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Detection and credibility of sentinel node in vulvar cancer: a single institutional study and short review of literature

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Abstract
Purpose To evaluate the detectability and credibility of sentinel lymph node (SLN) in vulvar cancer.
Methods With Tc99m-nanocolloid and methylene blue, we identified SLNs in 34 patients. In 27 cases both tracers were used, while in 7 only blue dye was used. Completion lymphadenectomy was performed in all patients. SLNs and non-SLNs were sent separately for pathologic evaluation.
Results At least one SLN was identified in all patients. Detection rate per groin was not significantly higher in the combined versus blue dye only technique (42/50 vs. 10/14, $p = 0.43$). 99m-Tc was not superior to blue dye in detecting SLN (42/50 vs. 50/64, $p = 0.65$). Midline location of the tumor did not seem to negatively affect the procedure. Four false negatives were observed in three patients with tumors >4 cm. Negative predictive value of SLN was 100% for grade I tumors ≤4 cm in patients ≤71 years.
Conclusion Tc-99m does not seem to be superior to methylene blue in the detection of SLN in vulvar cancer. Patients of younger age with small, well-differentiated tumors appear to be the most suitable candidates for lymphatic mapping.

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Introduction

Radical vulvectomy and inguinofemoral lymphadenectomy for the management of vulvar cancer are associated with high complication rates and long-term morbidity in the form of wound breakdown, lymphedema, cellulitis and recurrent erysipelas [1]. The initial standard approach to vulvar cancer was an en bloc resection of the vulva and groins with a single incision [1]. To reduce the complications associated with such a major surgical intervention, the triple incision technique was introduced with three separate incisions for removal of the central tumor and the inguinofemoral lymph nodes (LN), without compromising the prognosis [2]. A GOG study tried to assess whether a more conservative approach with only superficial lymphadenectomy could reduce morbidity. However, it had to close prematurely because of a high recurrence rate of 7.3% in the groins [3]. Furthermore, severe morbidity was not remarkably reduced.

Nodal metastasis represents the most important prognostic factor for recurrence and death, and is reported to be as high as 27% [4, 5]. Tumor size, depth of invasion and lymph vascular space involvement are all positively correlated with nodal disease [4]. Since diagnostic procedures such us ultrasound, CT, MRI, PET or fine needle biopsy by ultrasound guidance prove to be inaccurate predictors of LN status, the gold standard remains surgical excision and histological evaluation [6–14]. If not removed, they should at least be accurately assessed as being "negative", so that no nodal disease is left behind.

For all these reasons, during the last decade, the "sentinel lymph node" (SLN) concept has been introduced,

with the SLN considered as the "gate" for spread of the disease. Whether SLN can be detected and if its status represents an accurate predictor of inguinofemoral LN status still remain a controversial issue for most gynecologic oncology units, even after publication of a large multicenter study by Van der Zee et al. in 2008 [15].

In this current study, we tried to examine detectability of SLN by 99m-Tc-nanocolloid and methylene blue and determine its negative predictive value in correlation with size, grade, location of the tumor and age of patients.

Materials and methods

From February 2006 till January 2010, 82 patients were admitted to our department with histologic confirmation of vulvar cancer. Of these, only 34 met the inclusion criteria and entered this study after their informed consent. The study was approved by the scientific and ethical committee of our hospital. Inclusion criteria were: (a) squamous cell carcinoma, (b) depth of invasion more than 1 mm, (c) cancer verified by punch and not excisional biopsy, (d) tumors smaller than 8 cm. Patients with suspicious LNs on the preoperative clinical or imaging evaluation were excluded.

Technique

Of 34 patients, 27 underwent four intradermal peritumoral injections of 99m-Tc-nanocolloid 24 h before surgery (each injection containing 0.5 mCi in a volume of 0.3 ml). Thirty minutes after injection, lymphoscintigraphy followed and sentinel nodes as well as other nodes (second-echelon nodes, which did not seem to have direct lymphatic connection with the lesion) were demonstrated. The supposed to be sentinel nodes were marked on the skin of our patients with ink, so that they could be more easily identified on the day of surgery. On the next day after induction of general anesthesia and 10 min before groin dissection, methylene blue dye was injected intradermally around the tumor in a similar manner to 99m-Tc-nanocolloid in all 34 patients (4 injections containing 1 ml of methylene blue and 1 ml of normal saline 0.9% NaCl). A handheld γ-probe was used intraoperatively to identify the "hot" sentinel node (defined as the number of counts greater than 5% of that at the injection site or greater than 10% of the "hottest" sentinel node). A standard inguinal incision was performed and sentinel nodes were identified, removed and sent separately for pathologic evaluation. A sentinel node could be "hot" and blue, "hot" only or blue only. A completion dissection followed in all patients and the remaining inguinofemoral lymph nodes were removed and sent to the pathologist. After excision of the central tumor, the groins were scanned once more to make sure that no sentinel node was left behind.

All inguinal nodes were examined by conventional H–E staining. Sentinel nodes found to be negative by H–E were examined thoroughly by ultrastaging (more step sections every 250 μm and immunohistochemical staining with cytokeratins AE1/AE3, ZYMED, CA USA), so that no "micrometastasis" would be missed. All patients were staged according to FIGO 1994 classification for vulvar cancer and treated according to our protocols [16].

Statistical results were evaluated by SPSS using Fisher's exact probability test. Statistical significance was set at $p < 0.05$.

Results

A total of 34 patients with a mean age of 69.1 years (range: 35–86) entered our study and 64 inguinal node dissections were performed (4 patients with severe comorbidities and lateral tumors had unilateral groin dissection). Eighteen patients (53%) had stage I/II disease, while the remaining 16 (47%) had stage III/IV.

At least one SLN was identified in all patients and in 52 out of 64 dissections (detection rate 34/34–100% per patient, 52/64–81.2% per groin). In the 12 groin dissections, in which no SLN was identified (detection failure), there was no metastasis. These 12 groins were at the contralateral side of the primary tumor. Detection rate per lymphadenectomy was not higher in the 27 patients in whom both radiocolloid and blue dye were used compared to the 7 patients in whom only blue dye was used (84 vs. 71.4%, $p = 0.43$). Mean time between groin incision and SLN detection was also comparable between these two groups (10.1 min vs. 11.3 min).

A total of 80 SLNs were recognized in 64 lymphadenectomies and 18 contained metastasis (22.5%). Only one SLN of these 18 was initially negative with the conventional H–E staining and finally did contain a "micrometastasis", when it was ultrastaged. The average number of SLN identified was 1.25 per groin (range 0–5), while the average number of total lymph nodes and non-sentinel nodes removed per groin was 11.45 and 10.2, respectively. In the 27 cases, 69 SLNs were identified, in which both radiocolloid and blue dye were used. All of them were "hot" (100%) and 65 of them (94.2%) were also blue. One "hot" SLN that was not blue was metastatic.

Nineteen groins contained metastasis (Table 1). In 11 of them, the SLN was the only positive node, in 4 cases SLN and non-SLNs were affected by the disease, while 4 cases of "false negative" SLN were observed (2 of them in one patient with bilateral "false-negative" SLN).

Table 1 Status of SLN and non-SLN in dissected groins

Number of groins	SLN status	Non-SLN status
33	Negative	Negative
11	Positive	Negative
4	Positive	Positive
4	Negative	Positive

SLN sentinel lymph node

No significant differences were observed in the detection rate between the two tracers. At least one SLN was identified by Tc-99 m in 42/50 and by blue dye in 50/64 lymphadenectomies (84 vs. 78%, $p = 0.65$, Table 2). Furthermore, in metastatic groins, SLN was correctly identified in 13/17 for Tc-99 m and in 14/19 groins for blue dye (76 vs. 74%, p = 0.62, Table 3).

Overall, the negative predictive value of the SLN in our study was 89.2% (95% CI: 75–97%). When this was adjusted for grade, it was estimated to be 100, 89.4 and 84.6%, for grade I, II and III, respectively (all cases of false negatives concerned grade II/III tumors). In addition, negative predictive value was 100% for the 25 patients with tumors ≤4 cm and decreased to 50% for the remaining 9 with tumors >4 cm (all cases of false-negative sentinel node were observed in tumors of largest dimension 5, 5.5 and 8 cm). Concerning topography of the tumor, there was no case of false-negative SLN in the midline and posterior lesions. All these cases were observed in anterior lateral lesions. When we equally divided our study group according to age (17 patients ≤71 and 17 patients >71 years), we observed that there was no case of false-negative SLN for the younger women ≤71. Negative predictive value was 100% for this subgroup of patients (95% CI: 79–100%). Characteristics of false-negative cases are summarized in Table 4.

Table 2 SLN detection results with Tc-99m and methylene blue

SLN detection method	Groins with at least one SLN detected	
Tc-99 m	42/50(84%)	$p = 0.65$
Blue dye	50/64(78%)	

SLN sentinel lymph node

Table 3 SLN detection in metastatic groins

Number of groins with metastasis	19	
SLN correctly identified by Tc-99 m	13/17(76%)[a]	$p = 0.62$
SLN correctly identified by blue dye	14/19(74%)	

[a] Tc-99 m was not used in two groins containing metastasis

SLN sentinel lymph node

Discussion

Overall, there have been 21 reported series evaluating the credibility of the SLN in vulvar cancer [17–37]. In these studies, the SLN was identified with Tc-99m, blue dye or both, and completion lymphadenectomy followed in all patients. Authors, year of publication, number of patients, detection method and rate, as well as false negatives are summarized in Table 5.

Detection rate ranges from 75 to 100%, while in our study it was 100%. However, this decreased to 81.2% when the number of groins and not the number of patients was considered. Lindell et al. [37] reported a 97.4% detection rate per patient, but it was much lower when this was adjusted per lymphadenectomy (72.3%). Failure in identification of an SLN could be due to unilateral drainage of the tumor or a massively invaded node, which occludes the lymphatic vessels [29]. Since there was no metastasis in the 12 groins in which no SLN was identified, we have to assume that these tumors drained to one side only. Furthermore, in the three cases with false-negative SLN, non-SLNs with metastatic disease were massively invaded by tumor.

Tc-99m was not superior to blue dye for SLN detection in our series, although all of the previous studies comparing them showed the opposite [25–27, 29–37]. Detection rates were similar for Tc-99m and methylene blue. This was true even for the groins containing metastasis. Furthermore, the overall detection rate by blue dye was higher when compared with the detection rate in most studies [26, 36]. This could be attributed to the fact that we used methylene

Table 4 Characteristics of the three patients with false-negative sentinel nodes

Age	Tracer	Stage	Grade	Largest dimension of tumor (mm)	Tumor location	SLN	Groin LN
74	Tc + BD	III	II	80	Left anterior	1 neg. left	0/10 pos. right 1/7 pos. left
80	Tc + BD	IV	II	55	Left anterior	1 neg. right	3/9 pos. right 0/14 pos. left
86	Tc + BD	IV	III	50	Right anterior	4 neg. right	3/12 pos. right
						1 neg. left	3/20 pos. left

SLN Sentinel lymph node, *Tc* 99m-Technetium, *BD* Blue dye

Table 5 Literature review of SLN detection with completion inguinofemoral dissection

Author	Year	Patients	Detection method	Detection rate(%)	False negative
De Cesare et al. [17]	1997	10	Tc + BD	10/10(100)	0
Ansink et al. [18]	1999	51	BD	42/51(82)	2
Echt et al. [19]	1999	12	BD	9/12(75)	0
Bowles et al. [20]	1999	6	Tc	6/6(100)	0
De Hullu et al. [21]	2000	59	Tc + BD	59/59(100)	0
Sideri et al. [22]	2000	44	Tc	44/44(100)	0
De Cicco et al. [23]	2000	37	Tc	37/37(100)	0
Levenback et al. [24]	2001	52	BD	46/52(88)	0
Sliutz et al. [25]	2002	26	Tc + BD	26/26(100)	0
Moore et al. [26]	2003	21	Tc + BD	21/21(100)	0
Puig-Tintore et al. [37]	2003	26	Tc + BD	25/26(96)	0
Merisio et al. [28]	2005	20	Tc	20/20(100)	1
Louis-Sylvestre et al. [29]	2006	38	Tc ± BD	36/38(95)	1
Terada et al. [30]	2006	21	Tc + BD	21/21(100)	0
Hauspy et al. [31]	2007	41	Tc + BD	39/41(95)	1
Nyberg et al. [32]	2007	47	BD ± Tc	46/47(98)	0
Rob et al. [33]	2007	59	BD ± Tc	54/59(92)	1
Hampl et al. [34]	2008	127	BD ± Tc	125/127(98)	3
Camara et al. [35]	2009	17	Tc + BD	15/17(88)	1
Radziszewski et al. [36]	2010	56	Tc + BD	56/56(100)	8
Lindell et al. [37]	2010	77	BD ± Tc	75/77(97)	2
Our study		34	BD ± Tc	34/34(100)	3

Tc 99m-Technetium, *BD* Blue dye

blue, instead of the commonly used blue dyes. According to literature, patent blue V and isosulfan blue are considered more suitable for the procedure [38, 39]. Our detection rate was higher than that reported by Moore et al. [26] who used isosulfan blue and Radziszewski et al. [36] who used patent blue V (78 vs. 61% and 76%, respectively). Since methylene blue has a much lower cost compared to other dyes, its use in the SLN procedure should be reconsidered.

We decided to include nine patients with tumors greater than 4 cm, although this was not in accordance with the latest recommendations of the expert panel at the International Sentinel Node Society Meeting in 2008 [40], which we were not aware of at the beginning of our study. Four cases of false negatives were observed in three patients with tumors greater than 4 cm. Hampl et al. [34] reported three false negatives in 127 women with tumor sizes 1, 4 and 5.6 cm. Maybe some of the false negatives could have been avoided if more peritumoral injections of Tc-99m and blue dye had been performed in such large tumors. No false negatives were observed in well-differentiated (grade I) tumors, as reported in other studies [34].

Age $\leq$71 seems to positively affect the SLN procedure, since no false negatives were observed in this subgroup of patients. Although this has never been reported in literature, it can only be used as an observation, since the sample size is small. Maybe future studies focusing on the function of cutaneous lymph vessels and changes concerning age can reach conclusions. It seems only logical to us that a lymph vessel—such as any vessel—functions better in a younger patient and in that way can lead us safely to the actual SLN.

According to Louis-Sylvestre et al. midline lesions of the vulva must be treated with caution when lymphatic mapping procedure is used [29, 41]. In our series, no false negatives were observed in such topography of the tumor, although eight midline lesions were included.

Ultrastaging was performed in all SLNs found to be negative with the conventional H–E staining. Seventeen of them were positive with H–E, whereas ultrastaging revealed a "micrometastasis" in 1 out of the 63 remaining (1.58%). Similar results were reported by De Hullu et al. [21]. They detected by step sectioning and immunohistochemistry four additional metastases in 102 negative SLNs on routine examination (4/102, 4%), while Terada et al. [42] reported a higher percentage in their study (2/14, 14%). Recent data have shown that adding immunohistochemistry to ultrastaging with H–E for the evaluation of SLN does not increase the detection rate of "micrometastasis" [43]. This was also confirmed in our study, since the single case of "micrometastasis" was uncaptured by more step sections and not by immunohistochemistry.

In conclusion, Tc-99m does not seem to be superior to methylene blue in the detection of SLN in vulvar cancer. Considering that the blue dye technique is a cost-effective and 1-day procedure, its value for the procedure could be reconsidered. The midline position of the tumor did not seem to negatively affect the credibility of the procedure. SLN mapping seems to be more appropriate for small (<4 cm), well-differentiated (grade I) tumors and younger patients. In such cases, with a negative ultrastaged SLN, completion lymphadenectomy could be omitted and patients should be closely (every 2 months) followed up.

Conflict of interest We declare that we have no conflict of interest.

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