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Teaching Case

Complete and Durable Response After Radiation Therapy to Primary Tumor Site of a Patient With Metastatic Anorectal Mucosal Melanoma With Oligoprogression on Nivolumab

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Introduction

Mucosal melanoma is a rare subtype of melanoma, accounting for 1.4% of melanoma diagnoses in the United States.[1] Median overall survival from time of diagnosis for mucosal melanoma has historically been less than that of cutaneous melanoma in part owing to the frequency of occult presentation and the relative lack of evidence-based guidelines specific to mucosal histology.[2] Radiation therapy (RT) in mucosal melanoma has shown promise in certain settings but indications remain poorly defined.[3,4] Immune checkpoint inhibitors have shown excellent response rates in metastatic melanoma and are increasingly used for mucosal melanoma; however, most patients will eventually progress. Response patterns are highly variable among patients who respond to immunotherapy. Although a small group of patients will experience complete response, many patients will have other types of responses such as pseudoprogression (disease enlargement followed by shrinking) or oligoprogression (progression at a limited number of sites).[5-7] Patients with oligoprogression after treatment are of particular interest owing to the possibility of controlling the progressive disease with local therapy and achieving long-term survival. This concept has been demonstrated in retrospective studies of patients with melanoma; however, there have been no studies demonstrating this for patients with mucosal melanoma.[5,8]

Herein, we report a case of a 67-year-old woman with metastatic anorectal mucosal melanoma with primary site oligoprogression on nivolumab who was treated with RT to the primary site, which induced a complete, durable, and ongoing response of almost 3 years.

Case Presentation

The patient was a 67-year-old woman who initially presented with complaints of difficulty emptying her bowels. A colonoscopy revealed a tumor in her rectum, located 1.0 cm from the anal verge. A biopsy was consistent with primary melanoma of the anus, BRAF wild-type. Further staging workup included a computed tomography (CT) of the chest, abdomen, and pelvis with intravenous contrast (Fig 1), followed by a positron emission tomography (PET)/CT scan 1 week later (Fig 2). The primary lesion was noted to be 2.3 × 2.3 cm with a standardized uptake value (SUV) of 11.1 and

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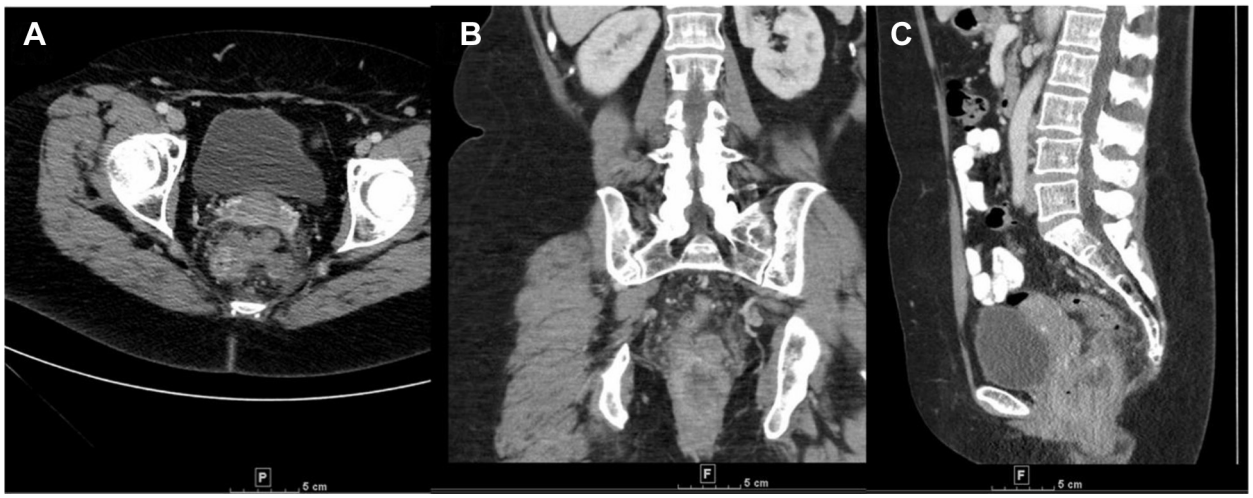

Figure 1 Initial staging computed tomography (CT) with contrast (A = axial, B = coronal, C = sagittal).

with marked thickening of the wall of the anorectum with extension to the anus. Two perirectal lymph nodes were noted (1.6 and 2.1 cm), in addition to 1 lymph node seen above the rectum just posterior to the sigmoid colon (1.5 × 1.0 cm). CT also revealed multiple low-density lesions in the liver: 1.1 cm and 1.0 cm in the right lobe (SUV 6.4) and 1.2 cm in the left lobe. A "left peri-rectal mass" was noted with an SUV of 12.8. An additional 1.2 cm presacral lymph node was noted with an SUV of 4.3. Hyperavidity was also noted in the right sacrum and right iliac bone (SUV 3.1). Biopsy of a liver lesion was performed and confirmed metastatic melanoma. Magnetic resonance imaging (MRI) of the head with intravenous contrast was negative for intracranial disease. Interval CT 4 weeks after initial imaging revealed an increase in the size of the primary to 2.5 cm, a bilobed perirectal mass 4.7 × 2.6 cm, and a new indeterminate 6-mm nodule in the right middle lobe of the lung.

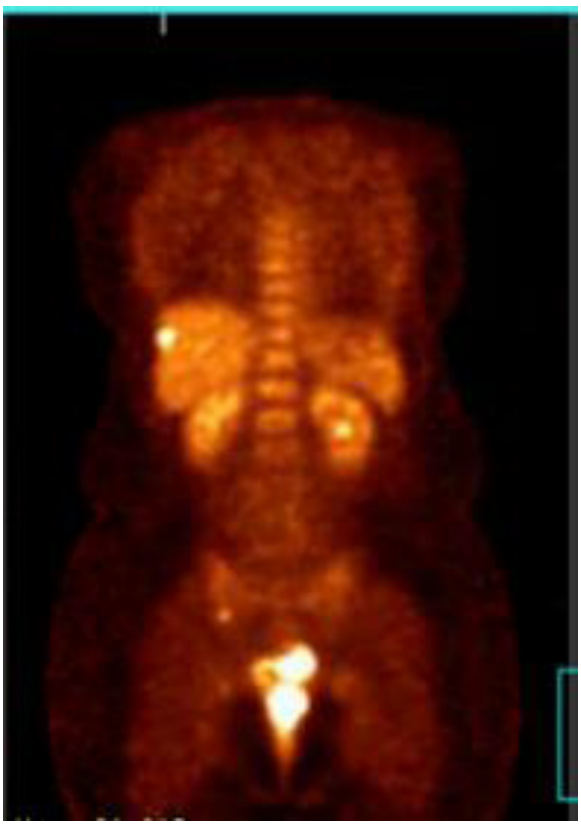

Figure 2 Initial staging positron emission tomography (PET)/computed tomography (CT).

Given her stage IV disease, she was started on combined ipilimumab and nivolumab on the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network EA6141 clinical trial; she was randomized to the control arm and did not receive sargramostim. After approximately 6 weeks of treatment, she developed mild hypophysitis and ipilimumab was discontinued and she was maintained on nivolumab alone every 2 weeks.

Ten weeks after starting treatment, interval restaging imaging was obtained with a CT of the chest, abdomen, and pelvis with intravenous contrast. The previously noted indeterminate right middle lobe nodule appeared to be nearly completely resolved. The liver metastases appeared significantly smaller. No new liver lesions were noted. The pelvic and presacral lymph nodes appeared much improved without any new adenopathy. The maximum thickness of the anorectal primary had decreased from 2.5 cm to 1.8 cm. Interval imaging 12 weeks later continued to show stable findings of treatment response with a stable hypodensity in the left lobe of the liver, no lesions in the right lobe of the liver, stable pelvic lymph nodes, and the primary appearing similar in size compared with prior. The previously noted left perirectal mass was also smaller (1.1 × 0.9 cm, previously 1.3 × 1.0 cm).

Follow-up CT imaging at 8 months after treatment initiation suggested progression of disease at the primary site with distant disease control. The anorectal mass had enlarged from 1.8 × 2.5 cm to 2.2 × 3.3 cm. Multiple

pelvic lymph nodes appeared slightly larger. Enlarging left and right inguinal nodes measuring 1.2 cm were noted representing a change compared with prior studies. The right liver mass continued to be nondiscernable and the left liver lesion was stable in size. An MRI of the pelvis with intravenous contrast (Fig 3) was obtained that elaborated an infiltrative tumor. A T2 enhancing mass was seen in the anus and lower rectum with transmural extension, invasion of the levator ani muscle on the right laterally, and extension through the pelvic floor musculature anteriorly. Abnormal tissue tracking cephalad was noted on the left, consistent with the infiltrating tumor. Overall, the findings were interpreted as representing progression of disease at the anorectal primary and adjacent lymph nodes and the patient was taken off trial. She was continued on maintenance nivolumab and referred to radiation oncology for consideration of local therapy, given her worsening symptoms of constipation and occasional bleeding. Clinically, rectovaginal septum induration secondary to malignancy was also appreciated at this time.

It was decided to deliver consolidative RT without interruption of maintenance nivolumab. Nine months after starting initial immunotherapy, 45 Gy in 3 Gy per fraction was delivered using a 3-field 3D conformal technique to the diagnostic MRI and CT simulation-defined primary site gross tumor volume with a 2.0 cm circumferential margin and a 3.0 cm superior/inferior margin without regional coverage (Fig 4). This was felt to be a regimen that would achieve a near definitive effective dose while being safe for the anal canal, with hypofractionation enabling a shorter treatment time and assisting in overcoming resistant melanoma.

RT was tolerated without issue. Interval CT imaging 3 months later demonstrated significantly decreased thickness of the primary anorectal lesion measuring 1.3 cm compared with 2.3 cm previously; perirectal lymph nodes also appeared smaller in size. MRI imaging 5 months after RT demonstrated circumferential submucosal thickening involving the distal rectum and anus without enhancing lesion, thought to be consistent with postradiation change; no lymphadenopathy was seen (Fig 5). A linear enhancing band extending from the anterior aspect of the anus through the external sphincter to the lower vagina/vulvar area was visualized and thought to represent a fistulous tract. Clinically, the patient reported improvement in caliber of stools. Serial CT, MRI, and interval MRI 6, 11, and 19 months after RT, respectively, continued to show stable findings.

A PET/CT obtained 21 months after RT showed minimal residual uptake in the anal canal with no associated mass. An interval PET/CT 4 months later showed stable (SUV 4.6) uptake in the region of the anal canal with no associated mass. A third interval PET/CT was obtained after a subsequent 8 months (33 months after RT and 42 months after the start of initial treatment), showing no areas of hypermetabolism. The patient's nivolumab was discontinued. The patient has enjoyed excellent performance status and has been without symptom or complaint.

Discussion

This case shows complete and durable response of metastatic anorectal mucosal melanoma to RT after primary site progression on nivolumab. Although there was radiographic concern for fistula after radiation, the patient has done well clinically, has not required any intervention for it, and it has improved over time.

This is a case of "oligoprogression" and supports the hypothesis that prolonged survival may be possible with treatment of limited progressive sites, similar to the paradigm that has been demonstrated in a prospective study of oligometastatic disease.[8-11] The optimal management of

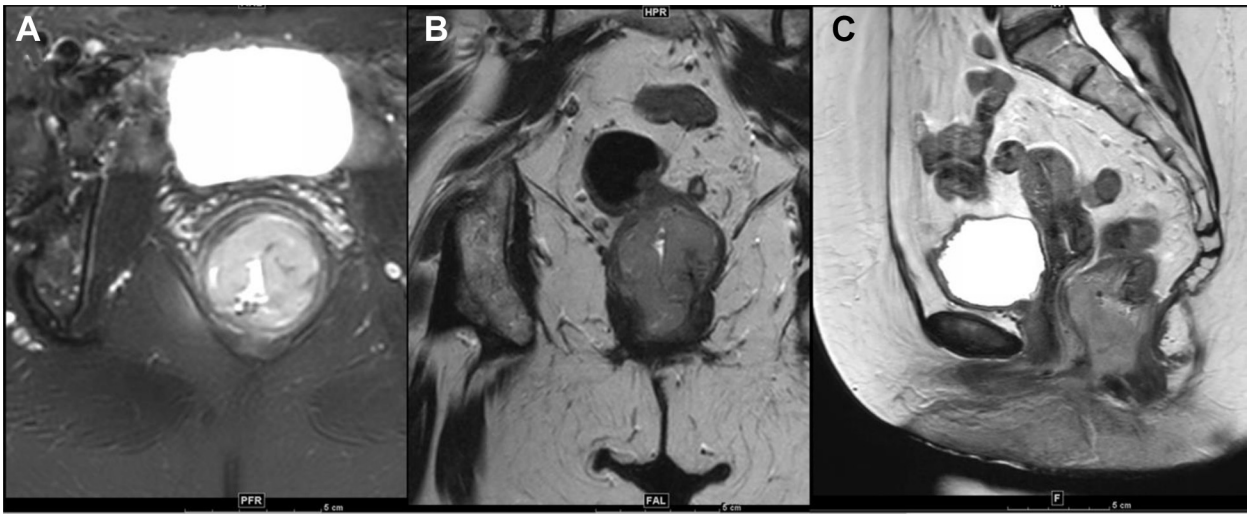

Figure 3 Preradiation therapy (RT) magnetic resonance imaging (MRI) with contrast (A = axial, B = coronal, C = sagittal).

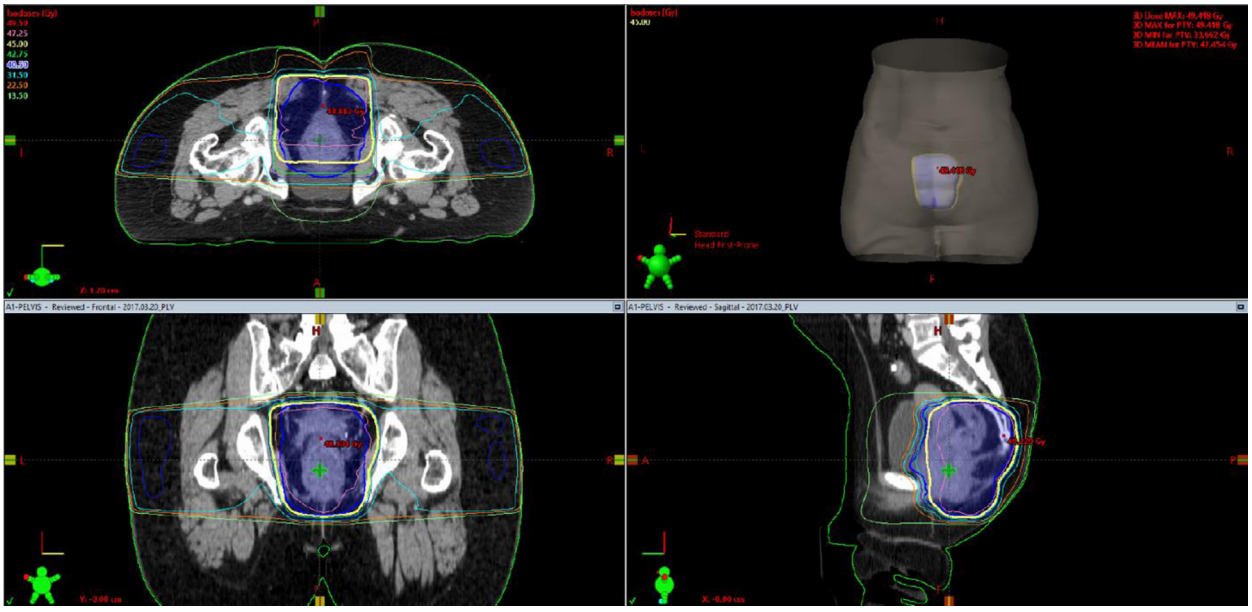

Figure 4 Radiation therapy treatment plan dose distributions (isodose curves).

oligoprogressive patients on immune checkpoint inhibitors remains poorly defined owing to the lack of prospective data. A PubMed search for the terms "oligoprogression" and "melanoma" yields only 2 results, both of which are retrospective and neither of which are specific to RT.[5,8] In the larger of the 2 retrospective studies, 52 patients met inclusion criteria of initial treatment with immune checkpoint inhibitor followed by progression at 1 to 3 sites. These patients were treated with a variety of local therapies. Three-year progression-free survival was 31%. Interestingly, improved progression-free survival was found in those with progression limited to previously established tumors.[8] Extrapolating these results to the presented case is difficult given the various other local therapy options included in their analysis such as ablation, surgery, and stereotactic body radiation therapy. This suggests that an optimal consolidative approach to oligoprogression may yet be elucidated, and our case highlights the potential of radiation immunotherapy combination in this situation. The excellent response of the patient in this case raises the possibility that RT may have advantages over other forms of local therapy when used in oligoprogressive patients receiving immune checkpoint inhibitors. One hypothesis for this synergy is the immunogenic effects of radiation, which include increased neoantigen expression, activation of the "cyclic GMP-AMP synthase/stimulator of interferon genes" pathway, and increased dendritic cell activation.[12] Given the strong biological rationale for the combination of radiation and immunotherapy[13] and the observation of such synergy in preclinical models,[14] treatment with both modalities is being investigated in numerous clinical trials (Table 1). Given that

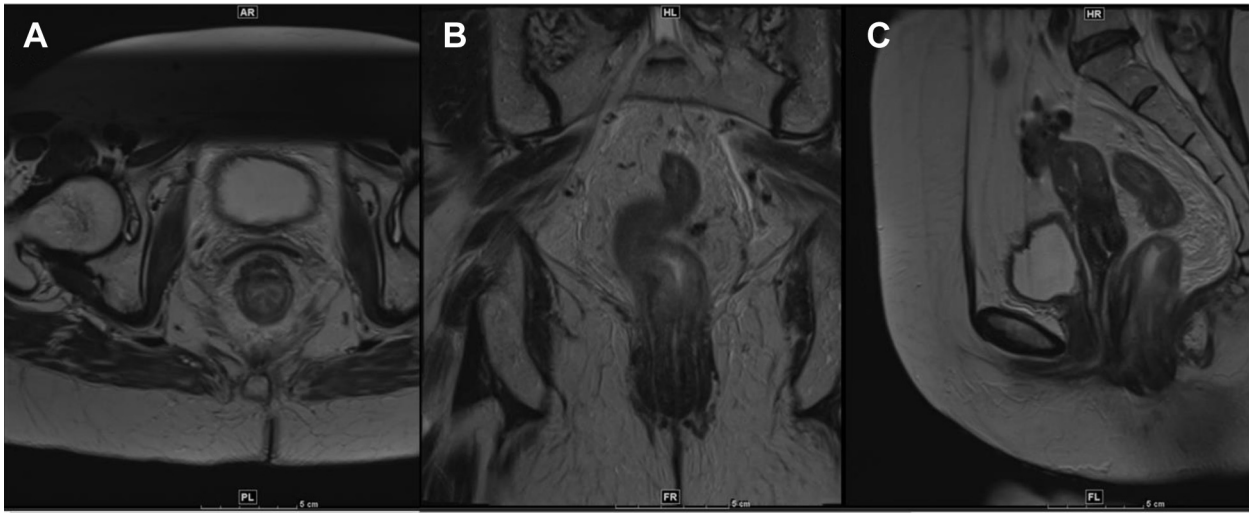

Figure 5 Five months post-radiation therapy (RT) magnetic resonance imaging (MRI) with contrast (A = axial, B = coronal, C = sagittal).

Table 1 Summary of relevant ongoing immunotherapy + melanoma clinical trials

NCT number	Title	Immunotherapy	Radiation	Phase	Estimated enrollment	Patient characteristics	Mucosal histology included	Primary outcome	Estimated start date	Estimated primary completion date	Estimated final completion date
NCT03758729	Phase II Study of Nivolumab in Combination With Radiation Therapy as Definitive Treatment for Patients With Locally Advanced, Unresectable Head and Neck Mucosal Melanoma	Nivolumab	2 Gy × 35	Single arm, phase II	26	Locally advanced, unresectable H&N mucosal melanoma	Yes, trial is specific for mucosal melanoma	Response rate (CR + PR)	September 1, 2019	March 2020	December 2020
NCT03646617	Ipilumumab and Nivolumab With or Without Hypofractionated Radiation Therapy in Patients With Metastatic Melanoma (RadVax)	Ipilumumab + nivolumab	8 Gy × 3 versus no radiation	Phase II	70	Metastatic melanoma, ECOG 0-1	Not specified	Safety	August 23, 2018	February 23, 2022	February 23, 2023
NCT04042506	SBRT as a Vaccination for Metastatic Melanoma	Nivolumab	8-10 Gy × 3	Single arm, phase II	15	Unresectable melanoma (any histology)	Yes	Safety	August 2019	March 2023	March 2028
NCT03340129	Anti-PD 1 Brain Collaboration + Radiation Therapy Extension (ABC-X Study)	Ipilumumab + nivolumab	SRS 16-22 Gy up-front versus salvage	Phase II	218	Cutaneous, acral, or mucosal melanoma with 1 or more brain metastases	Yes	Neurologic death	August 14, 2019	August 2022	August 2024
NCT04017897	The Combination of Anti-PD-1 With Radiation Therapy in Previously Untreated Metastatic Melanoma	Ipilumumab + nivolumab	Not specified	Phase II	52	Unresectable stage III - IV melanoma, ECOG <1, no prior systemic therapy	Yes	Overall response rate	July 3, 2019	July 2022	July 2022
NCT03850691	Radiation and Combination Immunotherapy for	Aldesleukin + nivolumab OR Aldesleukin +	Not specified	Phase II	44	At least 3 radiographically distinct lesions	No	Objective response rate, safety	May 28, 2019	December 2025	December 2025

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Table 1 (*continued*)

NCT number	Title	Immunotherapy	Radiation	Phase	Estimated enrollment	Patient characteristics	Mucosal histology included	Primary outcome	Estimated start date	Estimated primary completion date	Estimated final completion date
	Melanoma	ipilumumab + nivolumab				(>1.5 cm) previously refractory to standard immunotherapy					
NCT03354962	Induction of Immune-mediated aBscOpal Effect thrOugh STEreotactic Radiation Therapy in Metastatic Melanoma Patients Treated by PD-1 + CTLA-4 Inhibitors (BOOSTER MELANOMA)	Ipilumumab + nivolumab	SBRT versus no radiation	Phase I/II	120	Histologically proven unresectable stage III-IV melanoma. PD-L1 expression <1%	Yes	Dose limiting toxicities, abscopal effect	October 15, 2018	September 2022	March 2024

Abbreviations: CR = complete response; CTLA-4 = cytotoxic T-lymphocyte associated protein-4; ECOG = Eastern Cooperative Oncology Group; H&N = head and neck; OR = overall response; PD-1 = programmed cell death protein 1; PR = partial response; SBRT = stereotactic body radiation therapy; SRS = stereotactic radiosurgery.

our patient only had 1 oligoprogressive site, a nontarget site was not available at which an abscopal response to RT could be assessed. Observation of such an effect would have strengthened our ability to conclude RT-immunotherapy synergy was involved.[15]

It is notable that we achieved durable control given the mucosal histology in this case. Mucosal melanoma differs from cutaneous melanoma in presentation, diagnosis, and genetic profile.[16,17] Surgery with the potential to achieve negative margins is considered standard of care for these patients; however, this is often not feasible owing to anatomic location and the higher frequency of metastatic disease at presentation compared with cutaneous melanoma.[17,18] Other treatment options are similar to those available for cutaneous melanoma including radiation, chemotherapy, targeted small molecule inhibitors, and immunotherapy.[19] Notable differences in treatment involve the types of inhibitors available and the response to immunotherapy. Mucosal melanomas more frequently harbor KIT mutations as opposed to the BRAF mutations seen in cutaneous melanoma.[20,21] Retrospective studies have shown that the utilization of immunotherapy is increasing and it may provide superior results in mucosal melanoma compared with other treatment modalities, especially when combined with RT.[22,23] Response to immunotherapy, however, may also be lower for mucosal melanoma than for cutaneous melanoma, possibly owing to lower levels of tumor neoantigens.[24] A large retrospective study showed objective response rates to nivolumab of 23.3% and 40.9% for mucosal and cutaneous melanoma, respectively.[25] Given the decreased immunogenicity of mucosal melanoma and the ability of radiation to enhance immunogenicity,[12,24] melanoma with mucosal histology may derive great benefit from the addition of RT to immunotherapy. A retrospective study of 23 patients with head and neck mucosal melanoma treated with RT and immunotherapy reported target local control was highest with an RT and immunotherapy combination (94% at 1 year).[23] A prospective study of an RT/immunotherapy combination in this histology is ongoing with patients with mucosal melanoma included in many melanoma clinical trials (Table 1).[26,27]

Conclusions

Our illustrative single-case experience suggests the dramatic and durable control that may be achieved with a consolidative radiotherapeutic approach to oligoprogression on immunotherapy in a case of a typically poorer responding mucosal melanoma. The management of such patients remains poorly defined. Randomized trials investigating methods of controlling disease progression in the setting of immunotherapy are necessary.

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