Management of the axilla for early breast cancer:

a systematic review

September 2007

Management of the axilla for early breast cancer: a systematic review
was prepared and produced by:
National Breast and Ovarian Cancer Centre (NBOCC)*
Locked Bag 3 Strawberry Hills NSW 2012 Australia
Tel: +61 2 9357 9400 Fax: +61 2 9357 9477
Website: www.canceraustralia.gov.au

ISBN Online: 9781741271584

Recommended citation

Cancer Australia. Management of the axilla for early breast cancer: a systematic review. Cancer Australia, Surry Hills, NSW, 2011

Copies of Management of the axilla for early breast cancer: a systematic review can be downloaded from the Cancer Australia website: www.canceraustralia.gov.au

* In July 2011, National Breast and Ovarian Cancer Centre (NBOCC) amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

Acknowledgements

This review was developed by National Breast and Ovarian Cancer Centre (NBOCC)[†].

National Breast and Ovarian Cancer Centre gratefully acknowledges the support of all the individuals who contributed to the development of this review.

Funding

Funding for the development of this review was provided by the Australian Government Department of Health and Ageing.

Axilla Working Group

This review was developed with input from a multidisciplinary Working Group:

Associate Professor Sue Pendlebury (Chair)

Dr Melissa Bochner

Professor John Boyages

Ms Jenny Donovan

Dr Michelle Grogan

Dr Jane O'Brien

Dr Neil Wetzig

National Breast and Ovarian Cancer Centre Staff

The following people were involved in the development of this review:

Ms Katrina Anderson

Dr Karen Luxford

Dr Anne Nelson

Ms Alison Pearce

Ms Rosemary Vagg

Ms Heidi Wilcoxon

Dr Helen Zorbas

[†]In July 2011, National Breast and Ovarian Cancer Centre (NBOCC) amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

CONTENTS

List of tables

List of abbreviations

AD	axillary dissection
BC	breast cancer
BCT	breast conserving therapy
DBCG	Danish Breast Cancer Cooperative Group
DFS	disease-free survival
EBC	early breast cancer
FNA	fine needle aspiration
IBCSG	International Breast Cancer Study Group
LVI	lymphovascular invasion
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NBCC	National Breast Cancer Centre
NBOCC	National Breast and Ovarian Cancer Centre
N/A	not applicable
NPV	negative predictive value
NR	not reported
NS	not significant
OR	odds ratio
OS	overall survival
P/D ratio	ratio of positive nodes to nodes dissected
PET	positron emission tomography
PICO	Population, Intervention, Comparison, Outcomes
PMRT	post-mastectomy radiotherapy
Pts	patients
QoL	quality of life

RT	radiotherapy
SCF	supraclavicular fossa
SI	signal intensity
SNB	sentinel node biopsy
SUV	standardised uptake value
US	ultrasound
USPIO	ultra-small super paramagnetic iron oxide

Executive Summary

This systematic review was conducted to support an update of the Management of the Axilla section within the *Clinical Practice Guidelines on the Management of Early Breast Cancer* published in 2001.[1] The review includes evidence published between 2000 and 2007 about the management and treatment of the axilla in early breast cancer.

The review was divided into seven research questions incorporating two areas, staging and treatment. The staging sections compare axillary dissection to non-surgical methods and to four node sampling. The treatment sections encompass the extent of axillary dissection, prognostic significance of nodal involvement, long term outcomes of axillary treatment, comparisons of axillary dissection to axillary radiotherapy and the use of axillary radiotherapy after axillary dissection. Over 100 papers were included in the review, including 11 randomised controlled trials. The remaining were non-randomised studies including case series, diagnostic accuracy, prognostic and observational studies. Some papers provided information for multiple questions.

Staging

The majority of information regarding non-surgical staging of the axilla relate to the diagnostic accuracy of ultrasound or positron emission tomography (PET) compared with axillary dissection. The specificity for each of these modalities was often high, however both ultrasound and PET had low negative predictive value, therefore a negative result did not remove the need to undergo surgical staging of the axilla.

Four node sampling may be an accurate method to stage the axilla, however appeared to be associated with increased axillary recurrence compared to axillary dissection.

Treatment

The extent of axillary dissection was reported in two randomised trials, comparing level III dissection with level I or II dissection, respectively. No survival differences were observed between level III and the other levels of dissection, however longer operation times and more blood loss was reported with level III dissection.

The prognostic significance of nodal involvement was reported by number of excised nodes, ratio of positive to dissected nodes and number of uninvolved nodes. Studies on the number of excised nodes compared different numbers of nodes, making comparisons difficult, however higher ratios of positive to dissected nodes were consistently associated with decreased survival.

Long term data from randomised control trials showed no overall survival difference for axillary dissection or axillary radiotherapy compared to no axillary treatment for low-risk patients.

For the randomised trials which compared axillary dissection directly to axillary radiotherapy, no survival differences were observed. Rates of axillary recurrence appear higher in patients who were treated with axillary radiotherapy compared to axillary dissection, however differences were often not

statistically significant. Lymphoedema appeared to be reported more often with axillary dissection than axillary radiotherapy, however this was also not always statistically significant.

The use of axillary radiotherapy after axillary dissection was reported in papers investigating either radiotherapy to the axilla only or radiotherapy which targeted the axilla as well as other regional areas, therefore it is difficult to determine the effect that each targeted area, such as the axilla, contributes to outcomes. In high-risk patients, the addition of radiotherapy which targeted the axilla as well as other regional areas led to decreased rates of locoregional recurrence. The addition of radiotherapy to axillary dissection increased rates of lymphoedema. The subgroup of patients at high risk of axillary recurrence following axillary dissection is not well defined however some studies reported on predictors for locoregional recurrence.

Across the studies included in the systematic review, quality of life outcomes were not reported, in general. The most common adverse effects reported for axillary treatment were increased lymphoedema and arm morbidity. Ongoing trials are investigating axillary treatment for patients with positive sentinel nodes.

1 Background

National Breast Cancer Centre (NBCC)‡ published the second edition of *Clinical Practice Guidelines on the Management of Early Breast Cancer* in 2001.[1] To ensure currency of the guidelines, NBOCC is updating sections of these guidelines on a topic-specific basis. This review is to support the update of the Management of the Axilla section of the 2001 EBC guidelines. A guideline on the use of sentinel node biopsy for early breast cancer has been developed separately.

NBCC recommendations from 2001 guidelines:

- For women with early breast cancer, a level I or level II axillary node dissection should be standard.

The 2001 guidelines also reference recommendations from the Meeting on Axillary Dissection and Irradiation held at the Gold Coast, Australia, in September 1998:

- Omission of axillary dissection can be considered for some women.
- Axillary irradiation will reduce axillary recurrence.
- Where the risk of axillary recurrence is high axillary dissection and axillary irradiation should be considered.
- Management of the axilla should be determined by a multidisciplinary team in discussion with the patient. Patients should be informed of benefits and risks of axillary dissection and axillary irradiation.

‡ In February 2008, National Breast Cancer Centre (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

2 Methods

The objective of the review was to assess the evidence published in the literature since 2000 about the management and treatment of the axilla in early breast cancer.

The review was divided into seven questions incorporating two areas, staging and treatment:

Staging

What is the best method to assess the axilla?

1) **Non-surgical methods compared to axillary dissection**

2) **4-node sampling compared to axillary dissection**

Treatment

Axillary dissection or Axillary irradiation

3) **What is the optimal extent of axillary dissection?**

4) **What is the prognostic significance of the numbers of nodes involved and/or retrieved in axillary dissection?**

5) **What are the long-term outcomes of axillary dissection or axillary irradiation versus no axillary treatment?**

6) **What are the benefits of axillary dissection alone compared to axillary irradiation alone?**

7) **a. What are benefits of radiotherapy after axillary dissection?**

   b. Who should have irradiation to the axilla after axillary dissection?

2.1 Inclusion Criteria

Each research question was broken down into the following components: population, intervention, comparison and outcomes (PICO), see Appendix 1. A separate literature search was conducted for each question. Articles were included if they addressed the PICO criteria identified for each question.

2.2 Literature Search

Literature searches were conducted in each of the following electronic databases:

- Medline
- EMBASE
- PubMed.

Each question had an individual search strategy, using combined key terms which described the PICO defined for each question (see Appendix 2). The searches were limited to trials conducted in humans which were published from January 2000 to August 2007 in the English language.

Reference lists of relevant papers and personal files were also searched to identify additional citations. From each of the seven literature searches, articles were often identified by one search but considered relevant for another question. These articles were included into the papers for the other question as being identified by an additional source.

2.3 Exclusion Criteria

Papers were excluded if they met the following exclusion criteria:

- Not an original clinical study – including non-systematic reviews, editorials, letters, opinion pieces
- Inappropriate population – trials conducted in a population other than early breast cancer
- Inappropriate intervention – as identified for each question
- Inappropriate comparison – as identified for each question
- Inappropriate outcomes – as identified for each question
- Not English language
- Published prior to 2000

Based on these criteria, titles and abstracts were assessed to determine whether they met inclusion criteria for the relevant question. The full text of the included citations were retrieved and assessed to identify which met the inclusion criteria for the review (Tables 1 and 2).

Table 1. Number of included/excluded citations for each question

Question	1st round (titles/abstracts)	2nd round (full text)	Final included papers
1	222	67	37
2	160	16	4
3	210	22	7
4	238	27	20
5	232	13	5
6	245	20	9
7	199	32	17

Table 2. Papers identified from additional sources

Question	1st round	2nd round (full text)	Final included papers
1	-	6	3
2	-	3	3
3	-	14	2
4	-	7	8
5	-	-	-
6	-	8	0
7	-	20	13

2.4 Data Extraction

Data on the characteristics and the outcomes of the trials were extracted and tabulated for each question. Where multiple citations were identified for one trial, data from the most recent publication were used, unless further information could be gained from the older publication(s). If a paper reported on one combined analysis of data from two or more trials, it was classified as one trial.

2.5 Quality Assessment

Trials were classified into levels of evidence, as defined by the National Health and Medical Research Council (NHMRC), Levels of Evidence,[2] see Appendix 3. However, formal quality assessment was not performed.

Data has been included from all levels of evidence (unless specified otherwise), except for non-systematic (narrative) reviews and opinion pieces (including letters and editorials). However, where possible, information has been sourced from systematic reviews and randomised controlled trials as the highest levels of evidence (level I and II).

The results and discussion will be presented for each research question. The first two research questions relate to staging of the axilla, the remaining five questions regard the treatment and management of the axilla.

3 Non-surgical methods of staging the axilla

Axillary dissection (AD) is currently considered the gold standard for staging the axilla. The following non-surgical modalities for assessing the axilla were investigated: magnetic resonance spectroscopy (MRS), magnetic resonance imaging (MRI), ultrasound (US) and positron emission tomography (PET). In the trials the accuracy of staging the axilla of the non-surgical method was determined by comparing the lymph node status identified by the non-surgical method to the histological confirmation of lymph node status following axillary dissection (AD).

3.1 Results

The trials identified reported diagnostic accuracy of various techniques to stage the axilla. Two trials were identified which compared two non-surgical modalities to each other. One investigated MRI compared to PET, the other compared US to PET. The remaining trials investigated cohorts of patients who had axillary staging performed by one of the various non-surgical methods prior to surgical staging. It was noted that not all patients in these studies received axillary dissection, some patients were surgically staged using sentinel node biopsy only.

Each of the modalities investigated will be discussed in turn.

3.1.1 MRS

No relevant trials were identified which investigated the use of MRS to stage the axilla.

3.1.2 MRI

Three trials were identified which investigated the use of MRI to stage the axilla, including one paper which compared MRI to PET.

Description of studies

The trial comparing MRI to PET was small, containing only 10 patients.[3] Also the trial investigated used a non-standard method of MRI, ultra-small super paramagnetic iron oxide (USPIO)-enhanced MRI. The comparative trial is reported in section 3.1.5. The other two trials were diagnostic accuracy studies where patients were examined by dynamic contrast-enhanced MRI prior to planned level I/II axillary dissection.[4,5] Characteristics of the diagnostic accuracy trials are in Table 3.

Table 3. Characteristics of MRI trials

First author, year	Location	Study design – diagnostic accuracy	N	Population	Intervention	Reference standard
Kvistad, 2000[4]	Norway	Level II A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	65	Invasive breast cancer (T1-T4) Mean age: 59.4yrs (38-79yrs); pre- and post-menopausal	Preoperative MRI	AD
Murray, 2002[5]	UK	Level III-1 A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	47	Invasive breast cancer Tumour size: 5–31mm Mean age: 63yrs (50-87yrs)	Preoperative MRI	AD

Notes: AD – axillary dissection; MRI – magnetic resonance imaging

Overall results

Accuracy of staging

The accuracy of the MRI to detect lymph node metastases depended on what criteria were used to determine a positive lymph node. Here the best possible result, as defined in each trial, is presented in Table 4. The best result for the Kvistad trial was obtained when an abnormal signal intensity (SI) increase was observed (defined as >100% SI increase during the first post-contrast image compared with the pre-contrast SI value in the most contrast enhancing axillary lymph node).[4] The best result for the Murray trial was when Ef (the signal change in an enhancing node normalised to the signal in an adjacent area of axillary fat) < 0.21% and A (maximal cross sectional area) < 0.4cm^2 were used.[5]

Table 4. Accuracy of MRI to stage the axilla

Trial	N	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Kvistad, 2000[4]	65	83	90	83	90	88
Murray, 2002[5]	47	100	56	38	100	65

Notes: NPV – negative predictive value; PPV – positive predictive value

3.1.3 Ultrasound

One systematic review, one comparative study (US compared to PET), and nineteen diagnostic accuracy studies which investigated the use of ultrasound to stage the axilla were identified. Nodes which were identified as suspicious on ultrasound were often followed by fine needle aspiration (FNA) or core biopsy (CB) for confirmation of metastases.

Description of studies

One systematic review was identified[6] which includes 16 papers published between 1986 and 2003. Six of these papers have been published since 2000 and have been included in the current NBOCC review.

One comparative study was identified which compared US to PET[7] and is reported in section 3.1.5. Nineteen diagnostic accuracy studies have been identified which compare the accuracy of US compared to AD and/or SNB. Characteristics of the original diagnostic accuracy trials are in Table 5.

Table 5. Characteristics of ultrasound trials

First author, year	Location	Study design – diagnostic accuracy	N	Population	Intervention	Reference standard
Sato, 2004[8]	Japan	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	262	Primary breast cancer (T1: 35.9%, T2: 55.3%, T3: 8.8%) Mean age: 54.8yrs (21-83yrs)	Preoperative US	SNB + AD
Nori, 2007 [9]	Italy	Descriptive study	132	Breast cancer (98% invasive, 2% DCIS) Mean tumour size: 1.2cm (0.4cm-2.8cm)Mean age: 56.4yrs (28-88yrs)	Preoperative US +/- CB	SNB and/or AD
Sapino, 2003[10]	Italy	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	298	Breast cancer (90% invasive, 10% in situ)	Preoperative US	SNB or AD
Ciatto, 2007[11]	Italy	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	491 biopsies from 476 patients	Operable breast cancer (T1-2, N0-1) Mean tumour size: 2.1cm (0.4-4.9cm) Mean age: 52yrs (24-90yrs)	Preoperative US + FNA	SNB or AD
Deurloo, 2003[12]	Netherlands	Descriptive study	265	Invasive breast cancer Mean tumour size: 1.9cm (0.2-8cm) Mean age: 56yrs (27-91yrs)	Preoperative US +/- FNA	SNB and/or AD

First author, year	Location	Study design – diagnostic accuracy	N	Population	Intervention	Reference standard
Van Rijk, 2006[13]	Netherlands	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	726	Unifocal breast cancer (T1: 67% T2: 30%, T3: 22%, T4: 1%) Mean age: 58 yrs (18-94 yrs)	Preoperative US +/- FNA	SNB and/or AD
Kuenen-Boumeester, 2003[14]	Netherlands	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	183 aspirations (of 180 patients)	Primary breast cancer (T1: 72% T2: 28% T3: 0.5%)	Preoperative US + FNA	SNB and/or AD
Podkrajsek, 2005[15]	Slovenia	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	165	Primary breast cancer (T1a/b: 19% T1c: 42% T2: 33%, T3: 1%, DCIS: 5%) Mean age: 56yrs (26-80yrs)	Preoperative US +/- FNA	SNB or AD
Mathijssem, 2006[16]	Netherlands	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	131	Invasive breast cancer (T1 and T2: 95.7%)	Preoperative US +/- FNA	SNB or AD
Motomura, 2001[17]	Japan	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	60	Breast cancer (stage I or II) Median tumour size: 2cm (0.5-4cm) Median age: 50yrs (28-71yrs)	Preoperative US + FNA	SNB
Topal, 2005[18]	Turkey	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	39	Invasive breast cancer (T1: 49% T2: 49% T3: 2%) Mean age: 51yrs (36-78yrs)	Preoperative US + CB	AD

First author, year	Location	Study design – diagnostic accuracy	N	Population	Intervention	Reference standard
Krishnamurthy, 2002[19]	US	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	103	Breast cancer	Preoperative US + FNA	AD
Damera, 2003[20]	UK	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	166	Invasive breast cancer (T1: 22% T2: 39% T3: 39%) Median age: 56yrs (33-81yrs)	Preoperative US +/- CB	Axillary sampling and/or AD
Brancato, 2004 [21]	Italy	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	159	Breast cancer (Stage IA/B: 22.1% Stage IC: 38.7% Stage II>: 39.3%) Mean age: 59 (23-89yrs)	Preoperative US + FNA	SNB or AD
Hinson, 2007[22]	US	Descriptive study	112	Breast cancer at high risk for axillary metastases (grade III and size ≥ 1cm, or grade II and size ≥ 1.5 cm)	Preoperative US +/- FNA	SNB +/- AD
Mobbs, 2005[23]	US	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	71	Invasive breast cancer	Preoperative US + FNA	AD +/- SNB
Lumachi, 2006[24]	Italy	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	77	Primary breast cancer (T1b:7.8%, T1c: 61%, T2: 31.2%) Median age: 54yrs (36-70yrs)	Preoperative US	AD

First author, year	Location	Study design – diagnostic accuracy	N	Population	Intervention	Reference standard
Bedrosian, 2003[25]	US	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	208	Breast cancer (T1: 77%, T2: 15%) Mean age: 55.4yrs (26-91yrs)	Preoperative US +/- FNA	SNB +/- AD
Couto, 2004[26]	Portugal	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	55	Invasive breast cancer (T1 or T2, N0)	Preoperative US	AD

Notes: AD – axillary dissection; CB – core needle biopsy; FNA – fine needle aspiration; SNB – sentinel node biopsy; US – ultrasound

Overall results

Accuracy of staging

The accuracy of US and/or FNA/CB of finding or excluding metastases in the axilla was reported, see Table 6. Where results for ultrasound and ultrasound plus biopsy are reported separately, both are reported. The addition of FNA or CB tended to increase the accuracy of staging the axilla.

Table 6. Accuracy of ultrasound to stage the axilla

Trial	N	Technique	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Ciatto, 2007[11]	491 biopsies from 476 patients	US+FNA*	72.6	95.7	96.6	67.2	
Hinson, 2007[22]	112	US	81	69			
		US+FNA	82	100			
Nori, 2007[9]	132	US	45.2	86.6	61.3	77.2	73.5
		US+CB	91.6	100	100	66.6	92.8
Van Rijk, 2006[13]	726	US	35	82			
		FNA	62	99			
		US+FNA	21	99.8			
Mathijssen, 2006[16]	131	US	34	98.7	94.7	68.8	72.5
Lumachi, 2006[24]	77	US	67.6	80	75.6	72.7	74
Podkrajsek, 2005[15]	165	US	58	89	77	77	
		US+FNA	84	91	97	62	
Mobbs, 2005[23]	71	US	40	82	47	78	70
	61	US (>5mm)	80	82	47	95	82
Topal, 2005[18]	39	US+CB	90	100	100	66	92
Sato, 2004[8]	262	US	{44.6}	{97.3}	{92.6}	{70.2}	{74.8}
Brancato, 2004[21]	159	US (suspicious)	64.3	86.5	78.9	75.5	
		US+FNA	58.6	100	100	75.4	
Couto, 2004[26]	55	US	71.4	71.4	60	80.6	
Sapino, 2003[10]	298	US	{68.2}	{83.3}	{63.2}	{86.2}	{78.9}
		US+FNA*	{89.1}	{100}	{100}	{83.3}	{92.9}
Deurloo, 2003[12]	265	US+FNA*	{86}	{100}	{100}	{72.7}	{89.8}
Bedrosian, 2003[25]	208	US+FNA	25	100			
Damera, 2003[20]	166	US	55	82	74	65	
		US+CB	42	100	100	74	
Kuenen-Boumeester, 2003[14]	183 aspirations from 180 patients	US+FNA*	57	96	92	70	76

Trial	N	Technique	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Krishnamurthy, 2002[19]	103	US+FNA	86.4	100	100	67	79
Motomura, 2001[17]	60	US	50	92.1			76.7
		US+FNA	78.5	93.3			86.2
Ohta, 2000[7]**	32	US	65	100			79

Notes: CB – core biopsy; FNA – fine needle aspiration; NPV – negative predictive value; PPV – positive predictive value; US – ultrasound
Figures in {braces} were calculated by review authors. *Not including FNA data which was not informative/inadequate (neither positive or negative). **Data from single arm of comparative study reported in section 3.1.5.

3.1.4 PET

One systematic review and sixteen trials were identified which investigated the use of PET to stage the axilla. Two comparative trials were identified, one which compared PET to MRI, the other which compared PET to US.

Description of studies

One systematic review was identified[27] which includes papers evaluating use of PET both in the diagnosis of primary breast cancer and to evaluate axillary lymph node and sentinel node status. Twenty-four studies published between 1989 and 2004 investigated the use of PET to stage axillary and sentinel node status. Six of these papers which were published since 2000 have been included in the current review.

Two comparative studies were identified, one which compared PET to US,[7] the other compared PET to USPIO MRI.[3] The comparative trials are reported in section 3.1.5. Sixteen diagnostic accuracy studies have been identified which compare the accuracy of PET to stage the axilla to AD and/or SNB, the characteristics of these trials are in Table 7.

Table 7. Characteristics of PET trials

First author, year	Location	Study design – diagnostic accuracy	N	Population	Intervention	Reference standard
Kelemen, 2002[28]	USA	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	15	Invasive breast cancer Median tumour size 1.5cm (0.5-5cm) Median age: 60yrs (43-82yrs), most postmenopausal	Preoperative PET	SNB +/- AD
Van der Hoeven, 2002[29]	Netherlands	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	70	Operable breast cancer (T0: 6%, T1 53%, T2: 26%, T3 6%, T4: 4%) Mean age: 58yrs	Preoperative PET	SNB or AD
Chung, 2006[30]	USA	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	54 cancers in 51 patients	Invasive breast cancer (T1: 41%, T2: 44%, T3: 15%)	Preoperative PET	SNB or AD
Guller, 2002[31]	Switzerland	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	31	Breast cancer (T1:19pts T2: 12pts) Mean age: 64.8yrs (47-88yrs)	Preoperative PET	SNB
Fehr, 2004[32]	Switzerland	Level III-1 A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	24	Breast cancer ≤ 3cm Mean age: 56yrs (45-74yrs)	Preoperative PET	SNB + AD

First author, year	Location	Study design – diagnostic accuracy	N	Population	Intervention	Reference standard
Kumar, 2006[33]	USA	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	80	Breast cancer, mean tumour size: 1.64cm (0.2-6.9cm) Mean age: 52yrs (32-79) Menopausal status: premenopausal: 41%, perimenopausal: 14%, postmenopausal: 45%	Preoperative PET	SNB + AD
Barranger, 2003[34]	France	Level II A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	32	Breast cancer (T0: 28.1%, TI: 56.3%, T2: 15.6%) Mean age: 58yrs (29-77yrs)	Preoperative PET	SNB + AD
Veronesi, 2007[35]	Italy	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	236	Breast cancer (T1-T3) Median age: 49yrs (24-79yrs) Menopausal status: Premenopausal: 135, Postmenopausal: 100, 1 male patient	Preoperative PET	SNB and/or AD
Lovrics, 2004[36]	Canada	Level II A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	90	Breast cancer (stage I – II) Mean age: 56.4yrs	Preoperative PET	AD
Gil-Rendo, 2006[37]	Spain	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	275	Breast cancer (stage I – II) Mean tumour size: 2.3cm (0.3-4.9cm) Mean age: 50.6yrs (24-87yrs)	Preoperative PET	SNB and/or AD

First author, year	Location	Study design – diagnostic accuracy	N	Population	Intervention	Reference standard
Hubner, 2000[38]	US	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	87	Primary (35pts) and recurrent (57pts) breast cancer [only results for primary breast cancer reported in this review] Mean age: 59yrs	Preoperative PET	Routine histopathological methods
Greco, 2001[39]	Italy	Level II A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	167	Breast cancer (T1-2) Mean tumour size: 2.1cm (0.5cm-5cm) Mean age: 54yrs (28-84yrs)	Preoperative PET	AD
Rieber, 2002[40]	Germany	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	43	Suspected breast cancer Mean age: 52.9yrs (27-84yrs)	Preoperative PET	Histopathology
Yutani, 2000[41]	Japan	Level II A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	38	Primary breast cancer Mean tumour size: 2.1cm (0.4-4.5cm) Mean age: 51yrs (25-86yrs)	Preoperative PET (compared to pre-op SPECT)	AD
Schirrmeister 2001[42]	Germany	Level III-2 A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	117	Suspected breast cancer Mean age: 56.8yrs (28-86yrs) Premenopausal: 34pts Perimenopausal: 23pts Postmenopausal: 60pts	Preoperative PET	Histopathology

First author, year	Location	Study design – diagnostic accuracy	N	Population	Intervention	Reference standard
Wahl, 2004[43]	USA	Level III-1 A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	308	Invasive breast cancer (T1: 14%, T1a: 6.2%, T1b: 17.5%, T1c: 31.5%, T2: 25.6%, T3: 2.3%, Tx: 2.9%) Median age: 52yrs (27-82yrs) Menopausal status: premenopausal: 37.3%, perimenopausal: 4.5%, postmenopausal: 40.3%, surgical menopause: 17.2%	Preoperative PET	AD

Notes: AD – axillary dissection; PET – positron emission tomography; SNB – sentinel node biopsy

Overall results

Accuracy of staging

The accuracy of PET compared to AD and/or SNB from the identified trials are reported in Table 8.

Table 8. Accuracy of PET to stage the axilla

Trial	N	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Veronesi, 2007[35]	236	37	96	88	66	70
Gil-Rendo, 2006[37]	275	84.5	98.5	98.4	85.6	91.3
Kumar, 2006[33]	80	44	95	89		72
Chung, 2006[30]*	54 cancers in 51 patients	60	100	100	53	72
Stadnik, 2006[3]**	10	80	100	100	80	
Wahl, 2004[43]	308	61	80	62	79	
Lovrics, 2004[36]	90	40	97	75	89	
Fehr, 2004[32]	24	20	93	67	62	
Barranger, 2003[34]	32	20	100	100	58.6	62.5
Van der Hoeven, 2002[29]†	70	28	82			
Rieber, 2002[40]	43	80	95	94.1	95	87.5
Guller, 2002[31]	31	43	94	NR	67	NR
Kelemen, 2002[28]	15	20	90	NR	NR	NR
Greco, 2001[39]	167	94.4	86.3	84	95.3	89.8
Schirrmeister 2001[42]	117	79	92	82	91	89
Yutani, 2000[41]	38	50	100	100	73.3	78.9
Ohta, 2000[7]**	32	70	100			82
Hubner, 2000[38]	35‡	96	91			

Notes: NPV – negative predictive value; PPV – positive predictive value; NR – not reported
*Data by adopting a standardised uptake value (SUV) threshold of 2.3; **Data from single arm of comparative study reported in section 3.1.5; †PET considered positive if ≥2 observers read intense uptake (3), moderate (2) or faint (1); ‡Five patients were evaluated for both primary and recurrent tumours

3.1.5 Comparative trials

Two trials compared the use of two non-surgical methods of staging the axilla.

Description of Studies

One trial compared US and PET for staging the axilla in 32 patients[7] and the other trial compared a non-standard method of MRI, USPIO-enhanced MRI, and PET in 10 patients.[3]

Overall results

Diagnostic accuracy of US compared with PET for staging the axilla,[7] is presented in Table 9. The addition of PET and US improved sensitivity and accuracy of staging the axilla, however these differences were not statistically significant.

Table 9. Accuracy of PET compared to US to stage the axilla

	PET	US	PET+US
Sensitivity %	70	65	75
Specificity %	100	100	100
Accuracy %	82	79	85

Notes: PET – positron emission tomography; US – ultrasound

The accuracy of a non-standard method of MRI, USPIO-enhanced MRI, compared to PET,[3] is presented in Table 10. Combining MRI and PET gave an accuracy of 100%.

Table 10. Accuracy of MRI compared to PET to stage the axilla

	USPIO MRI	PET	PET+MRI
Sensitivity %	100	80	
Specificity %	80	100	
PPV %	80	100	
NPV %	100	80	
Accuracy %			100

Notes: MRI – magnetic resonance imaging; NPV – negative predictive value; PET – positron emission tomography; PPV – positive predictive value; USPIO - ultra-small super paramagnetic iron oxide

3.2 Discussion

Axillary dissection has been the gold standard for staging of the axilla, as numbers of nodes could be assessed as well as positivity or negativity. In the 2001 NBCC Guidelines for Early Breast Cancer,[1] non-surgical staging techniques such as MRI, ultrasound and PET had limited evidence to support their use. These techniques, as well as MRS, were re-assessed using the latest data available.

MRI

Results of MRI as a method of staging the axilla are best for negative predictive value, but continue to be less reliable in sensitivity and specificity than axillary dissection. As discussed in the Murray (2002) paper,[5] the implications of these results on practice are dependent on the purpose of the assessment. MRI staging showed good results in terms of excluding axillary metastases, however performs poorly in terms of identifying women with axillary metastases.[5]

The two studies identified comparing MRI with axillary dissection continue to demonstrate technical problems related to the technique. Movement related to respiration can limit the quality of the images obtained from MR imaging of the breast,[4] and may lead to misinterpretation, particularly of smaller lymph nodes.[5] In addition, general technical issues such as the design of breast coils not always being suitable for axilla imaging may also influence quality of images.[4]

Ultrasound

For the use of ultrasound to stage the axilla a larger body of data is available. Overall accuracy of ultrasound alone ranged from 70% to 82%, however accuracy approached 93% when ultrasound was performed in combination with fine needle aspiration or core biopsy. For those with palpable nodes, results for sensitivity and specificity were also improved. The findings suggest that, in patients with ultrasound-positive axillary nodes confirmed by fine needle aspiration or core biopsy, it may be appropriate to proceed to axillary dissection immediately, without initial sentinel node biopsy.

However, the significant difficulty encountered with ultrasound as a method of staging the axilla is the poor negative predictive value (usually <80%). Therefore a negative result on ultrasound plus fine needle aspiration or core biopsy, does not remove the need for surgical staging of the axilla.

Finally, a study comparing US with PET showed similar results for both techniques in relation to sensitivity, specificity and accuracy.[7]

PET

There are many trials investigating the role of PET as a method of staging the axilla. However, the picture overall is one of low sensitivity, and negative predictive value, although the technique does have high specificity and moderate positive predictive value. This indicates that the best clinical utility of this technique in non-surgical staging of the axilla may be for patients with positive PET predicting an involved axilla,[30] with specificity up to 100% (see Table 8 for reference). The use of PET to indicate patients with a PET-positive axilla for whom an ALND is more appropriate than a SNB (a new treatment in staging axillary lymph nodes), to minimise the number of procedures for the women, is a possibility given the high specificity seen across studies.[35]

4 Node-sampling method of staging the axilla

4.1 Results

4.1.1 Description of studies

Six trials were identified which investigated unguided axillary sampling (as opposed to SNB) compared to axillary dissection. These included randomised controlled trial data from one centre,[44,45] three comparative trials and two trials reporting on diagnostic accuracy. Characteristics of these trials are presented in Table 11.

Table 11. Characteristics of axillary sampling trials

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Chetty, 2000[44]	UK	RCT-prospective Level II - intervention	466	Operable breast cancer ≤4cm Median age: 54yrs	Axillary node sample n:234	Level III axillary node clearance n:232	Survival, local recurrence, morbidity
Lambah, 2001[45]	UK	Combined analysis of 2 RCTs Level II – intervention	855	Operable breast cancer (T1-3, N0-1, M0)	Four node sampling plus radiotherapy if node +ve	Level III axillary clearance	Axillary recurrence, survival
Kingsmore, 2005[46]	UK	Comparative-retrospective Level III-2 - intervention	2122 [317 received no axillary surgery]	Invasive breast cancer Median age: 58yrs (25-74yrs)	Axillary node sampling n:627	Axillary clearance n:1178	Recurrence, morbidity
Sinha, 2002[47]	UK	Comparative-retrospective Level III-2 - intervention	734	Invasive breast cancer	Axillary node sample n:384	Axillary clearance n:350	Overall survival, recurrence
Gui, 2005[48]	UK	Comparative-prospective Level III-2 - intervention	168	Breast cancer ≤3cm (TI: 118 pts T2: 50 pts) Median age: 54yrs (27-75yrs)	Sentinel node biopsy → axillary node sampling n:82	Sentinel node biopsy → axillary clearance n:86	Accuracy
Ahlgren, 2002[49]	Sweden	Study of diagnostic accuracy Level III-2 – diagnostic accuracy	415	Operable breast cancer (T0-3, N0-1,M0) Tumour size: 27% 0-10mm, 40% 11-20mm, 19% 21-30mm, 13% >30mm Median age: 24% <50yrs, 76% >50yrs Menopausal status: 27% pre-menopausal, 73% post-menopausal	Five node biopsy	Level I-II axillary dissection (following the five node biopsy)	Accuracy

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Tanaka, 2006[50]	Japan	Study of diagnostic accuracy Level III-2 – diagnostic accuracy	237	Primary breast cancer (stage I – II)	Four node sampling	Axillary clearance (following the four node sample)	Accuracy

Notes: RCT – randomised controlled trial

4.1.2 Overall results

Accuracy of staging

Two trials reported on the accuracy of node sampling in staging the axilla compared to axillary dissection,[49,50] see Table 12. These trials reported that sampling was an accurate method of staging the axilla. Ahlgren et al (2002) reported that sampling five nodes, compared to the first four sampled, did not greatly increase the sensitivity of the technique.[49]

Table 12. Accuracy of node sampling in staging the axilla

Trial	N	Technique	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	FN rate %
Ahlgren, 2002[49]	415	5 node sampling	97.3			98.5		
		4 node sampling*	96.0			97.8		
Tanaka, 2006[50]	237	4 node sampling	93.4	100	100	97.8	98.3	6.5

Notes: FN – false negative; NPV – negative predictive value; PPV – positive predictive value
*if only first four nodes were sampled instead of five

One trial reported on whether the addition of sampling to SNB provided any additional information on staging the sentinel node,[48] see Table 13. Gui *et al* (2005) report that the addition of axillary sampling to sentinel node biopsy does not provide any additional data on staging the sentinel node.[48]

Table 13. Accuracy of node sampling in staging the sentinel node

Trial	N	Technique	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	FN rate %
Gui, 2005[48]	165	SNB→AD	92.3			96.7		7.7
		SNB→AS	100			100		0

Notes: AD – axillary dissection; AS – axillary sampling; FN – false negative; NPV – negative predictive value; PPV – positive predictive value; SNB – sentinel node biopsy

Survival

Two centres report on survival outcomes, see Table 14. Lambah *et al* (2001)[45] report longer term outcomes for those in the Chetty (2000) trial[44] combined with data from patients enrolled in a mastectomy trial in the same centre. Sinha *et al* (2002)[47] stratified absolute survival by prognostic groups (good, moderate, poor) and found no significant differences between the sampled or the clearance group in any of the three groups (p=0.3, 0.8, 0.6 respectively), however they report a trend towards better survival in the sampled groups.

Table 14. Survival outcomes of axillary sampling compared to axillary dissection

First author, year	Median follow-up	Comparison (n)		Disease-free survival			Overall survival		
		Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Chetty, 2000[44]	4.1 years	AS (234)	AD (232)	5yr: 79.1%	5yr: 76.0%	0.68	5yr: 88.6%	5yr: 82.1%	0.2
Lambah, 2001[45]	9.4 years	AS Node –ve (283)	AD Node –ve (260)				5yr: 89.9%; 10yr: 84.6%; 15yr: 70.1%	5yr: 88.5%; 10yr: 77.6%; 15yr: 67.5%	0.36
		AS Node +ve (148)	AD Node +ve (164)				5yr: 76.4%; 10yr: 59.4%; 15yr: 51.7%	5yr: 75.7%; 10yr: 62.1%; 15yr: 51.1%	0.79
Sinha, 2002[47]	65.5 months	AS (384)	AD (350)						NS

Notes: AD – axillary dissection; AS – axillary sample; NS – not significant

Local recurrence

Two centres report on axillary and/or local recurrence, (Chetty 2000[44] and Lambah 2001[45] report results from same centre) see Table 15.

Table 15. Recurrence outcomes of axillary sampling compared to axillary dissection

First author, year	Median follow-up	Comparison (n)		Axillary recurrence			Local recurrence		
		Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Chetty, 2000[44]	4.1 years	AS (234)	AD (232)	7 axilla; 1 axilla + SCF	8 axilla; 0 axilla + SCF	0.94	15	14	0.97
Lambah, 2001[45]	9.4 years	AS Node –ve (283)	AD Node –ve (260)	5yr: 3.3%; 10yr: 6.8%	5yr: 1.6%; 10yr: 1.6%	0.017			
		AS Node +ve (148)	AD Node +ve (164)	5yr: 6.0%; 10yr: 9.4%	5yr: 3.0%; 10yr: 6.6%	0.086			
Kingsmore, 2005[46]	8 years	AS (627)	AD (1178)	Overall: 10%; node –ve: 7%; node +ve: 23%	Overall: 4%; node –ve: 2%; node +ve: 6%	<0.001; <0.001; <0.001			

Notes: AD – axillary dissection; AS – axillary sample; SCF – supraclavicular fossa

Kingsmore (2005)[46] also reported axillary recurrence stratified by the number of nodes examined, see Table 16.

Table 16. Axillary recurrence of axillary sampling compared to axillary dissection by number of nodes examined

First author, year	Patients	Subgroup	Comparison (n)		Axillary recurrence		
			Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*
Kingsmore, 2005[46]	Node -ve	1-3 nodes excised	AS (107)	AD (42)	9%	5%	
		≥ 4 nodes excised	AS (112)	AD (532)	5%	2%	
	Node +ve	1-3 nodes excised	AS (24)	AD (13)	33%	8%	
		≥ 4 nodes excised	AS (75)	AD (415)	20%	5%	

Notes: AD – axillary dissection; AS – axillary sample

Adverse events

Chetty *et al* (2000)[44] report on morbidity data with impairment of shoulder motion and arm swelling worse in axillary dissection groups compared to axillary sample. No difference was found in shoulder muscle power between the two groups. Impairment of shoulder motion improved over time however arm swelling persisted at three years.

Kingsmore *et al* (2005)[46] report that rates of lymphoedema were similar between those who had axillary sampling and those who had axillary clearance (5% vs. 6%, respectively). However the addition of radiotherapy to either of the surgical procedures increased the incidence of lymphoedema.

4.2 Discussion

Two non-randomised trials using axillary dissection as the reference standard reported that four node sampling was an accurate method for staging breast cancer.[49,50] The sampling of an additional node (Swedish five node sample technique compared to four node sampling) was found by Ahlgren (2002)[49] to add very little to the sensitivity of the technique (<2% improvement). The five node technique was also compared to axillary dissection and was found to be equivalent.

The addition of four node sampling to sentinel node biopsy, showed sampling provided no additional information to stage the axilla.[48]

Pooled randomised trial data showed no significant difference in 15-year overall survival between axillary sampling and axillary dissection.[45] For node negative women, significantly higher rates of axillary recurrence were observed in the axillary sampling group.[45] While higher rates were also observed in node positive women, this difference was not statistically significant.

Kingsmore (2005)[46] showed in a large retrospective, but non-randomised study, an increased axillary recurrence rate for sampling in node negative patients compared with axillary clearance (9% vs. 5%; p<0.001) when fewer than 4 nodes were sampled (5% vs. 2%; p=0.052). This diminished

when four or more nodes were sampled. For node positive patients, there was a large difference in recurrence rates between women who received sampling alone compared to axillary clearance, however this disappeared when radiotherapy was added.

5 Optimal extent of axillary dissection

5.1 Results

5.1.1 Description of studies

Two RCTs were identified investigating varying levels of axillary dissection, one which compares level I and level III dissection, the other compares level II with level III dissection (Table 17).

Non-randomised, descriptive trials investigated the difference between varying levels of dissection (Table 17) or numbers of excised nodes (Table 18).

Table 17. Study characteristics of levels of dissection trials

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Tominaga, 2004[51]	Japan	RCT Level II - intervention	1209	Breast cancer stage II (T2 N0 or T2 N1a, excluding N1b) Age:<40yrs: 115pts, 41-50yrs: 447 pts, 51-60yrs: 313pts, 61-70yrs: 253pts, >71yrs: 71pts Menopausal status: premenopausal: 567pts postmenopausal: 620pts	Level II dissection n:604	Level III dissection n:605	Survival, disease free survival, morbidity
Kodama, 2006[52]	Japan	RCT Level II - intervention	514	Breast cancer (T1-3, N0, N1a, N1b) Mean age: 51.6yrs vs. 50.6yrs Menopausal status: premenopausal: 125 vs. 131 postmenopausal: 131 vs. 127	Level I dissection n:256	Level III dissection n:258	Survival, recurrence, morbidity, distribution of nodes
Chua, 2002[53]	Australia	Descriptive study	320 dissections in 308 patients	Invasive breast cancer (T1-3, N0-1, M0) Median tumour size 18mm (2-85mm) Median age: 52yrs (20-92yrs)	Level III dissection (level I & II dissection levels marked intraoperatively)	N/A	Number involved nodes, distribution on nodes in each level
Iyer, 2000[54]	USA	Descriptive study – mathematical model	1652	Breast cancer (T1: 1155pts T2: 497pts) Median age: 55yrs (22-89yrs)	Axillary dissection (>10 nodes examined)	N/A	Accuracy, number of nodes excised
Kuru, 2006 [55]	Turkey	Retrospective cohort Level III-3 - prognosis	798	Invasive breast cancer (T1-3) Median age: 47yrs (24-76yrs) Menopausal status: premenopausal: 54% postmenopausal: 46%	Level I ± level II dissection n:530	Level III (± level II ± level I) dissection n:268	Number of nodes removed, number involved nodes
Saha, 2000[56]	USA	Descriptive study	302	Invasive breast cancer (T1: 96pts, T2: 169pts, T3: 18pts) Median age: 56yrs (24-89yrs)	Level I/II/III dissection	N/A	Level of surgery, nodes retrieved, number positive nodes

Notes: N/A – not applicable

Table 18. Study characteristics – numbers of nodes dissected

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Axelsson, 2000[57]	Denmark	Retrospective cohort Level III-3 - prognosis	4771	Invasive breast cancer ≤ 1cm 64% low-risk patients, clinically node-negative , grade I	Axillary dissection (level I/II)	Number of nodes removed	Nodes retrieved, positive nodes identified
Somner, 2004[58]	UK	Descriptive study	520	Invasive breast cancer with complete level III dissection performed	Level III dissection	N/A	Node retrieved, positive nodes identified
Schaapveld, 2004[59]	Netherlands	Retrospective cohort Level III-3 - prognosis	4715	Invasive breast cancer Median age: 60yrs (49-71yrs)	Axillary dissection	Number of nodes removed	Node retrieved, positive nodes identified

Notes: N/A – not applicable

5.1.2 Overall results

The two RCTs report on the impact of differing levels of dissection on survival, recurrence and morbidity.[51,52] The remaining trials report on the number of positive nodes identified with regards to levels of dissection or numbers of nodes excised.

Survival

Table 19. Survival outcomes of varying levels of axillary dissection

First author, year	Median follow-up	Comparison (n)		Disease-free survival			Overall survival		
		Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Tominaga, 2004[51]	7.2 years	Level II (604)	Level III (605)	5yr: 84.1%; 10yr: 73.3%	5yr: 84.5%; 10yr: 77.8%	5yr: 0.756* 10yr: 0.666*	5yr: 92.1%; 10yr: 86.6%	5yr: 92.5%; 10yr: 85.7%	5yr: 0.915*; 10yr: 0.931*
Kodama, 2006[52]	9.3 years	Level I (256)	Level III (258)	5yr: 83.1%; 10yr: 74.1%	5yr: 84.7%; 10yr: 76.6%	NS	5yr: 94.5%; 10yr: 87.8%	5yr: 93.6%; 10yr: 89.6%	NS

Notes: NS – not significant
* Intention-to-treat analysis

Local recurrence

Table 20. Recurrence outcomes of varying levels of axillary dissection

First author, year	Median follow-up	Comparison (n)		Axillary recurrence			Local recurrence		
		Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Tominaga, 2004[51]	7.2 years	Level II (604)	Level III (605)	19 (3.1%)*	14 (2.3%)*		114 (18.9%)**	108 (17.9%)**	0.646
Kodama, 2006[52]	9.3 years	Level I (256)	Level III (258)	1 (0.39%)	0	NS	13 (5.08%)	15 (5.81%)	NS

Notes: NS – not significant
* lymph node recurrence; ** any recurrence

Adverse events

Operation-related morbidity and post-surgical complications are reported in Tables 21 and 22, respectively.

Table 21. Operation-related morbidity of levels of dissection

First author, year	Comparison (n)		Duration of surgery (min)			Mean blood loss (ml)		
	Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Tominaga, 2004[51]	Level II (604)	Level III (605)	133	145	<0.001	216	250	0.001
Kodama, 2006[52]	Level I (256)	Level III (258)	60.5	77.0	<0.0001	48.1	62.1	<0.0001

Table 22. Post-surgical complications of levels of dissection

First author, year	Comparison (n)		Arm oedema			Shoulder disturbance		
	Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Kodama, 2006[52]	Level I (256)	Level III (258)	5.5%	5.8%	NS	8.2%	8.5%	NS

Notes: NS – not significant

The Tominaga RCT reported no significant differences between level II or level III axillary dissection with respect to arm pain, motor function, social functioning or pectoralis major muscle atrophy at 6, 12, 18 or 24 months after surgery.[51]

Number of reported positive nodes

Chua *et al* (2002)[53] reported on a cohort of patients who had level III dissection and examined the difference on the number of positive nodes identified if only level I or level II had been performed.

Similarly, Saha *et al* (2000)[56] reported the difference of the lymph node status detected from level I, II or III dissection. If only level I had been performed compared to level I/II, 15.9% patients' lymph node status would have been down-categorised. When level I/II/III was performed, 4.3% patients would have had their lymph node status up-categorised compared to level I/II dissection.

Table 23. Positive nodes identified by varying levels of dissection

First author, year	Level of dissection/number of nodes excised	Number (%) positive nodes					% positive nodes
		0	1-3	≥ 4	4-9	≥ 10	
Kuru, 2006[55]	1-10 nodes		76 (73)	28 (27)			
	11-15 nodes		136 (68)	64 (32)			
	16-20 nodes		100 (56)	80 (44)			
	21-25 nodes		68 (41)	98 (59)			
	≥26 nodes		84 (57)	64 (43)			
Schaapveld, 2004[59]	<6 nodes	176 (72)	61 (25)	9 (4)			
	6-9 nodes	769 (63)	339 (28)	121 (10)			
	10-14 nodes	1198 (61)	452 (23)	313 (16)			
	15-19 nodes	508 (57)	211 (24)	177 (20)			
	≥20 nodes	217 (46)	107 (23)	148 (31)			

First author, year	Level of dissection/number of nodes excised	Number (%) positive nodes					% positive nodes
		0	1-3	≥ 4	4-9	≥ 10	
Somner, 2004[58]	1-5 nodes 6-10 nodes 11-15 nodes 16-20 nodes 21-25 nodes 26-30 nodes						{33} {50} {58} 68 {67} {66}
Chua, 2002[53]	Level I dissection Level II dissection Level III dissection		97 (30) 94 (29) 92 (29)	44 (14) 48 (15) 51 (16)			
Saha, 2000[56]	Level I dissection Level I/II dissection Level I/II/III dissection	182 169 166	75 65 64		30 36 33	15 32 39	

Notes: Figures in {braces} estimated by authors from graphs presented in original paper

Axelsson (2000)[57] reports that four or more positive nodes were identified in 5% of cases. If 15 or more nodes were examined, this increased to 8%.

Iyer *et al* (2000)[54] report a mathematical model to predict the accuracy of detecting positive nodes based on the number of nodes excised. Approximately 20 nodes need to be excised to estimate up to three positive nodes with 90% probability of accuracy.

5.2 Discussion

The previous guidelines recommended a level I/II axillary dissection.[1]

In this current, updated search period there were two randomised trials identified. Neither trial found a difference for DFS or OS between level II and level III dissection[51] or level I and level III dissection.[52] Both trials found longer operation times and more blood loss for level III, but no differences in arm oedema or shoulder movement following dissection.

The non-randomised data during the updated search period demonstrated the differences in the number of nodes retrieved at all levels. The addition of level III does improve node retrieval somewhat.

The number of nodes to be excised for maximum accuracy was estimated to be approximately 20.

6 Prognostic significance of nodal involvement

6.1 Results

This question was divided into four sub-questions regarding nodal involvement:

a) Prognostic significance of number of excised nodes.
b) Prognostic significance of ratio of positive to excised nodes.
c) Prognostic significance of number of uninvolved nodes.
d) Sentinel node involvement as a predictor of further axillary involvement.

6.1.1 Description of studies

Nineteen trials were identified which investigated the prognostic significance of the number of excised nodes, the ratio of positive to excised nodes and/or the number of uninvolved nodes. Nine trials were identified which investigated sentinel node involvement as a predictor of further axillary involvement. Characteristics of these trials are presented in Table 24.

Number of nodes excised

Thirteen trials reported on how the number of nodes that were excised during dissection impacted on survival and/or recurrence. The numbers of nodes excised were examined either by grouping numbers of nodes together or analysing as a continuous variable. Trials compared varying numbers of excised nodes. In trials where all patients had node negative disease, total number of nodes excised = total number of uninvolved nodes.

Ratio of positive nodes to nodes dissected (P/D ratio)

Eleven trials report on the effect of the ratio of positive nodes to the number of nodes dissected, this will be referred to as the P/D ratio. Patients were divided into groups by quartile or by ratio. The median P/D ratio ranged from 7% to 21%.

Number of uninvolved nodes

Five trials investigated the effect of the number of uninvolved nodes on survival and recurrence.

Prediction of further nodal involvement

Some trials were identified which investigated the predictive value of sentinel nodes in detecting non-sentinel node involvement. The literature search strategy was not designed to identify these articles therefore the articles discussed may not represent a comprehensive list of all articles on this topic. Variables which were considered independent predictors of further axillary involvement on multivariate analysis in individual papers were reported.

Table 24. Study characteristics – prognostic significance of nodal involvement

First author, year	Location	Study design	N	Population	Intervention	Nodal involvement examined	Outcomes
Salama, 2005[60]	USA	Retrospective cohort Level III-3 - prognosis	1927	Local-regional breast carcinoma Node negative Median tumour size 1.5cm (0.1-7cm) vs. 2.5cm (0.1-15cm) Median age: 57yrs (22-89yrs) vs. 56yrs (23-89yrs)	Breast-conservation cohort n:1094 Mastectomy cohort n:833	Number of nodes excised	Survival, disease free survival
Mersin, 2003[61]	Turkey	Retrospective cohort Level III-3 - prognosis	270	Stage I or II Node-negative invasive breast cancer Tumour size <5cm Median age: 49yrs Pre- and postmenopausal	Modified radical mastectomy and complete axillary dissection	Number of nodes excised Patients who had lymph nodes <18 n:152 Patients who had lymph nodes >18 n:118	Survival, disease free survival
Megale Costa, 2004[62]	Brazil	Case series-prospective Level IV - prognosis	168	Breast cancer T stage: T1: 9%, T2: 64%, T3: 27% Clinical node status: mean 1 positive node (0-5) Median age: 50yrs (43-57yrs)	Adjuvant chemotherapy following lymph node excision	Ratio positive nodes to dissected nodes	Disease free survival, relapse
Kuru, 2006[63]	Turkey	Retrospective cohort Level III-3 - prognosis	801	Invasive breast cancer patients with T1-3 tumour and positive axillary lymph node Tumour size: <2cm: 17%, 2.1-5cm: 59%, >5cm: 24% Age: <35yrs: 14%, >35yrs: 86% Menopausal status: premenopausal: 54%, postmenopausal: 46%	Modified radical mastectomy	Nodes removed, Ratio positive nodes to dissected nodes	Survival
Camp, 2000[64]	USA	Retrospective cohort Level III-3 - prognosis	290	Node negative breast carcinoma Tumour size >2cm: 48% Age: <50yrs: 32%, >50yrs: 68%	Modified radical mastectomy (79%) Partial breast resection (21%)	<20 lymph nodes n:67 >20 lymph nodes n:223	Survival, uninvolved nodes

First author, year	Location	Study design	N	Population	Intervention	Nodal involvement examined	Outcomes
Shahar, 2004[65]	USA	Case series-retrospective Level IV - prognosis	339	Invasive breast cancer with one to three positive SLNs T stage: T1: 256pts vs. 54pts, T2: 9pts vs. 20pts Median age: 53yrs (29-88yrs) vs. 52yrs (27-72yrs)	Surgery first n:265 Neoadjuvant chemotherapy n:74	N/A	Sentinel node prediction of nodal involvement
Schaapveld, 2006[66]	Netherlands	Retrospective cohort Level III-3 - prognosis	5314	Invasive breast carcinoma	Mastectomy or breast conserving therapy and axillary dissection	Nodes examined, number of positive nodes	Survival
Truong, 2005a	Canada	Retrospective cohort Level III-3 - prognosis	542	T1–T2 breast cancer (T1: 44.8%, T2: 55.2%) 1-3 positive nodes Age: <45yrs: 17%, >45yrs: 83%	Mastectomy and adjuvant systemic therapy and axillary dissection without radiotherapy	Nodes examined, ratio of positive nodes to dissected nodes	Recurrence, survival
Truong, 2007[67]	Canada	Two cohorts – single arms of RCTs Level II - prognosis	544 (British Columbia n:82; MD Anderson Cancer Centre n:462)	Stage II or III breast cancer 1-3 positive nodes	Mastectomy and axillary dissection without radiotherapy	Ratio of positive nodes to dissected nodes	Recurrence
Van der Wal, 2002[68]	Netherlands	Retrospective cohort Level III-3 - prognosis	453	Stage I or II breast cancer Node negative or positive Mean age: 65.6yrs (29-92yrs)	Mastectomy or breast conserving therapy and radiotherapy and axillary dissection	Nodes examined, ratio of positive nodes to dissected nodes	Survival, metastases
Vinh-Hung, 2004[69]	International	Retrospective cohort Level III-3 - prognosis	83686	Invasive breast cancer (T1-2) Node negative (69%) or positive	Axillary dissection	Ratio of positive nodes to dissected nodes	Survival
Voordeckers, 2004[70]	Belgium	Retrospective cohort Level III-3 - prognosis	810	Breast cancer (T stage: T1: 29%, T2: 53%, T3: 9%, T4: 9%) Node positive Age: <50yrs: 33.5%, >50yrs: 66.5%	Local surgery (76% mastectomy, 24% breast conserving therapy) and axillary dissection	Ratio of positive nodes to dissected nodes	Survival

First author, year	Location	Study design	N	Population	Intervention	Nodal involvement examined	Outcomes
Weir, 2002[71]	UK	Retrospective cohort Level III-3 - prognosis	2278	Invasive breast cancer (T1-3) Tumour size: median 1.5cm (0.1-8cm) Node-negative Median age: 62yrs (19-89yrs)	Node negative without systemic therapy n:1468 Node negative with systemic therapy n:810	Excised nodes	Survival, relapse
Fortin, 2006[72]	Canada	Retrospective cohort Level III-3 - prognosis	1372	Node-positive breast cancer (T1–T2)	Breast conserving surgery with (n:477) or without radiotherapy (n:904)	Ratio of positive nodes to dissected nodes	Recurrence
Axelsson, 2000[57]	Denmark	Retrospective cohort Level III-3 - prognosis	4771	Invasive breast cancer with tumour size less than 10 mm	Mastectomy and axillary dissection (level I/II)	Excised nodes	Survival, relapse
Kamath, 2001[73]	USA	Case series-retrospective Level IV - prognosis	101	Invasive breast cancer (T1–T3)	Sentinel node biopsy plus axillary dissection	N/A	Sentinel node prediction of nodal involvement
Cserni, 2001[74]	Hungary	Retrospective cohort Level III-3 - prognosis	111	Primary operable breast cancer Median tumour size 2.3cm (0.1-6cm)	Sentinel node biopsy	Number of positive nodes	Sentinel node prediction of nodal involvement
Wada, 2006[75]	Japan	Case series-retrospective Level IV - prognosis	185	Breast cancer stage 0-II (T1b: 8pts, T1c: 61pts, T2: 116pts) Mean age: 52.6yrs Menopausal status: premenopausal 91pts, postmenopausal 94pts	Sentinel node biopsy plus axillary dissection	N/A	Sentinel node prediction of nodal involvement
Yu, 2005[76]	Taiwan	Case series Level IV - prognosis	286	Breast cancer T0-II Tumours <3cm (T stage: <1cm: 19.7%, 1-2cm: 40.3%, 2-3cm: 40%) Mean age: 44.3yrs (23-88yrs) Clinically node negative	Sentinel node biopsy plus axillary dissection	N/A	Sentinel node prediction of nodal involvement

First author, year	Location	Study design	N	Population	Intervention	Nodal involvement examined	Outcomes
Wong, 2000[77]	USA	Case series-retrospective Level IV - prognosis	722	Stage I-II invasive breast cancer (T1: 455pts, T2: 267pts) Age: <49yrs: 407pts, >50yrs 315pts Clinically node negative	Axillary dissection with ≥6 nodes removed	N/A	Sentinel node prediction of nodal involvement
Katz, 2006[78]	USA	Case series-retrospective Level IV - prognosis	224	Invasive breast cancer Sentinel node positive Tumour size: <1cm: 12%, 1.1-2cm: 44%, 2.1-5cm: 41%, >5cm: 3% Age: <40yrs: 9%, 41-69yrs: 79%, >70yrs: 12%	Sentinel node biopsy plus axillary dissection	N/A	Sentinel node prediction of nodal involvement
Karlsson, 2007[79]	International	Prospective cohort Level II - prognosis	6660	Breast cancer T1-3 Node negative or positive Tumour size: <2cm: 41%, >2cm: 55%, unknown: 4% Age: <40yrs: 12yrs, 40-59yrs: 61%, >60yrs: 27% Menopausal status: premenopausal: 53%, postmenopausal: 47%	Axillary dissection with ≥5 nodes removed	Uninvolved nodes	Survival
Kingsmore, 2003[80]	UK	Retrospective cohort Level III-3 - prognosis	4627	Invasive breast cancer Median age: 58yrs (25-74yrs)	Axillary surgery and with number of nodes stated	Excised nodes	Survival
Tan, 2005[81]	USA	Case series-retrospective Level IV - prognosis	86	Primary invasive breast cancer T stage: T1: 63%, T2: 37% Sentinel node positive Median age: 53.5yrs (31-84yrs)	Axillary dissection	N/A	Sentinel node prediction of further nodal involvement
Blancas, 2006[82]	Europe	Retrospective cohort Level III-3 - prognosis	1606	Pathologically node negative T1-T3 invasive breast cancer	Axillary dissection	Number of axillary lymph nodes examined	Survival

Notes: NA – not applicable

6.1.2 Overall results

Survival

Number of nodes excised

Six trials reported that smaller numbers of excised nodes were associated with reduced survival. However, four trials reported the opposite, with smaller numbers of excised nodes associated with improved survival,[61,64,70,83] two of which were statistically significant (using a larger cut-off for categorising the numbers of excised nodes).[61,64]

Weir *et al* (2002)[71] report that shorter overall survival was associated with fewer nodes removed (p=0.03). Fewer nodes removed was also associated with decreased regional relapse-free survival (p=0.01).

Axelsson *et al* (2000)[57] report that dissecting 1–9 nodes compared to ≥10 nodes was associated with decreased survival at 10 years, however this was not significant (p=0.06). Patients with 1–9 nodes dissected compared to ≥10 nodes dissected had significantly decreased 10-year relapse-free survival (p=0.0001).

Schaapveld *et al* (2006)[66] report that in patients with 1–3 positive nodes, examining less than 10 nodes resulted in significantly lower 5-year overall survival compared to examining 10 or more nodes (78.8% vs. 83.2%, p=0.008). Overall survival did not differ between number of nodes examined in node-negative patients or where ≥4 nodes were positive.

Table 25. Survival outcomes by number of nodes excised

First author, year	Nodal status	Nodes excised subgroups	Disease-free survival	p value	Overall survival	p value
Kingsmore, 2003[80]	Node -ve	i) 1-3 ii) ≥4			i) HR: 1.31 (95% CI: 1.07,1.60) ii) HR: 1	<0.01
	Node +ve	i) 1-3 ii) ≥4			i) HR: 1.85 (95% CI: 1.54,2.21) ii) HR: 1	<0.001
Axelsson, 2000[57]	Node -ve	i) 1-9 ii) ≥10	i) 5yr: 81%; 10yr: 71%† ii) 5yr: 88%; 10yr: 78%††	0.0001	i) decreased	0.06
Schaapveld, 2006[66]	1-3 +ve nodes	i) <10 ii) ≥10			i) 5yr: 78.8%* ii) 5yr: 83.2%*	0.008
Van der Wal, 2002[68]	Node -ve	i) <14 ii) ≥14			i) HR: 1 ii) HR: 0.40 (95% CI: 0.20,0.79)	0.03

First author, year	Nodal status	Nodes excised subgroups	Disease-free survival	p value	Overall survival	p value
Weir, 2002[71]	Node -ve	Continuous scale			Decreased when fewer nodes excised	0.03
Truong, 2005a[83]**	Node +ve	i) ≤10 ii) >10			i) 10yr: 60.3% ii) 10yr: 58.4%	0.51
Kuru, 2006[63]	Node +ve	i) ≤15 ii) >15			i) HR: 1 ii) HR: 0.62 (95% CI: 0.48,0.79)	<0.001
Voordeckers, 2004[70]	Node +ve	i) ≤15 ii) >15			i) HR: 0.84 (95% CI: 0.60,1.16) ii) HR: 1	0.28
Millis, 2002[84]	Node -ve	Continuous scale		0.8605†		
Mersin, 2003[61]	Node -ve	i) ≤18 ii) >18	i) 5yr: 92.5%; RR: 1 ii) 5yr: 70%; RR: 3.2 (95% CI: 1.7,5.9) ‡	<0.0001 ; 0.0005‡	i) 5yr: 98.3% RR: 1 ii) 5yr: 86.7% RR: 3.1 (95% CI: 1.2,8.5) ‡	0.009; 0.03‡
Camp, 2000[64]	Node -ve	i) <20 ii) ≥20			i) 5yr: 96.3% ii) 5yr: 84.7%	0.0007
Salama, 2005[60]	Node -ve – mastectomy	i) <4 ii) 4-9 iii) 10-20 iv) >20	i) 10yr: 70% ii) 10yr: 65% iii) 10yr: 79% iv) 10yr: 81%	0.0012		
	Node -ve – breast conservation	i) <4 ii) 4-9 iii) 10-20 iv) >20	i) 5yr: 90% ii) 5yr: 91% iii) 5yr: 92% iv) 5yr: 95%	0.07		
Blancas, 2006[82]	Node -ve	i) <6 ii) ≥6	i) 5yr: 82%; 10yr: 63% ii) 5yr: 86%; 10yr: 74%	0.014†		

Notes: *for patients with 1-3 positive nodes; **univariate analysis; † recurrence-free survival; ‡ multivariate analysis

Axelsson *et al* (2000)[57] also report that when ≥15 lymph nodes were removed the 5 years recurrence free survival was 87% and the 5 years survival was 93%.

Ratio of positive nodes to nodes dissected (P/D ratio)

Six trials reported that higher ratios of positive to dissected nodes were associated with reduced survival, see Table 26.

Megale Costa *et al* (2004)[62] report that patients with a ratio of positive to dissected nodes >30% has a significantly decreased disease-free survival compared to those with a ratio <30%.

Table 26. Survival outcomes by P/D ratio

First author, year	Median P/D ratio	Ratio subgroups	Disease-free survival	p value	Survival	p value
Kuru, 2006[63]	19%	i) ≤10% ii) >10-25% iii) >25%			i) HR: 1 ii) HR: 2 (95% CI: 1.39,2.88) iii) HR: 3.8 (95% CI: 2.74,5.50)	<0.001 <0.001
Megale Costa, 2004[62]	7%	i) 0% ii) 0-7% iii) 2-28% iv) 30-100%	i) 13.8% relapse ii) 17.2% relapse iii) 17.2% relapse iv) 51.7% relapse	<0.001		
Truong, 2005a[83]	18.7%	i) ≤10% ii) >10% iii) ≤20% iv) >20% v) ≤25% vi) >25%			i) 10yr: 64.6% ii) 10yr: 56.2% iii) 10yr: 62.9% iv) 10yr: 49.4% v) 10yr: 62.6% vi) 10yr: 43.4%	i) vs. ii): 0.03 iii) vs. iv): 0.002 v) vs. vi): <0.0001
Van der Wal, 2002[68]	20%	i) <20% ii) ≥20%			i) HR: 1 ii) HR: 2.1 (95% CI: 1.20,3.66)	<0.01
Voordeckers, 2004[70]	21%	i) ≤10% ii) 11-50% iii) >50%			i) HR: 0.54 (95% CI: 0.33,0.87) ii) HR: 1 iii) HR: 2.32 (95% CI: 1.64,3.30)	0.01 <0.0001
Vinh-Hung, 2004[69]		Continuous scale			Higher ratio associated with higher mortality HR: 1.015 (95% CI: 1.013, 1.017)	

Notes: CI – Confidence Interval; HR – Hazard Ratio; P/D – positive nodes to nodes dissected

Number of uninvolved nodes

Karlsson *et al* (2007)[79] reported that the number of uninvolved nodes has no impact on survival in node negative patients. However, for patients who were node positive, increasing numbers of uninvolved nodes were involved with improved survival, see Table 27.

Vinh-Hung *et al* (2004)[69] reported that the number of uninvolved nodes had no impact on survival for node negative or node positive patients.

Table 27. Survival outcomes by number of uninvolved nodes.

First author, year	Nodal status	Nodes uninvolved subgroups	Disease-free survival	p value	Survival	p value
Karlsson, 2007[79]	Node -ve pre-menopause	i) 1-10 ii) 11-14 iii) 15-18 iv) ≥19			i) 10yr: 76% ii) 10yr: 76.9% iii) 10yr: 81.7% iv) 10yr: 80.5%	0.63
	Node -ve post-menopause	i) 1-10 ii) 11-14 iii) 15-18 iv) ≥19			i) 10yr: 75.2% ii) 10yr: 76.5% iii) 10yr: 76.7% iv) 10yr: 79.5%	0.53
	Node +ve pre-menopause	i) 0-5 ii) 6-9 iii) 10-14 iv) ≥15			i) 10yr: 40% ii) 10yr: 57.7% iii) 10yr: 62.1% iv) 10yr: 67.6%	<0.0001
	Node +ve post-menopause	i) 0-5 ii) 6-9 iii) 10-14 iv) ≥15			i) 10yr: 31.3% ii) 10yr: 49.9% iii) 10yr: 59.2% iv) 10yr: 61.4%	<0.0001
Vinh-Hung, 2004[69]	Node -ve	i) <20 ii)≥20			i) {93%} ii) {92.7%}	
	Node +ve	i) <20 ii)≥20			i) {82%} ii) {81.3%}	

Notes: HR – Hazard Ratio; RR – Relative Risk. Figures in {braces} calculated by authors

6.1.3 Local recurrence

Number of nodes excised

Weir *et al* (2002)[71] and Axelsson *et al* (2000)[57] reported that axillary relapse rates were higher when fewer nodes were examined (p<0.001). Weir *et al* (2002)[71] also reported that having fewer nodes removed was also associated with increased regional relapse (p=0.01) but was not significantly associated with local or systemic relapse.

Table 28. Recurrence by number of nodes excised

First author, year	Nodal status	Nodes excised subgroups	Axillary recurrence	p value	Locoregional recurrence	p value
Weir, 2002[71]	Node -ve	Continuous scale	Higher when fewer nodes were examined	<0.001		NS
Axelsson, 2000[57]	Node -ve/+ve	i) 1-9 ii) ≥10	i) 1.3% ii) 0.4%	<0.001		
Truong, 2005a[83]*	Node +ve	i) ≤10 ii) >10			i) 10yr: 18.6% ii) 10yr: 15.2%	0.16
Mersin, 2003[61]	Node -ve	i) ≤18 ii) >18			i) 5.9%** ii) 27.1%**	<0.0001

Notes: NS – not significant
*univariate analysis data; ** local or distant relapse

Ratio of positive nodes to nodes dissected (P/D ratio)

Megale Costa *et al* (2004)[62] report that in a multivariate analysis, only the P/D ratio was an independent predictor of relapse (p<0.001). Two other trials reported higher P/D ratios were associated with higher rates of locoregional or axillary recurrence, Table 29.

Table 29. Recurrence by P/D ratio

First author, year	Median P/D ratio	Ratio subgroups	Axillary recurrence	p value	Locoregional recurrence	p value
Truong, 2005a[83]	18.7%	i) ≤10% ii) >10% iii) ≤20% iv) >20% v) ≤25% vi) >25%			i) 10yr: 11.6% ii) 10yr: 22.1% iii) 10yr: 14% iv) 10yr: 27.7% v) 10yr: 13.9% vi) 10yr: 36.7%	i) vs. ii): 0.02 iii) vs. iv): 0.001 v) vs. vi): <0.0001
Fortin, 2006[72]	25%	i) <40% ii) ≥40%	i) 1.54% ii) 4.5%	0.007		

Notes: P/D – positive nodes to nodes dissected

Number of uninvolved nodes

Table 30. Recurrence by number of uninvolved nodes

First author, year	Nodal status	Nodes involved subgroups	Axillary recurrence	p value	Locoregional recurrence	p value
Karlsson, 2007[79]	Node -ve pre-menopause	i) 1-10 ii) 11-14 iii) 15-18 iv) ≥19	NR		i) 10yr: 14.7% ii) 10yr: 11.7% iii) 10yr: 12.3% iv) 10yr: 10.9%	0.66
	Node -ve post-menopause	i) 1-10 ii) 11-14 iii) 15-18 iv) ≥19	NR		i) 10yr: 11.6% ii) 10yr: 8.4% iii) 10yr: 8.0% iv) 10yr: 6.2%	0.12
	Node +ve pre-menopause	i) 0-5 ii) 6-9 iii) 10-14 iv) ≥15	NR		i) 10yr: 31.2% ii) 10yr: 23.8% iii) 10yr: 21.6% iv) 10yr: 18.2%	<0.0001
	Node +ve post-menopause	i) 0-5 ii) 6-9 iii) 10-14 iv) ≥15	NR		i) 10yr: 31.2% ii) 10yr: 23.2% iii) 10yr: 18.1% iv) 10yr: 14.8%	<0.0001

Notes: NR – not reported

6.1.4 Prediction of axillary lymph node involvement

The following factors were most often reported as statistically significant predictors of further nodal involvement on multivariate analysis, see Table 31:

- Primary tumour size
- Lymphovascular invasion (LVI)
- Size of sentinel node metastases
- Number of positive sentinel nodes.

Table 31. Predictors of further axillary involvement

First author, year		**Characteristics***					
	Primary tumour size	*Histology (ductal vs. lobular)*	*LVI*	*Drainage*	*SN metastatic size*	*Number of positive SNs*	*Positive SN ratio*
Yu, 2005[76]	**<0.001**	0.139	0.051		**0.001**	**<0.001**	
Wong, 2000[77]	**0.03**		**<0.01**				
Shahar, 2004[65]	0.653		**0.005**	**0.031**	0.146	**0.013**	
Tan, 2005[81]						**0.014**	**0.030**
Katz, 2006[78]		**0.002**	**0.008**		**<0.001**	**0.003**	
Kamath, 2001[73]	**<0.005**				**<0.001**		
Wada, 2006[75]	**0.013**		**<0.001**		**<0.001**		
Truong, 2007[67]						0.14	0.06

Notes: LVI – lymphovascular invasion; SN – Sentinel Node.
*(statistically significant factors p<0.05)

Cserni *et al* (2001)[74] report that sentinel node metastatic size, location of sentinel node metastases and primary tumour size were predictors of axillary metastases.

Tan *et al* (2005)[81] reports that sentinel node involvement is associated with positive non-sentinel node involvement.

Vinh-Hung *et al* (2004)[69] report that the percentage of involved nodes is a useful indicator of nodal involvement in node positive patients.

6.2 Discussion

a) Prognostic significance of the number of excised nodes

There is conflicting evidence from 13 studies regarding the impact on survival of smaller numbers of nodes being excised, with studies showing significant results in both directions. Each study reports on different comparisons of number of nodes making interpretation difficult. However, the results for

axillary relapse are more consistent, although there are fewer studies examining this.[57,71] These show that having fewer nodes removed is associated with increased axillary relapse.

b) Prognostic significance of the ratio of positive to excised nodes (P/D ratio)

All six trials examining this question found a higher ratio of positive to dissected nodes had a decreased survival. The P/D ratio may also be an independent predictor of relapse.[62]

c) Prognostic significance of uninvolved nodes

For node negative patients, the number of uninvolved nodes does not impact on survival or locoregional recurrence.[79] For patients who are node positive, one study reported that an increased number of uninvolved nodes led to decreased recurrence and improved survival.[79]

d) Sentinel node involvement as a predictor of further axillary involvement

The following factors were most often reported as statistically significant predictors of further nodal involvement on multivariate analysis, see Table 31:

- Primary tumour size
- Lymphovascular invasion (LVI)
- Size of sentinel node metastases
- Number of positive sentinel nodes.

7 Long term outcomes of axillary dissection

7.1 Results

7.1.1 Description of studies

In reviewing the literature for this question it became clear that the original research question should be modified to examine the benefits of axillary treatment vs. no axillary treatment, and would therefore include studies of axillary dissection alone vs. no axillary treatment, as well as axillary irradiation alone vs. no axillary treatment.

Only randomised controlled trials (RCTs) were included in this question, due to the body of evidence available.

Two RCTs investigated axillary dissection compared to no further axillary treatment.[85,86] Two RCTs investigated axillary irradiation/radiotherapy including the axilla compared to no further axillary treatment.[87,88] One RCT provided information on both axillary dissection vs. no further axillary treatment and radiotherapy including the axilla vs. no further axillary treatment[89] (Tables 32 and 33).

For the purposes of reporting results 'axillary irradiation' refers to either radiotherapy to the axilla only or radiotherapy which included targeting the axilla as well as other regional areas. Details on how radiotherapy was given are in Table 33.

Table 32. Study characteristics of axillary dissection vs. no axillary treatment trials

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Fisher, 2002[89]	USA	RCT Level II - intervention	Total: 1665 Subgroup: 727	Primary operable breast cancer Subgroup: clinically node negative Low-risk	Mastectomy with axillary dissection (n:362)	Mastectomy without axillary dissection (n:365)	Survival, disease free survival, distant disease free survival, relapse free survival
Rudenstam, 2006[85]	US	RCT Level II - intervention	473	Clinically node-negative operable breast cancer Tumour size: <2cm 56%, >2cm 42% Age ≥60yrs: median 74yrs (60-91yrs) Low-risk	Primary surgery plus axillary clearance and tamoxifen n:234 NB 32% had breast radiotherapy	Primary surgery without axillary clearance followed by tamoxifen n:239	Survival, disease free survival, recurrence, QoL
Martelli, 2005[86]	Italy	RCT Level II - intervention	219	Early breast cancer and clinically negative axillary nodes Tumour size ≤2cm Age 65 to 80 years: median 70yrs Low-risk	Conservative breast surgery with axillary dissection and tamoxifen n:109	Conservative breast surgery without axillary dissection and tamoxifen n:110	Survival, recurrence

QoL – quality of life; RCT – randomised controlled trial

Table 33. Study characteristics of axillary irradiation vs. no axillary treatment trials

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Fisher, 2002[89]	USA	RCT Level II - intervention	Total: 1665 Subgroup: 717	Primary operable breast cancer Subgroup: clinically node negative Low-risk	Mastectomy with irradiation (n:352) Radiation therapy was administered with supervoltage equipment. Women with negative nodes received 5000 rad in 25 fractions; node-positive women received an additional boost of 10-20 Gy. A dose of 45 Gy in 25 fractions was delivered to both the internal mammary nodes and the supraclavicular nodes. Tangential fields were used to treat the chest wall with 50 Gy in 25 treatments.	Mastectomy alone (without axillary dissection) (n:365)	Survival, disease free survival, distant disease free survival, relapse free survival

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Veronesi, 2005[87]	Italy	RCT Level II - intervention	435	Breast cancer with no palpable axillary nodes Tumour size ≤1.2cm (<0.5cm 13.1%, 0.6-1cm 61.4%, 1.1-1.2cm 16.3%, 1.2-1.5cm 9.2%) Age >45yrs (<55yrs 40.2%, 56-65yrs 44.6%, >65yrs 15.2%) Low-risk	Breast conservation plus axillary radiotherapy n:221 All patients received breast treatment with two opposed tangential fields, non-parallel to avoid posterior beam divergence and minimise lung and heart irradiation. The fields were designed to avoid irradiation of the axillary nodes. Axillary radiotherapy patients only: The axillary region was irradiated with two parallel opposed fields (antero-posterior postero-anterior). The limits of the irradiation fields were: the upper border was the upper margin of the clavicle; the lateral border was the anterior axillary fold; the medial border was the margin of the vertebral bodies; and the inferior border was 0/5cm from the upper limit of the tangential breast fields. The total dose was 50 Gy in 25 fractions of 2 Gy each. The isocentre point was at the midplane or slightly anterior. The shoulder joint was properly shielded.	Breast conservation alone n:214 All patients received breast treatment with two opposed tangential fields, non-parallel to avoid posterior beam divergence and minimise lung and heart irradiation. The fields were designed to avoid irradiation of the axillary nodes.	Survival, recurrence
Morgan, 2002[88]	UK	RCT Level II - intervention	76	Operable (stage I or II) primary breast cancer, tumour grade III, with at least one node involved High-risk	Mastectomy and axillary sampling (3 nodes) followed by irradiation to the ipsilateral supraclavicular fossa and axilla n:36 Patients given radiotherapy were treated on a linear accelerator, with an 8 MV X-ray field encompassing the axilla and ipsilateral supraclavicular fossa. To the lower edge of this field an 8 MeV electron field was matched, the other limits of which were chosen to encompass the area previously covered by breast tissue. A dose of 45 Gy was given in 15 fractions to both fields.	Mastectomy and axillary sampling n:40	Survival, disease free survival, recurrence, morbidity

Notes: RCT – randomised controlled trial

7.1.2 Overall results

Survival

Survival outcomes for patients receiving axillary treatment (either axillary dissection or axillary irradiation) compared to no axillary treatment are presented in Table 34.

No statistically significant differences in DFS and OS were reported between those who had axillary dissection and those who received no further treatment.

Veronesi *et al* (2005)[87] reported more deaths in the group which received no further treatment compared to those who had axillary irradiation (p=0.005). Morgan *et al*[88] report improved DFS in those who received axillary irradiation compared to those who had no further treatment (p=0.043).

Table 34. Survival outcomes for axillary treatment compared to no axillary treatment

First author, year	Median follow-up	Comparison (n)		Disease-free survival			Overall survival		
		Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Axillary dissection vs. no axillary treatment									
Fisher, 2002[89]	25 years	AD (362)*	No AT (365)*	25yr: 22%	25yr: 21%		25yr: 25%	25yr: 26%	0.72
Rudenstam, 2006[85]	6.6 years	AD (234)	No AT (239)	6yr: 67%	6yr: 66%	0.69	6yr: 75%	6yr: 73%	0.77
Martelli, 2005[86]	5.1 years	AD (109)	No AT (110)				13 deaths	8 deaths	0.25
Axillary irradiation vs. no axillary treatment									
Fisher, 2002[89]	25 years	AI (352)*	No AT (365)*	25yr: 17%	25yr: 21%		25yr: 19%	25yr: 26%	0.60
Veronesi, 2005[87]	5.3 years	AI (221)	No AT (214)	5yr: 96.9%	5yr: 95.1%	0.30	2 deaths	12 deaths	0.005
Morgan, 2002[88]	12 years	AI (36)	No AT (40)	10yr: 39%	10yr: 15%	0.043	10yr: 39%	10yr: 25%	NS

Notes: AD – axillary dissection; AI – axillary irradiation; AT – axillary treatment; NS – not significant
* women with clinically negative nodes

Local recurrence

Table 35. Recurrence outcomes for axillary treatment compared to no axillary treatment

First author, year	Median follow-up	Comparison (n)		Axillary recurrence			Local recurrence		
		Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Axillary dissection vs. no axillary treatment									
Fisher, 2002[89]	25 years	AD (362)*	No AT (365)*	15 (4%)**	23 (6%)**		19 (5%)	26 (7%)	
Rudenstam 2006[85]	6.6 years	AD (234)	No AT (239)	2 (1%)	6 (3%)		9 (4%)	4 (2%)	
Martelli, 2005[86]	5.1 years	AD (109)	No AT (110)	0	2	NR	1	1	NR
Axillary irradiation vs. no axillary treatment									
Fisher, 2002[89]	25 years	AI (352)*	No AT (365)*	15 (4%)**	23 (6%)**		5 (1%)	26 (7%)	
Veronesi, 2005[87]	5.3 years	AI (221)	No AT (214)	1	3	0.295	1	1	0.979
Morgan, 2002[88]	12 years	AI (36)	No AT (40)				10yr: 25%	10yr: 65%	<0.001

Notes: AD – axillary dissection; AI – axillary irradiation; AT – axillary treatment; NR – not reported
* women with negative nodes; ** regional recurrence defined as supraclavicular, subclavicular, internal mammary nodes or ipsilateral axillary recurrence

Adverse events

The International Breast Cancer Study Group (IBCSG) study[85] reported quality of life/morbidity data on axillary dissection vs. no treatment for women over 60 years of age. The doctor reported assessments of the axillary dissection group had worse arm restriction (39% vs. 15%) and pain (23% vs. 7%) at the first post-operative visit, however differences disappeared after that. Arm circumference, lymphoedema and performance of daily activities were not significantly different between the groups. In the patient reported assessments, more restricted use of arm and numbness were worse at first post-operative visit for patients in the axillary dissection group but not after that. The axillary dissection group had a median of 13 nodes removed.

Morgan *et al* (2002)[88] report that two of the 36 irradiated patients reported clinically significant lymphoedema (recorded as mild or moderate). No cases of pulmonary fibrosis or radiation induced brachial plexus damage occurred.

7.2 Discussion

The previous NBCC early breast cancer guidelines[1] concluded that no group could routinely avoid axillary dissection. We therefore searched for updated data on axillary dissection versus no axillary dissection. Two additional trials that embrace the question of axillary treatment (with radiotherapy) versus none were retrieved as well, but were not specifically searched for.

The randomised data shows no OS difference for axillary dissection vs. no axillary dissection in low-risk patients. When treatment of the axilla is considered as dissection or radiotherapy versus no treatment, radiotherapy shows similar results for low-risk patients. The Morgan (2002) data[88] demonstrates that for high-risk disease, there was a trend toward positive impact of radiotherapy on OS. This data also shows that relapses are difficult to treat with >60% of patients who relapse having uncontrolled locoregional disease at death.

8 Axillary dissection alone compared to axillary radiotherapy alone

8.1 Results

8.1.1 Description of studies

Nine studies were identified which investigated axillary dissection alone in comparison with axillary irradiation alone, including four randomised controlled trials and three comparative studies and two retrospective case series. Characteristics of these trials are presented in Table 36.

For the purposes of reporting results ‘axillary irradiation’ refers to either radiotherapy to the axilla only or radiotherapy which included targeting the axilla as well as other regional areas.

Table 36. Study characteristics – axillary irradiation compared to axillary dissection

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Chetty, 2000[44]	UK	RCT Level II - intervention	466	Invasive breast cancer Tumour size ≤4cm Clinical node status: 151 pts vs. 168 pts node negative Age <70yrs (median 54yrs) Menopausal status: 139 pts vs. 144 pts postmenopausal	Axillary node sample with radiotherapy for node positive patients n:234	Level III axillary node clearance n:232	Survival, local recurrence, morbidity
Lambah, 2001[45]	UK	Combined analysis of 2 RCTs Level II – intervention	312	Operable breast cancer T1-3 Node positive	4 node sampling with axillary radiotherapy for node positive patients n:148	Level III axillary clearance n:164 (node positive patients only)	Axillary recurrence, survival
Fisher, 2002[89]	USA	RCT Level II - intervention	1665 Subgroup: 1300	Primary operable breast cancer Node negative or positive Age: ≥50yrs 70%	Mastectomy with irradiation (n:352 node negative; 294 node positive) Radiation therapy was administered with supervoltage equipment. Women with negative nodes received 5000 rad in 25 fractions; node-positive women received an additional boost of 10-20 Gy. A dose of 45 Gy in 25 fractions was delivered to both the internal mammary nodes and the supraclavicular nodes. Tangential fields were used to treat the chest wall with 50 Gy in 25 treatments.	Mastectomy with axillary dissection (n:362 node negative; 292 node positive)	Survival, disease free survival, distant disease free survival, relapse free survival

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Chua, 2001/2002[90,91]	Australia	Comparative-prospective Level III-2 - intervention	1158	Stage I or II breast cancer Clinical node status: N0: 96.9% vs. 93.9%, N1: 2.2% vs. 4.1% Median age: 64yrs (28-86yrs) vs., 48yrs (22-89yrs)	Regional lymphatic irradiation n:229	Axillary surgery n:782	Recurrence, relapse free survival, morbidity
Livsey, 2000[92]	UK	Retrospective cohort Level III-2 - intervention	2277	Breast cancer, 91% stage I, 7% stage II Median age: 54yrs (21-81yrs)	Radiotherapy to the axilla, infraclavicular and supraclavicular fossae n:1191 (52%) Two parallel opposing tangential fields were used to irradiate the whole breast, with a single anterior megavoltage field to irradiate the axilla, infra- and supraclavicular fossae. The regional lymph node field delivered 40 Gy in 15 daily fractions over 3 weeks	Axillary surgery alone n:517 (23%)	Survival, recurrence
Fujimoto, 2004[93]	Japan	Prospective cohort Level III-2 - intervention	1810	Breast cancer T1-2, Tumour size ≤5cm Node negative Median age: 48 yrs (24-87) and 46yrs (25-80yrs) vs. 43yrs (27-65yrs) Menopausal status: premenopausal 64.6% and 64% vs. 87.5%, postmenopausal 35.4% and 36% vs. 12.5%	Axillary radiotherapy n:1437 (Tangential field radiation n:1134; Three field radiation n:303) The maximal dose did not exceed 53 Gy.	Axillary dissection n:80	Survival, recurrence
Louis-Sylvestre, 2004[94]	France	RCT Level II - intervention	658	Invasive breast cancer Tumour size <3cm Node negative Age <70yrs (Mean: 50.6yrs vs. 52yrs) Menopausal status: premenopausal 205pts vs. 186pts, postmenopausal 127pts vs. 140pts	Axillary radiotherapy n:332 All patients received radiotherapy to the breast. Axillary radiotherapy patients: Irradiation to the breast was systematically associated with radiotherapy associated with	Axillary dissection n:326 All patients received radiotherapy to the breast.	Survival, disease free survival, recurrence

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
					radiotherapy to axillary and internal mammary lymph nodes. Axillary nodes received a 50 Gy dose; internal mammary nodes and supraclavicular nodes received a 45 Gy dose.		
Galper, 2000[95]	USA	Case series Level IV - intervention	418	Stage I or II invasive breast cancer (T1: 62% T2: 38%) Node negative Median age: 66yrs (29-88yrs)	Axillary radiotherapy alone n:292	N/A	Recurrence
Hoebers, 2000[96]	Netherlands	Case series-retrospective Level IV - intervention	105	Breast cancer Median tumour size: 20mm (5-50mm) Node negative Median age: 64yrs (38-84yrs) Menopausal status: 3 premenopausal	Breast conserving therapy and radiotherapy to the breast, axilla and supraclavicular lymph node areas	N/A	Survival, disease free survival, recurrence, morbidity

Notes: N/A – not applicable; RCT – randomised controlled trial

8.1.2 Overall results

Survival

No statistically significant survival differences were reported between patients treated with axillary irradiation alone compared to axillary dissection alone, see Table 37.

Table 37. Survival outcomes for axillary irradiation compared to axillary dissection

First author, year	Median follow-up	Comparison (n)			Disease-free survival			Overall survival		
			Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Lambah, 2001[45]	9.4 years	node +ve	AS→ AI (148)	AD (164)				5yr: 76.4%; 10yr: 59.4%; 15yr: 51.7%	5yr: 75.7%; 10yr: 62.1%; 15yr: 51.1%	0.79
Louis-Sylvestre, 2004[94]	15 years	Clinically node -ve	AI (332)	AD (326)	65.5%	64.3%	NS	73.8%	75.5%	NS
Fisher, 2002[89]	25 years	Clinically node -ve	AI (352)	AD (362)	17%	22%		19%	25%	0.38
		Clinically node +ve	AI (294)	AD (292)	12%	13%		14%	14%	0.49
Fujimoto, 2004[93]	13.4 years		AI (1437)	AD (80)				T1 10yr: 92.7%; T2 10yr: 89.1%	T1 10yr: 94.7%; T2 10yr: 92.5%	0.34; 0.34
Galper, 2000[95]	8 years		AI (292)	-	41%					
Hoebers, 2000[96]	3.4 years		AI (105)	-	5yr: 82%			5yr: 83%		

Notes: AD – axillary dissection; AI – axillary irradiation; AS – axillary sample; NS – not significant

Local recurrence

Table 38. Recurrence outcomes for axillary irradiation compared to axillary dissection

First author, year	Median follow-up	Comparison (n)			Axillary recurrence			Local recurrence		
			Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Lambah, 2001[45]	9.4 years	node +ve	AS→AI (148)	AD (164)	5yr: 6.0%; 10yr: 9.4%	5yr: 3.0%; 10yr: 6.6%	0.086			
Louis-Sylvestre, 2004[94]	15 years	Clinically node -ve	AI (332)	AD (326)	3%	1%	0.04	16.3%	17.2%	NS
Fisher, 2002[89]	25 years	Clinically node -ve	AI (352)	AD (362)	15 (4%)*	15 (4%)*		5 (1%)	19 (5%)	
		Clinically node +ve	AI (294)	AD (292)	33 (11%)*	22 (8%)*		3%	8%	
Chua, 2001/2002[90,91]	AI: 9.3 years; AD: 6.6 years		AI (229)	AD (782)	1.3% axilla ± SCF	1.0% axilla ± SCF	NS			
Livsey, 2000[92]	5.9 years		AI (1191)	AD (517)	5yr: 5.9%	5yr: 4.5%				
Fujimoto, 2004[93]	AI: 5.5 years; AD: 13.4 years		AI (1437)	AD (80)	2.4%	1.3%				
Galper, 2000[95]	8 years		AI (292)	-	1% regional			8% local		
Hoebers, 2000[96]	3.4 years		AI (105)	-	2					

Notes: AD – axillary dissection; AI – axillary irradiation; IBC – ipsilateral breast cancer; NS – not significant; SCF – supraclavicular fossa

* regional recurrence defined as supraclavicular, subclavicular, internal mammary nodes or ipsilateral axillary recurrence

Adverse events

Pneumonitis

Chua *et al* (2002)[91] reported that 4% of patients who received radiotherapy to the breast and regional lymphatics (SCF ± axilla) developed symptomatic pneumonitis, this was higher in those who had also received chemotherapy compared to those who did not have chemotherapy, though not statistically significant (8% vs. 3%, p=0.09).

Fujimoto *et al* (2004)[93] reported that radiation-induced pneumonitis occurred in six patients in the dissection group and 26 patients in the radiotherapy group (statistical significance not reported).

Neuropathy

Chua *et al* (2002)[91] reported that a brachial plexus neuropathy developed in 1% of patients given radiotherapy to the breast and regional lymphatics (SCF ± axilla), however these symptoms resolved completely within 30 months.

Lymphoedema

Table 39. Lymphoedema data

First author, year	Comparison (n)		Arm oedema		
	Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*
Chua, 2002[91]	AI (229)	AD (767)	6.1%	9.5%	NS
Chetty, 2000[44]	AS → AI (91)	AD (229)	{0.5%}	4%	
Fujimoto, 2004[93]	AI (1437)	AD (80)	0.07%	19%	<0.0001
Galper, 2000[95]	AI (292)	-	1%		
Hoebers, 2000[96]	AI (105)	-	4% subjective; 11% objective		

Notes: AD – axillary dissection; AI – axillary irradiation; AS – axillary sample; NS – not significant. Data in {braces} estimated by review authors

Quality of life

No information was reported on quality of life outcomes.

8.2 Discussion

The previous NBCC early breast cancer guidelines[1] recommended surgery as routine treatment (level I evidence), and added that axillary radiotherapy was equivalent (limited level II data).

The data is strongest from the randomised trials suggesting that axillary dissection and radiotherapy are equivalent in terms of OS and local control, with no overall survival differences observed.

One trial reported higher recurrence in the axillary radiotherapy arm for node negative patients.[94] In another trial, a similar result approached significance in node positive patients.[45] Other trials reported no significant difference in axillary or local recurrence between the groups.

Arm oedema appears to be higher in the axillary dissection alone patients, however this was often not statistically significant.

9 Axillary radiotherapy after axillary dissection

This question is divided into two subsections:

- What are the benefits of axillary radiotherapy after axillary dissection i.e. axillary dissection plus axillary radiotherapy compared to axillary dissection alone?
- Who should have irradiation to the axilla after axillary dissection i.e. should it be dependent on number of nodes involved and are there any other subgroups who may benefit?

9.1 Results

9.1.1 Axillary dissection + axillary radiotherapy versus axillary dissection alone

Description of studies

Two overview/recommendation papers were identified, a consensus statement from the National Institutes of Health[97] and clinical practice guidelines from the Canadian Medical Association.[98]

Two systematic reviews were identified.[99,100]

The remaining original trials were divided into those which compared axillary dissection plus radiotherapy to axillary dissection alone (7a), and those which provided some information on who may most likely benefit from axillary irradiation (7b). Some trials were identified which provided limited morbidity data on axillary dissection alone or with axillary irradiation. In many trials all patients were given breast irradiation (i.e. trials compared axillary dissection + breast irradiation and axillary dissection + breast & axillary irradiation) (Tables 40 and 44).

For the purposes of reporting results 'axillary irradiation' refers to either radiotherapy to the axilla only or radiotherapy which included targeting the axilla as well as other regional areas.

Table 40. Study characteristics - irradiation after axillary dissection

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Overgaard 2007,[101] Nielson 2006[102,103]	Denmark	Combined subgroup analysis from 2 RCTs Level II - intervention	3083	Pre- and post-menopausal high risk patients High-risk patients were defined as patients who were node positive and/or a T3 or T4 tumour and/or skin or deep fascia invasion	Mastectomy and axillary dissection followed by adjuvant systematic therapy and radiotherapy n:1538 Radiotherapy consisted of: 48-50Gy in 22-25 fractions in 5 weeks to the chest wall and regional lymph nodes (internal mammary nodes, peri-clavicular nodes, and the axilla)	Mastectomy and axillary dissection followed by adjuvant systematic therapy only n:1545	Survival, recurrence
Rutqvist, 2006[104]	Sweden	2 RCTs Level II - intervention	Premenopausal n:547	High risk patients All patients were required to have node-positive disease or a tumour diameter exceeding 30 mm	Mastectomy and axillary dissection followed by radiotherapy n:256 Radiotherapy target volume included the chest wall, axilla, supraclavicular fossa and the ipsilateral internal mammary nodes down to the fifth intercostals space.	Mastectomy and axillary dissection followed by adjuvant chemotherapy n:291	Survival, recurrence morbidity
			Postmenopausal n:679	High risk patients All patients were required to have node-positive disease or a tumour diameter exceeding 30 mm	Mastectomy and axillary dissection followed by radiotherapy n:148 Radiotherapy target volume included the chest wall, axilla, supraclavicular fossa and the ipsilateral internal mammary nodes down to the fifth intercostals space.	Mastectomy and axillary dissection followed by adjuvant chemotherapy n:182	

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Ragaz, 2005[105]	Canada	RCT Level II – intervention	318	Premenopausal patients with lymph node positive breast cancer treated by modified radical mastectomy and adjuvant chemotherapy	Mastectomy and axillary dissection followed by locoregional radiation therapy n:164 Radiation therapy was given by a five-field technique including the chest wall, axilla, supraclavicular field and internal mammary chain.	Mastectomy and axillary dissection n:154	Survival, recurrence, toxicity
Livsey, 2000[92]	UK	Retrospective cohort Level III-2 intervention	2277	Breast cancer, 91% stage I, 7% stage II, pre- and post-menopausal, median age: 54.3yrs (21-81yrs)	Axillary surgery followed by radiotherapy to the axilla, infraclavicular and supraclavicular fossae n:474 (21%) Two parallel opposing tangential fields were used to irradiate the whole breast, with a single anterior megavoltage field to irradiate the axilla, and infraclavicular and supraclavicular fossae.	Axillary surgery alone n:517 (23%)	Survival, recurrence
Grills, 2003[106]	USA	Prospective cohort Level III-2 - intervention	1500	Stage I–II breast cancer, pre- and post-menopausal	Breast conserving therapy followed by breast and regional lymphatic irradiation n:191 A nodal region was considered to have been irradiated if a minimal dose of 45 Gy was prescribed to the supraclavicular and Level III axillary lymph nodes or to the full axilla at a depth of 3–5 cm	Breast conserving therapy followed by breast irradiation n:1309	Survival, disease free survival, recurrence, toxicity

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Chua, 2002[91]	Australia	Retrospective cohort Level III-2 intervention	1158	Stage I–II breast cancer, pre- and post-menopausal, median age: 51yrs (22-89yrs)	Axillary surgery and regional lymphatic irradiation including the axilla n:136 Radiotherapy to axilla and supraclavicular fossa with or without internal mammary chain	Axillary surgery only n:782	Recurrence, relapse free survival, morbidity
Fodor, 2002[107]	Hungary	Prospective cohort Level III-2 intervention	249	T1/2 breast cancer and one to three positive nodes, pre- and post-menopausal	Mastectomy and axillary dissection followed by locoregional radiotherapy n:175 Radiotherapy to the chest wall and to the regional lymph nodes including the ipsilateral axilla, internal mammary region, and supraclavicular fossa.	Mastectomy and axillary dissection n:74	Recurrence
Lee, 2005[108]	Canada	Prospective cohort Level III-2 intervention	233	Women aged 70 years or over (median 75yrs) with high-risk breast cancer (tumours >5 cm or ≥4 positive axillary nodes)	Mastectomy followed by post-mastectomy radiotherapy n:147 Radiotherapy to the chest wall and regional nodes	Mastectomy only n:86	Survival, recurrence
Chang, 2007[109]	USA	Prospective cohort Level III-2 intervention	63	Breast cancer patients (stage II-IIIB) with ≥10 positive lymph nodes, pre- and post-menopausal	Mastectomy followed by systemic therapy and radiotherapy and supplemental axillary radiotherapy n:35 The chest wall, internal mammary nodes, and supraclavicular nodes were treated in every patient	Mastectomy followed by systemic therapy and radiotherapy without supplemented axillary radiotherapy n:28	Survival, disease free survival, recurrence

First author, year	Location	Study design	N	Population	Intervention	Comparator	Outcomes
Kwan, 2002[110]	Canada	Case series Level IV intervention	744 (467 respondents)	Invasive or in situ breast cancer	Axillary radiotherapy after dissection n:129 Radiation was given to the supraclavicular and axillary nodes in high-risk patients (more than three positive nodes, involved nodes greater than 2 cm in diameter, or presence of significant extranodal extension)	Axillary dissection n:240	Lymphoedema
Ververs, 2001[111]	Netherlands	Case series Level IV intervention	400	Breast cancer patients treated with axillary lymph node dissection (ALND), mean age: 59yrs (26-88yrs)	Axillary or supraclavicular radiotherapy after dissection n:68 Irradiation of the axilla and the supraclavicular region was recommended for patients with inadequate ALND, extracapsular extension of tumour growth or nodal involvement in the apex of the axilla.	Axillary dissection and no irradiation n:112	Nature and severity of arm complaints
Johansen 2000[112]	Denmark	Prospective cohort Level III-2 intervention	266	Stage I–IIIA breast cancer, pre- and postmenopausal Axillary radiotherapy was given for high-risk patients (tumour diameter >5 cm, and/or invasion to the skin or pectoral fascia, and/or involvement of axillary lymph nodes)	Axillary dissection and breast radiotherapy and radiotherapy to regional lymph nodes (axilla, supraclavicular fossa, infraclavicular region and internal mammary chain) for high-risk patients n:121	Axillary dissection and breast radiotherapy n:145	Treatment morbidity

Notes: RCT – randomised controlled trial

Overall results

The Canadian Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, 2004,[98] state that:

- Locoregional post-mastectomy radiotherapy (PMRT) is recommended for women with an advanced primary tumour (≥5cm, or tumour invasion of the skin, pectoral muscle or chest wall).
- Locoregional PMRT is recommended for women with 4 or more positive axillary lymph nodes.
- The role of PMRT in women with 1–3 positive axillary lymph nodes is unclear.
- Locoregional PMRT is generally not recommended for women with tumours <5cm or who have negative axillary nodes.
- Other patient, tumour and treatment characteristics, may affect locoregional control, but their use in specifying additional indications for PMRT is unclear.

Survival

The systematic review by Gebski *et al* (2006)[99] found that when looking at patients who received optimal post-mastectomy radiotherapy (40-60Gy in 2-Gy fractions or as a biologically equivalent dose to the chest wall, axillary lymph nodes, and the supraclavicular fossa with or without the internal mammary lymph nodes) had an improved survival (2.9% absolute survival increase) up to 10 years, compared with non-optimal radiotherapy (inadequate or excessive radiotherapy or inappropriate target volume). The review by Van de Steene *et al* (2000)[100] reported that when current techniques are used and treatment is given with standard fractionation, overall survival can be improved by surgical adjuvant radiotherapy.

Survival outcomes of axillary dissection plus axillary irradiation compared to axillary dissection alone from the original trials are presented in Table 41. One trial reported improved DFS in the radiotherapy arm.[105] Two trials reported reduced DFS with the addition of axillary irradiation to axillary dissection.[104,106] Two randomised trials reported improved OS in node positive patients.[101,105] The Danish Breast Cancer Cooperative Group (DBCG) 82 b&c randomised trials[101] found a survival benefit was seen in those who received axillary radiotherapy in both patients with 1–3 positive nodes and four or more positive nodes. One trial showed reduced OS in the axillary dissection plus axillary irradiation group.[106] The remaining trials did not report any statistically significant survival differences.

Table 41. Survival outcomes of axillary dissection + axillary irradiation compared to axillary dissection alone.

First author, year	Median follow-up	Patients	Comparison (n)		Disease-free survival			Overall survival		
			Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Overgaard, 2007[101] DBCG 82 b&c	18 years	≥ 8 nodes excised; node +ve	AD → AI (563)	AD (589)				15yr: 39%	15yr: 29%	0.015
		1-3 +ve nodes	AD → AI (276)	AD (276)				15yr: 57%	15yr: 48%	0.03
		≥4 +ve nodes	AD → AI (287)	AD (313)				15yr: 21%	15yr: 12%	0.03
Rutqvist, 2006[104]	18.4 years	Pre-menopausal high risk	AD → AI (256)	AD (291)	HR: 1.25	HR: 1	0.037	HR: 1.21	HR: 1	0.10
		Post-menopausal high risk	AD → AI (308)	AD (371)	HR: 0.92	HR: 1	0.28	HR: 0.91	HR: 1	0.38
Ragaz, 2005[105]	20 years	Premenopausal; node +ve	AD → AI (164)	AD (154)	35%	25%	0.009	47%	37%	0.03
Grills, 2003[106]	8.1 years		AD → AI (191)	AD (1309)	5yr: 68%; 10yr: 52%	5yr: 87%; 10yr: 73%	<0.001	5yr: 79%; 10yr: 61%	5yr: 91%; 10yr: 80%	<0.001
Lee, 2005[108]	5.5 years	≥70 years old	AD → AI (147)	AD (86)				10yr: 31.2%	10yr: 27.4%	0.32
Fodor, 2003[107]	189 months		AD → AI (175)	AD (74)				15yr: 52%	15yr: 41%	0.23
Chang, 2007[109]	9.5 years		AD → AI (35)	AD (28)	10yr: 36%	10yr: 39%		10yr: 41%	10yr: 31%	

Notes: AD – axillary dissection; AI – axillary irradiation; HR – hazard ratio.
*Recurrence-free survival

Local recurrence

Table 42. Recurrence outcomes of axillary dissection + axillary irradiation compared to axillary dissection alone.

First author, year	Median follow-up	Patients	Comparison (n)		Axillary recurrence			Locoregional recurrence		
			Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*	*Exp*	*Ctrl*	*p value*
Nielsen, 2006[102] DBCG 82 b&c	12.7 years		AD → AI (1538)	AD (1545)	1.2%	13.1%	<0.001	5%	30%	<0.001
Overgaard, 2007[101] DBCG 82 b&c	18 years	≥ 8 nodes excised; node +ve	AD → AI (563)	AD (589)				15yr: 6%	15yr: 37%	<0.001
		1-3 +ve nodes	AD → AI (276)	AD (276)				15yr: 4%	15yr: 27%	<0.001
		≥4 +ve nodes	AD → AI (287)	AD (313)				15yr: 10%	15yr: 51%	<0.001
Rutqvist, 2006[104]	18.4 years	Pre-menopausal	AD → AI (256)	AD (291)	2%	2%		14%	24%	0.048
		Post-menopausal	AD → AI (308)	AD (371)	1%	7%		12%	26%	<0.001
Ragaz, 2005[105]	20 years	Premenopausal node +ve	AD → AI (164)	AD (154)				10%	28%	<0.001
Grills, 2003[106]	8.1 years		AD → AI (191)	AD (1305)				5yr: 7%; 10yr: 8%	5yr: 1%; 10yr: 2%	<0.001
Livsey, 2000[92]	5.9 years		AD → AI (474)	AD (517)	7.3%	4.5%				
Lee, 2005[108]	5.5 years	≥70 years old	AD → AI (147)	AD (86)				10yr: 15.5%	10yr: 28%	0.04
Fodor, 2003[107]	189 months		AD → AI (175)	AD (74)				12%	23%	0.03
Chang, 2007[109]	9.5 years		AD → AI (35)	AD (28)	0	1 (4%)		1 (3%)	7 (25%)	

Notes: AD – axillary dissection; AI – axillary irradiation.
*Ipsilateral breast recurrence

Grills *et al* (2003)[106] analysed results by lymph node status and found that regional nodal irradiation reduced the 10-year actuarial rate of any regional nodal failure from 11% to 2% (p<0.041), and the rate of axillary failure from 5% to 0% (p<0.027) in patients with more than four positive nodes.

The DBCG 82 b&c randomised trials found that locoregional recurrence benefit more pronounced in radiotherapy group in patients with four or more positive nodes compared to those with one to three positive nodes.

Adverse events

Lymphoedema was reported more often in patients receiving both axillary dissection and axillary irradiation compared to those receiving axillary dissection alone, see Table 43.

Table 43. Lymphoedema following axillary dissection + axillary irradiation compared to axillary dissection alone.

First author, year	**Subgroup**	**Comparison (n)**		**Arm oedema**		
		Exp	*Ctrl*	*Exp*	*Ctrl*	*p value*
Ragaz, 2005[105]		AD → AI (164)	AD (154)	9.1%	3.2%	0.035
Chang, 2007[109]		AD → AI (35)	AD (28)	40%	14%	0.029
Grills, 2003[106]		AD → AI (191)	AD (1305)	10%	7%	
Kwan, 2002[110]		AD → AI (129)	AD (240)	30%	5%	<0.05
Johansen, 2000[112]	0-9 nodes removed	AD → AI (81)	AD (115)	12%*	4%*	
	≥10 nodes removed	AD → AI (40)	AD (30)	28%*	7%*	

Notes: AD – axillary dissection; AI – axillary irradiation; OR – odds ratio.
*Defined as arm volume change ≥ 2cm

Ververs *et al* (2001)[111] reported that patients with axillary or supraclavicular irradiation had more swelling or oedema compared to those who had no irradiation (OR: 3.57; 95% CI: 1.66 to 7.69).

Johansen *et al* (2000)[112] reported that overall 15% of patients reported pain (axilla/arm) grades 1-3. The percentage of patients reporting pain at these levels was highest at 28% in the group who had 10 or more nodes removed and had radiotherapy.

Quality of life

No information was reported on quality of life outcomes.

9.1.2 Subgroups suitable for axillary irradiation

Description of studies

None of these studies were specifically designed to address the question of which factors are prognostic of the impact of nodal irradiation on patients-relevant efficacy outcomes. The studies relate to the prognostic value of selected factors more broadly, not about how they influence the efficacy of nodal irradiation. The studies describe factors associated with locoregional recurrence, and therefore suggest suitability for the use of radiotherapy (which may or may not target the axilla) after dissection. Factors commonly considered were age, tumour size and stage, lymphovascular invasion (LVI), and hormone receptor status.

Table 44. Characteristics of trials suggesting patients suitable for irradiation

First author, year	Location	Study design	N	Population	Intervention	Prognostic factors considered	Outcomes
Truong, 2004[113]	Canada	Descriptive (for prognostic factors)	94	T1-2, node negative invasive breast cancer with positive surgical margins	Mastectomy with radiotherapy n:41 Mastectomy only n:53	Age, histology, tumour size, grade, LVI, oestrogen receptor status, number of nodes removed, systemic therapy	Survival, recurrence
Truong, 2005b[114]	Canada	Descriptive* (for prognostic factors)	821	T1-T2 breast cancer and one to three positive nodes	Mastectomy and axillary dissection without locoregional radiotherapy	Age, histologic findings, tumour location, size, and grade, lymphovascular invasion status, oestrogen receptor (ER) status, margin status, number of positive nodes, number of nodes removed, percentage of positive nodes, and systemic therapy use	Isolated LRR and LRR with or without simultaneous distant recurrence
Truong, 2005c[115]	Canada	Descriptive* (for prognostic factors)	1505	T1-T2, node negative breast cancer with clear surgical margins	Mastectomy without radiotherapy	Histologic features (ductal, lobular, other), T stage (T1, T2), histologic grade (1, 2, 3); LVI status, ER status, and number of axillary nodes removed (≤5, 6–10, 11–15, ≥16; and ≤10 vs. >10)	Locoregional recurrence, distant recurrence, breast cancer-specific survival, overall survival
Pejavar, 2006[116]	USA	Descriptive (for prognostic factors)	1920	Stage I and II invasive breast cancer	Axillary dissection followed by radiotherapy to the breast alone if pathologically node-negative (n:984), or to the breast and supraclavicular nodes if pathologically node-positive (n:346). In patients not undergoing axillary dissection, supraclavicular and axillary nodes were irradiated, with or without an additional internal mammary field n:590	Age, nodal status, race, histology, tumour stage, axillary dissection, margin status, family history, ER and PR status	Survival, recurrence

First author, year	Location	Study design	N	Population	Intervention	Prognostic factors considered	Outcomes
Strom, 2005[117]	USA	Descriptive (for prognostic factors)	1031	Stage I-IIIA breast cancer	Mastectomy with level I-II dissection without radiotherapy	Tumour stage, tumour size, number of involved nodes, number of nodes examined, LVI, percentage nodes, size of largest node, extranodal extension	Survival, disease free survival, recurrence
Yildirim, 2007[118]	Turkey	Descriptive (for prognostic factors)	502	T1-2 node negative invasive breast cancer, tumour size <5cm	All patients had level I, II and III axillary dissection without radiotherapy	Age, menopausal status, tumour size, histological type, histological grade, LVI, ER status, PR status, p53 status, cErbB2 status	Primary: locoregional and distant recurrence Secondary: survival, disease free survival
Stranzl, 2004[119]	Austria	Descriptive (for prognostic factors)	183	T1–3 breast cancer and1–3 involved axillary lymph nodes Median age: 58yrs (28–86)	BCT or mastectomy, axillary dissection, followed by irradiation to breast n:146 (79.8%) or chest wall n:37 (20.2%)	Age, tumour location, T-stage, tumour size, histologic grade, oestrogen receptor status, margin status, LVI, systemic therapy	Nodal failure, survival
Cheng, 2002[120]	Taiwan	Descriptive (for prognostic factors)	110	T1 or T2 primary breast cancer and 1–3 histologically involved axillary lymph nodes	Modified radical mastectomy with level I/II dissection without adjuvant radiotherapy	Age, menopausal status, medial/lateral quadrant of tumour location, T stage, tumour size, hormone receptor status, nuclear grade, extracapsular extension, LVI, and number of involved axillary nodes) and treatment-related factors (chemotherapy and hormonal therapy)	Locoregional recurrence, survival
Gruber, 2005[121]	Switzerland	Descriptive (for prognostic factors)	254	Node-positive breast cancer Median age: 56yrs (26–87) Extracapsular spread n:167; No extracapsular spread n:87	All patients had segmental mastectomy with axillary node dissection (level I, II, ± III); or modified radical mastectomy. All patients were irradiated locally, 78 patients had periclavicular and 74 axillary irradiation	Number of positive nodes, age, ER status, PR status, T-stage, grade, extracapsular spread, systemic therapy, radiotherapy	Relapse free survival
Floyd, 2006[122]	USA	Descriptive (for prognostic factors)	70	Node-negative breast cancer Tumour size ≥5cm (mean 6cm) Median age: 50yrs (29–87)	Patients were treated with mastectomy and adjuvant systemic therapies but without radiotherapy	Age, menopausal status, tumour size, LVI, number of lymph nodes sampled, systemic therapy, and hormone receptor status	Survival, disease free survival, locoregional failure

Notes: AD – axillary dissection; BCT – breast conserving treatment; ER – oestrogen receptor; LRR – locoregional recurrence; LVI – lymphovascular invasion ; PR – progesterone receptor; SCF – supraclavicular fossa. *These trials have been reported elsewhere in the review with a different study design.

Overall results

Survival

For the studies which reported overall survival rates, 5-year overall survival rates were more than 80%,[119,120,122] 10-year overall survival rates ranged from 58%[114] to 91%.[118]

Local recurrence

Rates of locoregional recurrence in the studies ranged from 1%[114] to 19%,[117] with chest wall and axilla being the most commonly reported sites of recurrence.

Predictors of locoregional recurrence

Commonly reported predictors of locoregional recurrence are reported in Table 45. Primary tumour size, lymphovascular invasion and number of positive nodes were most often reported as significant predictors of locoregional recurrence on multivariate analysis.

Truong *et al* (2005b)[114] report that age <45years, >25% of nodes positive, a medial tumour location and ER-negative status are independent predictors of locoregional recurrence.

Pejavar *et al* (2006)[116] report that young age, non-Caucasian race and pathologic nodal status were associated with increased risk of nodal relapse.

Node negative patients

Truong *et al* (2005c)[115] report that patients with Grade 3 disease and LVI or patients with Grade 3 disease, T2 tumours and no systemic therapy had a locoregional recurrence risk of approximately 20%. Truong *et al* (2004)[113] report that in those treated without post-mastectomy radiotherapy, node negative women with positive margins plus at least one of the following factors: age ≤50year, T2 tumour size, grade III histology, or LVI, locoregional recurrence rates of approximately 20% were observed.

Table 45. Predictors of locoregional recurrence

First author, year	Patients	Characteristics*									
		Age	*Primary tumour size*	*Grade*	*LVI*	*ECE*	*ER status*	*# of +ve nodes*	*P/D ratio*	*# of excised nodes*	*Systemic therapy*
Yildirim, 2007[118]	≤40 yrs		**0.05**		**0.004**						
	>40 yrs		**0.05**	**0.05**	**0.007**						
Floyd, 2006[122]	Tumours >5cm	NS	NS		**0.038**		NS			NS	NS
Pejavar, 2006[116]		**<0.001**		0.055			NS	**<0.001**			
Truong, 2005b[114]	1-3 +ve nodes	**0.001**		0.69	0.31		**0.01**	0.74	**0.05**	0.24	0.92

First author, year	Patients	Characteristics*									
		Age	*Primary tumour size*	*Grade*	*LVI*	*ECE*	*ER status*	*# of +ve nodes*	*P/D ratio*	*# of excised nodes*	*Systemic therapy*
Truong, 2005c[115]	Node – ve	0.92		0.78	**<0.001**		0.48			0.47	**0.01**
Gruber, 2005		0.27				0.62	0.14	**0.007**			0.43
Strom, 2005[117]**					**<0.001**	**0.001**		**<0.001**	**<0.001**		
Stranzl, 2004[119]	1-3 +ve nodes	0.402	**0.004**	0.144	0.164		**0.002**				
Cheng, 2002[120]	1-3 +ve nodes	0.25	**0.006**		0.11	0.25	0.16			0.96	

Notes: ECE – extracapsular extension; LVI – lymphovascular invasion; NS – not significant
*statistically significant factors p<0.05; **univariate analysis of supra/intraclavicular failure

9.2 Discussion

Two systematic reviews indicate that post-mastectomy radiotherapy can improve overall survival somewhat, and have a positive effect on locoregional recurrence rates. However, the addition of radiotherapy also increases the incidence of lymphoedema.

Not all trials report on axillary irradiation only, some trials reported radiation treatment which included the axilla along with chest wall, internal mammary nodes, peri-clavicular nodes etc. Therefore it is difficult to determine the effect that each target area, such as axilla, contributes to outcomes.

The subgroup of patients at high risk of axillary recurrence following axillary dissection is not well defined. Some studies report on predictors for locoregional recurrence and suggest that patients with these factors may be suitable to receive radiotherapy following axillary dissection.

10 Ongoing trials

The following clinical trials websites were searched to identify any additional studies on axillary treatment which have not yet reported.

- Australian Clinical Trials Registry (ACTR) http://www.actr.org.au/
- Clinical Trials.gov http://www.clinicaltrials.gov/
- Current Controlled Trials http://www.controlled-trials.com/
- National Research Register http://www.nrr.nhs.uk/
- National Cancer Institute http://www.cancer.gov/clinicaltrials.

Three randomised trials were identified as ongoing trials with each currently recruiting patients. Details of the trials are presented in Table 46. Both trials are investigating axillary treatment following identification of a positive sentinel node/micrometastases from SNB. Both trials are multicentre randomised trials. The AMAROS trial is being conducted throughout Europe and at November 2006 had recruited 61% of the total number of patients needed for the trial. The IBCSG-23-01 trial is an international trial with two participating centres in Australia. The SNAC II trial is based in Australia and New Zealand and is investigating sentinel node biopsy compared to axillary dissection in a broader group of patients than those examined in SNAC I. There is currently no indication when these trials are likely to report results.

Table 46. Ongoing studies

Title/trial name	Location/s	Status	Participants	Treatment	Objectives
Phase III Randomised Study of Complete Axillary Lymph Node Dissection Versus Axillary Radiotherapy in Sentinel Lymph Node-Positive Women With Operable Invasive Breast Cancer					
EORTC-10981-AMAROS, NCT0001461[123]	France, Italy, Netherlands, Poland, Slovenia, Switzerland, Turkey, UK (Wales)	Currently recruiting	• N=3485 • 1394 SN positive • 2091 SN negative • SNB performed in all patients	**Arm I**: SN –ve patients undergo no further surgery **Arm II**: SN +ve patients undergo complete ALND **Arm III**: SN +ve patients undergo radiotherapy 5 days a week for 5 weeks	Primary outcome: Axillary recurrence rates Secondary outcomes: morbidity, DFS, OS

Title/trial name	Location/s	Status	Participants	Treatment	Objectives
A randomised trial of axillary dissection versus no axillary dissection for patients with clinically node negative breast cancer and micrometastases in the sentinel node.					
CDR0000339581 **IBCSG-23-01** EU-20319 NCT00072293[124]	Australia, Brazil, Denmark, Italy, Peru, Slovenia, Switzerland	Currently recruiting	• N = 1960 • Female • any age • Clinically node negative cancer • Micrometastases in sentinel node	**Arm I**: Surgical resection of primary tumour with ALND **Arm II**: Surgical resection of primary tumour without ALND	Do micrometastases in the sentinel node warrant axillary clearance? Outcomes: DFS,OS, QoL
A randomised phase IIII study to determine in women with early breast cancer whether SN based management increases the risk of loco-regional recurrence and in particular, axillary recurrence, compared with axillary clearance in any subgroup of women					
SNAC II[125]	Australia & New Zealand	Currently recruiting	• N = 1012 • Female • Single or multiple ipsilateral BC • Primary BC may be less than or greater than 3cm	**Arm I:** Sentinel node biopsy with immediate standard axillary clearance **Arm II:** Standard axillary clearance	To determine if sentinel node based management increases the risk of loco-regional recurrence compared with axillary clearance in any subgroup of women Outcomes: OS, DFS

Notes: ALND – axillary lymph node dissection; BC – breast cancer; DFS – disease-free survival; OS – overall survival; QoL – quality of life; SN – sentinel node

Conclusions

Over 100 articles regarding the management of the axilla were included in this systematic review. Seven questions were included in two areas, staging and treatment of the axilla. Eleven randomised controlled trials were identified with information on both staging and treatment of the axilla. Much of the information on the management of the axilla was from non-randomised studies including case series, diagnostic accuracy, prognostic and observational studies.

Surgical staging is the most accurate way to assess axillary node involvement. No survival differences were observed between level III and the other levels of dissection, however longer operation times and more blood loss was reported with level III dissection. Long term data from randomised control trials showed no overall survival difference for axillary dissection or axillary radiotherapy compared to no axillary treatment for low-risk patients. For the randomised trials which compared axillary dissection directly to axillary radiotherapy, no survival differences were observed. In high-risk patients, the addition of radiotherapy which targeted the axilla as well as other regional areas led to decreased rates of locoregional recurrence.

Across the studies included in the systematic review, quality of life outcomes were not reported, in general. The most common adverse effects reported for axillary treatment were increased lymphoedema and arm morbidity. Ongoing trials are investigating axillary treatment for patients with positive sentinel nodes.

Appendix 1 PICO formulation of original research questions

Question 1:	**Non-surgical methods compared to axillary dissection to stage the axilla**

Population: Patients with early breast cancer

Intervention: non-surgical staging techniques including:
- Ultrasound
- Magnetic resonance imaging (MRI)
- Magnetic resonance spectroscopy (MRS)
- Positron-emission tomography (PET)

Comparison: axillary dissection

Outcomes: accuracy of staging (sensitivity, specificity), morbidity

Limits: English language
Published 2000 – 2007

Question 2:	**4-node sampling compared to axillary dissection to stage the axilla**

Population: Patients with early breast cancer

Intervention: 4-node axillary sampling

Comparison: axillary dissection

Outcomes: accuracy of staging (sensitivity, specificity), morbidity

Limits: English language
Published 2000 – 2007

Question 3:	**What is the optimal extent of axillary dissection?** • Level I vs. Level II vs. Level III clearance (related to numbers of node retrieved)

Population: Patients with early breast cancer

Intervention: Level I or II axillary dissection

Comparison: Level III axillary dissection

Outcomes: local recurrence, morbidity

Limits: English language
Published 2000 – 2007

Question 4:	**What is the prognostic significance of the numbers of nodes involved and/or retrieved in axillary dissection?**

Population: Patients with early breast cancer

Intervention: less nodal involvement

Comparison: more nodal involvement

Outcomes: local recurrence, survival

Limits: English language
Published 2000 – 2007

Question 5:	**What are the long-term outcomes of axillary dissection/irradiation vs. no treatment?** - Limit to RCT data

Population: Patients with early breast cancer

Intervention: axillary dissection/irradiation

Comparison: no further treatment

Outcomes: survival, local recurrence, quality of life

Limits: English language
Published 2000 – 2007
Randomised controlled trials

Question 6:	**What are the benefits of axillary dissection alone compared to axillary irradiation alone?**

Population: Patients with early breast cancer

Intervention: axillary irradiation alone

Comparison: axillary dissection alone

Outcomes: survival, local recurrence, toxicity, quality of life

Limits: English language
Published 2000 – 2007

Please note: This search is not limited to node-positive patients, however this population will be analysed separately.

Question 7:

a) What are benefits of radiotherapy after axillary dissection?

- I.e. Axillary dissection + radiotherapy vs. axillary dissection alone

b) Who should have irradiation to the axilla after axillary dissection?

- Regional nodal irradiation vs. no irradiation (post-mastectomy radiotherapy vs. none)
  - Dependent on number of nodes involved?
  - Other subgroups that might benefit – those at high-risk of axillary relapse/recurrence?

Population: Patients with early breast cancer, at high risk of axillary relapse/recurrence

Intervention: axillary dissection followed by radiotherapy/post-mastectomy irradiation

Comparison: axillary dissection followed by no further treatment

Outcomes: survival, local recurrence, toxicity, quality of life

Limits: English language
Published 2000 – 2007

Appendix 2 Search Terms used

Describing	Search Terms
Breast Cancer	(breast neoplasms/ or (breast and (cancer or carcinoma)))
Axilla	(((axilla/) and (lymph node excision)) or ALND or CLND or (axilla and (dissection or clearance or lymphadenectomy)))
Non-surgical methods to stage the axilla (Q1)	((ultrasound) or (MRI or magnetic resonance imaging/ or magnetic resonance imaging) or (magnetic resonance spectroscopy/ or magnetic resonance spectroscopy or MRS) or (PET or positron emission tomography/ positron emission tomography))
Axillary sampling (Q2)	(sampl$ and (axillary or axilla or nodes or node or nodal))
Levels of clearance (Q3)	((level and (clearance or dissection)) or (levels and (clearance or dissection)) or (level I) or (level II) or (level III))
Nodal involvement (Q4)	((((number or percent$ or proportion) and (node or nodes) and (retriev$ or excis$ or involv$)) or (nodal involvement)) and (prognosis/ or prognos$ or predict$))
Randomised controlled trials (Q5)	(Randomized Controlled Trial/ or “randomized controlled trial” or “randomized controlled trials” or “randomised controlled trial$” or “random$” or “random allocation” or “controlled clinical trial” or “controlled trial” or “double blind method” or “single blind method” or (“meta-analysis/” or “meta-analysis” or “meta analysis”) or “systematic review” or “pooled analysis”)
Axillary irradiation (Q6)	((axilla or axillary) and (radiation or radiotherapy or irradiation))
Postmastectomy radiation (Q7)	(((post-mastectomy or postmastectomy or post mastectomy) and (radiation or radiotherapy or irradiation or lymphatic irradiation/ or lymphatic irradiation)) and (((high-risk or high risk) and (relapse or recurrence)) or (neoplasm recurrence, local/)))

Notes: / MeSH term, $ Boolean terms

Appendix 3 NHMRC Levels of Evidence

NHMRC additional levels of evidence and grades for recommendations for developers of guidelines STAGE 2 CONSULTATION Early 2008 – end June 2009[2]

Table 1 NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question (including explanatory notes)

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial[9] • Cohort study • Case-control study • Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study[10] • Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic

reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

[5] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting *et al* 2003).

[6] Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

[7] At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

[8] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[9] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

[10] Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

[11] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer *et al*. 1999; Phillips *et al*. 2001.

References

1. National Breast Cancer Centre. Clinical practice guidelines for the management of early breast cancer. 2nd Edition. Canberra: Commonwealth of Australia 2001.

2. National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra Commonwealth of Australia 2009.

3. Stadnik TW, Everaert H, Makkat S, et al. Breast imaging. Preoperative breast cancer staging: comparison of USPIO-enhanced MR imaging and 18F-fluorodeoxyglucose (FDC) positron emission tomography (PET) imaging for axillary lymph node staging--initial findings. Eur Radiol. 2006;16(10):2153-60.

4. Kvistad KA, Rydland J, Smethurst HB, et al. Axillary lymph node metastases in breast cancer: Preoperative detection with dynamic contrast-enhanced MRI. Eur Radiol. 2000;10(9):1464-71.

5. Murray AD, Staff RT, Redpath TW, et al. Dynamic contrast enhanced MRI of the axilla in women with breast cancer: Comparison with pathology of excised nodes. Br J Radiol. 2002;75(891):220-8.

6. Alvarez S, Anorbe E, Alcorta P, et al. Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. AJR Am J Roentgenol. 2006;186(5):1342-8.

7. Ohta M, Tokuda Y, Saitoh Y, et al. Comparative efficacy of positron emission tomography and ultrasonography in preoperative evaluation of axillary lymph node metastases in breast cancer. Breast Cancer (Tokyo, Japan). 2000;7(1):99-103.

8. Sato K, Tamaki K, Tsuda H, et al. Utility of axillary ultrasound examination to select breast cancer patients suited for optimal sentinel node biopsy. Am J Surg. 2004;187(6):679-83.

9. Nori J, Vanzi E, Bazzocchi M, et al. Role of axillary ultrasound examination in the selection of breast cancer patients for sentinel node biopsy. Am J Surg. 2007;193(1):16-20.

10. Sapino A, Cassoni P, Zanon E, et al. Ultrasonographically-guided fine-needle aspiration of axillary lymph nodes: role in breast cancer management. Br J Cancer. 2003;88(5):702-6.

11. Ciatto S, Brancato B, Risso G, et al. Accuracy of fine needle aspiration cytology (FNAC) of axillary lymph nodes as a triage test in breast cancer staging. Breast Cancer Res Treat. 2007;103(1):85-91.

12. Deurloo EE, Tanis PJ, Gilhuijs KGA, et al. Reduction in the number of sentinel lymph node procedures by preoperative ultrasonography of the axilla in breast cancer.[see comment]. Eur J Cancer. 2003;39(8):1068-73.

13. van Rijk MC, Deurloo EE, Nieweg OE, et al. Ultrasonography and fine-needle aspiration cytology can spare breast cancer patients unnecessary sentinel lymph node biopsy. Ann Surg Oncol. 2006;13(1):31-5.

14. Kuenen-Boumeester V, Menke-Pluymers M, de Kanter AY, et al. Ultrasound-guided fine needle aspiration cytology of axillary lymph nodes in breast cancer patients. A preoperative staging procedure. Eur J Cancer. 2003;39(2):170-4.

15. Podkrajsek M, Music MM, Kadivec M, et al. Role of ultrasound in the preoperative staging of patients with breast cancer. Eur Radiol. 2005;15(5):1044-50.

16. Mathijssen IM, Strijdhorst H, Kiestra SK, Wereldsma JC. Added value of ultrasound in screening the clinically negative axilla in breast cancer. J Surg Oncol. 2006;94(5):364-7.

17. Motomura K, Inaji H, Komoike Y, et al. Gamma probe and ultrasonographically-guided fine-needle aspiration biopsy of sentinel lymph nodes in breast cancer patients. Eur J Surg Oncol. 2001;27(2):141-5.

18. Topal U, Punar S, Tasdelen I, Adim SB. Role of ultrasound-guided core needle biopsy of axillary lymph nodes in the initial staging of breast carcinoma. Eur J Radiol. 2005;56(3):382-5.

19. Krishnamurthy S, Sneige N, Bedi DG, et al. Role of ultrasound-guided fine-needle aspiration of indeterminate and suspicious axillary lymph nodes in the initial staging of breast carcinoma. Cancer. 2002;95(5):982-8.

20. Damera A, Evans AJ, Cornford EJ, et al. Diagnosis of axillary nodal metastases by ultrasound-guided core biopsy in primary operable breast cancer. Br J Cancer. 2003;89(7):1310-3.

21. Brancato B, Zappa M, Bricolo D, et al. Role of ultrasound-guided fine needle cytology of axillary lymph nodes in breast carcinoma staging. Radiologia Medica. 2004;108(4):345-55.

22. Hinson JL, McGrath P, Moore A, et al. The Critical Role of Axillary Ultrasound and Aspiration Biopsy in the Management of Breast Cancer Patients with Clinically Negative Axilla. Ann Surg Oncol. 2007:Epub 7 Aug; doi: 10.1245/s10434-007-9524-3.

23. Mobbs LM, Jannicky EAS, Weaver DL, Harvey SC. The accuracy of sonography in detecting abnormal axillary lymph nodes when breast cancer is present. Journal of Diagnostic Medical Sonography. 2005;21(4):297-303.

24. Lumachi F, Tregnaghi A, Ferretti G, et al. Accuracy of ultrasonography and 99mTc-sestamibi scintimammography for assessing axillary lymph node status in breast cancer patients. A prospective study. Eur J Surg Oncol. 2006;32(9):933-6.

25. Bedrosian I, Bedi D, Kuerer HM, et al. Impact of clinicopathological factors on sensitivity of axillary ultrasonography in the detection of axillary nodal metastases in patients with breast cancer. Ann Surg Oncol. 2003;10(9):1025-30.

26. Couto D, Dias M, Goncalo M, Pinto E, de Oliveira CF. Diagnostic value of ultrasound and color Doppler in identifying axillary lymph node metastases in patients with breast cancer. Eur J Gynaecol Oncol. 2004;25(5):568-70.

27. Byrne AM, Hill AD, Skehan SJ, McDermott EW, O'Higgins NJ. Positron emission tomography in the staging and management of breast cancer. Br J Surg. 2004;91(11):1398-409.

28. Kelemen PR, Lowe V, Phillips N. Positron emission tomography and sentinel lymph node dissection in breast cancer. Clinical Breast Cancer. 2002;3(1):73-7.

29. van der Hoeven JJ, Hoekstra OS, Comans EF, et al. Determinants of diagnostic performance of [F-18]fluorodeoxyglucose positron emission tomography for axillary staging in breast cancer. Ann Surg. 2002;236(5):619-24.

30. Chung A, Liou D, Karlan S, et al. Preoperative FDG-PET for axillary metastases in patients with breast cancer. Archives of Surgery. 2006;141(8):783-8; discussion 8-9.

31. Guller U, Nitzsche EU, Schirp U, et al. Selective axillary surgery in breast cancer patients based on positron emission tomography with 18F-fluoro-2-deoxy-D-glucose: not yet! Breast Cancer Res Treat. 2002;71(2):171-3.

32. Fehr MK, Hornung R, Varga Z, et al. Axillary Staging Using Positron Emission Tomography in Breast Cancer Patients Qualifying for Sentinel Lymph Node Biopsy. Breast Journal. 2004;10(2):89-93.

33. Kumar R, Zhuang H, Schnall M, et al. FDG PET positive lymph nodes are highly predictive of metastasis in breast cancer. Nuclear Medicine Communications. 2006;27(3):231-6.

34. Barranger E, Grahek D, Antoine M, et al. Evaluation of fluorodeoxyglucose positron emission tomography in the detection of axillary lymph node metastases in patients with early-stage breast cancer. Annals of Surgical Oncology. 2003;10(6):622-7.

35. Veronesi U, De Cicco C, Galimberti VE, et al. A comparative study on the value of FDG-PET and sentinel node biopsy to identify occult axillary metastases. Ann Oncol. 2007;18(3):473-8.

36. Lovrics PJ, Chen V, Coates G, et al. A prospective evaluation of positron emission tomography scanning, sentinel lymph node biopsy, and standard axillary dissection for axillary staging in patients with early stage breast cancer.[see comment]. Ann Surg Oncol. 2004;11(9):846-53.

37. Gil-Rendo A, Zornoza G, Garcia-Velloso MJ, et al. Fluorodeoxyglucose positron emission tomography with sentinel lymph node biopsy for evaluation of axillary involvement in breast cancer. Br J Surg. 2006;93(6):707-12.

38. Hubner KF, Smith GT, Thie JA, et al. The Potential of F-18-FDG PET in Breast Cancer. Detection of Primary Lesions, Axillary Lymph Node Metastases, or Distant Metastases. Clin Positron Imaging. 2000;3(5):197-205.

39. Greco M, Crippa F, Agresti R, et al. Axillary lymph node staging in breast cancer by 2-fluoro-2-deoxy-D-glucose-positron emission tomography: Clinical evaluation and alternative management. Journal of the National Cancer Institute. 2001;93(8):630-5.

40. Rieber A, Schirrmeister H, Gabelmann A, et al. Pre-operative staging of invasive breast cancer with MR mammography and/or PET: boon or bunk? Br J Radiol. 2002;75(898):789-98.

41. Yutani K, Shiba E, Kusuoka H, et al. Comparison of FDG-PET with MIBI-SPECT in the detection of breast cancer and axillary lymph node metastasis. J Comput Assist Tomogr. 2000;24(2):274-80.

42. Schirrmeister H, Kuhn T, Guhlmann A, et al. Fluorine-18 2-deoxy-2-fluoro-D-glucose PET in the preoperative staging of breast cancer: comparison with the standard staging procedures. Eur J Nucl Med. 2001;28(3):351-8.

43. Wahl RL, Siegel BA, Coleman RE, Gatsonis CG. Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET Study Group. J Clin Oncol. 2004;22(2):277-85.

44. Chetty U, Jack W, Prescott RJ, Tyler C, Rodger A. Management of the axilla in operable breast cancer treated by breast conservation: a randomized clinical trial. Edinburgh Breast Unit. Br J Surg. 2000;87(2):163-9.

45. Lambah A, Dixon JM, Prescott RJ, et al. Randomised study of axillary clearance versus four node sampling. Eur J Cancer. 2001;37(Suppl 5): 2.

46. Kingsmore DB, Hole DJ, Gillis CR, George WD. Axillary recurrence in breast cancer. Eur J Surg Oncol. 2005;31(3):226-31.

47. Sinha PS, Thrush S, Bendall S, Bates T. Does radical surgery to the axilla give a survival advantage in more severe breast cancer? European Journal of Cancer. 2002;38(11):1474-7.

48. Gui GP, Joubert DJ, Reichert R, et al. Continued axillary sampling is unnecessary and provides no further information to sentinel node biopsy in staging breast cancer. Eur J Surg Oncol. 2005;31(7):707-14.

49. Ahlgren J, Holmberg L, Bergh J, Liljegren G. Five-node biopsy of the axilla: An alternative to axillary dissection of levels I-II in operable breast cancer. European Journal of Surgical Oncology. 2002;28(2):97-102.

50. Tanaka K, Yamamoto D, Kanematsu S, Okugawa H, Kamiyama Y. A four node axillary sampling trial on breast cancer patients. Breast. 2006;15(2):203-9.

51. Tominaga T, Takashima S, Danno M. Randomized clinical trial comparing level II and level III axillary node dissection in addition to mastectomy for breast cancer. Br J Surg. 2004;91(1):38-43.

52. Kodama H, Nio Y, Iguchi C, Kan N. Ten-year follow-up results of a randomised controlled study comparing level-I vs level-III axillary lymph node dissection for primary breast cancer. Br J Cancer. 2006;95(7):811-6.

53. Chua B, Owen UNG, Taylor R, Boyages J. Is there a role for axillary dissection for patients with operable breast cancer in this era of conservatism? ANZ Journal of Surgery. 2002;72(11):786-92.

54. Iyer RV, Hanlon A, Fowble B, et al. Accuracy of the extent of axillary nodal positivity related to primary tumor size, number of involved nodes, and number of nodes examined. Int J Radiat Oncol Biol Phys. 2000;47(5):1177-83.

55. Kuru B & Bozgul M. The impact of axillary lymph nodes removed in staging of node-positive breast carcinoma. Int J Radiat Oncol Biol Phys. 2006;66(5):1328-34.

56. Saha S, Farrar WB, Young DC, Ferrara JJ, Burak WE, Jr. Variation in axillary node dissection influences the degree of nodal involvement in breast cancer patients. J Surg Oncol. 2000;73(3):134-7.

57. Axelsson CK, Rank F, Blichert-Toft M, Mouridsen HT, Jensen MB. Impact of axillary dissection on staging and regional control in breast tumors < or = 10 mm--the DBCG experience. The Danish Breast Cancer Cooperative Group (DBCG), Rigshisoutalet, Copenhagen, Denmark. Acta Oncol. 2000;39(3):283-9.

58. Somner JE, Dixon JM, Thomas JS. Node retrieval in axillary lymph node dissections: recommendations for minimum numbers to be confident about node negative status. J Clin Pathol. 2004;57(8):845-8.

59. Schaapveld M, Otter R, de Vries EG, et al. Variability in axillary lymph node dissection for breast cancer. J Surg Oncol. 2004;87(1):4-12.

60. Salama JK, Heimann R, Lin F, et al. Does the number of lymph nodes examined in patients with lymph node-negative breast carcinoma have prognostic significance? Cancer. 2005;103(4):664-71.

61. Mersin H, Yildirim E, Bulut H, Berberoglu U. The prognostic significance of total lymph node number in patients with axillary lymph node-negative breast cancer. Eur J Surg Oncol. 2003;29(2):132-8.

62. Megale Costa LJ, Soares HP, Gaspar HA, et al. Ratio between positive lymph nodes and total dissected axillaries lymph nodes as an independent prognostic factor for disease-free survival in patients with breast cancer. Am J Clin Oncol. 2004;27(3):304-6.

63. Kuru B. Prognostic significance of total number of nodes removed, negative nodes removed, and ratio of positive nodes to removed nodes in node positive breast carcinoma. Eur J Surg Oncol. 2006;32(10):1082-8.

64. Camp RL, Rimm EB, Rimm DL. A high number of tumor free axillary lymph nodes from patients with lymph node negative breast carcinoma is associated with poor outcome. Cancer. 2000;88(1):108-13.

65. Shahar KH, Hunt KK, Thames HD, et al. Factors predictive of having four or more positive axillary lymph nodes in patients with positive sentinel lymph nodes: Implications for selection of radiation fields. Int J Radiat Oncol Biol Phys. 2004;59(4):1074-9.

66. Schaapveld M, de Vries EG, van der Graaf WT, et al. The prognostic effect of the number of histologically examined axillary lymph nodes in breast cancer: stage migration or age association? Ann Surg Oncol. 2006;13(4):465-74.

67. Truong PT, Woodward WA, Thames HD, et al. The ratio of positive to excised nodes identifies high-risk subsets and reduces inter-institutional differences in locoregional recurrence risk estimates in breast cancer patients with 1-3 positive nodes: an analysis of prospective data from British Columbia and the M. D. Anderson Cancer Center. Int J Radiat Oncol Biol Phys. 2007;68(1):59-65.

68. van der Wal BC, Butzelaar RM, van der Meij S, Boermeester MA. Axillary lymph node ratio and total number of removed lymph nodes: predictors of survival in stage I and II breast cancer. Eur J Surg Oncol. 2002;28(5):481-9.

69. Vinh-Hung V, Verschraegen C, Promish DI, et al. Ratios of involved nodes in early breast cancer. Breast Cancer Res. 2004;6(6):R680-8.

70. Voordeckers M, Vinh-Hung V, Van de Steene J, Lamote J, Storme G. The lymph node ratio as prognostic factor in node-positive breast cancer. Radiother Oncol. 2004;70(3):225-30.

71. Weir L, Speers C, D'Yachkova Y, Olivotto IA. Prognostic significance of the number of axillary lymph nodes removed in patients with node-negative breast cancer. J Clin Oncol. 2002;20(7):1793-9.

72. Fortin A, Dagnault A, Blondeau L, Vu TT, Larochelle M. The impact of the number of excised axillary nodes and of the percentage of involved nodes on regional nodal failure in patients treated by breast-conserving surgery with or without regional irradiation. Int J Radiat Oncol Biol Phys. 2006;65(1):33-9.

73. Kamath VJ, Giuliano R, Dauway EL, et al. Characteristics of the sentinel lymph node in breast cancer predict further involvement of higher-echelon nodes in the axilla: a study to evaluate the need for complete axillary lymph node dissection. Arch Surg. 2001;136(6):688-92.

74. Cserni G. Sentinel lymph-node biopsy-based prediction of further breast cancer metastases in the axilla. Eur J Surg Oncol. 2001;27(6):532-8.

75. Wada N, Imoto S, Yamauchi C, Hasebe T, Ochiai A. Predictors of tumour involvement in remaining axillary lymph nodes of breast cancer patients with positive sentinel lymph node. Eur J Surg Oncol. 2006;32(1):29-33.

76. Yu JC, Hsu GC, Hsieh CB, Sheu LF, Chao TY. Prediction of metastasis to non-sentinel nodes by sentinel node status and primary tumor characteristics in primary breast cancer in Taiwan. World J Surg. 2005;29(7):813-8; discussion 8-9.

77. Wong JS, O'Neill A, Recht A, et al. The relationship between lymphatic vessell invasion, tumor size, and pathologic nodal status: Can we predict who can avoid a third field in the absence of axillary dissection? Int J Radiat Oncol Biol Phys. 2000;48(1):133-7.

78. Katz A, Niemierko A, Gage I, et al. Factors associated with involvement of four or more axillary nodes for sentinel lymph node-positive patients. Int J Radiat Oncol Biol Phys. 2006;65(1):40-4.

79. Karlsson P, Cole BF, Price KN, et al. The role of the number of uninvolved lymph nodes in predicting locoregional recurrence in breast cancer. J Clin Oncol. 2007;25(15):2019-26.

80. Kingsmore DB, Ssemwogerere A, Hole DJ, Gillis CR, George WD. Increased mortality from breast cancer and inadequate axillary treatment. Breast. 2003;12(1):36-41.

81. Tan YY, Fan YG, Lu Y, et al. Ratio of positive to total number of sentinel nodes predicts nonsentinel node status in breast cancer patients. Breast J. 2005;11(4):248-53.

82. Blancas I, Garcia-Puche JL, Bermejo B, et al. Low number of examined lymph nodes in node-negative breast cancer patients is an adverse prognostic factor. Ann Oncol. 2006;17(11):1644-9.

83. Truong PT, Berthelet E, Lee J, Kader HA, Olivotto IA. The prognostic significance of the percentage of positive/dissected axillary lymph nodes in breast cancer recurrence and survival in patients with one to three positive axillary lymph nodes. Cancer. 2005;103(10):2006-14.

84. Millis RR, Springall RJ, Hanby AM, Ryder K, Fentiman IS. A high number of tumor free axillary lymph nodes from patients with lymph node negative breast carcinoma is associated with poor outcome. Cancer. 2002;94(8):2307-9.

85. Rudenstam CM, Zahrieh D, Forbes JF, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol. 2006;24(3):337-44.

86. Martelli G, Boracchi P, De Palo M, et al. A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer: results after 5 years of follow-up. Ann Surg. 2005;242(1):1-6; discussion 7-9.

87. Veronesi U, Orecchia R, Zurrida S, et al. Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. Ann Oncol. 2005;16(3):383-8.

88. Morgan DA, Berridge J, Blamey RW. Postoperative radiotherapy following mastectomy for high-risk breast cancer. A randomised trial. Eur J Cancer. 2002;38(8):1107-10.

89. Fisher B, Jeong JH, Anderson S, et al. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med. 2002;347(8):567-75.

90. Chua B, Ung O, Boyages J. Treatment of the axilla in early breast cancer: past, present and future. ANZ Journal of Surgery. 2001;71(12):729-36.

91. Chua B, Ung O, Boyages J. Competing considerations in regional nodal treatment for early breast cancer. Breast Journal. 2002;8(1):15-22.

92. Livsey JE, Magee B, Stewart AL, Swindell R. Axillary recurrence following conservative surgery and radiotherapy in early breast cancer. Clinical Oncology. 2000;12(5):309-14.

93. Fujimoto N, Amemiya A, Kondo M, Takeda A, Shigematsu N. Treatment of breast carcinoma in patients with clinically negative axillary lymph nodes using radiotherapy versus axillary dissection. Cancer. 2004;101(10):2155-63.

94. Louis-Sylvestre C, Clough K, Asselain B, et al. Axillary treatment in conservative management of operable breast cancer: Dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. J Clin Oncol. 2004;22(1):97-101.

95. Galper S, Recht A, Silver B, et al. Is radiation alone adequate treatment to the axilla for patients with limited axillary surgery? Implications for treatment after a positive sentinel node biopsy. Int J Radiat Oncol Biol Phys. 2000;48(1):125-32.

96. Hoebers FJ, Borger JH, Hart AA, et al. Primary axillary radiotherapy as axillary treatment in breast-conserving therapy for patients with breast carcinoma and clinically negative axillary lymph nodes. Cancer. 2000;88(7):1633-42.

97. Eifel P, Axelson JA, Costa J, et al. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1-3, 2000. J Natl Cancer Inst. 2001;93:979-89.

98. Truong PT, Olivotto IA, Whelan TJ, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional post-mastectomy radiotherapy. CMAJ. 2004;170(8):1263-73.

99. Gebski V, Lagleva M, Keech A, Simes J, Langlands AO. Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective. J Natl Cancer Inst. 2006;98(1):26-38.

100. Van De Steene J, Soete G, Storme G. Adjuvant radiotherapy for breast cancer significantly improves overall survival: The missing link. Radiother Oncol. 2000;55(3):263-72.

101. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol. 2007;82(3):247-53.

102. Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Loco-regional recurrence after mastectomy in high-risk breast cancer-risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials. Radiother Oncol. 2006;79(2):147-55.

103. Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol. 2006;24(15):2268-75.

104. Rutqvist L & Johansson H. Long-term follow-up of the Stockholm randomized trials of postoperative radiation therapy versus adjuvant chemotherapy among 'high risk' pre- and postmenopausal breast cancer patients. Acta Oncologica. 2006;45(5):517-27.

105. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97(2):116-26.

106. Grills IS, Kestin LL, Goldstein N, et al. Risk factors for regional nodal failure after breast-conserving therapy: regional nodal irradiation reduces rate of axillary failure in patients with four or more positive lymph nodes. Int J Radiat Oncol Biol Phys. 2003;56(3):658-70.

107. Fodor J, Polgar C, Major T, Nemeth G. Locoregional failure 15 years after mastectomy in women with one to three positive axillary nodes with or without irradiation the significance of tumor size. Strahlentherapie und Onkologie. 2003;179(3):197-202.

108. Lee JC, Truong PT, Kader HA, Speers CH, Olivotto IA. Postmastectomy radiotherapy reduces locoregional recurrence in elderly women with high-risk breast cancer. Clin Oncol (R Coll Radiol). 2005;17(8):623-9.

109. Chang DT, Feigenberg SJ, Indelicato DJ, et al. Long-term outcomes in breast cancer patients with ten or more positive axillary nodes treated with combined-modality therapy: the importance of radiation field selection. Int J Radiat Oncol Biol Phys. 2007;67(4):1043-51.

110. Kwan W, Jackson J, Weir LM, et al. Chronic arm morbidity after curative breast cancer treatment: prevalence and impact on quality of life. J Clin Oncol. 2002;20(20):4242-8.

111. Ververs JM, Roumen RM, Vingerhoets AJ, et al. Risk, severity and predictors of physical and psychological morbidity after axillary lymph node dissection for breast cancer. European Journal of Cancer. 2001;37(8):991-9.

112. Johansen J, Overgaard J, Blichert-Toft M, Overgaard M. Treatment of morbidity associated with the management of the axilla in breast-conserving therapy. Acta Oncol. 2000;39(3):349-54.

113. Truong PT, Olivotto IA, Speers CH, et al. A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. Int J Radiat Oncol Biol Phys. 2004;58(3):797-804.

114. Truong PT, Olivotto IA, Kader HA, et al. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. Int J Radiat Oncol Biol Phys. 2005;61(5):1337-47.

115. Truong PT, Lesperance M, Culhaci A, et al. Patient subsets with T1-T2, node-negative breast cancer at high locoregional recurrence risk after mastectomy. Int J Radiat Oncol Biol Phys. 2005;62(1):175-82.

116. Pejavar S, Wilson LD, Haffty BG. Regional nodal recurrence in breast cancer patients treated with conservative surgery and radiation therapy (BCS+RT). Int J Radiat Oncol Biol Phys. 2006;66(5):1320-7.

117. Strom EA, Woodward WA, Katz A, et al. Clinical investigation: Regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. Int J Radiat Oncol Biol Phys. 2005;63(5):1508-13.

118. Yildirim E & Berberoglu U. Can a subgroup of node-negative breast carcinoma patients with T1-2 tumor who may benefit from postmastectomy radiotherapy be identified? Int J Radiat Oncol Biol Phys. 2007;68(4):1024-9.

119. Stranzl H, Peintinger F, Ofner P, et al. Regional nodal recurrence in the management of breast cancer patients with one to three positive axillary lymph nodes. Outcome of patients following tangential irradiation without a separate nodal field. Strahlentherapie und Onkologie. 2004;180(10):623-8.

120. Cheng JC, Chen CM, Liu MC, et al. Locoregional failure of postmastectomy patients with 1-3 positive axillary lymph nodes without adjuvant radiotherapy. Int J Radiat Oncol Biol Phys. 2002;52(4):980-8.

121. Gruber G, Menzi S, Forster A, et al. Sites of failure in breast cancer patients with extracapsular invasion of axillary lymph node metastases. No need for axillary irradiation?! Strahlenther Onkol. 2005;181(9):574-9.

122. Floyd SR, Buchholz TA, Haffty BG, et al. Low local recurrence rate without postmastectomy radiation in node-negative breast cancer patients with tumors 5 cm and larger. Int J Radiat Oncol Biol Phys. 2006;66(2):358-64.

123. National Cancer Institute Clinical Trials PDQ. EORTC-10981-AMAROS. Accessed: June 2007; Available at: http://www.cancer.gov/clinicaltrials/EORTC-10981.

124. National Cancer Institute Clinical Trials PDQ. IBCSG-23-01. Accessed: June 2007; Available at: http://www.cancer.gov/clinicaltrials/IBCSG-23-01.

125. Australian New Zealand Clinical Trials Registry. SNAC II. Accessed: July 2007; Available at: http://www.anzctr.org.au/trial_view.aspx?ID=484.