The role of sentinel node biopsy in male breast cancer

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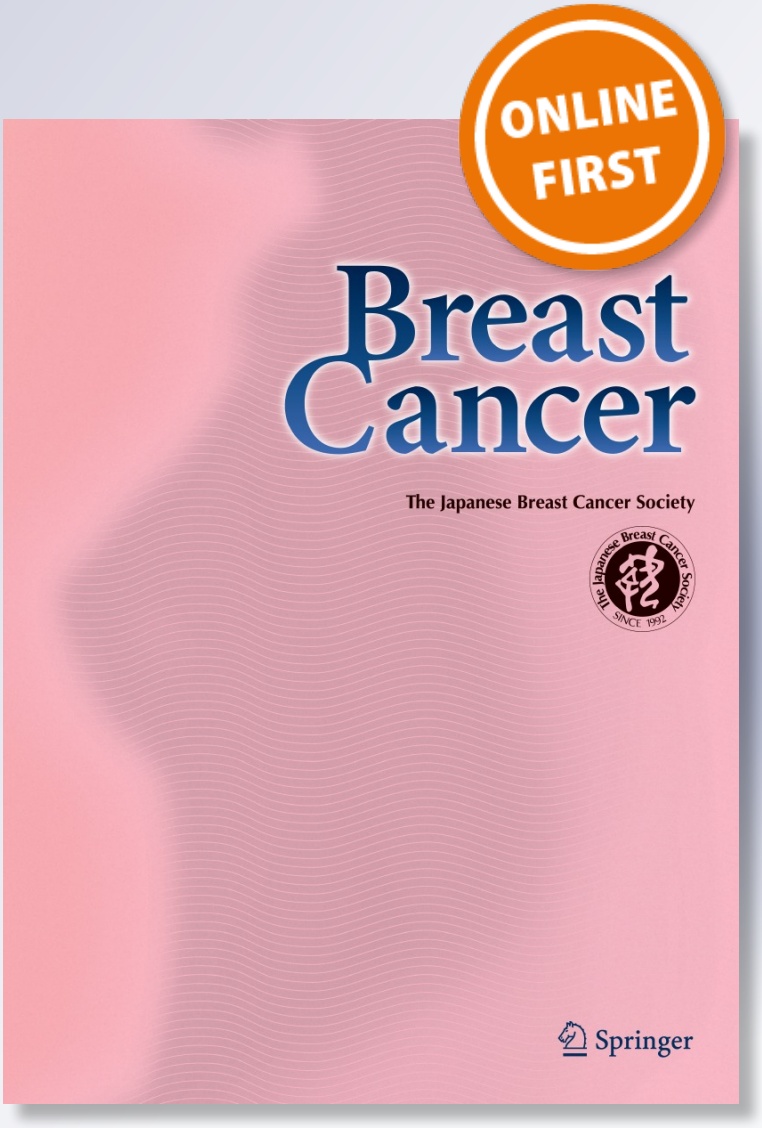

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ORIGINAL ARTICLE

The role of sentinel node biopsy in male breast cancer

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Abstract
Background Sentinel lymph node biopsy (SLNB) is a standard procedure in women with breast cancer. The risk of morbidity related to axillary lymph node dissection (ALND) is similar for men and women with breast cancer and SLNB could minimize this risk.
Methods Between January 2004 and August 2013, 25 men with primary breast cancer were operated on at the Bács-Kiskun County Teaching Hospital. These were reviewed retrospectively. SLNB was performed following lymphoscintigraphy with intraoperative gamma probe detection and blue dye mapping.
Results SLNB was successful in all 16 male patients (100 %), in whom it was attempted. The SLNs were negative in 4 cases (25 %) and were involved in 12. Intraoperative imprint cytology was positive in 9 of the 12 involved cases (75 %) and resulted immediate completion ALND. In 7 patients, the intraoperative imprint cytology was negative, with 3 false-negative results that resulted in delayed completion ALND. After a median follow-up of 48 months, there was only one axillary recurrence after ALND and none in the SLNB group.
Conclusions SLNB is successful and accurate in male breast cancer patients too. Although compared to women a larger proportion of men have positive nodes, for men with negative nodes, ALND-related morbidity may be reduced by SLNB. We recommend SLNB in male patients with breast cancer and clinically negative axilla.

Keywords Male breast cancer · Sentinel lymph node biopsy · Axillary block dissection

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Introduction

Male breast cancer (MBC) is a rare disease representing less than 1 % of all malignancies in men and only 1 % of all incident breast cancers (BC) [1–4]. Due to the rarity of male breast cancer, there is a lack of prospective clinical trials to define optimum treatment. Because of the low number of affected patients, treatment for MBC has been extrapolated from treatment protocols relating to breast cancer occurring in women. Mastectomy with axillary dissection is still the most commonly recommended procedure for MBC. There have been several reports on the use of sentinel lymph node biopsy (SLNB) in men, although the numbers of patients and length of follow-up

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have been limited [5–10]. The aim of our retrospective study was to investigate the role of SLNB in MBC.

Materials and methods

Selective axillary lymph node dissection based on the results of axillary SLNB was introduced in our hospital with the approval of the local ethical committee. Twenty-five MBC patients were operated on between January 2004 and August 2013. The majority of patients with MBC presented with a painless, subareolar mass, often associated with nipple retraction or discharge [11].

For most patients, the preoperative diagnosis of breast cancer was established by the combination of imaging (mammography and ultrasonography) and pathology, either fine needle aspiration (FNA) or core-needle biopsy (CNB) preceded by physical examination. Ultrasound-(US-) guided FNA was used as the first step for reaching a preoperative pathology opinion. Whenever the cytology results were non-conclusive CNB was performed as a next step, although some clinical settings (e.g., planned neoadjuvant treatment) resulted in CNB as a first approach. This stepwise diagnostic procedure is based on the availability of trained cytopathologists and cost-consciousness, as FNA cytology is faster and much cheaper in our setting. CNB allows a better distinction between invasive and in situ carcinoma and permits multiple immunohistochemical stains, and is therefore preferred over FNA biopsy of breast masses, but conclusive FNA may also help in the indication of definitive surgery. Axillary ultrasound (AXUS) routinely performed in all but a few patients at the beginning of the study period often helped in the demonstration of axillary lymph node involvement, as men were frequently diagnosed with locally advanced disease [12]. If an abnormal lymph node was noted during AXUS, FNA biopsy was done for preoperative staging and as an aid for decision making for neoadjuvant therapy. The FNA-based identification of metastatic nodal involvement resulted in the indication of axillary lymph node dissection (ALND).

Our technique of SLNB consisted of the intraparenchymal (intra- and/or peritumoral injection in 3–4 depots) administration of 60–90 MBq of a 99mTc-labeled colloid: either 200–600 nm particle size SENTISCINT (Medi-Radiopharma Kft., Érd, Hungary) or 40–80 nm particle size Nanoalbumon (Medi-Radiopharma Kft., Érd, Hungary) or Nanocoll (Gipharma, Saluggia, Italy). Superficial, periareolar injection of the radiocolloid according to the localization of the quadrant harboring the tumor was implemented as preferred method in January 2006.

Lymphoscintigraphy was generally performed 2 h after the administration of the radioactive tracer and the reading was often repeated the next day, shortly before surgery. The rationale for the second reading was the disappearance or late appearance of some hotspots, especially in the internal mammary (IM) region. The feasibility and utility of IM-SLNB was also studied during an overlapping period [13], and the disappearance of an IM-SLN representing hotspot resulted in no attempt to remove that lymph node. Only hotspots identifiable before starting surgery were looked for in the parasternal region, where the blue dye is not of much use in finding the SLNs [13].

Lymphoscintigraphic images were obtained in three standard positions: anterior, anterior oblique and lateral. After the induction of general anesthesia, 10–15 mins before the incision, 2 ml Patent Blue V dye (Laboratoire Guerbet, France) was injected intraparenchymally above the tumor. SLNB was performed before the removal of the primary carcinoma. To allow immediate axillary lymph node dissection (ALND) in patients with preoperatively detected metastasis, the SLNs sliced at about 2 mm intervals were evaluated by imprint cytology as a method of intraoperative assessment. After that, according to the tumor and patient characteristics, the primary breast tumor was removed by either breast conserving methods or by mastectomy. SLNs were defined as either blue nodes or nodes with an afferent blue lymphatic vessel pointing to them, or radioactive lymph nodes with an activity at least 10 times that of the background [14]. For the purpose of this study, lymph nodes suspicious on palpation during surgery were also included as SLNs [15]. Any of these features alone or in combination therefore identified a lymph node as SLN. Intraoperative identification of the SLNs was based both on gamma probe detection (C-Trak Surgical Guidance System, Care Wise Medical Products Corporation, Morgan Hill, CA, USA) and blue dye mapping. The final pathological evaluation of all SLNs included fixation in buffered formalin, embedding in paraffin and step sectioning at 250-μm intervals of all slices or unsliced lymph nodes smaller than 6 mm with hematoxylin and eosin staining of all, and immunostaining for cytokeratins of several levels [16]. With the exception of a few patients, ALND was also performed if metastases in the SLNs were discovered only in the permanent sections. The largest part of the study period used the 6th edition of the TNM classification of malignant tumors; consequently, this edition was used for staging purposes and the discrimination of metastases, micrometastases and isolated tumor cells (ITC) [17]. Statistical analysis for the comparisons included the student t test for continuous variables and the Chi-square test for categorical variables. The significance level chosen was $P < 0.05$.

Survivors were asked to complete a post-operative questionnaire about the subjective aspects of the disease. The questions referred to previous knowledge of the existence of MBC, family history, main apprehension when

finding out the diagnosis of breast cancer (surgery, chemo-hormone- or radiotherapy, work-related issues, sexual activity problems). The other set of questions referred to complaints relating to any motoric or sensorial disfunctions on the operated side (arm, hand). The last set of questions was about fears of breast cancer recurrence.

Results

A total of 25 consecutive male breast cancer patients were included in this review. Sixteen of them (64 %) had SLNB. The SLNB was successful in all cases. The remaining 9 patients (36 %) had primary ALND. The data of the 25 patients who had SLNB or ALND were analyzed in detail. The histological type of the tumors was as follows: invasive carcinoma of no special type (ductal carcinomas) ($n = 21$), invasive lobular ($n = 2$), invasive cribriform ($n = 1$) mixed invasive micropapillary carcinoma ($n = 1$). No significant differences were found between patients with SLNB or ALND in terms of age, tumor location, axillary involvement, tumor grade or estrogen receptor and HER-2 status (Table 1).

The only significant difference was in tumor size, with larger tumors found in the ALND patients. Breast conserving surgery was performed in only 1 patient.

Table 1 Characteristics of male breast cancers on a per intention to treat basis

Characteristic	ALND group ($n = 9$)	SLNB group ($n = 16$)	*P* value
Median age (years)	66	64.5	0.6
Tumor type			
IDC	8	13	0.25
ILC	1	1	
Other	0	2	
Tumor location			
Lateral or medial	1	2	0.92
Central	8	14	
Median tumor size (mm)	27	20	0.004
Axillary nodal status			
Negative	3	4	0.65
Positive	6	12	
Axillary ultrasound	5	12	
Tumor grade			0.053
I	1	2	
II	3	11	
III	5	3	
Estrogen receptor status		0	0.24
Positive	7	15	
Negative	2	1	
HER-2 receptor status			
Positive	8	16	0.17
Negative	1	0	

ALND axillary lymph node dissection, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *SLNB* sentinel lymph node biopsy

Male patients undergoing immediate ALND operation for breast cancer ($n = 9$)

The average age of the ALND group male patients was 66 years (range 48–82 years). All patients underwent mastectomy. Tumor location was central in the majority of patients, ($n = 8$) and lower upper quadrant ($n = 1$) in the remainder. The primary tumor ranged in size from 1.7 to 6 cm (average 2.7 cm). Four of the patients had large tumors: one measuring 4 cm and three measuring 6 cm. The axilla was clinically positive in two cases. Preoperative AXUS was used in 5 patients (55 %) and it showed pathologic lymph nodes in 2 cases. There was no axillary metastasis in 3 cases (33 %). The therapy used is summarized in Table 2.

The median follow-up in this group was 5 months (range 1–84). In one case, axillary lymph node metastases occurred in the opposite side two years after the initial

Table 2 Summary of treatment of male breast cancers (on treatment received bases)

Characteristic	ALND group ($n = 9$)	SLNB group ($n = 16$)
Type of the operation		
Mastectomy + ALND	9	
BCS + SLNB + I-ALND		1
Mastectomy + SLNB		4
Mastectomy + SLNB + I-ALND		8
Mastectomy + SLNB + D-ALND		3
Type of adjuvant systemic therapy		
Chemotherapy	5	8
Hormonal therapy	8	15
Type of radiation therapy		
WBI	3	3
WBI + RRT	6	8

ALND axillary lymph node dissection, *BCS* breast conserving surgery, *D-ALND* delayed completion axillary lymph node dissection, *I-ALND* immediate completion axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *WBI* whole breast irradiation, *RRT* regional radiotherapy

operation, and contralateral ALND was performed. Four patients died due to distant metastases and the progression of the disease after one, three, five and seven post-operative years, respectively.

Male patients undergoing SLNB operation for breast cancer ($n = 16$)

The average age of the SLNB group male patients was 64.5 years (range 47–76 years). Tumor location was central in the majority of patients, ($n = 14$) and lower outer quadrant ($n = 2$) in the remainder. The primary tumor ranged in size from 0.6 to 3.5 cm (mean 1.9 cm). All patients had a negative axillary status on physical examination. Preoperative AXUS was used in 12 patients (75 %) and it was negative in all of them. Preoperative lymphoscintigraphy was performed in all 16 patients and revealed drainage to the axilla in 15 of them, the axilla and the internal mammary region in the remaining 1 case. Intraoperatively, at least one axillary SLN was identified in all 16 patients (100 % identification rate). In one case, we found 4 macroscopically malignant SLNs by intraoperative palpation and decided for immediate ALND. The mean number of SLNs removed at operation was 1.5 (range 1–5), which is very much in keeping with our validation series from the nineties, where the mean number of SLNs was 1.3, the accuracy and false-negative rates were 99 and 3 %, respectively, with the dual labeling method [18].One IM-SLN and one intramammary SLN were excised during the study period. In the patient with the IM-SLN identified, this lymph node was free of metastasis, but the two axillary SNs of the patients were metastatic, one had a micrometastasis (MIC) and the other a macrometastasis (MAC). Therefore, ALND was performed and 17 further uninvolved axillary nodes removed. In the patient with an intramammary SLN, this node contained a MIC and ALND was done with the removal of 23 lymph nodes of which one harbored a MAC. In the SLNB group, intraoperative imprint cytology of the SLN was positive in 9 cases and in these we performed immediate completion ALND. In the remaining 7 patients, the intraoperative imprint cytology was negative. In 3 of them, the final histological examination proved SLN involvement (none belonged to the MAC category), and delayed completion ALND was done. Overall, the sensitivity and specificity of the intraoperative cytology were 75 % (95 % CI 47–91 %) and 100 % (95 % CI 51–100 %), respectively. The surgical and adjuvant treatments are listed in Table 2.

Of the 16 cases with successful SLNB, the SLN was involved in 12 patients (75 %); 9 patients had MAC, 2 patients had MIC, and 1 patient had isolated tumor cells (ITC). In the majority of successful cases, SLNs were identified by both blue dye and isotope (12 cases 75 %). In the case of SLN ITC, we could not find non-SLN involvement. In the MIC group, we found non-SLN involvement in one of the 2 patients. In the MAC group, non-SLN involvement was present in 4 of the 9 patients. The lymph node involvement in the ALND and the SLNB group of patients with MBC is summarized in Fig. 1.

The median follow-up time in the SLNB group was 68 months. None of the patients who underwent SLNB alone had an axillary recurrence during this time. Five of the 16 SLNB patients of this study died, one of distant metastases of breast cancer in the lung five years after the operation, and four of unrelated causes (pneumonia and cardiorespiratory insufficiency after 3, 7, 7 and 9 years after the operation, respectively).

The median follow-up time for all 25 patients was 48 months (range 1–140). Finally, ALND was performed in 21 patients. Five of these 21 patients had lymphedema (24 %), appearing after 1 ($n = 1$), 1.5 ($n = 2$) and 2 ($n = 2$) years after the operation. In 3 cases, the lymphedema receded significantly after one year of physiotherapy. A total of 9 patients have died.

Out of the surviving 16 patients, 15 have answered a post-operative questionnaire about the subjective aspects of the disease. The most interesting finding was that 13 (87 %) out of the 15 patients had no previous knowledge of the existence of MBC. Two patients had a positive family history: one's daughter and another's sister had breast cancer. The patients were most afraid of surgery and chemotherapy. The 4 patients who had undergone SLNB only did not complain of any motoric or sensorial problems on the operated side (arm, hand). Nine of the responding patients were in the ALND group. Eight of them complained of minor (5) or moderate (3) motoric or sensorial problems on the operated side (arm, hand) 0.12 of the questioned patients (80 %) are seriously worried about a possible relapse of the disease and are happy about being under follow-up care having regular check-ups done.

Discussion

Because of the lack and uselessness of general screening in this sex, MBC is rarely detected mammographically. It most manifests as a palpable mass, at a later stage and a larger tumor size. The majority of MBC patients undergo mastectomy because of the small breast size and subareolar location of most malignancies [19]. Because of the low incidence, treatment for breast cancer in men has been extrapolated from the experience of treatment of breast cancer in women, without the benefits of randomized trials. ALND is associated with a number of complications,

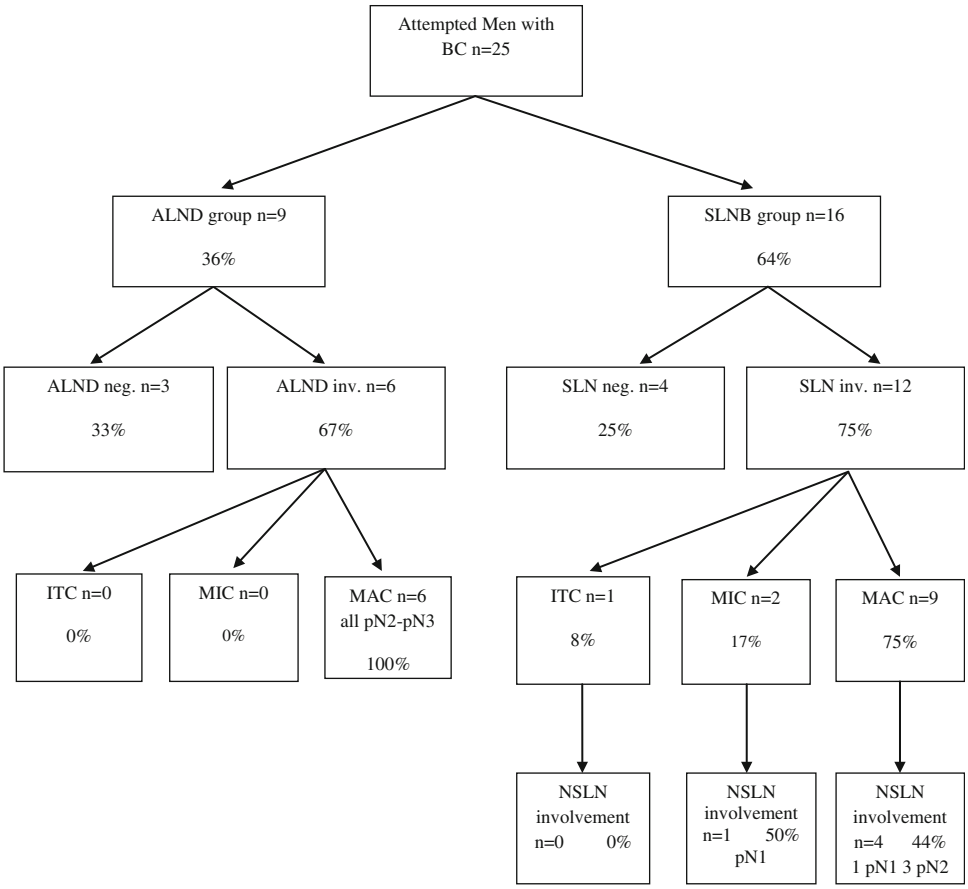

Fig. 1 Lymph node involvement in ALND and SLNB group of patients with MBC. *ALND* axillary lymph node dissection, *BC* breast cancer, *ITC* isolated tumor cells, *inv* involvement, *MAC* macrometastases, *MBC* male breast cancer, *MIC* micrometastases, *n* number, *neg* negative, *NSLN* non-sentinel lymph node, *SLN* sentinel lymph node, *SLNB* sentinel lymph node biopsy

including lymphedema, axillary paresthesia and decreased range of motion of the shoulder and arm. SLNB permits removal of a smaller number of lymph nodes that can be subjected to a more detailed pathologic examination, resulting in improved staging of the regional lymph nodes [20]. Randomized trials have also demonstrated decreased morbidity with SLNB compared to ALND, and SLNB has rapidly been incorporated into the treatment of women with early-stage breast cancer [21–27]. The first SLNB in MBC was reported in 1999 by Hill and colleagues [7] from the Memorial Sloan-Kettering Cancer Center. Since that report, its use has increased and there are several additional studies reporting on 6, 9, 16, and 18 patients [6, 8–10]. Since the experience was published in 2004, SLNB has been routinely offered to all male patients with breast cancer and clinically negative axillary nodes, according to the standard policy applied to women with breast cancer at the European Institute of Oncology, Milan, Italy [9]. Frequently, breast cancer in men is diagnosed at an advanced stage, making SLNB inappropriate, but still a considerable proportion of patients present with a clinically negative axilla, therefore making them candidates for a less invasive method of axillary staging.

At the beginning of the study period, mastectomy was performed with immediate ALND, without attempting SLNB. The reasoning behind this policy was as follows: the size of tumors in males is typically larger compared to females, larger tumors are more often accompanied by lymph node metastases, and there were insufficient data on the role of SLNB in male patients. This approach was used in 9 patients. The final histological examination of the ALND specimen proved to be negative in 3 of them. One of these cases was seen in 2004, at the beginning of the examined period, before the accumulation of sufficient evidence allowing SLNB in MBC. The second patient was 82 years old, and the avoidance of a possible second axillary operation in case of a metastatic SLN arguably deviated us from SLNB. The last patient had a 4-cm-large tumor and had a strong clinical suspicion of axillary metastases.

In our experience, 4 of 16 patients (25 %) who underwent SLNB were spared an unnecessary axillary dissection. Should SLNB been performed in all male patients with clinically negative axillae, 3 further men could have been spared the potential morbidity of ALND, and this rate could have been 7/25. As shown in Table 1, the group

Table 3 Summary of literature on male sentinel node biopsy in breast cancer

References	Number of patients	SLNB successful (%)	SLNB positive (%)	Median age (years)	Palpable mass (%)	Mean tumor size (cm)	Tumor histology (IDC) (%)	ER positive (%)	Mastectomy (%)
Flynn et al. [34]	78	97	49	60	77	1.9	83	98	–
Rusby et al. [35]	31	96	61	62	42	1.9	84	100	81
Boughey et al. [28]	30	100	37	62.5	80	2	83	97	100
Gentilini et al. [36]	32	100	19	58		<1 in 70 %	71	100	100
Our results	16	100	75	61	78	1.9	81	94	94

cm centimeter, *ER* estrogen receptor, *IDC* invasive ductus carcinoma, *SLNB* sentinel lymph node biopsy

treated with upfront ALND was not very much different from the one where SLNB was attempted, except for tumor size and the 2 cases where the axilla was clinically positive.

The SLN biopsy procedure is a technically feasible and accurate method of evaluating males with clinically node-negative BC [8, 28]. If an SLN is positive for metastatic disease, complete axillary node dissection has been recommended [29]. Owing to the relatively high rate of nodal involvement, intraoperative SLN examinations are of value. The sensitivity of imprint cytology found in our small series does not seem very gratifying, but is in line with the 63 % (95 % CI 57–69 %) pooled sensitivity of the method reported by a meta-analysis [30], and if only MACs are considered, the sensitivity goes up to an idealistic 100 %. Although the choice of intraoperative assessment should be based on local preferences and expertise [31], frozen sections seem somewhat better than imprint cytology [32], but both methods become worse with MICs. Quantitative molecular methods like one step nucleic acid amplification are probably the most sensitive methods, if one wants to detect virtually all MICs [33]. Table 3 shows details and main results of larger SLNB studies relating to MBC. Our experience is in keeping with the data summarized in Table 3. Compared to female patients, a larger proportion of male patients (75 %) have positive nodes, but for patients with clinically negative nodes, SLNB may reduce morbidities associated with ALND. The feed-back from the patients in our questionnaire shows that in the SLNB group patients had no motoric and sensory problems as opposed to the ALND group where a large majority complained about these, and this supports the idea that SLNB is associated with less morbidity than ALND in male patients too. A panel of the American Society of Clinical Oncology stated that "although the data are limited… it is unlikely that SLNB will be any less accurate in men than it is in women" [35]. The cumulative evidence from previously published and the current series support this notion. In the absence of stronger evidences based on larger numbers, it seems reasonable to recommend modified radical mastectomy as the gold standard in men, in whom an SLN cannot be identified.

We conclude that SLN operations in male patients with clinically node-negative BC are feasible and accurate and appear to be an appropriate alternative to routine ALND. Intraoperative evaluation of the SLN should be strongly considered in the surgical management of MBC patients.

Conflict of interest None declared.

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