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## Original Research Article

# Evaluation of the impact of individual and environmental factors on the prognosis of women with vulvar cancer



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## ARTICLE INFO

## Article history:

Received 17 June 2013

Received in revised form

6 August 2013

Accepted 12 September 2013

Available online 17 September 2013

## Keywords:

SCC of the vulva

Wound healing

Infection of wound

Recurrence

Menopause

## ABSTRACT

**Introduction:** Vulvar cancer is a rare type of cancer. In Poland in 2010 there were 491 cases of vulvar cancer. Prognostic factors that may influence the course of the disease and results of treatment can be divided into factors associated with tumor, individual factors of the patient (age, socioeconomic status, co-morbidities, body weight, motivation to comply) and environmental factors.

**Aim:** The purpose of this research was to evaluate the impact of individual and environmental factors on the prognosis of women with vulvar cancer, regardless of the clinical stage.

**Material and methods:** The study group consisted of 48 patients with invasive squamous cell carcinoma of the vulva treated surgically in the Department of Gynecological Oncology in Olsztyn in 1995–2008. Analysis included age, place of living, occupational status, marital status, obstetric history, co-morbidities, body weight, and healing of post-operative wound. Univariate analysis of the effect of these factors on survival and recurrence rates was performed.

**Results and discussion:** Univariate analysis showed a relationship between impaired post-operative wound healing and recurrence rate ( $p < .05$ ). Wound healing complicated by abscess formation occurred most frequently in patients with T2 stage tumor and did not correlate with lymph node involvement. No effect of age, body weight, age at menarche and age at menopause, and number of births on the presence or absence of recurrence was observed ( $p < .05$ ).

**Conclusions:** In patients with post-operative wound healing complications due to infection statistically significant worse survival rates have been observed. Vulvar cancer was repeatedly diagnosed 22 years after menopause, in its advanced stages (according to FIGO 1988). No correlation between survival rate and demographic factors, environmental factors, gynecological and obstetric history and co-morbidities was demonstrated. Difference between

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overall survival and disease-specific survival, that is, excluding deaths from causes unrelated to cancer, was 10%.

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## 1. Introduction

Vulvar cancer is a rare type of cancer. According to the National Cancer Registry, standardized incidence rate in 2010 was 1.1, when 491 new cases were reported.<sup>4</sup> Prognostic factors that may influence course of the disease and treatment results are divided into three groups: (1) factors associated with the tumor, (2) individual factors that characterize the patient and (3) environmental factors, in which the patient lives. The majority of researches concerns factors associated with characteristics of tumor invasion. However, according to researchers environment and lifestyle might be responsible for the development and course of neoplastic disease in up to 80%. Among individual factors one may identify: (1) demographic factors such as age, race, socioeconomic status, (2) factors that affect general health status such as concomitant diseases, body weight, immunodeficiency states, patient mental status and (3) motivation to begin and continue to comply with physician. Environmental factors of the patient are also relevant, such as highly specialized medical education of physician (that ensures quick diagnosis and adequate treatment), availability of medical care (that is comfortable and affordable access, short waiting time) and socioeconomic status of the patient.<sup>22</sup>

## 2. Aim

The purpose of this research was to determine, whether selected demographic and environmental features, regardless of clinical staging, affected prognosis of women with vulvar cancer admitted for surgical treatment.

## 3. Material and methods

### 3.1. Material

Study group consisted of 48 patients with squamous cell carcinoma (SCC) of the vulva treated surgically in the Department of Gynecologic Surgery in Olsztyn in 1995–2008. Data were collected from hospital records, outpatient medical records, from patients and their families. In the majority of patients ( $n=38$ ; 79.2%) radical excision of the vulva with inguinal-femoral lymphadenectomy was performed. According to the 1995 FIGO classification 37.5% of patients were diagnosed with stages III and IV disease. Information on the number of patients with various staging, according to FIGO and TNM, are presented in Table 1.

The observation time of all patients ranged between 12 and 158 months (average of 49.4 months), while observation time of patients cured ranged between 25 and 158 months (average of  $86.3 \pm 38.5$  months, median 80).

### 3.2. Statistical methods

Kaplan–Meier curves for overall survival were plotted. Differences between the two curves were compared with the use of log-rank test. In order to determine the impact of the chosen factors on survival, univariate Cox proportional hazards analysis was performed. For qualitative variables, depending on the number of subcategories,  $p$  value is the result of log-rank test (number of categories=2), or  $\chi^2$  test (number of categories >2). For quantitative variables hazard ratio (HR) was calculated. Univariate analyses of the impact of variables on the incidence of recurrence were performed. For qualitative variables  $p$  value was calculated for Pearson's  $\chi^2$  test of independence. Odds ratio (OR) was determined – standard deviation (SD), confidence interval (CI) and  $p$  value were defined. For quantitative variables U Mann–Whitney test was performed.  $P$  value less than .05 was considered statistically significant.

Analyses were conducted with the use of Statistica SoftStat 9.1.

## 4. Results

### 4.1. Environmental history

Average age of patients was  $67.1 \pm 11.9$  years (range 28–87 years; median 67.5). Increased incidence was noted in patients over 60 years of age (81.3%). The most numerous group constituted patients between 60 and 70 years of age – (41.7%) and between 75 and 80 years of age – (18.8%). Data are presented in Fig. 1.

The majority of patients were residents of the cities ( $n=37$ ; 77.1%). Only one-third of them came from rural areas. Marital status of the studied patients ( $n=48$ ) was as follows: 27 were married (56.3%), 16 were widows (33.3%) and 5 single (10.4%). At the time of admission only 3 patients were professionally active (6.3%). Among the remaining patients, 18 were pensioners (37.5%), 24 retired on disability benefit (50.0%) and 3 respondents declared themselves unemployed (6.3%).

**Table 1 – FIGO (1995) and TNM classification of SCC of the vulva.**

FIGO	TNM	No.	Total number of patients n (%)
Stage I	T1N0M0	13	13 (27.08)
Stage II	T2N0M0	17	17 (35.42)
Stage III	T1N1M0	1	10 (20.83)
	T2N1M0	9	
Stage IV	T1N2M0	1	8 (16.67)
	T2N2M0	7	
Total			48 (100.00)

4.2. Gynecological history

Patients had menarche between 12 and 18 years of age (average of 14 years). In the majority of women it occurred up to 15 years of age (83.3% of respondents). Menopause, in turn, occurred between 39 and 56 years of age (average of  $49.0 \pm 4.5$  years). In most women the disease presented after menopause ( $n=43$ ; 89.6%). Almost one-third of them ( $n=13$ ; 27.1%) had menopause before 48 years of age (Fig. 2).

In the study group, 28 women (58.3%) had from two to four deliveries, 11 women (22.9%) gave birth to five or more children and 7 women (14.6%) did not give birth (Table 2).

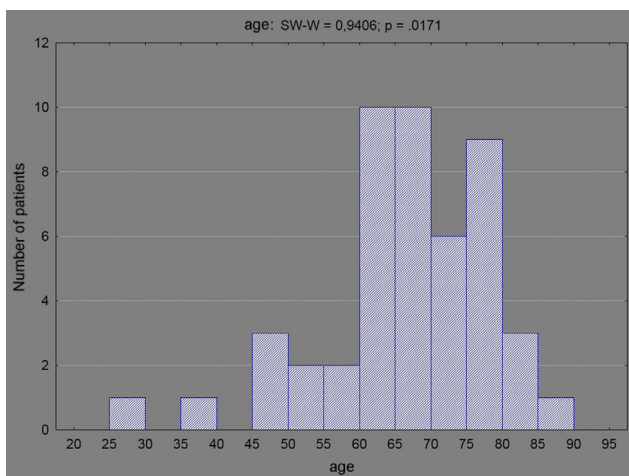


Fig. 1 – Age of patients with vulvar SCC who underwent surgical treatment.

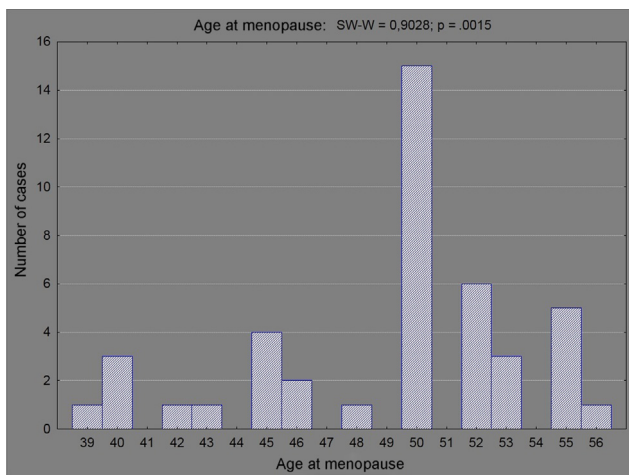


Fig. 2 – Age at menopause of women with SCC.

4.3. Co-morbidities

Factors aggravating surgical and adjuvant treatment, in addition to advanced age, include coexistence of other diseases. None of the patients suffered from any malignant disease, whereas many of them (70.8%) had other coexisting medical conditions: arterial hypertension – 27 patients (56.3%), coronary heart disease – 16 (33.3%), including myocardial infarct – 3 (6.3%), diabetes – 11 (22.9%), diseases of the central nervous system – 6 (12.5%), stroke – 1 (2.1), asthma – 3 (6.3%), sustained atrial fibrillation – 2 (4.2%), and varicose veins of the lower limbs – 19 (39.6%).

Body mass index (BMI) of patients was also calculated. Patients with normal body weight accounted for 25.0% of patients ( $n=12$ ). The remaining 75.0% of patients ( $n=36$ ) had BMI above 25, while half of them ( $n=18$ ; 37.5% of total) were overweight and half ( $n=18$ ; 37.5%) obese (including second degree obesity – 10.4%). In the study group no underweight women were identified. Mean BMI was 28. Cross-section of the study group according to BMI is presented in Fig. 3.

4.4. Healing of postoperative wounds

In 12 patients (25.0%) post-operative wounds were healing by primary intention. None of these patients had recurrence. In 28 patients (58.3%) healing of vulva and inguinal wounds was complicated by suppurative process and they were healing by granulation. Culture of the collected specimen most frequently identified the following bacteria: *Escherichia coli* (10 cases), *Proteus mirabilis* (6), *Enterococcus fecalis* (5),

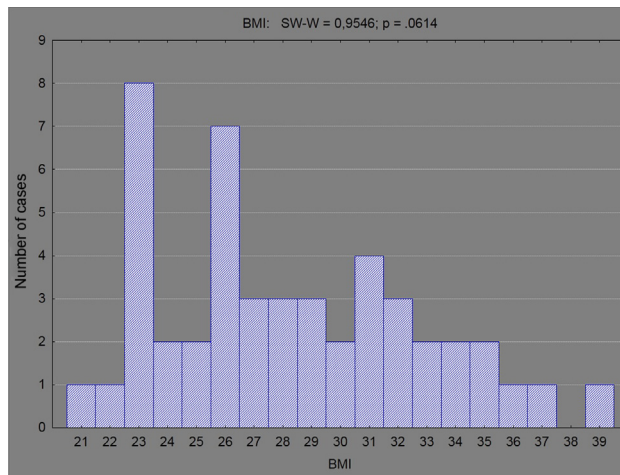
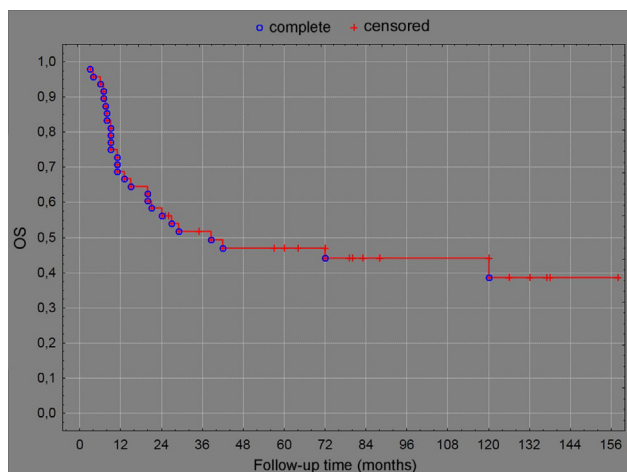


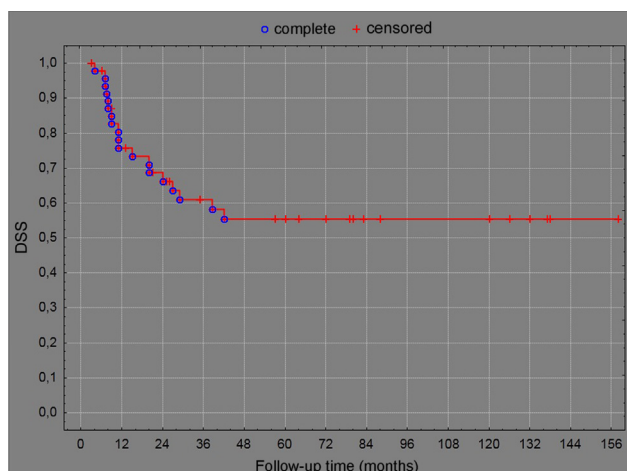
Fig. 3 – BMI differences of SCC vulvar cancer patients.

Table 2 – Summary of the selected descriptive statistics of the study group.

Feature	Average	Median	Min	Max	SD
Age, years	67.13	67.50	28	87	11.85
Menarche, years	14.25	14.00	12	18	1.62
Menopause, years	49.21	50.00	39	56	4.51
Number of deliveries, n	3.23	3.00	0	11	2.58



**Fig. 4 – OS Kaplan–Meier curve for SCC vulvar cancer patients.**



**Fig. 5 – DSS Kaplan–Meier curve for SCC vulvar cancer patients.**

*Streptococcus agalactiae* (4), *Klebsiella pneumoniae* (3) and *Staphylococcus aureus* (3).

#### 4.5. Assessment of overall survival

Kaplan–Meier curves for patients overall survival (OS) and disease-specific survival (DSS) were plotted. DSS excludes deaths unrelated to cancer. Obtained data are shown in Figs. 4 and 5. OS after 12, 36 and 60 months was 68.8%, 51.7%, and 45.8%, and DSS 76.1%, 61.0% and 54.2%, respectively.

#### 4.6. Impact of the selected factors on overall survival

Univariate analyses of the impact of the selected factors on overall survival were performed. Results are summarized in Tables 3 and 4.

The impact of FIGO stage on overall survival is presented in Fig. 6.

A relationship between TNM stage and wounds infection was evaluated ( $\chi^2$  test). It was concluded that infection

**Table 3 – Impact of qualitative variables on patients OS.\***

Variable	Number of categories	P value
Stage according to FIGO 1995	5	.0027
Place of living	2	.2556
Marital status	3	.5890
Occupational status	4	.7342
Co-morbidities	2	.0789
Menopause	2	.4585
Wound infection	2	.0015
Lymphedema	2	.9903
Deliveries	5	.8728
Miscarriages	3	.8487

\* Depending on the number of categories in  $p$ -value column there is a log-rank test result (number of categories = 2) or  $\chi^2$  test result (number of categories > 2). Statistically significant parameters have been highlighted ( $p < .05$ ).

correlates ( $p = .02$ ) with tumor size and does not correlate with lymph node involvement ( $p = .11$ ). Univariate analysis has confirmed the effect of type of wound healing on survival. Patients with prolonged healing of postoperative wounds complicated by infection had a statistically significant worse survival than patients with normal wound healing (Fig. 7).

Univariate analysis of the impact of individual qualitative and quantitative factors on recurrence was performed. Obtained data are summarized in Table 5.

Pearson's  $\chi^2$  test of independence (at the significance level  $\alpha = .05$ ) indicated the relationship between recurrence and healing of inguinal wounds complicated by infection. Univariate analysis ( $U$  Mann–Whitney test) showed no statistically significant impact of age (.5839), body weight (.7556), age at menarche and age at menopause (.9914 and .2416, respectively) or number of deliveries on recurrence rate (.9743).

## 5. Discussion

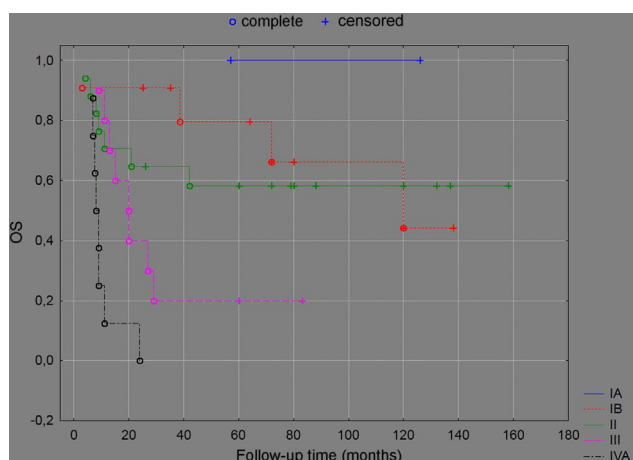
Sample, on which analyses were performed, was quite small but included the majority of patients operated on for carcinoma of the vulva in Warmia–Masuria Province in 1995–2008.

Mean age of patients was 67.1 years (median 67.5 years) and was higher than the mean age of patients treated in Silesia (62 years).<sup>20</sup> In Gdansk and Krakow similar median age was demonstrated – 67 years.<sup>2,18</sup> According to the National Cancer Registry in Poland the majority of cases of vulvar cancer are found in women aged 70–79 years.<sup>4</sup>

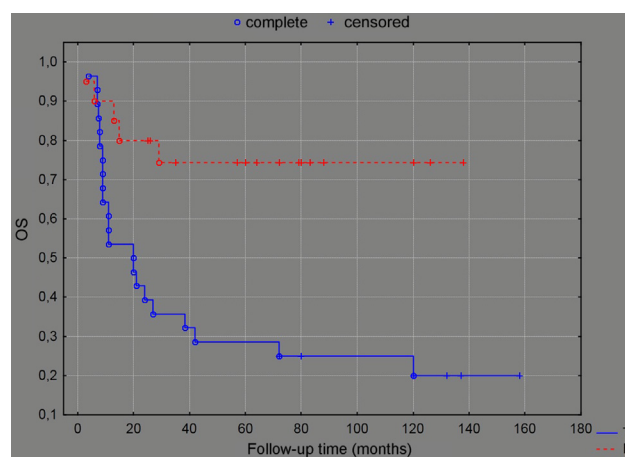
In the study material, in nearly 90% of women the disease occurred after menopause. Average time between the last menstrual period and reporting for treatment was 22 years. According to some sources, in patients with vulvar cancer last menstrual period occurred 5–6 years earlier than in general female population.<sup>7</sup> In the material of Clinic of Gynecologic Oncology in Gdansk, 27% of patients were postmenopausal.<sup>8</sup> Median age of menarche was 14 and did not differ from the average in Poland. No clear association of

**Table 4 – Impact of quantitative variables on patients OS (univariate Cox proportional hazards models).**

Variable	HR	Lower HR 95% CI	Upper HR 95% CI	P value
Age	1.04	1.00	1.08	.0685
BMI	1.04	0.95	1.13	.4093
Menarche, years	1.16	0.94	1.44	.1619
Menopause, years	0.99	0.91	1.09	.9051
Deliveries	0.98	0.84	1.15	.7988



**Fig. 6 – OS Kaplan–Meier curves for SCC vulvar cancer patients following surgery by FIGO 1995 staging system ( $\chi^2$  test –  $p = .0027$ ).**



**Fig. 7 – OS Kaplan–Meier curves for patients with normal wound healing vs. inguinal wound infection (log-rank test –  $p = .0015$ ). N – cases with normal wound healing, T – cases with infection of inguinal wound.**

these parameters and vulvar cancer, as well as survival of patients in the study group, was demonstrated. In the literature it is assumed that vulvar cancer has no significant correlation with sex hormones.<sup>17</sup> A potential association between carcinogenesis on the vulva and hormonal disorders related to menopause and advanced age is demonstrated.<sup>20</sup>

Univariate analysis showed no statistically significant impact of age on survival of women in the study group. It should be noted, however, that the group was too small to divide it into age subgroups. Impact of age on survival of patients with vulvar cancer was analyzed in several studies but the results are inconclusive. Authors have observed a trend towards worse treatment results in patients at a more advanced age.<sup>15</sup> Data show that survival of vulvar cancer women younger than 40 years of age was significantly higher (96%) than in patients above 65 years of age (72%).<sup>6,16</sup> High survival rates for younger women might have been associated with diagnosis made in the early stages of the disease.<sup>6,9</sup> Women aged 80 years are more frequently diagnosed with cancer in advanced stages. Treatment plan is then frequently individualized and modified due to general condition, physical function and concomitant diseases, which according to the authors resulted in the reduction of OS.<sup>9,21</sup> However, in our material patients above 75 years of age presented at early stages of the disease according to FIGO (11 out of 14 patients). Analysis of patients treated in the Centre of Oncology in Krakow showed a relationship between OS and age. In case of patients below 70 years of age OS was 54.7% and in older patients it decreased to 30.5%.<sup>2</sup>

In our material, we did not demonstrate the impact of place of living, marital status or occupational status of the patient on survival or recurrence rate. Most of patients were citizens, similarly as in Gdansk site.<sup>8</sup> The majority of women participating in the study were out of work. They were pensioners or retired on disability benefit due to incapacity to work resulting from concomitant diseases. Approximately 56% of women were married. According to the data of Central Statistical Office of Poland (GUS) 60% of population of Warmia–Masuria Province lives in cities. At the end of 2012 in this province GUS reported the highest unemployment rate in Poland – 21.2% compared to 13.4%. A delay of the region in relation to road, rail and telecommunication infrastructure is also observed. This is important to the fact that attempts of different researchers to determine a relationship between socioeconomic status and OS of patients with gynecologic cancers did not bring any firm conclusions. Special Report of the American Cancer Society evaluating such conditions stated that patients with lower socioeconomic status have worse survival rates and in at least half of cases such differences result from late diagnosis of cancer. Delayed diagnosis, on the other hand, resulted from imperfection of educational programs, conviction on ineffectiveness of free treatment and observed in this group general tendency to pessimism and fatalism in the estimation of curability of cancer, which discouraged them from treatment.<sup>11,13</sup> Respondents from the study group and their families claimed that

**Table 5 – Results of univariate analysis of the impact of qualitative variables on recurrence rate.**

Variable	Number of categories	Relation	OR	ASE	Lower 95% OR	Upper 95% OR	P value OR	P value $\chi^2$
Tumor status	2	T2 vs. T1	2.68	0.70	0.67	10.63	.1621	.1340
Nodal status	3	N1 vs. N0	5.30	0.81	1.08	26.00	.0400	.0002
		N2 vs. N0	62.33	1.55	2.99	1298.83	.0076	
Place of living	2	C vs. V	0.31	0.69	0.08	1.18	.0863	.0731
Marital status	3	Widowed vs. married	2.76	0.64	0.79	9.68	.1134	.2631
		Single vs. married	1.55	0.93	0.25	9.55	.6337	
Occupational stats	4	Retired vs. pensioner	1.77	0.63	0.51	6.12	.3675	.7954
		Unemployed vs. pensioner	1.15	1.14	0.12	10.79	.9001	
		Employed vs. pensioner	1.15	1.14	0.12	10.79	.9001	
Co-morbidities	2	Y vs. N	1.28	0.64	0.37	4.49	.6949	.6682
Menopause	2	Y vs. N	0.44	0.89	0.08	2.52	.3602	.3454
Wound infection	2	Y vs. N	7.17	0.70	1.82	28.31	.0049	.0022
Lymphedema	2	Y vs. N	2.08	0.64	0.59	7.30	.2546	.2463
Number of deliveries	5	1 vs. 0	1.67	1.28	0.14	20.48	.6898	.5242
		2 vs. 0	0.60	0.96	0.09	3.96	.5957	
		3 vs. 0	0.29	1.04	0.04	2.27	.2409	
		4 vs. 0	0.89	0.89	0.16	5.13	.9007	
Number of miscarriages	3	1 vs. 0	1.47	0.73	0.35	6.12	.5944	.2986
		2 vs. 0	4.20	1.04	0.55	32.10	.1667	

the availability, distance and travel costs affected decisions on continuation of treatment and postoperative care. Radiotherapy has been available in Olsztyn since 2003. Previously, patients that required adjuvant therapy were referred to the sites located in adjacent provinces. Numerous patients abandoned treatment or decided on treatment only after recurrence of cancer, when palliative treatment did not give the expected results. Even after Gynecologic Oncology Group study #37 of 1986 better survival rates for patients with regional lymph nodes metastases were observed when surgical treatment was supplemented with radiation therapy on inguinal and pelvic area.<sup>1</sup>

According to the literature, arterial hypertension and diabetes often coexist (25%–40%) in patients with vulvar cancer, but are not independent risk factors for the disease. These conditions, together with obesity, are considered poor prognostic factors that reduce survival.<sup>19</sup> Some authors have shown higher risk of vulvar cancer in overweight women, others did not find such relationship.<sup>3,12</sup> In our material, no correlation between body weight and survival or recurrence rate was found.

Treatment of patients with vulvar cancer is associated with high risk of complications. Long-lasting non-healing postoperative wounds, lymphatic cysts formation, excessive lymph flow, occurrence of infection and abscess formation lead to immobilization of patients and cachexia. In the literature infection of post-operative wounds is reported in 11%–58% of patients.<sup>10,14</sup> The authors have emphasized significant prolongation of treatment of infectious post-operative wounds after

inguinal lymphadenectomy in comparison to peri-operative infections after other non-oncological surgeries in women.<sup>5</sup> None of the patients in our group died due to post-operative septic complications. In patients with infected wounds recurrence rates were more than seven times higher than in patients with normal wound healing processes ( $p=.0022$ ). None of the patients, in whom the wound healed by first intention, had recurrence.

## 6. Conclusions

In patients with infectious complications of post-operative wound healing a statistically significant worse survival ratio was observed than in patients with normal wound healing processes. Analysis shows correlation between this factor and recurrence risk. Wound healing complicated by infection was more frequently observed in patients with T2 tumor than in patients with T1 tumor and it did not correlate with lymph node involvement.

In the study group no distinguishing features were observed in comparison to other study groups of patients with vulvar cancer. Diagnosis of vulvar cancer on average 22 years after menopause in its most advanced stages draws attention.

No correlation between survival of patients with vulvar cancer and demographic factors, environmental factors, gynecologic and obstetric history and co-morbidities was demonstrated. Difference between OS and DSS, that is after exclusion of deaths unrelated to cancer, was 10%.

Patients from Warmia–Masuria Province were admitted for treatment in advanced stages, did not continue adjuvant therapy and did not come back for recommended follow-ups. Thus, it seems important to promote education of both women and primary healthcare personnel.

### Conflict of interest

None declared.

### REFERENCES

- [1] Barnes EA, Thomas G. Integrating radiation into the management of vulvar cancer. *Semin Radiat Oncol.* 2006;16(3): 168–176.
- [2] Blecharz P, Karolewski K, Bieda T, Klimek M, Pudelek J, Kojs E, et al. Prognostic factors in patients with carcinoma of the vulva – our own experience and literature review. *Eur J Gynaecol Oncol.* 2008;29(3):260–263.
- [3] Brinton LA, Nasca PC, Mallin K, Baptiste MS, Wilbanks GD, Richard RM. Case-control study of cancer of the vulva. *Obstet Gynecol.* 1990;75(5):859–866.
- [4] Centrum Onkologii Warszawa. *Krajowy Rejestr Nowotworów.* Available from: [epid.coi.waw.pl/krn](http://epid.coi.waw.pl/krn).
- [5] Elg SA, Carson LF, Brooker DC, Carter JR, Twigg LB. Infectious morbidity after radical vulvectomy. *Infect Dis Obstet Gynecol.* 1994;2(3):130–135.
- [6] Ghebre RG, Posthuma R, Vogel RI, Geller MA, Carson LF. Effect of age and comorbidity on the treatment and survival of older patients with vulvar cancer. *Gynecol Oncol.* 2011;121(3): 595–599. <http://dx.doi.org/10.1016/j.ygyno.2011.02.005>.
- [7] Green Th. Carcinoma of the vulva. A reassessment. *Obstet Gynecol.* 1978;52(4):462–469.
- [8] Konefka T. *Ocena wyników leczenia chorych na raka płaskonabłonkowego sromu z uwzględnieniem możliwości zastosowania zabiegów oszczędzających [rozprawa doktorska] [Evaluation of treatment results of patients with squamous cell carcinoma of the vulva including possible use of conservative treatment] [doctoral dissertation].* Gdańsk; 1997 [in Polish].
- [9] Kumar S, Shah JP, Bryant CS, Imudia AN, Morris RT, Malone JM. Comparison of younger vs older women with vulvar cancer in the United States. *Am J Obstet Gynecol.* 2009;200(5): e52–e55. <http://dx.doi.org/10.1016/j.ajog.2008.09.869>.
- [10] Leminen A, Forss M, Paavonen J. Wound complications in patients with carcinoma of the vulva. Comparison between radical and modified vulvectomies. *Eur J Obstet Gynecol Reprod Biol.* 2000;93(2):193–197.
- [11] Oonk MH, Hullu JA, Hollema H, Mourits MJ, Pras E, Wymenga AN, et al. The value of routine follow-up in patients treated for carcinoma of the vulva. *Cancer.* 2003;98(12):2624–2629.
- [12] Parazzini F, Moroni S, Negri E, La Vecchia C, Dal Pino D, Cavalleri E. Selected food intake and risk of vulvar cancer. *Cancer.* 1995;76(11):2291–2296.
- [13] Parham GP, Hicks ML. Gynecologic cancer among the socioeconomically disadvantaged. *Cancer Suppl.* 1995;76 (suppl 10):2176–2180.
- [14] Rodolakis A, Diakomanolis E, Voulgaris Z, Akrivos T, Vlachos G, Michalakis S. Squamous vulvar cancer: a clinically based individualization of treatment. *Gynecol Oncol.* 2000;78(3 Pt 1): 346–351.
- [15] Rutledge FN, Mitchell MF, Munsell MF, Atkinson EN, Bass S, McGuffee V, et al. Prognostic indicators for invasive carcinoma of the vulva. *Gynecol Oncol.* 1991;42(3):239–244.
- [16] Saraiya M, Watson M, Wu X, King JB, Chen VW, Smith JS, et al. Incidence of in situ and invasive vulvar cancer in situ in the US, 1998–2003. *Cancer.* 2008;113(suppl 10):2865–2872. <http://dx.doi.org/10.1002/cncr.23759>.
- [17] Sherman KJ, Daling JR, McKnight B, Chu J. Hormonal factors in vulvar cancer. A case-control study. *J Reprod Med.* 1994;39(11): 857–861.
- [18] Sznurkowski JJ, Emerich J. Characteristic features of recurrences of squamous cell carcinoma of the vulva. *Ginekol Pol.* 2010;81(1):12–19.
- [19] Tyring SK. Vulvar squamous cell carcinoma: guidelines for early diagnosis and treatment. *Am J Obstet Gynecol.* 2003;189 (suppl 3):S17–S23.
- [20] Urban A, Wala D, Miszczyk L, Suwiński R. Ocena wyników leczenia złośliwych nowotworów sromu w materiale operacyjnym chorych Kliniki Ginekologii i Położnictwa w Bytomiu [Evaluation of treatment results of vulvar cancer in postoperative material of patients of the Clinic of Obstetrics and Gynecology in Bytom]. *Współcz Onkol.* 2002;6(7):458–463 [in Polish].
- [21] Vlastos AT, Usel M, Beffa V, Petignat P, Nayround-Caspar I, Bouchardy C, et al. Treatment patterns of vulvar cancer in the elderly. *Surg Oncol.* 2004;13(4):187–191.
- [22] Zwierko M, Wronkowski Z. Epidemiologia [Epidemiology]. In: Markowska J, Mądry R, eds. *Zarys ginekologii onkologicznej [Gynecological oncology]*, Vol. 1. Poznań: Temida; 2012:39.