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Primary squamous cell carcinoma of the vagina: Prognostic factors, treatment patterns, and outcomes

Susan M. Hiniker [a], Audrey Roux [b], James D. Murphy [c], Jeremy P. Harris [a], Phuoc T. Tran [d], Daniel S. Kapp [a], Elizabeth A. Kidd [a,*]

[a] Department of Radiation Oncology, Stanford University, Stanford, CA, USA
[b] Department of Radiation Oncology, Hopital Maisonneuve-Rosemont, Montreal, Quebec, Canada
[c] Department of Radiation Oncology, University of California-San Diego, San Diego, CA, USA
[d] Department of Radiation Oncology, Johns Hopkins Hospital, Baltimore, MD, USA

HIGHLIGHTS

- We analyzed a large series of patients with squamous cell carcinoma of the vagina treated with definitive radiation therapy.
- We found that total radiation dose over 70 Gy is associated with improved survival and locoregional control.
- None of the patients treated with IMRT have experienced locoregional recurrence or grade 3–4 toxicities.

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ABSTRACT

Objective. Primary squamous cell carcinoma (SCCA) of the vagina is a rare malignancy with limited data to guide treatment. We evaluated prognostic factors and outcomes for patients with primary vaginal SCCA treated with definitive radiation therapy at a single institution.

Methods. A retrospective analysis was performed on patients treated for primary vaginal SCCA from 1959 to 2011.

Results. Ninety-one patients with primary vaginal SCCA were treated with definitive radiation therapy. Thirty-eight patients had FIGO stage I, 28 stage II, 13 stage III, and 12 stage IV disease. The mean total dose was 70.1 Gy. Two-year overall survival (OS), locoregional control rate (LRC), and distant metastasis-free survival by stage were, respectively: stage I: 96.2%, 80.6%, 87.5%; stage II: 92.3%, 64.7%, 84.6%; stage III: 66.6%, 44.4%, 50.0%; and stage IV: 25.0%, 14.3%, 25.0%. Treatment with total dose over 70 Gy was associated with improved OS ($p = 0.0956$) and LRC ($p = 0.055$). There was a significant difference in median dose received by patients who developed grade 3/4 toxicity compared to those who did not (82.9 Gy versus 70.0 Gy, $p = 0.0019$). None of the 10 patients treated with IMRT experienced locoregional recurrence or grade 3/4 toxicity. Tumor size larger than 4 cm was associated with worse OS ($p = 0.0034$) and LRC ($p = 0.006$).

Conclusions. Our analysis suggests that the optimal dose for definitive treatment of SCCA of the vagina lies between 70 and 80 Gy. Treatment with IMRT may allow for dose escalation with reduced toxicity and excellent LRC. Tumor size over 4 cm is associated with inferior outcomes and may require additional treatment modalities.

Introduction

Primary squamous cell carcinoma (SCCA) of the vagina is a rare disease, with an estimated incidence of less than 3000 new cases annually in the US, and accounts for less than 2% of all gynecologic malignancies [1]. Due to the anatomy of the region, surgery as primary treatment modality is generally felt to be too morbid except in early-stage disease involving the upper posterior vagina [2]. The mainstay of treatment is typically definitive radiation therapy with external beam radiation and/or brachytherapy, as well as more limited surgery in select cases. The addition of concurrent cisplatin-based chemotherapy to radiation is also increasingly being incorporated into therapy [3]. However, due to the rarity of disease, there have been no randomized prospective trials to guide treatment decisions, and the few published retrospective series provide limited information regarding outcomes with modern multimodality approaches [4,5].

* Corresponding author at: Department of Radiation Oncology, Stanford Cancer Center, 875 Blake Wilbur Drive, Stanford, CA 94305-5847, USA. Fax: +1 650 725 8231.
E-mail address: ekidd@stanford.edu (E.A. Kidd).

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Our objective was to evaluate the prognostic factors, management and outcomes for patients with primary SCCA of the vagina treated with definitive radiation therapy at a single institution, including current treatment patterns utilizing intensity modulated radiation therapy (IMRT), concurrent chemotherapy, and pre-treatment FDG-PET scans. Here we report our experience with definitive radiation therapy as treatment for primary SCCA of the vagina in 91 patients.

Methods and materials

Patient characteristics

This study was approved by the Stanford Institutional Review Board. We reviewed the hospital, radiation oncology, and pathology records of patients with biopsy-proven primary vaginal cancer diagnosed between May 1959 and December 2011 and initially identified 131 patients. From these, we identified 91 patients with SCCA of the vagina treated with radiotherapy in the Department of Radiation Oncology, Stanford University Medical Center, Stanford, CA, USA. Only patients with invasive squamous cell carcinoma histology were included. We excluded patients with cervical or vulvar involvement. Pretreatment evaluation included complete patient history, physical examination, standard laboratory studies, and imaging studies depending on treatment era and stage of disease. Patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines. Stages IVA and IVB were combined into stage IV for analysis.

Treatment methods

All 91 patients received definitive radiation therapy with external beam radiation therapy (EBRT), brachytherapy, or a combination of the two. A total of 67 patients were treated with EBRT via whole pelvis irradiation through individually shaped portals using an anterior–posterior (AP)/posterior–anterior (PA) or a four-field technique (AP/PA and opposed laterals). Pelvic doses ranged from 30 to 62 Gy. An additional 10 patients treated since 2000 received intensity-modulated radiation therapy (IMRT). Twenty-two patients received radiation to the inguinal nodes as well. The technical details of these treatments have been previously described [6].

Fourteen patients were treated with brachytherapy alone. Brachytherapy was delivered by either intracavitary or interstitial techniques. Forty-three patients were treated with intracavitary brachytherapy. Intracavitary therapy was delivered using vaginal cylinders, vaginal ovoids, or colpostats containing radium-226 or cesium-137. Vaginal cylinder doses were prescribed to treat at depth of 5 mm or at vaginal mucosa. Twenty-eight patients were treated with interstitial brachytherapy, of which two were high dose rate (HDR). Interstitial brachytherapy was administered with implanted stainless steel needles afterloaded with customized strength iridium-192 ribbons. Interstitial dose was prescribed to treat at the contour covering the tumor volume. The implant technique and dosimetry have been previously described [7,8]. A total of 13 patients were treated with HDR brachytherapy. HDR doses were converted into 2 Gy LDR equivalents using the methodology of Nag and Gupta in order to calculate total dose [9].

A total of 10 patients had a vaginal resection and 13 patients received chemotherapy as part of their treatment. Blood counts were checked prior to treatment and/or weekly during treatment. Since 1984, our policy has included packed red blood cell transfusions to maintain a hemoglobin level above 10 g/dL.

Patient follow-up

Following treatment, patients were re-evaluated during regularly scheduled clinical visits. At our institution, patients are recommended to return for clinic visits every 3 months for the first 2 years of follow-up, then every 4–6 months until year 5 with annual visits afterwards. Follow-up data was obtained by examination, reviewing data from referring physician, or by correspondence with patients or their relatives. Patients were censored at the date of their last follow-up. Surveillance imaging including computed tomography (CT), PET and magnetic resonance (MR) imaging were performed at the discretion of the treating physician. Evaluation of treatment response was assessed by clinical exam primarily. Radiographic studies were referenced when available. Complications were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistical analysis

Patients were categorized by known prognostic factors, stage, and radiation dose. Kaplan–Meier estimates of overall survival and disease-free survival (DFS) including DFS according to site of the first failure (locoregional or distant) were calculated. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC). Log-rank test and Cox regression analysis were used to determine association with patient characteristics, tumor features, and treatment methods for univariate and multivariate analyses, respectively. Wilcoxon rank-sum test was used to assess association of dose with grade 3 or 4 toxicity.

Results

Patient characteristics

The mean follow-up time was 57.6 months (range 1–290.7). Patient characteristics are detailed in Table 1. The mean age was 64.3 years (range 33–99). The most common presenting symptom was vaginal

Table 1
Patient characteristics.

Age at diagnosis (years)	Mean (range)	64.3 (33–99)
Ethnicity	White	62 (68.1%)
	Hispanic	9 (9.9%)
	Asian	9 (9.9%)
	African–American	1 (1.1%)
	Other	10 (11.0%)
Smoking history	Never	31 (34%)
	Past	9 (9.9%)
	Current	13 (14.3%)
	Unknown	38 (41.8%)
Prior hysterectomy	Yes	46 (50.5%)
Surgical resection	Yes	10 (10.9%)
Vaginal location	Whole	18 (19.8%)
	Upper 1/3	42 (46.2%)
	Middle 1/3	10 (11.0%)
	Distal 1/3	21 (23.1%)
Pretreatment hemoglobin (g/dL)	Mean (range)	12.3 (8.7–14.4)
Hemoglobin during treatment (g/dL)	Mean (range)	12.2 (9.2–14.4)
Stage	I	38 (41.8%)
	II	28 (30.8%)
	III	13 (14.2%)
	IV	12 (13.1%)
Tumor Size	≤4 cm	53 (58,2%)
	>4 cm	38 (41.8%)
Total dose (Gy)	Mean (range)	70.1 (6.0–127.0)
Radiation Modality	EBRT only	21 (23.1%)
	EBRT/interstitial BT	24 (26.4%)
	EBRT/intracavitary BT	33 (36.2%)
	Interstitial BT only	3 (3.3%)
	Intracavitary BT only	9 (9.9%)
	IS and IC BT	1 (1.1%)
IMRT	Yes	10 (11.0)
Chemotherapy	Yes	13 (14.2%)
Treatment decade	<1960	1 (1.1%)
	1960–1969	20 (22.0%)
	1970–1979	11 (12.1%)
	1980–1989	27 (29.7%)
	1990–1999	13 (14.3%)
	2000–2011	19 (20.9%)

EBRT, external beam radiation; BT, brachytherapy; IS, interstitial; IC, intracavitary.