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Research Article

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Survival Rate after Individualized Approach in Treatment of Vulvar Cancer: A Ten-Year Single Institution Experience

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Abstract

Objective: The aim of the study was to evaluate overall survival and recurrence-free survival rate in patients with squamous cell vulvar cancer after applying an individualized therapeutic approach.

Methods: The concept of individualized therapeutic approach in the treatment of squamous cell vulvar cancer was defined and 113 patients with the diagnosis were studied. All these patients were diagnosed, operated on and followed up at the Clinic of Gynecologic Oncology of the University Hospital Pleven, Bulgaria. Treatment was individualized and more conservative surgical techniques were applied when possible. The Kaplan-Meier method was used to estimate overall survival and disease-free survival rates.

Results: Application of individualized approach resulting in: The 5-year survival rate was 73%, and the 10-year survival rate was about 67%. The five-year disease-free survival rate was about 57%, and ten-year disease-free survival rate was about 43%.

Conclusion: High rates can be achieved through applying more conservative surgical techniques and individualized therapeutic approach in patients with vulvar cancer.

Keywords

Vulvar cancer; Survival; Individualized approach; Lymph node dissection

Introduction

Malignant vulvar tumors are rare and account for less than 5% of all cancers of the female genitalia. Squamous cell carcinoma is diagnosed in 90% of cases of vulvar tumors. Epidemiological characteristics of vulvar squamous cell carcinoma is equally unfavorable for European countries, the US and Bulgaria. A significant increase in pre-cancer diseases - Vulvar Intraepithelial Neoplasia (VIN) and VIN-related carcinomas in young females has been established during the last decades [1-3]. In Bulgaria, a two-fold rise of the incidence of vulvar cancer during the last 20-25 years was found, and the significance of this rare tumor localization is increasing. Surgery is the main treatment method. However, major changes in management have occurred since 1980. At the beginning of the 20th century, patients usually sought medical attention at an advanced stage of the disease and surgical techniques were not that well developed. The five-year survival rate used to be 20 -25% [4]. Later, Taussig in the USA (1940) and Way in Great Britain (1948) developed and applied *en bloc* resection of the vulva and the inguinal femoral and iliac lymph nodes. They reported a five-year survival rates in 60 to 70% in their cases. This aggressive surgical treatment was commonly applied for about 40 years due to the high survival rates achieved [5-8]. The concept of this "standard" treatment for all patients in all stages, implying aggressive surgical techniques has changed over the years. New, more conservative surgical approaches have been tried and adopted. These techniques need as effective as the aggressive ones, and sparing enough for the patients, aiming to reduce postoperative complications, genital disfigurement and improve life quality after surgery. More conservative surgery is possible only if individualized approach to each patient is applied. Our understanding of epidemiology, the way the disease spreads, prognostic factors and data on survival rates in cases of vulvar cancer is predominantly derived from retrospective observations and very few prospective studies on the squamous cell carcinoma [9]. Vulvar cancer is a surgically staged disease and surgery remains the main treatment method. Although principles of individualized approach have been adopted and more conservative surgical techniques are applied, a significant part of the patients do not receive adequate surgical treatment and staging, mostly associated with absence of inguinofemoral lymph dissection (LD) [10-12]. and treatment in non-specialized hospitals. The main reason for these practices is the lack of generally accepted criteria for assessment and selection of a definite surgical procedure, the lack of consensus in defining the inguinal lymph dissection procedure [13] and the lack of consensus as regards the exact topographic anatomical terminology [14,15]. The aim of the study was to evaluate and analyze overall and recurrence-free survival against the background of individualized approach in treatment of squamous cell vulvar carcinoma.

Materials and Methods

The clinical group studied included 113 patents with squamous cell vulvar carcinoma, who were diagnosed, treated and followed up at the Clinic of Oncologic Gynaecology at the Oncology Center of the University Hospital Pleven in the period between January 2000 and July 2010. The mean age of the patients was 67.64 ± 11.42, age range 28-87. All patients receive primary surgical treatment. Surgical staging was performed using the criteria International Federation of Gynecology and Obstetrics (of FIGO) and the TNM classification of the Union for International Cancer Control (UICC) [16]. The patients underwent thorough clinical examination, vulvoscopy and colposcopy, image diagnostic procedures including lung X-ray, ultrasound of pelvis and abdominal organs, computer tomography, rectoscopy and cystoscopy. Decision on postoperative radiotherapy or radiotherapy in combination with chemotherapy was made by a medical board including an oncogynaecologist, chemotherapist and a radiation therapist. Patients with invasive carcinoma who did not undergo inguinal lymph dissection were given radiotherapy of the inguinal region and the pelvis. Follow-up was performed according to the recommendations of the National Oncology Hospital – Sofia

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as follows: one month after surgery, every three months for two years, every six months for five years and once a year – after the fifth year. Information was collected from medical records, the cancer registry at the University Hospital in Pleven and the Bulgarian National Cancer Registry. Recurrence of the disease was registered as between the date of operation and date of histological verification of a newly developed squamous vulvar carcinoma, at least three months following surgery. Defining the histological type of the tumor and the stage of histological differentiation was made according to the WHO classification of tumors [17]. The surgical method was the method of choice of treatment for vulvar cancer. The appropriate surgical treatment had two targets: the primary tumor and the inguinofemoral lymph nodes. When superficial inguinal lymph dissection was performed, both groups of superficial lymph nodes were dissected: those along inguinal ligament and those along great saphenous vein. When dissection of deep femoral lymph nodes was performed, all nodes located in the oval fossa and medially to the femoral vein were removed. The femoral fascia was preserved and the sartorius muscle was not transpositioned. Pelvic dissection was performed transperitoneally, on the side of the tumor or only on the side of enlarged nodes as visualized with CT scan. It included resection of outer iliac, inner iliac and obturated lymph nodes. The collected data was processed using SPSS 13.0.1. P values less than 0.05 were considered significant. We applied descriptive and variation analysis on the investigated characteristics. The Kaplan-Meier method was used to analyze overall survival and disease-free survival rates.

Results

Patients with squamous cell vulvar carcinoma received surgical interventions for the primary tumor as follows: 1. Deep total (radical) vulvectomy with or without separate incisions for lymph node dissection – 68 patients (60.18%); 2. *En-bloc* radical vulvectomy with bilateral LD without vulvar reconstruction – 10 patients (8.85%). 3. Modified radical vulvectomy (hemivulvectomy, partial vulvectomy) – 25 patients (22.12%); 4. Wide local excision – 3 patients (2.65%); 5. Total (simple) vulvectomy or partial (simple) vulvectomy - 5 patients (4.43%); 6. En-bloc resection with reconstruction – 2 patients (1.77%). Of the 113 patients included in the study, 106 (93.8%) had invasive vulvar cancer, and 7 patients (6.2%) had microinvasive carcinoma (depth of invasion less than 1 mm). Lymph node dissection was performed on 77 patients (72.64%) with invasive carcinoma (depth greater than 1 mm). Lymph dissection in the inguinal region was either ipsilateral (21 patients), or bilateral (56 patients). As regards degree of radical resection, lymph node resections performed included: 1. Inguinal (superficial LD) – 24 patients (31.16%); 2. Inguinofemoral (superficial and deep LD) – 50 patients (64.93%); 3 Inguinofemoral and pelvic (superficial, deep and pelvic LD) – 3 patients (3.89%). Surgical interventions were performed by the same team of six surgeons qualified in obstetrics, gynecology and oncology. Data analysis was performed using the Kaplan-Meier method. The event investigated was the death of the patient from the studied disease (cancer specific death). The mean follow-up time was 38.96 ± 34.34 months (between 1 and 125 months), the mean overall survival was 91.41 ± 5.41 months in 95% CI (80.00 - 102.01 months).

Table 1 presents survival rates calculated using the Kaplan-Meier method. It should be noted that: 1. Of the 113 patients with squamous cell vulvar cancer, 28 patients (25%) died of the disease, and the cause of death was different in 19 (17%) of the cases. 2. The highest mortality was registered between the 4th and 8th postoperative months – 8 cases (28.6%), followed by 7 deaths (25%) between the 8th and 12th postoperative months. 3. Most of deaths – 23 (82.1%) occurred within the first 24 months following surgery. 4. The one-year survival rate was 85%, the three-year survival rate was about 73%, the five-year survival rate was also about 73%, and the ten-year survival rate was approximately 67%. The maximum survival registered was 125 months, a little higher than 10 years.

Figure 1 represents the cumulative probability of survival. The vertical segments present the so-called "censured", i.e. cases excluded because of a variety of reasons - death unrelated to the disease, lack of observation or survival after the follow-up period. The figure shows that the steepest descent of the curve is related to the first postoperative year. After that, the decrease of cumulative survival probability decreases more slowly to reach a comparatively good level – the probability of higher than a 10-year survival is about 70%. The cumulative death risk (Figure 2) increased most rapidly between the 1st and 12th postoperative month, i.e. most deaths occurred during the first postoperative year. Analysis of the disease-free survival rate was performed by Kaplan-Meier method because of differences in time of inclusion and duration of follow-up. The event investigated was the onset of tumor recurrence. The mean duration of follow-up for onset of recurrence was 35.56 ± 33.60 months, in the interval of 1 to 125 months, and the mean survival rate without tumor recurrence was 76.13 ± 5.88 months in 95% CI, varying between 64.40 and 87.66 months. Table 2 presents disease-free survival, evaluated by method of Kaplan-Meier. It illustrates that: 1. Of the 113 patients followed up, 40 (35.4%) had recurrences. 2. The earliest onset of recurrence was found between the 3rd and 4th postoperative month. 3. The highest rate of the event investigated was seen during the first postoperative year – 24 cases (60%). 4. Most of all events – 32 (80%) occurred within the first 36 months following surgery. 5. The 3-year disease-free survival rate was about 66%, the 5-year was about 57%, and the 10-year was about 43%. 6. The maximum disease-free survival was 125 months, a little more than 10 years. Figure 3 illustrates the curve of cumulative probability of disease-free survival rate. The vertical segments represent the so-called "censured" cases, i.e. patients excluded because they could not be followed up, died or were free of the disease at the end of the observation period. The figure shows that the drop of the cumulative survival rate was sharpest during the first postoperative year, the curve was a little less steep during the following two years and survival rates reached to a comparatively low level – the probability for a disease-free survival rate after ten years was about 43%. The curve of cumulative risk for disease recurrence (Figure 4) ascends most quickly during the first 12 months, and then continues to rise, though more slowly.

Discussion

Data on overall survival in our study are similar to those reported by authors at the end of the 20th century and the first decade of the 21st century [18-29]. All authors reported 5-year survival values which averaged 70%. Unlike our data, that of Homesley were 79% for the same index [25], and Chan reported an impressive 83.1% overall survival rate [30]. It should be noted, however, that in the study of Chan [30], 51% of the patients had FIGO stage I vulvar carcinoma and the mean age of the patients surgically treated was 59.9 years. In our study, the patients with FIGO stage I were only 28.3%, and the mean age was about 68 years. The cumulative survival curves in our study and that of Raspagliesi have similar patterns (Figure 1) and reach levels that are almost identical [28]. It is worth noting that the level of the 5-year survival reported by authors stayed the same during the years, though at the end the 1980s and the beginning

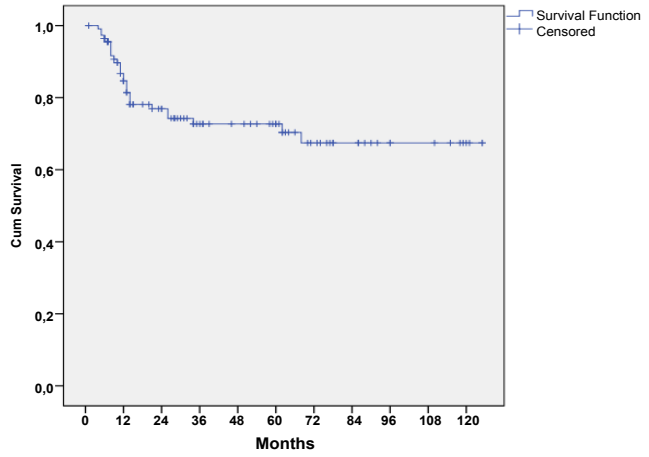

Figure 1: Cumulative survival function.

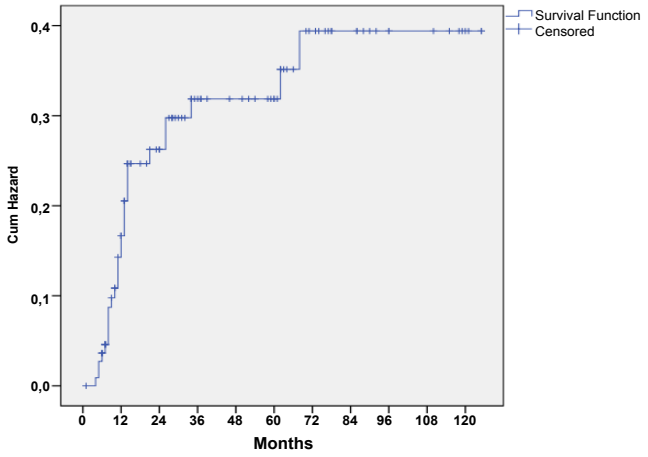

Figure 2: Cumulative hazard survival function.

Table 1: Kaplan-Meier product limit estimation of the survival function.

Time (months)	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
	Estimate	Std. Error		
4	0.991	0.009	1	111
8	0.917	0.027	9	95
12	0.846	0.035	16	79
24	0.769	0.043	23	58
36	0.727	0.047	26	43
48	0.727	0.047	26	39
60	0.727	0.047	26	32
72	0.674	0.056	28	21
84	0.674	0.056	28	15
96	0.674	0.056	28	9
108	0.674	0.056	28	7
120	0.674	0.056	28	3
125	0.674	0.056	28	0

Table 2: Table of disease-free survival rate by method of Kaplan-Meier.

Time (months)	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
	Estimate	Std. Error		
3	0.991	0.009	1	111
6	0.902	0.028	11	97
9	0.834	0.036	18	85
12	0.773	0.041	24	71
24	0.724	0.045	28	54
36	0.664	0.050	32	39
48	0.610	0.055	35	33
60	0.571	0.058	37	26
72	0.543	0.062	38	17
84	0.501	0.070	39	12
96	0.501	0.070	39	8
108	0.501	0.070	39	8
120	0.429	0.089	40	2
125	0.429	0.089	40	0

of the 1990s a real change had begun, aiming at more conservative surgical treatment for vulvar cancer. During that period, many teams throughout the world adopted the principles of individualized approach and began to apply modified surgical treatment. The fact that survival rates stayed the same, as that achieved with a block radical vulvectomy is encouraging. Moreover, even higher survival rates have been reported lately. When analyzing the disease-free survival rate, the event investigated was that of onset recurrence, the time to the end of follow-up or the time till the death of a patient. The study did not include patients with a persisting malignant process after surgery. The facts revealed by statistical analysis are extremely important and make it necessary to perform regular checkups for 2 years following

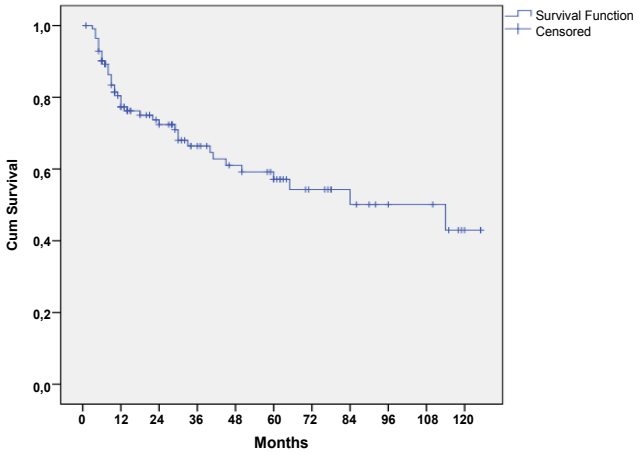

Figure 3: Function of disease-free survival rate.

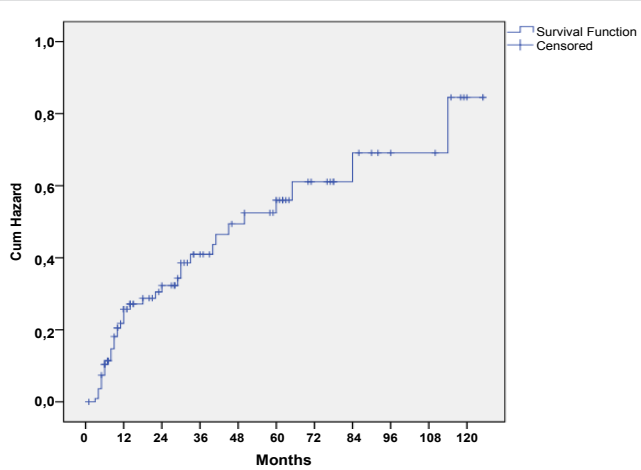

Figure 4: Function of disease recurrence risk.

surgery. On the basis of these facts, we believe that follow up checkups of the group of patients at risk for recurrence should be performed every two months during the first year, and every three months for the next two years. Vulvar cancer is a rare condition and, when diagnosed at an early stage it can be completely cured. Significant postoperative physical and mental disease rates were seen in the past, and today the situation is not that different. The philosophy of cancer treatment in the 21st century is focused on reducing the incidence of these diseases and retaining organ function without compromising the treatment outcome. This requires individualized approach, including careful choice of treatment for both the primary tumor and the regional lymph nodes [31,32]. Summing up data from the literature available and our own experience, we suggest the following definition of individualized approach to treatment of vulvar cancer: *a therapeutic strategy involving planning and carrying out basic and additional treatment appropriate for a particular patient, based on her physical and performance status and the clinical and morphological characteristics of the primary tumor and the regional lymph nodes. The aim of the strategy is to achieve high survival rate, a minimum of complications and acceptable life quality.* The attempts to reduce complications from aggressive surgery for vulvar cancer make it necessary to find out modifications of the surgical procedure [33]. There was no consensus on the criteria a patient should meet to be a candidate for conservative surgery. However, it is generally agreed that patients with T1 tumors and non-suspected inguinal lymph nodes are the right candidates [27]. The development of this concept over the years has resulted in validating sentinel lymph biopsy for tumors as large as 4 to 6 cm. To substantiate the application of individualized approach in treatment for squamous cell vulvar carcinoma, we analyzed the criteria used in making decisions on the treatment.

Criteria regarding the primary tumor

Early vulvar cancer is defined by the presence of T1 and T2 tumors and unsuspicious inguinal lymph nodes. In cases with T1 tumors, the major criteria were anatomical localization, its location in relation to major central anatomical structures and the state of the vulva. In our study, the patients with T1 tumors were 34 (30.1%). The surgical techniques applied included modified radical vulvectomy (MRV), triple incision resection and wide local resection. MRV was applied in 17 cases, and wide local resection was used in 3 cases Although the tumors were 2 cm in size, or smaller, radical vulvectomy (three-incision) was performed in 14 cases. In these cases, we did not apply the even more sparing MRV and wide local excision because of the proximity of the tumors to the median line, the state of tissues close to the tumor and the presence of multiple foci. It should be noted that MRV was performed on 4 patients with unilateral multiple foci of T1 tumor on the labia majora. We believe that despite the presence of multiple foci, hemivulvectomy is appropriate in carefully evaluated cases of T1 tumors with multiple foci.

We established that when such surgical interventions were chosen, statistically significant higher overall and disease-free survival rates were found in the group of patients with T1 tumors. None of the patients underwent en- bloc radical vulvectomy. The patients operated on for T2 tumors were 58 (51.3%), the major criteria in determining the type of surgical intervention being: tumor size, its location in relation to the central structures (level of lateralization) and presence of multiple foci. In 44 (76%) of the patients with T2 triple-incision technique was applied and MRV was performed on 7 patients only. Hemivulvectomy was applied in cases of T2 tumors sizing 3-5 cm, all of the tumors were well lateralized. Only one patient had a multiple foci lesion. Seven of the patients with T2 had a poor performance status and they received the most sparing surgical technique possible: 3 patients underwent simple vulvectomy, 2 patients received MRV and triple-incision technique was performed on 2 patients. The low Karnovski index is important in making a decision so far as to avoid en-bloc resection in poor health patients or in choosing a more conservative procedure. *En-bloc* resection was carried out on 4 patients with anteromedian localization of T2 tumors. Locoregional control of the disease in cases with T2 tumors and 2-cm tumor-free surgical margins can be achieved mostly by using a triple-incision technique. When in doubt whether such control would be achieved using this technique, the more aggressive en bloc resection was applied.

We believe that the method of choice for T2 tumors is radical triple-incision vulvectomy but one should always keep in mind that there are T2 patients with well lateralized and smaller lesions, measuring 3-5 cm. Such patients can have right or left hemivulvectomy. A higher statistically reliable overall and disease-free survival was found for the patients with T1 and T2 tumors after MRV. Moreover, their hospital stay was significantly shorter and they had a statistically reliable smaller number of postoperative complications as compared to the patients in whom the other two

surgical techniques were applied. Therefore, when a patient meets the criteria to undergo hemivulvectomy, this opportunity should be not overlooked. *En bloc* resection and triple incision techniques were used in most of the patients with T3 tumors. The study included only the patients that we found suitable for primary surgery. When possible, the triple incision technique was applied, having in mind that this would imply fewer complications and shorter hospital stay. When in doubt about achieving locoregional control of the disease using the more conservative technique, we performed en-bloc vulvectomy. Deterioration in physical and performance status was a limiting factor for performing en-bloc vulvectomy. In some cases the most aggressive technique was combined with construction of an artificial anus. It should be noted that the higher the T-stage was in the patients we studied, the more often en-bloc resection was applied. En bloc vulvectomy was applied in only 4 out of 58 patients with T2 tumors, whereas it was performed on 7 out of 20 patients with T3 tumors. En bloc resection was applied as primary surgery in only one patient, diagnosed with aT4 tumor.

Assessment criteria regarding lymph dissection

When discussing the opportunities regarding the type of inguinal lymph dissection in patients with vulvar cancer, three facts should be considered:

The only patients which are practically at no risk for lymph node metastases are those in whom the invasion into the stroma are less than 1mm;

In patients with a recurrence in the non-dissected inguinal region, fatal outcome is likely in more than 90% of the cases [34-38];

The necessity for ipsilateral or bilateral lymphadenectomy is based on the tumor laterality.

An appropriate inguinal lymph dissection is an independent major factor to reduce mortality in cases of vulvar cancer. In patients with T1 and T2 tumors and invasive squamous cell carcinoma definitely confirmed by histology before surgery, the relevant lymph dissection is recommendable. In cases of suspected microinvasive cancer and a T1 tumor, wide local excision is performed, with at least 1 cm tumor-free surgical margins and waiting for final histology. In cases of stromal invasion deeper than 1mm, lymphadenectomy relevant to the particular case is performed [39,40]. Despite the importance of lymph dissection and the agreement stated by all authors, in real practice lymph dissection is not performed on a great portion of patients with the disease. According to literature data, the situation is almost identical in countries throughout the world: inguinal lymph dissection is not performed in 43% - 89% of such patients [12,41]. The reasons pointed out for this approach included omission of data records (retrospective inquiries), increased incidence of microinvasive carcinoma (FIGO Ia), registering cases of VIN-III as invasive, underlying diseases associated with high anesthesiology risk, and incompetence. We did not find exact information regarding non-performance of lymph dissection in Bulgaria but we support the opinion that the situation is similar to that in other countries. The most exact data on the incidence of Ia stage have been reported in single-institution studies or papers, accounting for about 5% to maximum 10% of vulvar cancers [42-44]. Contraindications associated with accompanying morbidity are reported as the most common reason for non-performance of lymph dissection but in fact they are not the major reasons. This is supported by Falconer [10] who stated that the frequency of lymphadenectomy varied according to American Society of Anesthesia (ASA) Score. Notwithstanding this relationship, the frequency of lymph dissection was 67% in the group of the most favorable score – 1 or 2. We support the view of these authors, namely that despite the high percentage of accompanying diseases in patients with vulvar cancer, patients can tolerate a relevant type of surgery, including lymph dissection. The greatest opportunities for individual approach in lymph dissection exist in cases with T1 and T2 tumors. The criteria we used to select the patients included laterality and size of the tumor, and involvement of the lymphovascular space. In cases of lateralized T1 or T2 tumor, unilateral superficial lymph dissection was performed and node samples were collected for prompt frozen section histology. In case lymphatic metastases, bilateral inguinofemoral dissection of superficial and deep lymph nodes was performed. When frozen section histology proved the lymph nodes were not metastatic, dissection was limited to unilateral removal of the two groups (horizontal and vertical) superficial nodes. In cases of central location of T1 and T2 tumors less than 5 cm in size, bilateral total inguinofemoral node dissection was performed with frozen section. If frozen section results made it necessary, lymph nodes located in fossa ovalis medially to *v. femoralis* were dissected. In the presence of T1 and T2 tumors less than 4-5 cm in size and inguinal lymph nodes suspicious for metastases, CT scan of pelvis and retroperitoneal lymph node was performed prior to operation. Depending on the CT scan results, bilateral inguinal dissection of superficial and deep lymph nodes was performed. Pelvic extraperitoneal lymph dissection was performed on 3 patients on account of CT scans revealing enlarged lymph nodes and/or presence of N1 or N2 in the inguinal region. In all other cases of T1 and T2 tumors, bilateral inguinofemoral dissection of superficial and deep lymph nodes was performed, and pelvic lymph node dissection was carried out on three of these patients. In cases with T3 and T4 tumors, bilateral inguinofemoral lymphadenectomy was performed using either triple-incision technique or en bloc vulva resection.

After evaluating the final results from the approach to treatment applied for vulvar cancer, we made the following conclusions:

Despite the more conservative surgical techniques we applied to treat a selected group of patients with squamous cell vulvar carcinoma, we achieve a high 5-year survival rate, as well as high disease-free survival rate.

Our results regarding the frequency of recurrence and disease-free survival rate are very close to those achieved by other institutions, where individualized approach and more conservative surgery for vulvar cancer are applied.

Application of conservative surgery requires adhering to strict evaluation criteria for each clinical case.

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