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Guidelines

Axillary Surgery Following Neoadjuvant Chemotherapy – Multidisciplinary Guidance From the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology and British Society of Breast Radiology☆

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Abstract

Aims: These multidisciplinary guidelines aim to provide clinically helpful, evidence-based recommendations on the surgical management of the axilla in patients who have received neo-adjuvant chemotherapy for early breast cancer.
Materials & methods: Following a review of published evidence, a writing group representing all disciplines quorate within a breast cancer multidisciplinary meeting prepared the guidelines.
Key recommendations: In patients presenting with clinically node negative axillae, sentinel node biopsy (SNB) may be performed prior to or on completion of neo-adjuvant chemotherapy (NACT). In patients presenting with clinically node positive axillae, SNB may be safely considered following completion of NACT. Four nodes should be removed with dual mapping. If evidence of complete pathological response of previous metastases is seen, axillary radiotherapy may be offered. If residual cancer (isolated tumour cells, micro- or macrometastes) is seen within the SNB, offer axillary node dissection.

Keywords: Axillary radiotherapy; axillary surgery; neoadjuvant chemotherapy; sentinel node biopsy

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Introduction

Sentinel node biopsy (SNB) aims to stage the axilla and avoid unnecessary axillary lymph node dissection (ALND) and associated morbidity in patients with invasive breast cancer without lymph node disease. The performance of SNB in patients who receive neoadjuvant chemotherapy (NACT) has been controversial. This guidance, based on the best available evidence, has been written to assist multidisciplinary teams in managing such patients.

It is recognised that some patients may wish/need to be managed differently due to patient choice/other factors. The risks and benefits of alternative approaches need to be discussed with patients and documented in the medical records. Ideally, these patients should receive extended follow-up so that longer term outcome is recorded. Ultimately, the multidisciplinary team will be responsible for the treatment choices offered to each patient.

Node-negative Disease at Presentation (cN0)

The identification and false-negative rates in patients presenting with node-negative disease (normal clinical and radiological assessment of the axilla) are comparable whether carried out before or after NACT [1,2].

Sentinel Node Biopsy before Neoadjuvant Chemotherapy

SNB before NACT in cN0 patients can establish the presence of unexpected lymph node involvement and, hence, the possible need for subsequent axillary lymph node treatment (ALND or adjuvant radiotherapy according to local protocol). This may also facilitate planning in patients considering immediate reconstruction.

Patients with unexpected macrometastases in upfront SNB, on current evidence, should proceed with ALND or axillary radiotherapy after the completion of NACT. Some of these patients may fulfil criteria for entry into the POSNOC study (www.posnoc.co.uk) and be offered entry into this trial. Repeat SNB after NACT is not recommended, as there is a low identification rate of 60% and a 50% false-negative rate [3].

Patients who present as cN0 and are found to have a negative SNB do not require any axillary treatment.

Patients with micrometastases or isolated tumour cell clusters within SNB carried out before NACT do not routinely undergo further axillary treatment [4]. These patients are treated according to established guidelines [5,6].

The disadvantage of upfront SNB is the certainty of two surgical procedures; initially for SNB, and then subsequent therapeutic breast surgery after NACT. Outwith the POSNOC trial, patients with macrometastases before NACT are committed to ALND and/or axillary radiotherapy post-chemotherapy, regardless of the response to NACT.

Also, in cN0 patients with unexpected SNB macrometastases, there is a loss of information on the response in nodal metastases, which has strong independent prognostic significance to the response in the breast. The Residual Cancer Burden, an increasingly used calculation within trials to quantify residual disease in the neoadjuvant setting (with good correlation to survival outcomes) is not valid in patients who have malignant nodes removed before chemotherapy.

Sentinel Node Biopsy after Neoadjuvant Chemotherapy

For SNB after NACT, the reported detection rate is 96% with a false-negative rate of 6% [2]. Patients who present as cN0 and are found to have a negative SNB after NACT (i.e. showing no evidence of previous nodal positivity) do not require any further axillary treatment. Patients who present as cN0 and are found to have unexpected evidence of previous node positivity after NACT should be managed as discussed in section Evidence of a Complete Pathological Response in the Sentinel Node Biopsy after Neoadjuvant Chemotherapy in Previously cN1 Patients. Patients presenting as cN0 but who are found to have unexpected isolated tumour cells, micrometastatic or macrometastatic disease within the SNB after NACT should be managed as discussed in section Malignant Sentinel Node Biopsy in Patients who have Completed Neoadjuvant Chemotherapy: the Role of Completion Axillary Lymph Node Dissection.

There is emerging evidence that the prognostic value of SNB carried out after chemotherapy is higher than SNB carried out before NACT [4,7,8]. A further advantage of carrying out SNB after NACT is that only one surgical procedure will usually be necessary.

To summarise, in cN0 patients, SNB may be carried out before or after NACT. However, practice is moving towards it being carried out after NACT for patient benefit [9].

Node-positive Disease at Presentation (cN1)

This guidance applies to those patients who have needle biopsy-proven lymph node metastases at presentation and then proceed to NACT. At presentation, on ultrasound assessment of the axilla, radiologists should report the number of axillary nodes that appear to be involved and any ultrasonographic evidence of extranodal spread [10].

All patients who present with node-positive disease should be re-discussed at the multidisciplinary team meeting on the completion of NACT to decide the most appropriate axillary treatment.

Following NACT, the response within axillary nodal metastases may correlate with that seen within the breast [11,12]. This is most effectively seen in patients with triple-negative invasive cancers [9] or with the addition of

pertuzamab to trastuzamab during NACT for those with HER2-positive cancers [13].

Many patients could be safely considered for SNB after NACT despite presenting with cN1 disease [9,14]. Axillary ultrasound may be used to identify residual nodal disease after the completion of NACT [15].

Some patients, for example those noted at presentation to have clinically or radiologically extensive involvement of the axillary nodal region, may be felt by the multidisciplinary team to still require ALND. Examples of such patients may include patients who present with fixed, matted axillary nodes (cN2 axillary disease as defined by the American Joint Committee on Cancer staging [16]).

Surgical Considerations

In patients presenting with proven cN1 disease, the false-negative rate of SNB after NACT is inversely correlated to the number of lymph nodes removed at the time of SNB and it is recommended that three or more nodes are removed to minimise the false-negative rate [3,9]. Early evidence suggests that marking an involved node before chemotherapy and subsequent retrieval of this marked node will further reduce the false-negative rate [17]. Further trials are needed to confirm this finding and to standardise protocols.

Lymph Node Mapping

Studies consistently show that dual mapping with radioactive colloid and blue dye results in lower false-negative rates than if only one mapping agent is used [3,18]. We recommend that dual mapping be deployed for SNB in patients after NACT.

If at the time of surgery there is no mapping of blue dye or radioactive colloid apparent, then axillary node clearance should be carried out and the patient should be consented for this.

Evidence of a Complete Pathological Response in the Sentinel Node Biopsy after Neoadjuvant Chemotherapy in Previously cN1 Patients

The Royal College of Pathologists provides guidance for the handling and reporting of specimens following NACT [19]. Evidence of downstaging with complete pathological response within the lymph nodes may include fibrosis or scarring within the SNB specimen [8].

There is no firm evidence base to advise on the treatment of patients presenting with biopsy-proven axillary node metastases who then are found, after NACT, to have a complete pathological response in their SNB (ypN0). Until there is an improved evidence base for this group of patients (ypN0 on post-NACT SNB) they should be offered axillary radiotherapy.

Evidence-based management of these patients will develop with the results of trials currently underway. The NSABP B-51/Radiation Therapy Oncology Group 1304 study [20] will examine, in patients who have an axillary pathological complete response after NACT, whether the addition of regional nodal irradiation is of benefit. In the UK, the proposed ATNEC study will explore the same clinical question.

Malignant Sentinel Node Biopsy in Patients Who Have Completed Neoadjuvant Chemotherapy: the Role of Completion Axillary Lymph Node Dissection

Both the Royal College of Pathologists and the World Health Organization classify micrometastases and isolated tumour cell clusters within sentinel lymph nodes after NACT (ypN1mi and ypN0i+) as residual chemoresistant disease. There is evidence that low volume axillary disease present after NACT is associated with a worse outcome [21]. Furthermore, after NACT, even low volume residual disease in SNB may also indicate a higher likelihood of non-sentinel node metastases [22].

The results of the AMAROS trial [23], which showed non-inferiority of axillary recurrence rates after axillary radiotherapy compared with axillary dissection in early breast cancer patients, cannot be extrapolated to higher tumour burden patients (e.g. Ultrasound Scan guided Fine Needle Aspiration (USS FNA) or core biopsy positive) in the neoadjuvant setting. This study included isolated tumour cells and micrometastases within the SNB (40% of those recruited). Further evidence for the axillary management of patients after NACT is awaited from the Alliance Trial (clinicaltrials.gov/ct2/show/NCT01901094), which randomises to axillary dissection versus axillary radiotherapy after the completion of NACT.

Therefore, at present, completion ALND rather than axillary radiotherapy remains the general standard of care in these patients. Axillary radiotherapy may be considered in individual cases according to patient wishes and multidisciplinary team assessment.

Use of One Stop Nucleic Acid Amplification for Intraoperative Assessment of Sentinel Nodes in Patients after the Completion of Neoadjuvant Chemotherapy

Evidence for one stop nucleic acid amplification (OSNA) in this specific clinical scenario is conflicting with data supporting [24] and discouraging [25] its use. OSNA is not calibrated for the detection of isolated tumour cells, which constitute clinically significant disease in the neoadjuvant context. It is not possible to comment on the presence of fibrosis indicating a response or regression of previous node involvement. Therefore, until further evidence confirming the safety of OSNA in patients completing NACT is available, the writing committee do not support its use for

intraoperative sentinel lymph node biopsy assessment in such patients outside of clinical trials.

Summary

Clinically Node-negative Axilla (cN0)

1. In many cN0 patients, SNB may be carried out before or after NACT with equivalent prognostic information.
2. In cN0 patients with unexpected sentinel node metastases, SNB after NACT may be of increased prognostic value compared with upfront SNB.

Clinically Node-positive Axilla (cN1)

1. Patients can be safely considered for SNB after NACT. Four nodes should be removed with dual mapping.
2. If SNB shows evidence of a complete pathological response within the nodes offer axillary radiotherapy.
3. If SNB shows isolated tumours cells, micrometastases or macrometastases, offer ALND.
4. Patients presenting with extensive axillary node metastases (clinically/radiologically) may, after multidisciplinary team discussion, need to proceed to ALND on the completion of NACT.

Conflicts of Interest

The authors declare no conflict of interest.

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