

Prognostic Impact and Therapeutic Implications of Sentinel Lymph Node Micro-Metastases in Early-Stage Breast Cancer Patients

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The prognostic value of sentinel lymph node (SLN) micro-metastases and the question whether patients with SLN micro-metastases should undergo axillary lymph node dissection remain a matter of great debate. Based on the current literature and on our own data, we provide suggestive evidence that SLN micro-metastases in early stage breast cancer patients appear to have prognostic value and should impact the decision-making regarding adjuvant therapy, however, do not necessarily require further surgical treatment.

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BACKGROUND

Sentinel lymph node (SLN) procedure has become the standard axillary staging method for early-stage breast cancer patients. As the SLN accurately reflects the nodal status of the axilla, only patients with SLN macro-metastases routinely undergo axillary lymph node dissection (ALND), while patients with negative SLN can be spared the substantial (short- and long-term) morbidity of ALND [1][2]. Additionally, due to the more accurate histopathologic examination of SLN, micro-metastases are detected with increasing frequency in SLN. However, the prognostic value of SLN micro-metastases and the question whether patients with SLN micro-metastases should undergo ALND remain a matter of great debate. While the American Society of Clinical Oncology (ASCO) guidelines recommend ALND for patients with SLN micro-metastases, only about one-quarter of ASCO members questioned would actually recommend ALND, as evidenced by a recent survey [3]. In previous investigations [4,5], we presented our prospective data on an unselected and consecutive group of early-stage breast cancer patients with negative SLN or SLN micro-metastases undergoing SLN procedure only. Omitting ALND in patients with SLN micro-metastases was found to be safe, as no axillary recurrence and no distant metastases were found in these patients after a median follow up of 77 months [4]. However, recurrences may occur late in the course of the disease. Therefore, we have updated the clinical long-term outcome in this group of early-stage breast cancer patients with negative SLN or SLN micro-metastases undergoing SLN procedure only as an invited review for this issue of the *Journal of Surgical Oncology* Data presented are based on a median follow-up of over 97 months.

PATIENTS AND METHODS

Between 1998 and 2002, 234 consecutive patients with 236 early-stage breast cancers were prospectively enrolled in this study. Eligibility criteria were (1) palpable breast cancer ≤ 3 cm and (2) absence of clinically palpable axillary lymph nodes. Written informed consent was obtained from all patients. Patients' characteristics and the technical details have been described previously [4,5]. Briefly, the SLN

procedure was performed using a combination of a radiolabeled colloid (Nanocol[®]) and a lymphotropic blue dye (Lymphazurin[®]). Frozen section was routinely performed intraoperatively. On permanent section, SLN were examined using step sectioning, staining with H&E, and immunostaining with pan-cytokeratin antibodies (Lu-5 or CK22). Patient with SLN micro-metastases did not undergo completion ALND or radiation to the axilla. The decision regarding an eventual adjuvant therapy was strictly based on the recommendation of the St. Gallen Consensus Conferences [6,7]. The presence of SLN micro-metastases did not impact this decision-making. For statistical analysis, the χ^2 -test was used for comparisons of dichotomous variables, and the log-rank test for comparisons of survival curves. All tests were two-sided. Statistical significance was defined as $\alpha < 0.050$.

RESULTS

The SLN identification rate was 95% (224/236). Seventy-four (33%) patients had SLN macro-metastases, 27 (12%) patients SLN micro-metastases, and 123 (55%) patients no SLN metastases. The use of adjuvant systemic therapy (hormone or chemo- or a combined therapy) did not significantly differ between the groups of patients with SLN micro-metastases and those without SLN metastases (96.2% and 86.2%, respectively, $P = 0.091$). None of the patients with SLN micro-metastases or with negative SLN were lost to follow-up. Median

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TABLE I. Axillary Recurrence Rate in Patients With Detection of SLN Micro-Metastases and Without ALND

Refs.	Type	n	Size of nodal infiltrate (mm)	FU	Ax rec	Patient sample
Liang et al. [11]	Retro	4	<2	14 ^b	0	Selected
Ganaraj et al. [12]	Prosp	17	<2	30 ^b	0	Selected
Guenther et al. [13]	Prosp	16	<2	32 ^c	0	Selected
Fant et al. [14]	Retro	27	<2	30 ^b	0	Selected
Fournier et al. [15]	Retro	6	≤2	12 ^b	0	Selected
Fan et al. [16]	Retro	27	≤2	29 ^c	1	Selected
Schrenk et al. [17]	Prosp	16	>0.2 and ≤2	48 ^c	0	Selected
Carlo et al. [18]	Prosp	21	<2	60 ^c	0	Selected
Chagpar et al. [19]	Retro	12	>0.2 and ≤2	40 ^c	0	Unselected ^d
Haid et al. [20]	Prosp	6	>0.2 and ≤2	47 ^c	0	Selected
Hwang et al. [21]	Retro	90	>0.2 and ≤2	30 ^c	0	Selected
Pernas et al. [22]	Prosp	45	>0.2 and ≤2	60 ^c	0	Unselected
Pugliese et al. [23]	Retro	76	^a	77 ^c	0	Selected
This study	Prosp	27	>0.2 and ≤2	98 ^c	0	Unselected

FU, follow-up (months); Ax rec, axillary recurrence (n); retro, retrospective; prosp, prospective. (Modified and updated after Ref. [4])

^aMetastases detected by immunohistochemistry only.

^bMean.

^cMedian.

^dHistopathological review of primarily negative SLN.

follow-up was 97.7 months (range 3.6–133.7 months). In the SLN micro-metastases group, none of 27 patients (0.0%) experienced an axillary recurrence, as compared to 1/123 patients (0.8%) in the SLN negative group ($P = 1.000$). Similarly, no patients with SLN micro-metastases developed distant metastases (0.0%), whereas 9/123 (7.3%) SLN negative patients were found to have a distant disease recurrence ($P = 0.075$). Eight-year overall survival was 88.7% and 86.7% for the SLN micro-metastases and the SLN negative group ($P = 0.803$), respectively. Eight-year disease-free survival was 88.7% and 78.9%, respectively ($P = 0.313$).

DISCUSSION

Based on a follow-up of over 97 months—the longest one in the literature—we provide suggestive evidence that early-stage breast cancer patients with SLN micro-metastases treated with SLN procedure alone do not have an increased axillary or distant disease recurrence rate as compared to patients with negative SLN. Therefore, the SLN procedure is not only an accurate staging tool, but also appears to provide excellent local control, at least when combined with adjuvant systemic therapy. Moreover, patients with SLN micro-metastases had similar 8-year overall and disease-free survival rates in our investigation compared to those with negative SLN.

There are two cardinal, fundamentally different questions regarding SLN micro-metastases in early-stage breast cancer patients [8]:

- (1) Should these patients receive adjuvant treatment?
- (2) Should these patients undergo a completion level I and II ALND?

A recent retrospective New England Journal of Medicine publication [9] answers question #1: de Boer et al. compared large cohorts of early stage breast cancer patients with isolated tumor cells or micro-metastases in the SLN who did or did not receive adjuvant treatment. In this investigation, adjuvant therapy was found to be associated with significantly improved disease-free survival. Similarly, in the present investigation 26/27 patients (96.2%) with SLN micro-metastases received adjuvant systemic therapy, even though the decision for administration of adjuvant therapy was not based on the presence of SLN micro-metastases.

Question #2 was addressed in the present study. To our knowledge, our prospective investigation presents the longest follow-up in the

literature of an unselected cohort of consecutive, early-stage breast cancer patients with SLN micro-metastases, in whom an ALND was systematically omitted (Table I). No regional or distant recurrences occurred in any of the 27 patients with SLN micro-metastases during a median follow-up of over 97 months. Our findings were confirmed by a recent publication by Bilimoria et al. [10]. Based on a large national cancer database, 2,203 patients with microscopic nodal metastases were identified. No significant differences with respect to axillary recurrence and survival were found between patients who underwent completion ALND versus those who did not.

It is well known and extensively described in the literature that the short- and long-term complications after ALND are dramatically higher than after SLN procedure alone [1]. Therefore, it is imperative that breast cancer surgeons carefully consider whether or not an ALND is indicated and of any benefit at all to the patient.

CONCLUSIONS

In summary, based on the current literature and our own data, SLN micro-metastases in early stage breast cancer patients appear to have prognostic value and should impact the decision-making regarding adjuvant therapy, however, do not necessarily require further surgical treatment.

These conclusions are well supported by the American College of Surgeons Oncology Group Study ACOSOG Z 0011 [24,25].

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