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ORIGINAL ARTICLE

The clinical role of micrometastatic disease in sentinel lymph nodes in breast cancer

A. Golubovic[1], M. Ranisavljevic[1], D. Djilas[2], B. Stoiljkovic[3], V. Selakovic[1], Z. Radovanovic[1], D. Bogdanovic[1], A. Plzak[1]

[1]Department of Surgical Oncology, [2]Department of Radiology, [3]Department of Pathology, Institute of Oncology, Sremska Kamenica, Novi Sad, Serbia

Summary

Purpose: *Complete axillary lymph node dissection (cALND) is the standard procedure in treating the patients with tumor-positive sentinel nodes (SLNs). However, approximately half of these patients have not additional metastases in their axilla and therefore do not benefit from cALND. Our aim was to examine the outcome of patients with tumor-positive SLNs without cALND.*

Methods: *All patients (n=591) were women with clinically $T_{1-2}N_{0-1}M_0$ breast cancer. SLN marking was performed with blue dye (Patentblau V) and radiotracer (antimony sulfide marked with Tc^{99m}). Both contrast media were applied peritumorally or periareolarly. After SLN biopsy all patients underwent breast-conserving surgery or mastectomy with or without lymph node dissection of level I and II (depending on SLN status).*

Results: *In 37 (17.84%) out of 185 patients cases SLNs contained micrometastases. In 19 of 37 cases (57.58%) cALND was performed, and in 14 (42.42%) was not. The mean and median duration of follow-up were 50.59 and 55 months, respectively (range 4-108). Two cases without cALND developed ipsilateral enlarged lymph nodes at 26 and 59 months. Biopsy showed that the enlarged nodes were tumor-free. In all other cases with micrometastases in SLNs neither axillary lymphadenopathy nor distant metastases were seen. After performing surgical treatment, all patients received adjuvant chemotherapy or hormonotherapy and radiotherapy.*

Conclusion: *Patients with SLN micrometastases who had not undergone cALND showed no regional recurrence and distant metastases. ALND is not necessary for regional control in patients with micrometastatic or isolated tumor cells in SLNs. By avoiding cALND the number of complications was reduced and the quality of life was improved.*

Key words: axillary node dissection, breast cancer, isolated tumor cells, micrometastases, sentinel lymph nodes

Introduction

The presence of metastases in axillary lymph nodes in breast cancer is still one of the most important prognostic factors. Before the introduction of axillary SLN biopsy, lymph nodes were routinely dissected, and this approach was the gold standard in the surgical treatment of breast cancer [1-5].

The SLN sampling procedure in breast cancer was pioneered by the surgical oncologist Armando Giuliano, in 1994 [1], and confirmatory trials followed soon after.

At the Department of Surgical Oncology of our Institute SLN biopsy is a standard procedure since 1999, with over 700 SLN biopsies having been performed.

SLN biopsy includes identification, and then extirpation and histopathological study on fresh frozen preparations. Presence of metastasis in lymph nodes is one of the most significant prognostic factors [1-5].

SLN biopsy is indicated in patients with tumor size < 3 cm, without clinical and imaging suspicion of lymphadenopathy.

SLNs can be identified by radioguided lymphatic mapping and/or by visualisation of the nodes with vital blue dyes. Overall, radioisotopic mapping of the SLNs with the use of a handheld gamma probe gives better results than blue dye. Identification rates were 92% with radioguided lymphatic mapping, 81% with vital blue dyes and 93% with both methods, while false-negative rates were 7, 9 and 5%, respectively [1-5]. There

Correspondence to: Andrija Golubovic, MD, PhD. Bogoboja Atanackovica, 21000 Novi Sad, Serbia. Tel: +381 216335336, E-mail: ogolubovic2412@gmail.com

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is growing evidence that using both methods in combination - blue dye and radioisotope - very high identification rates can be achieved and fewer SLN may be missed compared with single-method mapping [1,3,5].

Therefore, histopathological evaluation of these nodes can be an accurate predictor of other metastases in the same lymph node basin, and can guide the regional and systemic treatment. ALND and its morbidity can be avoided in patients in whom SLN proved negative [1-3].

Micrometastases in axillary SLNs can be divided into 2 groups: isolated groups of tumor cells without stroma (<0.2 mm) and real micrometastases (0.2-2.0 mm) with stroma [6-10].

The Dutch MIRROR study [7] is the largest cohort study on micrometastases and isolated tumor cells in SLN. The findings of this study showed that isolated tumor cells and micrometastases produce different outcomes and should not be treated the same way by clinicians. If isolated tumor cells in SLNs are found cALND should not be performed, but if real micrometastases (0.2-2.0 mm) are found cALND should be performed.

After 5 years of follow-up, patients who were found with isolated tumor cells in SLNs and who did not subsequently undergo cALND did not have a significantly higher rate of axillary recurrence than similar patients who did undergo cALND (2.3 vs. 1.6% [1,9-11]). Also, it would be advisable that patients with micrometastases to be followed more frequently in cases where no cALND was performed.

The importance of the presence of micrometastases in SLNs in relation to survival of patients with breast cancer has not yet been precisely determined, and therefore there is no clear consensus on what should be done in such cases.

The purpose of this study was to see whether it would be possible to omit axillary dissection in cases of *ex tempore* positive histology confirming the existence of micrometastases in SLNs, no matter whether the isolated groups of tumor cells or real micrometastases, and couple this condition with the patient disease-free and overall survival.

Methods

This retrospective study was performed at the Department of Surgical Oncology from January 2002 to December 2010. All patients were women with clinically $T_{1-2}N_{0-1}M_0$ breast cancer. The study included 591 patients who had undergone SLN biopsy. Preoperative diagnosis was obtained with physical examination, mammography, ultrasonography and FNA cytology or core biopsy.

Preoperatively, all patients were administered dual contrast media (radiotracer+blue dye). Radiotracer was antimony sulphide marked with Tc^{99m}, and the blue dye was Patentblau V (Byk Gulden, Atlanta, USA). Both types of contrasts were administered subcutaneously above the primary tumor, and in some cases paraareolarly (localization of primary tumor near the axilla, multifocal or multicentric tumors) with thin needles (25 G). Radiotracer was administered 2-16 h preoperatively, and blue dye 15 min before surgery. Radioactivity of the injected radiotracer was 0.3 mCi (11.1 MBq). For the detection of the accumulated radioactivity in the SLN, we used intraoperative handheld gamma counter to identify nodes with the greatest numerical and sound activity, by probe of 10 mm in diameter. The color was visually identified.

After processing the surgical antiseptic procedures preoperative percutaneous measurement of the following areas was carried out: internal mammary group, supraclavicular, infraclavicular and axillary lymph node group. Firstly, we performed extirpation of SLN, and then all patients underwent breast-conserving surgery or mastectomy with or without cALND of level I and II, depending on SLN status.

Immediately after the extirpation, SLNs were sent for intraoperative frozen section evaluation. Ten sections of SLNs were obtained from each block of tissue and stained with haematoxylin and eosin (H&E) or immunostained for epithelial membrane antigen (EMA). The remaining SLN tissue was fixed in formalin and embedded in paraffin, and the embedded tissue blocks were stained with H&E or immunostained for EMA; these preparations were compared with frozen section results.

Statistical analysis

All data were grouped, statistically analysed, and presented as Tables and Figures. Fisher's exact test, Pearson's x^2 test and Student's t-test were used to compare data between groups. Values of $p<0.05$ were considered as statistically significant. The SPSS program was used for statistical analysis.

Results

Three hundred and twenty-two (54.48%) patients were premenopausal and 269 (45.52%) postmenopausal with median age 57 years (range 25-84; Figure 1).

Breast-conserving surgery was performed in 550 patients and in 41 patients subcutaneous mastectomy with immediate reconstruction was carried out.

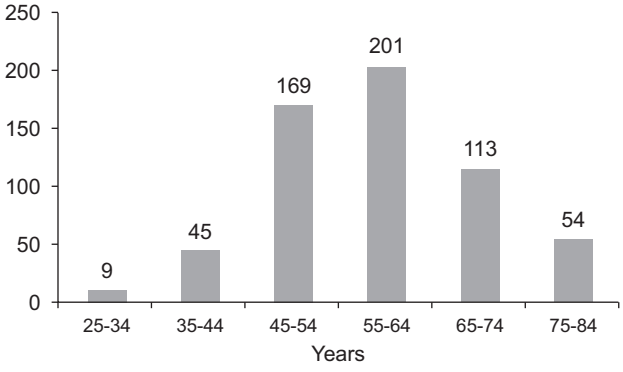

Figure 1. Patient age distribution.

Solitary tumor was present in 539 (91.2%) cases, multifocal tumors in 27 (4.57%), multicentric in 21 (3.55%) and bilateral in 4 (0.68%) patients. Ductal carcinoma was encountered in 63.79% of the cases, lobular in 28.43%, medullary in 1.18%, and other histological types in 1.35% cases. In 31 (5.25%) patients ductal carcinoma *in situ* (DCIS) was identified, and SLN biopsy was performed because of the large size of the DCIS field, or suspected high-grade forms (Figure 2).

SLN biopsy was negative in 406 (68.7%) patients. In this group most of the patients (n=208; 51.5%) had T1c tumor stage. SLN biopsy was positive in 185 (31.3%) patients. The most frequent tumor stage in this group was T1c (n=96; 51.08%; Table 1). The mean number of extirpated SLNs in both groups (SLN positive and SLN negative) was 1.84 (median 1, range 1-6). The mean number of dissected axillary lymph nodes in the group with positive SLNs on paraffin embedded tissue sections was 18.49 (median 17, range 8-28 after cALND). The mean number of dissected axillary lymph nodes with metastases in SLN-positive patients was 6.59 (paraffin embedded tissue preparations) and the mean number of dissected axillary lymph nodes without metastases in the same group was 11.8 (paraffin embedded tissue sections).

In 50 (27.03%) patients SLN was the only metastatic lymph node in the axilla after cALND. In 33 (17.84%) cases SLN contained micrometastases (22; 66.67% patients with <0.2 mm and 11; 33.33% with 0.2-2.0 mm). In 19 cases (57.58%) cALND was performed, and in 14 (42.42%) was not. The mean duration of follow-up was 50.59 months (median 55, range 4-108). During that time there were 2 cases with ipsilateral enlarged lymph nodes (26 and 59 months) in patients without cALND. Biopsy showed that the nodes were tumor-free. In all other cases with micrometastases neither local lymphadenopathy nor systemic metastases were registered. All patients with SLN micrometastases received adjuvant radiotherapy, chemotherapy and hormonotherapy after the surgical treatment.

Systemic metastases in SLN-positive patients (macrometastases >2 mm) developed mostly in bones (39.13%), liver (21.74%), lungs (13.04%) and brain (4.35%). Three (13.04%) patients died due to distant metastases. In the group with micrometastases (0.2-2 mm) in SNL, no distant metastases developed.

In patients with negative SLN biopsy there were 2 cases with distant metastases (1 in the liver and 1 in the bones; Table 2).

There was a statistically significant difference between patients with micro (0.2-2.0 mm) and macrometastases (>2.0 mm) in SLN ($p < 0.05$), while between patients with SLN micrometastasis (both <0.2 mm and 0.2-2.0 mm) and patients with negative SLN no such difference was observed ($p > 0.05$).

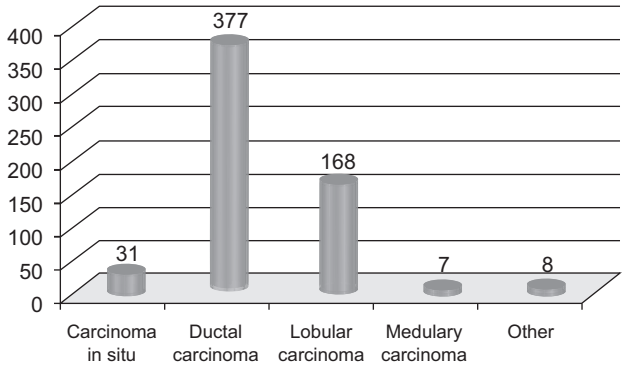

Figure 2. Histological tumor types.

Discussion

For more than 2 decades, SLN biopsy in breast cancer patients is used to predict axillary lymph node status avoiding cALND if possible [1-5].

Yet, questions persist about the implications of micrometastases (0.2-2.0 mm) in SLNs.

The question is whether each immunohistochemistry (IHC)-positive cell in the node characterizes this node as positive. Does that mean that the presence of micrometastases has prognostic value? Could one say

Table 1. Tumor (T) classification in groups with positive and negative SLN

T stage (cm)	*Negative SLN*		*Positive SLN*		*Total*	
	Patients, N	*%*	*Patients, N*	*%*	*Patients, N*	*%*
T1a: 0.1 - 0.5	27	4.57	6	1.02	33	5.58
T1b: 0.5 - 1.0	84	14.21	17	2.88	101	17.09
T1c: 1.0 - 2.0	208	35.19	96	16.24	304	51.44
T2: 2.0 - 3.0	74	12.52	53	8.97	127	21.49
T2: 3.0 - 4.0	13	2.20	13	2.20	26	4.40
Total	406	68.70	185	31.30	591	100

SLN: sentinel lymph node

Table 2. Distant metastases according to SLN status

	Positive SLN				*Negative SLN*		*Total*	
	Macrometastases (>2 mm)		*Micrometastases (0.2-2 mm)*					
Metastases	*Patients, N*	*%*	*Patients, N*	*%*	*Patients, N*	*%*	*Patients, N*	*%*
Bones	9	39.13	0	0	1	4.35	10	43.48
Liver	5	21.74	0	0	1	4.35	6	26.09
Lungs	3	13.04	0	0	0	0	3	13.04
Brain	1	4.35	0	0	0	0	1	4.35
Death	3	13.04	0	0	0	0	3	13.04
Total	21	91.30	0	0	2	8.70	23	100

SLN: sentinel lymph node

that the presence of one micrometastasis necessarily predicts the presence of others? The question is also whether the multistep pathologic sectioning of biopsy specimens of SNL and IHC have influenced the staging of disease or its treatment [1,6-12].

The first question was examined in a recent report [1] by researchers at Los Angeles Medical Center, who described 25 cases with IHC-positive epithelial cells in SLNs in patients with breast cancer, which normally indicates that cancer has spread to the lymph nodes. In all cases the cells appeared benign, and in 22 of the 25 cases the cell clusters had features similar to small, noncancerous tumors called intraductal papillomas, often found in needle core biopsy or surgical biopsies. According to the authors, the most likely explanation for the findings was that the biopsy itself helped the migration of benign breast epithelial cells into axillary lymph nodes, an observation that has been reported by other researchers as well [13]. The authors also concluded that IHC-positive cells in SLNs do not automatically indicate spreading of cancer to the lymph nodes.

SLN biopsy in this study was performed mostly in solitary tumors sized up to 3 cm, from which it follows that breast-conserving surgery was by far the most frequent operation performed (n=549 patients). Tumors > 3 cm in size had the same percentage of positive and negative SLNs, no matter whether the clinical, ultrasonographic and mammographic evaluation were negative.

After histological analysis of the primary cancer in all patients, ductal carcinoma was encountered in 63.79% of the cases, lobular in 28.43%, 1.18% in medullary, and other histological types in 1.35% cases, very close to the global distribution of histological types of breast cancer. In 31 (5.25%) patients DCIS was identified, and SLN biopsy was performed because of the large size of the DCIS field, or suspected high-grade forms.

Breast carcinoma was mostly found in T1c stage (304 patients; 51.44%), coinciding with other authors' data [1-7].

In 50 (27.03%) patients SLN was the only axillary lymph node with metastasis after cALND. When considering the need for dissection of other axillary nodes in the presence of micrometastatic SLN, the fact that for all positive SLN (micro+macrometastases) the SLN is the only positive axillary node in 28-40% of the cases (and even more) depending on the stage of disease should be taken into account [8,10,13-16].

In this study 33 (17.84%) cases SLN contained micrometastases. In 19 cases (57.58%) cALND was performed, and in 14 (42.42%) was not. The mean duration of follow-up was 50.59 months (median 55, range 4-108). During that time there were 2 cases of ipsilateral axillary nodal enlargement at 26 and 59 months in patients without cALND but biopsy showed tumor-free nodes. All other cases with micrometastases were without enlarged lymph nodes or distant metastases. Available evidence suggests that micrometastases and isolated tumor cells in SLNs have no prognostic value [13-20]. If SLN biopsy reveals no additional disease, patients' survival with isolated tumor cells or micrometastases is the same as in those with node-negative disease. All patients with SLN micrometastases should have minor surgical treatment with adjuvant radiotherapy, chemotherapy and hormonotherapy.

So far, the present study has shown that in patients with SLN macrometastases, systemic metastases developed mostly in bones (39.13%), liver (21.74%), lungs (13.04%) and brain (4.35%). Three (13.04%) cases succumbed due to distant metastases. In the group with micrometastases, no distant metastases developed. In patients with negative SLN biopsy there was one case with metastasis in the liver and one in bones. Statistical analysis of these data showed significant difference between patients with micro and macrometastases ($p < 0.05$); no such difference ($p>0.05$) has been observed between patients with micrometastases and patients with negative SLN biopsy.

If ALND in patients with micrometastases fails to identify involvement beyond the SLN, the disease should be considered node-negative, and adjuvant ther-

apy should be based on the primary tumor's prognostic features.

Available evidence suggests that micro metastases and isolated tumor cells in SLNs have no prognostic value [5-10]. Patients with isolated tumor cells or micrometastases survive at the same rate as those with node-negative disease [5-10,13-17]. If cALND is performed in patients with micrometastases, and reveals no metastases in the remaining axilla, such cases should be considered as SLN-negative and adjuvant therapy should be based in relation to the primary tumor prognostic characteristics.

Conclusion

1. Patients with SLN micrometastasis who do not undergo ALND have zero incidence of regional recurrence.
2. The percentage of detected micrometastases in the SLN positive patients was 18%.
3. Cases with SLN micrometastases should be surgically treated like tumor-free SLNs; cALND is not required in patients with SLN micrometastases (presence of isolated cancer cells).
4. Avoiding cALND reduces the number of complications and improves the patient quality of life.
5. It is an open question whether the presence of SLN micrometastases suggests administration of adjuvant systemic treatment or postoperative therapy should be based on the prognostic characteristics of the primary tumor and host factors.

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