

**American College of Radiology
ACR Appropriateness Criteria®**

MANAGEMENT OF VAGINAL CANCER

Expert Panel on Radiation Oncology–Gynecology: Larissa J. Lee, MD¹; Anuja Jhingran, MD²; Elizabeth Kidd, MD³; David K. Gaffney, MD, PhD⁴; Higinia Rosa Cardenes, MD, PhD⁵; Mohamed A. Elshaikh, MD⁶; Beth Erickson, MD⁷; Nina A. Mayr, MD⁸; David Moore, MD⁹; Ajmel A. Puthawala, MD¹⁰; Gautam G. Rao, MD¹¹; William Small Jr, MD¹²; Mahesh A. Varia, MD¹³; Andrew O. Wahl, MD¹⁴; Aaron H. Wolfson, MD¹⁵; Catheryn M. Yashar, MD¹⁶; William Yuh, MD.¹⁷

Summary of Literature Review

Introduction

Primary carcinoma of the vagina is a rare malignancy, representing 3% of all gynecologic cancers, and is diagnosed in an estimated 2,900 women annually in the United States [1]. The majority of primary vaginal cancers are squamous cell carcinomas, which are frequently associated with human papillomavirus infection [2,3]. Given the rarity of this disease, prospective trials of patients with vaginal cancer have not been feasible, and evidence for treatment relies on single institutional reports of clinical outcomes spanning several decades. Due to these limitations, management guidelines for vaginal cancer are currently extrapolated from reported clinical experience and prospective studies of cervical and anal cancer, given the similarities in disease etiology and desire for organ preservation.

Staging

Staging for vaginal cancer relies on the clinical evaluation, according to the Federation of Gynecology and Obstetrics (FIGO) system, which allows for chest radiographs, examination under anesthesia with bimanual and rectovaginal examination, cystoscopy and/or proctoscopy (in patients with urinary or rectal symptoms), and intravenous pyelogram to evaluate for hydronephrosis [4]. By the FIGO system, tumors that involve the cervix or vulva are not considered vaginal cancers and are classified as cervical or vulvar primaries. As in cervical cancer staging, FIGO encourages the use of advanced imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), to guide therapy, although in historic series and resource-poor settings the imaging findings may not be used to determine the stage in order to preserve the FIGO system.

Given its superior soft-tissue resolution, MRI is particularly useful in delineating tumor size and extent and is more sensitive than physical examination in assessing paravaginal or parametrial involvement in patients with cervical cancer [5,6]. Primary vaginal tumors are best visualized on T2-weighted imaging and appear hyperintense [7]. Visualization of the vaginal tumor may be improved with the instillation of vaginal gel or a dry vaginal tampon, which distends the vaginal walls and allows for assessment of the tumor thickness.

PET imaging has become a standard diagnostic tool in the initial staging of cervical cancer and for post-treatment surveillance [8-10]. PET has shown a similar applicability for vaginal cancer, as its sensitivity for detecting primary vaginal tumors and involved inguinal or pelvic lymph nodes is greater than that of CT alone [11]. CT may be used to delineate the disease extent and evaluate for nodal and distant metastatic spread, although its sensitivity is modest compared to MRI and PET. CT is primarily used for 3-D conformal treatment planning for radiotherapy delivery. (See [Variant 1](#).)

¹Principal Author, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, Massachusetts. ²Co-Author, University of Texas, MD Anderson Cancer Center, Houston, Texas. ³Co-Author, Stanford Cancer Center, Stanford, California. ⁴Co-Author and Panel Chair, University of Utah Medical Center, Salt Lake City, Utah. ⁵Panel Vice-chair, Indiana University Medical Center, Indianapolis, Indiana. ⁶Henry Ford Health System, Detroit, Michigan. ⁷Medical College of Wisconsin, Milwaukee, Wisconsin. ⁸Ohio State Comprehensive Cancer Center-James Cancer Hospital, Columbus, Ohio. ⁹Indiana University School of Medicine, Indianapolis, Indiana, American College of Obstetricians and Gynecologists. ¹⁰Long Beach Memorial Medical Center, Long Beach, California. ¹¹University of Maryland School of Medicine, Baltimore, Maryland, American Society of Clinical Oncology. ¹²The Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois. ¹³University of North Carolina School of Medicine, Chapel Hill, North Carolina. ¹⁴University of Nebraska Medical Center, Omaha, Nebraska. ¹⁵University of Miami, Miami, Florida. ¹⁶University of California San Diego, San Diego, California. ¹⁷Ohio State University, Columbus, Ohio.

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Reprint requests to: Department of Quality & Safety, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191-4397.

Treatment of Early-Stage Vaginal Cancer

Early-stage vaginal cancer is defined as an invasive disease confined to the vaginal mucosa and/or paravaginal tissues (FIGO stages I–II). The treatment approaches for early-stage disease include surgical resection or definitive radiotherapy. The advantages of surgery are the preservation of ovarian and sexual function and elimination of the risk of radiation-associated malignancy [12]. Lesions that are well-circumscribed in the upper vagina may be amenable to conservative excision or upper vaginectomy, which is performed in conjunction with radical hysterectomy for patients with an intact uterus. Bilateral pelvic lymph node dissection is required, given the extensive lymphatic network of the vagina and the risk of occult nodal spread. Surgical series have reported rates of pathologic nodal involvement that range from 6%–14% for stage I disease and from 26%–32% for stage II disease [13,14]. For distal vaginal lesions, the surgical approach involves total vaginectomy, or vulvovaginectomy, and inguinofemoral lymph node dissection. Anterior, posterior, or total exenteration is performed less commonly for early-stage disease, as radiation therapy is the preferred modality for organ preservation.

Surgical series have reported 5-year survival rates ranging from 53% to 92% [14–19] for women with early-stage disease who were treated with conservative excision or partial or total vaginectomy. These reports show a survival advantage for surgery over definitive radiotherapy, although selection bias is inherent, as patients with larger tumors and comorbid disease were less likely to be surgical candidates [14,16–19]. In a study from the National Cancer Data Base, the 5-year survival rate was 90% for women with stage I disease who were treated with surgery alone, compared with 63% who received definitive radiotherapy [2]. Similar results from a Surveillance, Epidemiology, and End Results analysis found an increased risk of mortality among stage I patients who received definitive radiotherapy compared with those who were treated surgically, with an adjusted hazard ratio of 1.5 [20]. Survival outcomes for stage II disease also favor surgery in these population-based studies, although the difference is not statistically significant. However, patients with stage II disease are more likely to require total vaginectomy or an exenterative procedure to obtain negative surgical margins [18]. Laparoscopic radical vaginectomy with the construction of a neovagina has been proposed as an organ-sparing surgical alternative [21]. Neoadjuvant chemotherapy has also been used as a downstaging method prior to radical surgery. In a study of 11 patients with FIGO stage II disease who were treated with 3 cycles of neoadjuvant cisplatin and paclitaxel prior to radical vaginectomy and pelvic lymphadenectomy, complete and partial clinical response rates were 27% and 64%, respectively, and 73% were disease-free at the last follow-up [22]. In patients with an incomplete resection or pathologically involved lymph nodes, adjuvant radiotherapy is delivered with 5-year survival rates of 100% for stage I disease and 40%–69% for stage II disease [14,16–18]. (See [Variant 2](#).)

Large, institutional series of definitive radiotherapy for early-stage vaginal cancer have reported 5-year cause-specific survival rates of 40%–92% for stage I disease and 35%–78% for stage II disease (see [Appendix 1](#)) [23–31]. In patients with superficial stage I lesions, brachytherapy alone has been used with 5-year survival rates of 53%–100% [24,27,28,31,32]. Pelvic failure rates following brachytherapy alone range from 14% to 33% [24,27]. Although several studies have shown no difference in outcome from adding external beam radiation therapy (EBRT) to brachytherapy for stage I disease [27,31,32], others have advocated for using that combination in patients with higher grade and infiltrative lesions, given the increased risk of local-regional failure [29,33,34]. In stage II disease, the combination of EBRT and brachytherapy has been associated with improved pelvic control and survival [27]. The predominant pattern of failure following definitive radiotherapy is locoregional, similar to that of surgery.

Treatment of Locally Advanced Disease

Advanced-stage vaginal cancer is primarily managed with definitive radiation therapy with cause-specific survival rates that range from 23%–59% for stage III disease and from 0%–25% for stage IV disease (see [Appendix 1](#)) [23–31]. Corresponding pelvic control rates are 62%–71% and 12%–30%, respectively. EBRT alone or in combination with intracavitary or interstitial brachytherapy has been used to deliver definitive radiation doses. In a series from MD Anderson Cancer Center, 66% of women with advanced-stage lesions were treated with EBRT alone and received lower cumulative delivered doses than those treated with a brachytherapy boost [24]. Pelvic control and survival outcomes were not statistically different by radiation treatment modality, and 83% of relapses were locoregional. In contrast, the clinical experience from the Mallinckrodt Institute favored a combined modality approach of EBRT and intracavitary/interstitial brachytherapy for patients with locally advanced disease [27]. The pelvic control rates for stage III disease were comparable between these large series.

Use of neoadjuvant chemotherapy prior to radical surgery has been studied in randomized trials of patients with locally advanced cervical cancer, and no detectable survival advantage was found [35]. Case reports and small series of neoadjuvant chemotherapy for locally advanced vaginal cancer have been published, although experience is limited and most patients relapsed and died [24,36]. Up front exenteration may also be considered for patients with resectable advanced-stage disease, an approach that may provide palliation in the setting of rectovaginal or vesicovaginal fistula in otherwise localized disease. (See [Variant 3](#) and [Variant 4](#).)

Concurrent Chemoradiotherapy

Given the high rates of pelvic failure, the use of concurrent chemoradiotherapy has been adopted for vaginal cancer based on the survival gains observed in several randomized trials of locally advanced cervical cancer [37-39]. Although there have been no prospective trials in patients with vaginal cancer, institutional reports support the feasibility of chemoradiotherapy. In a study of 14 patients with predominately early-stage disease, radiation therapy was delivered with concurrent 5-fluorouracil (5-FU) (continuous infusion over 4 days) alone or in combination with bolus cisplatin (100 mg/m²) or mitomycin C (10 mg/m²) [40]. At 5 years, the cause-specific survival rate was 93%, and 1 patient had local failure. Another series that was comparable in size and composed of patients with early- and late-stage disease reported a local control rate of 92% and a 5-year progression-free survival rate of 75% with the use of concurrent weekly cisplatin (40 mg/m²) [41]. A cohort of 26 patients with predominately locally advanced disease was treated with definitive radiotherapy and concurrent 5-FU with or without mitomycin C or weekly single-agent cisplatin. This series reported a 5-year survival rate of 50%, and pelvic failure was documented in 31% of the patients [25].

Radiation Technique

EBRT for vaginal cancer is typically delivered to the pelvis with a 45 Gy dose using a 4-field or anterior-posterior-posterior-anterior (AP-PA) beam arrangement. CT simulation allows for the use of 3-D conformal treatment planning to improve target coverage and dose homogeneity, while minimizing the normal tissue dose. Conventional field borders, blocks, and multileaf collimators may be set using bony landmarks and may be adjusted based on the contoured target volume and normal tissue structures. In the absence of nodal involvement, the superior field border covers the upper extent of the external iliac lymph node region, which generally corresponds to the L5/S1 interspace. The inferior field border covers the full vaginal length. The elective nodal volume for vaginal cancer should encompass the external iliac, internal iliac, and obturator lymph nodes. If the tumor involves the superior half of the posterior vaginal wall or rectovaginal septum, the presacral and perirectal nodes are also included. For cases with distal vaginal involvement, the inguinal lymph nodes are at risk and are treated bilaterally along with the pelvic nodal groups. The gross target volume (GTV) for the primary site is defined based on physical examination findings and the local extension as identified by CT, MRI, and/or PET. The clinical target volume (CTV) for the primary tumor represents the adjacent regions at risk for microscopic spread, including the GTV with a 1–2-cm margin, full vaginal length, and paravaginal tissues.

An additional boost dose may be delivered to the primary site or the involved lymph nodes using a 3-D conformal technique or intensity-modulated radiation therapy (IMRT). The use of IMRT for vaginal cancer has not been evaluated, and, if used, tumor regression and movement of the vagina with organ filling should be considered in the planning process, as the vaginal apex may be displaced by 1.5–2 cm on average in the AP direction [42,43]. In patients with locally advanced disease treated with EBRT alone, a parametrial or nodal boost is frequently delivered to the pelvic side wall or involved lymph node(s) to a cumulative dose of 55–66 Gy, whereas the primary tumor receives approximately 64–70 Gy [24,27]. Due to limited published data, the use of stereotactic body radiotherapy (SBRT) for treating gynecologic malignancies is considered investigational.

Brachytherapy

The choice of the brachytherapy modality is based on the residual tumor thickness following pelvic radiation therapy. Vaginal cylinder brachytherapy is appropriate for residual disease measuring <5 mm in thickness, whereas interstitial implants are performed for bulky residual tumors. The most common brachytherapy modalities used in clinical practice are low-dose-rate (LDR), high-dose-rate (HDR), and pulsed-dose-rate delivery. HDR and LDR intracavitary brachytherapy have comparable local control, survival, and complication rates [44]. For cylinder brachytherapy, the full vaginal length typically receives a cumulative dose of 60–65 Gy, while the region of the tumor is boosted an additional 10–20 Gy [45]. For interstitial brachytherapy, the cumulative delivered dose ranges from 70–85 Gy, and the recommended dose schedules are described elsewhere [46]. For treatment planning based on 3-D, simulation with MRI or fusion of MR images with CT simulation at

the time of interstitial brachytherapy has been reported with favorable outcomes [47]. For CT-based planning, the placement of fiducial markers may be used to demarcate the superior, inferior, and lateral extent of the tumor for contouring purposes.

Treatment Considerations

As in cervical cancer, retrospective studies have identified a prolonged overall treatment time and lower hemoglobin level as treatment-related factors associated with poor survival for vaginal cancer [30,48]. The ACR consensus panel recommends the completion of definitive radiotherapy within 8–9 weeks and transfusion as needed to maintain hemoglobin levels of >10–11 gm/dL to promote tumor oxygenation. Individual management decisions for vaginal cancer are based on the patient's extent of disease, the presence of comorbid illness, and the desire to maintain ovarian and/or sexual function. In patients with metastatic disease or poor functional status, palliative radiotherapy may play an important role in alleviating the pain and bleeding associated with uncontrolled pelvic disease [49].

Follow-up

The standard follow-up for vaginal cancer involves a clinical examination every 3 months for 2 years, then less frequent intervals thereafter. Based on the practice for locally advanced cervical cancer, consideration of post-treatment PET/CT surveillance is reasonable for patients with initial bulky disease.

Summary

- Due to the rarity of vaginal cancer, treatment recommendations are extrapolated from single institutional reports and prospective studies of cervical and anal cancer.
- Advanced imaging modalities, such as MRI and PET/CT, may be used to delineate the tumor size and extent, evaluate nodal or distant metastatic spread, and perform post-treatment surveillance.
- For early-stage disease, surgery or definitive radiotherapy results in similar outcomes, although EBRT and brachytherapy are preferred for organ preservation.
- The addition of concurrent weekly cisplatin should be considered for all patients with advanced-stage disease and for the majority of patients with early-stage disease.
- When available, cylinder or interstitial brachytherapy is the preferred modality to deliver an additional boost dose to the primary tumor.
- In patients with metastatic disease, bleeding and/or pain palliation may be achieved with a hypofractionated radiation course.

Supporting Documents

- [ACR Appropriateness Criteria® Overview](#)
- [Evidence Table](#)

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Appendix 1. Summary of Definitive Radiation Therapy Series for Vaginal Cancer.

Institution Study years	Number of patients	Stage distribution	5-year pelvic control	5-year DSS	5-year OS	Notes
M.D. Anderson Cancer Center [24] 1970-2000	193; All SCC	I-26% II-50% III/IV-24%	I-86% II-84% III/IV-71%	I- 85% II-78% III/IV-58%	58% for entire cohort	There is no difference in pelvic control or DSS by RT modality or dose.
Mallinckrodt [27] 1953-1991	192; 89% SCC	I-31% IIA-33% IIB-18% III-10% IVA-8%	Crude rates: I- 86% IIA-66% IIB-56% III-65% IVA-27%	10-yr DFS: I-80% IIA-55% IIB-35% III-38%	-	There is improved tumor control with EBRT + brachytherapy for stage II patients.
Princess Margaret Hospital [25] 1974-1989	153; (128 RT, 17 S) 87% SCC	0-10% I-26% II-25% III-27% IV-13%	Crude rate: 65% for entire cohort	I/II-77% III/IV-56%	58% for entire cohort	An RT dose >70 Gy is prognostic on UVA for improved survival.
Krakow [31] 1965-1988	125; 90% SCC	I-26% II-30% III-32% IV-12%	-	I-73% II-54% III-23% IV-0%	-	There were high failure rates (27%) with brachytherapy alone for stage I disease.
Institut Gustav Roussy [23] 1970-2001	91; 100% SCC	I-29% II-38% III-29% IVA-4%	I- 79% II-79% III-63%	I-83% II-76% III-52%	I-65% II-62% III-42%	The clinical response to RT was prognostic
Vienna [32] 1986-1998	86; 88% SCC	I-20% II-44% III-23% IV-6%	-	I-92% II-57% III-59% IV-0%	I-41% II-43% III-37% IV-0%	The majority received HDR brachytherapy
University of Maryland [29] 1957-1975	88; 95% SCC	I-10% IIA-26% IIB-16% III-30% IV-9%	Crude rates: I-89% IIA-87% IIB-64% III-65% IV-12%	I-88% IIA-78% IIB-50% III-42% IV-0%	-	
Stanford [30] 1959-2005	78; 100% SCC	I-42% II-29% III-17% IV-11%	I-83% II-76% III-62% IV-30%	I-92% II-68% III-44% IV-13%	-	
Tata Memorial [28] 1984-1993	75; 93% SCC	I-7% IIA-49% IIB-20% III-19% IV-5%	Crude rate: 83% for entire cohort	5-yr DFS I-40% IIA-55% IIB-60% III-50% IVA-25%	50% for entire cohort	The response to RT was prognostic for improved DFS: 68% for CR, 35% for PR, and 18% for SD

DSS = Disease-specific survival; OS = overall survival; DFS= disease-free survival; SCC = squamous cell carcinoma; CR = complete clinical response; PR = partial clinical response; RT = radiation therapy; SD = stable disease; EBRT = external beam radiotherapy.

Clinical Condition: Management of Vaginal Cancer

Variant 1: 52-year-old woman with remote hysterectomy for cervical dysplasia and 1- x 1.5- x 1 cm invasive SCC involving right vaginal fornix without paravaginal extension.

Treatment	Rating	Comments
Pretreatment Evaluation		
X-ray chest	6	
CT abdomen and pelvis	7	
MRI abdomen and pelvis	8	
CT chest	6	
FDG-PET/CT whole body	8	
Cystoscopy	4	
Definitive Treatment		
Upper vaginectomy and pelvic node dissection	6	
Brachytherapy alone	2	
EBRT alone	3	
EBRT and brachytherapy	8	
Local excision and EBRT	5	
Chemoradiotherapy (EBRT alone)	3	
Chemoradiotherapy (EBRT and brachytherapy)	8	
Following EBRT to 45 Gy, residual disease measured <5 mm in thickness		
Brachytherapy Technique		
Vaginal cylinder	8	
Interstitial implant	4	
Brachytherapy Modality		
Low-dose-rate	8	
High-dose-rate	9	
Pulsed-dose-rate	8	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Management of Vaginal Cancer

Variant 2: 68-year-old woman with FIGO stage II SCC of distal vagina, 3 x 3 x 4 cm in size involving suburethral area. No nodal involvement or distant disease by PET/CT.

Treatment	Rating	Comments
Definitive Treatment		
EBRT alone	3	
EBRT and brachytherapy	8	
Chemoradiotherapy (EBRT alone)	3	
Chemoradiotherapy (EBRT and brachytherapy)	8	
Vulvovaginectomy with anterior exenteration	3	
Radiation Therapy Technique		
2D RT	3	
3D conformal RT	8	
IMRT	8	
Elective Nodal Coverage		
Pelvic nodes only	3	
Pelvic and bilateral inguinal nodes	8	
Low pelvic and bilateral inguinal nodes	6	
Superior Field Border (nodal CTV)		
L5/S1 (or bifurcation of common iliacs)	7	
L4/L5 (or bifurcation of aorta)	6	
Mid-SI joint	5	
Bottom of SI joint	3	
Residual disease measured 2 cm in thickness following EBRT to 45 Gy with concurrent chemotherapy		
Method of Boost		
3D conformal	3	
IMRT	5	
Cylinder brachytherapy	2	
Interstitial brachytherapy	8	
Cumulative Delivered Dose with EBRT Boost (If brachytherapy not performed)		
60-65 Gy	5	
70-75 Gy	7	
80-85 Gy	3	
Cumulative Delivered Dose with Brachytherapy Boost		
60-65 Gy	3	
70-75 Gy	7	
80-85 Gy	7	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Management of Vaginal Cancer

Variant 3: 65-year-old woman with FIGO stage III SCC of the vagina with full-length involvement and pelvic sidewall extension measuring 5 x 7 x 7 cm. PET/CT shows bulky primary disease and a 2- x 3 cm external iliac lymph node but no distant metastases.

Treatment	Rating	Comments
Definitive Treatment		
EBRT alone	3	
EBRT and brachytherapy	5	
Chemoradiotherapy (EBRT alone)	5	
Chemoradiotherapy (EBRT and brachytherapy)	8	
Neoadjuvant chemotherapy followed by RT	3	
Neoadjuvant chemotherapy followed by radical surgery	2	
Exenteration with postoperative RT for close/positive margins	2	
Palliative RT	3	
Concurrent Chemotherapy		
Weekly cisplatin	8	
Bolus cisplatin and 5FU	6	
Cisplatin and gemcitabine	3	
Weekly paclitaxel	3	
Superior Field Border (nodal CTV)		
L3/L4 (cover low para-aortics)	7	
L4/L5 (or bifurcation of aorta)	7	
L5/S1 (or bifurcation of common iliacs)	3	
L1/L2 (cover renal hilum)	3	
After 45 Gy EBRT with concurrent chemotherapy, the primary vaginal disease measures 3 x 4 x 4 cm and nodal disease measures 1 x 1 cm.		
Boost to Pelvic Nodal Disease		
No boost	2	
Pelvic sidewall boost to 54-60 Gy with midline block	6	
Conformal nodal boost to 60-66 Gy	7	
IMRT nodal boost to 60-66 Gy	8	
Boost to Primary Vaginal Disease		
Conformal boost to vaginal CTV to 65-75 Gy	5	
IMRT boost to vaginal CTV to 65-75 Gy	7	
Interstitial brachytherapy to vaginal CTV to 70-85 Gy	8	
Vaginal cylinder brachytherapy to 70-85 Gy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Management of Vaginal Cancer

Variant 4: 85-year-old woman with FIGO stage IVB SCC of the vagina with pelvic sidewall fixation, pain, and vaginal bleeding. PET/CT shows FDG-avid lymphadenopathy in the pelvis, inguinal nodes, and mediastinum, as well as pulmonary metastases. Karnofsky performance status is 50.

Treatment	Rating	Comments
Primary Management		
Palliative radiotherapy	8	
Palliative chemotherapy	3	
Chemoradiotherapy	3	
Palliative exenteration	1	
Best supportive care with pain management	5	
Radiation Fields		
Primary tumor volume with 2 cm margin	7	
Pelvis only	5	
Pelvis and involved inguinal nodes	6	
Pelvis, inguinal and para-aortic nodes	3	
Radiation Dose		
10 Gy in single fraction	4	
3.7 Gy BID for 2 days q2 weeks to 44.4 Gy	7	
30 Gy in 10 fractions	7	
50 Gy in 25 fractions	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		