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Teaching Case

Complete Response After Stereotactic Body Radiation Therapy With Concurrent Immunotherapy for Vaginal Melanoma

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Mucosal melanomas represent 1.3% of all melanomas. Of those, 18% arise within the female genital tract (FGT).[1,2] Unique molecular profiles were identified for vulvar and vaginal melanomas (VM) compared with non-gynecologic melanomas, suggesting mucosal melanomas (MM) of the FGT represent a distinct melanoma subtype.[3] Vaginal melanomas are particularly rare, making up only 19.8% of FGT melanomas compared with vulvar primaries (76.7%).[4] Although no formal staging system exists for VM, clinical staging from cutaneous melanomas has been adapted as follows: localized (stage I), lymph node involvement (stage II), disseminated disease (stage III).[5] Tumor size and lymph node involvement have been correlated with survival in vaginal melanoma.[2,6-8] Unfortunately, VM has a poor overall prognosis, with 5-year overall survival rates of 5% to 25%.[9,10] These poor outcomes are attributed to occult location, often multifocal disease with surrounding atypia, advanced disease in close proximity to critical anatomic pelvic structures, and rich submucosal lymphovascular channels with predilection for nodal spread.[2,11]

Given the rarity of VM and paucity of data, optimal management remains in question.[6,12] Retrospective analyses combined with data extrapolated from cutaneous or other MM guide current recommendations regarding surgical, systemic, and radiation therapies (RTs). Primary surgical resection via wide local excision with negative margins is preferred, though the survival benefit of surgery has been debated.[6,13] Advanced tumor size, multifocal disease, and proximity to bladder, urethra, rectum, and anus increase the technical challenge of achieving R0 surgical margin. Extensive radical surgery to achieve wider margins has not improved survival, and recommendations for pelvic and/or inguinal staging are lacking.[12,14,15] Despite aggressive multimodality therapy including primarily surgical management with or without adjuvant RT, outcomes remain poor for VM with high rates of distant recurrence.[1,8,9,15-17] Immunotherapy (IO)

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shows promise in treating MM with objective response rates of ~x223C20% and ~x223C75% of responders with some degree of durable response.[18-20] Therefore, treatment selection is challenging given the need to balance the morbidity of local therapies with the propensity for distant metastatic disease and overall poor outcomes.

Within this context, improvements in both local and systemic therapy are needed. We present 2 cases of vaginal melanoma treated at different comprehensive cancer centers using a multimodality approach of IO and stereotactic body radiation therapy (SBRT) with or without surgical debulking, and review current management controversies.

Case Presentation

Case 1

A 56-year-old G3 P3 woman with no significant past medical history presented with vaginal pressure and postcoital bleeding. Physical examination at presentation showed a 2 cm mass protruding at the anterior vaginal wall just proximal to the introitus.

Biopsy revealed ulcerated melanoma, invasive to a depth of at least 3.1 mm, at least Clark level IV (BRAF and KIT negative) without perineural invasion or lymphovascular invasion. Staging magnetic resonance imaging (MRI) of the pelvis demonstrated a large mass at the vaginal introitus, extending superiorly along the right and left vaginal fornices, and abutting the posterior urethra without intervening fat plane (Fig 1A and 1B). Positron emission tomography (PET)/computed tomography (CT) demonstrated an fluorodeoxyglucose-avid vaginal mass with superior extension to the cervix (Fig 1C). PET/CT and brain MRI were both negative for lymph node involvement and distant metastatic disease.

After multidisciplinary discussions, she initiated combination ipilimumab (3 mg/kg intravenously [IV] every 3 weeks) and nivolumab (1 mg/kg IV every 3 weeks for 4 cycles, then 480 mg IV every 4 weeks until maximum benefit). She had a partial response with symptomatic improvement after initial cycles of combination IO, and after cycle 4, she continued with nivolumab monotherapy. Restaging CT of the chest and MRI of the abdomen and pelvis demonstrated stable vaginal disease and no evidence of metastatic disease.

After cycle 8 of nivolumab monotherapy, she underwent anterior vaginectomy for debulking before RT. Multifocal lesions were identified and all visible lesions were debulked. Pathology redemonstrated melanoma with sarcomatoid features.

After maximal debulking, she was planned to undergo SBRT. Three gold seeds were placed in the vaginal wall to mark out the proximal and distal extent of gross residual disease and a third seed inserted out of plane with the others for daily setup alignment. She was simulated supine, frog-legged, in an alpha cradle, with full and empty bladder using CT and MRI with contrast. Using the diagnostic MRI presurgery coregistered to the planning CT and MRI, the original extent of gross disease and the residual gross disease was delineated. The clinical target volume (CTV) was the entire length of the vagina, resulting in a nearly 1.0-1.5 cm margin around the gross tumor volume (GTV). A planning target volume (PTV) margin of 0.3 cm was isometrically applied. Total prescription dose was 30 Gy delivered in 5 fractions every other day with cone beam CT (CBCT) for alignment with attention to gold seeds and PTV, though real-time tumor tracking was not used. A volumetric-modulated arc therapy plan using 6X photons with 2 arcs created an acceptable plan meeting all normal structure constraints (Table 1) and excellent target coverage (Fig 1D). Daily setup included full bladder and empty rectum. Full bladder was obtained with 16 oz of fluid intake 1 hour before each treatment. Patient were instructed to have a bowel movement before arrival to treatment. If full rectum or rectal gas was noted on pretreatment CBCT distending rectum >0.5 cm in diameter from empty at simulation, patients were removed from table and asked to evacuate. There was not a need for use of pretreatment enema or rectal tube, but this was available if needed.

She tolerated treatment well without significant side effects. After RT, she developed abdominal cramping and diarrhea for 1 week, which self-resolved. Three weeks after RT, she developed grade 2 radiation perineal dermatitis (National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0), which resolved with Aquaphor (Beiersdorf AG) and Domeboro soaks (Advantice Health). Follow-up MRI obtained 3 months post-RT showed no abnormal soft tissue remaining at the site of previously seen malignancy in the vagina. Physical examination at 8 months post-RT recorded maintained vaginal length and caliber without any mucosal abnormality, discoloration, discharge, or bleeding. PET/CT 6 months post-RT demonstrated no evidence of disease (Fig 2). She completed 15 cycles of nivolumab monotherapy and has been on surveillance with no evidence of disease at last follow-up, now 16 months post-RT. There were no long-term toxicities attributable to radiation noted to date.

Case 2

An 80-year-old G2 P2 female with chronic kidney disease, uveitis, and prior hysterectomy for benign disease presented with significant vaginal bleeding. Outpatient examination showed large fungating vaginal mass filling and nearly prolapsing through the vagina. Biopsy showed malignant melanoma (*BRAF* mutation negative and *KIT*

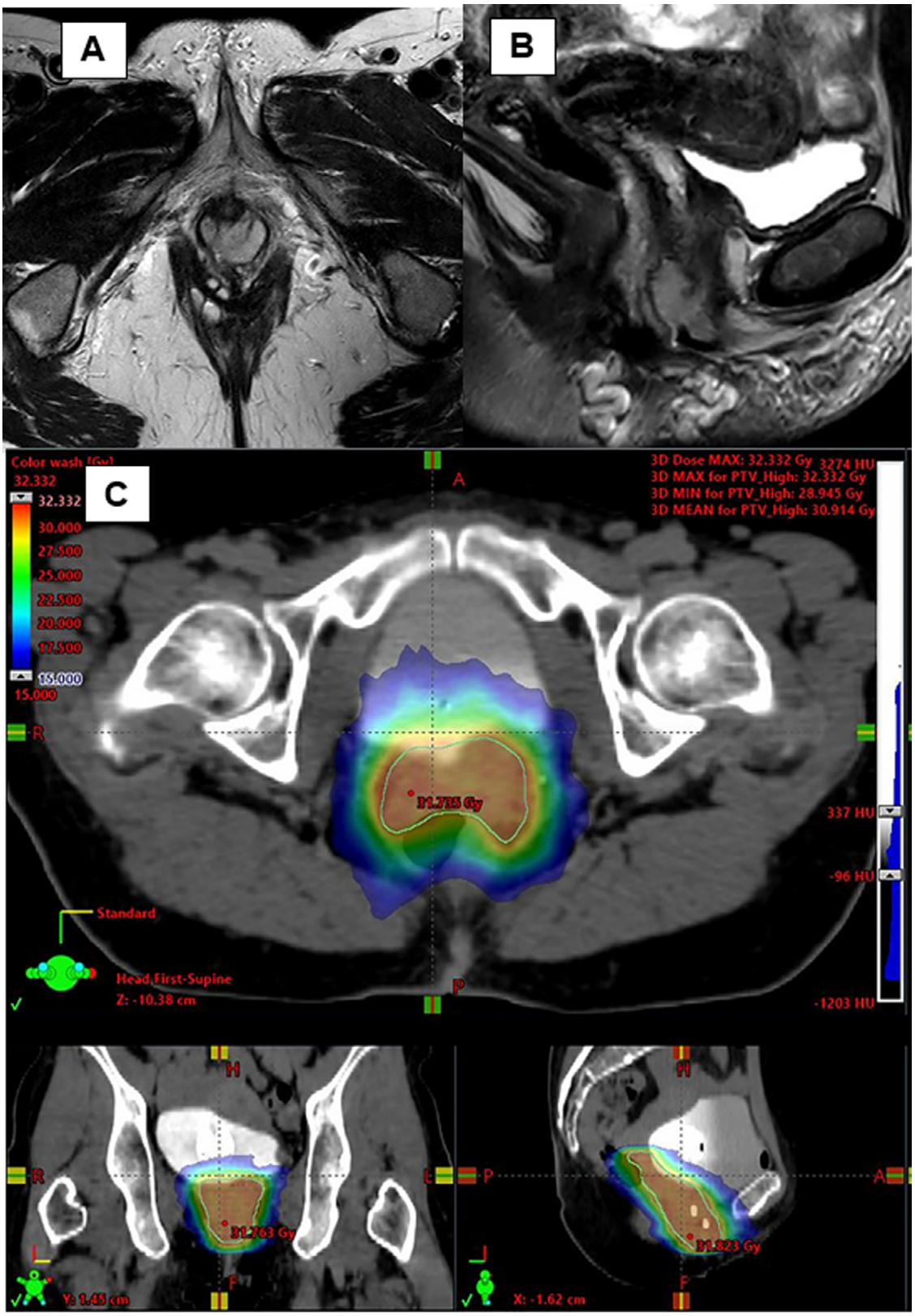

Fig. 1 Case 1: Initial diagnostic staging scans demonstrate large mass at vaginal introitus, abutting posterior urethra on (A) axial T2-weighted MRI and (B) sagittal T2-weighted MRI. (C) After immunotherapy and maximal debulking, radiation treatment plan encompassing entire length of vagina in PTV (cyan) to total dose of 30 Gy in 5 fractions.

Abbreviations: MRI = magnetic resonance imaging; PTV = planning target volume.

Table 1 Vaginal stereotactic body radiation therapy planning dose constraints

Normal structures and goals		
Normal structures	**Priority**	**Parameter planning limit**
Small bowel	1	D0.1cc[Gy] ≤ 27 D1cc[Gy] ≤ 25
Bladder	1	D0.1cc[Gy] ≤ 35 D0.5cc[Gy] ≤ 32 V26Gy[cc] ≤ 50 V26Gy[%] ≤ 25
Rectum	1	D0.1cc[%] ≤ 38 D1cc[Gy] ≤ 36 D2cc[Gy] ≤ 35 V36Gy[%] ≤ 5 V32Gy[%] ≤ 10 V20Gy[%] ≤ 50
Colon_sigmoid Colon	1	D0.1cc[Gy] ≤ 30 D1cc[Gy] ≤ 28
Femur_head	3	V22Gy[%] ≤ 5 V22Gy[cc] ≤ 10
Skin	3	D0.1cc[Gy] ≤ 20
Urethra	3	D0.5cc[Gy] ≤ 40

mutation negative, variant of uncertain significance in *JAK2*). MRI pelvis revealed 6.3 × 6.5 × 9.2 cm anterior vaginal mass eroding into the posterior bladder (Fig 3A and 3B). Staging PET/CT showed disease in the vagina, retroperitoneal and pelvic nodes, and lungs, and a caudate liver lesion (Fig 3C).

She was initiated on 200 mg flat-dose pembrolizumab every 3 weeks and referred for palliative RT after no significant improvement in her symptoms and worsening of the vaginal lesion after cycle 3. The patient underwent CT and MRI-simulation supine, frog-legged, in a Vac-Lok bag (Civco). Scans were performed with full bladder and empty rectum with magnesium citrate bowel preparation the night before. The GTV was delineated on fused MRI. The entire vaginal length was contoured as CTV and 0.3 cm expansion to make the PTV. The PTV was treated to 30 Gy in 5 fractions using 2 coplanar arcs respecting constraints indicated herein (Table 1). A hotspot of 114% was allowed but was placed in the GTV. Daily setup included full bladder and empty rectum with the same protocol used earlier for patient 1. Verification consisted of orthogonal pair alignment to bone and CBCT shift to match on the GTV. The patient continued on pembrolizumab during SBRT.

By fraction 3, the patient noticed significantly decreased odor and bleeding. Two weeks posttreatment, her symptoms included grade 1 dermatitis in the medial thighs and groin and grade 1 diarrhea, which self-resolved. Six weeks posttreatment, restaging PET/CT showed complete metabolic response to all locoregional and distant sites of disease (Fig 4), indicating complete response locally and possible abscopal effect for distant disease. Local response was confirmed by pelvic examination. At 25 months after completion of RT and 29 months since diagnosis, the patient remains without evidence of disease on physical examination and PET/CT scan, and she continues on maintenance flat dose pembrolizumab. The patient has long-term grade 1 vaginal dryness attributable to radiation.

Discussion

We present 2 cases of vaginal melanoma managed with multimodality IO and SBRT with or without surgical debulking. Both patients are alive and recurrence free after RT. The second patient demonstrated a possible abscopal effect where all distant disease regressed after treating the index vaginal lesion even as the patient was progressing on initial immunotherapy. Both women recovered from acute toxicities including grade 1 to 2 dermatitis. Of note, the potential for increased skin toxicity when combining RT and IO for vulvovaginal melanoma has been previously reported.[21]

Multimodality management for VM remains key given that 80% to 90% of VMs recur with variable patterns of failure depending on up-front management.[8,9,22] With resection alone, locoregional and distant failures occurred in 45% and 55% of patients, respectively, whereas the addition of adjuvant RT was found to have 7% locoregional and 73% distant failures.[8] Effective therapies for recurrence are lacking, and evolving efforts focus on improving neoadjuvant and adjuvant therapies.

Traditional cytotoxic chemotherapies play a limited role in melanoma treatment.[12] BRAF mutations are generally less often found in mucosal melanomas compared with cutaneous melanomas. Conversely, KIT mutations are generally more frequent. Neither of the previous patients harbored these mutations, and subsequently they were not candidates for targeted BRAF- or KIT-inhibitors.[23] Immunotherapy improves overall survival in cutaneous metastatic melanoma.[24] Pooled analyses demonstrate durable responses of MM to pembrolizumab, ipilimumab, and nivolumab, though lower efficacy in mucosal compared with cutaneous melanomas.[19,25] These pooled analyses do not break down MM by primary site, but several prospective single-center series demonstrate FGT mucosal melanoma response rates of 20% to 28.5% with IO.[20,26] Recent results are encouraging with combination IO and RT for these patients.[14,27]

Exact mechanisms of interaction between IO and RT are incompletely characterized, though responses are attributed to potential synergistic immune modulation.[28,29] Melanoma is relatively radioresistant with high intrinsic repair capacity at lower RT doses.[30-32] With a low α/β ratio, hypofractionation with dose-escalation offers a theoretical advantage and improved local control of metastatic melanoma compared with conventional fractionation.[33] Enhanced immunogenicity of SBRT is likely multifactorial,

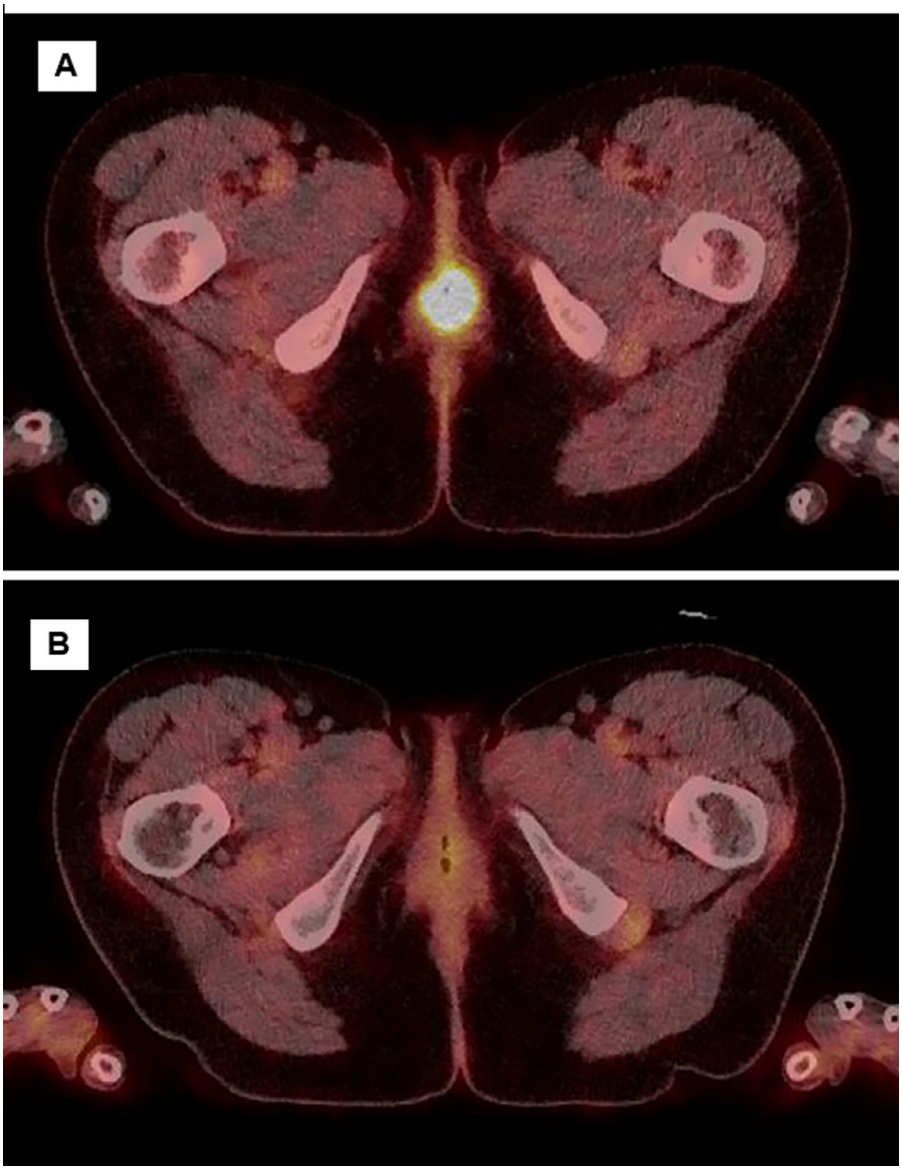

Fig. 2 Case 1: PET/CT before (A) and 3 months post-RT (B) showing complete radiographic response.
Abbreviations: PET/CT = positron emission tomography/computed tomography; RT = radiation therapy.

including cytoreductive effects in combination with release of tumor-associated antigens and modulation of the host immune system and tumor microenvironment.[27,34-37]

When considering focal RT, heterogeneity exists in RT regimens with variable target and nodal coverage, sequencing, external beam versus brachytherapy, treatment technique, dosing, fractionation, and image guidance.[9,13,14,38] In the series by Schiavone et al, both neoadjuvant SBRT and conventionally fractionated RT were used.[14] McGuire et al reported complete local remission following salvage external beam and interstitial brachytherapy boost.[38] In addition to conventionally fractionated approaches, when considering elective coverage of pelvic or inguinal lymph nodes, we note the safety and precedence for hypofractionated RT in the setting of short-course neoadjuvant RT for rectal cancer.[39] The incidence of occult nodal involvement is not well known, and risks of pelvic or inguinal coverage should be considered in the context of potential benefit.

Technical considerations for SBRT in both cases include the coregistration of pelvic MRI simulation with contrast both preimmunotherapy and postimmunotherapy to delineate initial and residual disease extent. Given the high conformality of SBRT in combination with volumetric and maximum dose constraints of the bladder and rectum (Table 1), both patients were treated with full bladders and empty rectums (similar to prostate SBRT). Based on our experience, a daily empty rectum was the most critical variable to overcome. CTV included the entire length of the residual vagina, given the multifocal

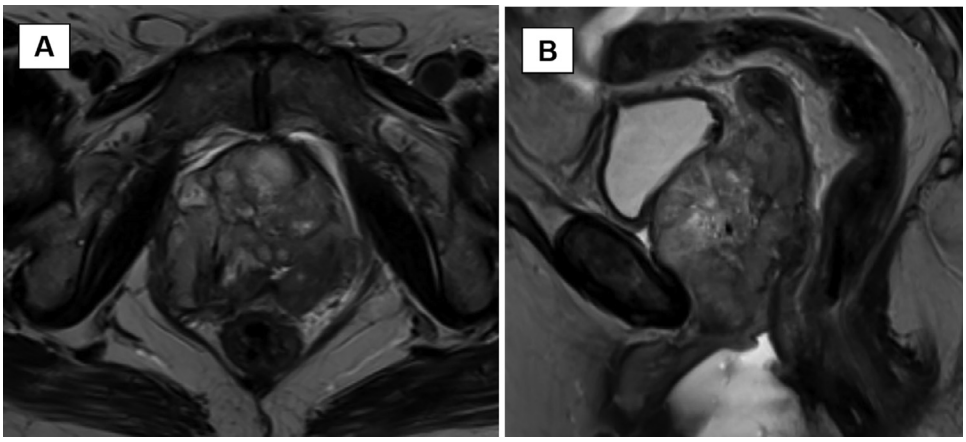

Fig. 3 Case 2: Initial diagnostic scans. (A) axial T2-weighted MRI, (B) sagittal T2-weighted MRI, and (C) fused axial PET/CT.
Abbreviations: MRI = magnetic resonance imaging; PET/CT = positron emission tomography/computed tomography.

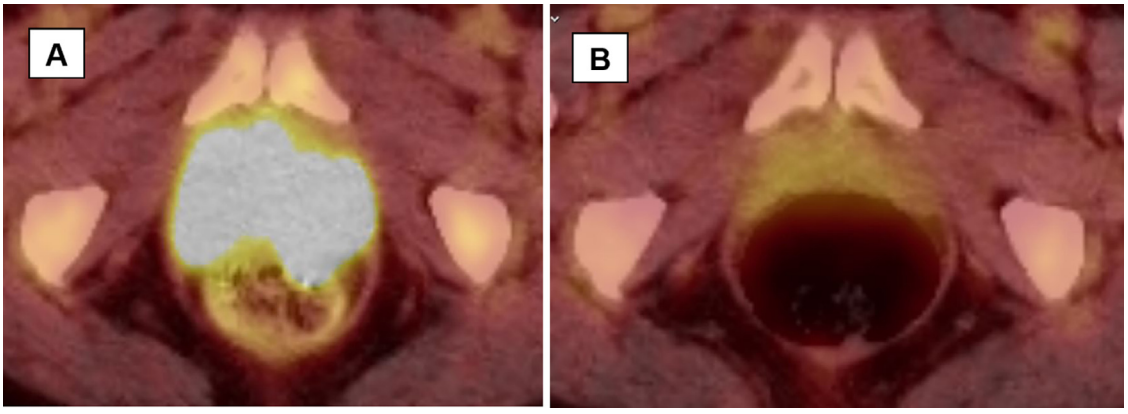

Fig. 4 Case 2: Follow-up axial fused PET/CT before (A) and after (B) irradiation demonstrating complete response in vaginal disease post SBRT. Air is noted in rectum in posttreatment scan.
Abbreviations: PET/CT = positron emission tomography/computed tomography; SBRT = stereotactic body radiation therapy.

nature of disease and that even higher doses subject the distal vagina to toxicity. A PTV margin of 3 mm was used with alpha cradle or Vac-Lok and with daily CBCT.

Considering the rarity of vaginal melanomas, their poor outcomes, and limited evidence with treatment variability, we encourage multidisciplinary management discussions. The incorporation of IO, surgery, and ultrahypofractionated RT appears safe and effective in this case report. Further high-quality prospectively collected evidence is needed to guide recommendations for optimal RT approaches, particularly when combined with IO.

Conclusions

Stereotactic body radiation therapy with concurrent immunotherapy with or without surgical debulking was a safe and effective treatment option for local therapy for vaginal melanoma while on systemic therapy. In this rare disease entity, multidisciplinary discussions should consider this approach in select patients with good performance status and localized disease. Patients with vaginal melanoma should also be encouraged to enroll on clinical trials.

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