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Research Article

Retrospective Analysis of Patients Treated for Vaginal Cancer at the Brazilian National Cancer Institute

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Abstract

Vaginal cancer (VC) is a rare neoplasm. Few studies have been published on its natural history, prognostic factors, and treatment.

The objective was to provide a review of institutional cases and information on therapeutic patterns and survival of VC patients treated at the Brazilian National Cancer Institute.

Patients with the diagnosis of VC between 2005-2015 were included. Demographics, histology, tumor grade, stage, and treatment modalities were retrospectively collected.

Twenty-nine women were enrolled and divided into three treatment groups: chemotherapy plus external radiotherapy followed by brachytherapy or not (group 1), external radiotherapy followed by brachytherapy or not (group 2) and surgery (group 3). Mean OS for the whole group was 5.0 years (95%CI, 3.8–6.2); 4.9 years (95%CI, 3.7–6.2) for group 1; 1.8 years (95%CI, 0.7–2.9) for group 2 and 6.3 years (95%CI, 4.3–8.3) for group 3 (p=0.011).

Despite the low number and heterogeneity of patients included in this analysis, treatment modality significantly affects a woman's risk of mortality from VC.

Keywords: Vaginal cancer, Gynecologic cancer

Introduction

Vaginal cancer (VC) was first identified as a unique entity by Graham and Meigs in 1952 [1]. Since then, very few case series have been reported, and to date, there is still minimal information on its natural history, prognostic factors, and treatment. VC accounts for 3% of malignant neoplasms of the female genital tract. In the United States, 5,170 new cases were estimated in 2018, with 1,330 deaths [2]. There is no official data of VC incidence and death rates in Brazil.

VC is most likely to occur in older women and approximately 50% of cases present in patients older than 70 years. Squamous cell carcinoma (SCC) is the most common histological subtype, accounting for nearly 80% of all cases in some reports [3]. Recognized factors that increase a woman's lifetime risk of VC include younger age at first intercourse, the number of lifetime sexual partners, smoking, in utero diethylstilbestrol (DES) exposure [4,5] and human papillomavirus (HPV) infection [6,7].

Due to its low incidence, there are no randomized phase III trials to define the optimal treatment of primary VC. As the most common subtype of VC is SCC and its etiology is identical to cervical cancer (CC) (mainly due to HPV subtypes 16 and 18 infection), the therapy is defined extrapolating data from CC studies, which has a much higher incidence. Overall, the treatment is multimodal; surgical excision is the most widely used therapy for FIGO stage I tumors. However, radiation therapy may be appropriate for patients with tumors larger than 2 cm and lesions within the lower or middle third of the vagina due to the difficulty to achieve negative margins with surgery [8,9]. For locally advanced disease (FIGO stages II to IVA), concomitant external radiotherapy and chemotherapy followed by brachytherapy is generally the treatment of choice, similarly to that used in CC [10-12].

This paper provides a review of a single-institution cases and information on therapeutic patterns and survival of VC patients treated at the Brazilian National Cancer Institute (INCA).

Material and Methods

Patient selection and data collection

This study was approved by the Ethics in Human Research Committee of INCA, Rio de Janeiro, Brazil (approval number: CAAE 52065115.8.00005274), and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Patients with the diagnosis of VC between 2005 and 2015 were identified through internal database, and the charts were reviewed. Clinical data including demographics, histology, tumor grade, stage, and treatment modalities were retrospectively collected. All patients in this study were treated at INCA, older than 18 years old, diagnosed with primary vaginal squamous cell carcinoma or adenocarcinoma and received surgery, radiotherapy, chemotherapy or any combination with curative intent. Data concerning disease progression or recurrence and its treatment were also collected.

Statistical analysis

Progression-free survival (PFS) was measured from the first treatment day to either first progression or death or the date of the last contact for patients who are alive and disease-free; overall survival (OS) was estimated from the time of the first treatment day until death or, for living patients, the last available follow-up, in both cases using Kaplan-Meier method; $p < 0.05$ was considered statistically significant. All analyses were performed with the SPSS software, version 18.0 (IBM, São Paulo, Brazil).

Results

A total of 29 women with histologically proven primary VC were identified and all of them were enrolled into this study. The median age at initial diagnosis was 62 years old (range 34 – 84 years old), and the most frequent histology was SCC (82.8%). The distribution of FIGO stage at diagnosis was stage I (41.4%), II (37.9%) and III (20.7%). Most patients were white (62.1%), married or widow (34.5% each) and postmenopausal (89.7%). The median age at first intercourse was 17 years old (range 12 – 27 years old), the median number of sexual partners in lifetime was 3 (range 1 – 10 partners), and pregnancies were 4.5 (range 1 – 13 pregnancies). Most women did not have history of smoking (89.6%), and 44.8% of cases represented patients with incomplete elementary school. Patients' characteristics are shown in Table 1.

For this analysis, patients were divided into three treatment groups, all with curative intent: those who received chemotherapy plus external radiotherapy followed by brachytherapy or not (group 1), those who received external radiotherapy followed by brachytherapy or not (group 2) and those who had surgery only (group 3). Treatment modalities are summarized in Table 2.

External radiotherapy doses ranged from 45 to 50.4 Gy and brachytherapy doses ranged from 28 to 42 Gy. Weekly cisplatin 40mg/m^2 was the treatment of choice when chemotherapy was used in combination (no other regimens were used in this cohort of patients).

Mean PFS was 4.9 years (95% CI, 3.6 – 6.3) for the whole studied population; 4.5 years (95% CI, 3.1 – 5.8) for group 1; 2.1 years (95% CI, 0.7 – 3.6) for group 2 and 5.3 years (95% CI, 2.8 – 7.8) for group 3 ($p = 0.970$).

Mean OS for the whole group was 5.0 years (95% CI, 3.8 – 6.2); 4.9 years (95% CI, 3.7 – 6.2) for group 1, 1.8 years (95% CI, 0.7 – 2.9) for group 2 and 6.3 years (95% CI, 4.3 – 8.3) for group 3 ($p = 0.011$), as seen in figure 1.

Mean PFS was 5.2 years (95% CI, 3.3 – 7.0) for patients with FIGO stage I disease, 4.3 years (95% CI, 2.7 – 6.0) for stage II and 3.0 years (95% CI, 1.3 – 4.7) for patients with stage III ($p = 0.6$). There were no deaths among patients with stage I disease and the mean OS was 2.8 years (95% CI, 1.4 – 4.2) for patients with stage II disease and 1.5 years (95% CI, 0.7 – 2.3) for patients with stage III disease ($p = 0.742$).

Table 1: Patients characteristics.

	N = 29	%
Age, years		
Median	62	
Range	34 – 84	
Histology		
Squamous cell carcinoma	24	82.8
Adenocarcinoma	5	18.2
Tumor grade		
1	4	13.8
2	11	38.0
3	4	13.8
Unknown	10	34.4
FIGO stage		
I	12	41.4
II	11	37.9
III	6	20.7
IV	0	0
Race		
Black	3	10.3
White	18	62.1
Others	8	27.6
Marital Status		
Married	10	34.5
Single	5	17.2
Widow	10	34.5
Divorced	4	13.8
Menopause		
Yes	26	89.7
No	3	10.3
Number of sexual partners		
Median	3	
Range	1 – 10	
Number of pregnancies		
Median	4.5	
Range	1 – 13	
Age at first intercourse, years		
Median	17	
Range	12 – 17	
Smoking		
Yes	3	10.4
No	26	89.6
Education		
Illiterate	1	3.4
Incomplete primary school	13	44.8
Complete primary school	6	20.7
Incomplete/complete high school	6	20.7
University	3	10.4
Total	29	100

Among 12 patients diagnosed with stage I disease, 5 were treated with surgery, 5 were treated with chemoradiation with or without brachytherapy and 2 were treated with radiotherapy with or without brachytherapy. Among 11 patients diagnosed with stage II disease, 6 received chemoradiation with or without brachytherapy, one was treated with surgery and four were treated with external radiotherapy with or without brachytherapy. Three patients diagnosed with stage III disease received treatment based on chemoradiation with or without brachytherapy and other three patients with radiotherapy with or without brachytherapy.

Among patients with stage I disease treated with surgery, five patients had no recurrence and 3 out of 7 of those treated without surgery recurred. Nine patients had disease progression or recurrence: 6 locoregional, two locoregional with distant metastasis and 1 with distant metastasis. One patient had disease progression during the treatment with curative intent. Most of the patients who had disease progression or recurrence received first-line palliative treatment, except two (one who was waiting for surgical deliberation by the time of data collection for this study and one due to poor performance status). Four out of 6 patients with locoregional recurrence received local treatment (surgery or chemoradiation). The other 3 patients with distant metastasis received palliative treatment with carboplatin and paclitaxel.

Discussion

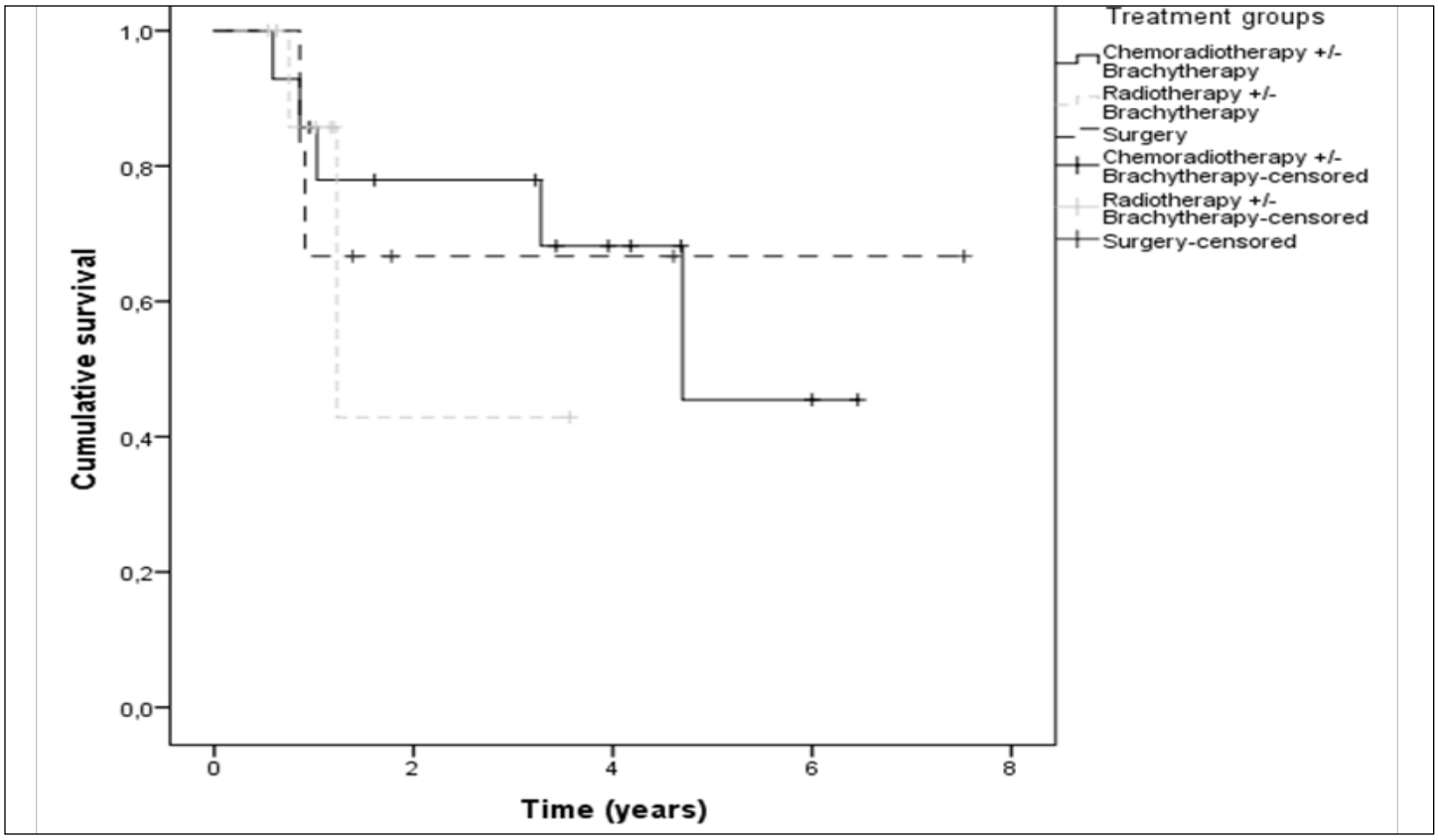
Primary VCs are very rare malignancies. As in many other sites, the treatment for VC requires individualization because of different presentations and how the treatment can affect surrounding organs [8,11]. Treatment is guided by disease stage and international guidelines. In general, surgery is recommended with adjuvant therapy for early stages and concomitant chemoradiation for unresectable disease. At INCA, surgery, chemoradiation with or without brachytherapy and external radiotherapy with or without brachytherapy alone were used as treatment modalities for patients with primary VC.

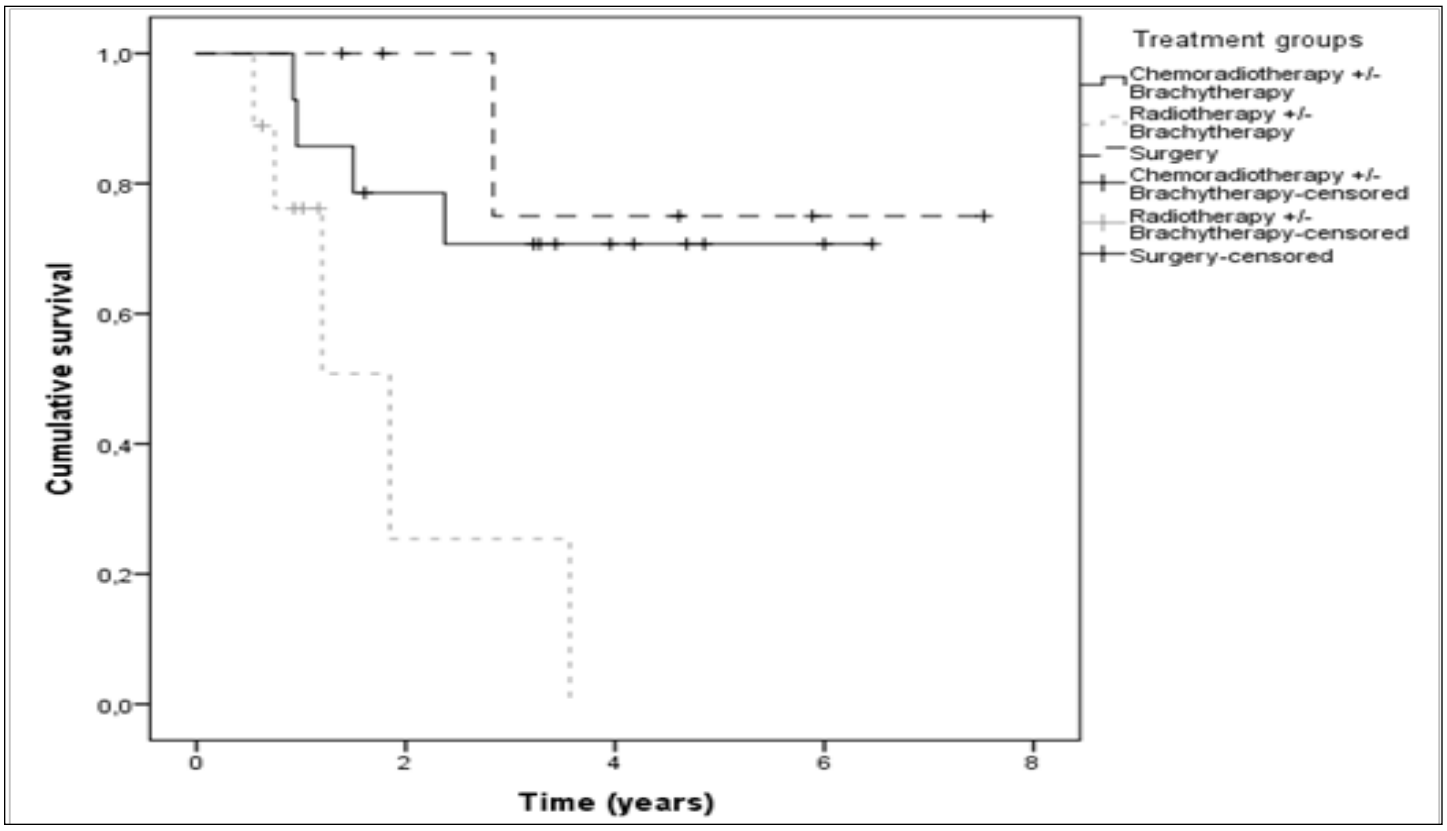
Tumor histology distribution was 82.8% of SCC and 18.2% of ad-

Table 2: Treatment modality.

Groups	n	%
Chemoradiotherapy +/- Brachytherapy	14	48.3
External radiotherapy +/- Brachytherapy	9	31.0
Surgery	6	20.7
Total	29	100

Figure 1: A - Progression-free survival; B – Overall survival.





enocarcinoma, similar to the literature data [3]. Most of the patients were diagnosed with stage I disease, and the median age at diagnosis was 62 years old, a little younger than generally mentioned in the literature data [7].

Progression-free survival and OS differed according to the modality of therapy received. Surgery had better results, probably because these patients had a more initial disease (in most cases, stage I). The group that received treatment based only on radiotherapy with or without brachytherapy had the worst survival which may be explained by the fact that most of these patients had stage II or III disease and worse clinical conditions, which prevented them from receiving chemotherapy. The results for PFS and OS were not statistically significant according to FIGO stages due to the low number and heterogeneity of patients included in this analysis.

It is surprising to note that 7 out of 12 patients with stage I disease were treated with a combination of chemoradiation or radiotherapy alone since the standard of care in this scenario is surgery (wide local excision with sentinel lymph node assessment). Explanations could be the poor performance status at diagnosis or any other medical condition that preclude them from receiving the standard of care therapy.

Shah et al. [9] conducted a retrospective study using data from 17 population-based cancer registries that participate in Surveillance, Epidemiology, and End Results (SEER) program with 2,149 women diagnosed with primary VC between 1990 and 2004. They found that 5-year disease-specific survival for women with stage I tumors was 84% (95% CI, 82 – 87%), 75% for stage II tumors (95% CI, 70 – 79%) and 57% for women with advanced disease (95% CI, 50 – 52%). In their study, only 10% of women that underwent surgery had a radical approach, lower than historically reported. At INCA, 1 out of 6 women who underwent surgery had a radical approach (16%). Stock et al., in a review of 100 cases from 1962-1992, found that treatment with surgery was a significantly favorable prognostic factor for PFS when compared to patients treated with radiation therapy alone, especially in patients with stages I - II disease ($p < 0.001$) [13]. Shah et al. [9] found, in a stratified analysis of the effect of treatment modality by stage, that stage I patients did worse when treated with radiation alone or a combination of both radiation and surgery. Wiebren et al. [8] conducted a retrospective review of 84 patients to define the role of surgery in managing patients with primary VC. Forty-five (66%) out of 84 patients reviewed had SCC, and 67% of the patients were treated with surgery alone, and 33% were treated with radiotherapy alone. With a median follow-up of 45 months, the 5-year and 10-year OS were, respectively, 74 and 58%. For stage I, the figures were 91 and 70%. They concluded that initial VC (stages I and II) have good outcomes in terms of survival and tumor control when treated with initial surgery followed by selective radiotherapy.

Modern treatment increasingly incorporates concurrent chemotherapy with radiation, but due to the lack of prospective studies, it is very difficult to determine if this leads to improvements in outcomes in VC treatments. Dalryumple et al. [12] report on concurrent chemoradiation in a series of 14 patients with stage I-III invasive SCC VC, mostly stage II patients [10], and found that 9 patients had no evidence of disease at 74-168 months. Samant et al. [14] report a series of 12 patients with primary VC who were treated with radiotherapy plus weekly cisplatin. They reported a 5-year OS of 66% and locoregional PFS of 92%. Nashiro et al. [15] reported outcomes of a series of 6 patients with locally advanced (stage III) VC treated with chemoradiation and found that all of them achieved a clinical complete response and four of them remained disease free at 18-55 months.

In this retrospective single-institution analysis, patients were treated with surgery or a combination of chemotherapy, radiotherapy and brachytherapy. Less than half of patients in stage I was treated with surgery and those treated with chemoradiation appeared to have more recurrences. The retrospective nature of this study raises the possibility of bias and justifies the lack of some collected variables.

Author Contribution

All authors equally contributed with the study design, data collection and analysis and writing the manuscript.

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