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Original Research

# TNM classification and the need for revision of pN3a breast cancer

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**Abstract** ***Background:*** According to the seventh edition of tumour-node-metastasis (TNM) classification, pN3a status in breast cancer patients consists of presence of an infraclavicular lymph node metastasis (LNM) and/or presence of ≥10 axillary LNMs. The aim of this study was to determine whether prognosis of pN3a based on at least an infraclavicular LNM differs from ≥10 axillary LNMs.

***Methods:*** Data were obtained from the Netherlands Cancer Registry. All patients were diagnosed between 2005 and 2008 with primary invasive epithelial breast cancer and pN2a or pN3a status as pathologic result. Patients with pN3a were subdivided in pN3a based on at least an infraclavicular LNM or ≥10 axillary LNMs. Disease-free survival (DFS) included any local, regional or contralateral recurrence, distant metastasis or death within 5 years. Kaplan–Meier curves provided information on 5-year DFS and 8-year overall survival (OS). In addition, Cox proportional hazards model was used to measure the effect of relevant clinicopathological variables on DFS and OS.

***Results:*** A total of 3400 patients with pN2a and 1788 patients with pN3a were included. In 83 patients, pN3a was based on at least an infraclavicular LNM (4.6%) and in 1705 patients because of ≥10 axillary LNMs (95.4%). After multivariable analyses, DFS and OS were

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inferior in patients with pN3a based on ≥10 axillary LNMs compared to infraclavicular LNM (DFS 48.8% versus 63.8%, hazard ratio [HR] 1.59, p = 0.036; OS 46.6% versus 63.9%, HR 1.46, p = 0.042). Furthermore, pN2a and pN3a based on infraclavicular LNM had comparable DFS and OS.

***Conclusion:*** PN3a status based on an at least an infraclavicular LNM is rare, yet its prognosis is superior to ≥10 axillary LNMs. Reclassification of infraclavicular LNM in the next TNM should therefore be considered into pN2a.

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## 1. Introduction

In 1958, the first edition of the tumour-node-metastasis (TNM) classification of malignant tumours of the breast was published by the Union for International Cancer Control (UICC) in order to achieve worldwide consensus for the classification of, eventually, each solid tumour type [1]. Subsequently, this classification system was revised each decade to implement new insights. For instance, the introduction of neoadjuvant systemic therapy, sentinel lymph node biopsy, immunohistochemical staining and the method of pathologic nodal staging [2].

Regarding pathologic nodal staging, axillary lymph node metastases (LNMs) were divided into three categories in the fifth edition of the TNM classification: pN0 (0 axillary LNMs), pN1 (movable axillary LNMs) and pN2 (fixed axillary LNMs) [3]. After revision in sixth edition, the number of axillary LNMs was incorporated as key element in the classification, as impaired prognosis was demonstrated in the presence of an increasing number of axillary LNMs [4]. This resulted in four categories: pN0 (0 axillary LNMs), pN1a (1–3 axillary LNMs), pN2a (4–9 axillary LNMs) and pN3a (≥10 axillary LNMs) [5]. Furthermore, a study by Newman *et al.* observed a worse disease-free (DFS) and overall survival (OS) in patients with infraclavicular (level III) and axillary LNMs compared to patients with axillary LNMs only (DFS 50% versus 68%; OS 58% versus 83%, respectively) [6]. As a consequence, the UICC decided to redefine infraclavicular LNM as pN3a in the sixth edition; in contrast to earlier, when an infraclavicular LNM was considered equivalent to other axillary LNMs in the fifth edition. Currently pN3a nodal status consists of patients with ≥10 axillary LNMs and of patients with infraclavicular LNM [7].

The combination of both groups within pN3a suggests that their prognosis is similar [8,9]. However, no study thus far analysed this assumption. Therefore, the purpose of this study is to determine whether the prognosis of pN3a breast cancer patients based on at least an infraclavicular LNM is different compared to patients with ≥10 axillary LNMs and to patients with 4–9 axillary LNMs.

## 2. Material and methods

### 2.1. Data collection

Data were obtained from the Netherlands Cancer Registry (NCR), managed by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR collects data of all patients diagnosed with any type of cancer in the Netherlands, after a notification of the PALGA ('Nationwide network and registry of histo- and cytopathology in the Netherlands') system. Afterwards, trained data collection registrars from the NCR extracted data from patients' records concerning patient characteristics, treatment and follow-up.

In this study, all patients diagnosed between 2005 and 2008 with primary invasive epithelial breast cancer and pN2a or pN3a statuses as the final pathologic result were included. Exclusion criteria were synchronous breast cancer, distant metastases at time of diagnosis (or within 91 days) or an unknown number of LNMs. Patients without surgery were also excluded. Data were collected on age, tumour type, receptor status, surgical procedures, systemic therapy, radiation therapy and pathological results, including pathologic TNM classification and the number of LNMs. For a period of 5 years after diagnosis, the first breast cancer event was registered, which consisted of any local, regional or contralateral recurrence or distant metastasis.

Patients with pN3a were divided into two subgroups according to the number of LNMs, to simulate pN3a based on infraclavicular or ≥10 axillary LNMs. Patients with nine or less positive lymph nodes required at least one infraclavicular LNM to be considered pN3a, while patients with ≥10 positive lymph nodes required at least 10 axillary LNMs (with or without infraclavicular LNMs).

### 2.2. Treatment

According to the national guideline of 2005, regional treatment depended on nodal status: sentinel lymph node biopsy (SLNB) in case of clinically node negative status, based on physical examination (axillary ultrasound was common but not mandatory at that time), or

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