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RESEARCH

Regional Disease Control in Selected Patients with Sentinel Lymph Node Involvement and Omission of Axillary Lymph Node Dissection

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Abstract Whether an axillary lymph node dissection (ALND) is needed for breast cancer patients with minimal sentinel lymph node (SLN) involvement is arguable despite recent data supporting the omission of axillary clearance in these patients. Data on disease recurrence of 111 patients with SLN involvement and no ALND were analysed. Patients with minimal SLN involvement were assessed for their risk of non-SLN metastasis by means of several nomograms. The series included patients with isolated tumour cells ($n=76$), micrmetastasis ($n=33$) and macrometastasis ($n=2$) who were followed for a median of 37 months (range 12–148 months). Six patients died, 3 of disease and 3 of unrelated causes. Eight further patients had breast cancer related events: 1 local breast recurrence and seven distant metastases. No axillary regional recurrence was detected. Disease related events were not associated with the risk of non-SLN metastasis. The presented data suggest that omitting ALND in patients with low volume SLN metastasis may be a safe procedure, and support the observation that systemic disease recurrence may not be associated with axillary recurrence or the risk of NSLN involvement predicted by nomograms.

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Introduction

The surgical treatment of breast cancer has substantially changed during the last decades. Lymph node status was the most important single prognostic factor of the disease and lymph nodes were removed for diagnostic (prognostic) and therapeutic purposes. Sentinel lymph node biopsy (SLNB) has widely become the standard surgical procedure for axillary staging of clinically node-negative patients, and preoperative clinical assessment has often been supplemented with axillary ultrasound and fine needle aspiration (or needle core biopsy) of suspicious nodes. If the SLNs contain no metastasis, no further axillary treatment is envisaged, and the omission of axillary lymph node dissection (ALND) in patients with negative SLNs has proved to be safe [1–5]. On the other extreme, clinically detected metastases in the axillary lymph nodes still require surgery, generally in the form of ALND.

Although a positive SLN led to an ALND in most patients, evidence suggests that a majority of SLN-positive patients do not have further lymph node involvement [6, 7]. It is even evident that further lymph node involvement does not manifest itself in recurrent disease in the majority of patients, provided adjuvant therapies are used according to current standards [1, 8–10]. Therefore, omission of ALND has been a trend in at least a subset of SLN-positive patients for several years, even before the publication of the results of the American College of Surgeons Oncology Group (ACOSOG) trial Z-0011 [11–13].

Recent guideline recommendations acknowledge that limited SLN involvement does not necessarily require ALND in all patients [14, 15], and suggest that there is no need for

ALND if the SLN involvement is at most micrometastatic [14, 15]. In contrast, the largest retrospective series of micrometastatic SLN patients suggest that there is a small minority of patients with SLN micrometastasis who have a significant risk and incidence of non-SLN (NSLN) involvement [16]. Nomograms devised for the prediction of NSLN metastasis in patients with micrometastatic SLNs suggest over 30 % or close to 50 % risk at their extremes [17–19]. On the basis of multivariate models, several factors affect the risk of NSLN involvement beside the size of the SLN metastasis [16–20]. Therefore, the omission of ALND in all micrometastatic SLN patients might be negligent. This is why follow-up data of patients with limited SLN involvement but no ALND is still important [15]. The present study summarizes the follow-up data of such patients at a single institution.

Patients and Methods

After the introduction of SLNB in August 1997 and a rather long learning period, early breast cancer patients presenting with clinically node-negative disease presenting at the Bács-Kiskun County Teaching Hospital were routinely offered SLNB from October 2000. The technique of SLNB involved a dual tracer lymphatic mapping with vital blue dye (Patent blue, earlier Byk Gulden, Konstanz, Germany, later Laboratoires Guerbet, France) and 99mTechnecium labelled colloidal albumin (Sentiscint or Nanoalbumon, Medi-Radiopharma Kft., Érd, Hungary or Nanocoll, Gipharma, Saluggia, Italy) administered peritumorally or intratumorally [21], and/or periareolarly. After periareolar injection of the tracers had been introduced, at least one of the tracers was preferably given peri- or intratumorally. Non-palpable tumours were preferably removed with intratumoral radiocolloid administration and radioguided occult lesion localization.

Sentinel nodes were subjected to intraoperative assessment by imprint cytology [22], and initially negative nodes were further processed for permanent histology. This included step sectioning of the sliced SLNs and cytokeratin immunohistochemistry (IHC) at multiple levels. Initially the SLNs were sectioned till the extinction of the tissue blocks [23], but from July 2012, after an initial trimming, only three layers separated by 250 microns were taken with IHC at the beginning and the end of the 3 steps.

All patients with positive SLN findings on intraoperative or final histology were offered ALND. Isolated tumour cells/clusters (ITC) were considered negative nodal findings in this respect, according to the TNM recommendations, and patients with minimal nodal involvement belonging to this category were generally not offered ALND. From January 2009, a number of micrometastatic patients were also spared ALND [24], and a few patients with larger metastases also skipped completion ALND by not consenting to this operation.

Radiotherapy and systemic therapy was given according to national guidelines valid at the time of their management. All patients undergoing breast conserving surgery had adjuvant whole breast irradiation complemented with boost irradiation when the margins were close. Axillary radiotherapy was given to 29 patients (9 with SLN ITC, 19 with SLN micrometastasis and 1 patient with axillary macrometastasis). Systemic therapy involved hormonal treatment in 75 patients (44 with SLN ITC, 30 with SLN micrometastasis and 1 patient with axillary macrometastasis), chemotherapy in 13 patients (10 with SLN ITC and 3 with SLN micrometastasis), their combination in 19 patients (13 with SLN ITC and 6 with SLN micrometastasis). Seven patients with HER-2 positive tumours also received trastuzumab as part of their adjuvant treatment (5 with SLN ITC and 2 with SLN micrometastasis).

Patients were followed as outpatients, and follow-up included six monthly mammographic and ultrasonographic assessment (including the examination of the axilla) in the first three years, and yearly imaging controls thereafter. Clinical controls were scheduled every 6 months in the first five years following breast surgery. Patients lost to follow-up within the first 12 months were not considered suitable for this retrospective analysis. The Kaplan-Meier survival estimates were used for overall, disease free and breast cancer specific survivals.

Patients with SLN metastatic involvement not larger than 2 mm were analysed for the risk of NSLN involvement with 3 nomograms devised for micrometastatatic disease [17–19]. A low risk of NSLN involvement was defined as a nomogram predicted risk not greater than 10 %. Accordingly, a nomogram based risk of more than 10 % was classified as high risk. For the fourth predictive tool, the presence of 0 or 1 of 5 risk factors (tumour size >2 cm, lymphovascular invasion, hormone receptor negativity, localisation in the upper outer quadrant, involved SLN ratio >33 %) was used to define low risk patients with micrometastatic SLNs, as this was associated with around 10 % frequency of NSLN metastasis in the original description [16]. Likewise, for SLNs harbouring ITC, the presence of 0–1 of 3 risk factors (age younger than 40 years, tumour size >2 cm, involved SLN ratio of 100 %) were considered to have low risk of NSLN metastasis [16]. Disease related events of patients classified as having high versus low risk were compared with the Fisher exact test, and the significance level of the two sided test was set at $p<0.05$ (VassarStats, Richard Lowry, Vassar College, Poughkeepsie, New York, USA; http://vassarstats.net).

All patients gave an informed consent. Data were anonymized and the institutional data safety monitor approved their handling in such a way. The institutional ethical

committee of Bács-Kiskun County Teaching Hospital approved this non-interventional retrospective analysis.

Results

Between October 2000 and December 2012, 111 patients with demonstrated SLN involvement did not undergo an ALND and had at least 12 months of follow-up. The characteristics of the patients are summarized in Table 1. The majority of the patients had only ITC involvement of the SLNs, but 30 % had micrometastasis and 2 patients had metastasis larger than 2 mm.

The median follow-up was 37 months (range: 12–148 months). During this period, 6 patients died, 3 of disseminated disease with multiple distant metastases (68, 70 and 117 months after surgery, respectively), and 3 of unrelated causes (62, 90 and 90 months after surgery, respectively). All the 3 patients who died of disease had only ITC category SLN involvement. Eight further patients had breast cancer related events: 1 local breast recurrence in a patient with initial ITC involved SLN, managed surgically with repeated SLNB and 2 negative SLNs, and 7 distant metastases (bone 3, lung 1, lung and liver with or without bone 2, cerebellum 1). Of the latter patients with distant metastasis, the SLN originally harboured ITCs ($n=3$), micrometastasis ($n=3$) and macrometasasis ($n=1$). No axillary regional recurrence was detected in any of the 111 patients. The disease free survival (DFS), overall survival (OS) and breast cancer specific survival (BCSS) curves based on the Kaplan-Meier estimates are shown in Fig. 1. The 5-year estimates for DFS, OS and BCSS were 85.7 % (standard error, SE: 0.06), 100 % (SE: 0.0) and 100 % (SE: 0.0), respectively.

The nomogram based risks of non-SLN involvement in relation to the follow-up events are shown in Table 2. The nomograms predict for further nodal involvement beyond the SLN. Since there were no regional recurrences, local and distant relapses were analysed in this setting, in keeping with the notion that lymph node metastases are traditionally considered relevant prognosticators of the disease, and a predicted higher risk could reflect a worse outcome. There was no significant difference in the rate of relapse in patients classified as having a high or a low risk of NSLN metastasis, independently of the nomogram or predictive tool used.

Table 1 Basic characteristics of the patients analyzed

Characteristic	
Mean age (year)	60.5
Mean invasive tumour size (mm)	16
pT1mic	1
pT1a	3
pT1b	15
pT1c	57
pT2	32
pT3	3
Tumour Grade	
I.	21
II.	46
III.	44
ER-positive	92
ER-negative	9
PR-positive	81
PR-negative	30
HER-2-positive	10
HER-2-negative	101
LVI	19
SLN ITC	76
SLN MIC	33
SLN MAC	2

ER, Oestrogen receptor; HER-2, Human epidermal growth factor receptor 2; ITC, Isolated tumour cell/cluster; LVI, Lymphovascular invasion; MAC, Macrometastasis; MIC, Micrometastasis; PR, Progesterone receptor; SLN, Sentinel lymph node

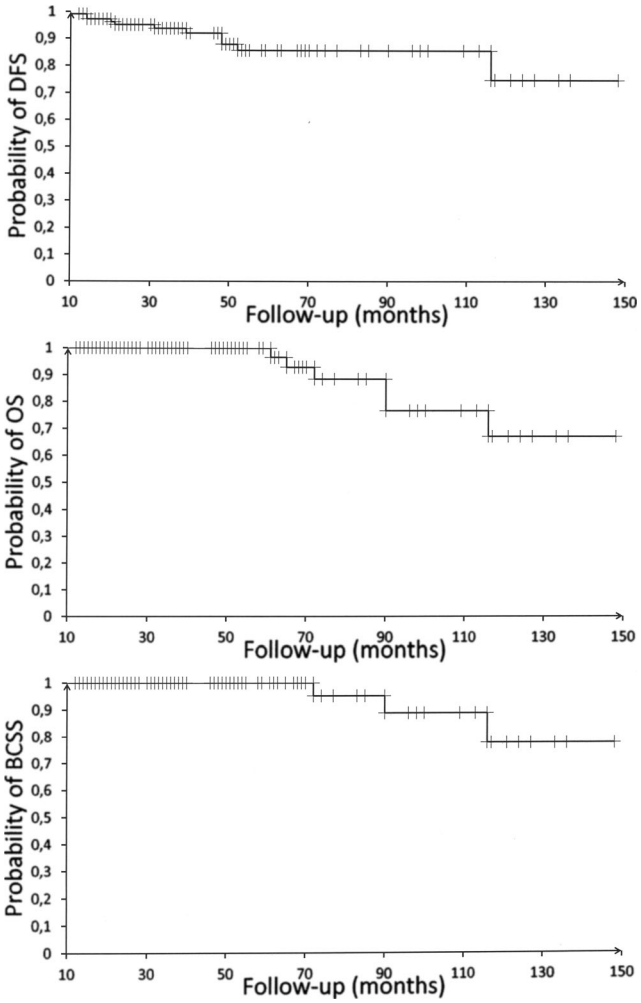

Fig. 1 Kaplan-Meier survival curves for the study population *DFS*, Disease free survival; *OS*, Overall survival; *BCSS*, Breast cancer specific survival

Table 2 Distribution of patients with low volume metastatic SLN involvement according to their risk of NSLN metastasis based on the prediction by different predictive tools

Nomogram	Low risk (≤10 %)	High risk (>10 %)	p[a]
French 4-variable nomogram [17]			
NED	53	45	
REC	7 (11.7 %)	4 (8.2 %)	0.75
Helsinki nomogram [18]			
NED	67	31	
REC	6 (8.2 %)	5 (13.9 %)	0.50
French 5-variable nomogram [19]			
NED	77	21	
REC	7 (9.5 %)	4 (16 %)	0.45
Danish risk factors based [16]	[b]	[b]	
NED	67	32	
REC	6 (9.0 %)	4 (12.5 %)	0.73

NED, No evidence of disease; *REC*, Recurrent disease. (Numbers in parentheses reflect the percentage of patients who experienced local or distant recurrence of their disease in the given risk category.)

a: Fisher exact test (two-sided); b: low risk defined as 0 or 1 risk factor and high risk defined as having >1 risk factors for both MIC and ITC. (For details on risk factors, see Materials and Methods)

Discussion

Lymph node status is still considered one of the most powerful prognostic factors in breast cancer. Besides being a qualitative prognosticator (metastastic lymph nodes or a positive nodal status versus the lack of metastases, i.e., a negative nodal status) it is also a quantitative one. A greater tumour burden in the regional lymph nodes reflects worse prognosis, and conversely, a smaller tumour burden means smaller and even questionable disadvantage in prognosis. The involvement of NSLNs is influenced by several factors among which the size / degree of the SLN involvement is one of the most important. Low-volume SLN metastases of the micrometastatic category are associated with NSLN positivity in 10–15 % of the cases [25], a proportion which is confirmed by the data of recent clinical trials [8–10], but as highlighted in the introduction, depending on the combination of several factors, this may double or triple in a minority of patients [16–19]. In this respect ITCs do not seem much better, as on average, they are suggested to be associated with NSLN involvement in about 12 % of the cases according to a meta-analysis [26]. It must also be remembered that until recently, the distinction between ITC and micrometastasis by pathologists was far from perfect [27, 28]. Taking all this together, analysing patients with SLN micrometastasis or ITC together makes sense.

Although current trends favour the omission of ALND in many patients with minimal SLN involvement, including all with SLN micrometastasis [14, 15], this approach may ignore a small minority of patients who could potentially benefit from further axillary treatment [16, 24]. This makes follow-up studies of patients with involved SLNs but no ALND important.

One of the first studies of the kind reported no axillary recurrence for a selected group of SLN micrometastatic patients with favourable prognostic profile during a median follow-up period matching the present one [29]. Likewise, this series also included mainly patients deemed to have a low risk of further nodal involvement, including many with SLN ITC only. Unlike in other studies, some patients with omitted ALND and receiving radiotherapy to the breast following breast conservation, also got irradiation of the axillary region, which we believe to constitute an overtreatment in patients with low risk of axillary NSLN involvement. In keeping with the results of the first similar report [29], no axillary recurrence occurred during the follow-up period, but 11 breast cancer related events were noted, including 3 deaths from metastatic disease. The results of clinical trials looking at the safety of omitting ALND in patients with minimal SLN involvement [8–10] also point to a very low rate of axillary recurrence after a somewhat longer median follow-up, and the occurrence of local (in breast) and systemic disease recurrence. This seems unrelated to the manifestation of recurring axillary cancer (Table 3), and also to the predicted risk of NSLN involvement on the basis of predictive tools devised for low volume SLN metastasis patients (Table 2).

Table 3 Follow-up events of patients with SLN involvement and no ALND in published reports

Study, 1st author	Patients	MAC/MIC/ITC	Median follow-up (months)	Axillary recurrence	Breast recurrence	Metastasis	DOD	DOOC
Meretoja [29]	48	0/22/26	37	0	1	2	1	9
Present	111	2/33/76	37	0	1	10	3	3
Galimberti [10]	467	0/467/0	60	5	8	25	0	2
Sola [9]	116	0/116/0	62	2	0	1	0	0
Giuliano [8]	359	160/199/ni	75	4	8	ni	ni	ni

DOD, Dead of disease; *DOOC*, Dead of other (unrelated) causes; *ITC*, Isolated tumour cell/cluster; *MAC*, Macrometastasis; *MIC*, Micrometastasis; ni: no information. (Studies listed according to length of median follow-up

The presented retrospective data suggest that omitting ALND in patients with low volume SLN metastasis may be a safe procedure, and support the observation that systemic disease recurrence may not be associated with axillary recurrence or the risk of NSLN involvement predicted by nomograms.

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Conflict of Interest The authors have no conflict of interest to report.

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