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Effect of age and comorbidity on the treatment and survival of older patients with vulvar cancer

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Abstract

Objective—To determine the disease characteristics and comorbidities predictive of vulvar cancer specific mortality and five year overall survival among older women, ages 65 and above.

Methods—A retrospective analysis was conducted of women diagnosed with vulvar cancer at a single regional cancer center from 1989 to 2003, with a follow up to 2009. Treatment records were extracted for: demographics and treatment information, Eastern Cooperative Oncology Group (ECOG) performance status and Charlson comorbidity index score. Probability of death from vulvar cancer was estimated using cumulative incidence, treating death by other known and unknown causes as competing risks. Predictors of overall survival were determined using multivariate Cox regression analyses.

Results—One hundred forty-six women were identified, with a median age at diagnosis of 79 years (range 65–95). Median follow up was 5.0 years (range 0.1–16.7 years). The cumulative incidence of vulvar cancer-specific mortality was 13% (95% CI: 0.08–0.19) at year one, 24% (95% CI: 0.17–0.31) at year three and 26% (95% CI: 0.19–0.33) at year five. Use of adjuvant therapy or surgical procedure performed did not differ by age at diagnosis ($p=0.807$ and 0.663) according to age group (65–74, 74–84 and 85+). Increasing age, Charlson comorbidity index score, lymph node involvement and type of surgery performed were associated with increased risk of death from any cause (all $p<0.05$).

Conclusion—Among women aged 65, vulvar cancer specific mortality was most significant in the first three years after diagnosis. Conversely other causes of mortality which can be attributed to comorbid conditions steadily increased with time.

Keywords

Vulvar cancer; Comorbidity; Treatment outcome

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Conflict of interest statement

The authors have no conflicts of interest to declare.

Introduction

Advancing age has been identified as a prognostic indicator for survival from vulvar cancer. Vulvar cancer is diagnosed at a median age of 69 years; the incidence of which begins to rise after age 50, then increases sharply after age 70 [1,2]. The life expectancy of women in the United States (US) as of 2006 has extended to the 8th decade of life and women at ages of 65, 75, and 85 years can expect to live, on average, another 20, 12, and 7 years respectively [3]. As the number of women in the US above the age of 65 increases, addressing unique aspects of cancer care among the elderly is of significance.

Analysis of US Federal Cancer Registry data from 1998 to 2003 found the 5-year relative survival rate from vulvar cancer in women less than 40 years of age to be significantly higher (96%) than for women above 65 years of age (72%) [1]. The high survival rate can, in part, be attributed to the large percentage of women who are diagnosed with early stage disease when the potential for cure is highest [4,5]. Women above the age 50 and in particular those greater than 75 years of age, experience a decreased vulvar cancer specific survival compared to a younger aged cohort [6-8].

The standard treatment for vulvar cancer involves radical vulvectomy with or without inguinal lymph node dissection. Adjuvant postoperative radiation therapy and chemotherapy have shown benefit in women with advanced vulvar cancer [9,10]. Although advances in the standard of care for treatment of vulvar cancer have improved survival, these treatments often invoke morbidity. The management of the elderly patient (7th and 8th decade of life) is therefore often individualized based on the patient's performance status and comorbid conditions [8,11].

The trend of decreased survival in older women with invasive vulvar cancer has been attributed to increased comorbid conditions, poor performance status, and lack of appropriate referral. Beyond the clinically significant prognostic marker of lymph node involvement, the Eastern Cooperative Oncology Group (ECOG) performance status below that of fully active (0 score) has been associated with the use of nonstandard therapies [12]. The Surveillance, Epidemiology, and End Results (SEER) Program data from 1988 to 2005 shows that women less than 50 years of age were more likely to receive standard therapy including surgical resection while women older than 50 years tended to receive modified therapy with radiation resulting in differing survival rates of 87% and 52%, respectively [6].

In the current study we examined the treatment patterns of vulvar cancer in older women, ages 65 and above, from a single institution. The primary goal of this study is to determine disease and treatment characteristics that are predictive of mortality from vulvar cancer. We also explored predictors of overall survival, including all causes of death.

Patients and methods

We performed a retrospective analysis of vulvar cancer patients diagnosed from January 1989 to December 2003 at the Masonic Cancer Center (MCC) at the University of Minnesota using a tumor registry, with follow up to December 2009. Institutional Review Board approval was obtained prior to study initiation. Inclusion criteria included women 65

years or older diagnosed with pathologically confirmed invasive adenocarcinoma or squamous cell carcinoma of the vulva. Exclusion criteria included diagnosis of vulvar intraepithelial neoplasia (VIN) or lichen sclerosis. Clinical data was abstracted from outpatient and hospital charts.

Data extracted included: age, place of residence (nursing home or other), previous cancer diagnosis, and estimated distance to the MCC as determined by recording of zip code. Patients were grouped as residing within 30 mi or beyond from the MCC. ECOG performance status score, a 5 point scale that measures the ability to carry out normal daily activities (0) to being bed bound (4), was retrospectively assessed by two independent abstractors [13]. Charlson comorbidity index score was assigned to each patient based on review of documented medical diagnosis from the initial outpatient chart record or from the initial hospital admission. Charlson comorbidity index is tabulated from nineteen comorbid conditions which have assigned weights of 1, 2, 3, or 6, based on mortality risk for patients with the comorbid condition compared to mortality risk for those without [14]. All patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) system [15]. Treatment follow up data was obtained by review of outpatient charts and cancer registry data.

One-hundred forty six women diagnosed with vulvar cancer were included in this analysis. Demographics and disease characteristics for all patients were summarized. Age at diagnosis was collapsed into three groups: 65–74, 75–84 and over 85 years old for the purposes of this analysis as categorized by the U.S. Census Bureau. Disease stage, surgery performed and the use of adjuvant therapy were compared across age groups using chi-squared and Fisher's exact tests. Patient deaths were divided into three categories: death from vulvar cancer, death from other known cause or death from unknown cause. Event times were calculated from the date of first diagnosis of vulvar cancer to the event or the date of last contact for patients still alive.

The probability of death from vulvar cancer was estimated using cumulative incidence, treating deaths by other known and unknown causes as competing risks. Differences in the incidence of death from vulvar cancer by age at diagnosis were analyzed using Gray's test. Fine and Gray competing risks regression was used for multivariate analyses [16]. Predictors of overall survival (death from all causes) were determined using multivariate Cox regression [17]. Variables considered in the multivariate analyses included age at diagnosis (65–74/75–84/85+ years), FIGO stage (I/II/III/IV), previous cancer (yes/no), surgery (radical vulvectomy only/local excision only/unilateral or bilateral inguinal lymph node dissection (LND)/radical vulvectomy+inguinal LND), adjuvant therapy (none/chemotherapy only/radiation only/chemotherapy and radiation), lymph node involvement (yes/no), and Charlson comorbidity index score (0/1/2+). Final models were chosen using backward selection, removing variables with p-values >0.10. Performance status and place of residence were not included as possible covariates because of high correlation with other variables. Two patients with missing stage information and six with unknown lymph node involvement were excluded from the multivariate analyses.

All *p* values were two-sided and considered to be statistically significant if less than 0.05. All analyses were performed using SAS version 9.2 and R version 2.7.

Results

Patient demographics and clinical variables

One hundred and forty six women with vulvar cancer diagnosed over a fifteen year time period (1989–2003) were identified. The median age at diagnosis was 79 years (range 65–97). Thirty-three women were 85 years of age or older, of which 10 were 90 years or older. The women were primarily on Medicare (98%), lived within 30 mi of the clinic (56%), and were fully active (80%) with an ECOG performance status of 0 (Table 1). A Charlson comorbidity index score of 0 was recorded for 79 women (54%), score of 1 for 37 women (25%) and score of 2 for 30 women (21%). Thirteen women (9%) were nursing home residents and the majority of them (75%) had an ECOG performance status of 3 or 4. These women were more likely to have a Charlson comorbidity index score of 2. Common comorbid conditions were congestive heart failure, diabetes, peripheral vascular disease and chronic pulmonary disease. A history of previous cancer diagnosis was reported by 30 (21%) of the women.

The predominant histologic subtype was squamous (143; 98%). The most common surgical procedure performed was radical vulvectomy with either unilateral or bilateral inguinal lymph node dissection (111; 76%), resulting with no histological metastasis to lymph nodes (103; 74%). FIGO stages I and II were the most common clinical stages (93; 65%) with the majority of patients receiving no adjuvant therapy (106; 73%).

The median follow up for the group was 5.0 years (range 0.1–16.7 years). Of the 146 patients, 44 (30.1%) were alive at last contact, 44 (30.1%) died from vulvar cancer, 49 (33.6%) died from other known causes and 9 (6.2%) died from an unknown cause. Other known causes of death include cardiovascular events, cerebrovascular disease and diabetes.

Vulvar cancer-specific mortality

The cumulative incidence of vulvar cancer-specific mortality was 13% (95% CI: 0.08–0.19) at year one, 24% (95% CI: 0.17–0.31) at year three and 26% (95% CI: 0.19–0.33) at year five (Fig. 1). Most of the deaths from vulvar cancer occurred in the first three years following diagnosis whereas the cumulative incidence of death from other causes increased steadily over time. Competing risks regression found age at diagnosis, disease stage, lymph node involvement, type of surgery performed and use of adjuvant therapy were all significantly associated with the risk of vulvar cancer-specific death in both univariate (data not shown) and multivariate models (Table 2). In particular, older age, higher disease stage, lymph node involvement, surgery removing lymph nodes only and receiving only chemotherapy or radiation therapy were associated with a greater risk of death (all $p < 0.01$). These non-standard therapies were employed in individual cases at the discretion of the treating physician, but were equally distributed among the three age groups.

In our population, the data do not suggest that the use of adjuvant therapy or the type of surgical procedure performed differed by age at diagnosis ($p = 0.807$ and 0.663 respectively;

Table 3). Although limited by the small number of patients, FIGO stages III and IV present at a slightly higher proportion among the 65–74 year olds (44%), compared to 75–84 year olds (29%) and 85 year and older patients (36%) in this study population.

The cumulative incidence of death from vulvar cancer was most elevated among women 85 years and older and lowest among women 75–84 years old when comparing by age group ($p=0.016$; Fig. 2A). As expected, death from other causes increased with each increasing decade in age ($p=0.008$; Fig. 2B).

Overall survival

The predictors of overall survival in the final Cox regression model included age at diagnosis, disease stage, lymph node involvement, Charlson score and the type of surgery performed (Table 4). As expected, increasing age, disease stage and lymph node involvement were associated with increased risk of death from any cause (all $p<0.05$). Patients with Charlson scores of 1 and 2+ had an increased risk of death of almost 2 and 3 times, respectively, compared to patients with a Charlson score of 0 ($p=0.0006$). The proportion of patients with Charlson scores of 0, 1 and 2+ surviving to/past 5 years from diagnosis were 0.66 (95% CI: 0.54, 0.75), 0.55 (95% CI: 0.37, 0.69) and 0.27 (95% CI: 0.12, 0.44), respectively.

Discussion

We examined the treatment patterns of women age 65 and above with vulvar cancer at a single regional cancer center. In this study population, vulvar cancer specific mortality was most significant in the first three years after diagnosis. Conversely other causes of mortality which can be attributed to comorbid conditions steadily increased with time. Age was a significant predictor of vulvar cancer specific mortality among women 85+ years, although women 65–74 and 75–84 had similar cancer mortality risk. Our data supports previous SEER database studies reporting increased cancer associated mortality and decreased overall survival with advancing age [6,7].

In this study, there was no difference in treatment patterns in women with vulvar cancer based on age. Women in the 85+ age group were able to undergo standard surgical treatment with radical vulvectomy and inguinal lymph node dissection with follow up adjuvant treatment. Age bias in the surgical and adjuvant treatment of the older 65+ population is well documented [18,19]. Previous studies on vulvar cancer outcome among older women are limited by high rates of non-standard surgical evaluation[8]. In the study by Stroup et al., less than 1% of Stage I and 55% of stage II underwent evaluation of regional lymph node status [7]. Lymph node involvement is a well documented significant and critical marker of survival and our data supports this consensus [4,20].

Competing causes of mortality must be acknowledged at the time of diagnosis and treatment of vulvar cancer among older patients. Within this study population, woman with Charlson comorbidity index score of 2+ experienced decreased overall survival. In a large study of 17,712 patients with prospectively documented concurrent conditions, the number of co-existing conditions and the severity of those conditions was documented to have significant

impact on survival [21]. The Charlson comorbidity index score and the ECOG performance status are often utilized to provide an overall assessment of health [7,12]. Attempts to measure the impact of multiple medical conditions on the individual patient tolerance of cancer treatment and survival has been limited by the lack of validated comorbidity assessment tool that can be efficiently utilized in the oncology clinic setting.

Our study has some limitations. Due to inherent bias in a retrospective medical record review approach, women diagnosed with vulvar cancer and selectively not referred into the cancer center are not represented in this study. The data obtained concerning co-existing medical conditions while detailed is confined to clinic and hospital-based medical record information. The small sample size may underestimate potential differences in vulvar cancer specific mortality and overall survival between the three designated age groups.

In a disease such as vulvar cancer in which the median age of diagnosis is 69, cancer care must take into account age and comorbidity. Studies on aging are highlighting the ever increasing lifespan of the older woman. Although increasing age by decade is significant to vulvar cancer mortality, our data supports low rates of mortality for optimally early staged patients. As we expand our understanding of the impact of comorbid conditions on cancer treatment in older patients, further research should be supported in developing clinically relevant comorbidity assessment tools.

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Fig. 1.
Cumulative incidence of death by cause: vulvar cancer or other known cause.

Fig. 2.

The cumulative incidence of death from vulvar cancer or other known causes by age at diagnosis. (A) Vulvar cancer specific mortality by age of diagnosis. (B) Other cause specific mortality by age of diagnosis.

Table 1

Demographic and clinical characteristics (N = 146).

Variable	N	%
Age at diagnosis		
65–74	43	29.45
75–84	70	47.95
85+	33	22.60
Year of diagnosis		
1989–1994	47	32.19
1995–1999	66	45.21
2000–2003	33	22.60
Insurance		
Medicare	143	97.95
Other	3	2.05
Type of residence		
Nursing home	13	8.90
Other	133	91.10
Distance of residence from university clinic		
Within 30 mi	82	56.16
Greater than 30 mi	62	42.47
Unknown	2	1.37
ECOG performance status		
0 (Fully active)	117	80.14
1 (Restricted in physically strenuous activity)	13	8.90
2 (Ambulatory and capable of self-care)	2	1.37
3 (Capable of only limited self-care)	8	4.48
4 (Complete disabled)	6	4.11
Charlson score		
0	79	54.11
1	37	25.34
2+	30	20.55
Histology		
Squamous carcinoma	143	97.95
Adenocarcinoma	3	2.05
Disease stage (FIGO)		
Stage I	45	31.25
Stage II	48	33.33
Stage III	37	25.69
Stage IV	14	9.72
Unstaged	2	
Lymph node involvement		
No histological involvement	103	73.57

Variable	N	%
Involvement	37	26.43
Unknown	6	
Adjuvant therapy		
None	106	72.60
Chemotherapy only	1	0.68
Radiation only	15	10.27
Chemotherapy and radiation	24	16.44
Surgeries performed		
Radical vulvectomy only	26	17.81
Local excision only	6	4.11
Unilateral or bilateral inguinal LND	3	2.05
Radical vulvectomy + inguinal LND	111	76.03

Table 2

Predictors of vulvar cancer-specific mortality.

	Hazard ratio (95% CI)	p-value
Age at diagnosis-category		0.0046
65–74 years old ^a	1.0	
75–84 years old	0.38 (0.18, 0.84)	
85+ years old	1.79 (0.78, 4.09)	
Stage		0.0009
I ^a	1.0	
II	0.85 (0.31, 2.34)	
III	0.62 (0.20, 1.94)	
IV	3.17 (1.14, 8.80)	
Lymph node involvement		< 0.0001
None ^a	1.0	
Lymph node involvement	7.47 (3.09, 18.04)	
Surgery performed		< 0.0001
Radical vulvectomy only ^a	1.0	
Local excision only	3.77 (0.75, 18.85)	
Unilateral or bilateral inguinal LND	12.77 (2.52, 64.64)	
Radical vulvectomy + inguinal LND	2.08 (0.49, 8.83)	
Adjuvant therapy		<0.0001
None ^a	1.0	
Chemo or radiation therapy only	59.86 (19.21, 186.54)	
Chemo and radiation therapy	0.84 (0.36, 2.00)	

^aReference group.

Table 3

Treatment employed in patients by age at diagnosis (N = 146).

	<u>65–74 years old</u>		<u>75–84 years old</u>		<u>85+ years old</u>		p
	N	%	N	%	N	%	
Disease stage (FIGO)							0.639
Unstaged	1	2.33	1	1.43	0	0.00	
I	14	32.56	23	32.86	8	24.24	
II	9	20.93	26	37.14	13	39.39	
III	13	30.23	14	20.00	10	30.30	
IV	6	13.95	6	8.57	2	6.06	
Adjuvant therapy							0.807
None	29	67.44	53	75.71	24	72.73	
Chemotherapy only	0	0.00	1	1.43	0	0.00	
Radiation only	4	9.30	7	10.00	4	12.12	
Chemo and radiation	10	23.26	9	12.86	5	15.15	
Surgery							0.663
Radical vulvectomy only	7	16.28	10	14.29	9	27.27	
Local excision only	1	2.33	3	4.29	2	6.06	
Unilateral or bilateral inguinal LND	1	2.33	2	2.86	0	0.00	
Radical vulvectomy + inguinal LND	34	79.07	55	78.57	22	66.67	

Table 4

Predictors of overall survival (all causes of death).

Variable	Hazard ratio (95% CI)	P
Age category		<0.0001
65–74 years old ^a	1.0	
75–84 years old	1.38 (0.81, 2.35)	
85+ years old	5.75 (3.06, 10.84)	
Stage		0.048
I ^a	1.0	
II	0.98 (0.58, 1.66)	
III	1.32 (0.58, 2.99)	
IV	3.71 (1.26, 10.90)	
Lymph node involvement		0.024
None ^a	1.0	
Lymph node involvement	2.59 (1.13, 5.96)	
Charlson score		0.0006
0 ^a	1.0	
1	1.88 (1.12, 3.14)	
2+	3.03 (0.70, 5.39)	
Surgery performed		0.010
Radical vulvectomy only ^a	1.0	
Local excision only	1.93 (0.52, 7.16)	
Unilateral or bilateral inguinal LND	7.17 (1.78, 28.90)	
Radical vulvectomy+inguinal LND	0.85 (0.45, 1.59)	

^aReference group.