

Near complete remission of a locally advanced giant melanoma of the vulva following hypo-fractionated radiotherapy and immune checkpoint inhibitors: A case report

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Abstract. Melanoma is known to be insensitive to radiotherapy; however, the present study reports the case of a patient with vulvar malignant melanoma in which near complete remission of the target area was observed after implementing immune checkpoint inhibitors (ICIs) and hypo-fractionated radiotherapy (HFRT). The patient was treated with an intensity-modulated radiation therapy technique that delivered a hypo-fractionated dose of 3,000 cGy in six fractions. After 3 days, the patient underwent immunotherapy with two cycles of 240 mg triprizumab every 2 weeks. Tumors that underwent radiotherapy had markedly decreased in size and a near complete remission of the melanoma was observed 4 months after radiotherapy. However, the metastases in the liver and lungs continued to grow, new metastases appeared in the abdominal subcutaneous tissue and enlarged lymph nodes were observed in the pelvic area. The results of the present study indicated that ICIs and HFRT exert a marked local effect, but no abscopal effect.

Introduction

Vulvar malignant melanoma (VMM) often arises from the malignant transformation of a vulvar pigmented nevus and augurs a poor prognosis (1). VMM is characterized by the presence of a vulvar mass that may be accompanied by persistent itching, pain, tenderness, ulcers and bleeding, and the melanoma may spread directly, through local lymph nodes or give rise to distant metastases via the bloodstream. The most commonly affected primary sites are the labia minora, clitoris and perineum, and most lesions are hyperpigmented (2-4). In

fact, melanosis plays an important role in melanoma progression, as it can attenuate the efficacy of radiation, chemotherapy and immunotherapy (5).

VMM is a rare gynecological malignancy that has been understudied due to its extremely low incidence and lack of clear high-risk factors. Surgery, including both wide local excision and radical surgery, is the primary treatment method for VMM (6,7). However, due to the location of the lesions, it is occasionally difficult to meet the negative margin distance for resection. Radiotherapy is only recommended for patients with advanced inoperable disease or for patients with recurrence of metastasis after surgery. However, melanoma is generally considered to be insensitive to radiotherapy and disease remission rates are higher than expected (8). Strategies under investigation to improve response rates include simultaneous immune checkpoint inhibitor (ICI) therapy. ICIs are effective in the treatment of metastatic vulvar and vaginal melanomas (1). Preclinical studies have shown that the combination of radiotherapy with ICIs is more effective than either treatment modality alone (9-13). In addition, targeted therapy continues to be important for patients with advanced or metastatic tumors with well-defined target mutations (13). For example, encorafenib in combination with binimetinib is considered to be the first-line treatment for unresectable or advanced VMM with BRAF V600E/K mutations.

In the present study, a case of advanced giant VMM is reported for which treatment included hypo-fractionated radiotherapy (HFRT) combined with ICIs. The patient was evaluated for 4 months after HFRT and a near complete remission (CR; CR is defined by 100% resolution of the lesion) of the melanoma in the radiotherapy target area was observed. This result is contrary to the general notion that melanoma is insensitive to radiotherapy, so the feasibility of combining ICIs with HFRT is also briefly discussed.

Case report

Patient. A 77-year-old woman presented to the Department of Oncology, Affiliated Hospital of Southwest Medical University (Luzhou, China) with discomfort in the vaginal opening, recurrent bloody discharge and vulvar masses in September 2019. Pathology confirmed the vulvar mass were a malignant

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melanoma with hyperpigmentation, which did not carry BRAF mutations. The immunohistochemical profile was HMB45⁺, Melan-A⁺, S-100⁺, Ki-67⁺ (30%) and p53⁺ (90%) (Fig. 1). The patient did not undergo treatment for financial reasons and the vulvar mass enlarged, with the patient also experiencing vulvar ulceration, vaginal bleeding and paroxysmal pain in the lower abdomen. The melanoma was staged as T4N0Mx using the American Joint Committee on Cancer Melanoma Tumor-Node-Metastasis Staging System (8th Edition) (14) and could not be treated surgically.

In August 2020, the patient was prescribed four cycles of triprizumab (240 mg on day 1), dacarbazine (300 mg on days 1-5) and vincristine (2 mg on day 1) (Fig. 2). In November 2020, the patient received 3,000 cGy (at six fractions over 12 days, every other day) of radiation therapy to the perineal tumors and the left inguinal lymph nodes (Fig. 3), and was also treated with intensity-modulated radiation therapy (IMRT). The primary tumor of the vulva corresponded to the gross target volume (GTV), and the left inguinal lymph nodes were referred to by the GTV of the nodes; the maximal dose (Dmax) delivered was 3,000 cGy, with target coverage of 95%. Regarding the organs at risk, the Dmax deliveries were 393 cGy to the right femur, 1,264 cGy to the left femur, 3,389 cGy to the pelvis, 3,396 cGy to the bladder and 3,242 cGy to the rectum. After 3 days, two cycles of triprizumab (240 mg, administered every 2 weeks) were prescribed. In December 2020, the patient was prescribed three cycles of triprizumab (240 mg on day 1), paclitaxel (210 mg on day 1) and nedaplatin (90 mg on day 1).

After four cycles of triprizumab, dacarbazine and vincristine, the CT scan showed that the perineal mass (63 mm in diameter) (Fig. 4) and the left inguinal lymph node (34 mm in diameter) were enlarged, with irregular soft tissue density shadowing. Multiple solid nodules of different sizes were also noted in both the lungs and in the liver (the diameter range is provided in Table I). The disease was evaluated as progressive disease (PD; as defined by a target lesion with a maximal diameter that increased at least $\geq 20\%$, or new lesions).

After HFRT and two cycles of triprizumab, a reduction in the size of the masses (among them, the perineal tumor was ~ 58 mm, while the inguinal lymph node tumor was ~ 26 mm) was noted, and the disease was evaluated as stable disease (where the target lesion reduction did not reach a partial response or its increase did not reach PD). The absolute lymphocyte count (ALC) was markedly elevated after HFRT and ICIs (Fig. 5) and the patient experienced severe gastrointestinal adverse reactions.

After 4 months of HFRT, a CT scan revealed that the tumors that had received HFRT experienced marked shrinkage (the perineal tumor was ~ 12 mm, while the inguinal lymph node tumor was ~ 4 mm), which was evaluated as near CR (Fig. 6). However, the metastases in the liver and lungs continued to grow, new metastases appeared in the abdominal subcutaneous tissues and enlarged lymph nodes were observed in the pelvic area; therefore, overall disease state was evaluated as PD. The patient then received palliative care and died from liver failure after 1 month.

Pathological methods

Hematoxylin and eosin staining. The tissues were fixed in 10% formalin at 37°C for 1-2 h and sectioned to 3-4 mm.

The tissues were then stained with hematoxylin at 37°C for 8-15 min and with eosin at 37°C for 2-5 min. The tissues were observed with a light microscope at x100 magnification.

Immunohistochemistry. Tissues were embedded in paraffin and fixed in 10% formalin at 37°C for 1-2 h, before sectioning to 3-4 mm. Methanol hydrogen peroxide (3%) was used as the blocking reagent at 37°C for 10 min. The following primary antibodies were used at 37°C for 60 min: HMB45 (1:1,000; cat. no. ZM-0187), MelanA (1:1,000; cat. no. ZM-0398), S-100 (1:1,000; cat. no. ZM-0224), Ki-67 (1:1,000; cat. no. ZM-0166), p53 (1:1,000; cat. no. ZM-0408) (all OriGene Technologies, Inc.). Goat anti-mouse IgG polymer III (1:200; cat. no. 220426S935c; Fuzhou Maixin Biotech. Co., Ltd.) was used as the secondary antibody at 37°C for 30 min. The results were observed using a light microscope at x200 magnification.

Discussion

Radiotherapy is able to control local lesions, and the recommended modality for VMM is IMRT (15). The conventional fractionation schedule is 1.8-2.0 Gy/session, five times/week, with a clinical target volume (CTV) of 45-50 Gy/25 sessions in the area of the vulvar lesions and a local push volume of 60-70 Gy to the primary visible lesions and metastatic lymph nodes (16). Due to issues such as the lubrication of the vulva, the poor tolerance of skin mucosa to radiation, a large vulvar tumor and metastases to the lymph nodes, it is difficult to achieve a satisfactory dose distribution for radiotherapy. As the aforementioned factors make it difficult for vulvar cancer to receive the appropriate radiation dose, the effect of simple radiotherapy for vulvar cancer is poor and the local recurrence rate is high (8).

The treatment landscape for advanced and metastatic melanoma has changed markedly with the introduction of ICIs. Trials with programmed cell death protein 1 (PD-1) inhibitors have shown significantly improved response rate (28.5%) in patients with un-resectable or metastatic melanoma (4,17). The principal function of these inhibitors is to block the interaction between immune cells and tumor cells that express immune checkpoint proteins, thus hampering the inhibitory effect of tumor cells on immune cell function. ALCs and absolute eosinophil counts are important biomarkers for melanoma treatment that encompasses ICIs (13,18). Despite promising outcomes in a phase III clinical trial, a complete response is infrequent, and most patients who respond eventually exhibit progression (18). Thus, outcomes still can be improved in these patients.

Previous studies demonstrated that tumor size was significantly correlated with the efficacy of immunotherapy (i.e., smaller tumor loads correlated with higher immunotherapy efficacy) (19,20), and that HFRT reduced tumor loads and exhibited specific immunogenicity (21,22). Thus, the combination of HFRT and ICIs to enhance the radiotherapy-induced antitumor T-cell response comprises a viable modality. This approach has been applied to numerous tumor types with satisfactory results, particularly lung cancer (23-25). Shaverdian *et al* (23) reported that patients with advanced lung cancer who had undergone radiotherapy prior to immunotherapy manifested longer progression-free survival (4.4 vs. 2.1 months) and overall survival (10.7 vs.

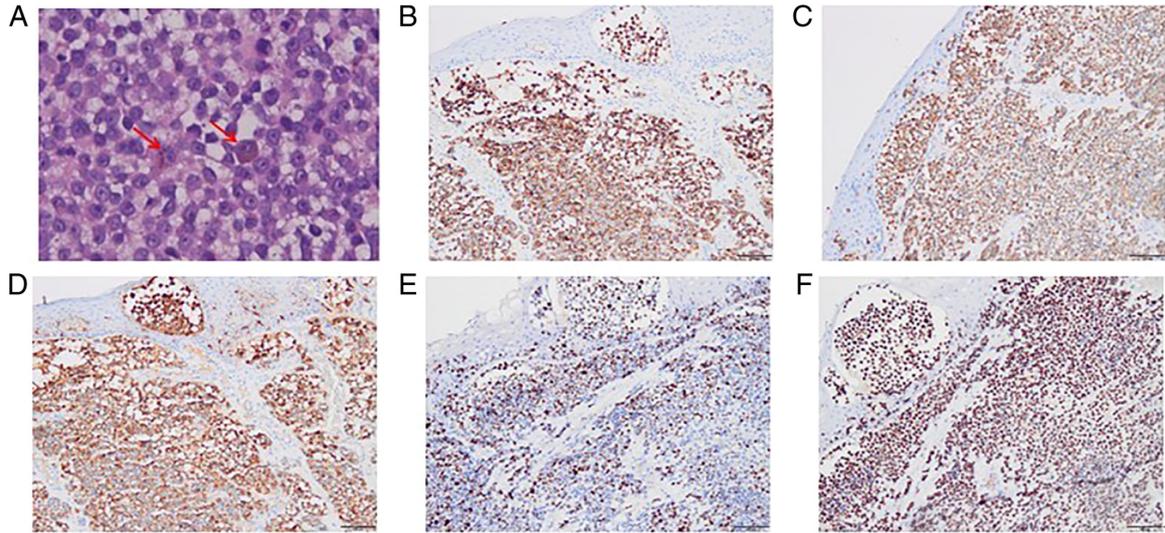


Figure 1. Histopathology and immunohistochemistry. (A) Pathology (magnification x200; hematoxylin and eosin staining) shows pigmentation in the cytoplasm of melanoma cells (indicated by red arrows). (B-F) Immunohistochemistry (magnification x100) was performed by immunoenzymatic cytochemistry and showed positive results for tumor markers (B) HMB45, (C) Melan-A, (D) S-100, (E) Ki-67 (30%) and (F) p53 (90%).

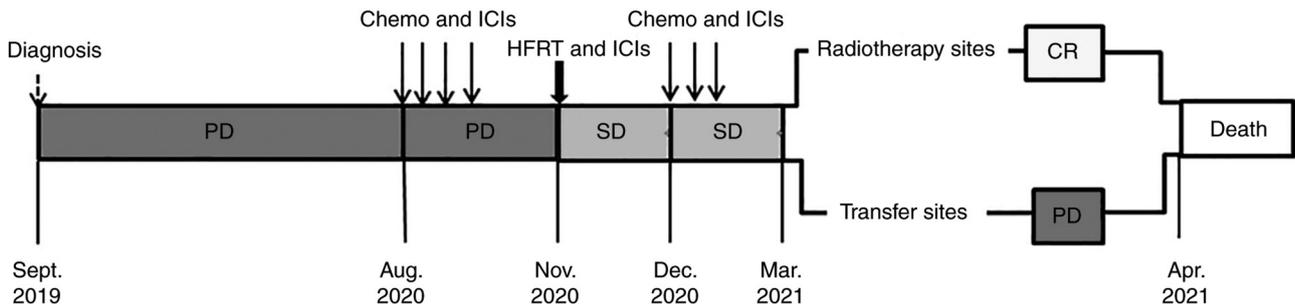


Figure 2. Clinical timeline. PD, progressive disease; SD, stable disease; CR, complete remission; HFRT, hypo-fractionated radiotherapy; ICIs, immune checkpoint inhibitors.

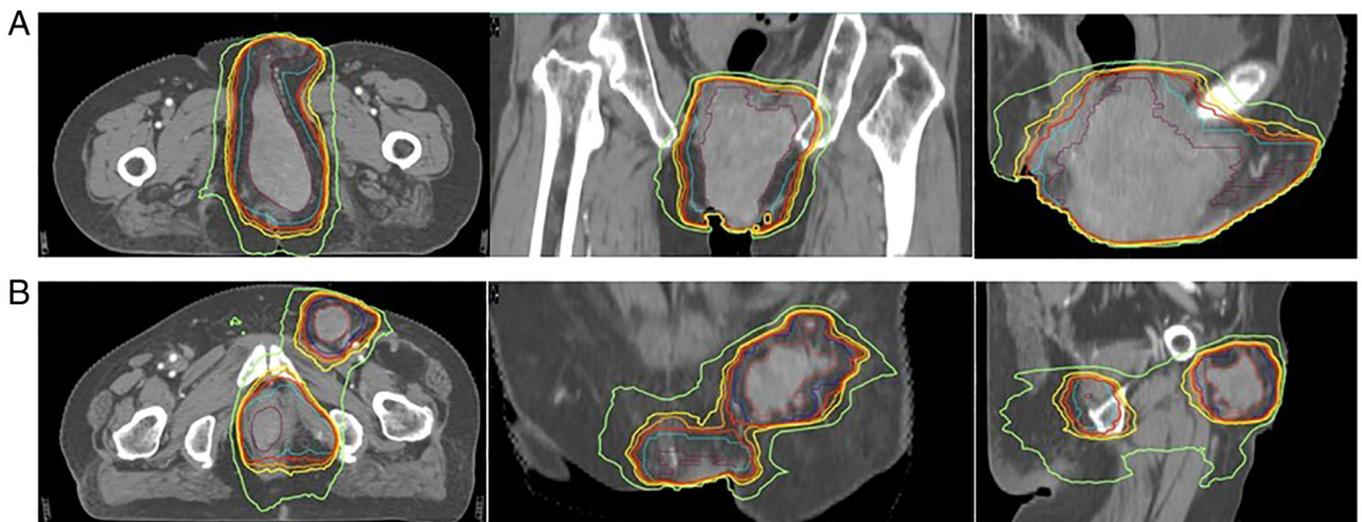


Figure 3. CT simulation images for radiotherapy planning. (A) The target volume encompassing the perineal tumor and (B) the inguinal lymph nodes. The isodose lines represent total doses of 3,000 cGy (red), 2,850 cGy (orange), 2,700 cGy (yellow) and 2,100 cGy (green).

5.3 months) times. A study by Theelen *et al* (24) on non-small cell lung cancer revealed that the 1-year survival rate from

immunotherapy combined with radiotherapy increased from 18 to 36% compared with the immunotherapy-only group.

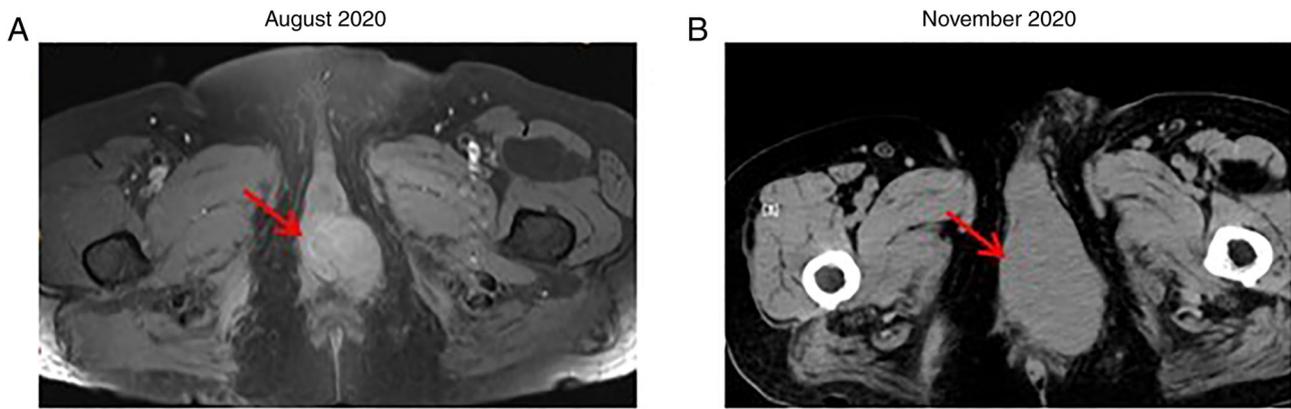


Figure 4. CT images of perineal tumors. (A) CT scan of the perineal melanoma before treatment and (B) after 3 months of chemotherapy combined with immune checkpoint inhibitor treatment. Perineal melanoma (indicated by red arrows) was significantly enlarged according to the Response Evaluation Criteria in Solid Tumors and evaluated as disease progression.

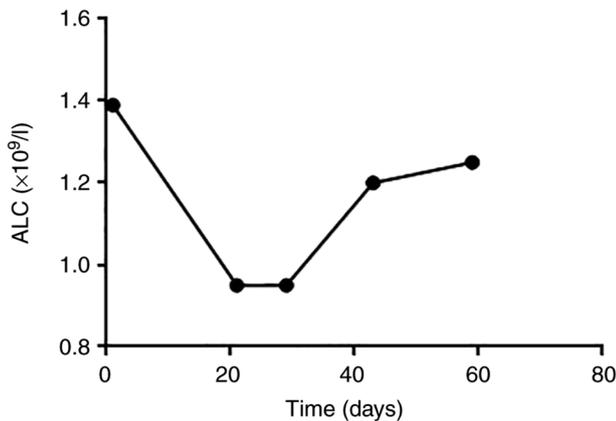


Figure 5. Change in the ALC before and after HFRT combined with ICIs. HFRT was prescribed from days 15 to 26, and ICIs were prescribed on days 30 and 45. ALC, absolute lymphocyte count; HFRT, hypo-fractionated radiotherapy; ICI, immune checkpoint inhibitor.

However, compared with other tumor types, melanoma is not sensitive to radiotherapy, so the same radiotherapy and immunotherapy combination may have different therapeutic effects.

In previous years, there have been some reports on the combination of radiotherapy and immunotherapy in melanoma, but the segmentation modes and doses have been different. A consensus on the use of combined therapy has not yet been formed (26-30). A retrospective study showed higher response rates (33% compared with 23%) in patients with immune concurrent radiotherapy compared with immunotherapy alone (29). Ahmed *et al* (30) showed that stereotactic radiotherapy combined with PD-1 may have a synergistic effect on brain metastatic melanoma. Compared with non-reproductive melanomas, vulvar and vaginal melanomas have unique features in terms of their molecular biology and type of gene mutation, so the prognosis is very different.

There are few reports concerning this combination therapy for vaginal melanoma. Parisi *et al* (31) reported that a patient with vaginal melanoma achieved CR after HFRT combined with ICIs. Schonewolf *et al* (32) presented two cases of vaginal

melanoma, where both patients achieved CR. The patients were treated at different comprehensive cancer centers using a multimodality approach of immunotherapy and stereotactic body radiation therapy, with or without surgical therapy. However, there have been no reports on combination therapy for vulvar melanoma treatment.

Based on the aforementioned theoretical basis and the present research results, we propose to improve treatment efficacy for advanced melanoma through use of local radiotherapy in combination with ICIs. In the present case, the patient received chemotherapy combined with ICIs, but the results revealed that the combined therapy did not achieve satisfactory results. The patient did not consent to gross pathology images being captured of the results at this point. The patient then received HFRT combined with ICIs, and the results showed that the perineal tumor and inguinal lymph node tumors that underwent HFRT shrank significantly, almost reaching CR, and indicating that this combination exerted a marked local effect. As aforementioned, melanoma is insensitive to radiotherapy, with an α/β value of only 0.6 (8). According to the present segmentation method, the 2 Gy fractionated radiation equivalent dose was ~ 64 Gy, which was not enough to allow the melanoma mass to regress. Therefore, the patient reached near CR of the perineal and left inguinal lymph node tumors. This may be since HFRT caused presumed antigen release and stimulated the ICIs to exert better efficacy, in contrast to follow-up chemotherapy and ICIs. After treatment with HFRT and ICIs, there was an increase in ALC, one biomarker that is associated with improved survival rates in patients with ICI-treated melanoma. This indicated that HFRT modulated the efficacy of ICIs, as was also shown in previous studies (9-12).

In contrast to the perineal and inguinal lymph node tumors, the metastases of the liver and lungs increased, the lymph nodes in the pelvic area enlarged and new metastases appeared in the abdominal subcutaneous tissue. These observations indicated the absence of an abscopal effect, which may have been due to the heterogeneity of the tumor and the tumor microenvironment. Thus, the release of neoantigens and effector T cells produced by radiotherapeutic

Table I. Change in size of the perineal tumor, inguinal lymph node tumor, and liver and lungs metastases before and after treatment.

Clinical stage	Perineal tumor, mm	Inguinal lymph node tumor, mm	Liver		Lungs	
			Diameter range, mm	Severity of metastases	Diameter range, mm	Severity of metastases
At diagnosis	31	10	/	/	/	/
Before chemotherapy and ICIs	55	29	8-15	+	3-4	+
After chemotherapy and ICIs (before HFRT and ICIs)	63	34	6-24	+++	3-8	+++
After HFRT and ICIs	58	26	4-27	++++	1-14	++++
After 4 months of HFRT and ICIs	12	4	1-31	+++++	1-17	+++++

+ indicates the severity of liver/lung metastases, with more symbols indicating more serious liver/lung metastasis. ICIs, immune checkpoint inhibitors; HFRT, hypo-fractionated radiotherapy.

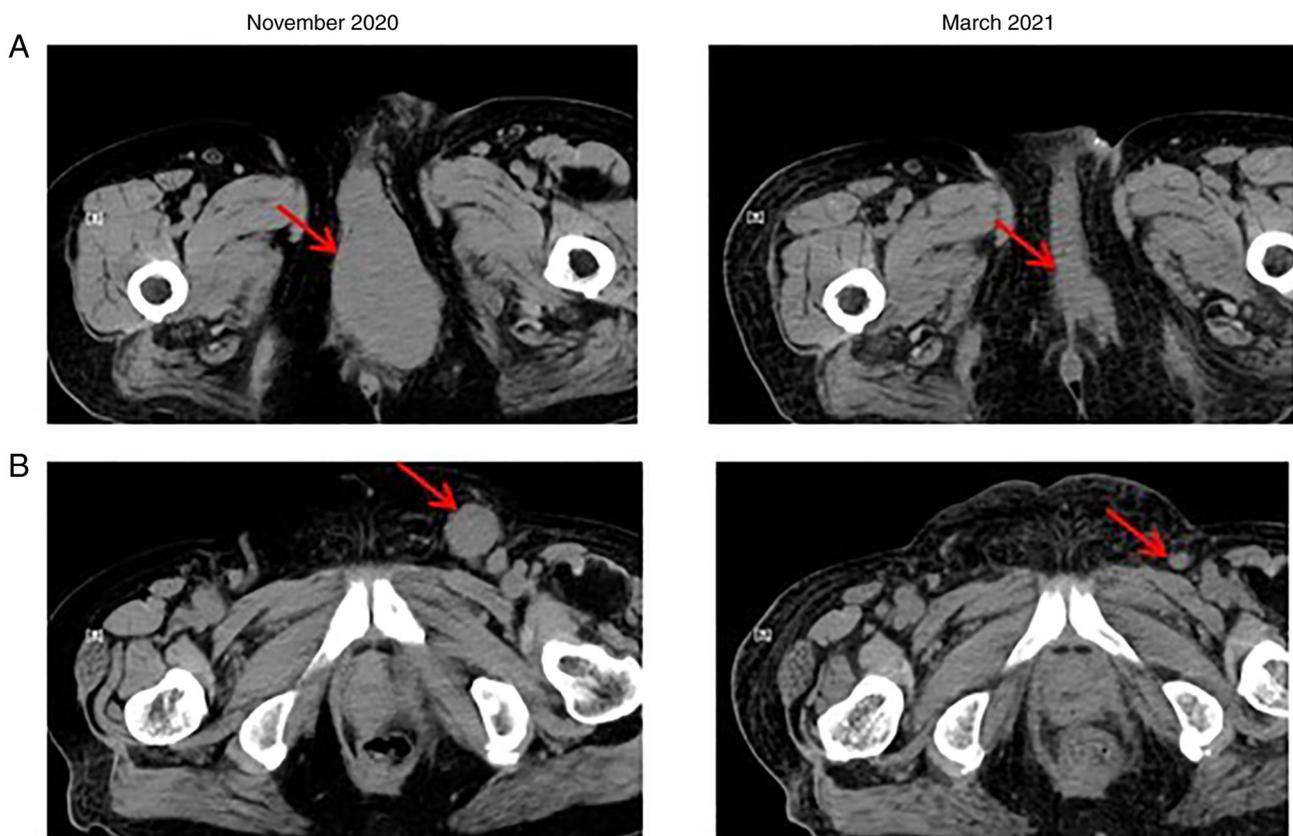


Figure 6. CT images of perineal tumors and inguinal lymph nodes. (A) CT scans of perineal melanoma (indicated by red arrows) and (B) inguinal lymph nodes (indicated by red arrows) before treatment and 4 months after hypo-fractionated radiotherapy combined with immune checkpoint inhibitor treatment. Perineal melanoma and inguinal lymph nodes were markedly reduced in size and nearly achieved complete remission according to Response Evaluation Criteria in Solid Tumors.

application to a single lesion does not appear sufficient to produce effects on all metastases, and it is questionable as to whether it is possible to stimulate the abscopal effect by combining other treatments with HFRT and ICIs. It is clear that additional studies need to be conducted to confirm this. In addition, the present patient was initially diagnosed with vulvar melanoma and had no melanoma elsewhere. Whether

there is a difference in the efficacy of HFRT combined with ICIs in melanomas of different organs/areas also requires further study.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SC made substantial contributions to the acquisition and analysis of data, and drafted the manuscript. CX and QD contributed to implementing the treatment and the collection of case information. XD made substantial contributions to the acquisition and analysis of data, and revised the study critically for important intellectual content. HY made substantial contributions to conception and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SC and HY confirm the authenticity of all the raw data. All authors have all read and approved the final manuscript, and agree with its submission.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient's husband for publication of this manuscript and all accompanying images after the patient had succumbed to the disease.

Competing interests

The authors declare that they have no competing interests.

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