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Management of the axilla after neoadjuvant chemotherapy for clinically node positive breast cancer: A nationwide survey study in The Netherlands

G. Vugts [a,b,*], A.J.G. Maaskant-Braat [c], W.K. de Roos [d], A.C. Voogd [b,e,f], G.A.P. Nieuwenhuijzen [a]

[a] Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands
[b] Department of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands
[c] Department of Surgery, Maxima Medical Centre, Veldhoven, The Netherlands
[d] Department of Surgery, Gelderse Vallei Hospital, Ede, The Netherlands
[e] Department of Epidemiology, Maastricht University, Maastricht, The Netherlands
[f] GROW – School for Oncology and Developmental Biology, Maastricht, The Netherlands

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Abstract

Background: Axillary pathologic complete response (pCR) to neoadjuvant chemotherapy (NAC) is achieved in a substantial part of clinically node positive breast cancer patients. Treatment of the axilla after NAC varies widely, and new techniques to spare patients from an axillary lymph node dissection (ALND) are being introduced.
Methods: This Dutch nationwide survey regarding treatment of the initially clinically node positive axilla in patients receiving NAC was conducted amongst 148 surgical oncologists during November 2014–June 2015, to survey the diagnostic work-up, axillary mapping and willingness to omit ALND.
Results: Axillary ultrasound was considered a standard procedure in the diagnostic work-up by 99% of participants. The majority of 70% of participants stated that ALND could possibly be omitted in node positive patients with a favourable response to NAC. A positive correlation was observed between the total amount of patients treated, versus patients receiving NAC ($P < 0.01$). A total of 93 respondents performed axillary response evaluation after NAC, using imaging (72%), excision of localized lymph nodes (56%) or sentinel node biopsy (SNB; 45%). Decision-making in omitting ALND was influenced by the presence of N2–3 disease, patient age and type of breast surgery. Multivariable analysis showed that clinicians who administered NAC more often, were more likely to omit ALND ($P < 0.01$).
Discussion: The majority of surgeons are inclined to omit ALND in case of an axillary pCR. A large variety of techniques is being used to identify a pCR. The lack of consensus on this topic indicates the need for guidelines based on the best available evidence.

Keywords: Breast cancer; Neoadjuvant chemotherapy; Axillary treatment; Axillary lymph node dissection; Pathological complete response

Introduction

In breast cancer patients, clinically positive axillary lymph nodes (i.e. proven with axillary ultrasound and fine-needle aspiration/core needle biopsy) are an unfavourable prognostic sign.[1,2] A node-positive axilla is associated with a higher risk of recurrent and metastatic disease, and consequently a lower overall survival rate. Historically, the axilla was treated with aggressive surgery, after the discovery of its function in regional lymph drainage and the possibility of harbouring tumour deposits.[3,4] However, over the last decades a shift is being observed towards less invasive axillary treatment. With the introduction of the sentinel node biopsy (SNB) and axillary radiotherapy, axillary lymph node dissection (ALND) can be prevented in a substantial part of the patients with clinically node-negative breast cancer.[5–8] The next clinical dilemma in

* Corresponding author. Catharina Hospital, Department of Surgery, Postbus 1350, 5602 ZA Eindhoven, The Netherlands. Tel.: +31 (0)6 38 33 55 10.
E-mail address: guusje.vugts@catharinaziekenhuis.nl (G. Vugts).

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axillary treatment concerns the optimal management of patients with a clinically positive axilla.

Neoadjuvant chemotherapy (NAC) is a treatment modality that is increasingly being used in breast cancer patients, especially in those with locoregionally advanced tumours.[9–11] As a result, an axillary pathologic complete response (pCR) is observed in 20–42% of the clinically node-positive patients.[12–15] In HER2-positive disease it is even more pronounced, with an axillary pCR in as much as 74% of patients.[16] In patients with clinically node-positive breast cancer, an axillary pCR is associated with a more favourable survival.[14,17] It seems rational to assume that aggressive surgical treatment of the axilla with an ALND might be omitted in patients in whom an axillary pCR is achieved, since the axilla has already been cleared of tumour deposits by systemic treatment. This could spare patients from treatment-related morbidity, such as upper limb oedema and shoulder dysfunction. However, the current guidelines still recommend the performance of an ALND in all patients with clinically node-positive breast cancers, regardless of their response to NAC.[18] One of the main issues is the identification of an axillary pCR. Several recent and on-going trials have been initiated to evaluate imaging modalities to identify patients with an axillary pCR in whom ALND might be omitted. The use of imaging techniques only, however, has not shown to predict an axillary pCR accurately; MRI has not been extensively studied and PET-CT has a reported accuracy of 72%.[13,19] SNB after NAC has been studied for its suitability for response monitoring as well, but has a relatively low identification rate of around 80% and a relatively high false negative rate (12–14%), which was even higher when only one sentinel node was harvested (24–32%).[20,21,23] Therefore, SNB after NAC appears not suitable yet for axillary response monitoring after NAC. In the Dutch MARI (Marking the Axilla with Radioactive Iodine seeds) trial, clinically positive lymph nodes were marked with radioactive iodine seeds. These localized nodes (so-called 'MARI nodes') were removed and examined by a pathologist after NAC. The MARI node predicted response to NAC correctly in 97%, with a FNR of only 7%.[22] The high FNR of SNB after NAC alone, shown in the American College of Surgeons Oncology Group Z1071 trial also led to studies on SNB combined with targeted axillary dissection (TAD).[24] TAD uses the same principle as the MARI procedure, marking axillary lymph nodes with clips instead of radioactive iodine seeds. In the trial, the sentinel node as well as the targeted node were resected. The FNR of this procedure was 7.4% if the targeted node was the exact same node as the sentinel lymph node.[24]

Since these novel strategies in the management of clinically node positive patients have not been incorporated in guidelines yet, the clinical landscape seems to be divided. Some clinicians still follow the standard guidelines, whereas others have adopted techniques that should still be considered as experimental. Since there is no national or international consensus on this topic, this survey was conducted to assess the current diagnostic and therapeutic management of clinically node-positive patients receiving NAC among Dutch breast surgeons.

Methods

Participants

This Dutch nationwide survey study regarding treatment of the clinically node-positive axilla after NAC was conducted among the members of the Dutch Society of Surgical Oncology (NVCO) within the period of November 2014 up to June 2015. They received a message by e-mail containing the goals of the survey, and were asked to participate through an enclosed link to the online survey. One and two months after the first invitation to participate, a reminder was sent to all NVCO members. In December 2015, a total of 593 NVCO members were registered. A total of 509 of the registered NVCO members were surgical oncologists and 46 were surgical residents. The dedicated breast cancer surgery subgroup of the NVCO has 116 listed members. Due to the anonymous character of this survey, we do not have information on the amount of respondents being a member of this breast cancer surgery subgroup.

Survey

The online survey consisted of a maximum of 29 questions, depending on which answers were filled out. In Appendix I, all survey questions are enclosed. Answers to the questions were multiple choice, and at the end of the survey surgeons could add any comments or questions related to the survey.

Statistical analysis

Statistical analysis of the data was performed using SPSS Statistics, version 22. For continuous variables such as age, number of patients treated per hospital and proportion of patients receiving NAC, medians were calculated. For the correlation between number of patients treated per hospital and proportion of patients receiving NAC, the Pearson correlation index was calculated. A multivariable analysis was performed to assess the influence of doctor-related factors (gender, years of experience, type of hospital, number of patients receiving NAC) on the decision to omit ALND after NAC. For all analyses, a P-value <0.05 was considered statistically significant.

Results

Participant characteristics

A total of 148 participants filled out the online survey. The majority of 136 participants were surgical oncologists