

Vulvar cancer in Iran: Retrospective study over 20 years (1998-2018)

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ABSTRACT

Background: We did not have any data about vulvar cancer — as a fourth cause of gynecological cancer in the worldwide — in our country. **Study Design:** Our study is designed to evaluate the frequency, stage and outcome of patients with vulvar cancer. **Materials and Methods:** In this retrospective observational study, we studied patients' records with diagnosis of vulvar cancer who referred to department of gynecology oncology, Emam-Khomeini Hospital (EKH), Tehran, Iran, between January 1998 and December 2018. A total of 106 cases of vulvar cancers were found in the records of outpatient oncology clinic of medical university of Tehran university. Survival was estimated using the Kaplan-Meier analysis with SPSS version of 24. **Results:** Mean age of the 106 patients in the study was 59.2 years. The most site of tumor involvement was major labial (39.1%). Vulvar cancer significantly was more in multiparous ($P < 0.001$) and menopause patients ($P < 0.001$). Squamous Cell Carcinoma was the most pathology of vulvar cancer (72.2%). Ninety patients (84.9%) had surgery as a primary treatment and 48 (53.3%) of these patients received adjuvant radiotherapy or chemoradiation after surgery. Mean duration of patient's follow up was 82.4 ± 68.3 month. Five-year survival of our patients in all stages was 71%. **Conclusions:** Our findings are located between developed and underdeveloped countries. Our patients are diagnosed nearly in earlier stages of disease and 84.9% of them had surgery as a primary treatment, so earlier surgery resulted in good survival of patients.

Keywords: Chemoradiation, radical surgery, survival, vulvar cancer

Introduction

Vulva cancer is a rare and fourth cause of gynecological cancer with prevalence around 4% worldwide. The most histologic type of vulvar cancers are squamous cell carcinomas, which account for 90% of all types.^[1]

The incidence is higher among old and postmenopausal patients.^[2] Mean age of women with vulvar cancer is between 64 and 70 years.^[3]

Vulvar intraepithelial neoplasia (VIN), HPV infection, squamous hyperplasia, lichen sclerosis, smoking, and immunosuppression were mentioned as risk factors.^[4]

There is a strong correlation between disease survival with lymph node status and the stage of disease.^[5] Recent studies showed that the disease is diagnosed at the early stage without lymph node involvement, the survival rate reached to 90%.^[6] Although, surgery is the gold standard of treatment, conservative surgery such as local excision of tumor with free margin rather than decrease of psychosexual consequence and morbidity of groin lymph node dissection than radical vulvectomy is preferred. Chemotherapy and radiotherapy are the other modalities for unresectable disease.^[7]

In Iran as a developing country we have no survey on vulvar cancer incidence or prevalence and long-term Survivals. Our study was carried out to determine demographic, treatment modalities, and survival rate of patients with vulvar cancer at medical university of Tehran, main referral center of gynecologic cancer of country over a period of 20 years.

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Materials and Methods

In this retrospective cohort study, we evaluated medical records of patients with vulvar cancer who referred during 20 years (1998–2018) to Oncology and Gynecology department of Emam-Khomeini Hospital (EKH) of medical university of Tehran — the main referral center for gynecological cancer throughout the country — Iran. Patients with pathologically report of vulvar cancer entered into study.

Demographic data such as age, parity, menopaosity state, history of medical disease, age onset of cancer, signs and stage of disease, treatment modalities, and so on were recorded with questionnaire.

Staging in our study was performed based on clinical examination, imaging, and pathological report after a complete surgery.

Vulvectomy or radical local excision of tumor and inguinofemoral lymphadenectomy were done for early stage (stages I and II) vulvar cancer.

Cases with stage III that had tumor resection capability were under initial surgery, those who were unable to be resected because of proximity to the urethra and anus were under three chemotherapy sessions, and then surgery was performed for them.

Patients with stage IV of disease referred for chemotherapy or radiotherapy. Adjuvant radiotherapy after surgery was done for patients with pathology of positive lymph node, size of tumor >4 cm or if the tumor-free surgical margins were <8 mm and further excision was not possible.

The outcome of patients (recurrence, death, and alive) were evaluated by a phone call. Recurrence time was calculated from last date of treatment up to time of recurrence diagnosis. Disease-free survival was considered as the date of primary treatment to date of death, or ended to palliative treatment.

Patients who did not respond to a call and their file information was incomplete, their being alive or dead was checked by referring to the site of Behesht Zahra Organization (State Death Registration System).

The study was approved by the Committee for Ethics of Tehran University of Medical Science. (IR.TUMS.IKHC.REC.1397.166).

The authors of the study were committed to the principles of the Helsinki Convention. Data were analyzed with IBM SPSS statistics version 24. Means were compared using Student's *t*-test. Survival analysis was performed using Kaplan-Meier test. $P < 0.05$ was considered statistically significant.

Results

A total of 106 women presented to EKH with vulvar cancer between January 1998 and December 2018. The mean age of patients was 59.2 years (range 23-86 years). As age

Table 1: Demographic data of patients

	Number	Percentage (%)	P
Age range (years)			0.03
<30	3	2.8	
30-39	7	6.6	
40-49	17	16	
50-59	21	19.8	
60-69	22	20.8	
70-79	26	24.5	
80-89	10	9.4	
Mean age	59.2±14.7		
Parity			0.0001
Nulliparous	8	7.5	
Multiparous	98	92.5	
Parity, median (range)	5 (0-13)		
Menopausal status			0.0001
Premenopausal	17	15.1	
Postmenopausal	85	80.2	
Pap smear			0.001
Normal	103	97.2	
Abnormal	3	2.8	
Past medical Hx			0.0001
Yes (HTN, diabetes)	22	20.8	
No	84	79.2	

Table 2: Annual distribution of patients with vulvar cancer

Year	Number of cases (n)	Percentage (%)
1998	4	4.1
1999	2	2.1
2000	3	2.8
2001	5	4.7
2002	3	2.8
2003	6	5.7
2004	4	3.8
2005	7	6.6
2006	9	8.5
2007	8	7.5
2008	9	8.5
2009	4	3.8
2010	3	2.8
2011	3	2.8
2012	6	5.7
2013	3	2.8
2014	3	2.8
2015	4	3.8
2016	6	5.7
2017	8	7.5
2018	6	5.7
Total	106	100.0
Mean	5.3 case per year	

distribution presented in Table 1, only 25% of patients were <50 years. Most incidence of vulvar cancer was diagnosed in the year 2006 [Table 2]; the average per year was 5.3 cases.

Vulvar cancer significantly was more in multiparous patients than nulliparous ($P < 0.001$) and menopause patients than premenopause ($P < 0.001$). Details of demographic data are shown in Table 1.

The most obvious manifestation of vulvar cancer in our patients was a mass with most sign of pruritus. The most site of tumor involvement was major labial (39.1%), minor labial (27%), and clitoris (17.5%) respectively.

Squamous cell carcinoma was the most pathology of vulvar cancer in this study [Table 3].

Table 4 presents details of primary treatments for patients. Ninety patients (84.9%) had surgery as a primary treatment, 48 (53.3%) of them received adjuvant radiotherapy or chemoradiation after surgery. Sixteen patients (15.1%) had Chemoradiation as a primary treatment because of advanced-stage cancer of FIGO stage IV.

Eighty two (77.4%) patients had radical vulvectomy+ bilateral inguinofemoral lymphadenectomy, five (4.7%) hemivulvectomy, and two (1.2%) had wide local excision.

Table 3: Pathology of vulvar cancer

	Number	Percentage (%)
SCC	79	74.5
Adenocystic	8	8.2
Adenocarcinoma	5	5.2
Melanoma	3	3.1
Paget	2	2.1
Verrucous Carcinoma	4	4.1
Others	5	5.2
Total	106	100

Table 4: Stages of vulvar cancer and primary treatment

Stage of disease	Number of cases n=106	Surgery n=90	NACT n=11	RT n=44	CT n=8	Chemoradiation n=10
I	31	31	1	1	0	0
II	17	17	1	4	0	1
III	42	41	7	35	3	4
IV	16	0	2	4	5	5

Table 5: Summary of our findings in comparison with similar studies

	Our study	Okolo et al. ^[16]	Dadzie et al. ^[20]	Butt et al. ^[3]	Singh et al. ^[12]	Dittmer et al. ^[21]	Hunter ^[22]	Kehila et al. ^[23]
Duration of study	1998-2018	1981-2008	2000-2014	2001-2014	2004-2014	1973-2000	1952-1966	1998-2014
Country	Iran	Nigeria	Ghana	South Africa	India	Germany	Oxford	Tunisia
Number of patients	106	78	52	180	41	2685	361	76
Mean age of patients	59.2 year	49.7 year	56.3 year	52.5 year	52 year	72 year	-	65.4 year
Pathology of SCC	74.5%	73.6%	84%	-	97.56%	88%	-	94.7%
Primary surgery	84.9%	-	9.6%	62.7%	48.7%	-	31%	100%
Overall five-year survival	76%	-	36.7%	58.8%	-	50%	56%	58.3%

In all, 58 patients answered our phone calls and 55 cases (43.1%) had recurrence: 2 (12.5%) of patients without surgery and 23 (25%) with primary surgery treatment ($P = 0.1$). Mean duration of patients' follow up was 82.4 ± 68.3 (1–200) month.

Five-year survival of patients in all stages was 76% [Figure 1]. Mean time of recurrence was 20 month (1-72 month). Two-year survival in those who had recurrence <2 years was 25% versus those who did not (87%).

Discussion

There is paucity of information on vulvar cancer epidemiology and prognosis in Iran, as an upper-middle income country^[8] located in middle east with a wide area and almost 80 million population. This is the only study in Iran on vulvar cancer. Over a period of 20 years, we founded 106 patients of primary cancer of vulva at EKH. Annual incidence in our study was 5.3 per cases. These findings proved rarity of vulvar tumors as the fourth gynecological cancer.^[7]

Mean age of our patients was 59.2 ± 14.7 years. It was resemble to Amavi et al.^[9] study. Mean age in US^[10] was 68 years and 70 years in Ciszko study^[11] [Table 5].

The most number of patients was in the age range of 70–79 years, 10 years older than Indian people in Singh et al.^[12] study and similar to US^[10], and European countries^[13].

In Okeke et al.^[14] study, this prevalence in Nigerian patients were found in fifth and sixth decades.

Vulvar cancer is the elderly disease in Iran. Only one fourth of our patients were below 50 years. It is comparable with Buttman-Schweiger^[13] and Baantrup^[15] findings, which were 11.5% and 23%, respectively.

SCC was the most pathology (74.5%). Like 73% in Okolo study^[16] and 75% in Schuurman et al.^[17]

Vulvar cancer is seen in two age groups of the elderly and young people. In the elderly and menopause, it usually occurs in chronic illnesses associated with the P53 gene mutations, which is observed in advanced countries with high life expectancy. Another type is related to the HPV virus and observed in young people.^[18]

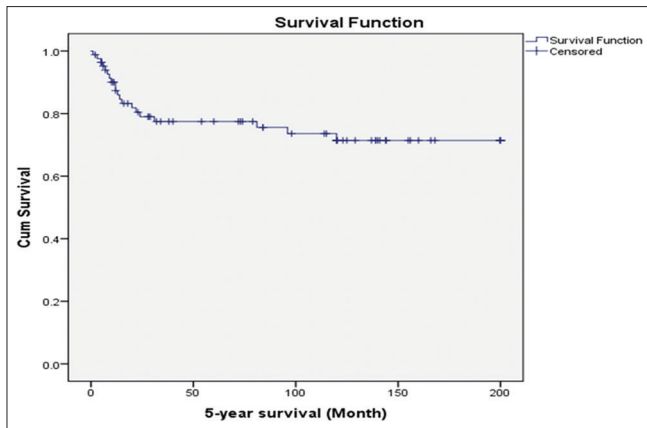


Figure 1: Overall five-year survival of patients with vulvar cancer

In our study, only three abnormal pap smears were observed. According to this finding and the lower probability of HPV patients, occurring vulvar cancer in higher ages in statistical population can be justified.

In our study, 54.7% of women diagnosed at stages III and IV which was similar to other studies. According to FIGO, in Ciszko study^[11], 68% of cases vulvar cancer was detected in II, III or IVa stage. Moreover, 39% of patients in Amavi study^[9] and 53.3% in Butt *et al.*^[3] were at stages III and IV.

Our finding is in contrast with Stroup *et al.*,^[19] 90% of cases were diagnosed in early stages, and 25% with stages III and IV.

Almost half of our patients referred in stages III and IV, which may be for referring to gynecologists for examination and check-up in elderly people in cities and rural areas is rarely done due to cultural issues, a sense of shame of showing genital area to other, lack of awareness and financial resources. Hence, most patients have suspicious unbearable symptoms when refer.

Five-year survival was 73% in the surgical group that was upper than other studies [Table 5]. Studies have shown that surgery leads to survival up to 90%.^[20] One possible reason for this is that the number of people who were under surgery was higher than all other studies in our study (84.9%), because all patients in stage III except one case that was under chemoradiation due to high age and underlying disease, other cases that had tumor resection capability were under initial surgery. This finding confirms the effectiveness of surgery as an initial treatment in patients with vulvar cancer.

In Singh study,^[12] all patients of stage III were under chemoradiation. [Table 5]

In Dadzie's study^[20] in Ghana, 70% of patients were in stage IV and only 9% of patients were under initial surgery and overall five-year survival was 36.7%, which is in a worse situation than Iran.

However, 53.3% of our patients needed radiotherapy after surgery, which was 40.7% in Butt *et al.*^[3] study.

Two-year survival rate was 37.5% in the group treated with non-surgical procedures. Six out of 16 people died, but the exact time of death was not measurable due to lack of proper follow up.

The most amount of type of operation in our study was radical vulvectomy + Ind, which can also contribute to the survival rate in the study, although postoperative morbidity in this type of surgery increases.

Vulvectomy surgery was performed with three incisions, one in the vulvar area and two in the groin regions for inguinofemoral lymphadenectomy. Studies have shown that this surgical technique will reduce the severity of postoperative complications.^[12]

In our study, patients from different cities and distant ways were referred to our health center. After surgery, due to lack of good financial support and the medical costs, they came back to health centers of their city for post-surgical following and we could not investigate morbidity after surgery or other therapies on these patients.

The results of our study, Iran is placed among developed and non-developed countries in terms of the prevalence of vulvar cancer, the mean age of the disease, the response to therapeutic modalities, and the survival rate.

Limitations

Owing to the change in the telephone number, it was not possible to make phone calls to many people and to be aware of the current situation of these people.

As patients did not come back after surgery, we could not access the pathologic reports of some of these patients and information such as lymph node and marginal involvement in all patients could not be assessed. We did not have good assessment of long-term morbidity of surgery or other modalities.

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Conflicts of interest

There are no conflicts of interest.

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