

No Axillary Lymph Node Dissection in Breast Cancer Patients with Sentinel Lymph Node Micrometastasis

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ABSTRACT

Follow-up data of a series of 75 breast cancer patients with sentinel node (SN) micrometastases only (between 0.2 and 2 mm) and favorable histopathological features of the primary tumor (well-differentiated, T1 tumors without lymphovascular invasion) who refused completion axillary lymph node dissection (ALND) or who were unsuitable for surgery were assessed in order to detect the rate of axillary recurrence after an adjuvant chemo- and/or hormonal adjuvant treatment was given. The great majority of patients (81.3%) did not undergo ALND due to the existence of favorable histopathologic factors while the rest were equally distributed among over 75-year-old women (10.6%) and patients at a high surgical risk due to comorbid conditions (9.3%). Sixty-six patients (88%) underwent conservative treatment (lumpectomy followed by adjuvant breast radiotherapy) while the remaining nine patients (12%) had total mastectomy; 72 out of 75 patients (96%) received some forms of adjuvant chemo- and/or hormone-therapy. After a median follow-up of 38 months (range 12 - 84 months), nine out of 75 patients (12%) had a disease relapse, only one of them (1.3%) being affected by an axillary recurrence in the untreated axilla three years after primary surgery. On these grounds, completion ALND could be safely omitted in patients with SN micrometastasis and favorable histopathological characteristics of the primary neoplasm due to the very low rate of axillary recurrence with no detrimental effect on survival.

KEYWORDS

Sentinel Lymph Node; Axillary Lymph Node Dissection; Breast Cancer

1. Introduction

Sentinel lymph node (SN) biopsy has become the standard of care as staging procedure in clinically node-negative breast cancer patients in order to achieve a more selective approach to completion axillary lymph node dissection (ALND) [1-3]. In many instances, however, especially in the case of SN micrometastasis, the rate of non-SN involvement after completion ALND is rather low with an observed pooled proportion of 20.2%, as reported in the meta-analysis by *Cserni et al.* [4]. These figures may be even lower in patients with more favorable histopathological features, such as those with well-differentiated T1 tumors (<2 cm) without lympho-vas-

cular invasion (LVI) [5,6]. Although ALND provides additional prognostic information such as the number of involved lymph nodes, which may be useful only for the planning of post-operative radiotherapy, and may decrease the rate of regional recurrences, its impact on survival seems negligible coupled with an increased morbidity as compared to SN biopsy alone [7-12].

For these reasons, the therapeutic benefit of a completing ALND has gradually lost much of its interest. Actually, ALND may be considered optional in the following clinical setting: 1) patients with 1 - 2 tumor-positive SN and favorable histopathological features, for whom the planning of adjuvant systemic therapy is unlikely to be affected; 2) elderly patients; and 3) patients with serious comorbid factors [13,14].

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In the present study, we revised the follow-up of a series of breast patients with SN micrometastasis and favorable histopathological features of the primary tumor who refused completion ALND after an informed consent was given or who were unsuitable for surgery due to comorbid conditions, in order to assess the rate of axillary recurrence after an adjuvant chemo- and/or hormonal adjuvant post-operative treatment.

2. Patients and Methods

Between January 2005 and December 2012, 1743 patients with early-stage (clinical T₁₋₂ N₀ M₀) breast cancer underwent SN biopsy as part of their standard treatment at the Breast Unit of the IRRCS “Azienda Ospedaliera Universitaria San Martino-IST” of Genoa. Clinical, histopathological, and follow-up data were collected into an institutional database; 75 patients with SN micrometastases only (between 0.2 and 2 mm) who did not undergo ALND were retrospectively identified, and they represented the specific target of this study. SN micrometastases were usually detected at definitive histological examination. ALND was not performed due to patient’s refusal of the operation after an informed consent was given about the existence of favorable histopathological features of the primary tumor (*i.e.*, T1 breast cancer with Scarff-Bloom-Richardson (SBR) grade well (G1) or moderately differentiated (G2), and no lymphovascular (LVI) invasion); moreover, patients over 75 years of age or with comorbid conditions that would have seriously increased the operative risk were usually regarded as not eligible for ALND. All patients underwent an adjuvant systemic treatment according to national guidelines [15]. The study protocol was approved by the Ethic Committee of the Institute.

As regards the detection and histology of SN, a standard procedure was adopted, as previously described [16]. Pathological staging was defined according to the International Union Against Cancer (UICC) TNM classifications of malignant tumors [17]. The following variables were retrospectively reviewed in the specific database: patients’ characteristics (age at diagnosis, menopausal status), tumor features (tumor size, histological type, SBR grade, LVI, Ki-67 proliferative index, c-ERBB2 expression, hormonal expression), and adjuvant treatments (chemotherapy, endocrine therapy, post-operative radiotherapy). Follow-up data included the length of follow-up and the analysis of the pattern of failure.

3. Results

The characteristics of patients and the histopathological features of the primary tumor are reported in **Table 1**. Overall, 75 patients were included in the present analysis; the mean patient age was 68 years (range = 47 - 78, SD =

Table 1. Characteristics of the patients and breast tumor description.

Characteristic	Total patients (n = 75)	
	No.	%
Age at diagnosis, years		
<50	17	22.6
50 - 70	25	33.3
>70	33	44.1
Menopausal status		
Yes	59	78.6
No	16	21.4
Tumor size, mm		
1 - 20	61	81.3
>20	14	18.7
Histological type		
Non-lobular	60	80.0
Lobular	15	20.0
SBR grade		
I	37	49.3
II	32	42.6
III	6	8.1
LVI		
No	65	86.6
Yes	10	13.4
Ki-67 proliferative index		
≤10%	33	44.0
>10%	42	56.0
c-ERBB2 expression		
Negative	57	76.0
Positive (+)	8	10.6
Highly positive (++/+++)	10	13.4
Hormonal expression		
ER-positive/PgR-positive	60	80.0
ER-negative/PgR-positive	-	-
ER-positive/PgR-negative	8	10.6
ER-negative/PgR-negative	7	9.4
Adjuvant chemotherapy		
Yes	50	66.6
No	25	33.4
Adjuvant endocrine therapy		
Yes	67	89.3
No	8	10.7
Adjuvant radiotherapy		
Yes	66	88.0
No	9	12.0

ER, Estrogen receptor; PgR, Progesterone receptor; LVI, lymphovascular invasion; SBR, Scarff-Bloom-Richardson; c-ERBB2, HER-2/neu.

10.5 years). The mean size of the primary tumor was 12 mm (range = 6 - 24, SD = 4.5 mm). The mean number of

SN examined per patient was 1.6 (range = 1 - 3, SD = 0.9). The great majority of patients (61 out of 75 = 81.3%) did not undergo ALND due to the existence of favorable histopathologic factors (T1, and G1/G2, and no LVI), the remaining being equally distributed among over 75-year-old patients (7 out of 75 = 9.3%) and patients at high surgical risk due to comorbid conditions (7 out of 75 = 9.3%). Sixty-six patients (88%) underwent conservative treatment (lumpectomy followed by adjuvant breast radiotherapy) while the remaining nine patients (12%) had total mastectomy; 72 out of 75 patients (96%) received some form of adjuvant chemo- and/or hormone-therapy.

The median duration of follow-up was 38 months (range 12 - 84 months); follow-up was 2 - 5 years in 60 patients (80%). Nine out of 75 patients (12%) had a disease relapse (Table 2); one of them (1.3%) had an axillary recurrence in the untreated axilla three years after primary surgery, and she underwent therapeutic ALND with an uneventful recovery thereafter.

4. Discussion

SN biopsy has substantially replaced ALND for the pathological staging of the axilla in patients with clinically node-negative breast cancer; this procedure has a more than satisfactory accuracy, thus allowing to reserve ALND in patients with tumor-positive SN only, with reduced overall postoperative morbidity and improved quality of life [1-3,18,19]. Noteworthy, in 38% to 67% of patients with tumor-positive SN undergoing completion ALND the only tumor-involved lymph node is just the SN; hence, most patients would not benefit at all from ALND [20-22]. This rate is likely to increase over time thanks to earlier diagnosis of breast cancer due to the widespread use of screening mammography, as the risk of axillary metastases is close to 10% in tumors of less than 1 cm [21,22]. Noteworthy, in patients with SN micrometastasis the rate of tumor-positive nodes at completion ALND drops down to 0% and 2.8% when the tumor size is less than 1 cm and between 1 and 2 cm, respectively [23,24]. Moreover, the selection of patients eligible for systemic adjuvant treatment is currently influenced by various patient- and tumor-related factors, such that axillary lymph node status, as well as the extent of lymph node involvement, no longer determines this decision analysis [25].

Overall, these figures are progressively limiting the need of performing a therapeutic ALND, according to current perspective on the natural history of breast cancer that would suggest the usefulness of ALND as for survival in clinically node-negative patients. Actually, the 25-year report of the randomized trial B-04 initiated in 1971 failed to show any survival advantage from removing occult positive nodes at the time of initial surgery

Table 2. Follow-up data.

Length of follow-up	No.	%
1 year	8	10.6
2 year	10	13.4
3 year	18	24.0
4 year	22	29.3
5 year	10	13.4
>5 year	7	9.3
Failure		
No	69	92.0
Yes	6	8.0
Site of first event		
Local	1	1.3
Local + regional nodes	1	1.3
Regional node recurrence	1	1.3
Contralateral breast	2	2.6
Distant	4	5.3
Total	9	12.0

[26]. Recently, the role of completion ALND in patients with a tumor-positive SN has been further challenged by the results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, confirming the excellent regional control of SN biopsy without ALND in selected patients with early-stage breast cancer [8,9]. For these reasons, ALND may be considered optional in the following clinical setting: 1) patients with 1 - 2 tumor-positive SN and favorable histopathological features, for whom the planning of adjuvant systemic therapy is unlikely to be affected; 2) elderly patients, and 3) patients with serious comorbid factors [13,14].

On these grounds, a series of patients with SN micrometastasis and favorable histopathological features of the primary tumor who refused completion ALND or unsuitable for surgery due to comorbid conditions were investigated in order to assess the rate of axillary recurrence and its consequence as for subsequent disease relapse. Notwithstanding the rather limited sample of patients due their selective accrual in this study, our findings confirm that the rate of axillary recurrence is very low (1.3%), in agreement with previous report ranging from 1% to 3%; mostly, no further recurrence occurred following a delayed therapeutic ALND [7,8,27,28]. Moreover, almost all patients underwent adjuvant chemo- and/or hormone-therapy so that the prognostic information supplied by completion ALND looks negligible in the treatment decision planning.

5. Conclusion

In our view, these results well match with existing literature data so that: 1) completion ALND could be safely omitted in patients with SN micrometastasis and favora-

ble histopathological characteristics of the primary neoplasm; 2) its role should be further assessed in patients with more aggressive prognostic features and/or with SN macrometastasis, and 3) ALND should be reserved to clinically node-positive breast cancer patients or with axillary recurrence in an untreated axilla.

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List of Abbreviations (In Order of Comparison)

ALND: Axillary Lymph Node Dissection
 SN: Sentinel Node
 G: Grade
 LVI: Lympho-Vascular Invasion
 SD: Standard Deviation
 ER: Estrogen Receptor
 PgR: Progesterone Receptor
 SBR: Scarff-Bloom-Richardson
 c-ERBB2: HER-2/neu