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Original article

Predictors for extensive nodal involvement in breast cancer patients with axillary lymph node metastases☆

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ABSTRACT

Purpose: Various prediction models have been developed to predict the risk of having no additional axillary metastases in patients with a positive sentinel lymph node biopsy (SLNB), thereby disregarding patients with a positive ultrasound-guided lymph node biopsy (UGLNB). However, in the post-Z0011 trial era it is important to identify all patients with extensive nodal involvement for whom axillary treatment might still be beneficial. Therefore, the aim of this study is to identify factors predicting extensive nodal involvement (≥3 positive nodes) in the axilla, with the emphasis on the method of axillary staging: node positivity by UGLNB versus SLNB.

Methods: All patients diagnosed with invasive breast cancer between January 2006 and December 2011 at the Máxima Medical Center were included. Univariate and multivariate logistic regression analyses were performed.

Results: We included 302 cases, representing 301 node positive patients, of whom 177 cases had 1 or 2 positive lymph nodes and 125 cases had ≥3 positive lymph nodes. Multivariate analyses showed that a positive UGLNB (OR = 5.10; 95%CI = 2.78–9.36), lymphovascular invasion (OR = 3.60; 95%CI = 1.79–7.23) and a larger tumor size (OR = 1.03 per mm increase; 95%CI = 1.00–1.06) were significantly associated with extensive nodal involvement in patients with invasive breast cancer.

Conclusion: This study shows that a positive axilla, determined by UGLNB, is the most important factor for predicting further extensive nodal involvement. Hence, the role of axillary staging by ultrasound should be redefined since it might play an important role in selecting patients who may still benefit from axillary treatment.

Introduction

Axillary status is the strongest prognostic indicator in invasive breast cancer [1–5]. Prior to the introduction of the sentinel lymph node biopsy (SLNB) and the ultrasound guided lymph node biopsy (UGLNB), axillary lymph node staging was performed through a complete axillary lymph node dissection (ALND). However, an ALND can cause significant morbidity, such as lymphedema, dysesthesia, impairment of mobility and paresthesia.

The American College of Surgeons Oncology Group conducted a randomized trial (ACOSOG Z0011 trial) in which they studied the disease-free survival and mortality in selected patients with sentinel node positive breast cancer treated with versus without an ALND. This trial showed that an ALND may be omitted in patients with clinical $T_{1-2}N_0M_0$ breast cancer, a positive sentinel node and treated with breast conservation therapy and adjuvant systemic therapy [6]. The question is whether these results are also applicable to patients with a positive UGLNB, since current guidelines

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state that a positive UGLNB is an indication for an immediate ALND. In a previous article we described that patients with a positive UGLNB had poorer/less favorable tumor characteristics and a worse (disease-free) survival, irrespective of clinical palpability of the axillary lymph nodes. We therefore concluded that omitting an ALND is as yet only applicable in patients with a positive SLNB [7].

Treatment of the axilla in patients who do not fit the criteria of the Z0011 trial conclusions and/or in case of extensive nodal involvement might therefore still be of importance for local disease control. However, there is still some ambiguity on the definition of extensive nodal involvement, since the Z0011 trial defined extensive nodal involvement as having 3 or more positive axillary lymph nodes, whereas international guidelines concerning the necessity for additional (axillary) treatment define it as having 4 or more positive nodes (pN_2 in the TNM-classification).

Hence, this study aims to identify factors predicting the presence of extensive nodal involvement in patients with node positive breast cancer, with the emphasis on the method of axillary staging (ultrasound guided lymph node biopsy versus sentinel node procedure), in order to select patients who might still benefit from additional axillary treatment by either ALND or radiotherapy.

Patients and methods

This study included patients diagnosed with primary invasive breast cancer in the period between January 2006 and December 2011 at the Máxima Medical Center. Data were retrieved from the population-based Eindhoven Cancer Registry and medical charts of patients. In accordance with Dutch guidelines, all patients with newly diagnosed breast cancer were also referred to the radiologist for sonographic evaluation of the breast tumor and ipsilateral axilla. Ultrasound guided biopsies were performed on the breast tumor and suspicious axillary lymph nodes. Multiple histological biopsies of the breast tumor were performed using a 14 Gauge or 18 Gauge needle. Suspicious lymph nodes were biopsied for cytological analysis using a 21 Gauge hollow needle. If pathological analysis showed that the axillary biopsy was positive, patients were referred for an immediate ALND. If the results were negative or inconclusive, patients underwent a SLNB. In the period described in this study, a SLNB was considered to be 'positive' if macrometastases, micrometastases and/or isolated tumor cells had been proven by pathological evaluation after which these patients underwent an ALND. For the current research question, patients were eligible if they had cytologically or histologically proven axillary lymph node metastases after an UGLNB or after a SLNB, respectively. Patients with stage IV breast cancer, those treated with neoadjuvant systemic therapy, patients with a clinical N_2 or N_3 axillary nodal status or patients who did not undergo a complete ALND were excluded. Patients with bilateral carcinoma were considered as separate observations.

Data analyses

Clinical data included in the analysis were age, body mass index BMI, year of diagnosis, lateralization of the tumor, clinical palpability of the axillary lymph nodes, method of axillary staging and type of surgery (mastectomy or breast conserving). Histopathological data collected on the tumor included tumor size in millimeters, tumor type, tumor grade using the Nottingham-modification-scale, lymphovascular invasion and the presence of estrogen or progesterone receptors and HER2-status. Estrogen (ER) and progesterone (PR) status were considered positive if 10% or more of tumor cells contained the appropriate receptors. Multifocality was also included in the analysis as a covariate and was defined as tumors occurring in multiple sites in the breast. Due to missing data in the pathological reports, it was not possible to make a clear distinction between multifocality and multicentricity. When available, sonographic data retrieved by UGLNB consisted of number of visible lymph nodes, size of lymph nodes, described sonographic characteristics of lymph nodes (pathologically enlarged, suspicious, enlarged cortex, irregular shaped) and method of biopsy (cytological or histological). Histopathological data on the axillary lymph nodes included the number of resected (positive) sentinel lymph nodes and the number of resected (positive) non-sentinel lymph nodes.

The total number of resected (positive) lymph nodes was computed by adding the total number of resected lymph nodes during axillary lymph node dissection to the number of resected lymph nodes during the sentinel node procedure, if applicable. In this study extensive nodal involvement was defined as the presence of 3 or more positive lymph nodes as proposed by the ZOO11 trial. In addition, we performed analyses in which extensive nodal involvement was defined as 4 or more positive lymph nodes, as stated in the guidelines for axillary treatment. All analyses were performed on patients with a positive SLNB and UGLNB combined, as well as subgroup analyses within the ultrasound positive group. We also performed subanalyses on the value of lymph node palpability in predicting extensive nodal involvement. Univariate analyses were performed using logistic regression analysis. Variables with a p-value of $\leq$0.10 in univariate analyses were entered in a stepwise backward procedure in the multivariate logistic regression model. In this multivariate model a p-value of $\leq$0.05 was considered statistically significant. Data were analyzed using IBM SPSS statistics version 21.

Results

From January 2006 until December 2011, 1281 cases of invasive breast cancer without metastatic disease were treated at the Máxima Medical Center, with a median age of the patients of 54 years (22–97 years). In 431 (33.6%) cases metastases were found in the axillary lymph nodes of which 129 cases were excluded for various reasons as listed in Fig. 1.

Hence, a total of 302 cases with breast cancer, representing 301 patients, were analyzed including 177 patients with 1 or 2 positive lymph nodes and 125 patients with 3 or more positive lymph nodes. The median age of this study population was 60 years. All patients except one were female.

Descriptive analyses

Table 1 shows frequencies of clinicopathological characteristics in relation to the extent axillary lymph node involvement. Of the 302 patients with positive axillary lymph nodes removed during ALND, 86 (28.5%) had extranodal extension, 235 (77.8%) had macrometastases in one or more the lymph nodes and 52 (17.2%) had metastases in one or more level-III-nodes. Subanalyses on the value of lymph node palpability in predicting extensive nodal involvement (3 or more positive nodes) showed a sensitivity of 66.7%, a specificity of 64.3%, negative predictive value of 68.5% and a positive predictive of 62%.

Univariate and multivariate analyses

Table 2 shows the results of both the univariate and multivariate regression analyses. After univariate analyses the following variables were entered into the multivariate model: method of axillary staging (ultrasound versus sentinel lymph node procedure), palpability of axillary lymph nodes, type of surgery (breast conserving therapy versus radical mastectomy), tumor size in