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Minimal risk of macrometastases in the non-sentinel axillary lymph nodes in breast cancer patients with micrometastatic sentinel lymph nodes and preoperatively ultrasonically uninvolved axillary lymph nodes

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Abstract

Micrometastases in the sentinel lymph node (SLN) carry a considerable risk of macrometastases in the non-sentinel lymph nodes (NSLN), resulting in axillary lymph node dissection (ALND). Preoperative ultrasound (US) examination of the axillary lymph nodes combined with a fine-needle aspiration biopsy (FNAB) has been proved to discover metastases in the axillary lymph nodes. The aim of our study was to assess the risk of macrometastases in NSLN in patients with micrometastatic SLN after a preoperative US examination of the axillary lymph nodes. The study included 36 patients in whom, after preoperative axillary US, micrometastases in the SLN were revealed and ALND was subsequently performed. At final histopathology, no macrometastases were discovered in the NSLN. In four patients, additional micrometastases were discovered in the NSLN. In conclusion, the risk of macrometastases in the NSLN in patients with preoperatively ultrasonically uninvolved axillary lymph nodes is minimal.

Keywords: Breast cancer; Sentinel node; Micrometastases; Non-sentinel lymph nodes

1. Introduction

Axillary lymph node status remains the most important prognostic information in breast cancer patients [1]. Routinely, axillary lymph node dissection (ALND) is performed to obtain the lymph node status. However, ALND is associated with severe side-effects [2]. In order to avoid these side-effects, sentinel lymph node biopsy (SLN) has become a widely accepted alternative [3]. A SLN biopsy allows the staging of the axillary lymph node basin with minimal side-effects. It is also a more exhaustive lymph node examination compared with routine ALND. As a result, micrometastases are frequently discovered in the SLN.

However, the clinical importance of micrometastases in the SLN is unknown [4]. Several reports showed that micrometastasis in the SLN is associated with a considerable risk of macrometastatic deposits in the non-sentinel lymph nodes (NSLN) [5–8]. This risk can be as high as 16% [5]. Therefore, ALND remains the standard treatment in micrometastatic SLN patients. Preoperative ultrasound (US) of the axilla and US-guided fine-needle aspiration biopsy (FNAB) of suspicious lymph nodes have been shown to be effective in discovering

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and verifying metastases in lymph nodes and thereby also reduces the need for SLN biopsy [9–12]. We recently confirmed these findings [13].

The aim of our study was to assess the risk of macrometastases in NSLN in patients with micrometastatic SLN, where the preoperative US examination of the axilla had not confirmed lymph node metastases.

2. Patients and methods

From November 2001 until January 2004, SLN biopsy was successfully performed in 457 breast cancer patients at the Institute of Oncology, Ljubljana. Eligibility criteria for the SLN biopsy were: (i) monofocal breast cancer; (ii) tumour size <30 mm; (iii) clinically non-palpable lymph nodes. Of 457 patients, 67 had micrometastases and 40 had isolated tumour cells (ITC) in the SLN(s) on the final histopathological examination. The preoperative US examination of the axillary lymph nodes was performed in 56 of 107 patients with micrometastases or ITC in the SLN(s); in eight of these patients FNAB was also performed, but was negative for malignancy. All patients signed an informed consent form.

The criteria for inclusion were: (1) preoperative US examination of the axillary lymph nodes showing no axillary pathology and negative FNAB of the lymph nodes (when performed); (2) successful SLN biopsy; (3) only micrometastases or ITC found in the SLN at the final histopathological examination; (4) subsequent, ALND.

Twenty patients with micrometastases in the SLN who preferred not to undergo ALND were excluded from the study.We therefore, included 36 patients in our study.

For preoperative US examination of the axilla, a Power Vision 8000 ultrasound scanner (Toshiba, Japan) with a 9–12 MHz linear probe was used.

The sentinel node procedure has been already described in detail elsewhere in [14]. Briefly, on the morning of surgery, 30–60 MBq of ^{99m}Tc labelled nanocolloid (Nanocol®) in 0.2 ml saline, divided in two doses, was injected peritumorally at two sites. Then, dynamic and static lymphoscintigraphy was performed. The first hot spot in regional lymph-node basins was considered to represent the SLN and was marked on the skin. In the operating theatre, only few minutes before surgery, 1ml of blue dye (Blue Patente V; Laboratorie Guerbet, Aulnaysous-Bois, France) was injected peritumorally at the same two sites. Surgical dissection of the SLN was guided by a hand-held gamma probe (Navigator GPS System, USSC, Watertown, Massachusetts, USA) and/or by the blue-stained afferent lymphatic channel. The identified SLN was excised and measured for *ex-vivo* radioactivity. Additional hot nodes were removed until the ratio of the background radioactivity to the hottest *ex-vivo* SLN was less than 10%.

The excised SLNs were examined intraoperatively with touch imprint cytology (TIC). Details of the TIC are described elsewhere in [14]. If TIC was positive, ALND was performed immediately.

All slices of the SLN were then formalin-fixed and embedded in paraffin. The slides were examined with haemotoxylin & eosin(H & E) staining. For all negative SLNs, serial sections were evaluated with H & E and cytokeratin immunohistochemical (IHC) staining at 250 μm. IHC staining was performed using the avidin–biotin–peroxidase complex method with commercially obtained monoclonal anti-cytokeratin antibody, clone MNF 116 (Dako, Glostrup, Denmark).

According to the TNM staging system, the metastatic deposits with sizes ranging between 0.2–2 mm were considered micrometastases, and those with sizes less than 0.2 mm as ITC [15].

All NSLN were sectioned transversely at 2–3 mm, entirely embedded and examined with one H & E staining per paraffin block. Results are reported on a per patient basis.

3. Results

The mean patient age was 50 years (range 24–76 years, median age 50 years). The mean tumour diameter was 18 mm (range 4–80 mm, median 16.5 mm). Histologically, 32 tumours were invasive ductal carcinomas, three were invasive lobular carcinomas and one was a mixed invasive ductal and lobular carcinoma. Hormonal receptor status was positive in 32 patients and negative in four patients (Table 1).

Altogether 64 SLN were removed, (range 1–4). The mean number of SLN removed was 1.8 per patient. The mean number of the NSLN was 17.2 (range 7–36). We found no macrometastases in the NSLN. In four patients, additional micrometastases were found in only one NSLN. In all patients with additional micrometastases in the NSLN, the SLN metastases size was $\geqslant$ 1 mm (Table 1).

4. Discussion

The presence of NSLN metastases raises questions when making treatment decisions after the finding of a positive SLN. Numerous studies have addressed the likelihood of NSLN metastases [7,8,16–18]. In a recent meta-analysis of 11 studies, the authors concluded that five individual characteristics are associated with an increased likelihood of additional NSLN metastases: SLN metastasis greater than 2 mm, extra nodal extension, tumour size greater than 2 cm, more than one positive SLN, and lymphovascular invasion of the primary tumour [7]. The important conclusion was that, in any

Table 1
Clinicopathological characteristics of the patients and their tumours

ID	Age (years)	Tp (mm)	T type	Grade	ER (%)	PR (%)	HER-2 (+)	Number of SLN	SLN metastas. size (mm)	No of +ve SLN	All lnn	No of all +ve lnn	No of macromet. NSLN	No of micromet. NSLN
1	51	9	IDC	2	90	100	–	3	0.6	1	21	1	0	0
2	46	22	IDC	3	90	90	++	3	0.9	1	13	1	0	0
3	52	11	IDC	2	90	10	+++	1	0.6	1	34	1	0	0
4	38	15	IDC	3	80	70	++	2	0.4	1	20	1	0	0
5	41	19	IDC	3	50	70	–	1	ITC (<0.2)	1	30	1	0	0
6	61	21	ILC	2	0	0	+++	2	0.6	2	15	2	0	0
7	74	15	IDC	1	100	10	+	1	1.9	1	15	2	0	1
8	46	20	IDC	3	100	90	+++	1	1.5	1	20	1	0	0
9	76	19	IDC	2	100	90	++	1	0.3	1	13	1	0	0
10	55	17	IDC	3	60	60	++	1	0.5	1	12	1	0	0
11	43	19	IDC	1	30	90	–	1	1.0	1	24	1	0	0
12	47	80	ILC	1	80	90	–	3	1.2	2	39	3	0	1
13	63	25	IDC	3	95	10	–	3	1.3	1	10	1	0	0
14	55	26	IDC	3	0	0	–	3	1.8	3	24	3	0	0
15	45	7	IDC	2	40	50	–	1	1.2	1	21	1	0	0
16	49	23	IDC	2	50	70	–	2	0.3	1	15	1	0	0
17	51	8	IDC	2	60	70	–	2	0.3	1	18	1	0	0
18	45	10	IDC	3	80	0	–	3	1.2	2	16	2	0	0
19	56	12	IDC	1	100	30	–	2	ITC (<0.2)	1	16	1	0	0
20	56	15	IDC	2	100	15	–	1	0.4	1	22	1	0	0
21	55	17	IDC	2	60	50	–	1	2.0	1	19	1	0	0
22	48	18	IDC	1	100	100	–	1	1.0	1	17	1	0	0
23	40	8	IDC	1	80	80	+++	1	1.0	1	12	2	0	1
24	36	7	IDC	3	0	0	+++	1	0.3	1	19	1	0	0
25	55	10	IDC + ILC	1	90	50	+	1	1.1	1	22	1	0	0
26	50	25	ILC	2	80	20	–	2	ITC (<0.2)	2	11	2	0	0
27	57	23	IDC	2	0	0	–	1	ITC (<0.2)	1	13	1	0	0
28	54	16	IDC	2	60	10	–	1	1.6	1	19	1	0	0
29	50	21	IDC	2	90	70	–	3	1.7	1	13	1	0	0
30	46	9	IDC	3	90	90	–	1	0.3	1	12	1	0	0
31	60	9	IDC	2	20	60	–	1	1.8	1	18	1	0	0
32	53	14	IDC	3	80	5	–	1	ITC (<0.2)	1	6	1	0	0
33	24	19	IDC	2	50	50	–	3	2.0	3	33	3	0	0
34	45	25	IDC	2	20	0	++	2	2.0	2	29	3	0	1
35	37	4	IDC	2	40	90	–	3	0.3	1	19	1	0	0
36	51	12	IDC	2	100	30	++	4	0.3	1	20	1	0	0

T, tumour; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, oestrogen receptor status; PR, progesterone receptor status; SLN, sentinel lymph node; Metastas, metastases; ITC, isolated tumour cells; +ve, positive; Lnn, lymph nodes; Macromet, macrometastases; Micromet, micrometastases; NSLN, non-sentinel lymph nodes.

combination of the five variables, the calculated risk of additional NSLN remains substantial. The investigators from Memorial Sloan Kettering Cancer Center have recently presented an algorithm to assess the likelihood of additional NSLN metastases based on eight different clinicopathological variables [16]. Although it is, by far, the best model to date, as the authors themselves acknowledged, it does not estimate perfectly the risk of NSLN metastases. We believe that, the algorithm should be tested in other institutions before it is used worldwide.

We paid particular interest to the association of the NSLN metastases risk and the SLN metastasis size; in the SLN micrometastatic group, the risk of NSLN metastases ranged from 13–22% in the studies included in the meta-analysis [7]. In a recent report, French investigators reported the risk of additional NSLN metastases in the SLN micrometastatic group of only 6.5% (8/123) [8]. In the study published by Viale and colleagues [5], the risk of additional NSLN metastases in the micrometastatic SLN was as high as 22.0% (24/109); most of the NSLN metastases were macrometastases (18/24), leading to the conclusion that an ALND should be performed in patients with micrometastatic SLN who are treated outside of clinical trials.

In the present study, we have shown for the first time the low risk of NSLN macrometastases in the axillary lymph nodes of the micrometastatic SLN patients, in whom the preoperative high quality US examination of the axillary lymph nodes (combined with the US guided FNAB in US suspicious lymph nodes) did not confirm involved axillary lymph nodes. However, due to small numbers of the patients included in our study, we can not rule out the possibility of finding macrome-

tastasis in the NSLN in the future. Nevertheless, our results indicate that the risk is minimal.

We focused only on the risk of additional NSLN macrometastatic disease because the adverse effect of macrometastatic disease in axillary lymph nodes is well documented [1], although the most appropriate local treatment is still a matter of debate; some authors showed that ALND can be safely omitted in selected patients [19], others, however, argue that the patients with limited tumour burden in axillary lymph nodes could have a survival benefit following ALND [20]. The clinical importance of micrometastases in axillary lymph nodes remains controversial [4].

The US assessment has the advantage of being a direct measure of metastatic lymph node involvement. This is in contrast to the imprecise probability calculations used in other studies. In our series, NSLN metastases were found in only four cases; all of them were micrometastases. We are well aware that it is very likely that some micrometastases were overlooked as the NSLN lymph nodes were examined by a standard method. Nevertheless, this means that, in our series, patients with exclusively micrometastatic disease are included. Therefore, if the axilla was left untreated after finding a micrometastatic SLN, no macrometastases were missed. This information can be of crucial importance when discussing further treatment plans with the patient. Furthermore, it also creates a subgroup of patients in whom the biological importance of micrometastatic disease can be studied in a prospective manner. One of the important questions today is the biologically relevant cut-off size of the micrometastases. It has been already proposed that a 1 mm cut-off for micrometastases could be more appropriate than the 2 mm used today by the TNM/American Joint Committee on Cancer (AJCC) system [21]. SLN micrometastases <1 mm had significantly less NSLN involvement than metastases >1 mm [5,6]. However, these questions need to be further clarified by prospective clinical research. Currently, the International Breast Cancer Study Group (IBCSG)is enrolling patients with micrometastatic SLN into the randomised study (IBCSG 23), comparing axillary dissection versus no axillary dissection.

Besides US, other imaging techniques have been tested for axillary lymph node assessment, like positron emission tomography (PET) scans [22]; however, a recent report showed discouraging results for PET in the staging of axillary lymph nodes [23]. At our institution, we prefer to use US due to its low cost and good results.

5. Conclusion

The risk of macrometastases in the NSLN of breast cancer patients with a micrometastatic SLN is minimal in patients with preoperatively ultrasonically uninvolved axillary lymph nodes. Thus, a purely micrometastatic patient population can be created that is suitable to research the biological importance of axillary lymph nodes micrometastases.

Conflict of interest

None declared.

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