

Clinical results of vulvar cancer treatment in early stages based on sentinel lymph node biopsy and classic surgical treatment in the Institute of Oncology of Vilnius University between 2011 and 2013

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Background. Radical vulvectomy accompanied by bilateral inguinal lymph nodes dissection (ILND) has been performed to treat cancer for a long time but, due to various short and long term postoperative complications, alternatives have been found. The objective was to compare the clinical results of vulvar cancer treatment in early stages based on sentinel lymph node(s) biopsy (SLNB) and classic surgical treatment and to evaluate the radiological safety of SLNB.

Materials and methods. Retrospective study involved 26 patients with clinical stage I–II of vulvar carcinoma treated in the Institute of Oncology, Vilnius University, between 2011 and 2013. The women were divided into two groups: 14 patients underwent a reduced surgical treatment based on the SLNB method, and 12 patients underwent a classic surgical treatment.

Results. After SLNB and intraoperative histological examination, 9 patients in the first group underwent radical tumour excision, while the others underwent ipsilateral or bilateral ILND. Final histological examination detected metastases in lymph nodes in 4 patients from the first group and 3 patients from the second group. The average surgery duration on the patients undergoing only SLNB and radical tumour excision was 77.2 minutes, and the classical surgery took 177.7 minutes. Average exposure levels measured in the first group reached up to 1 µSv/hour.

Conclusions. Surgery treatment based on SLNB for patients with early stages of vulvar carcinoma can reduce the extent of surgical interventions. Exposure limits to the patients and staff were safe.

Key words: vulvar cancer treatment, sentinel lymph node, technetium (99mTc) albumin nanocolloid, vital blue dye

INTRODUCTION

The past few decades have witnessed a methodical evolution in vulvar cancer surgery. Radical vulvec-

tomy with bilateral inguinal lymph nodes dissection (ILND) has been replaced by less invasive surgical methods with the efficiency and treatment results no worse than those of the classic surgery (1). After the classic surgical treatment, an average of 3 operated patients out of 10 suffer from wound infection or dehiscence and 30–70% suffer from lymphedema

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of the lower limbs and / or recurrent erysipelas for the rest of their lives (2). It has been found that the main prognostic factor of vulvar carcinoma is the presence of metastases in regional lymph nodes and, therefore, bilateral ILND has been performed for a long time. Despite radical surgery, groin recurrence was evidenced in 1 to 10% of cases (3). However, 25 to 35% of patients with an early stage of vulvar carcinoma will have lymph node metastases. The publication of the results of the multicentre GROINSS-V study in 2008 and later examinations have shown that the sentinel lymph node biopsy method is reliable, the sensitivity is high and the 3-year survival rate of the patients is 97%, the incidence of early and late post-operative complications is 3–4 times less, and the groin recurrence rate does not reach 2.3% (3, 4). According to Holschneider and co-authors, modern principles of vulvar carcinoma treatment include: individualisation of treatment; in case of monofocal tumours minimally invasive surgery is purposeful (5). The Institute of Oncology of Vilnius University has applied lymphoscintigraphy since 2000 mostly in staging of breast cancer and melanoma. Since May 2012, sentinel lymph node biopsy (SLNB) using the double-mapping (preoperative lymphoscintigraphy and vital blue dye) method has been applied in diagnostics of vulvar carcinoma. The objective of this study was to evaluate the clinical results of vulvar cancer treatment in early stages based on SLNB and classic surgical treatment.

MATERIALS AND METHODS

This retrospective study involved 26 patients with clinical stage I–II of vulvar carcinoma, who had been treated in Oncogynecology Department of the Institute of Oncology, Vilnius University, in Vilnius, Lithuania, between January 2011 and December 2013. Vulvar carcinoma of these patients was histologically confirmed (depth of invasion was greater than 1 mm) preoperatively. Based on the results of examination, palpation and instrumental tests (by ultrasound, magnetic resonance imaging and / or computed tomography), clinical stage I–II of vulvar carcinoma was diagnosed in the examined patients. During the preoperative examination, none of the patients had any clinically palpable inguinal lymph nodes or typical radiological signs of metastases. The women were divided

into two groups based on the surgical treatment method. In the first group, 14 patients underwent a reduced surgical treatment based on SLNB (between May 2012 and December 2013). In the second group, 12 patients underwent a classic surgical treatment (between January 2011 and April 2012).

Sentinel lymph node detection

Sentinel lymph node was localized by the double-mapping method using a radiotracer and blue dye.

1. Radionuclide lymphoscintigraphy

The location and number of sentinel lymph nodes was determined by preoperative lymphoscintigraphy (LSG). For 14 patients, the radiotracer was injected one day before the planned surgery (on average 14.2 hours before the surgery). ^{99m}Tc albumin nanocolloid (Nanocoll, GE Healthcare S. r. l.) was used for LSG.

The radiotracer was injected subcutaneously in four spots around a vulvar tumour. The volume of the radiotracer in one injection was 0.1 ml. LSG was performed by a dual-head SPECT/CT gamma camera Siemens Symbia T6 (Siemens AG Medical Solutions, Germany) equipped with low-energy high-resolution collimators. Multiple static images were acquired for the visualisation of the sentinel lymph node, followed by the SPECT/CT of the pelvic area. Spiral computed tomography was performed using low-dose scan protocols (X-ray tube current of computed tomography 21 mA). The correction of SPECT reconstruction, attenuation and fusing of SPECT and CT images were performed using the Esoft 2000 program package (Siemens AG Medical Solutions, Germany). SLN localization, number and size were evaluated in planar, SPECT and fused SPECT/CT images.

2. Vital blue dye

Vital blue dye was injected to localize the sentinel lymph node. About 15–20 min before the surgery, 0.5–1 ml of isosulfan blue dye (Patentblau V 2.5%) was injected subcutaneously in four spots around the primary tumour.

Radiation dosimetry

In order to evaluate exposure levels during SLNB, the staff of the operating room had personal digital radiation dosimeters Polimaster PM1621.

The incision site for SLNB was specified using a surgical gamma probe with a wireless detector (Neoprobe 2300). Separating subcutaneous tissues by layers, sentinel lymph node(s) were identified using a sterile coated detector. Harvested sentinel node(s) showed up to 20% activity of the injection site. After excision of sentinel lymph node(s), the area of regional lymph nodes was repeatedly checked with the gamma probe for possible “hot” spots to confirm that all sentinel lymph node(s) had been removed. If the dissection of sentinel node(s) was successful, the surgical gamma probe did not show any radioactivity in the surgical wound or it did not exceed 10% of radioactivity that was recorded before the removal of the sentinel node. The removed material was sent for urgent histological examination. In case of metastatic lesions in sentinel lymph node(s), unilateral or bilateral ILND was performed.

Surgical treatment

The extent of the surgery was determined by the location and size of vulvar tumour. All patients underwent radical tumour excision by making incisions at the distance of at least 2 cm from the tumour's edge. In the first group of patients, SLNB was taken from the groins by separate 3–4 cm incisions. Sentinel node(s) were dissected and sent for intraoperative histological examination. In case of positive sentinel lymph node(s), the incisions in groins were extended and inguinal lymph nodes were dissected. In the second group of patients, bilateral ILND was taken.

Histological tests

Sentinel lymph node(s) dissected during the surgery were sent for urgent histological examination. During the operation, micro slides of tissues were prepared using the frozen section technique, sections of 10 micrometres were dyed with haematoxylin and eosin (HE). Later all examined lymph

nodes were fixed in 10% formalin solution and embedded in paraffin and routine preparations of 2–3 micrometres dyed with HE were made. Immunohistochemical staining for S-100 and monoclonal HMB-45 antibodies were used to detect micro-metastases.

Methods of statistical analysis

The data of examinations were processed by the statistical program SPSS 15.0 for Windows. Averages of the analysed variables were compared using the Student's (t) test and chi-square test. Quantitative characteristics were expressed as an average and its standard deviation (SD) was calculated. The analysis results were considered statistically significant when the value of the probability of an error was $p < 0.05$ and very significant when the value of the chance of an error was $p < 0.001$.

RESULTS

The data of 26 patients were analysed. The data on patients' characteristics, types of vulvar tumour and histology details are presented in Table 1.

In the first group, 14 examined women underwent SLNB together with radical vulvar tumour excision. During LSG, sentinel lymph node(s) were identified in 13 out of 14 (92.6%) patients. This method did not visualize sentinel lymph node(s) in only one patient (7.4%). The mean number of scintigraphically identified sentinel lymph nodes was 2.1 (range 1–3). During LSG, sentinel lymph nodes were visualized in both groins only in one patient (7.4%). Average total activity of ^{99m}Tc -nanocolloid for LSG was approximately 59 MBq (range 47–68 MBq) when performed on the day before surgery and 25 MBq (range 22 and 27 MBq) on the day of surgery.

During the surgery, sentinel lymph node(s) were found in all patients. The SLNB of one patient that was not visible on LSG imaging was found blue

Table 1. Patients' characteristics, types of vulvar tumour and histological details

	First group (N14)	Second group (N12)	p
Age, years, mean (range)	71.6 (54–90)	72.2 (52–89)	0.87
Vulvar cancer histology			
Squamous cell carcinoma, cases (%)	14 (100)	11(91.7)	0.27
Vulvar melanoma, cases (%)	–	1(8.3)	
Tumour size, mm, mean (range)	34.8 (10–66)	32.8 (5–80)	0.85
Depth of invasion, mm, mean (range)	6.1 (1–15)	10.8 (1–45)	0.27

stained during the surgery. This woman underwent bilateral ILND for oncological safety reasons, no metastasis were found in this case. None of the patients experienced any local or systemic complications related to the injection of radionuclide or vital dye. After intraoperative histological examination, groin surgery was confined to SLNB in 9 patients out of 14 (64.3%) with negative nodes. Metastases were detected in 4 (28.6%) patients (two patients with two sentinel lymph nodes with metastases and two with 1 sentinel lymph node with metastases). From them, 3 (21.4%) women underwent bilateral ILND.

All 12 women of the second group (100%) underwent radical incision of the tumour and bilateral ILND. After postoperative histological examination, metastases were detected in 3 (25%) patients. There was no statistically significant difference ($p = 0.84$) between the proportions of metastases in these groups.

The data on vulvar and groin surgeries and distribution of cases based on FIGO (International Federation of Gynecology and Obstetrics) stages are presented in Tables 2 and 3.

The average duration of surgery of the patients who only underwent SLNB and radical tumour excision was 77.2 minutes ($SD \pm 23.5$), while together with unilateral or bilateral ILND and radical tumour excision the surgery was prolonged up to 177.7 min ($SD \pm 44.9$); this difference is statistically significant $p < 0.0001$.

Average exposure levels to the surgeon, anaesthetist, scrub nurses and operating room nurses were measured with digital dosimeters and reached up to 1 μ Sv/hour.

DISCUSSION

Our research confirmed the opinion expressed in literature that the localization of sentinel lymph node(s) by the double-mapping method is valuable in determining metastases in regional lymph nodes when they cannot be detected by non-invasive methods (clinically and / or by radiological methods). Although it is quite a new method in vulvar cancer treatment, more and more sources refer to the possibilities of this method.

Moore and co-authors examined 36 patients enrolled into their study with 35 of them undergoing a SLNB. 56 biopsy procedures of sentinel lymph nodes in total were performed on 4 patients found to have inguinal metastasis by sentinel lymph nodes. The results of metastatic disease were negative in 31 patients with a total of 46 SLNBs. The median follow-up has been 29 months (range 8 to 51) with 2 groin recurrences for a groin recurrence rate of 4.3% and a recurrence rate per patient of 6.4%. There have been no reports of complications. The authors have concluded that the recurrence rate for patients undergoing inguinal sentinel node(s) dissection alone is low. These patients did not experience any complications as seen with complete groin

Table 2. Vulvar and groin surgery

	First group (N14)	Second group (N12)	p
Vulvar surgery			
Tumor excision, cases (%)	5 (35.7)	–	0.0006
Total vulvectomy, cases (%)	9 (64.3)	12 (100)	
Lymph surgery			
SLNB, cases (%)	9 (64.3)	–	0.0009
Unilateral ILND, cases (%)	1 (7.1)	–	
Bilateral ILND, cases (%)	4 (28.6)	12 (100)	

Table 3. Distributions of cases based on FIGO (International Federation of Gynecology and Obstetrics) stages, cases (%)

	First group (N14)		Second group (N12)		P
	Clinical	Pathological	Clinical	Pathological	
IA	3 (21.4)	1 (7.1)	4 (33.3)	2 (16.7)	0.78
IB	10 (71.4)	9 (64.3)	7 (58.4)	6 (50)	0.95
II	1 (7.1)	0	1 (8.3)	1 (8.3)	0.37
III A	0	3 (21.4)	0	2 (16.7)	–

node dissections (6). SLNB should be considered as an option for evaluation of inguinal nodes for metastatic disease.

In our study, the incidence of postoperative complications was not analysed.

In a multicentre observational study, Van Der Zee and co-authors (3) performed the SLNB procedure on 403 assessable patients. 259 patients with unifocal vulvar cancers with diameters of <4 cm and negative sentinel lymph nodes were followed without additional therapy for a median of 35 months. Six groin recurrences (2.3%) were observed and the 3-year survival of these patients was 97%. The authors concluded that SLNB should be offered to selected patients with early stages of vulvar cancer as a means to avoid the postoperative morbidity associated with ILND. The double-mapping method is more advantageous than dyeing of sentinel lymph nodes with vital dye only.

Between 2003 and 2006, in Germany, 7 oncology centres investigated 127 women with primary T1-T3 vulvar cancer who were included in the study and treated using sentinel node removal after the application of (99m) Tc nanocolloid and / or blue dye. Subsequently, a complete ILND and an adequate vulvar surgery were performed on all women. Sentinel lymph nodes were examined by routine pathologic examination followed by step-sectioning and immunohistochemistry if negative. The SLNB procedure was successful in 125 out of 127 cases and in 2 cases no sentinel nodes were detected. 21 patients received unilateral ILND and 103 women had the surgery of both groins. In 39 women out of 127, positive lymph nodes in one or both groins were identified (30.7%). In 36 women, sentinel nodes were also positive (sensitivity 92.3%). There were 3 cases with a false negative sentinel node (false negative rate: 7.7%), all of these women having tumours in the midline position. This study shows that the identification of sentinel lymph nodes in vulvar cancer is feasible, though not very accurate depending on tumour location and size. The false negative rate seems to be acceptable if the procedure is restricted to stage 1 tumour with the clinically negative lymph node status (7).

During testing by Devaja et al., lymph nodes were detected by the double-mapping method in 98.3% of cases and accumulated vital dye in 93.3% cases (4). Our results have demonstrated that these methods are equivalent with blue dye having a small

advantage (92.6% SLN found by double-mapping and 100% by accumulated vital blue dye). When sentinel lymph nodes were not detected by LSG, at least 1 lymph node that accumulated vital dye was usually found during the surgery or detected by a radionuclide sensor (8). The cases were reported in our research when SLN that accumulated radionuclide could not be seen during LSG but was detected due to accumulated vital dye.

There is an on-going important scientific discussion on the evaluation of radiation exposure to the patients and staff when using radionuclide nanocolloid. Average exposure levels to the surgeon, anaesthetist, scrub nurses and operating room nurses were measured with digital dosimeters and reached up to 1 μ Sv/hour. According to published sources, the average exposure levels to operating-room staff were less than 1 μ Sv per one procedure during sentinel lymph node biopsy of patients with skin melanoma or breast cancer (9–11). The recommendations of the European Society of Nuclear Medicine state that the monitoring of operating room staff for professional exposure and additional measures of screening from ionizing radiation are not necessary. The exposure to staff performing the examination of surgical material is also low and additional monitoring with personal dosimeters is not necessary (12, 13). The opinion of the patients is also important. Women with early stages of vulvar tumour who underwent radical ILND reported worse quality of their lives (14). However, about 80% of them would prefer radical surgery if they knew before the surgery that the possibility of mistakes during SLNB was 1 in 100 cases (14). It shows that, in addition to a thorough preoperative examination of the patient, an attentive conversation and a fully informed consent are necessary in all cases.

CONCLUSIONS

1. Surgery treatment based on SLNB for the patients with early stages of vulvar carcinoma can reduce the extent and duration of surgical interventions.

2. Exposure levels to the patients and staff did not exceed normal limits, i. e. the method was safe to the patients and staff.

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**ANKSTYVOS STADIJOS VULVOS VĖŽIO
GYDYMO, PAGRĮSTO SENTINELINIŲ
LIMFMAZGIŲ BIOPSIJA IR KLASIKINIŲ
CHIRURGINIŲ GYDYMU, KLINIKINIAI
REZULTATAI VILNIAUS UNIVERSITETO
ONKOLOGIJOS INSTITUTE 2011–2013 METAIS**

Santrauka

Įvadas. Radikali vulvektomija ir abiejų pusių kirkšnių limfonodektomija ilgą laiką buvo taikoma gydant vulvos vėžį, tačiau dėl daugelio ilgalaikių ir trumpalaikių pooperacinių šios procedūros komplikacijų yra ieškoma alternatyvių gydymo metodų. Šio tyrimo tikslas – įvertinti ankstyvų stadijų vulvos vėžio gydymo klinikinius rezultatus taikant chirurginį gydymą, paremtą sentinelinių limfmazgių biopsija (SLB), ir klasikinių chirurginių gydymą, taip pat įvertinti sentinelinių limfmazgių dvigubo kontrastavimo radiologinį saugumą.

Darbo metodika ir medžiaga. Atlikta retrospektyvinė Vilniaus universiteto Onkologijos instituto Onkochirurgijos centre 2011–2013 m. nuo I–II klinikinės stadijos vulvos vėžio gydytų 26 pacienčių ligos istorijų analizė. Pacientės buvo suskirstytos į dvi grupes: pirmos grupės pacientėms operacijos apimtį nulėmė

SLB, antros grupės pacientėms atliktas radikalus vulvos naviko pašalinimas ir abipusė kirkšnių limfonodektomija.

Rezultatai. Po SLB ir skubaus jų histologinio ištyrimo devynioms pirmos grupės pacientėms buvo radikaliai pašalintas navikas, kitoms operacijos apimtis padidinta iki vienpusės ar abipusės kirkšnių limfonodektomijos. Galutiniu histologiniu tyrimu metastazės limfmazgiuose nustatytos keturioms pirmos grupės pacientėms ir trims antros grupės pacientėms. Operacijos trukmė, atliekant tik radikalų naviko pašalinimą ir SLB, vidutiniškai truko 77,2 minutės, o atliekant vienpusę ar abipusę kirkšnies limfonodektomiją, vidutinė operacijos trukmė buvo 177,7 min. Vidutinė pacientės ir personalo apšvitos dozė neviršijo 1 $\mu\text{Sv/val}$.

Išvados. SLB paremta gydymo taktika gali sumažinti chirurginių intervencijų apimtį pacientėms, sergančioms pradinėmis vulvos vėžio stadijomis. Apšvitos dozės pacientei bei personalui buvo saugios.

Raktažodžiai: vulvos vėžio gydymas, sarginis limfmazgis, Technecio ($^{99\text{mTc}}$) albumino nanokoloidas, mėlynasis audinių dažas