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Intraoperative training on the techniques of sentinel node biopsy in breast cancer

THESE

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Abstract

Key words: breast cancer, sentinel node biopsy, axillary lymph node dissection, learning curve.

Principles: Surgeon's experience is crucial for proper application of sentinel node biopsy (SNB) in patients with breast cancer. A 20-30 cases learning curve of sentinel node (SN) and axillary lymph node dissection (ALND) was widely practiced. In order to speed up this learning curve, surgeons may be trained intraoperatively by an experienced surgeon. The purpose of this report is to evaluate the results of this procedure.

Methods: Patients with one primary invasive breast cancer (cT1-T2[<3 cm]cN0) underwent SNB based on lymphoscintigraphy using technetium Tc 99m colloid, intraoperative gamma probe detection, with or without blue dye mapping. This was followed by completion ALND when SN was positive or not found. SNB was performed by one experienced surgeon (teacher) or by 10 junior surgeons trained by the experienced surgeon (trainees). Four groups were defined: (i) SNB with immediate ALND for the teacher's learning curve, (ii) SNB by the teacher, (iii) SNB by the trainees under the teacher's supervision, and (iv) SNB by the trainees alone.

Results: Between May 1999 and December 2007, a total of 808 evaluable patients underwent SNB. The SN identification rate was 98% in the teacher's group, and 99% in the trainees' group ($p = 0.196$). SN were positive in respectively 28% and 29% of patients ($p = 0.196$). The distribution of isolated tumor cells, micrometastases and metastases was not statistically different between the teacher's and the trainees' groups ($p = 0.163$).

Conclusion: These comparable results confirm the success with which the SNB was taught. This strategy avoided the 20-30 SNB followed by immediate ALND early required per surgeon.

Introduction

Axillary staging is the most important prognostic factor for selection of appropriate adjuvant therapy, for locoregional recurrence and for long-term survival in breast cancer patients and was traditionally achieved by axillary lymph node dissection (ALND) [1, 2]. With the trend towards earlier detection and presentation of breast cancer, most patients do not have lymphatic metastases at diagnosis. Herein lies an irony: with widespread use of breast conservative surgery, the ALND carries a great morbidity [3, 4, 5].

Methods for accurately staging the axilla remain dominated by sentinel node biopsy (SNB), which is now accepted as a standard of breast surgery [6]. The aims of SNB include avoiding the unnecessary removal of uninvolved lymph nodes with standard ALND, preventing the morbidity of ALND and improving the pathologic examination by focusing on fewer lymph nodes [7, 8]. Risks of arm and shoulder morbidity (eg. pain, lymphedema and sensory loss), drainage, length of hospital stay, and time to resumption of normal day-to-day activities after surgery decrease significantly in patients undergoing SNB compared to patients undergoing ALND [2, 9].

Using a radiocolloid alone, Krag et al. first reported SNB in 18 out of 22 patients with breast cancer [10]. Using vital blue, Giuliano et al. were able to localize SN in 114 out of 174 patients (65.5%) [11]. Then the concept that sentinel node (SN) could be localized in breast cancer and that it was predictive of the axillary status was validated [12, 13, 14, 15]. Moreover it is now established that rates of clinical regional recurrence in patients with negative SNB, who had not proceeded to ALND, range from 0 to 1.4% [6, 16, 17,].

The identification of SN is directly related to the surgeon's experience. Performance and technical failure data are correlated with the number of cases. A study demonstrated that an average of 23 procedures are required for a surgeon to achieve a SNB success rate of 90% and that 53 cases allow to reach 95% [18]. A 20-30 cases learning curve is widely recommended [19, 20, 21].

We tried to speed up this learning curve, surgeons being trained in operative room by one instructor. The purpose of this report is to evaluate the procedure by comparing SN identification rates, SN status, the number of micrometastases or metastases of patients operated by the teacher and by the trainees.

Material and methods

Between May 1999 and December 2007, 808 patients with one primary invasive breast cancer (cT1-T2[<3 cm]cN0) underwent a sentinel node biopsy (SNB) with one experienced surgeon (teacher) or with 10 junior surgeons, trained by the teacher (trainees), the patients having given their informed consent.

In the Centre Hospitalier Universitaire Vaudois and in four community hospitals, four groups were defined: (i) SNB with immediate ALND for the teacher's learning curve, (ii) SNB by the teacher, (iii) SNB by the trainees under the teacher's supervision and (iv) SNB by the trainees alone. Training was based on 5-10 cases per surgeon. The criteria of patient selection, the parameters of success of the sentinel node (SN) procedure and the lymph node metastases were compared in all groups but the reported p-values are only compared between group (ii) and (iv).

Lymphatic mapping was obtained by peritumoral or periareolar injection of 2-5 ml technetium 99m colloid and lymphoscintigraphy, performed the day before surgery. Location of SN was achieved in the operative room with a hand-held gamma probe (Neoprobe®), with or without peritumorally blue dye injection. SNB was performed prior to the breast surgery, allowing an intraoperative examination of the SN using the touch imprint cytology technique [22]. Completion ALND of levels I and II was performed when SN was positive for metastasis or when the SN could not be identified. SN were assessed for the presence of metastases by both hematoxylin and eosin (H&E) staining and cytokeratine immuno-histochemistry (IHC).

Results

After having completed his learning curve of 40 sentinel node biopsies (SNB) followed by completion axillary lymph node dissection (ALND), the teacher operated 138 patients. 10 trainees operated 159 patients under the teacher's supervision, and then 471 patients alone.

Patients' characteristics are listed in Table 1. The median age was 56±11 (ranging from 28 to 85 years) in the teacher's group and 60±12 (ranging from 26 to 92 years) in the trainees' group. Ductal carcinoma was the most frequent type. Stage IC (11-20 mm) was the most common. Grade 1 differentiation was diagnosed in 38% of patients in the teacher's group and in 28% of patients in the trainees' group, whereas grade 2 was found in respectively 36% and 53% of patients, and grade 3 in respectively 26% and 19% of patients ($p = 0.003$).

The SN identification rate of the teacher and the trainees was respectively 98% and 99% (Table 2). SN was positive for metastasis in 31% of patients in the teacher's group and in 29% in the trainees' group ($p=0.092$). Then ALND was performed. ALND was performed in 3 patients in the teacher's group and in 4 patients in the trainees' group, because no SN was detected. Lymph nodes (LN) were negative in the 3 patients of the teacher's group, and positive in 3 out of 4 patients in the trainees' group. Isolated tumor cells or micrometastases were detected in 130 patients (54%) and metastases were detected in 113 patients (46%) out of 243 patients with positive LN. Even if isolated tumor cells and micrometastasis were proportionally more frequent in the teacher's group (70%) than in the trainees' group (53%) (Table 3), the overall percentage of women with positive LN was not statistically different ($p = 0.833$), thus confirming that the SNB technique was correctly taught. Postoperative evaluation revealed distant metastases in 12 patients; SN was positive in all of them.

Discussion

The primary aims of breast cancer surgery are to obtain local and regional control of the cancer and gather sufficient information to make an accurate prediction of the risk of distant metastasis in order to guide systemic therapy. This has traditionally been achieved by lumpectomy and axillary lymph node dissection (ALND). A meta-analysis compared mastectomy or lumpectomy plus radiation with or without ALND and reported a significant pooled survival benefit of 5.4% (95% CI 2.7%-8.0%, $p<0.01$) favouring ALND [23]. Although this meta-analysis suggests a significant survival benefit with ALND, evolving approaches in surgical management, radiotherapy, adjuvant systemic therapy and screening practices may limit the magnitude of survival benefit on women treated with current breast cancer therapy [24]. Other data tend to diminish the conclusions of this meta-analysis. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 study, a 25-year follow-up failed to show a significant difference in overall survival between the groups with and without ALND (25% v. 26% respectively) [25]. Rates of distant disease-free survival were respectively 46% and 43% in the groups with and without ALND (HR = 1.10, 95% CI 0.89-1.35) [25]. Moreover, ALND has significant short- and long-term morbidities, the most significant being lymphedema [7].

In comparison, sentinel node biopsy (SNB) is a minimally invasive technique to stage the axilla in breast cancer, and randomized trials comparing SNB and ALND have demonstrated a significantly reduced morbidity in SNB compared to ALND [2,9,26]. Moreover, SNB reflects the status of the axilla in 97-99% of cases [27, 28], and many studies validated the technique demonstrating a high sentinel node (SN) identification rate (>90%) and low false negative rates (ranging from 5.1 to 9.8%) [6, 13, 27, 29, 30] (Table 4). When the SN is free of tumor, the probability of non-SN involvement is <0.1% [37]. A further benefit of SNB is the possibility of targeting intensive histopathological examination by analysis of multiple sections of the nodes with the use of immunohistochemicals (IHC), which increases the sensitivity of detection [7, 38].

Preoperative identification of SN is highly predictive of the success of the subsequent procedure [7] thanks to identification of an unexpected drainage route, especially

non-axillary LN [15, 39, 40]. In this series, when SN were detected with the radiotracer, the SNB succeeded in 99% of patients. Patient selection, timing as well as location of injection of radionucleide may influence the SN identification [41]. The SN identification rate is higher and the false negative rate is lower when the radiocolloide is used alone or in combination with blue dye than when blue dye is used alone [35, 42]. This labeling technique with blue dye is now abandoned in our breast unit, since it caries a risk of allergy (ranging from trivial skin rashes to life threatening anaphylaxis) in 1-2% of patients [43, 44].

In this series, failure to identify SN was probably due to metastases in 3 out of 4 patients in the trainees' group, since grossly metastatic disease may cause a blockage to the flow of lymphatic fluid through the afferent lymphatics. Potential candidates for SNB should have clinically negative axillary LN (cN0), or a negative core or fine needle aspiration biopsy of any clinically suspicious axillary LN(s) [45]. We have no explanation for the other 4 failures of SN identification, even if other reasons for failure may include age and high BMI [8, 46, 47], but these parameters were not analyzed.

Adequate surgeon education has been identified as a critical factor for the successful application of new surgical procedures, although the required experience still remains controversial. Early study of SNB advocated a training set of 60 to 80 cases to achieve acceptable SN identification rate and to minimize false-negative events [48]. Subsequent studies advocated performance of 20 to 30 consecutive SNB followed by ALND and defined a minimal success rate of 85% for the identification of SN based on observed learning curves at pioneering institutions [19, 21, 49-52]. Bass et al. reported that an average of 23 patients per surgeon is required to achieve a 90±4% success rate and that 53 patients are required to obtain a success rate of 95±2% [53]. An English structured program called 'New Start' was developed to teach the SN technique [2]. Surgeons were trained on-site for 5 cases. Then they had to perform an audit series of 25 SNB and immediate ALND. The aim of the audit series was to verify that the surgeon with the assistance of the multidisciplinary team was able to identify the SLN in >90% of patients [2]. The American Society of Breast Surgeons SLNB Consensus Statement supports performing 20 cases of SNB and ALND and states that the use of mentoring, proctored cases and formal training in

accredited continuing medical education courses may reduce the personal case experience necessary to achieve optimal results [21]. We may wonder whether it is ethical to subject a woman to ALND, if she is candidate for SNB alone, purely for the purposes of surgical education. Along with others, we support the complete abandon of the learning curve [54]. The comparable results between the teacher and the trainees confirm the success with which the SNB was taught. In this series, 10 trainees were enrolled. Traditionally, they would have to operate an average of 250 patients during their learning curve. Thanks to our mentoring technique, 70% of patients (175 of the 250 pN0(sn) patients) were spared of ALND.

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Table 1: Patient characteristics

	Teacher learning (%)	Teacher (%)	Trainees learning (%)	Trainees taught (%)	All (%)	*p*-value
Median age (years)	59±12	56±11	59±11	60±12	59±11	0.031
Stage						
T1a	1 (2)	15 (11)	20 (13)	44 (9)	77 (10)	0.236
T1b	12 (30)	40 (29)	33 (21)	116 (25)	201 (25)	
T1c	17 (43)	62 (45)	78 (49)	233 (49)	390 (48)	
T2	9 (23)	19 (14)	26 (16)	76 (16)	130 (16)	
T3	1 (2)	2 (1)	2 (1)	2 (1)	7 (1)	
Differenciation						
G1	17 (42)	52 (38)	55 (34)	129 (27)	253 (31)	0.003
G2	15 (38)	49 (35)	71 (45)	249 (53)	384 (48)	
G3	8 (20)	36 (26)	30 (19)	90 (19)	164 (20)	
Unknown	0 (0)	1 (1)	3 (2)	3 (1)	7 (1)	
Histology						
Ductal	32 (80)	110 (80)	111 (70)	348 (74)	601 (75)	0.290
Lobular	4 (10)	16 (12)	18 (12)	55 (11)	93 (12)	
Tubulous	3 (8)	7 (5)	9 (6)	19 (4)	38 (5)	
Mucinous	1 (2)	0 (0)	7 (4)	7 (2)	15 (2)	
Ductal & lobular	0 (0)	4 (3)	7 (4)	31 (7)	42 (5)	
Other	0 (0)	1 (1)	7 (4)	11 (2)	19 (2)	
Palpable						
Yes	14 (35)	64 (46)	72 (45)	242 (51)	392 (49)	0.012
No	26 (65)	74 (54)	79 (50)	211 (45)	390 (48)	
Unknown	0 (0)	0 (0)	8 (5)	18 (4)	26 (3)	
Surgery						
Lumpectomy	40 (100)	124 (90)	150 (94)	433 (92)	747 (92)	<0.001
Mastectomy	0 (0)	14 (10)	9 (6)	38 (8)	61 (8)	
Distant metastases						
No	39 (98)	134 (97)	157 (99)	466 (99)	796 (99)	0.123
Yes	1 (2)	4 (3)	2 (1)	5 (1)	12 (1)	

Table 2. Sentinel nodes characteristics

	Teacher learning (%)	Teacher (%)	Trainees learning (%)	Trainees taught (%)	All (%)	*p*-value
Identification rate	39 (98)	135 (98)	154 (97)	467 (97)	795 (99)	0.196
SN not found	1 (2)	3 (2)	5 (3)	4 (1)	13 (2)	0.003
Metastases						
Positive SN	11 (28)	43 (31)	44 (28)	138 (29)	236 (29)	0.092
Positive ALND with no SN found	0 (0)	0 (0)	4 (3)	3 (1)	7 (1)	
Total	11 (28)	43 (31)	48 (30)	141 (30)	243 (30)	0.833

Table 3. Isolated tumor cells, micrometastases and metastases in sentinel nodes

	Teacher learning (%)	Teacher (%)	Trainees learning (%)	Trainees taught (%)	All (%)	*p*-value
Isolated tumor cells (IHC)	0 (0)	9 (21)	6 (13)	22 (16)	37 (15)	0.163
Micrometastases (IHC)	2 (18)	2 (5)	2 (4)	14 (10)	20 (8)	
Micrometastases (H&E)	2 (18)	19 (44)	14 (29)	38 (27)	73 (30)	
Metastases (H&E)	7 (64)	13 (30)	26 (54)	67 (47)	20 (8)	
Total	11 (100)	43 (100)	48 (100)	141 (100)	243 (100)	

Table 4 : SN identification in the literature

Author	Publication year	Number of patients In the study	SN identification Rate [%]	False negative [%]	Negative predictive value [%]
Krag [10]	1993	22	82	0	100
Giuliano [11]	1994	174	66	12	96
Giuliano [31]	1997	107	93	0	100
Günther [32]	1997	145	71	10	96
Veronesi [12]	1997	163	98	5	98
Cox [14]	1998	466	94	1	99
Krag [15]	1998	443	93	11	96
Veronesi [28]	1999	376	99	7	94
Fraile [33]	2000	2569	91	2	97
McMasters [34]	2000	562	90	6	98
Cody [35]	2001	4333	90	5	-
Posther [8]	2005	5327	99	-	-
Povoski [36]	2007	371	95	-	-
This series	2009	808	98	-	-