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Prognostic impact of clinical tumor size on overall survival for subclassifying stages I and II vaginal cancer: A SEER analysis

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HIGHLIGHTS

- A review of patients with stage I/II vaginal cancers was performed.
- Data was obtained from a national population-based repository.
- Multivariable analyses found tumor size was an independent predictor of survival.
- Confirmatory investigations are needed before revising existing staging systems.

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ABSTRACT

Purpose. This study accessed the Surveillance, Epidemiology and End Results (SEER) database to determine if tumor size is an independent predictor of overall survival (OS) for patients with stages I and II vaginal cancer (VC).

Materials and methods. We identified in the SEER database, patients with available tumor size having stage I or II squamous cell histology from January 2004 through December 2012 with minimum follow-up of six months. Univariate analyses (UA) and multivariable analyses (MVA) evaluated the effect of several prognostic factors, including tumor size, regarding OS.

Results. 529 SEER patients were found with recorded tumor sizes, of which 293 (55.4%) were stage I and 236 (44.6%) stage II. UA found the following significant prognostic factors of worse OS: tumor size >2 cm (HR = 1.80, $p = 0.02$) and older age at diagnosis ($p < 0.001$) in stage I; and tumor size >2 cm (HR = 2.13, $p = 0.04$) and older age at diagnosis ($p < 0.001$) in stage II. Estimates of 5-year OS in patients with tumor size ≤2 cm vs. >2 cm were 79.2% vs. 66.1% in stage I ($p = 0.0187$) and 80.9% vs. 51.2% in stage II ($p = 0.0369$). MVA confirmed about double risk of death for patients with tumor size >2 cm (HRs: 1.88 in stage I and 2.06 in stage II).

Conclusions. Tumor size seems to predict OS outcome in patients with stages I/II VC. Further confirmatory investigations are recommended to firmly establish its incorporation into currently accepted staging criteria for these patients.

1. Introduction

Vaginal cancer (VC) remains an extremely rare gynecological malignancy that will give rise to approximately 4070 new cases and account for about 910 deaths for 2015 in the United States (U.S.) [1]. The anatomic boundaries of the vagina include the vulva distally and the cervix proximally. Tumor involvement of these two latter sites must be excluded before a given lesion can be considered as a primary vaginal malignancy. The staging of this disease is primarily clinical as developed by the International Federation of Obstetrics & Gynecology (FIGO) and the American Joint Committee on Cancer (AJCC). Both of these staging systems have been largely unchanged for many years [2]. Squamous cell carcinoma is the most common histological subtype of gynecological cancers, comprising nearly 80% of all reported cases of primary VC [3].

This present investigation study centered on the hypothesis that clinical tumor size at diagnosis could further differentiate overall survival (OS) of patients with FIGO stage I and/or II squamous cell

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carcinomas of the vagina. The rationale behind this approach for refining clinical staging by tumor size was derived from the updated FIGO staging of cervical cancer, which stratified prognosis by tumor size at most 4 cm versus greater than 4 cm for stage IIA, which did correlate with survival outcome [4].

2. Materials and methods

This current study was initiated in response to a current task force mandate for updating the AJCC (American Joint Committee on Cancer) Staging of VC, in which several of the co-authors of this manuscript (AHW, RG, LP) were participants as part of the panel for creating the 8th Edition for AJCC Staging of VC. The study data was acquired from the April 2015 release of the Surveillance, Epidemiology and End Results (SEER) database covering diagnostic years 1973 to 2012. This data published by the National Cancer Center Institute is a compilation of female genital databases from all 18 population-based SEER cancer registries from around the U.S. (about 28% of the U.S. population) [5]. All patient data was sent de-identified; thus, no approval from any Institutional Review Board was indicated for conducting this inquiry.

Initially we selected 866 from the 667,467 patients in the four "FEMGEN" databases in the SEER 1973–2012 Research Data (November 2014 release), applying the following selection criteria: (1) primary vaginal squamous cell carcinomas (primary site C529 and histology variant codes 8070 to 8078); (2) clinical stage I (T1N0M0) or II (T2N0M0) disease according to the AJCC 6th Edition [6]; (3) reported sources from hospital inpatient units, outpatient radiation or medical oncology centers, physician/private medical practitioner's offices, and nursing/convalescent home/hospice units; (4) diagnostic years 2004 to 2012; and (5) minimum OS of six months. From this subset of 866 patients, we excluded an additional 337 (38.9%) subjects who did not had documented clinical tumor size (in centimeter [cm]).These selection criteria yielded a study cohort of 529 patients of which 528 were confirmed by histology and one by cytology. The reporting source was hospital inpatient units in 520 patients (98.3%), outpatient treatment centers for three patients, and physician/private medical practitioner/nursing/convalescent home/hospice units for six patients.

The primary endpoint of interest was overall survival (OS) in months, defined from date of diagnosis to date of death or to date of last contact for living patients (censored observations). Besides vital status, other variables selected for analyses included the following: age at diagnosis, race/ethnicity, AJCC stage, tumor size (in cm), number of primary cancers, indicators (yes, no) of VC as the only primary in patient's lifetime, surgery of primary vaginal cancer, regional lymph node surgery, and use of radiation treatment. The details regarding the techniques of surgical management and radiation therapy for study patients were not the subject of this review. Furthermore, chemotherapy use was not included since no information on chemotherapy for the primary VC was available from the SEER database.

Descriptive statistics of demographics and disease-related variables were conducted for the overall study cohort and separately for stage I and stage II disease groups. The distributions of selected variables by stage were compared using chi-square test or Fisher's exact test [7]. Mean age and mean tumor size between stages were compared using Student's *t*-test [7]. Survival curves were estimated using the Kaplan-Meier method [8]. The log-rank test [8] was used to evaluate the effect of tumor size and other potential prognostic factors, considering all patients together and separately by stage I and II disease groups. Univariate analyses (UA) and multivariable analyses (MVA), using Cox proportional hazards regression modeling [7] were conducted. Hazard Ratio (HR) estimates and corresponding 95% confidence intervals (CIs) from univariate and multivariable models were reported. All tests were two-sided. The statistical analyses were conducted in SAS version 9.4 for Windows (SAS Institute, Cary, NC).

3. Results

Table 1 depicts the demographic and other notable patient and tumor characteristics in the SEER database of the selected 529 total patients for this study, of which 293 (55.4%) were stage I and 236 (44.6%) had stage II disease. At diagnosis, stage II patients were significantly older than stage I patients [mean age 66.4 versus (vs.) 63 years-old ($p = 0.005$), median age 66 vs. 62 years-old, and more distributed in older age-decade categories ($p = 0.047$)]. In addition, patients in stage I were managed more often with primary site surgery (57% vs. 25.8%), $p < 0.0001$) and/or regional lymph node surgery (16% vs. 6.8%, $p = 0.001$) than stage II patients. Of note, subjects diagnosed with stage I disease were less commonly treated without radiation therapy than stage II patients (65.2% vs. 94.1%, $p < 0.0001$). There was a significantly higher number of deaths in stage II than in stage I patients (37.3% vs. 22.9%, $p < 0.001$).

Table 2 breaks down the study patients by clinical tumor size at diagnosis. The mean and median tumor size for all 529 patients was 3 cm (range: 0.1 cm–9.5 cm). Patients with stage I primary VC had significantly smaller tumor sizes than those in stage II [mean 2.4 cm vs. 3.8 cm ($p < 0.0001$), median 2.2 cm vs. 4 cm]. All three potential cutpoints for tumor size (2 cm, 3 cm, and 4 cm) showed significantly larger tumor sizes in stage II than in stage I disease. For example, almost half (51.2%) of stage I VC cancers were greater than 2 cm in size

Table 1
Demographic and other characteristics of study patients.

Variable	All patients		Stage I		Stage II		P
	N	%	N	%	N	%	
Total patients	529	100	293	100	236	100	NA
Age at diagnosis, in years							
Mean (SD)	64.5	(13.9)	63.0	(14.1)	66.4	(13.5)	0.005
Median (range)	64	(27, 95)	62	(30, 95)	66	(27, 94)	
<50	81	15.3	54	18.4	27	11.4	0.047
50–59	119	22.5	73	24.9	46	19.5	
60–69	134	25.3	66	22.5	68	28.8	
70–79	105	19.8	56	19.1	49	20.8	
≥80	90	17.0	44	15.0	46	19.5	
Race/ethnicity							
Non-Hispanic White	370	69.9	204	69.6	166	70.3	0.548
Hispanic White	67	12.7	38	13.0	29	12.3	
Black	60	11.3	30	10.2	30	12.7	
Other (1 unknown included)	32	6.0	21	7.2	11	4.7	
VC as the only primary							
Yes	294	55.6	150	51.2	144	61.0	0.234
No	235	44.4	143	48.8	92	39.0	
Radiation[a]							
Yes	413	78.1	191	65.2	222	94.1	<0.001
No	116	21.9	102	35.8	14	5.5	
Primary site surgery							
Yes	228	43.1	167	57.0	61	25.8	<0.001
No	301	56.9	126	43.0	175	74.2	
Regional lymph node surgery							
Yes	63	11.9	47	16.0	16	6.8	0.001
No	465	87.9	245	83.6	220	93.2	
Missing	1	0.2	1	0.3	–	–	
Survival status							
Dead	155	29.3	67	22.9	88	37.3	<0.001
Alive	374	70.7	226	77.1	148	62.7	

Note: Stage I = T1N0M0 and stage II = T2N0M0 per guidelines of the American Joint Committee on Cancer (AJCC); N = number; SD = standard deviation; P = p-value from chi-square test or Student's *t*-test; NA = not applicable.

[a] Radiation unknown in 5 patients converted to four "Yes" (Radiation = recommended, unknown if administered), and one "No" (Radiation = not recommended, unknown if radiation administered).