Amit Goyal,
Consultant Oncoplastic Breast Surgeon & Associate Professor, Royal Derby Hospital, Derby.

Correspondence address:
E: amit.goyal@nhs.net

POSNOC

POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy. A randomised controlled trial of axillary treatment in women with early stage breast cancer who have metastases in one or two sentinel nodes

Women with early breast cancer that has spread to the first one or two lymph glands (sentinel nodes) will receive chemotherapy or endocrine therapy (hormone therapy), or both. Radiotherapy is given to the breast in all women who undergo breast conserving surgery, and to the chest wall in some who undergo mastectomy. These treatments are called adjuvant therapy.

Currently, these women also have treatment to their axilla. This treatment is either a second operation to remove all the lymph glands in the axilla (axillary node clearance), or radiotherapy to the axilla.

Axillary treatment and arm morbidity

Axillary treatment is recommended for these women on the assumption that it reduces the risk of axillary recurrence, and might improve survival. Axillary node clearance is usually a second operation, but some hospitals use intra-operative sentinel node assessment and so perform axillary node clearance at the same time as breast conserving surgery or mastectomy. A drain is left in the wound for a few days afterwards. The operation lasts one to two hours and requires a stay in hospital of one to two days.

Axillary radiotherapy is given five days a week for three to five weeks based on the local protocols. Axillary radiotherapy is offered only in some specialist centres, and some women may need to travel a considerable distance.

Axillary treatment damages the drainage channels of the lymphatic system. Fluid called lymph begins to collect in the arm and doesn't drain in the normal way. So the arm and hand may swell. This swelling is called lymphoedema. One in five women may have lymphoedema in the arm after axillary treatment. Lymphoedema can be painful and make it difficult to move the arm. It cannot be completely cured, and without treatment it may get worse. Lymphoedema can start at any time after the armpit treatment. Also, one in three women may have numbness or pain; and one in five may experience shoulder stiffness [1-7]. These problems can be upsetting, impair quality of life and are costly to the NHS in terms of rehabilitative treatments (such as physiotherapy and lymphoedema clinics).

Adjuvant therapy

The systemic adjuvant therapy is now so effective for early breast cancer that axillary treatment may offer no additional protection against axillary recurrence, and so may be overtreatment. This hypothesis is supported by several small studies [8].

In the past, information from axillary node clearance with regard to the number of nodes with cancer was used to guide systemic therapy. However, decisions about these adjuvant therapies are now more commonly based on biological tumour markers and molecular determinants of prognosis and predictors of treatment benefit. Early data from the EORTC AMAROS trial [9] suggests that the 'extent' of nodal involvement does not affect the decision to administer systemic therapy.

There is variability in practice in relation to the use of post-mastectomy radiotherapy and radiotherapy to the supraclavicular fossa region. The degree of axillary nodal involvement is a significant driver and women with cancer spread to four or more nodes are candidates for chest wall and supraclavicular fossa radiotherapy [10]. This information will be absent if axillary node clearance is omitted. The proportion of patients having four or more positive lymph nodes in the AMAROS trial was low (8%) [11]. This figure is estimated to be lower than 5% in the POSNOC trial as ultrasound node negative patients have a lower axillary tumour burden [12].

Evidence from systematic reviews and randomised trials

Axillary treatment may now be over treatment for early breast cancer; as diagnosis tends to be earlier so patients present with smaller tumours and a low axillary tumour burden; adjuvant therapy has improved and is better at preventing breast and axillary recurrence [13]; and sentinel node biopsy has

already removed the lymph nodes most likely to have metastasis [14]. Moreover, if adjuvant therapy includes radiotherapy to the breast or chest wall, the lower axilla will be treated inadvertently as it is included in the tangential irradiation field, and some lower level axillary nodes may be removed at mastectomy [15].

There are three randomised trials assessing axillary treatment. The first [16] was a three arm study that recruited 1079 clinically node-negative women. They were randomised to receive either radical mastectomy (mastectomy with axillary node clearance), or total mastectomy with axillary irradiation, or total mastectomy alone without axillary treatment. Women had larger tumours, higher axillary tumour burden compared with today's patients and they did not routinely receive adjuvant systemic therapy. All three arms had similar 25 year overall survival, suggesting that axillary treatment did not improve survival.

The second study [17] randomised 435 clinically node-negative women to breast conservation without axillary treatment or breast conservation plus axillary radiotherapy. Axillary recurrence was low in both groups (no axillary treatment 1.5% vs. 0.5% axillary radiotherapy). Both arms had similar disease free survival.

In the third more recent trial [18] patients with tumours less than 5cm in size, treated by breast conserving surgery and whole breast radiotherapy, with sentinel node metastases, were randomised to axillary node clearance (n=445) or not (n=446). Axillary recurrence was low, and there were no clear differences between the two groups (axillary clearance 0.5% vs. no axillary clearance 0.9%) at 6.3 years. The trial was terminated before its targeted accrual. There was a potential for bias in this study as the radiation oncologists were aware of the treatment allocation, and it is not reported whether this influenced their decision about how much of the axilla to treat with tangential radiotherapy. Generalisability of the results is limited as some centres recruited fewer than five patients, axillary recurrence was not a pre-specified endpoint, mastectomy patients were excluded, and the trial protocol did not mirror NHS practice.

A recent meta-analysis [8] of randomised trials and observational studies which included patients who had sentinel node biopsy concluded that more evidence is needed to guide management of the axilla in patients with early breast cancer and sentinel nodes metastasis.

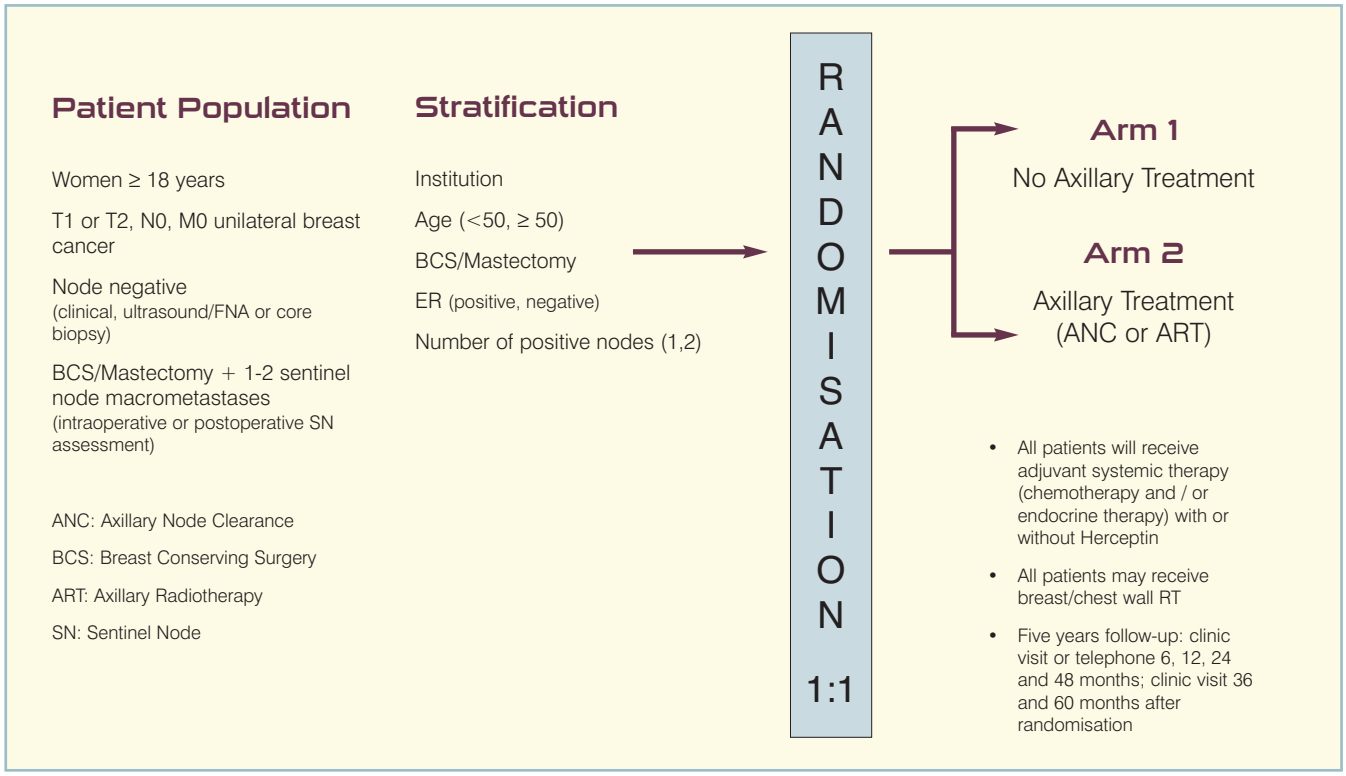
Why we need a trial now

Biological factors may be more important for recurrence than surgical removal or radiation eradication of axillary nodes. If axillary surgery is merely a staging or diagnostic procedure, then adverse effects are likely to be minimal if it is omitted and sentinel node biopsy alone is used to guide subsequent treatment in women with early stage breast cancer who have one or two sentinel node metastases. Also, axillary treatment (axillary node clearance or axillary radiotherapy) was introduced several decades ago without formal evaluation and is associated with significant short- and long-term morbidity. Since axillary treatment was introduced, chemotherapy and endocrine therapy have dramatically improved outcome. Therefore, it is timely to assess whether adjuvant therapy alone is an acceptable alternative to adjuvant therapy plus axillary treatment.

POSNOC trial

POSNOC is a pragmatic, randomised, multicentre, non-inferiority trial. Recruitment starts July 2014.

Aim: For women with early stage breast cancer and one or two sentinel node macrometastases, to assess whether adjuvant therapy alone is no worse than



adjuvant therapy plus axillary treatment, in terms of axillary recurrence within five years.

Patient Population: Women with unifocal or multifocal invasive breast cancer, largest primary lesion ≤5cm, clinically and ultrasound node negative, who undergo sentinel node biopsy (SNB) and have 1 or 2 sentinel node macrometastases (›2mm), with no extranodal extension.

Interventions: The study will compare adjuvant therapy alone with adjuvant therapy plus axillary treatment (axillary node clearance or axillary radiotherapy).

Primary Outcome: Axillary recurrence at five years.

Secondary Outcomes: Arm morbidity, quality of life, anxiety, local (breast or chest wall) recurrence, regional (nodal) recurrence, distant metastasis, time to axillary recurrence, axillary recurrence free survival, disease free survival, overall survival, contralateral breast cancer, non-breast malignancy, economic evaluation.

Sample Size and Follow-up: 1900 participants. Participants will be followed up for five years.

Adjuvant Therapy: All participants will receive adjuvant systemic therapy (chemotherapy and/or endocrine therapy). All participants may receive breast/chest wall radiotherapy. Axillary and supraclavicular fossa radiotherapy is not allowed when randomised to adjuvant therapy alone.

Conclusion

POSNOC Trial aims to address an important clinical question of axillary management in a randomised setting. For further information regarding participation in this important multicentre trial please contact the POSNOC trial team on 0115 884 4924 or email: posnoc@nottingham.ac.uk. ●

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