Sentinel node biopsy in breast cancer: short time results show appropriate regional control

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Sentinel node biopsy becomes a standard diagnostic and therapeutic tool in breast cancer in certain indications, while in other indications its validity is still reviewed. The authors present their experience with this method. In the years 2000-2006 700 patients underwent surgery. 704 sentinel node biopsies were performed (bilaterally in 4 cases), 7 times surgery was unsuccessful. In the unsuccessful cases immediate axillary lymph node dissection (ALND) was performed. 985 sentinel nodes were found, the average was 1.4 nodes, maximum 6 nodes. In 7 patients contralateral ALND for node positive contralateral cancer was necessary along with sentinel node biopsy. A positive sentinel lymph node (SLN) was found in 188 (26.9%) patients. A strong correlation between tumor size and lymph node positivity was found, 5.3% in pT1a, and 40.4% in pT2, respectively. The sentinel node metastases could be divided according to their size. The number of affected further nodes did correlate with this size, yet with the exception of isolated tumor cell detection, small size metastases did not exclude the possibility of further affection. Our findings support the role of sentinel node biopsy in breast cancer. 332 patients reached at least 2 years of follow up by the time of statistic evaluation, 2.5% of SLN negative and 5.6% of SLN positive patients experienced a recurrence. All of these recurrences were distant with no regional (axillary) involvement to this date. We conclude that sentinel node biopsy is not only a safe and accurate diagnostic tool, but it also provides acceptable regional control of the disease.

Key words: Breast cancer, sentinel node biopsy, staging, recurrence, lymphadenectomy

In the last decade, sentinel node biopsy (SNB) became an accepted staging tool in various solid cancers, especially in melanoma and breast cancer. In these two diagnoses, where regional lymph node clearance produces serious morbidity, SNB can offer accurate pathological staging.[1]

Every new technique solves some problems as well as discovers some new ones. So does even sentinel node biopsy in breast cancer.

Sentinel node biopsy revokes the necessity of axillary clearance in node negative patients. This concerns approximately 70% of operable breast cancers, so the impact of this simple fact is substantial.

SNB helps solve the mystery of "skip metastases", as the lymphatic spread does not respect axillary levels, and it only respects anatomy.[2]

SNB solves the problem of extraaxillary lymphatic spread.

SNB enables to find extremely tiny lymphatic metastases due to the possibility of examining lesser amount of tissue, thus improving the sensitivity of the staging process. Upstaging due to SLN investigation increases the number of cases who should receive anti-cancer drugs, and consequently reduces the distant relapse rate.[3]

On the other hand, the SNB approach introduces new problems and questions. Some of these questions have been at least partially answered.

Several technical details, such as the proper site of injection of blue dye and radiolabeled colloid, proper use in multifocal and multicentric lesions, and possibility of frozen section biopsy are studied.

The most important questions from the point of view of a surgeon are indications, contraindications and consequences: Is it necessary to perform an axillary clearance in positive sentinel node? What kind of affection should be considered positive? Is SNB safe enough? Does SNB offer appropriate regional control?

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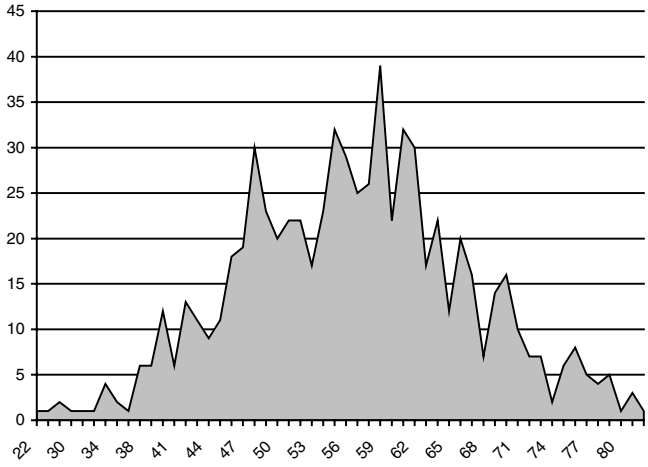

Figure 1. Age distribution of operated patients

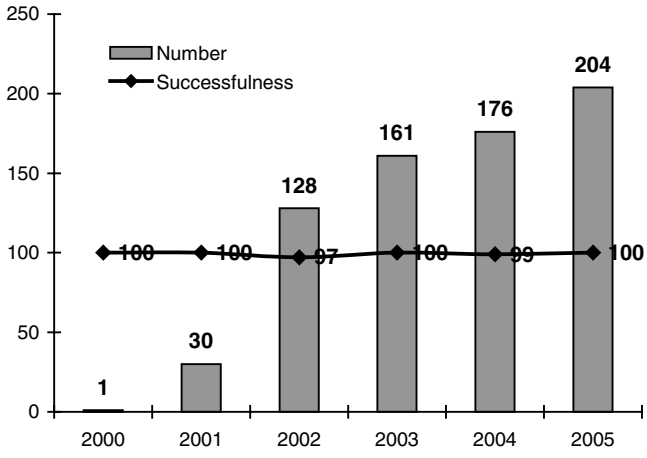

Figure 2. Numbers of operations and success rate

We would like to share our experience and offer clues to answer some of these questions.

Patients and methods

Sentinel node biopsy technique in breast cancer was introduced at our institute in the year 2000, following six years of daily use in melanoma with 99% of success rate and no more than 3% of false negativity during long term observation.

The indications for sentinel node biopsy were:

- Operable early breast cancer
- Size of the tumor up to 4 cm (clinically)
- Histologically verified invasive cancer, newly added high grade noninvasive ductal carcinoma (DCIS) [[4], [5], [6]]
- Absence of lymphatic metastases in ultrasonography
- No further selection is performed, excluded are only very old patients with extremely high operation risk and patients who refuse this method
- Patients with SNB after neoadjuvant chemotherapy are considered experimental and were excluded from this study, nevertheless our experience is good, in accordance with literary experiences. [[7], [8]]

The technique of sentinel lymph node identification is a combination of the radionavigation method and blue dye method. Lymphoscintigraphy is performed using the one day protocol:

the Tc Nannocoll is injected peritumorally in the early morning of the operation day, the operation follows after 2-5 hours. In the operation theatre blue dye injection (Bleu Patenté) is added. The combination method produces significantly better results than each individual method alone and should be considered standard. [[9], [10]]

The operation includes identification of the sentinel lymph node(s) and removal thereof, usually along with the primary tumor. The type of the breast operation depends on the size of the tumor, the size of the breast, and on the presence of satellites of extended intraductal component. The most frequently performed operation is lumpectomy, but in necessary cases even simple mastectomy is combined with SNB.

We rely on the definitive histological examination of the sentinel lymph node. Frozen sections are performed only in rare cases of a macroscopically suspect sentinel node. These cases are extremely rare due to regular ultrasonographic examination of the axilla preoperatively.

All patients are followed up and their status is periodically checked. The periodical examinations always include a clinical examination. Yearly chest X-ray, liver ultrasonography, bone scintigraphy, breast (if present) and axillary ultrasonography are all part of the follow-up. Further examinations are indicated depending on clinical status.

This analysis reflects the status at the beginning of the year 2006. Figure 1 shows the age distribution. (Fig. 1)

Results

In the years 2000-2006 700 patients underwent surgery. A total 704 sentinel node biopsies were performed (bilaterally in 4 cases). The surgery was unsuccessful in 7 patients. In the unsuccessful cases immediate axillary lymph node dissection (ALND) was performed. 985 sentinel nodes were found, with an average of 1.4 node, and a maximum of 6 nodes. In 7 patients contralateral axillary clearance for node positive contralateral cancer was necessary along with sentinel node biopsy.

In 23 cases parasternal sentinel node was removed, with one case of unwanted chest opening. In 6 cases an intramammary sentinel node was found.

In all cases of positive sentinel lymph node (except of the parasternal and intramammary localizations) a complete consequent ALND followed.

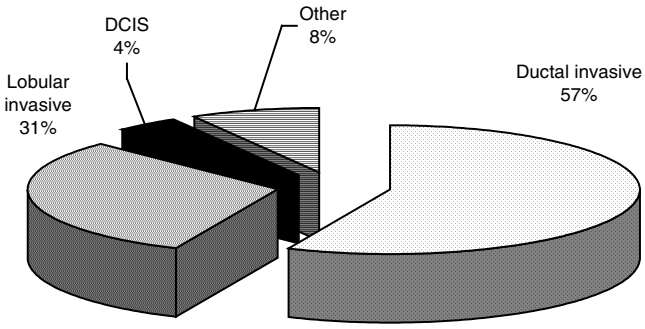

Figure 3. Histological types of breast cancer (simplified)

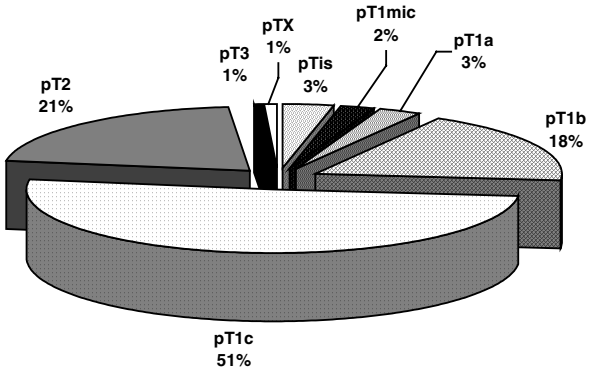

Figure 4. The size of primary tumors

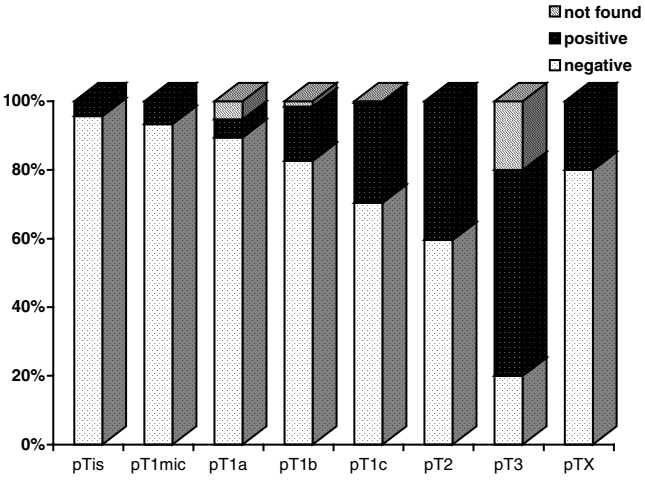

Figure 5. The correlation between sentinel node affection and tumor size

332 patients have reached at least 2 years of follow up by the beginning of 2006. These patients are evaluated in these short term results.

The number of patients undergoing surgery per year was growing quickly, partially due to the launch of the mammographic screening in the Czech Republic.

The success rate of sentinel node recognition stays nearly at 100%. (Fig. 2)

As for the histological types of breast cancer, invasive ductal carcinoma is dominating, followed by lobular invasive carcinoma. Figure 3 is simplified and considered only informative. (Fig. 3)

Figure 4 shows the distribution of the tumor sizes. The most frequently diagnosed size was pT1c, with the fraction of minor tumors growing slowly over the years.

Although our original indication for SNB requires tumors up to 4 cm in size, the postoperative classification did record even several pT3 tumors. (Fig. 4)

Sentinel lymph node was positive in 188 (26.9%) patients. As expected, a strong correlation between lymph node positivity and tumor size was found.(Tab. 1) (Fig. 5)

In many cases the sentinel lymph node remains the only affected node even after subsequent axillary dissection. Finding clues to identify these patients could lower the number of lymphadenectomies. The simplest sign could be the size of the metastasis in the sentinel lymph node.

We could divide the metastases into 6 groups based on their size: Isolated tumor cells (ITC), Single micrometastasis, micrometastases, intracapsular macrometastasis(es), extracapsular macrometastasis(es), diffuse infiltration.(Fig.6)

We found no further affected nodes in patients with ITC. In the remaining four groups further metastases were not rare,

Table 1. Positivity of sentinel nodes in correlation to tumor size

pT	total	positive
pTis	23	4,3%
pT1mic	15	6,7%
pT1a	19	5,3%
pT1b	127	15,7%
pT1c	352	29,0%
pT2	146	40,4%
pT3	5	60,0%
pTX	5	20,0%

Table 2. Number of further affected nodes in correlation with the sentinel node metastasis size

	No. of sentinel nodes	No. of further affected nodes	%
Isolated tumor cells	4	0	0%
Micrometastasis	49	7	14.3%
Micrometastases	27	4	14.8%
Intracapsular	92	33	35.9%
Extracapsular	11	6	54.5%
Diffuse	3	2	66.7%

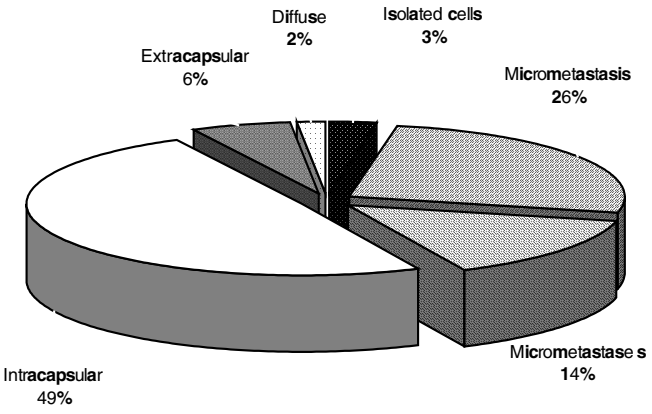

Figure 6. The size of the sentinel lymph node metastases

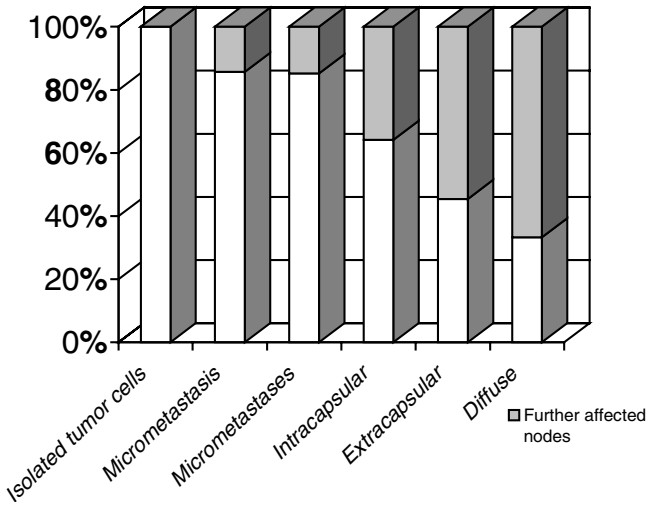

Figure 7. Affection of further lymph nodes in correlation with sentinel lymph node metastasis size

as even in the micrometastasis group over 14% of patients demonstrated further metastases in the dissection specimen. (Tab. 2) (Fig.7)

Out of the 332 patients with follow up period of 2 years and longer 11 patients experienced a recurrence. In all cases the recurrences were distant metastases to the lung, liver, bone, or brain. (Fig.8)

During the follow up in all patients we found no regional recurrence in spite of the sentinel lymph node positivity.

The following Table 3 shows the status of these patients, where NED means no evidence of disease, AWD alive with disease, DOD dead of disease, DWOD dead without disease and LOST means lost from follow up. (Tab.3)

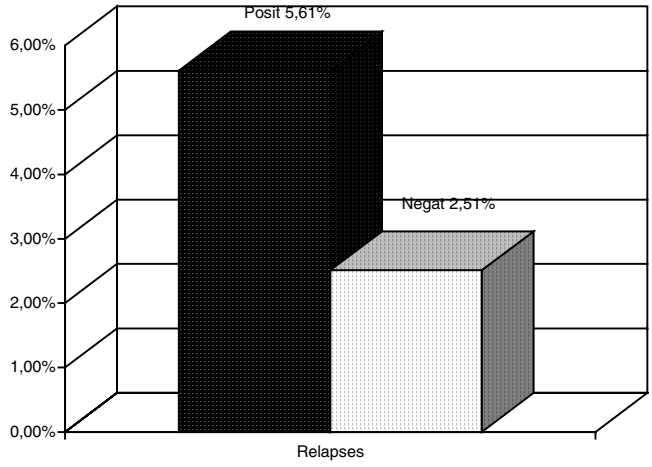

Figure 8. Overall relapses in correlation with sentinel lymph node status

Discussion

The lymph node status still remains the strongest prognostic factor in breast cancer and despite of numerous attempts no substitution for pathological lymph node staging was discovered. Therefore, the I-II level ALND remains the gold standard for pathological breast cancer staging. ALND is an often underestimated surgical procedure. To be performed correctly, it requires a skilled surgeon and operation time of 40 – 90 minutes. This procedure brings significant risk of vascular and nerve damage, long lasting seroma formation and not uncommon long term lymph edema problems.[11] In early breast cancer in approximately 70% of axillae no metastases are found, with all the described risks and problems gratuitous. The second aim of ALND is to obtain regional control. Axillary recurrences are painful and sometimes difficult to treat, yet they remain extremely rare.

The main goal of sentinel node biopsy in breast cancer is avoiding unnecessary ALND. The operation time for sentinel node biopsy in skilled hands is 10-30 minutes, with the exception of parasternal sentinel nodes removal. The complication rate is very low, the most frequent complications being com-

Table 3: Status of the patients in follow up

SLN status	NED	AWD	DOD	DWOD	LOST	
Negative	228(95.4%)	4(1.7%)	2(0.8%)		5(2.1%)	239(71.8%)
Positive	79(88.8%)	4(4.5%)	1(1.1%)	1(1.1%)	4(4.5%)	89(26.8%)
Not found	4(100%)					4(1.2%)
	311(93.7%)	8(2.4%)	3(1.6%)	1(0.8%)	9(2.7%)	332

mon wound problems (minor bleeding, inflammation, minor seroma). In rare cases a minor lymph edema can be found.

The main questions in introducing sentinel node biopsy in breast cancer are:

– Is the accuracy of staging at least comparable to ALND?
– Is the regional control comparable to ALND?
– Is it necessary to perform ALND in positive sentinel nodes? If yes, than in which cases?

The accuracy of staging has been repeatedly confirmed by many studies [[12], [13], [14], [15]]. The most feared problem is represented by false negative sentinel lymph node biopsies, in which a negative node, marked as sentinel node, is accompanied by another "non-sentinel" node, containing metastases. The false negative rate has been shown not to exceed 5% [16].

Several studies demonstrate comparable regional recurrence rates when comparing patients with obligatory ALND versus patients with sentinel node biopsy and subsequent ALND in case of positive sentinel lymph node only. Some studies even present a lower rate of regional relapses in case of SLN biopsy with subsequent ALND. This can be explained by radiotherapy involving a part of the axilla during breast conservation therapy. A positive effect of chemotherapy and/or hormonotherapy in these cases is possible as well [17].

In patients with a positive sentinel node, axillary clearance represents the standard procedure. Due to high number of patients with metastases solely in the SLN, possibilities of omitting ALND in these cases are still repeatedly discussed.

Several models calculating risk of involvement of other nodes were proposed, yet to this day, none of them could be widely accepted. Our data show that even in case of a solitary micrometastasis in the SLN nearly 15% of patients are diagnosed with further metastases. The same number of nonsentinel positive nodes is referred by Kamath et al. [18]. Katz et al. most recently tried to find some clues in 1133 patients.[[19], [20]]

Our findings correspond with those of other authors, who failed to find a simple way to identify patients with positive sentinel lymph node and negative other nodes. One possible way could be use of a longer radioactive tracer application protocol and removal of all radioactive nodes, representing a "sentinel chain". [21] A similar, albeit less sophisticated approach can be sampling of 3 further nodes in cases of positive sentinel node, with a reported accuracy of 87% [22].

Reynolds et al. [23] suggested using a combination of tumor size and sentinel node metastasis size. Based on the analysis of 222 cases he proposes the possibility of omitting ALND in patients with tumors smaller than 2 cm and with micrometastasis (i.e. metastasis up to 2mm). Applying this approach to our data (pT mic – pT1c plus micrometastasis), 9,1% of patients matching this criteria had further nodal metastases. However, if the criteria were narrowed to pTmic – pT1b plus micrometastasis, the selection would work and no further nodal metastasis would be found.

In our cases of isolated tumor cells, no further metastases were found to this day. In these cases ALND could probably be omitted. This corresponds also with the TNM classification, which classifies these cases as pN0.

Similarly, van Rijk et al.[24] report a group of 2150 patients with sentinel node biopsy, with positive sentinel node detected in 649 patients (30%). Of these 649 patients, 148 had (23%) micrometastases and 105 (16%) submicrometastases. Of the 148 patients with micrometastases, 106 underwent ALND and additional metastases were found in 20 patients (19%).

Another question is the true benefit of ALND in patients with proven nodal micrometastasis, even in cases with other nodes affected. Although an approximately 5% false negativity can be expected, the regional recurrence rate is extremely low, even peculiar. More authors refer similar results in this regard. [[24], [26], [27], [28]]

The sentinel node biopsy becomes an accepted diagnostic and even therapeutic tool in breast cancer. Its accuracy and staging abilities are outstanding. In combination with ALND in SLN positive cases it brings excellent regional control. On the other side it significantly reduces the most feared side effects of breast cancer surgery.

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