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Association of the number of sentinel lymph nodes harvested with survival in breast cancer

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Abstract

Aims: In patients with breast cancer, the association between the number of sentinel lymph node (SLN) removed and survival is poorly known. Our objective was to evaluate this association on disease-specific survival (DSS).

Methods: Data of 144 517 patients with invasive T1-3M0 breast carcinoma and initial treatment with SLN biopsy were extracted from the SEER database. Univariate and multivariate analyses were performed.

Results: The number of SLNs harvested and the completion of axillary lymph node dissection (ALND) were not associated with DSS improvement for patients without metastatic nodes. After adjustment, patients with three SLNs had a better DSS than did other groups (HR of 0.73 CI 95% [0.60–0.88], $p = 0.001$). This result was mainly driven by the group of patients with one metastatic LN. When patients had two or more metastatic LNs, there was no difference in DSS according to the number of SLNs or to completion of ALND.

Conclusions: The number of SLN harvested was associated with DSS. According to DSS, the optimal number of SLNs harvested was three in this large series, thereby calling into question the understaging or undertreatment of SLN biopsy in which only one or two SLNs are harvested but also the therapeutic effect of completion ALND.

Keywords: Breast cancer; Sentinel lymph node; Axillary lymph node dissection; Axillary nodal staging; Positive lymph node management

Introduction

Breast cancer is the most common cancer worldwide in females and is the first cause of cancer mortality among women.[1] In early breast cancers (EBCs), lymph node status is the main prognostic factor and determines adjuvant treatments.[2,3] Before the 1990s, axillary lymph node dissection (ALND) was used for axillary staging and had prognostic value helping physicians choose the appropriate adjuvant treatment. However, ALND causes the functional impairment of the upper limb and impairs the quality of life.[4,5] Krag et al. described for the first time in 1993 the technique of sentinel lymph node biopsy (SLNB).[6] Since that time, the SLNB has been developed and standardised. The completion of ALND when the sentinel lymph node (SLN) is free of tumour has no benefits in terms of local recurrence.[7–9] For those cases, SLNB avoids useless ALND with less morbidity and similar rates of local recurrence

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and survival.[5,10] Currently, for EBC the standard axillary staging is based on SLNB followed by ALND if the SLN shows evidence of metastasis.[3,11,12]

In the literature, the number of SLNs removed is highly variable, ranging from one to more than ten depending on the study, with an average of three SLNs removed by procedure.[6,13–15] Removing the maximum number of SLNs reduces the rate of false-negatives and optimises the adjuvant treatments; however, morbidity increases to rates closer to that of ALND when the number of SLNs removed increases.[16]

Several studies have evaluated the diagnostic accuracy of SLNB according to the number of SLNs harvested. Ban et al. and Zakaria et al. found that 100% of patients with metastatic SLN were identified after resection of the first four SLNs.[17,18] Similarly, Yi et al. found a threshold of 5 SLNs for identifying 99% of patients with metastatic SLNs.[13] None of these studies included none correlated the number of SLNs removed to the survival of patients.

The objective of this study was to evaluate the association between the number of SLNs harvested and survival in patients with ductal or lobular invasive breast cancer.

Patients and methods

Database and study population

All patients with a diagnosis of breast cancer confirmed by pathology were identified in the SEER (Surveillance, Epidemiology, and End Results database) database of the National Cancer Institute in the United States (U.S.). Data were obtained from all 17 U.S. registries participating in the SEER program with SEER*Stat software, version 8.0.4 (www.seer.cancer.gov/seerstat). All the information was publicly available, de-identified and exempt from review by our Institutional Review Board. The SEER registries collected the following information prospectively: patient demographics, primary tumour site, pathology, stage at diagnosis, initial treatment of the tumour and an updated follow-up of overall and specific survival (OS and DSS, respectively). They do not include information on lymphovascular invasion, adjuvant systemic chemotherapy and endocrine therapy and disease-free survival. These registries are demographically representative of the general population in the U.S.[19]

Population characteristics

The criteria for inclusion in the study were diagnosis of breast cancer between January 1, 2003 and December 31, 2008, histology of invasive ductal or lobular carcinoma according to WHO classification and confirmed by pathology, TNM tumour stage between T1 and T3, surgical treatment first by lumpectomy or mastectomy locally followed by evaluation of the axillary SLNBs alone or combined with ALND.[20,21] Patients were excluded if their tumour was of a histological type other than ductal or lobular invasive carcinoma, if they had carcinoma in situ, tumour stage T4, metastasis at diagnosis (stage M1), no axillary staging, ALND without prior SLNB or missing data on the staging of the axilla, preoperative radiotherapy or neoadjuvant chemotherapy.

In the SEER database, micrometastasis was defined as ipsilateral axillary lymph node involvement detected by immunohistochemistry with at least one micrometastasis greater than 0.2 mm and all micrometastases less than or equal to 2 mm. Isolated tumour cells (cluster of cells less than or equal to 0.2 mm) were classified as pN0 (pN−).

Statistical analysis

Statistical analyses were performed using R Studio software (« R », version 3.0.0, Cran, http://cran.cict.fr/index.html). Descriptive analyses were performed with the nonparametric Mann–Whitney test for continuous variables and the Chi-squared test for categorical or nominal variables. Disease specific survivals (DSS) were compared with the log-rank test. Multivariate survival analyses were performed according to the Cox model (proportional hazard model). This model can express the instantaneous risk of death due to breast cancer as a function of time (t) and covariates, given that the death did not occur before time t. The covariates were age, sex, ethnicity, histologic tumour type, grade, TNM tumour stage, oestrogen receptor status, number of sentinel lymph nodes harvested, number of positive lymph nodes, type of breast surgery and complementary radiation therapy. Non-informative variables in the Cox model were excluded from the final model using the method of Lawless and Singhal. All of the tests were two-tailed, and P values <0.05 were considered to indicate significant differences.

Results

According to selection criteria, the study group for statistical analysis consisted of 144,517 patients. The patients and tumour characteristics are presented in Table 1. The surgical axillary staging procedure and pathology results are presented in Table 2.

Regardless of LN involvement, patients who had received SLNB combined with ALND had a shorter DSS than patients who had received SLNB alone ($p < 0.0001$) (Table 3). In a univariate model, the HR increased with the number of SLNs harvested without statistical significance. Patients who received ALND had an increased HR compared to patients from whom only one SLN was harvested (HR = 1.89 CI 95% [1.70–2.09], $p < 0.0001$) (Table 4).

For pN− patients, the DSS were similar beyond the SLNB groups whatever the number of SLN harvested (97%–97.8%, $p = 0.19$) and between SLN groups and ALND group. For pN+ patients, there was a shorter DSS when patients had received ALND ($p < 0.0001$) (Table