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Review

Axillary reverse mapping in N0 patients requiring sentinel lymph node biopsy – A systematic review of the literature and necessity of a randomised study

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ABSTRACT

Objectives: Axillary reverse mapping (ARM) is a technique to map and preserve arm lymphatics which may be damaged during surgery, resulting in lymphoedema.
This work systematically reviews the incidence of lymphoedema following sentinel lymph node biopsy (SLNB) + ARM, compared to SLNB alone, for clinically node negative disease, as well as recurrence rate, other morbidity and the feasibility and difficulties of ARM.
Materials and Methods: The following databases were searched: PubMed, Embase, Cochrane Library. Abstracts submitted to recognised societies dedicated to research in oncology were included. Studies were eligible if performed within the last 10 years; ARM was used in any form; ARM performed during SLNB ± axillary lymph node dissection (ALND). Studies were analysed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
Results: No studies were found meeting the initial inclusion criteria. Therefore, studies reporting use of SLNB + ARM (i.e. no comparison to SLNB) were reviewed. A second search was performed to identify studies reporting outcome following SLNB alone. Twelve studies reported data on patients undergoing SLNB + ARM and 23 studies on patients undergoing SLNB. Incidence of lymphoedema following SLNB + ARM was quoted between 0-4% and 0–63.4% following SLNB. Few studies commented on recurrence rate. Studies included were of mainly low level of evidence.
Conclusion: Evidence is beginning to emerge for the use of ARM in order to reduce lymphoedema following axillary surgery. However, data regarding oncological safety of ARM is not clear and randomised controlled trials, with adequate follow-up, need to be performed to determine this.
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1. Introduction

1.1. History

At the turn of the century, breast cancer treatment in the UK moved from axillary lymph node dissection (ALND) [1] to four-node axillary sampling [3]. Even with this reduction in lymph node removal, it was estimated that 60–70% of patients with early breast cancer have no axillary disease and therefore, preservation of these lymph nodes outweighs removal [1,2,4]. In the last ten years or so [5,6] the concept of selecting only the first lymph node(s) draining the breast – the sentinel lymph node(s), has become commonplace. Current National Institute for Health and Care Excellence (NICE) guidance [7] states that minimally invasive surgery should be performed where possible for patients with no evidence of lymph node involvement and this should be by sentinel lymph node biopsy (SLNB).

1.2. Lymphoedema

The reported incidence of lymphoedema following ALND ranges from 6% to as high as 77% [1]. SLNB has helped to reduce the incidence of lymphoedema to between 2 and 7%, without impacting on overall survival [8,9].

The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) multicentre randomised trial in clinically node-negative breast cancer patients, compared those who underwent

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SLNB (n = 515) to those who received standard axillary staging procedure (n = 516) [10]. SLNB was associated with reduced arm morbidity and better quality of life over a 12-month period, with no compromise in efficacy, measured by axillary recurrence rate, local recurrence and survival.

Data on comparable survival between patients undergoing ALND and those having SLNB alone, has been demonstrated in the Phase III study Z0011 trial by The American College of Surgeons Oncology Group [11]. This prospective multi-centre trial compared overall survival between patients with positive sentinel lymph nodes, randomised to receive either ALND or no further axillary treatment following SLNB. At 1 year, lymphoedema was reported subjectively by 13% (37 of 288) of patients after SLNB + ALND and 2% (6 of 268) after SLNB alone ($p < 0.001$). There were no significant differences between the two groups for overall survival, disease-free survival, 5 year in-breast or nodal recurrence.

1.3. Concept of axillary reverse mapping

It is hypothesised that there are distinct non-overlapping nodes which drain the arm and the breast respectively [12]. Therefore, by tracing the two different pathways, a technique known as axillary reverse mapping (ARM), it is theoretically possible to resect axillary nodes alone and their draining lymphatics from the breast, subsequently leading to a reduced rate of lymphoedema occurrence following axillary surgery.

ARM involves injection of a radioactive substance, by blue dye, fluorescent dye or radioisotope into the axilla, to highlight the lymphatic drainage pattern of the upper limb. Therefore, lymphatics draining solely the arm can be avoided, as far as clinically able and lymphatics draining the breast alone can be removed as clinically indicated [13].

ARM can be used in N0 patients requiring SLNB or N+ patients requiring ALND.

1.4. Oncological safety of ARM

Studies to date suggest that ARM is feasible in clinical practice [13,14]. Data regarding safety in terms of recurrence; disease-free survival; and absolute benefit in preventing lymphoedema, is lacking. The hypothesis of this review is that the incidence of lymphoedema following SLNB + ARM compared to SLNB alone will be significantly reduced, without increasing regional recurrence of the disease.

2. Methods and results

This research undertook the form of a systematic review of the literature.

Following the initial search strategy as will be described, there were no articles found making comparisons between SLNB + ARM and SLNB alone, for clinically node negative disease. However, there were studies which did investigate the use of SLNB + ARM on its own, either as descriptive studies or compared to ALND + ARM.

In order to compare the incidence of lymphoedema following SLNB + ARM to SLNB alone, a second literature review was conducted looking at SLNB alone and data collected on incidence of lymphoedema, recurrence rate and other reported morbidity.

The data from the two searches were then compared.

2.1. Search 1 – methods

2.1.1. Search strategy

Studies reporting use of ARM in SLNB procedures compared to SLNB alone, were reviewed. The following online databases were searched for relevant literature: PubMed, Embase, Cochrane Library. Abstracts submitted to recognised international societies dedicated to research in oncology, including the American Society of Clinical Oncology, the San Antonio Breast Cancer Symposium and the St. Gallen Oncology Conferences, available online, were included.

SLNB has become commonplace in routine practice in the last decade, therefore, the search was limited to those studies published within the past 10 years (1st December 2005–31st December 2015). Studies were restricted to those published in English language and performed in humans. The last search was conducted on 7th February 2016.

The search terms used were: axillary reverse mapping, breast cancer, lymphoedema, sentinel lymph node biopsy.

Inclusion criteria:

- Performance of ARM defined as simultaneous mapping of the breast and axilla
- ARM performed during SLNB with or without completion ALND
- Clinical trial using patient data
- Full-text article or abstract

Exclusion criteria:

- Studies which failed to fulfil inclusion criteria or ARM not used in methodology
- No relation to breast cancer
- Patient data not used
- Duplicate study
- Restricted access to study report/data
- Review article, letter to the editors, editorial report, case report

2.1.2. Data extraction

Data was extracted from the selected studies using a data extraction form. All data was extracted directly from the study text. No further statistical analysis was made where data was not presented.

Data was collected on: publication details; study design; number of participants; number undergoing SLNB/ALND; follow-up period; participant age; ARM technique; stage of tumour; primary breast cancer treatment; ARM node or lymphatics identification and preservations rate; ARM crossover node identification rate; excised ARM nodes and node-positive rate; method of measurement of lymphoedema, incidence of lymphoedema; in-breast and in-axillary recurrence rates; other reported morbidity following the procedure: sensory disturbance; pain; impairment of arm mobility; uniqueness of the study; limitations of study.

2.1.3. Critical appraisal

Once relevant studies were identified and data collected, the studies were assessed using the system proposed by Harbour and Miller [15]. The quality of cohort studies was assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias [17].

2.1.4. Statistical analysis

All extracted data were tabulated and presented as percentages.

2.2. Search 1 – results

Using the initial search strategy, no studies were found meeting the inclusion criteria as outlined above (Fig. 1).

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