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Review

The changing role of axillary treatment in breast cancer: Who will remain at risk for developing arm morbidity in the future?

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ABSTRACT

Primary aim is to give an overview of changes in axillary staging and treatment of breast cancer patients. Secondly, we aim to identify patients with a high arm/shoulder morbidity risk, and describe a strategy to improve early detection and treatment.

Recent and initiated studies on axillary staging and treatment were evaluated and clustered for clinically node negative and clinically node positive breast cancer patients, together with studies on pathology, detection and (surgical) prevention and treatment of lymphedema.

For clinically node negative patients, the indication for axillary lymph node dissection in sentinel node positive patients is fading. On the contrary, clinically node positive patients are routinely subjected to an axillary lymph node dissection, in combination with other therapies associated with an increased lymphedema risk, such as mastectomy, adjuvant radiation- and (taxane-based) chemotherapy. Techniques for prevention, early detection and (surgical) treatment of lymphedema are being developed.

Axillary staging and treatment in breast cancer patients with a clinically node negative status will become less invasive, thereby reducing the incidence of morbidity. Nevertheless, in patients with a clinically node positive status, aggressive treatment will still be required for oncologic control. For these patients, a surveillance program should be implemented in order to apply (curative) surgical treatment for lymphedema.

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Introduction

Breast cancer treatment is in the process of moving towards an era of more conservative axillary treatment. Studies have shown that in selected patient populations, less extensive axillary surgery does not increase the regional recurrence rate, nor does it decrease overall survival [1–3]. The main advantage of a conservative approach towards axillary surgery is the reduction in treatment-related morbidity.

Of all, lymphedema has the highest incidence amongst axillary treatment related morbidities in breast cancer and is perceived as disabling. Swelling of the affected arm, symptoms of heaviness, paresthesia and decreased range of motion contribute negatively to the quality of life [4,5]. Studies have revealed several patient- and treatment related risk factors for breast cancer related lymphedema (BCRL), with most evidence pointing towards the axillary lymph node dissection (ALND) as an important risk factor. Other risk factors include greater number of dissected lymph nodes, mastectomy, high body mass index, adjuvant radiation therapy, and taxane-based chemotherapy [4,6].

For a long time, ALND was considered standard treatment for all breast cancer patients. Fifteen years ago, the sentinel lymph node biopsy (SLNB) replaced the ALND in patients with a clinically node negative status, resulting in significantly lower axillary morbidity rates, without compromising regional recurrence rates and overall

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survival [7,8]. Completion ALND was up until shortly considered the standard treatment in patients with a positive sentinel lymph node (SLN). Currently, there is a decline in the indication for completion ALND in patients with SLN metastases, and the clinical relevance of the SLNB in certain patient groups is being debated.

The primary aim of this paper is to give an overview of current and expected future changes in axillary staging and treatment, and to estimate the impact of these changes on the incidence of arm/shoulder morbidity, and of BCRL in particular. Secondly, we aim to identify the group of patients still high at risk for BCRL and to describe a strategy to improve early detection and treatment.

The changing role of axillary staging and treatment

Clinically node negative breast cancer patients

The standard preoperative lymph node staging consists of physical examination of the axilla, and according to the ESMO breast cancer guideline, combined with an axillary ultrasound [9]. If negative, a patient is considered clinically node negative, an SLNB is performed, and until recently, followed standardly by a completion ALND in patients with a positive SLN. The reported BCRL rate after completion ALND is 20%, and 6% after SLNB-only [4]. Several randomized trials have been performed with the aim to investigate whether completion ALND in patients with metastatic SLNs could be replaced by less invasive treatment or even omitted.

In the AMAROS trial, clinically T1-2N0 breast cancer patients with SLN metastases were randomized to completion ALND or axillary and periclavicular radiation therapy [3]. This trial has demonstrated that axillary and periclavicular radiation therapy provided a five-year regional recurrence rate of 1.03% that is comparable to 0.54% in the completion ALND group. Most patients were treated with breast conserving therapy (82%) and received adjuvant systemic therapy (90%). At five years, the BCRL rate following axillary radiation therapy was significantly lower than following completion ALND based on clinical signs (11 vs. 23%; $p < 0.0001$), as well as based on an arm circumference increase of $\geq 10\%$ (6% vs. 13%; $p = 0.0009$). The higher BCRL rate in the completion ALND-arm might partly be explained by the fact that 6% of these patients underwent axillary and periclavicular radiation therapy as well, compared to 2% of patients in the radiation therapy-arm that received both therapies [3]. In this subgroup of patients, the BCRL rate was 58%. Further, it is uncertain whether the stated advantage for axillary and periclavicular radiation therapy will persist over time, as side effects of radiation therapy evolve over a more prolonged time course than surgical side effects [10].

In the ACOSOG Z0011 trial, clinically T1-2N0 patients with 1–2 macrometastatic SLNs treated with breast conserving therapy were randomized to completion ALND or no completion ALND [2]. Results revealed a regional recurrence rate of 0.9% at five years after treatment for patients in whom the completion ALND was omitted compared to 0.5% in the completion ALND group, while it was estimated that 27% of the patients had residual nodal disease [2]. Furthermore, overall survival was not compromised by not performing a completion ALND in this patient population. However, adjuvant systemic treatment was administered to 96% of the patients. Side effects such as seroma, paresthesia or lymphedema, were reported in 70% of patients in the completion ALND-arm, and in 25% after SLNB alone in the first year after randomization ($p \leq 0.001$) [11].

The IBCSG 23-01 trial also randomized clinically T1-2N0 patients to completion ALND or no completion ALND, though only in case of a micrometastasis in the SLN [1]. Breast conserving treatment was performed in 91% of the patients, a mastectomy in 9% and adjuvant systemic treatment was administered to 96% of the

patients. The ALND-specimen of patients in the control arm contained additional lymph node metastases in 11% of the cases, but again, the regional recurrence rate after omitting the completion ALND was low (1.1%) and comparable to the completion ALND group (0.2%).

The AMAROS, ACOSOG Z0011 and IBCSG 23-01 trial were underpowered, as events occurred less common than anticipated [1–3]. Nevertheless, these trials suggest that for clinically node negative breast cancer patients, a completion ALND is no longer indicated in case of 1–2 macrometastatic SLNs when treated with breast conserving therapy and adjuvant systemic treatment [2], and neither in the case of a micrometastatic SLN when treated with mastectomy and adjuvant systemic treatment [1]. Furthermore, axillary-with or without periclavicular radiation therapy instead of a completion ALND might be beneficial in terms of morbidity risk for mastectomy patients with a macrometastasis in the SLN [3].

Thus, the incidence of BCRL in the clinically node negative patient group is likely to decrease in the coming years due to omitting completion ALND in the majority of patients with SLN metastases. The incidence is expected to decrease even further in the future when results of several ongoing randomized trials become clear. One of these trials is the Dutch BOOG 2013-07 trial that randomizes clinically T1-2N0 breast cancer patients with macrometastatic SLNs treated with mastectomy, to completion axillary treatment or no further axillary treatment [12]. Several other independent randomized controlled trials are investigating the safety of omitting the SLNB in clinically T1-2N0 breast cancer patients with negative axillary ultrasound findings who are treated with breast conserving therapy: the Dutch BOOG 2013-08, the Italian SOUND, and the British SNIPE trial [13–15]. The hypothesis that the SLNB could be safely omitted in this patient population derives from the fact that residual lymph node metastases in 11–27% of patients in the ACOSOG Z0011 and IBCSG 23-01 trials in whom completion ALND was omitted, did not result in a worse regional recurrence- and overall survival rate [1,2].

Despite the developments of minimizing or even no longer performing invasive staging and treatment of the axilla, we should remain mindful that patients with a clinically node negative status could still develop BCRL with the risk ranging from 6 to 20% [4]. As described earlier, type of breast surgery, a high body mass index, and adjuvant therapy could influence this risk [4,6].

Clinically node positive breast cancer patients

Breast cancer patients with preoperatively biopsy-proven nodal metastases or with palpable lymph nodes that are highly suspicious for malignancy, are considered clinically node positive [16]. In most of these patients an ALND should be performed according to ASCO and ESMO guidelines [9,17]. These patients are consequently at a high risk for developing severe BCRL, especially since a clinically node positive status is associated with a larger primary tumor, more often requiring a mastectomy, adjuvant chemotherapy and radiation therapy.

Adjuvant chemotherapy is frequently indicated in patients with nodal metastases and in patients without nodal metastases but with poor prognostic factors based on primary tumor characteristics, such as tumor grade and diameter. Nowadays, chemotherapy schedules containing taxanes are standard of care. Several studies have shown that taxanes are associated with generalized edema during treatment that can persist and increase the risk of BCRL [18–20].

The indication for adjuvant radiation therapy of the chest wall, axilla and periclavicular region is based on the risk of disease relapse and type of breast surgery, but in case of a pathological node negative or N1 status, there is no consensus amongst

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