JBUON 2015; 20(2): 492-497
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Can we use frozen section analysis of sentinel lymph nodes mapped with methylene blue dye for decision making upon one-time axillary dissection in breast carcinoma surgery in developing countries?

Igor Djurisic[1], Nada Santrac[1], Marko Buta[1], Merima Oruci[1], Ivan Markovic[1, 2], Srdjan Nikolic[1, 2], Milan Zegarac[1], Radan Dzodic[1, 2]

[1]*Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade;* [2]*Medical School, University of Belgrade, Belgrade, Serbia*

Summary

Purpose: *To evaluate the accuracy of intraoperative frozen section analysis (FSA) of sentinel lymph nodes (SLNs) mapped using methylene blue dye (MBD) and its usefulness for selecting patients with breast carcinomas and positive axillary lymph nodes (ALNs) for one-time axillary dissection.*

Methods: *152 female patients with T1/T2 breast carcinomas and clinically negative ALNs were selected for mapping using MBD (1%) from October 2010 to December 2011. Patients underwent FSA of mapped SLNs and ALN dissection. The accuracy of SLN-FSA was tested by comparing these findings with the definite histopathology (HP) of SLNs, as well as of other ALNs. Sensitivity, specificity, positive and negative predictive values were calculated.*

Results: *There was a 98%-match between FSA and definite HP findings of SLNs, suggesting high accuracy of FSA in this series. None of 3 patients with false-negative SLNs on FSA had additional axillary nodal metastases. One out of 20 (5%) patients with metastases in other ALNs had "clear" SLNs, both on FSA and definite HP (false-negative). Accuracy reached 94.1%.*

Conclusions: *SLN-FSA enables adequate selection of patients for one-time axillary node dissection. MBD mapping technique is cheap, feasible and enables easy and precise detection of the first draining ALNs. Using FSA of SLNs mapped with MBD, patients with breast carcinoma benefit from complete surgical treatment during one hospitalization, the risk of undergoing anaesthesia twice is reduced, as well as the treatment cost, which is important in developing countries.*

Key words: *axillary dissection, breast cancer, developing countries, frozen section analysis, methylene blue dye mapping, sentinel lymph nodes*

Introduction

ALN status determines to a great extend the need for adjuvant therapy for breast cancer and consists the most important single prognostic factor for recurrence and survival [1]. Sentinel lymph node biopsy (SLNB) has been introduced two decades ago as a useful method for staging ALNs in patients with invasive breast carcinoma [2]. Since then, the use of SLNB is increasing and has become the gold standard for preoperative N0 patients [3]. Current treatment guidelines suggest completion ALND only in cases with histologically positive SLN after previous surgery [4-8]. However, the financial and administrative implications as well as potential complications for patients from two-step breast cancer surgery in developing countries should not be neglected.

Correspondence to: Igor Djurisic, MD. Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Pasterova 14, Belgrade 11 000, Serbia. Tel: +381 64 148 49 49, Fax: +381 11 2685 300, E-mail: dr_igor_djurisic@yahoo.com, drigordjurisic@gmail.com
Received: 28/10/2014; Accepted: 22/11/2014

The aim of this study was to evaluate the accuracy of intraoperative FSA of SLNs mapped using MBD technique and its predictive value for selecting breast cancer patients for one-step axillary nodal dissection.

Methods

Before the beginning of this research, all patients with breast cancer were treated with complete ALND according to local protocols, while SLNB was performed occasionally. In 2009, the British Association of Surgical Oncologists guidelines suggested SLNB technique as adequate approach for axillary staging. Based on these suggestions, surgeons should have a minimum of 30 cases series, with >90% SLN identification rate and <10% case negative rate [9]. Quality surgery can only be achieved with high volume practice.

This observational study was conducted at theSurgical Oncology Clinic of the Institute for Oncology and Radiology of Serbia (IORS), from October 2010 to December 2011. Female patients with T1 or T2 breast carcinomas, clinically negative ALNs and no distant metastases were selected for lymph node mapping using MBD (1%).Patients with locally advanced and inflammatory breast cancer, patients who had neoadjuvant chemotherapy, previous breast surgery for non-malignant conditions orprevious axillary procedures, patients with recurrent breast cancer, as well as pregnant or lactating patients were not subjected to SLNB, since there was insufficient level of evidence for these clinical circumstances in the current ASCO recommendations [5]. Finally, patients with failure to stain any ALN during the procedure were also excluded. The revised 2009 TNM classification (7th Edn) was used for disease clinical and histopathological staging.

SLN-FSA findings were compared with the final SLN-HP and the final HP of other lymph nodes from the axillary dissected tissue (non-SLNs) was registered. Patients with non-SLN metastases and FSA-negative SLNs were specifically observed.

Statistics

The Statistical Package for Social Sciences (SPSS Inc, Chicago, Ill) version 17.0 software was used for statistical analyses. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were calculated. Additional parameters observed in this study were number of SLNs identified and their position in the axilla (Berg's level 1 vs Berg's level 2). Several parameters were tested in correlation to SLNs number and location: MBD injection site (periareolar vs peritumoral), MBD injection time (5 vs 10 vs 20 min before the incision of the skin) and MBD volume (0.2 vs 0.5 vs 1.0 ml), in order to try to optimize the vital dye mapping technique. Pearson's x^2 test was used for this analysis and the statistical significance level was set at p=0.05.

Results

Patient characteristics

All 152 patients with breast carcinoma were females, aged from 33 to 82 years, with a mean of 56.74 years (±SD 11.53). Clinically, 101/152 (66.4%) patients had tumors not larger than 20mm in size, while 51/152 (28.1%) had tumors from 2 to 5cm in size. The majority of the patients (120/152; 78.9%) were treated with conservative operation (quadrantectomy, SLNB and ALND), and 32/152 (21.1%) had either Madden's modified radical mastectomy (23/32; 71.9%) or nipple-sparing mastectomy with immediate breast reconstruction, SLNB and ALND (9/32; 28.1%).

Histopathology findings

The patient distribution by HP characteristics of breast carcinomas and lymph node status are shown in Table 1. The majority of tumors were of ductal type (60%, including medullary and tubular subtypes), moderately differentiated (82%), with rarely verified lymphovascular invasion (<5%) and a mean size 15.78 mm (±7.30). In total, 183 (1-4) SLNs were excised and analyzed intraoperatively. Other details regarding lymph nodes HP are given in Table 2.

Methylene blue dye mapping technique

Details regarding the technique of mapping

Table 1. Pathological characteristics of tumors

Characteristics	*N (%)*
Tumor size (mm)	
Mean (SD)	15.78 (7.30)
Median (range)	15 (1-48)
Tumor type	
Invasive ductal carcinoma (IDC)	74 (48.7)
Invasive medullary carcinoma (IDC-M)*	5 (3.3)
Tubular carcinoma (IDC-T)*	10 (6.6)
Invasive lobular carcinoma (ILC)	63 (41.4)
Tumor grade	
1 (low)	17 (11.2)
2 (intermediate)	125 (82.2)
3 (high)	10 (6.6)
Lymphovascular invasion	
No	145 (95.4)
Yes	7 (4.6)
Pathological T	
pT1a	10 (6.6)
pT1b	26 (17.1)
pT1c	87 (57.2)
pT2	29 (19.1)

SD: standard deviation, * IDC subtypes

Table 2. Pathological characteristics of axillary lymph nodes

Characteristics	*N (%)*
Axillary lymph node status (pN)	
Negative (pN0)	121 (79.6)
Positive	31 (20.4)
Sentinel lymph nodes – frozen section	
Negative	125 (82.2)
Positive	27 (17.8)
Sentinel lymph nodes – definite pathology	
Negative	122 (80.3)
Positive*	30 (19.7)
Non-sentinel lymph nodes - number	
Total (range)	2 337 (3-33)
Per patient (SD)	15.38 (4.94)
Non-sentinel lymph nodes–definite pathology	
Negative	132 (86.8)
Positive	20 (13.2)

*one positive SLN in 29/30 (96.7%) of the patients and two positive SLNs in 1/30 (3.3%) of the patients. SD: standard deviation

Table 3. Methylene blue dye mapping technique and characteristics of sentinel lymph nodes

Vital dye injection technique	*N (%)*
Methylene blue dye – injection site	
periareolar	141 (92.8)
peritumoral	11 (7.2)
Methylene blue dye – injection time (min)*	
5	113 (74.3)
10	33 (21.7)
20	6 (4.0)
Methylene blue dye – volume (ml)	
0.2	5 (3.3)
0.5	131 (86.2)
1.0	16 (10.5)
Sentinel lymph nodes characteristics	
Sentinel lymph nodes - localization**	
level 1	132 (86.8)
level 2	20 (13.2)
Sentinel lymph nodes	
total number (range)	183 (1-4)
per patient (SD)	1.2 ± 0.53
Sentinel lymph nodes pathologically identified	
1	128 (84.2)
2	19 (19.5)
3	3 (2.0)
4	2 (1.3)

*time to skin incision, **Berg's categories of axillary lymph nodes; SD: standard deviation

and biopsy of identified SLNs are shown in Table 3. The vast majority of patients (93%) had periareolar injection of MBD. In 86% of the cases a single 0.5ml dose of MBD was used. The majority of surgeons (74%) injected MBD 5 min before the skin incision. A total of 183 SLNs were identified, 1.2 SLNs per patient (range 1-4). In 87% of the patients, SLNs were identified in the Berg's level 1.There was no statistically significant difference between MBD injection site, time or volume and localization of SLNs in the ipsilateral axilla or number of SLNs identified (Pearson's x^2 test, $p>0.05$).

Sentinel lymph node biopsy and frozen section analysis - method's accuracy

Comparison of FSA and definite HP findings on SLNs (Table 2) showed concordance in 98% of the patients, since there were 3 patients with false-negative SLNs on FSA (Table 3). This suggests the high accuracy of FSA in this series.

The predictive value of SLN-FSA concerning the positivity of other axillary lymph nodes (non-SLNs) was calculated. None of the 3 patients with false-negative SLNs on FSA had non-SLN metastases on definite HP examination. Non-SLNs metastases were present in 20/152 (13.2%) patients. In total, 19/20 (95%) patients were correctly identified by FSA of SLNs as true-positive (sensitivity). The specificity of the method was 93.9%. The SLNB with MBD and intraoperative FSA accurately selected patients for ALND in 94.1% of the cases. A probability that non-SLN metastases were present in patients with positive SLNs was 70.4% (PPV), while negative SLN findings predicted absence of non-SLN metastases in 99.2% of patients (NPV). There was a false negative rate of 5% observed in the study, meaning that one of the 20 patients identified on definite HP with non-SLN axillary metastasis had "clear" SLNs, both on FSA and definite HP.

Discussion

Elective ALND for breast cancer was the only adequate method for evaluation of locoregional status of the disease up until mid-1990s when SLNB was introduced. Since then, the use of SLNB has increased [3], as well as variations in patient selection and mapping technique applied.

Several points regarding SLN mapping technique are matters of dispute in the literature. Tracers used for SLN mapping are numerous, as well as techniques for SLNs detection. All techniques carry certain difficulties in everyday practice (adverse reactions, costs, availability, complexity).

Fluorescence-guided SLN biopsy using indocyanine green, as well as use of radioactive colloids and preoperative lymphoscintigraphy are costly and not always available. The price for Technetium is $60/g, while 30ml of MBD (1%) costs only $4.50. While series of papers report allergic reactions to vital dyes, especially patent blue V and isosulfan blue [10,11], many authors point out MBD as a safer and less expensive dye [12-14], with high efficacy for mapping. Adverse reactions after intradermal injection of MBD have been reported in the literature and involve skin and fat inflammation or necrosis [15-17], interference with pulse oximetry [18] and pulmonary edema [19]. There were two reports of anaphylaxis after MBD injection in female adults with breast carcinoma [20,21] and one report in a 6-year-old child with melanoma [22]. However, these adverse reactions are rare in the literature, given the frequency and the wide use of MBD. In our institution, MBD is widely used in melanomas and thyroid carcinomas [23-26] as a standard technique for SLN mapping for almost a decade and there have been no reports of any adverse reactions whatsoever. It is a hypo-allergic, low-cost vital dye demonstrating high success in lymph node staining. Disputes about the "ideal" tracer injection site and tracer type (vital dyes vs radiocolloids) for identification of "true SLN" date back to the late 1990s [28]. Our patients were operated by several surgeons at that time, and since the SLNB method had only recently been introduced in IORS, differences in the vital dye injection technique should be expected. However, these differences in MBD injection site, time and volume did not affect the location and the number of SLNs identified (Pearson x^2 test, $p>0.05$).

The SLN identification rates vary from 95 to 97% in the most recent trials [5,29]. Results from the validation phase of the ALMANAC trial show accuracy of 97.6% and sensitivity of 93.3% [30]. Both surgeon and pathologist are recognized as important factors for identification of SLNs and SLNB accuracy [31]. Several researchers [30,32] found that removal of more than one SLN might improve accuracy. In this study, 1-4 lymph nodes (1.2 per patient) were removed. A review by Chen and Wu [31] reported occult lymph node metastases in 7-33% of SLN-negative patients found by serial HP sectioning, which might suggest that multiple-level sectioning with immunohistochemistry provides more accurate lymph node staging [33]. In our Institute we perform intraoperative FSA of identified and excised SLNs for over a decade in thyroid carcinomas and melanomas. In our experience, trained pathologists can achieve high accuracy of FSA. Concordance of FSA and definite HP on SLNs in our study was seen in 98% of the cases. Three patients were wrongly identified as having "clear" SLNs on intraoperative FSA. However, they had no other axillary metastases on definite HP. Practice guidelines suggest that in cases with positive SLNs completion ALND should be performed [4,6,7]. In the literature, additional non-SLN metastases are present in approximately 50% of SLN-positive patients [34] – in our series in 63.3% (19/30) of the patients. The SLNB method with MBD and intraoperative FSA accurately selected patients for one-time ALND in 94.1% of the cases. In this way, out of the total of 152 patients, 19 (12.5%) with additional metastases outside SLNs would have had benefit of intraoperative examination of SLNs being given one-time axillary dissection. Only one patient would have been misdiagnosed as disease-free axillary lymph nodes since she had "clear" SLN both on FSA and definite HP, with metastasis in one other ALN. False-negative SLN rates vary in the relevant literature from 0–29% (lower than 13% in the majority of studies) [34]. This might explain axillary recurrences reported in SLN-negative patients with breast carcinoma in up to 1.15% [35-37]. Quality control procedures aim to achieve false-negative rates of 5% or lower [5]. False-negative rate in this study was 5%.

Several clinical trials [29,30,38,39] demonstrated that SLNB vs ALND in early breast carcinoma reduces lymphedema and arm morbidity risk, whilst shortening the postoperative hospital stay. On the other hand, there was no significant increase in locoregional recurrence or survival, not even with longer follow-up [29,38]. Verry et al. [40] suggested an analytic model to estimate the 20-year effectiveness and cost-effectiveness of SLNB vs ALND in patients with early breast carcinoma. Based on this, SLNB generated an additional 8 quality-adjusted life years and saved 883,000$ per 1000 patients over 20 years. However, it was less effective when false-negative SLN rate was over 13%.

The results of this observational study concur with data obtained by many international studies regarding accuracy of SLNB method in the staging of axillary lymph nodes.What authors would like to point out is the high accuracy of frozen section analysis in the detection of true metastases in SLNs which enables adequate selection of patients for one-step axillary dissection. Furthermore, MBD mapping technique for lymph nodes is a cheap and feasible method that enables easy and precise detection of the first draining lymph nodes in the axillary fossa. Frozen section analysis of SLNs mapped with MBD in patients with breast carcinoma leads to completion of surgical treatment in a single hospitalization. In this way, the benefits of SLNB are maintained and second procedure is avoided, with obvious advantages regarding possible complications and costs.

References

1. Javid SH, He H, Korde LA, Flum DR, Anderson BO. Predictors and outcomes of completion axillary node dissection among older breast cancer patients. Ann Surg Oncol 2014;21:2127-2180.
2. Veronesi U, Paganelli G, Galimberti V et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet 1997;349:1864-1867.
3. Heneghan HM, Prichard RS, Devaney A et al. Evolution of breast cancer management in Ireland: a decade of change. BMC Surg 2009;9:15.
4. Veronesi U, Paganelli G, Viale G et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003;349:546-553.
5. Lyman GH, Giuliano AE, Somerfield MR et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005;23:7703-7720.
6. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Breast, version 2. 2008.
7. Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2014:32:1365-1383.
8. Dzodic R, Markovic I, Guduric B, Buta M, Kosovac O, Djurisic I. Hirurgija raka dojke – Postupak sa limfnim nodusima pazušne jame /Breast cancer surgery - Treatment of axillary lymph nodes/. In: Dzodic R, Neskovic-Konstantinovic Z, Guduric B (Eds): Rak dojke /Breast cancer (1st Edn). Belgrade: Kuca znanja; 2014, pp 47-153.
9. Surgical guidelines for the management of breast cancer. Association of Breast Surgery at BASO 2009. Eur J Surg Oncol 2009;35(Suppl 1):S1-S22.
10. Kaufman G, Guth AA, Pachter HL, Roses DF. A cautionary tale: anaphylaxis to isosulfan blue dye after 12 years and 3339 cases of lymphatic mapping. Am Surg 2008;74:152-155.
11. Medicines and Healthcare Products Regulatory Agency (MHRA). Blue dyes: risk of serious allergic reactions. Drug Safety Update 2012;5:7:A2. Available from: http://www.mhra.gov.uk 2012;5:A2.
12. Zakaria S, Hoskin TL, Degnim AC. Safety and technical success of methylene blue dye for lymphatic mapping in breast cancer. Am J Surg 2008;196:228-233.
13. Varghese P, Abdel-Rahman AT, Akberali S, Mostafa A, Gattuso JM, Carpenter R. Methylene blue dye-a safe and effective alternative for sentinel lymph node localization. Breast J 2008;14:61-67.
14. Mukherjee A, Kharkwal S, Charak KS. Assessment of the efficacy and safety of methylene blue dye for sentinel lymph node mapping in early breast cancer with clinically negative axilla. Arch Int Surg 2014;4:6-10.
15. Stradling B, Aranha G, Gabram S. Adverse skin lesions after methylene blue injections for sentinel lymph node localization. Am J Surg 2002;184:350-352.
16. Salhab M, Al Sarakbi W, Mokbel K. Skin and fat necrosis of the breast following methylene blue dye injection for sentinel node biopsy in a patient with breast cancer. Int Semin Surg Oncol 2005;2:26.
17. Bleicher RJ, Kloth DD, Robinson D, Axelrod P. Inflammatory cutaneous adverse effects of methylene blue dye injection for lymphatic mapping/sentinel lymphadenectomy. J Surg Oncol 2009;99:356-360.
18. Piñero A, Illana J, García-Palenciano C, Cañizarese F, Canteras M, Cañadillas V. Effect on oximetry of dyes used for sentinel lymph node biopsy. Arch Surg 2004;139:1204-1207.
19. Teknos D, Ramcharan A, Oluwole SF. Pulmonary edema associated with methylene blue dye administration during sentinel lymph node biopsy. J Natl Med Assoc 2008;100:1483-1484.
20. Jangjoo A, Forghani MN, Mehrabibahar M, Sadeghi R. Anaphylaxis reaction of a breast cancer patient to methylene blue during breast surgery with sentinel node mapping. Acta Oncol 2010;46:877-878.
21. Oomah S, Dembinski T, Becker A, Kalicinsky C. Prolonged elevation of serum tryptase resulting from intraoperative anaphylaxis to methylene blue. Allergy Asthma Clin Immunol 2010;6 (Suppl 2):P29.
22. Wahid FN, Malkan AD, Pappo A, Wright BB, Adefeyisan S, Sandoval JA. Severe anaphylactic shock due to methylene blue dye. J Ped Surg Case Reports 2014;2:117-118.
23. Dzodic R, Markovic I, Inic M et al. Sentinel lymph node biopsy may be used to support the decision to perform modified radical neck dissection in differentiated thyroid carcinoma. World J Surg 2006;30:841-846.

24. Dzodic R, Markovic I, Stanojevic B et al. Surgical management of primary thyroid carcinoma arising in thyroglossal duct cyst: an experience of a single institution in Serbia. Endocr J 2012;59:517-522.
25. Dzodic R, Oruci M, Besic N et al. Sentinel lymph node biopsy in thyroid papillary and medullary microcarcinomas. Endocr Abstr 2014;35:1090.
26. Santrac N, Besic N, Buta M et al. Lymphatic drainage, regional metastases and surgical management of papillary thyroid carcinoma arising in pyramidal lobe--a single institution experience. Endocr J 2014;61:55-59.
27. Dzodic R, Buta M, Markovic I et al. Surgical management of well-differentiated thyroid carcinoma in children and adolescents: 33 years of experience of a single institution in Serbia. Endocr J 2014 Aug 12. [Epub ahead of print].
28. Linehan DC, Hill AD, Akhurst T et al. Intradermal radiocolloid and intraparenchymal blue dye injection optimise sentinel node identification in breast cancer patients. Ann Surg Oncol 1999;6:450-454.
29. Krag DN, Anderson SJ, Julian TB et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010;11:927-933.
30. Mansel RE, Fallowfield L, Kissin M et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. (Erratum in: J Natl Cancer Inst 2006;98:876). J Natl Cancer Inst 2006;98:599-609.
31. Chen J, Wu J. Management strategy of early-stage breast cancer patients with a positive sentinel lymph node: With or without axillary lymph node dissection. Crit Rev Oncol/Hematol 2011;79:293-301.
32. Zakaria S, Degnim AC, Kleer CG et al. Sentinel lymph node biopsy for breast cancer: how many nodes are enough? J Surg Oncol 2007;96:554-559.
33. Pargaonkar AS, Beissner RS, Snyder S, Speights VO Jr. Evaluation of immunohistochemistry and multiple-level sectioning in sentinel lymph nodes from patients with breast cancer. Arch Pathol Lab Med 2003;127:701-705.
34. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. Cancer 2006;106:4-16.
35. Langer I, Marti WR, Guller U et al. Axillary recurrence rate in breast cancer patients with negative sentinel lymph node (SLN) or SLN micrometastases: prospective analysis of 150 patients after SLN biopsy. Ann Surg 2005;241:152-158.
36. Smidt ML, Janssen CMM, Kuster DM, Bruggink EDM, Strobbe LJA. Axillary Recurrence After a Negative Sentinel Node Biopsy for Breast Cancer: Incidence and Clinical Significance. Ann Surg Oncol 2005;12:29-33.
37. Andersson Y, de Boniface J, Jönsson PE et al. Swedish Breast Cancer Group; Swedish Society of Breast Surgeons. Axillary recurrence rate 5 years after negative sentinel node biopsy for breast cancer. Br J Surg 2012;99:226-231.
38. Veronesi U, Paganelli G, Viale G et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. Lancet Oncol 2006;7:983-990.
39. Canavese G, Catturich A, Vecchio C et al. Sentinel node biopsy compared with complete axillary dissection for staging early breast cancer with clinically negative lymph nodes: results of randomized trial. Ann Oncol 2009;20:1001-1007.
40. Verry H, Lord SJ, Martin A et al. Effectiveness and cost-effectiveness of sentinel lymph node biopsy compared with axillary node dissection in patients with early-stage breast cancer: a decision model analysis. Br J Cancer 2012;106:1045-1052.