

Online ISSN: 2682-2628
Print ISSN: 2682-261X

IJC CBR

INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH

<https://jcbr.journals.ekb.eg>

Editor-in-chief

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PUBLISHED BY

EACR EGYPTIAN ASSOCIATION
FOR CANCER RESEARCH

Since 2014

Predicting causes of death among vulvar cancer patients; SEER database analysis

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ABSTRACT

Background: This study aims to identify causes of death among vulvar cancer patients diagnosed in the period between 2004 and 2013, using the Surveillance, Epidemiology, and End-Results (SEER) Program. **Patients Methods:** Data of 3769 Women with vulvar cancer, aged 40 years or more were extracted. Causes of death were categorized into vulvar cancer death, other cancer death, and other causes of death. The statistical analysis was performed using R (Version 3.4.0) utilizing the survival package (Version 2.41-3) and competing for the risk package. **Results:** At the end of the follow-up period, 2520 patients (66.9%) were alive while 1249 patients (33.14%) were dead. Of the 1249 deaths, 632 (50.6%) were attributed to vulvar cancer, 184 (14.7%) to other cancers, and 433 (34.66%) to other causes of death. Cardiovascular diseases and other gynecological cancers were the most common causes of death after vulvar cancer representing 16.65% and 5.28% of all deaths respectively. Advanced disease stage and more than three positive lymph nodes were associated with an increased risk of death due to other cancers. Simple and total surgeries were associated with lower risk. Non-cancer-related deaths were higher in unmarried women or in those who underwent surgical treatment. **Conclusions:** Non-cancer causes in addition to cancers other than vulvar cancer account for half of all deaths that occurred among patients diagnosed with vulvar cancer. Cardiovascular diseases and other gynecologic cancers are the most significant causes of death after vulvar cancer.

Keywords: Causes of death, Competing Mortality, SEER, Vulvar cancer

Editor-in-Chief: Prof. M.L. Salem, Ph.D. - Article DOI: 10.21608/jcbr.2022.115165.1242

ARTICLE INFO

Article history

Submitted: November 21, 2021

Revised: May 24, 2022

Accepted: May 30, 2022

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INTRODUCTION

Vulvar cancer is a relatively rare disease that represents about 5% of all gynecologic malignancies, and about 1% of all women-related malignancies (Tabbaa et al. 2012). The American cancer society anticipated that 6,070 women will be diagnosed and about 1,280 will die from vulvar cancer in 2019. (ACS. 2002). Postmenopausal women are the most susceptible to being affected by vulvar cancer with a mean age of diagnosis of 70 years (van der Velden et al. 1995; Messing and Gallup 1995). However, younger women exhibit an increase in the incidence rate of vulvar cancer, in recent decades with a median age of 50-55

years at diagnosis (Messing and Gallup 1995; Woelber et al. 2009).

Squamous cell carcinoma is the most frequently diagnosed histological type of vulvar cancer, accounting for 86% followed by melanoma, sarcoma, basal cell carcinoma, and adenocarcinoma (Stroup et al. 2008). Human papillomavirus (Growdon and Del Carmen 2008) infection, other sexually transmitted diseases (causing vulvar intraepithelial neoplasia (VIN)), multiple sexual partners, early sexual debut, and tobacco smoking are more frequent risk factors at a young age. While vulvar non-neoplastic epithelial disorders (VNED) are more frequent in old age (Canavan and Cohen 2002).

Although the scarcity of vulvar cancer affects the patients' lives severely (Lai et al. 2014), most vulvar cancer-specific deaths occur in the first three years after diagnosis (Ghebre et al. 2011; Akhtar-Danesh, Elit, and Lytwyn 2014). Despite improved survival of vulvar cancer with the standard treatment, the comorbidities of elderly patients still represent an obstacle affecting their survival (Ghebre et al. 2011). Therefore, personalized management of the disease should be considered while taking into account the complications, age, and performance status (Vlastos et al. 2004).

The objective of this retrospective study was to use the Surveillance, Epidemiology and End-Results (SEER) program to analyze the causes of death among a population-based sample of vulvar squamous cell carcinoma patients who were diagnosed in the period between 2004 - 2013

METHODS

Data source: According to our agreement with SEER program, we obtained the data from The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database were used for this analysis. SEER is a population-based cancer registry that covers about 30% of the United States population and includes data about patient demographics, cancer site, stage, and survival (SEER 2016).

Patient characteristics: Data of 3769 Women diagnosed with vulvar cancer between 2004 and 2013 were extracted using the SEER*Stat software version 8.3.4. (SEER version 8.3.4) Selected patients had microscopically confirmed invasive primary malignant tumor of the vulva; histologically defined as in-situ and Squamous cell carcinoma (coded as 8070-8078) according to the WHO International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes (ICD-O-3 2012). Other histological subtypes were excluded due to small numbers.

Women with age at diagnosis of 40 years or more, race recorded as white, black, and other races, and marital status recorded as married, unmarried, and unknown were included. The first primary tumor only was included in the analysis with the exclusion of cases with no

active follow-up or cases diagnosed on autopsy or death certificate only. Only cases in the research database and all the SEER 18 registries were used for the analysis.

Stages of the disease were classified as Stage 0, Stage I, Stage II, Stage III and Stage IV according to the American Joint Committee on Cancer/staging system; 6th edition (ACS. 2002) as the 7th edition of the AJCC staging system was only available for cases diagnosed after 2010. Tumor grades were defined as: Grade I: well-differentiated, Grade II: moderately differentiated and Grade III: Poorly/undifferentiated.

Surgical modalities were identified according to SEER surgery codes: (SEER 2015)

- No Surgery (0)
- Local tumor destruction/ excision (10-27)
- Simple/partial surgical removal of the primary site (30)
- Total surgical removal of the primary site; enucleation (40)
- Debulking (50)
- Radical surgery (60)

SEER records the cause of death based on death certificate data. Causes of death of vulvar cancer patients were categorized into:

- Vulvar cancer death
- Other cancers death
- Other causes of death: cardiovascular diseases (disease of heart, hypertension without heart disease, cerebrovascular diseases, atherosclerosis, aortic aneurysm and dissection), other chronic diseases (chronic obstructive pulmonary disease and allied conditions, diabetes mellitus, Alzheimer's disease, chronic liver disease and cirrhosis, nephritis, nephrotic syndrome and nephrosis) and other causes of death. Patients with unknown data about age, race, tumor size, lymph node status, treatment modalities or cause of death were excluded.

Statistical Analysis

The statistical analysis was calculated using R (Version 3.4.0) utilizing the survival package (Version 2.41-3) and competing for risk package

(CMPRSK, Version 2.2-7). Confidence intervals for proportions are based on normal approximations. Multivariate analysis for the overall survival uses the Cox proportional hazard model. Cumulative incidence estimates and curves are based on Gray's method. Competing risk regressions are based on Fine and Gray's method. Patients who underwent debulking as a surgical modality (n=8) were excluded from the analysis. All statistical tests were two-sided. P values below 0.05 were considered statistically significant.

Ethics approval

We adhered to the ethical statements of our agreement with SEER program. No institutional review board (IRB) or ethics approval was required according to SEER contract.

RESULTS

We identified 3769 women diagnosed with vulvar cancer and met the selection criteria in the period from 2004 to 2013. At the time of diagnosis, 36.56% of patients aged less than 60 years and 63.44% were aged 60 years or older. The majority of women included were whites (88.6%) followed by blacks (8.1%) and other races (3.3%). The study included 363 (9.6%) patients presented with stage 0, 1125 (29.8%) patients with stage I, 1070 (28.4%) patients with stage II, and 846 (22.4%) patients with stage III, 365 (9.7%) patients with stage IV tumors. Table 1 displays the clinical and demographic characteristics of vulvar cancer patients.

Frequency of causes of death

At the end of the follow-up period, 2520 patients (66.9%) were alive while 1249 patients (33.14%) had died. Of the 1249 deaths, 632 (50.6%) were attributed to vulvar cancer, 184 (14.7%) to other cancers, 433 (34.66%) to other causes of death. Among deaths that occurred due to other cancers, gynecological cancers (vaginal cancer, cervical cancer, ovarian cancer, uterine cancer and cancers of other female genital organs) were the most common (n=66, 5.28%) followed by unspecified cancers (n=46, 3.68%) and lung cancer (n=30, 2.4%). Other causes of death included cardiovascular diseases (n=208, 16.65%), other chronic diseases (n=98, 7.85%) and other causes of death (n=127, 10.17%).

When stratified by stage, 90.1% (95% CI, 87-93.2%) of stage 0 patients, 82% (95%CI, 79.7-84.2%) of stage I patients, 65.4% (95% CI, 62.6-68.3%) of stage II patients, 52.6% (95% CI, 49.2-56.49%) of stage III patients and 34.5% (95% CI, 29.6-39.4%) of stage IV patients were alive at time of last follow-up. Vulvar cancer was the most common cause of death among patients with stage III and stage IV representing 59.35% and 71.55% respectively, while non-vulvar cancer deaths were more common among patients with stage I and stage II representing 66% and 59.2% respectively.

Table 2 shows the frequency of causes of death among vulvar cancer patients stratified by disease stage. The incidence of vulvar cancer death increased rapidly in the first two years after diagnosis and then stabilized. Death due to other cancers and other causes of death continued to rise during the follow-up period. However, Vulvar cancer remained the leading cause of death overtime. The five-year mortality rates due to specific causes were 19.53% (95% CI, 18.08% - 20.97%) for vulvar cancer deaths, 5.68% (95% CI, 4.8% - 6.56%) for other cancers deaths and 13.22% (95% CI, 11.91% - 14.53%) for other causes of death. (Figure 1)

Figure 2 displays the annual frequency of deaths from vulvar cancer and other causes based on the number of years since diagnosis. Vulvar cancer had been the leading cause of death in the first year after diagnosis in stage II. It had been the leading cause of death in stage III and stage IV for two and three years after diagnosis with vulvar cancer. In stage 0 and stage I, other causes of death were predominant.

Effect of Treatment on what???

Vulvar cancer deaths in patients who received radiotherapy were significantly higher than in those who didn't receive radiation (62.2% v.s.42.1%, $P < 0.05$). In Patients who had no surgery, vulvar cancer deaths account for (63.3%) of all causes of death. While in Patients who underwent surgery, radical surgery had the highest frequency of vulvar cancer death followed by total surgery then patients who underwent simple surgery (55.2%, 50.2% and 43.9% respectively, $P < 0.05$).

Factors predicting the overall survival and causes of death in the studied population

Several patient and disease characteristics were found to affect the overall survival and causes of death among vulvar cancer patients.

Multivariate Cox proportional hazards model for the overall survival of patients with vulvar cancer showed that tumor stage, number of positive lymph nodes, surgical modalities and marital status are independent predictive factors of the survival of patients with vulvar cancer. Advanced disease stage, more positive lymph nodes, no surgical treatment and unmarried women were associated with worsened survival. Although statistically significant, the effect size of age and tumor size is small. Radiation therapy and tumor grade were found to be collinear with tumor stage and are not independent predictors of survival (Table 3). Competing risk analysis showed that older age is associated with an increased risk of all causes of mortality (Table 4).

Vulvar cancer mortality is higher among patients of the white race, with advanced disease stages, more positive lymph nodes and no surgical treatment. Factors associated with increased risk of death due to other cancers included advanced disease stage and more than three positive lymph nodes. Simple and total surgeries were associated with lower risk. Non-cancer-related deaths were higher in unmarried women and those who underwent surgical treatment.

DISCUSSION

To our knowledge, this is the first population-based study to review causes of death amongst vulvar cancer patients. We identified 3769 patients diagnosed with vulvar cancer in the period from 2004 to 2013 recorded by the SEER database. At the end of the follow-up period, 66.9% of patients were alive and 33.14% died. Vulvar cancer deaths accounted for 50.6% of all death causes, while other causes of death accounted for 49.4%. Vulvar cancer has relatively good survival rates compared to many other cancers and the crucial problem may be attributed to the morbidity and the severe affection of patients' life more than death.

In the current study population, vulvar cancer-specific mortality showed a significant rise in the first two years after diagnosis then tends to be stable. On the other side, mortality due to other cancers and other causes of death showed a gradual increase with time. Cancers other than vulvar cancer which contribute to decreased survival among vulvar cancer survivors represented 14.7% of all deaths. Gynecological cancers were the most common, even more than lung cancer (5.28% vs. 2.4% respectively). The correlation between several gynecologic cancers and HPV could be a reasonable explanation which is considered a significant risk factor of vulvar cancer (Growdon and Del Carmen 2008). As vulvar cancer affects mainly advanced age women (Rauh-Hain et al. 2014) presence of associated comorbidities is frequent which is considered a competing cause of death (Ghebre et al. 2011; Piccirillo et al. 2004)

Cardiovascular diseases are one of the most critical causes of death in patients with gynecological cancers. In our findings, cardiovascular diseases were the most frequent cause of death after vulvar cancer representing (16.65%) of all deaths. They were the most prevalent cause of death in endometrial cancer patients (Ward et al. 2012) while they come second after cancer itself, even with a small proportion, as a cause of death among ovarian cancer patients (Dinkelspiel et al. 2015). This can be explained by the effect of aging on increasing the risk of occurrence of both gynecological cancers and cardiovascular diseases. Other factors participate in this increased risk of cardiovascular diseases death including the cardiotoxic effect of the cancer therapies and also the psychological distress (Aleman et al. 2014; Schoormans et al. 2016).

This study shows increased mortality of old age women due to all causes of death not only cancer itself, this outcome comes in agreement with the study by N. Akhtar-Danesh et al. which showed that the relative survival ratio decreases with age (Akhtar-Danesh et al 2014). The decrease in relative survival ratio in cancer patients might be attributed to age and comorbidities which may drive undertreatment as a preferable choice (Akhtar-Danesh et al 2012).

Table 1. Demographics and clinical criteria of vulvar cancer patients (SEER 18 registries, 2004 – 2013)

Variables		Total	(%)
		3769	
Race	White	3338	88.6
	Black	305	8.1
	Other	126	3.3
Age group	40-49	560	14.9
	50-59	818	21.7
	60-69	747	19.8
	70-79	746	19.8
	80+	898	23.8
Marital Status	Married	1469	39.0
	Unmarried	2123	56.3
	Unknown	177	4.7
Histology	SCC	3406	90.4
	In-situ	363	9.6
Tumor Stage	Stage 0	363	9.6
	Stage I	1125	29.8
	Stage II	1070	28.4
	Stage III	846	22.4
	Stage IV	365	9.7
Tumor Grade	Grade I	1071	28.4
	Grade II	1674	44.4
	Grade III	1024	27.2
Regional LN Positive	0	1473	39.1
	1-3	608	16.1
	>3	128	3.4
	No LN examined	1560	41.4
Surgical Type	No Surgery	358	9.5
	Local Tumor destruction/excision	569	15.1
	Simple/ Partial Surgical Removal	1364	36.2
	Total Surgical Removal	538	14.3
	Debulking	8	.2
	Radical Surgery	932	24.7
Radiation	Yes	1094	29.0
	No	2675	71.0

Table 2. Frequency of causes of death among vulvar cancer patients stratified by stage

Causes of death	All		Stage 0		Stage I		Stage II		Stage III		Stage IV	
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Alive	2520	66.9% (68.4,65.4)	327	90.1% (93.2,87)	922	82% (84.2,79.7)	700	65.4% (68.3,62.6)	445	52.6% (56,49.2)	126	34.5% (39.4,29.6)
Vulvar Cancer	632	16.8% (18,15.6)	3	0.8% (1.8,0)	69	6.1% (7.5,4.7)	151	14.1% (16.2,12)	238	28.1% (31.2,25.1)	171	46.8% (52,41.7)
Other Cancer	184	4.9% (5.6,4.2)	3	0.8% (1.8,0)	32	2.8% (3.8,1.9)	52	4.9% (6.1,3.6)	56	6.6% (8.3,4.9)	41	11.2% (14.5,8)
Other Causes	433	11.5% (12.5,10.5)	30	8.3% (11.1,5.4)	102	9.1% (10.7,7.4)	167	15.6% (17.8,13.4)	107	12.6% (14.9,10.4)	27	7.4% (10.1,4.7)

Table 3. Multivariate analysis of overall survival of vulvar cancer patients

Variables	HR	Lower CI	Upper CI	P Value
Age	1.0495	1.0447	1.0543	< 0.001
Race				
White	Referent			
Black	0.9673	0.7633	1.2259	0.783
Other	0.6142	0.4352	0.8669	0.006
Marital Status				
Married	Referent			
Unmarried	1.1835	1.042	1.3442	0.01
Unknown	1.0854	0.7968	1.4785	0.603
Stage				
Stage 0	Referent			
Stage I	1.9556	1.354	2.8247	< 0.001
Stage II	3.7519	2.602	5.4099	< 0.001
Stage III	4.9381	3.3503	7.2783	< 0.001
Stage IV	8.9259	5.9797	13.3236	< 0.001
Regional nodes positive				
0	Referent			
1-3	1.7918	1.4392	2.2308	< 0.001
>3	3.1825	2.4019	4.2167	< 0.001
No LN examined	1.7597	1.4948	2.0716	< 0.001
Surgery				
No Surgery	Referent			
Local tumor destruction/ excision	0.5259	0.4158	0.6651	< 0.001
Simple/partial surgical removal of primary site	0.4298	0.3491	0.529	< 0.001
Total surgical removal of primary site; enucleation	0.4371	0.3464	0.5517	< 0.001
Radical surgery	0.5077	0.4112	0.6267	< 0.001
Radiation				
Yes	Referent			
No	1.1103	0.9562	1.2893	0.17

HR: Hazard Ratio, CI: Confidence Interval

Table 4. Multivariate Analysis of factors associated with specific causes of death among Vulvar Cancer Patients

Variables	Vulvar Cancer Deaths			Other cancers Deaths			Other causes of death		
	HR	(95% CI)	P Value	HR	(95% CI)	P Value	HR	(95% CI)	P Value
Age	1.032	(1.026-1.039)	< 0.001	1.02	(1.01-1.03)	< 0.001	1.05	(1.04-1.06)	< 0.001
Race									
White	Referent			Referent			Referent		
Black	0.67	(0.45-0.98)	0.04	1.40	(0.82-2.40)	NS	1.25	(0.84-1.84)	NS
Other	0.66	(0.37-1.19)	NS	2.03	(1.05-3.93)	0.04	0.61	(0.32-1.18)	NS
Marital Status									
Married	Referent			Referent			Referent		
Unmarried	0.88	(0.73-1.05)	NS	1.21	(0.87-1.69)	NS	1.54	(1.23-1.94)	< 0.001
Unknown	1.02	(0.65-1.60)	NS	1.10	(0.48-2.50)	NS	1.07	(0.62-1.85)	NS
Stage									
Stage 0	Referent			Referent			Referent		
Stage I	7.15	(2.22-23.03)	< 0.001	4.56	(1.36-15.28)	0.01	0.92	(0.60-1.42)	NS
Stage II	14.74	(4.58-47.48)	< 0.001	6.44	(1.91-21.66)	0.003	1.34	(0.87-2.07)	NS
Stage III	19.89	(6.04-65.46)	< 0.001	6.32	(1.81-22.10)	0.004	1.40	(0.83-2.37)	NS
Stage IV	38.65	(11.67-128.03)	< 0.001	7.38	(2.08-26.13)	0.002	0.80	(0.43-1.50)	NS
Tumor Size	1.001	(0.999-1.003)	NS	1.002	(0.999-1.005)	NS	1.0007	(0.999-1.003)	NS
Regional nodes positive									
0	Referent			Referent			Referent		
1-3	2.18	(1.59-2.98)	< 0.001	1.37	(0.76-2.46)	NS	0.91	(0.60-1.39)	NS
>3	2.64	(1.75-3.98)	< 0.001	3.62	(1.86-7.04)	< 0.001	0.99	(0.51-1.90)	NS
No LN examined	1.53	(1.19-1.97)	< 0.001	1.97	(1.29-2.99)	0.002	1.25	(0.98-1.61)	NS
Surgery									
No Surgery	Referent			Referent			Referent		
Local destruction	0.43	(0.29-0.64)	< 0.001	0.65	(0.37-1.15)	NS	1.97	(1.23-3.16)	0.01
Simple surgery	0.41	(0.30-0.55)	< 0.001	0.47	(0.27-0.79)	0.01	1.77	(1.14-2.76)	0.01
Total Surgery	0.45	(0.32-0.64)	< 0.001	0.50	(0.28-0.90)	0.02	1.79	(1.11-2.89)	0.02
Radical Surgery	0.52	(0.39-0.71)	< 0.001	0.68	(0.40-1.17)	NS	1.54	(0.97-2.43)	NS
Radiation									
Yes	Referent			Referent			Referent		
No	0.995	(0.79-1.26)	NS	0.73	(0.50-1.07)	NS	1.13	(0.87-1.48)	NS

CI: Confidence Interval, NS: Not significant (P value > 0.05)

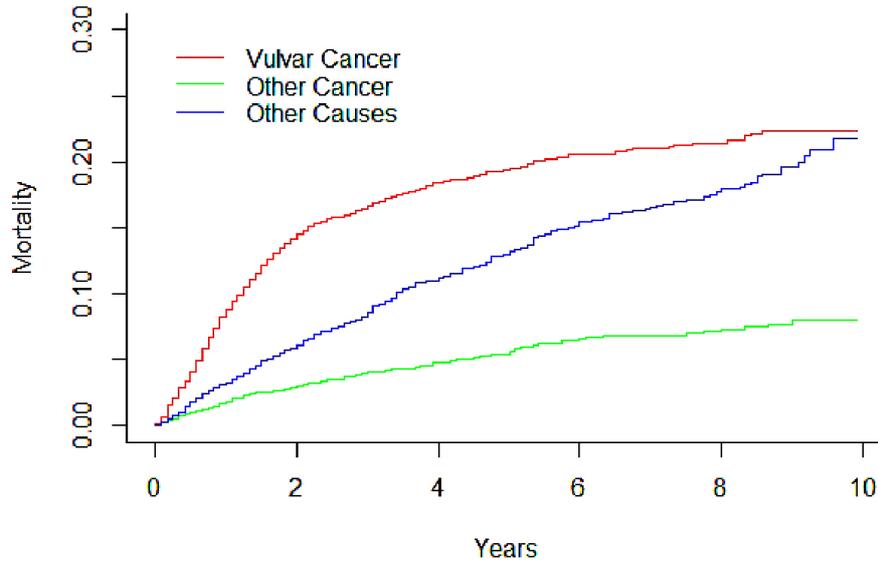


Figure 1. Cumulative incidence of mortality among vulvar cancer patients

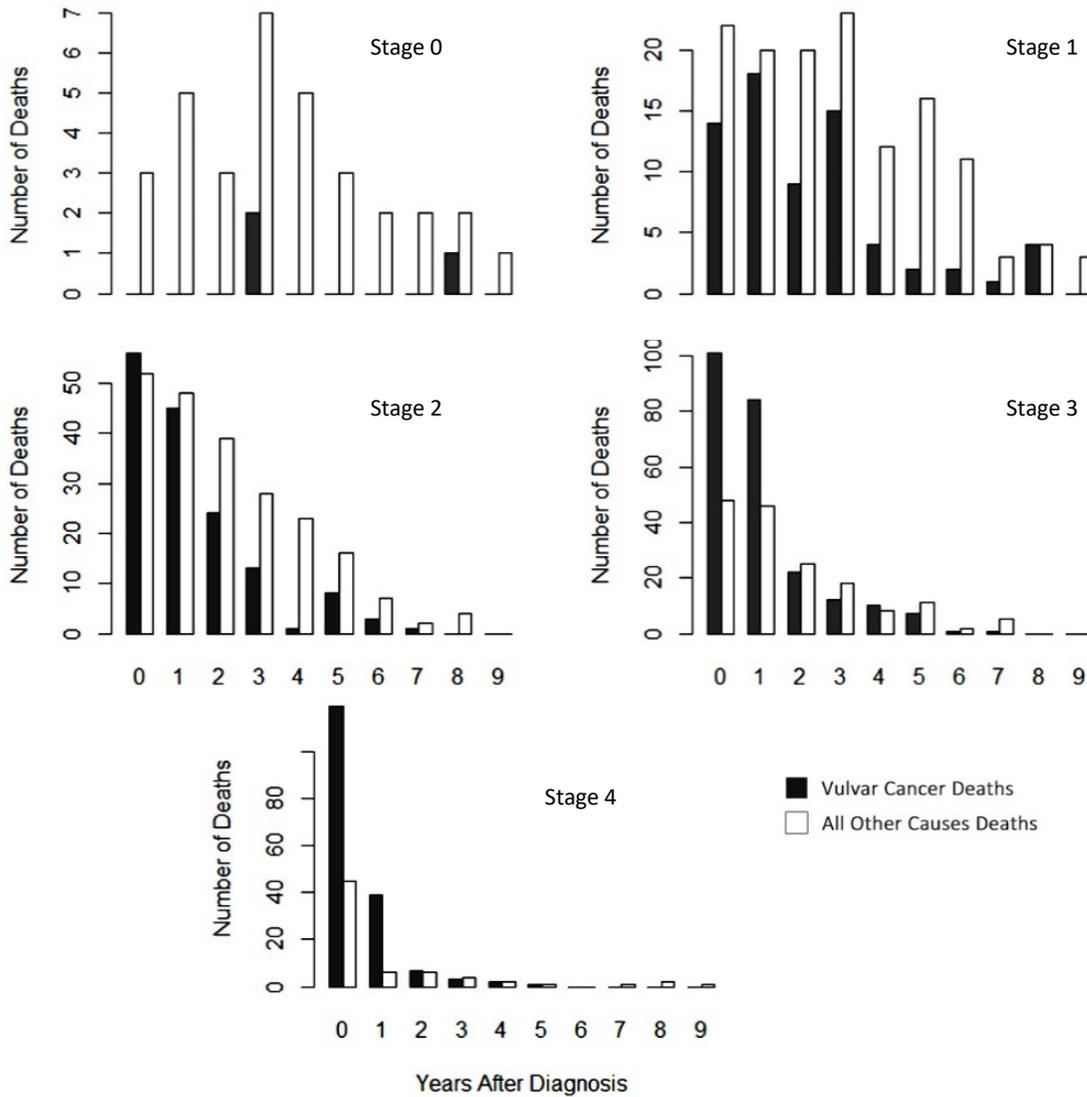


Figure 2. The frequency of causes of death by years after diagnosis among vulvar cancer patients stratified by stages

However, Kumar et al. suggested that old age women should not be assumed to have worse survival than younger women based on age only; at a young age, women with some cancers (e.g. breast cancer) (Maggard et al. 2003) may have worse survival than older ones. Moreover, age may affect genetic, pathologic, therapeutic, environmental, or societal variables of the disease, which in turn may influence disease outcomes (Kumar et al. 2009).

Surgical modalities should be put into consideration as we found that type of surgery is an independent predictor of overall survival. Patients who have no surgical treatment exhibit the worst survival. In contrast with our findings, a study by Rottmann et al. suggested that the type of surgery has no significant effect on overall survival (Rottmann et al. 2016). To our knowledge, few studies investigated the relationship between the type of surgery and survival, so this point may need further investigation.

Our results revealed that the positive lymph nodes count is an important predictor of survival; three or more positive lymph nodes were accompanied by worse survival. In consistency with our findings, Baiocchi et al. suggested in a study of 234 vulvar cancer patients that the presence of three positive lymph nodes or more worsens the five-year overall survival in comparison with one or two positive lymph nodes (Baiocchi et al. 2013). Also, Polterauer et al. studied 1727 patients and showed that overall survival is worth with three or more positive lymph nodes (Polterauer et al. 2017).

Multiple studies addressed the influence of marital status on cancer-specific survival and overall survival in patients with different types of common cancers (Kravdal 20; Aizer et al. 2013; Goodwin et al. 1987). Not only survival but also tumor progression, nodal stage, metastasis and susceptibility to treatment were found to be better in married than unmarried women according to Aizer et al (Aizer et al. 2013) Social support is considered the most fundamental factor provided by marriage to cancer patients at all and the most acceptable explanation (Kravdal 2001).

Our population-based study displayed that unmarried women have less overall survival than married ones which is in the same context as the previous studies. In addition, unmarried women in our study experienced increased mortality due to other diseases rather than cancer itself. Wu et al. analyzed the impact of the marital status of vulvar cancer patients between 2004 and 2013 utilizing the SEER database. In accordance with our results, their study showed that widowed patients exhibited worse vulvar cancer-specific survival than married, single and divorced patients supporting psychosocial support and personalized care as a precious aide for the elderly group (Wu et al. 2018).

Undeniably our study has some limitations. First, we obtained the causes of death information via the cause of death variable in SEER, which is based on death certificate data. This might be one limitation due to potential misclassification of the cause of death (German et al. 2011; Yang, Shen, and Sakamoto 2013). However, prior work by Chung-Yuan Hu et al. reported acceptable validity (Yang, Shen, and Sakamoto 2013).

Second, SEER database lacks data about some factors which may affect patients' survival and prognosis. It does not provide information about comorbidities that increase by age affecting the survival of elderly patients, so it could be a possible confounder and it becomes harder to know the probable influence of cancer and associated diseases on each other; that elderly patients commonly die from other causes rather than their vulvar cancer which results in an apparent decrease in survival. It also lacks data on chemotherapy. Therefore, we could not evaluate the effect of chemotherapy on survival or the combination of chemotherapy with surgery and radiotherapy. Additionally, we could not evaluate the possible confounders that may influence the prognosis e.g. HPV infection, sexual partners' count and tobacco use as their data are not available in the SEER database.

CONCLUSION

Non-cancer causes in addition to cancers other than vulvar cancer account for half of all deaths that occurred among patients diagnosed with

vulvar cancer. Cardiovascular diseases and other gynecologic cancers are considered the most significant causes of death after vulvar cancer. In clinical practice, Individualized management of vulvar cancer patients is recommended putting into consideration the patient's age, complications, co-morbid conditions and the preference of the attending consultant.

AUTHOR CONTRIBUTION STATEMENTS

Richard Leu and Basel Refky conceived the presented idea and design of the manuscript. Reem Yousef, Sarah Antar and Ahmed Nazzal, Gehad Tawfik wrote the first draft. Basel Refky revised the draft. Mona Hosh and Mahmoud Warda did the statistical work and verified the analytical methods Mohamed T Hafez did the scientific revision, verified the final draft and submitted the final manuscript.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest. This article is self-funded by the authors.

FUNDING

This study is self-funded and did not receive financial support from any funding source.

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