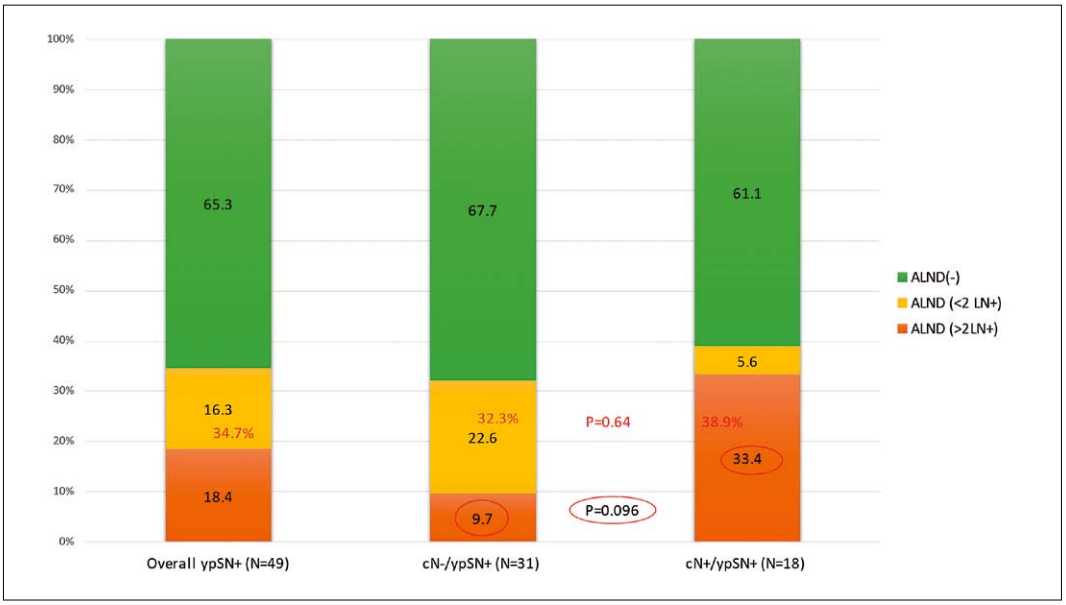

Figure 1 The risk of additional nodal involvement and the massive nodal involvement

SLNB procedure was performed in 146 patients (65.8% of all study population), and SLN metastasis was detected in 49 cases. However, additional positive lymph nodes were detected in only 18 ALND specimens and in half of those cases less than 3 additional positive non-SLN were involved i.e., the risk of additional nodal involvement in SLN positive population following NST was 34.7% and the risk of clinically significant nodal involvement of non-SLNs was 18.4%. In addition, the overall risk of additional nodal involvement was not significantly different between cN0 and cN1-2 subgroups (Pearson Chi-square, p=0.64), as well as the risk of massive nodal involvement, although the last one demonstrated a trend toward it (Fisher exact one-tailed test, p=0.096); both shown in figure 1.

The overall risk of non-sentinel lymph node involvement in the sentinel node-positive group of patients following NST is 34.7% and it is not correlated with the nodal status at presentation (32.3% vs. 38.9%, p=0.64). However, there is a trend toward significant lower risk of the massive non-sentinel node involvement (defined as more than 2 non-sentinel lymph nodes involved in addition to sentinel node metastasis) among the patients presented with uninvolved axilla compared to those diagnosed with nodal disease (9.7% vs. 33.4%, p=0.096)

In almost ¼ of positive SLN (22.4%), in both cN0 and cN1-2 groups, only micro-metastasis were detected, but ALND was performed due to current recommendations. Nevertheless, in neither ALND sample we did not discover additional disease i.e., in the present analysis, a strong correlation exists between the size of SLN metastasis and the risk of additional nodal disease (Fisher exact one-tailed test, p=0.027) as well as among the number of SLN involved and the risk of non-sentinel lymph nodes involvement (Fisher exact one-tailed test, p=0.016), as shown in figures 2 and 3.

The risk of non-sentinel lymph node involvement in sentinel lymph node-positive patients is significantly higher for patients with the macrometastatic disease compared to those with only micro-metastasis detected in the sentinel lymph node (0% vs. 25.8%, p=0.027) and is gradually increasing with the number of sentinel lymph nodes affected.

The risk of non-sentinel lymph node involvement is significantly higher in a group of patients with more than 2 sentinel lymph nodes affected compared to those with up to 2 lymph nodes involved with metastatic disease (16.2% vs. 66.7%, p=0.016)

Of all standard elements of the histopathological report for CNB specimen, as well as for the surgical specimen (ER, PR and HER2 status, Ki67,

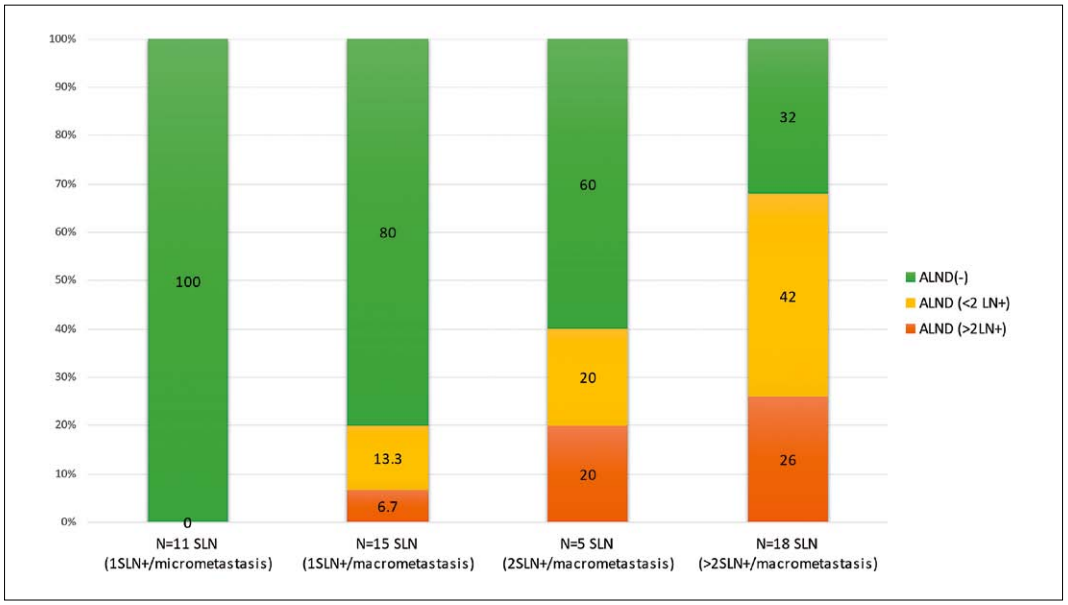

Figure 2 The risk of additional nodal involvement and massive nodal involvement is related to the size of the metastasis and the number of involved sentinel lymph nodes

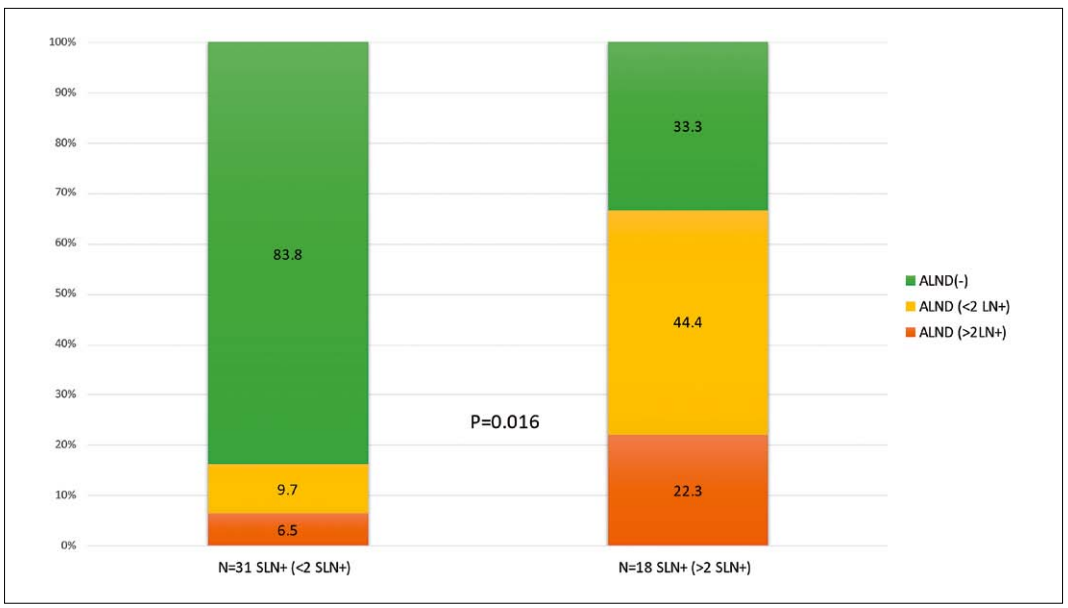

Figure 3 The risk of additional nodal involvement is significantly higher in cases where metastasis is detected in more than 2 SLN.

presence of lymphatic vascular invasion, grade, cellularity, immunophenotype, TILs, and size of the residual disease in the breast), in this analysis only 2 had shown statistically significant correlation with the risk of non-SLN involvement in the SLN positive cases; percentage of TILs in the surgical breast tissue specimens (Mann-Whitney U test, p=0.012; negative correlation) and the size of the residual disease in the breast (Mann-Whitney U test, p=0.014; positive correlation).

DISCUSSION

Uninvolved axilla in 56.8% of the whole post-NST population and the conversion rate of 44.5% in a cN1-2 group are strong arguments for the adoption of SLNB procedure in the neoadjuvant setting of BC treatment, not only for the early-stage BC patients but also for those patients diagnosed with the axillary metastasis.

According to our analysis, as well as the literature data, post-NST MRI of the axilla, with a false positive rate of 39.5%, is not the optimal method to guide the decision-making process for surgical management of the axilla(19,20). Neither imaging method is jet proven to be enough reliable for axillary staging following NST, including PET-CT and AUS(21-23). However, reliable pre-treatment AUS, with the underestimation rate of only 2.8%, for ypN2-3 status in the cN0 population, could be a very helpful tool in the further decision-making process for those SLN positive patients following NST diagnosed with cN0 disease.

In all relevant BC treatment guidelines(11,12), ALND is still considered a mandatory procedure in all cases of SLN involvement following NST, irrespective of nodal status at presentation. As in the upfront surgery setting, due to underestimation of AUS, 20-30% of patients diagnosed as cN0 (29% in the present analysis), would eventually have metastatic disease detected in SLN. If treated without NST, ALND would be omitted for the majority of those patients, and AxRT would be recommended for those with a higher risk of recurrence. However, following NST, in the same group of patients, ALND is still obligatory for all cases with metastasis detected in SLN, irrespective of its size and the number of SLN involved. The former literature data(13,24) did not show a correlation with the size of SLN metastasis and the risk of non-SLN involvement, and the overall risk in those previous analyses was significantly higher than the average of 30% documented in the upfront surgery studies(1-6). However, our results did not confirm those findings.

The overall risk of additional nodal involvement for SLN positive patients of 34.7%, calculated in our analysis, is not significantly different from the risk in the Z0011, AMAROS, and OTOASOR trials(1-4). In all mentioned trials, this risk did not translate in any clinical significance after a long-term follow-up period, however, the clinical significance following NST is jet unknown and should merely be determined by several ongoing prospective randomized controlled trials(25-28).

However, while waiting for the results of those trials, we should consider omitting ALND for the SLN-positive patients diagnosed with uninvolved axilla, as the risk for ypN2-3 status in the whole cN0 population is only 2.8%.

Could we offer AxRT instead of ALND for selected subgroups of post-NST SLN-positive patients diagnosed as cN1-2? There was no significant difference in the overall risk of additional nodal involvement among SLN-positive cN0 and cN1-2 patients in the present analysis. However, the risk of massive non-SLN involvement was higher in a cN1-2 group, although did not reach statistical significance, probably due to the small sample size. Nevertheless, the risk of non-sentinel lymph node involvement was found to correlate well with the size of SLN metastasis as well as with the number of involved SLNs in both groups. In addition, a strong correlation between the size of the residual disease and the presence of TILs in the breast tissue specimen is found in this analysis as well as in the literature data(29-32). Although new clinical and pathological biomarkers are needed in this field, those presented in our study could already be implemented in the decision-making process.

CONCLUSION

Due to the implementation of the SLNB procedure in the neoadjuvant setting, as well as with optimal multidisciplinary patient selection, unnecessary ALND is already avoided in 60.7% of the cN0 group and could be avoided for 44.3% of the cN1-2 group. However, it may be additionally omitted in both groups, by respecting clinical and pathological biomarkers of low risk for non-SLN involvement in post-NST SLN-positive patients. According to our results, the most powerful biomarkers are the size of the SLN metastasis, the number of involved SLN and nodal status at presentation, presence of TILs in the post-NST surgical breast tissue specimen and the size of the residual disease in the breast.

Considering that the analysis has included all the patients treated in our institution since the SLNB implementation in the neoadjuvant setting,

we have already included the above mentioned biomarkers of the low risk in our multidisciplinary decision-making process, with the goal of omission of unnecessary ALND.

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Sažetak

AKSILARNU LIMFADENEKTOMIJU TREBALO BI IZOSTAVITI KOD BOLESNICA SA KARCINOMOM DOJKE I MINIMALNOM REZIDUALNOM BOLESTI U SENTINEL LIMFNOM ČVORU NAKON NEOADJUVANTNOG SISTEMSKOG LIJEČENJA

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Uvod: U modernom kirurškom pristupu liječenja kacinoma dojke SLNB je univerzalno prihvaćeni standard. Izostavljanje ALND, u slučajevima sa metastazom pronađenom u do dva sentinel limfna čvora, ne utječe na onkološke ishode kod primarno kirurški liječenih pacijentica, Međutim, svaka metastaza detektirana u sentinel limfnom čvoru nakon provedenog neoadjuvantnog sistemskog liječenja još uvijek se smatra apsolutnom indikacijom za ALND.

Pacijenti i metode: Sve pacijentice operirane zbog karcinoma dojke u Kliničkom Bolničkom Centru (KBC) Rijeka nakon provedene neoadjuvantne kemoterapije, u periodu od 2017. do 2020., uključene su u ovu retrospektivnu analizu.

Rezultati: SLNB je učinjena kod 151 od 222 uzastopne pacijentice, a metastaza u sentinel čvoru pronađena je u 49 slučajeva. Rizik metastatske bolesti u ne-sentinel limfnim čvorovima kod sentinel-pozitivnih pacijentica je 34.7%, međutim isključivo u slučajevima sa makrometastazom u sentinel čvoru. Nadalje, kod skupine pacijenica dijagnosticiranih sa klinički i radiološki negativnom aksilom, rizik od ypN2-3 statusa je samo 2.8%

Zaključak: Nakon neoadjuvantne kemoterapije ALND je *overtreatment* u 65.3% sentine-pozitivnih pacijentica. Izostavljanje ALND uz zračenje aksile nakon provedenog neoadjuvantnog liječenja je opcija koju bi trebalo razmotriti za sentinel-pozitivne bolesnice sa mikro-metastazom u sentinel čvoru, kao i za bolesnice sa malim volumenom makrometastatske bolesti u sentinel limfnim čvorovima, a koje su inicijalno dijagnosticirane sa klinički negativnom aksilom.

KLJUČNE RIJEČI: *rak dojke, neoadjuvantna kemoterapija, biopsija sentinel limfnog čvora*