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ScienceDirect

EJSO 40 (2014) 1195–1202

EJSO the Journal of Cancer Surgery

www.ejso.com

Impact of sentinel node tumor burden on outcome of invasive breast cancer patients

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Accepted 3 August 2014
Available online 20 August 2014

Abstract

Background: The tumor status of the axillary lymph nodes is one of the most important prognostic factors in women with early breast cancer (BC). Sentinel lymph node (SLN) biopsy has become the standard staging procedure for patients with invasive BC, largely replacing axillary lymph nodes dissection (ALND). The exact impact on prognosis of SLN tumor burden is still object of controversy. The aim of this study was to correlate the tumor burden in the SLN with the outcome in a large cohort of women.
Patients and methods: 1040 consecutive patients with clinical stage I–III invasive BC were prospectively collected on our Institutional BC database from January 2001 to January 2007. Patients were stratified into the following four groups based on the tumor burden of the SLN: macrometastases, tumor deposit ≥2 mm; micrometastases, tumor deposit ≥0.2 mm and <2 mm; isolated tumor cells (ITC), isolated tumor cells or tumor deposit <0.2 mm; negative, in case of patients with no evidence of tumor.
Results: At a median follow-up of 8.5 years, the tumor burden of SLN metastases resulted significant predictor of DFS ($P < 0.0001$) and OS ($P = 0.042$). Multivariate analysis showed that the tumor burden of SLN metastases and Ki 67 proliferative index maintained the statistical significance.
Conclusion: Patients with SLN micrometastases or ITC, do not seem to have a worse DFS or OS compared with SLN negative cases. There is a significant decrease in DFS and OS in patients with macrometastatic disease in the SLN.

Keywords: Invasive breast cancer; Micrometastases; Macrometastases; Sentinel lymph node; Tumor burden; Lymphadenectomy

Introduction

Breast-conserving therapy is nowadays considered the gold standard approach thanks to randomized prospective trials and provides equivalent survival compared with total mastectomy.[1,2] The tumor status of the axillary lymph nodes is one of the most important prognostic factors in women with early breast cancer (BC).[3] Since the 1990s, the sentinel lymph node (SLN) biopsy has become the standard staging procedure for patients with invasive BC, replacing axillary lymph nodes dissection (ALND).[4]

SLN metastases are currently categorized as isolated tumor cells (ITC), micrometastases or macrometastases depending upon the size of the largest tumor deposit in the SLN following the seventh edition of the American Joint Committee on Cancer (AJCC).[5]

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http://dx.doi.org/10.1016/j.ejso.2014.08.471
0748-7983/

The exact impact on prognosis of SLN tumor burden is still object of controversy; contradictory findings have been published about the prognostic impact of SLN micrometastases.[6–9]

Furthermore, recent data have been questioning the need of a completion ALND in patients with SLN showing micrometastases or macrometastases: a large retrospective review including more than 7000 women demonstrated nearly equal recurrence rate between patients with micro- and macrometastases. The results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 changed the landscape of axilla management in BC patients, suggesting the omission of ALND in a subgroup of patients with SLN macrometastases that receive adjuvant systemic therapy and whole breast irradiation (WBI).[10]

The aim of this study was to correlate the tumor burden in the SLN with the outcome in a large cohort of women who were all subjected to SLNB.

Patients and methods

Patients

1360 consecutive patients with clinical stage I–III invasive BC were prospectively collected on our Institutional BC database from January 2001 to January 2007. Exclusion criteria form analyses were: ductal carcinoma in situ, contralateral or recurrent BC, neoadjuvant chemotherapy, clinical suspicious lymph nodes, or stage IV disease at diagnosis. All patients signed an informed consent form. The final analyses was performed on a total of 1040 cases.

Our Breast Unit multidisciplinary team has discussed all the cases. In our Department the patients undergo a whole-life follow-up.[11,12] In brief, outpatient clinics examinations are programmed every 6 months until 5 years from BC diagnosis, then yearly until 10 years and thereafter every two years.

Pathology methods

In our Institute, specialized expert pathologists, dedicated to BC specimens' evaluation, perform pathology assessment.

Our techniques for pathological methods have previously been described.[13,14] In brief, estrogen receptor (ER) status, progesterone receptor (PgR) status, and Ki-67 labeling index determined with the MIB1 monoclonal antibody were assessed; for ER and PgR status two categories (negative/positive) were considered according to well-established cut-off values (10% for both ER and PgR).[15]

HER2 immunohistochemistry (IHC) expression was scored as follows: 0, no staining or faint membrane staining; 1+, faint membrane staining in >10% of tumor cells, incomplete membrane staining; 2+, weak to moderate membrane staining in >10% of tumor cells; and 3+, intense circumferential membrane staining in >10% of tumor cells. HER2 scores of 0 and 1+ were considered negative. HER2 IHC 3+ and fluorescent in situ hybridization (FISH) – amplified tumors were considered positive. All IHC 2+ tumors and indeterminate tumors were tested for gene amplification by FISH. Histological tumor grading was assessed according to Elston and Ellis.[16] Concerning Ki-67, we used a validated[17,18] cut-off value of 20% to distinguish Ki-67 high from Ki-67 low, although the ideal threshold has not been identified yet, and vary widely from 1 to 28.6%.[18]

Patients were stratified into the following four groups based on the tumor burden of the SLN: macrometastases, tumor deposit ≥2 mm identified by hematoxylin eosin (HE); micrometastases, tumor deposit ≥0.2 mm and <2 mm identified by HE; isolated tumor cells (ITC), isolated tumor cells or tumor deposit <0.2 mm detected by IHC or HE; negative, in case of patients with no evidence of tumor with HE and IHC stain. BC were staged according to the histological type and the TNM Classification of malignant tumors.[5]

Table 1
Main individual characteristics of 1040 invasive breast cancer patients stratified by sentinel lymph node tumor burden.

Feature	Negative SLN (n = 878)	ITC SLN (n = 63)	Micrometastases SLN (n = 66)	Macrometastases SLN (n = 33)	p-Value[a]
Mean age, years (SD)	58.7 (10.9)	59.1 (11.5)	57.5 (11.6)	53.9 (11.1)	**0.032**
pT 2–3, n (%)	132 (15.1)	10 (15.9)	7 (10.6)	12 (36.4)	**0.006**
LVI presence	94 (10.7)	7 (11.1)	28 (42.4)	14 (42.4)	**0.0001**
Nuclear grade 3	193 (22.0)	13 (20.6)	14 (21.2)	10 (30.3)	0.70
ER positive status	784 (89.3)	57 (90.5)	58 (87.9)	29 (87.9)	0.96
PgR positive status	697 (79.4)	52 (82.5)	53 (80.3)	26 (78.8)	0.94
HER2 positive status	92 (11.7)	5 (8.1)	16 (25.0)	7 (21.9)	**0.006**
Ki 67 ≥20%	198 (22.6)	17 (27.0)	20 (30.3)	7 (21.2)	0.45
Adjuvant CT	141 (16.1)	11 (17.5)	35 (53.0)	25 (75.8)	**0.0001**
Adjuvant HT	647 (73.7)	49 (77.8)	55 (83.3)	24 (72.7)	0.33

Abbreviations: SLN, sentinel lymph node; ITC, isolated tumor cells; pT, pathological tumor stage; LVI, lymph vascular invasion; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CT, chemotherapy; HT, hormonal therapy.
Bold values represent the statistically significant p-Value <0.05.
[a] p-Value from Kruskal Wallis test or chi-square test, as appropriate.