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Internal mammary sentinel nodes: Ignore, irradiate or operate?

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ABSTRACT

Introduction: This study describes the results of internal mammary chain (IMC) biopsy, identifying factors that predict 'hot spots' and nodal metastases for patients in whom mapped IMC nodes were routinely dissected.

Methods: The nodal basin and status of every axillary and IMC site identified by lymphoscintigraphy were examined. Binary logistic regression analysed the relationship of several patients and tumour factors with IMC hot spots and metastases.

Results: Ninety of 490 patients (18.4%) had IMC sentinel lymph nodes (SLNs) identified by lymphatic mapping and dissected, and 20 of these (22.2%) were found to have metastases. Mapping to the IMC was most likely for women aged under 35 years (29.4%) ($p = 0.117$), women aged 35–44 (22.6%) ($p = 0.034$) or those with medial (23.7%) or central tumour location (22.2%) ($p = 0.014$; $p = 0.062$, respectively). Predictors of IMC positivity included age <35 years ($p = 0.063$), grade 3 histology ($p = 0.018$) and lymphatic vascular invasion (LVI) ($p = 0.032$). Although IMC positivity was more likely with positive axillary nodes, this trend was not significant.

Conclusion: We identified several factors (age <35 years, tumour grade and LVI) that independently predict IMC SLN identification and positivity for patients with stage I or II breast cancer. Where IMC hot spots are not dissected, we predict IMC positivity of 50% or more for young women (<35 years) or women with high grade or LVI positive tumours, and these women may benefit from more intensive chemotherapy and radiotherapy to the IMC.

1. Introduction

The use of lymphatic channel mapping to identify the first draining nodes or sentinel lymph node (SLN) for patients with breast cancer has been rapidly adopted as the standard of care for the staging and management of early breast cancer. For some women, the analysis of the SLN may yield as much or more staging information than from a complete axillary dissection. Histological examination of the sentinel node (or nodes) is often more detailed with finer sections and the use of immunohistochemical techniques. This comprehensive technique may reveal micrometastases that may not have been identified during the examination of nodes from a routine axillary dissection without a SLN biopsy.

Lymphatic mapping has the added advantage of identifying sentinel nodes in extra-axillary sites, typically the internal mammary chain (IMC) or nodes that 'skip' level 1 and drain to level 2 or 3 of the axilla, or, rarely, to the supraclavicular fossa (SCF) or opposite axilla. Management of patients whose SLNs were identified as being in the IMC remains controversial, particularly as detection rates may vary according to the lymphoscintigraphy technique used.[1] Some hold the opinion that

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detection of disease in the IMC may not alter treatment or prognosis, but increases the risk of complications. Although doubts have been expressed about the use of extra-axillary sentinel node biopsy (SNB) for staging patients with breast cancer,[2] internal mammary node involvement is an adverse prognostic indicator of increased distant metastases and reduced survival, even in the absence of axillary disease.[3–5]

The case for IMC biopsy is based on an assumption that treatment to all regional node sites may improve outcome. Studies of post-mastectomy radiotherapy, many of which included radiation to the IMC, have shown that reductions in breast cancer mortality are associated with increases in rates of loco-regional control.[6] It, therefore, makes intuitive sense to maximise disease control not only in the axilla but also in the IMC region. Although recurrences are rare in the IMC region, one cannot exclude an increased rate of metastatic disease due to secondary seeding from persistent disease, as argued by Hellman in his 'spectrum theory'.[7] Evidence from both the Early Breast Cancer Trialists' Group meta-analysis[8] and Orr's meta-analysis of axillary node dissection[9] shows a positive association between loco-regional control and survival. Although it is likely that the benefit from prevention of an IMC recurrence would be small, the use of systemic treatment because of unsuspected IMC disease or more intensive chemotherapy regimens because of disease in both the axilla and IMC nodal basins may also enhance survival in these circumstances.

The proportion of patients with a SLN mapped in the IMC varies between studies, possibly reflecting different radio-isotope injection techniques. Sub-dermal or sub-areolar injections appear to track quickly to the axilla, but extra-axillary nodes are less often localised with this technique.[10,11] However, intra-tumoural or sub-tumoural injection methods using ultrasound guidance, as used in our centre, allow identification of an extra-axillary node in up to 40% of patients.[12,13]

Identification of a SLN within the IMC following the lymphoscintigraphy may present the clinician with treatment options for the IMC basin including excision, radiation or observation. This study examines a series of patients who underwent surgery to a sentinel node identified by lymphatic mapping within the IMC to help determine the probability of disease at this location. This may assist clinicians to assess which of the three treatment options may be most appropriate for an individual patient in their own clinical setting.

2. Materials and methods

A total of 577 consecutive women with T1–T3 invasive breast carcinoma and clinically impalpable nodes underwent SLN biopsy between July 1998 and January 2005.

Lymphoscintigraphy was performed at either Westmead Public Hospital or an associated private hospital. Lymphatic mapping followed 0.2 ml injection of technetium-99-antimony-labelled sulphur colloid. The tracer was placed peri-tumourally either by palpation or by using ultrasound guidance for impalpable tumours. In patients in whom an excision biopsy had previously been performed, the tracer was injected either around the areola or adjacent to the biopsy cavity. The dose (5–40 MBq) was adjusted according to the estimated delay between imaging and surgery, and tumour location was recorded for all patients. The majority of tumours (54.7%) were located in the lateral one-third of the breast; a tumour in the medial one-third of the breast was reported for 97 patients (19.8%) with the remainder in the central one-third (25.5%).

Nuclear scan images were obtained at 15 and 45 min after injection, in planes at right angles to each other, and the site of every draining node, including extra-axillary sites, was marked on the skin. The operation was performed at one of three locations (Westmead Public Hospital or two private hospitals) by one of five consultant surgeons or by the surgical fellow under the supervision of a consultant. Sentinel nodes were identified using a Navigator gamma probe (Tyco Healthcare, Pembroke, Bermuda) and 2 ml intra-operative blue dye (Patent Blue V 2.5%, Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA, USA), which was injected into the peri-tumoural tissue.

The nodal basin of each SLN removed was recorded: axilla level 1 (L1), beyond level 1 (axilla level 2 or 3) and IMC. Every potential SLN site identified by lymphoscintigraphy was examined. Any blue node or any 'hot' lymph node whose gamma count exceeded the background count by 10 times was considered a sentinel node and was removed. Immediate levels 1–3 axillary clearance was performed for all patients if no sentinel node was identified or if imprint cytology of the sentinel node identified malignant cells. Each axillary lymph node level was sent separately for histological examination.

Patients with positive axillary sentinel nodes on formal histology using either haematoxylin and eosin or immunohistochemistry sections were offered a second operation to complete the axillary dissection. Patients who were found to have a histologically positive IMC node were treated by more intensive chemotherapy consisting of taxane-based regimens, and by radiotherapy to the IMC, SCF and the breast or chest wall.

2.1. *Statistical analysis*

A comparison was made between the lymphoscintigram mapping results and the nodal basin dissected. Of 577 patients, 87 (15.1%) were excluded from full analysis on the basis of one of three categories: failure to identify or dissect any lymph node ($n = 41$, 7.1%); failure to retrieve any lymphoid tissue and fat retrieved ($n = 7$, 1.2%) or failure to dissect or retrieve nodal tissue from every nodal basin identified by lymphoscintigraphy ($n = 39$, 6.8%). A total of 490 patients met all study criteria.

Individual variables were selected (patient age, lymphoscintigraphy injection method, tumour location and histological factors including tumour size, histological grade and lymphovascular invasion [LVI]), and were classified by the following standards: age at diagnosis (<35 years, 35–49 years or $\geqslant$50 years), injection method (palpation, ultrasound guided or other [peri-areolar or around a biopsy cavity ($n = 17$)]), tumour location (lateral, central or medial), tumour size ($\leqslant$10 mm, 11–20 mm, 21–50 mm or >50 mm), histological grade (1, 2 or 3) and LVI (no or yes). Chi-square and binary logistic regression were used to analyse the relationship of

these variables to the presence of IMC uptake on the lymphoscintigram and histological positive IMC metastases after a biopsy.

3. Results

Between June 1998 and January 2005, 577 patients underwent sentinel node biopsy. Sentinel node biopsy was unsuccessful in 41 patients, and in seven patients, no lymphoid tissue was retrieved. Another 39 patients were excluded from this analysis because the tumours drained to the axilla and the IMC, but lymphoid tissue was removed only from the axilla. Therefore, 490 of 577 patients (84.9%) had nodal tissue removed from every nodal basin draining the tumour. In 90 patients (18.4%), the IMC contained a sentinel node that was successfully dissected.

Up to six sentinel nodes were removed from each potential SLN site, which was identified by lymphoscintigraphy. The median age of patients was 54 years (range 27–93 years). During surgery, the pleura of two patients was accidentally breached, without any adverse effects following closure of the pectoral muscle while the anaesthetist held the patient in forced expiration. There were no other significant complications, and no patient required a chest drain. The addition of IMC dissection in 90 of the patients upstaged 12 (13.3%) to node positive and identified another eight (8.9%) patients with two nodal basin disease who underwent more intensive treatment, including more cycles of chemotherapy as well as radiation therapy.

Patient age, tumour location and lymphoscintigraphy injection methodology all influenced the probability of tumour drainage mapped as being to the IMC. This was most likely for women aged less than 35 years at diagnosis (29.4%) (odds ratio [OR] 2.460, $p = 0.117$) and for women aged 35–44 (22.6%) (OR 1.766, $p = 0.034$), medial (23.7%) (OR 2.131, $p = 0.014$) or central tumour location (22.2%) (OR 1.741, $p = 0.062$) or following ultrasound guided peri-tumoural injection of radiocolloid (20.8%) (OR 2.132, $p = 0.017$). Primary histological tumour characteristics including pathological size, grade and LVI had no significant impact on the probability of SLN identification in the IMC, although there was a trend for a higher frequency in women with tumours 50 mm or over (Table 1).

A total of 90 patients (18.4%) had IMC nodes mapped as draining the tumour and dissected; of these, 20 (22.2%) had disease present at final pathology. A total of 124 IMC nodes were dissected (mean 1.38). Factors identified by multivariate analysis as predictors of IMC positivity by histopathology included age <35 years at diagnosis (60%) (OR 13.008, $p = 0.063$), histological grade 3 (45.5%) (OR 30.211, $p = 0.018$)

Table 1 – Predictors of lymphoscintigraphy mapping to the internal mammary chain (n = 88[a]).

Patient and tumour characteristics	*n*	(%)	IM hot spots (%)	Univariate analysis		Multivariate analysis	
				Odds ratio	*p*-Value	Odds ratio	*p*-Value
All	490	100	18.0	–	–	–	–
Patient age (years)							
<35	17	3.5	29.4	2.367	0.121	2.460	0.117
35–49	159	32.4	22.6	**1.663**	**0.039**	**1.766**	**0.034**
⩾50	314	64.1	15.0	1	–	1	–
Lymphoscintigraphy injection technique							
By palpation	141	28.8	12.8	1	–	1	–
Ultrasound guided	274	55.9	20.8	**1.839**	**0.037**	**2.132**	**0.017**
Other	72	14.7	18.1	1.542	0.275	1.586	0.288
Tumour location[b]							
Lateral	268	54.7	13.8	1	–	1	–
Central	117	23.9	22.2	**1.736**	**0.050**	1.741	0.062
Medial	97	19.8	23.7	**1.889**	**0.031**	**2.131**	**0.014**
Pathological tumour size (mm)							
⩽10 (T1a,b)	114	23.3	17.5	1	–	1	–
11–20 (T1c)	244	49.8	16.4	0.931	0.813	0.923	0.807
21–50 (T2)	122	24.9	19.7	1.163	0.652	0.943	0.878
>50 (T3)	9	1.8	44.4	3.800	0.062	3.632	0.090
Histological grade							
1	162	33.1	14.2	1	–	1	–
2	188	38.4	17.6	1.287	0.394	1.145	0.673
3	140	28.6	22.9	1.791	0.054	1.523	0.221
Lymphovascular invasion[c]							
No	320	67.8	17.8	1	–	1	–
Yes	152	32.2	19.1	1.088	0.739	0.962	0.895

Figures in bold are statistically significant ($p < 0.05$).

a Patients who mapped on lymphoscintigraphy to the IMC basin ($n = 88$). Two patients had a hot spot identified at the time of surgery.

b Tumour location not included in eight patients (multifocal $n = 7$ and unknown $n = 1$).

c Lymphovascular invasion not recorded by the pathologist for 18 patients.

or the presence of LVI (46.7%) (OR 6.398, $p = 0.032$). Although IMC positivity was more likely to be seen in the presence of axillary nodal disease (34.8%), compared with the absence of axillary nodal disease (17.9%) this trend did not reach statistical significance on univariate or multivariate analysis. Patients with medial tumours had a higher rate of IMC positive nodes (34.8%) compared to patients with central (14.8%) or lateral tumours (21.1%) (p = NS) (Table 2).

Table 3 summarises the probability of finding an IMC positive node based on age, tumour location, histological grade or LVI, sub-grouped by the status of the axillary sentinel node of 77 patients whose lymphatic mapping showed sentinel nodes in the axilla and IMC. For a patient with a histological grade 3 tumour, where the axilla was positive, the probability of disease in the IMC sentinel node was 54.5% and 38.9% when the axilla was negative. For a grade 1 or 2 tumour, the probability of a positive IMC node was only 5.6% when the axilla was negative and was 16.7% when the axilla was positive. Similarly, the presence of LVI in the primary tumour was more likely to be associated with an IMC positive node when the axilla was positive (50%) than when the axilla was negative (12.2%). Although the sample of very young patients was small, they had a 50% probability of IMC disease, irrespective of their axillary status.

4. Discussion

This study demonstrates that a large proportion (90 of 490, 18.4%) of patients who have a SNB procedure may have radio-isotope tracer draining to the IMC basin. The clinician is then faced with a dilemma as to whether to ignore, irradiate or operate on this region. This report summarises factors

Table 2 – Predictors of IM node positivity (n = 90).

Patient and tumour characteristics	*n*	(%)	IM positivity (%)	Univariate analysis		Multivariate analysis	
				Odds ratio	*p*-Value	Odds ratio	*p*-Value
All	90	100	21.1	–	–	–	–
Patient age (years)							
<35	5	5.6	60.0	**8.786**	**0.030**	**13.008**	**0.063**
35–49	37	41.1	27.0	2.169	0.160	1.139	0.889
⩾50	48	53.3	14.6	1	–	1	–
Lymphoscintigraphy injection technique							
By palpation	19	21.1	36.8	1	–	1	–
Ultrasound guided	58	64.4	20.7	0.447	0.162	0.220	0.160
Other	13	14.4	7.7	6.143	0.089	0.139	0.046
Tumour location[a]							
Medial	23	25.6	34.8	1	–	1	–
Central	27	30.0	14.8	0.599	0.487	0.252	0.232
Lateral	38	42.2	21.1	1.507	0.438	1.786	0.560
Pathological tumour size (mm)							
⩽10 (T1a,b)	20	22.2	10.0	1	–	1	–
11–20 (T1c)	41	45.6	26.8	3.30	0.148	0.319	0.405
21–50 (T2)	25	27.8	24.0	2.842	0.235	0.115	0.135
>50 (T3)	4	4.4	25.0	3.0	0.420	0.227	0.465
Histological grade							
1	23	25.6	8.7	1	–	1	–
2	34	37.8	8.8	1.016	0.987	0.588	0.698
3	33	36.7	45.5	**8.750**	**0.008**	**30.211**	**0.018**
Lymphovascular invasion							
No	58	65.9	10.3	1	–	1	–
Yes	30	34.1	46.7	**7.853**	**<0.0001**	**6.398**	**0.032**
Extensive intra-duct component							
EIC negative	72	80.0	23.6	1	–	1	–
EIC positive	18	20.0	16.7	0.647	0.529	0.077	0.079
Hormone receptor status							
ER positive	20	22.2	22.9	1	–	1	–
ER negative	70	77.8	20.0	0.844	0.787	0.135	0.233
PR positive	31	34.4	23.7	1	–	1	–
PR negative	59	65.6	19.4	0.772	0.636	0.789	0.863
Axillary sentinel node status							
Node negative	67	74.4	17.9	1	–	1	–
Node positive	23	25.6	34.8	2.444	0.099	3.905	0.186

Figures in bold are statistically significant ($p < 0.05$).

a Tumour location not included for two patients (multifocal $n = 1$ and unknown $n = 1$).

Table 3 – Decision analysis.

Questions	Patient age (years)			Tumour location		Histological grade		Lymphovascular invasion	
	<35	35–49	⩾50	Medial or central	Lateral	1 or 2	3	LVI negative	LVI positive
Number in sub-group	17	159	314	214	268	350	140	320	152
Question 1									
Will the sentinel node map to the IMC (alone or with axilla)?									
Percentage mapped to the IMC	29.4	23.3	15.3	23.4	14.2	16.3	23.6	18.1	19.7
Number mapped to the IMC	5	37	48	50	38	57	33	58	30
Question 2									
If there is an IMC hotspot, will there be IMC metastases?									
Percentage IMC positive (%)	**60**	27	14.6	24.0	21.1	8.8	45.5	10.3	46.7
Number with IMC positivity	3	10	7	12	8	5	15	6	14
Question 3									
The axilla and IMC both mapped, but only the axilla was dissected									
Will the IMC be positive if …									
….the axilla is positive?[a] (%)	**50**	36.4	30	33.3	40	16.7	**54.5**	12.5	**50**
(Number IMC +ve, axilla +ve)	1	4	3	4	4	2	6	1	7
….the axilla is negative?[b] (%)	**50**	18.2	13.3	19.4	13.6	5.6	38.9	33.3	12.2
(Number IMC +ve, axilla –ve)	1	4	4	6	3	2	7	5	4

Values in bold indicate where the probability of IMC metastases exceeds 50%.
a % Given as a proportion of the patients who mapped to IMC and axilla, and had axillary metastases.
b % Given as a proportion of the patients who mapped to IMC and axilla, and had no axillary metastases.

which may predict IMC metastases to help guide the clinician in their own setting based on the findings from a series, in which the IMC sentinel node is routinely dissected.

In the ALMANAC multi-centre study, only 9.7% of the recruited patients had IMC hot spots, and fewer than half (45%) of these had any attempt at nodal dissection.[14] The conclusion of that publication (that IMC dissection does not add to the staging characteristics of the patient) may be flawed, given the large number of ineligible patients. Indeed, the surgical approach to the IMC can be performed without additional complications and appears to improve nodal staging.[15,16] More recent single-centre studies have reported 16.7% of patients with IMC hot spots, and an IMC positivity rate of 23.6%.[17]

The identification of IMC metastases affected radiotherapeutic treatment decisions with extension to the radiotherapy field in 17 patients (20.0%). Six (7.1%) patients were also treated with additional chemotherapy. In many hospitals, it is a common practice to give radiotherapy to patients with a primary cancer over a certain size, or in a medial quadrant or when the axilla is involved. Many of these patients will probably not have internal mammary metastases. Removing their sentinel nodes will prevent these patients from undergoing radiotherapy which will not benefit them. Therefore, we believe that failure to dissect these nodes may affect breast cancer staging and influence patient management.

This single-centre study has numerous strengths. It draws on consecutive patients treated in a large regional breast cancer centre, thus ensuring that there is no bias in patient selection. All lymphoscintigraphy injections and scanning were performed according to a local standard protocol in two hospitals, and only patients in whom every nodal basin was dissected and nodal tissue retrieved were included for analysis.

Within our series, the IMC node positivity rate was 22.2%. These values are consistent with other published data.[16,17] The addition of IMC dissection upstaged 12 (13.3%) patients to node positive and identified another eight (8.9%) patients with two nodal basin disease. These patients (3.9% of total) all received additional radiotherapy to the internal mammary nodes, SCF and breast or chest wall, and eight patients received additional adjuvant chemotherapy because of the poorer prognosis associated with two positive nodal basins.[3]

We have demonstrated that patient age (<35 years), tumour location (central or medial) and lymphoscintigraphy injection methodology (ultrasound localised) all influence the probability of a sentinel node being found in the IMC. The use of ultrasound to place the tracer in the sub-tumoural tissue may allow lymphatic channels that drain directly to the IMC to take up the tracer,[18] and thus may explain the high proportion of patients who have IMC sentinel nodes in this cohort.

Tumour histological characteristics have no impact on lymphatic drainage patterns. Although small tumours (<10 mm) appeared to have lower rates of IMC node positivity, this was not true in multivariate analysis. This result is in contrast to analysis of node positivity in the axillary basin, where there is a linear relationship between tumour size and rates of node positivity.[19] Patient age (<35 years), grade 3 histology, and LVI are independently associated with IMC metastases, particularly when the axilla has positive nodes.

Our policy of dissecting the IMC sentinel node allows for improved staging, potential improvements in regional control, and the potential to increase long-term survival and the identification of patients who may benefit from IMC radiation. Although the incidence of a recurrence in the IMC region is uncommon, the morbidity associated with extension of a recurrent node into the sternum or adjacent rib is significant and subsequent disease control can be difficult.[20]

Our approach to IMC dissection and IMC irradiation is supported by recently published research demonstrating

improved patient survival for patients with a positive IMC sentinel node. Veronesi found that patients with internal mammary metastases treated with radiotherapy and appropriate systemic treatment showed an excellent survival of 95% at 5 years.[21] However, this policy of removing the node is obviously not applicable in all clinical settings, because expertise varies. Three variables, i.e. patient age (<35 years), histological grade (grade 3) and LVI, are independently associated with IMC metastases, and prophylactic IMC radiotherapy may be considered, particularly when the axilla is positive.

Conflict of interest statement

None declared.

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REFERENCES

1. Benda RK, Cendan JC, Copeland EM, et al. Should decisions on internal mammary lymph node irradiation be based on current lymphoscintigraphy techniques for sentinel lymph node identification? *Cancer* 2004;**100**:518–23.
2. Victorzon M, Hämäläinen E, Svartback M, Lantto A. Extra-axillary sentinel node biopsy in breast cancer staging – is it necessary? *Eur J Surg Oncol* 2003;**29**:604–6.
3. Veronesi U, Cascinelli N, Greco M, et al. Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. *Ann Surg* 1985;**202**:702–7.
4. Nime FA, Rosen PP, Thaler HT, Ashikari R, Urban JA. Prognostic significance of tumor emboli in intramammary lymphatics in patients with mammary carcinoma. *Am J Surg Pathol* 1977;**1**:25–30.
5. Ege GN, Clark RM. Internal mammary lymphoscintigraphy in the conservative management of breast carcinoma: an update and recommendations for a new TNM staging. *Clin Radiol* 1985;**36**:469–72.
6. Voordeckers M, Van de Steene J, Vinh-Hung V, Storme G. Adjuvant radiotherapy after mastectomy for pT1–pT2 node negative (pN0) breast cancer: is it worth the effort? *Radiother Oncol* 2003;**68**:227–31.
7. Hellman S. Karnofsky Memorial Lecture. Natural history of small breast cancers. *J Clin Oncol* 1994;**12**:2229–34.
8. Clarke M, Collins R, Darby S, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**366**:2087–106.
9. Orr R. The impact of prophylactic axillary node dissection on breast cancer survival – a Bayesian meta-analysis. *Ann Surg Oncol* 1999;**6**:109–16.
10. Nieweg OE. Lymphatics of the breast and the rationale for different injection techniques. *Ann Surg Oncol* 2001;**8**(9Suppl):71S–3S.
11. Roumen RM, Geuskens LM, Valkenburg JG. In search of the true sentinel node by different injection techniques in breast cancer patients. *Eur J Surg Oncol* 1999;**25**:347–51.
12. Shimazu K, Tamaki Y, Taguchi T, et al. Lymphoscintigraphic visualization of internal mammary nodes with subtumoral injection of radiocolloid in patients with breast cancer. *Ann Surg* 2003;**237**:390–8.
13. Wu CT, Morita ET, Treseler PA, et al. Failure to harvest sentinel lymph nodes identified by preoperative lymphoscintigraphy in breast cancer patients. *Breast J* 2003;**9**:86–90.
14. Mansel RE, Goyal A, NewcombeRG: ALMANAC Trialists Group. Internal mammary node drainage and its role in sentinel lymph node biopsy: the initial ALMANAC experience. *Clin Breast Cancer* 2004;**5**:279–84.
15. van der Ent FW, Kengen RA, van der Pol HA, Povel JA, Stroeken HJ, Hoofwik AG. Halsted revisited: internal mammary sentinel lymph node biopsy in breast cancer. *Ann Surg* 2001;**234**:79–84.
16. Estourgie SH, Tanis PJ, Nieweg OE, Valdés Olmos RA, Rutgers EJ, Kroon BB. Should the hunt for internal mammary chain sentinel nodes begin? An evaluation of 150 breast cancer patients. *Ann Surg Oncol* 2003;**10**:935–41.
17. Madsen E, Gobardhan P, Bongers V, et al. The impact on post-surgical treatment of sentinel lymph node biopsy of internal mammary lymph nodes in patients with breast cancer. *Ann Surg Oncol* 2007;**14**:1486–92.
18. Suami H, Pan WR, Mann GB, Taylor GI. The lymphatic anatomy of the breast and its implications for sentinel lymph node biopsy: a human cadaver study. *Ann Surg Oncol* 2008;**15**:863–71.
19. Laura S, Coombs NJ, Ung O, Boyages J. Tumour size as a predictor of axillary node metastases in patients with breast cancer. *ANZ J Surg* 2006;**76**:1002–6.
20. Brennan M, Boyages J. BCI Case Study: Internal Mammary Lymph Node Involvement, Case No. 03/01, 2003 Case Studies, September 2003. <http://www.bci.org.au/index.php?option=com_content&task=view&id=95&Itemid=91> [accessed 21.06.08].
21. Veronesi U, Arnone P, Veronesi P, et al. The value of radiotherapy on metastatic internal mammary nodes in breast cancer. Results on a large series. *Ann Oncol* 2008;May 7 [Epub ahead of print].