Klinično-patološke značilnosti pacientk z rakom zunanjega spolovila, zdravljenih v obdobju od 1994 do 2017 v Univerzitetnem kliničnem centru Maribor

Clinicopathologic characteristics of patients with vulvar cancer treated between 1994 and 2017 at the University Medical Centre Maribor

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Izvleček

Namen: *Rak zunanjega spolovila je ena najredkejših oblik raka. Predstavlja 3–7 % vseh rakov rodil. Osemdeset odstotkov žensk, ki zbolijo, je starejših od 60 let. Namen raziskave je bil oceniti značilnosti bolnic z rakom zunanjega spolovila, analizirati epidemiologijo, opisati klinične značilnosti, načine zdravljenja in dejavnike, ki vplivajo na razvoj raka zunanjega spolovila.*

Metode: *Retrospektivna raziskava je zajela bolnice, ki smo jih obravnavali v Univerzitetnem kliničnem centru Maribor zaradi raka zunanjega spolovila v obdobju od leta 1994 do 2017. Zbrali*

Abstract

Purpose: *Vulvar cancer is one of the rarest forms of cancer. Vulvar cancer represents 3%–7% of all gynecologic cancers. Eighty percent of patients with vulvar cancer are > 60 years of age. The purpose of the current study was to evaluate the characteristics of patients with vulvar cancer, analyze the epidemiology, and describe the clinical characteristics, treatment modalities, and factors that influence the development of vulvar cancer.*

Methods: *This retrospective study included patients treated at the University Medical Centre Maribor for vulvar cancer between 1994 and 2017. Patient de-*

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smo podatke, ki so se nanašali na demografske značilnosti, značilnosti bolezni, klinične značilnosti, histopatološke karakteristike ter način zdravljenja. Podatke smo statistično obdelali in ocenili povezavo med različnimi demografskimi značilnostmi, tumorskimi karakteristikami, zdravljenjem in dejavniki tveganja.

Rezultati: *Zbrali smo podatke 124 bolnic, ki so bile stare od 22 do 92 let. Povprečna starost bolnic je bila 71 let. Prepoznali smo 6 različnih vrst tumorjev, med katerimi je bil ploščatocelični karcinom najpogosteje zabeležen histološki tip raka. Pri 45 bolnicah je bil odvzet bris za testiranje na okužbo z virusom HPV. Okužbo s HPV smo odkrili pri 71 % (32/45) testiranih bolnic.*

Zaključek: *Ugotovili smo, da je pri bolnicah, zdravljenih zaradi raka zunanjega spolovila v UKC Maribor, najpogostejša oblika raka ploščatocelični karcinom. Eden izmed dejavnikov tveganja za raka zunanjega spolovila je nedvomno tudi okužba z virusom HPV. HPV 16 je bil najpogosteje diagnosticiran tip HPV med našimi bolnicami. Za celovitejše in reprezentativnejše zaključke bi bilo potrebno vključiti še bolnice iz drugih predelov Slovenije.*

mographics, disease characteristics, clinical features, histologic findings, and type of therapy were recorded. Associations among various demographic factors, tumor characteristics, treatments, and risk factors of vulvar cancer were evaluated.

Results: *We collected data from 124 patients between 22 and 92 years of age. The average age of the patients was 71 years. Six different tumor types were identified, of which the most common histologic type of vulvar cancer was squamous cell carcinoma. Forty-five patients were tested for the presence of HPV types, which was confirmed in 71% (32/45) of the tested patients.*

Conclusion: *Squamous cell carcinoma was the most common form of vulvar cancer in patients treated at the University Medical Centre Maribor. Undoubtedly, one of the risk factors for vulvar cancer is HPV infection. HPV 16 was the most frequently diagnosed HPV type in our patients. For more comprehensive and more representative conclusions, data from other medical centers in Slovenia should be included.*

INTRODUCTION

Vulvar cancer is a rare malignancy and represents 3%–7% of gynecologic cancers (1–3). The number of newly diagnosed cases in Slovenia per year from 2010-2014 was 44 [4.2/100.000] (1). Vulvar cancer most often affects women > 70 years of age (2). Over the past few decades, the incidence of vulvar intraepithelial neoplasia (VIN) and invasive vulvar cancer (IVC) has increased in European countries and worldwide, particularly among younger women (2–6). An increased incidence of VIN and IVC was evident in Slovenia in 2003, which coincided with the launch of the Slovenian cervical cancer screening program and registry [ZORA] (1).

Squamous cell carcinoma (SCC) accounts for > 90% of malignant vulvar tumors. Basaloid and warty variants associated with the regular type of VIN are more common in younger women and are associated with human papilloma virus (HPV) infection (7). HPV 16 and 18 are the most frequently reported genotypes that induce these lesions (8). In contrast, keratinizing

variants arising from chronic vulvar dermatosis, such as lichen sclerosus, are associated with differentiated VIN, but not HPV, and generally affect older women (7). It is important to note, however, that all women with oncogenic HPV do not develop vulvar cancer. Therefore, additional factors, such as lifestyle data and decreased immune function, might be important risk factors (8).

Although the incidence of vulvar cancer is low, it is an important disease with an impact on women's health and quality of life that should not be underestimated. No retrospective studies have been conducted in Slovenian patients with vulvar cancer to date. As the second largest tertiary center in Slovenia, our patients receive primary surgical treatment in the Department of Gynecologic and Breast Oncology of University Medical Centre Maribor and are referred to the Institute of Oncology Ljubljana for radiotherapy and/or chemotherapy, if required.

The aim of this study was to review vulvar cancers recorded in our tertiary center over a 24-year period (1994–2017) to document the vulvar cancer status in the population of northeastern Slovenia.

PATIENTS AND METHODS

This retrospective study included 124 patients from northeastern Slovenia treated in the Division of Gynecology and Perinatology of University Medical Centre Maribor for vulvar cancer from January 1994 to December 2017. The study included all cases of vulvar cancer histologically-confirmed by biopsy or excised tissue specimens. Demographic data, medical histories, and cancer treatment data were collected using pre-defined written forms digitalized by custom Microsoft Access databases. IBM SPSS Statistics (version 21) was used for statistical evaluation.

Due to the retrospective nature of this study, approval by the Ethics Committee was not required.

RESULTS

A total of 124 patients diagnosed with vulvar cancer between 1994 and 2017 were identified. The highest number of patients treated per year at UKC Maribor was between 2015 and 2017 (n=24; Figure 1). Time-series analysis using Holt's trend method showed a trend toward an increased incidence from 2003.

Patients ranged in age from 22–92 years (median age, 71 years), with the majority between 72 and 81 years (Figure 2). The medical histories of 20 patients were significant for a previous malignancy. Only 17 patients (14%) had no co-morbidities. Co-morbidity data were obtained from the patient histories and medical records. The most common co-morbidities among patients with vulvar cancer were arterial hypertension (36%), diabetes mellitus (15%), and obesity (8%).

Patients usually presented with a lesion (46%), pain (28%), vaginal discharge (27%), and pruritus (27%). Other symptoms were less frequent (Figure 3).

The most frequently diagnosed histologic type of vulvar tumor was SCC (88.7%), followed by basocellular carcinoma (4%) and non-defined carcinoma (3.2%). The remaining 4% of patients had rare histologic types, including adenocarcinoma of cylindrical cells, malignant melanoma, and endodermal sinus tumor.

The stage of vulvar cancer was assessed according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) stage classification system (Figure 4). Cases diagnosed prior to the new classification were translated into the 2009 FIGO stage classification

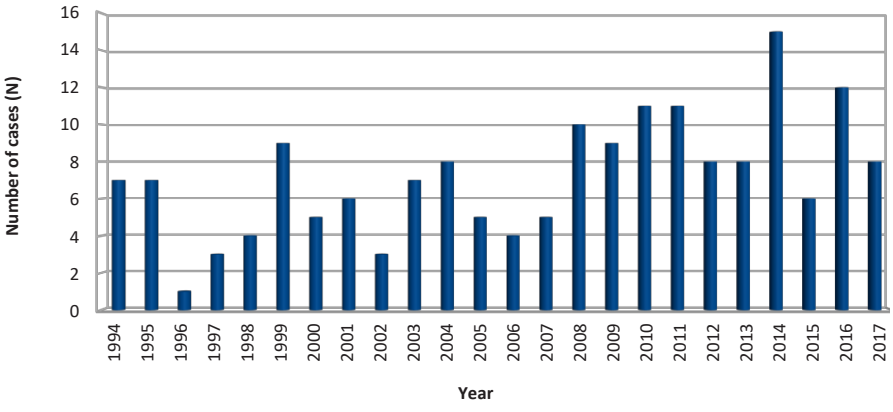

Figure 1. *Yearly occurrence of vulvar cancer between 1994 and 2017 at UKC Maribor.*

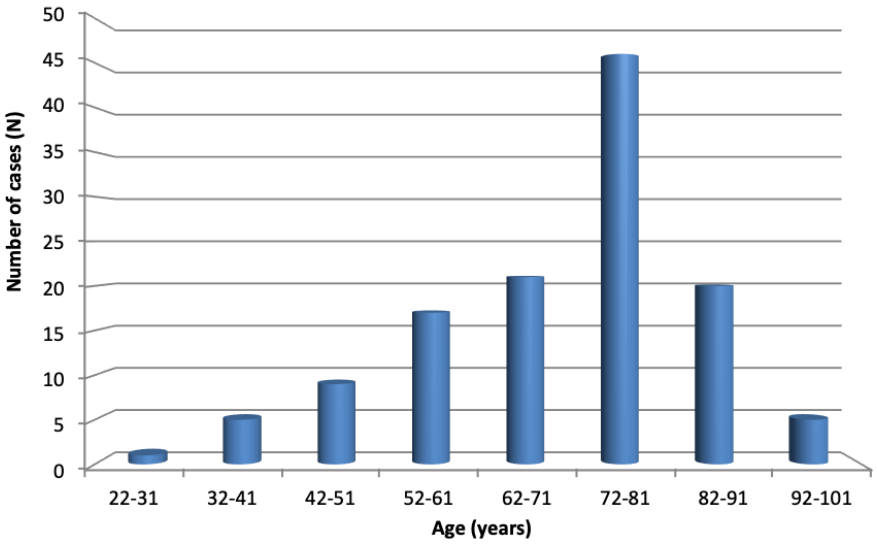

Figure 2. *Age distribution of patients with vulvar cancer at UKC Maribor between 1994 and 2017.*

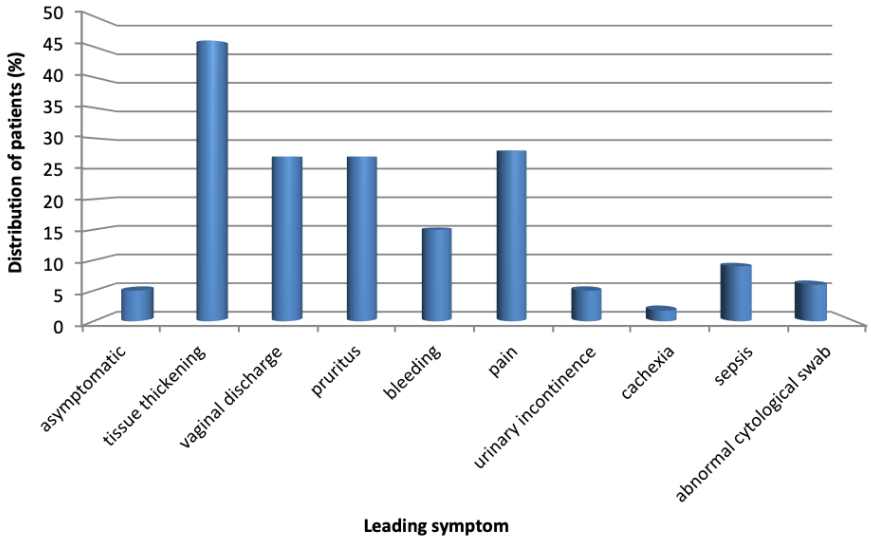

Figure 3. *Presenting symptoms in patients with vulvar cancer.*

system using the clinical parameters in our database.

HPV testing was performed in 45 patients. Thirteen patients were HPV-negative (29%), while the remaining patients tested positive for one or more HPV types. The most common type was HPV 16, followed by HPV 18, 31, and 33 (Table 1).

Surgical treatment, including wide local excision and inguinofemoral lymphadenectomy or sentinel node biopsy, were the most common primary treatment modalities performed in 86% of the patients. The initial treatment was primary radiotherapy in 5% of the patients and the initial treatment was a combination of primary radiotherapy and chemotherapy in 2% of the patients. The initial surgical treatment was followed by adjuvant radiotherapy or a combination of radiotherapy and chemotherapy in 7% of the patients.

DISCUSSION

The current study is the first retrospective analysis to address the epidemiologic, clinical, and pathologic characteristics of patients with vulvar cancer treated in a single clinical center in Slovenia. The epidemiologic characteristics of the patients in this study were consistent with recent international data, which usually involve postmenopausal women with an age range of 65–70 years (8). The average age in our population was slightly higher (71 years). Figure 1 shows a tendency toward a growing number of cases diagnosed per year from 2003, which was confirmed using the Holt's trend method. This observation is in agreement with previously published data and was attributed to the increasing incidence of vulvar cancer to the implementation of ZORA, the Slovenian cervical cancer screening program and registry (1).

In most cases, genital cancer is a lesion accompanied by symptoms, such as pruritus, bleeding, discharge, and pain, which was also confirmed in our study population (9).

A typical distribution by histologic type of cancer was depicted in a retrospective study conducted in the Netherlands based on cancer registry data of 5680 women, as follows: 81% of cases were SCCs; 8% were basal cell carcinomas; 6% were melanomas; and

5% were other types of cancer (10). Like other studies, we also confirmed that vulvar SCC was the most common histologic type of vulvar cancer (confirmed in 88.7% of our patients). In contrast, vulvar melanoma, which has been reported to be the second most common neoplasm of the vulva, occurred in only 1.6% of our study patients (10).

Because the most common symptoms of vulvar cancer are lesions in 46% of patients, pain in 28%, and discharge and pruritus in 27%, vulvar cancer is usually diagnosed in an early stage when the cancer is still confined to the primary site. According to the Netherlands Cancer Registry, patients are most often diagnosed at an early stage [59% in stages I and II] (11). The Cancer Registry of the Republic of Slovenia reported 58 new cases of vaginal cancer in 2017 (12). Cancer was diagnosed at a localized stage in 26 women (44.8%), while in 29 patients (50.0%) the tumor growth was regional (12). In the current study, 63% of patients were classified in the first two stages according to the FIGO stage classification system.

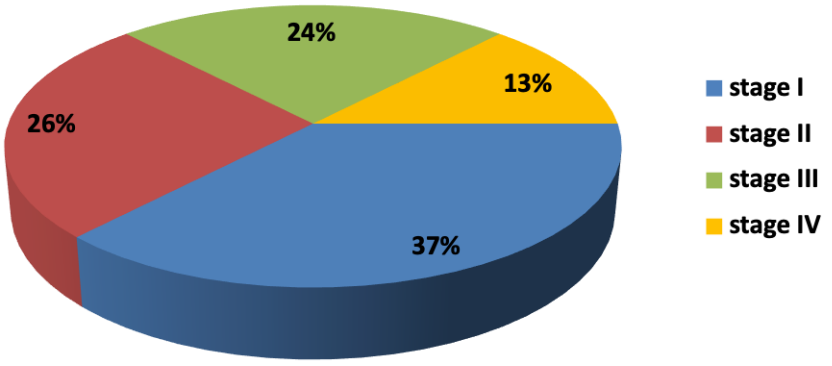

Figure 4. *FIGO stage classification of vulvar cancer diagnosed between 1994 and 2017 at UKC Maribor.*

Table 1. *HPV type distribution in 45 vulvar cancer specimens tested for HPV*

HPV type	N (45)	%
No HPV infection	13	29
Single HPV infection	2	4.4
HPV16	2	4.4
HPV18	0	0
HPV31	0	0
HPV33	0	0
Multiple HPV infection	30	66.6
HPV16&HPV18	16	53
HPV16&HPV18&HPV31	0	0
HPV16&HPV18&HPV31&HPV33	14	47

HPV is involved in one of at least two pathways leading to vulvar SCC: HPV-associated; and HPV-independent (13). According to del Pino (13), these two types of vulvar SCC have different epidemiologic, pathologic, and clinical characteristics, and should therefore be considered two separate entities. Rakislova et al. (14) stated that the percentage of HPV-positive vulvar SCCs range from 18%–75% depending on the geographic area. HPV-associated tumors affect relatively young women and arise from high-grade intraepithelial lesions that are identical to other HPV-associated pre-malignant lesions of the anogenital region. HPV-positive tumors tend to be of the basaloid (prevalence of HPV = 84%) or warty types (prevalence of HPV = 76.5%), whereas HPV-independent tumors tend to be the keratinizing type (prevalence of HPV = 13.8%); however, there is a frequent overlap between these histologic types (15). The prognostic role of HPV in vulvar SCC is still a matter of debate; however, increasing evidence suggests that HPV-associated tumors are less aggressive (14). A large meta-analysis by Faber et al. (16) included > 5000 vulvar cancer patients; the prevalence of HPV was 39.7%. Our HPV-tested patients had a higher percentage of positive results.

Among HPV-positive cases, the predominant high-risk HPV type was 16, followed by 33 and 18, once again demonstrating geographic heterogeneity. In a recent Austrian study, 23% of vulvar cancers tested positive for HPV DNA, and HPV 16 was present in 76%, followed by HPV 31 and HPV 33 (17). HPV 16 also had the highest prevalence in our population, followed by HPV 18.

Lichen sclerosus is a chronic inflammatory disease that has traditionally been considered a pre-cancerous lesion, although malignant transformation is observed in only 4%–6% of patients (18). Lichen sclerosus is a frequent finding in the skin adjacent to HPV-independent vulvar SCC; however, the mechanisms involved in the pathogenetic pathway from lichen sclerosus to cancer have not been elucidated (13, 18). Hypertension, hypothyroidism, and type II diabetes mellitus are more frequent in the Italian population with lichen sclerosus than among the general population. (19). These findings led Virgili et al. (19) to conclude that metabolic factors and lifestyle have key roles in the pathogenesis of genital lichen sclerosus among genetically-predisposed patients. Of note, some co-morbidities in the Virgili et al. (19) study were the most common co-morbidities in our vulvar cancer patients.

The gold standard for surgical treatment of vulvar carcinoma was previously a radical vulvectomy followed by en bloc resection of the inguinal, and sometimes, pelvic lymph nodes. Today, a more individualized and less radical approach is preferred, including wide excision and inguinofemoral lymphadenectomy or sentinel node biopsy. Operative treatment is preferred whenever feasible (stages I and II, locally advanced disease [stages III and IVA]), otherwise primary chemoradiation is recommended (10). Surgical treatment was feasible in 93% of our patients with vulvar carcinoma. Decisions about adjuvant treatment were based on the findings at the time of surgery, and was necessary in 7% of our patients.

CONCLUSIONS

Vulvar cancer most often affects older women; however, the incidence is on the rise across all age groups. Early detection and histologic examination of any suspicious lesion is required for early diagnosis and successful treatment.

Because a high percentage of vulvar cancers is related to HPV infection, vulvar cancer may be prevented by prophylactic HPV vaccination. Although HPV 16 accounts for the majority of cases, other HPV types play an important role in the development of HPV-associated disease. Therefore, vaccines should cover a wide range of genotypes to reduce the incidence of vulvar pre-cancerous lesions and vulvar cancer.

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