



Identification of the sentinel lymph node in the SNAC-1 trial

Amira A. Elmadahm,* Peter G. Gill,*† Melissa Bochner,*† Val J. Gebiski,‡ Diana Zannino,‡ Neil Wetzig,§ Ian Campbell¶, Martin Stockler,‡**†† Owen Ung,‡‡ John Simes‡** and Roger Uren**

*Department of Surgery, University of Adelaide, Adelaide, South Australia, Australia

†Royal Adelaide Hospital, Adelaide, South Australia, Australia

‡NHRMC Clinical Trial Centre, The University of Sydney, Sydney, New South Wales, Australia

§Wesley Medical Centre, Brisbane, Queensland, Australia

¶Waikato Hospital, Waikato, New Zealand

**Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

††Sydney Cancer Centre, Royal Prince Alfred and Concord Hospitals, Sydney, New South Wales, Australia and

‡‡Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

Key words

breast neoplasm/surger, lymphoscintigraphy, patent blue V, sentinel lymph node biopsy.

Correspondence

Professor Peter G. Gill, Department of Surgery, University of Adelaide, North Terrace, Adelaide, SA 5000, Australia. Email: nicki.bator@health.sa.gov.au

A. A. Elmadahm MBChB, MPhil; **P. G. Gill** MBBS, MD (Adel), FRACS; **M. Bochner** MBBS, MS, FRACS;

V. J. Gebiski BA, MStat, RANZCR (Honorary);

D. Zannino BSc (Hons), MSc (Research); **N. Wetzig** MBBS, FRACS; **I. Campbell** BHB, MBChB, FRACS;

M. Stockler MD, MSc; **O. Ung** MBBS, FRACS;

J. Simes BSc (Med) (Hons), MBBS (Hons), MD, SM, FRACP; **R. Uren** MBBS, MD, FRACP, DDU.

Accepted for publication 7 December 2013.

doi: 10.1111/ans.12527

Abstract

Background: A combination of scintigraphy and a lymphotropic dye (patent blue dye (BD)) is the recommended technique to detect the sentinel lymph node (SLN) in early breast cancer. This study determined the effect of clinical factors on SLN identification in the sentinel node biopsy versus axillary clearance (SNAC) trial.

Methods: A total of 1088 women were registered. Lymphatic mapping was performed using preoperative lymphoscintigraphy (LSG) and gamma probe (GP) combined with peritumoural injection of patent BD (971 patients) or BD alone (106 patients).

Results: SLNs were identified in 1024 women (94%), localized with LSG in 779 (81.4%), and were identified by GP in 879 (91.8%). The BD identified SLNs in 890 of 1073 (82%) women. Three patients had allergic reactions. BD detected the SLNs in 141 of 178 women with negative LSG mapping and in 44 of 79 women with no hot SLNs detected intraoperatively. Age, body mass index (BMI) and tumour presentation (screen detected versus symptomatic) were significantly related to the identification of the SLN. For BD, the primary tumour location was significantly related to identification rate. The detection of blue SLN was significantly lower in women with inner quadrant tumours.

Conclusion: The combined technique resulted in a high identification rate. BD contributed to the identification of the SLNs in patients where LSG and GP failed to identify the sentinel node. Special attention to these techniques is needed in particular groups of patients such as those with high BMI, screen-detected primary tumours and tumour located in the inner quadrants.

Introduction

Sentinel lymph node biopsy (SLNB) is used for the lymph node status exploration in women early breast cancer and clinically negative nodes. Currently, a combination of preoperative lymphoscintigraphy (LSG) mapping, intraoperative gamma probe (GP) and blue dye (BD) mapping is recommended for optimal detection of the sentinel lymph nodes (SLNs).

BDs were used in the early studies of SLNB before the introduction of radioactive colloids.¹ They include patent blue V (PBV) and isosulfan blue. PBV is used in textile industries and as a food colorant, which can result in sensitization.² Many studies have sug-

gested that the detection of the SLN using a combination of BD with a radioactive tracer is superior to single-agent detection.^{3–6} Others maintained that a high identification rate can be achieved by mapping the lymphatics with BD alone.⁷

The BD can cause allergic reactions mediated via immunoglobulin E.² The reported incidence of allergic reactions varies from 0.007% to 2.7%.⁸ Other adverse effects include blue discoloration of skin and interference with oximeter readings.⁹

The aim of our analyses is to define the contribution of each detection technique on the identification of SLNs in women involved in the sentinel node biopsy versus axillary clearance (SNAC) trial who were randomized to either SLNB with axillary clearance only if

the removed SLNs were positive (SLNBM group) or SLNB followed by immediate axillary clearance (AC).

Methods

The design and conduct of the SNAC trial were described previously.¹⁰ A total of 1088 women were randomized and their data, which were collected prospectively, combined for this analysis. SLNs were identified as previously described. Further, 2–4 mL of antimony sulphide colloid (20–40 MBq technetium-99) was injected preoperatively and a similar volume of PBV dye was injected via a peritumoural route after induction of anaesthesia.

Statistical analysis

Statistical analysis was carried out using SPSS software package, version 18 (SPSS Inc., Chicago, IL, USA). Chi-square test was used for analysis of the correlation of SLN identification with categorical variables including the clinical and histological features of primary tumours and with nominal data of clinical presentation such as associated illness. Binary logistic regression was used to analyse continuous variables (age, body mass index (BMI) and the primary tumour size). *P*-values less than 0.05 were considered statistically significant. All tests were two-tailed. All tumour characteristics, site and patient-related variables were included in the univariate analyses and only significant variables were included in multivariate analyses.

Results

The protocol for SLN mapping was identical in both groups, which were randomized prior to surgery. The results have therefore been combined as a single group in our analyses. The clinical and surgical characteristics of the women involved in the SNAC trial have been previously described.¹⁰

BD injection was used to detect the SLNs in 98% of all patients (*n* = 1073), whereas 88% of all patients underwent preoperative LSG and intraoperative GP. BD injection was used as the sole detection technique in 106 patients. A combination of preoperative LSG and intraoperative GP and BD injection was used in 940 patients (87%).

Overall outcomes of SLNB

The SLN was identified in 1024 patients (94.6%). Ninety-three per cent of SLNs removed were located in the axilla and 5.7% in the internal mammary chain. Eighty-eight patients (8.6%) had internal mammary SLN removal and preoperative LSG identified the internal mammary SLNs in 74 patients (7.2%).

Localization of SLNs with preoperative LSG

Preoperative LSG was used in 957 patients and detected SLNs in 779 patients (identification rate of 81.4%). The median number of SLNs visualized was 1.39. One node was removed in 56% of patients who underwent this technique; two nodes in 30%; and three or more in 9.2%. Preoperative mapping failed in 178 patients: no SLN was ultimately detected in 37 patients, whereas 141 of these had successful detection of SLN with intraoperative techniques (Fig. 1). SLN localization failed more often in elderly and obese

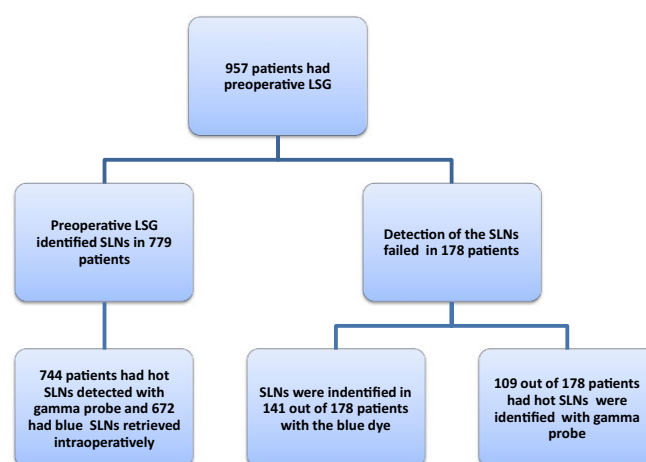


Fig. 1. Outcomes of sentinel lymph node (SLN) detection in patients who underwent preoperative lymphoscintigraphy (LSG).

women and those who had any associated co-morbidity (Table 1). Multivariate analysis demonstrated that age (*P* < 0.0001, odds ratio (OR): 0.948, 95% confidence interval (CI): 0.929–0.966) and BMI were the only significant predictors of SLN detection with LSG (*P* < 0.0001, OR: 0.944, 95% CI: 0.916–0.972) (Table 1).

Outcome of SLN identification with PBV dye

Blue SLNs were removed in 890 of 1073 patients (82.9%). The median number of removed blue SLNs was 1 (range 0–6). One blue SLN was removed in 85% of all patients who had blue SLN, two in 29.6% of patients and three SLNs in 9.4% of patients. More than three blue SLNs were retrieved in 2.8% of patients. Allergic reactions from the use of BD were reported in three patients (0.3%).¹⁰

The identification rate among patients who had BD injection only as the identification technique was 85.8% (91 of 106 patients). The median number of retrieved blue SLNs was 1 (range 0–3).

The results of univariate analyses of the clinical and pathological factors influencing the detection of blue SLNs are shown in Table 2.

Multivariate analysis revealed that BMI, tumour site, age and oestrogen receptor status were significant predictors of blue SLN detection. The *P*-values and odds ratios of multivariate analysis are shown in Table 3.

Detection of sentinel nodes with the GP

The GP was used to detect SLNs in 958 patients; hot nodes were identified in 879 patients (92%) (Fig. 2). The number of hot SLNs ranged from 0 to 7. The median number of hot nodes removed was 1. The use of the intraoperative GP significantly improved the detection of sentinel nodes (*P* < 0.0001, OR: 5.331, 95% CI: 2.997–9.484).

The GP identified SLN in 747 of 779 patients who had SLN visualized with LSG and 109 of the 178 patients who had no SLN detected (Fig. 1). Failure to detect a SLN with preoperative LSG resulted in failed intraoperative detection by the GP in 39% (69/178) of patients compared with 2.5% (18/729) of those with a positive LSG. The difference is highly significant (*P* < 0.001, OR: 257, 95% CI: 15.35–46.7).

Table 1 Outcomes of univariate analysis of clinicopathological features that influence the detection of SLN with preoperative lymphoscintigraphy

Features	Total no. of patients in each subgroup	No. of patients with localized SLN on preoperative LSG (% from each subgroup)	No. of patients with unsuccessful detection of SLN (% from each subgroup)	P-value
Age (years)				
≤30	6	6 (100)	0 (0)	<0.001
31–49	196	182 (92.9)	14 (7.1)	
50–69	636	507 (79.7)	129 (20.3)	
≥70	120	85 (70.8)	35 (29.2)	
BMI				
18.5–25	313	282 (90)	31 (10)	<0.001
>25–30	286	223 (78)	63 (22)	
>30	281	214 (76.2)	67 (23.8)	
Co-morbidity				
No associated illnesses	543	454 (83.6)	89 (16.4)	<0.05
Presence of co-morbidity	414	325 (78.5)	89 (21.5)	

BMI, body mass index; LSG, lymphoscintigraphy; SLN, sentinel lymph node.

Table 2 Outcomes of univariate analyses of clinical and pathological factors influencing the detection of the blue SLN

Features	Total no. of patients in each subgroup	No. of patients who had blue SLN identified (% from the total number of patients in each subgroup)	No. of patients who had no SLN detected with blue dye (% from the total number of patients in each subgroup)	P-value
Age (years)				
≤30	6	6 (100)	0 (0)	<0.001
31–49	230	207 (90)	23 (10)	
50–69	711	566 (97.6)	145 (20.4)	
≥70	136	110 (80.9)	26 (19.1)	
BMI				
18.5–25	348	314 (90.2)	34 (9.8)	<0.001
>25–30	322	273 (84.8)	49 (15.2)	
>30	316	242 (76.6)	74 (23.4)	
Clinical presentation				
Symptomatic	454	394 (86.8)	60 (13.2)	<0.05
Screen detected	619	494 (79.8)	125 (20.2)	
Tumour site				
Upper outer quadrant	530	462 (87.2)	68 (12.8)	<0.001
Upper inner quadrant	192	145 (75.5)	47 (24.5)	
Central	119	103 (86.6)	16 (13.4)	
Lower inner quadrant	92	65 (70.7)	27 (29.3)	
Lower outer quadrant	140	113 (80.7)	27 (19.3)	
Oestrogen receptor status				
Oestrogen receptor positive	864	732 (84.7)	132 (15.3)	<0.05
Oestrogen receptors negative	182	143 (78.6)	39 (21.4)	

BMI, body mass index; SLN, sentinel lymph node.

In 79 patients, the GP failed to detect hot SLNs (8.2%), and in 34 of 79 patients, no SLN was detected even with other techniques. BD detected SLNs in 44 patients who had no hot SLNs identified (Fig. 2).

The multivariate analysis revealed that the detection of hot SLNs was significantly lower in those who had prior open biopsy ($P = 0.003$). The identification rates in patients who were diagnosed with core biopsy, cytology and open biopsy were 91%, 93.8% and 82.2%, respectively. The primary tumour site, age and BMI were also significant predictors.

Detection of the SLN with the combined technique

Thirty-one centres used a combination of BD and scintigraphy. Nine hundred forty patients underwent preoperative LSG mapping fol-

lowed by intraoperative GP and BD injection to detect SLNs. The identification rate was high in this group (96.4%). The median number of removed SLNs was 1.7.

The patient distribution and univariate analysis of the combined techniques are shown in Table 4.

Multivariate analysis showed that the BMI and the site of the primary tumour were significant predictors (Table 5).

Overall outcomes of SLN detection in the SNAC trial

The analysis of overall outcomes includes all patients and is inclusive of all techniques of detection. Univariate analyses revealed that age, BMI, associated co-morbidity, mode of presentation and palpability of primary tumour were significant factors. On multivariate analysis, only BMI (OR: 0.945, 95% CI: 0.902–0.989) and the mode

Table 3 Results of multivariate analyses of clinicopathological factors influencing the detection of the blue sentinel lymph nodes

Features	P-value	Odds ratio	95% confidence interval	
			Lower	Upper
Age	<0.01	0.973	0.956	0.991
BMI	<0.001	0.944	0.917	0.972
Tumour presentation	<0.01	1.603	1.086	2.366
Tumour site†	<0.01			
Upper outer quadrant	>0.05	1.240	0.712	2.162
Upper inner quadrant	>0.05	0.613	0.331	1.132
Central	>0.05	1.034	0.498	2.148
Lower inner quadrant	<0.05	0.403	0.201	0.808
Oestrogen receptors status	<0.01	0.548	0.356	0.845

†The lower outer quadrant site is the reference site. BMI, body mass index.

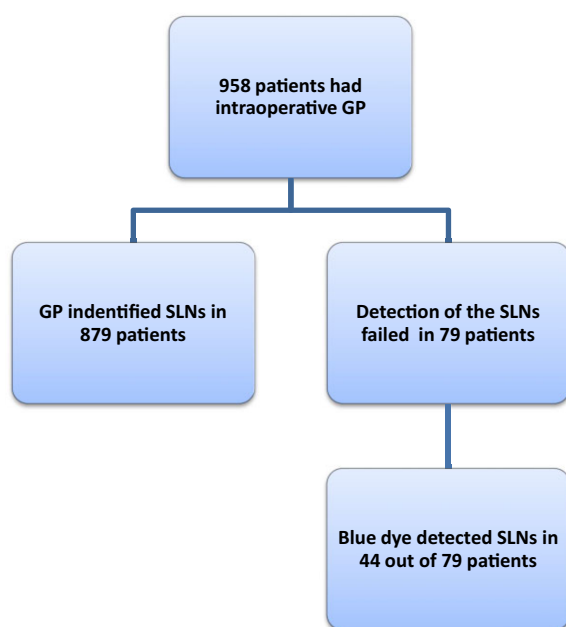


Fig. 2. Illustrates the outcomes of the intraoperative gamma probe (GP). SLN, sentinel lymph node.

of presentation of the primary tumours (OR: 0.461, 95% CI: 0.204–1.043) were significant predictors of the SLNB outcomes (Table 6).

Identification and retrieval of involved SLNs

Three hundred sixty-five sentinel nodes contained metastases. The involved SLNs were identified in 267 patients who had a combined technique and the total number of involved SLNs in this group was 324 nodes. The details for 12 nodes were missing. Using the GP, 94.4% of all positive SLNs were detected; 86.4% of all positive nodes were blue nodes and 82.7% of positive sentinel nodes were seen on the preoperative LSG. Nine of the involved SLNs (2.8%) were identified only with the BD technique and 6 of the involved SLNs (1.9%) were detected only with GP.

The involved SLN were categorized according to their order of removal. More than three quarters (279 of 365) of all positive SLNs were the first node removed. Seventy-three out of 365 of all positive sentinel nodes were the second-retrieved SLN (20%), 13 positive nodes (3.5%) were the third-retrieved SLN and only one node was the fourth node.

Discussion

Our study has delineated the contribution of the various techniques used in the SNAC trial and has immediate relevance to the practice of SLNB in Australasia.

Our findings confirmed that SLN identification was highest using the combined technique and support its continued use.^{3–6,11} A high BMI was correlated with a lower detection rate of the SLN, consistent with other studies.^{12,13} However, the clinical impact of the obesity was only marked in patients when the BMI exceeded 30.

The SLNs were visualized in 81% of patients who underwent mapping with LSG. Although the detection rate was lower than that anticipated, it is consistent with the rates reported in other multi-centre trials with a similar design such as the ALMANAC trial (69.3%, 490/707 patients).¹⁴ The detection of internal mammary and extra-axillary nodes was also less than anticipated, compared with a rate of 36% using a peritumoural injection route in results from a centre with dedicated nuclear medicine personnel.¹⁵ The SNAC trial results, however, reflect the outcomes achieved across a range of institutions and personnel. They do, however, indicate that continued monitoring of the technique may be appropriate to ensure continuing quality assurance. The lower detection of internal mammary SLNs in the SNAC trial may also be attributed to the inconsistency of peritumoural injection of the tracers as more than half of patients had screen-detected primary tumours and many were impalpable (the use of ultrasound to direct the tracer injection was neither specified nor recorded in the SNAC trial protocol). The identification of SLNs with LSG decreased in obese and older patients, but we found no correlation between primary tumour characteristics and detection of the SLN with preoperative LSG.

Our results support the continued use of preoperative LSG as it enhances the identification of non-axillary nodes particularly internal mammary nodes, which may lead to a change in adjuvant therapy and also can indicate to the surgeon when multiple SLNs are expected.¹⁶ Furthermore, the failure of identification of a hot node on the LSG can alert the surgeon to an increased risk of failure to identify the SLN with the GP and to include BD in the procedure.

Detection of hot SLNs was significantly correlated with age, BMI, method of diagnosis and site of the primary tumour. The location of the primary cancer was the only independent tumour-related factor that predicted SLN identification, which may reflect a longer transit time of tracer movement in the case of inner quadrant cancers.

Table 4 Outcomes of univariate analyses of clinicopathological factors of women who had sentinel lymph node biopsy using the combined technique (lymphoscintigraphy, gamma probe and blue dye)

Features	Total no. of patients in each subgroup	No. of patients who had the combined technique (% from the total number of patients in each subgroup)	No. of patients with unsuccessful detection of SLN (% from the total number of patients in each subgroup)	P-value
Age (years)				
≤30	194	192 (99)	2 (1)	<0.05
31–49	623	595 (95.5)	28 (4.5)	
50–69	117	111 (94.9)	6 (5.1)	
≥70	194	192 (99)	2 (1)	
BMI				
18.5–25	307	300 (97.7)	7 (2.3)	<0.01
>25–30	284	276 (97.1)	8 (2.8)	
>30	274	257 (93.8)	17 (6.2)	
Tumour presentation				
Symptomatic	397	389 (98)	8 (2)	<0.01
Screen detected	543	516 (95)	27 (5)	
Co-morbidity				
No associated illness	532	520 (97.7)	12 (2.3)	<0.01
Presence of associated illnesses	408	384 (94.1)	23 (5.6)	
Presence of diabetes mellitus	58	53 (91.4)	5 (8.6)	<0.05
Absence of diabetes mellitus	872	842 (96.6)	30 (3.4)	
Presence of hypertension disorder	205	191 (93.2)	14 (6.8)	<0.01
Absence of hypertension disorder	725	704 (97.1)	21 (2.9)	
Tumour site				
Upper outer quadrant	463	455 (98.3)	8 (1.7)	<0.01
Upper inner quadrant	166	153 (92.2)	13 (7.8)	
Central	107	101 (94.4)	7 (6.5)	
Lower inner quadrant	75	71 (94.7)	4 (5.3)	
Lower outer quadrant†	129	125 (96.9)	4 (3.1)	

†The lower outer quadrant site is the reference site. BMI, body mass index; SLN, sentinel lymph node.

Table 5 Multivariate analyses of factors influencing the identification of sentinel lymph node with the combined technique

Features	P-value	Odds ratio	95% confidence interval	
			Lower	Upper
BMI	<0.01	0.924	0.874	0.976
Tumour site†	<0.01			
Upper outer quadrant	>0.05	1.023	0.212	4.926
Upper inner quadrant	>0.05	0.198	0.043	0.915
Central	>0.05	0.276	0.054	1.422
Lower inner quadrant	>0.05	0.308	0.054	1.756

†The lower outer quadrant site is the reference site. BMI, body mass index.

It may also reflect lymph drainage to internal mammary nodes only. Interestingly, prior open biopsy was associated with an increased risk of failure of SLN identification with the GP. Similar results were reported by Estourgie *et al.*¹⁷

The BD technique identified a SLN in 890 of 1073 patients (82%). BD had an important salvage role in the SNAC trial when SLN identification failed using the GP and LSG. Blue SLNs were retrieved in 56% and 79% of patients with unsuccessful identification of the SLN with the GP and LSG, respectively. The use of BD is recommended in patients who have unsuccessful SLN detection utilizing the radioactive tracer in order to improve the detection rate.^{18,19} Degnim *et al.* first suggested that BD could have a role in the detection of the SLN in a small series when the identification failed using a radioactive tracer.¹⁹ White *et al.* confirmed this and reported a low rate of severe anaphylactic reactions

ranging from 0.06% to 0.4%.²⁰ Thus, there is merit in the use of patent blue in a combined technique, which could outweigh concerns about allergic reactions. Australian data reported in a survey of members of the BreastSurgANZ group similarly reported a low incidence of anaphylactic reactions to BD in 0.15%.²¹ Age and BMI were again significant predictors of SLN detection using this technique. These findings are consistent with the results of Cody *et al.*²² and Nos *et al.*,²³ who used the peritumoural injection route.

Overall, SLNB was an accurate regional staging procedure in the SNAC trial. Our analyses suggest that particular attention should be directed to this technique in the presence of particular clinical factors such as obesity, a cancer located in the inner quadrant or a screen-detected primary tumours. BD enabled the detection of SLN when use of scintigraphy and GP failed and retention of its use in a

Table 6 Multivariate analysis of clinical and pathological characteristics of women who had sentinel lymph node biopsy in the SNAC trial regardless of the techniques used

Clinical features	No. of patients who had no SLN identified (% of patients with unsuccessful detection of SLN) (n = 57)	Total no. of patients in the SNAC trial (% of failure rate in each subgroup out of total patients in the trial)	P-value
BMI*			
18.5–25	10 (17.5)	337 (3)	<0.05
>25–30	16 (28)	331 (4.8)	
>30	26 (45.6)	321 (8)	
Clinical presentation of primary tumour			
Symptomatic	13 (22.5)	461 (2.8)	<0.05
Screen detected	44 (77.2)	627 (7)	

BMI, body mass index; SLN, sentinel lymph node; SNAC, sentinel node biopsy versus axillary clearance. * indicate missing data.

combined technique is recommended. The removal of three SLNs provides accurate information on nodal status without more extensive dissection.

Acknowledgements

The SNAC trial was supported by grants from the National Breast Cancer Foundation, the Department of Health and Ageing and the National Health and Medical Research Council.

References

- Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann. Surg.* 1994; **220**: 391–8.
- Scherer K, Bircher AJ, Figueiredo V. Blue dyes in medicine – a confusing terminology. *Contact Dermatitis* 2006; **54**: 231–2.
- Albertini JJ, Lyman GH, Cox C *et al.* Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996; **276**: 1818–22.
- Rahusen FD, Pijpers R, van Diest PJ, Bleichrodt RP, Torrengra H, Meijer S. The implementation of the sentinel node biopsy as a routine procedure for patients with breast cancer. *Surgery* 2000; **128**: 6–12.
- Radovanovic Z, Golubovic A, Plzak A, Stojiljkovic B, Radovanovic D. Blue dye versus combined blue dye-radioactive tracer technique in detection of sentinel lymph node in breast cancer. *Eur. J. Surg. Oncol.* 2004; **30**: 913–7.
- Koukouraki S, Sanidas E, Askoxilakis J *et al.* Is there any benefit from sentinel lymph node biopsy using the combined radioisotope/dye technique in breast cancer patients with clinically negative axilla? *Nucl. Med. Commun.* 2009; **30**: 48–53.
- Varghese P, Mostafa A, Abdel-Rahman AT *et al.* Methylene blue dye versus combined dye-radioactive tracer technique for sentinel lymph node localisation in early breast cancer. *Eur. J. Surg. Oncol.* 2007; **33**: 147–52.
- Bézu C, Coutant C, Salengro A, Daraï E, Rouzier R, Uzan S. Anaphylactic response to blue dye during sentinel lymph node biopsy. *Surg. Oncol.* 2011; **20**: e55–9.
- Govaert GAM, Oostenbroek RJ, Plaisier PW. Prolonged skin staining after intradermal use of patent blue in sentinel lymph node biopsy for breast cancer. *Eur. J. Surg. Oncol.* 2005; **31**: 373–5.
- Gill G. Sentinel-lymph-node-based management or routine axillary clearance? One-year outcomes of sentinel node biopsy versus axillary clearance (SNAC): a randomized controlled surgical trial. *Ann. Surg. Oncol.* 2009; **16**: 266–75.
- Hung WK, Chan CM, Ying M, Chong SF, Mak KL, Yip AWC. Randomized clinical trial comparing blue dye with combined dye and isotope for sentinel lymph node biopsy in breast cancer. *Br. J. Surg.* 2005; **92**: 1494–7.
- Derossis AM, Fey JV, Cody III HS, Borgen PI. Obesity influences outcome of sentinel lymph node biopsy in early-stage breast cancer. *J. Am. Coll. Surg.* 2003; **197**: 896–901.
- Straalman K, Kristoffersen US, Galatius H, Lanng C. Factors influencing sentinel lymph node identification failure in breast cancer surgery. *Breast* 2008; **17**: 167–71.
- Mansel RE, Goyal A, Newcombe RG. Internal mammary node drainage and its role in sentinel lymph node biopsy: the initial ALMANAC experience. *Clin. Breast Cancer* 2004; **5**: 279–84.
- Noushi F, Spillane AJ, Uren RF *et al.* High discordance rates between sub-areolar and peri-tumoural breast lymphoscintigraphy. *Eur. J. Surg. Oncol.* 2013; **39**: 1053–60.
- Dupont EL, Salud CJ, Peltz ES *et al.* Clinical relevance of internal mammary node mapping as a guide to radiation therapy. *Am. J. Surg.* 2001; **182**: 321–4.
- Estourgie SH, Valdés Olmos RA, Nieweg OE, Hoefnagel CA, Rutgers EJT, Kroon BBR. Excision biopsy of breast lesions changes the pattern of lymphatic drainage. *Br. J. Surg.* 2007; **94**: 1088–91.
- Goyal A, Newcombe RG, Mansel RE *et al.* Role of routine preoperative lymphoscintigraphy in sentinel node biopsy for breast cancer. *Eur. J. Cancer* 2005; **41**: 238–43.
- Degnim AC, Oh K, Cimmino VM *et al.* Is blue dye indicated for sentinel lymph node biopsy in breast cancer patients with a positive lymphoscintigram? *Ann. Surg. Oncol.* 2005; **12**: 712–7.
- White V, Harvey JR, Griffith CDM, Youssef M, Carr M. Sentinel lymph node biopsy in early breast cancer surgery – working with the risks of vital blue dye to reap the benefits. *Eur. J. Surg. Oncol.* 2011; **37**: 101–8.
- Wong A, Spillane A. Patent Blue V dye anaphylaxis: experience of Australian and New Zealand surgeons. *ANZ J. Surg.* 2014; **84**: 37–41.
- Cody HSL, Fey J, Akhurst T *et al.* Complementarity of blue dye and isotope in sentinel node localization for breast cancer: univariate and multivariate analysis of 966 procedures. *Ann. Surg. Oncol.* 2001; **8**: 13–9.
- Nos C, Fréneaux P, Guilbert S, Falcou MC, Salmon RJ, Clough KB. Sentinel lymph node detection for breast cancer: which patients are best suited for the patent blue dye only method of identification? *Ann. Surg. Oncol.* 2001; **8**: 438–43.