**Case 11: Controversy of Adjuvant Locoregional Therapy for Node-Positive Anal Mucosal Melanoma**

A 73-year-old woman presented with a 1-year history of a growing anal mass with intermittent bleeding. A nononcologic transanal excision revealed malignant melanoma (5 × 2.8-cm) with Breslow thickness 19 mm, mitotic rate of 12/mm2, positive margins, and molecular markers (KIT positive, BRAF V600E negative). Magnetic resonance imaging of the pelvis and 18F- fluorodeoxyglucose positron emission tomography/computed tomography showed a fluorodeoxyglucose-avid single right inguinal lymph node (LN) measuring 1.4 cm in the short axis that was suspicious for metastatic disease (Fig. 1). Flexible sigmoidoscopy showed absence of gross residual disease at the excision site and intact sphincter preservation. Multidisciplinary recommendation was to forgo further surgical resection in favor of adjuvant radiation therapy for local control/sphincter preservation. Immediate LN dissection was deferred in favor of immunotherapy. Radiation therapy was delivered to the perianal primary to 30 Gy in 5 fractions using volumetric modulated arc radiation therapy, twice weekly (Fig. 2). Acute side effects included Common Terminology Criteria for Adverse Events v4 grade 2 diarrhea, including transient fecal incontinence and dermatitis. She was then initiated on ipilimumab and nivolumab. Six months later, she continues to have stability of the inguinal LN as her only site of measurable disease; however, she was hospitalized for immunotherapy-related autoimmune encephalitis.

Fig. 1: Magnetic resonance T1 postcontrast axial image demonstrating a single right inguinal lymph node after a nononcology excision of the anal primary.

Fig. 2: Adjuvant radiation therapy plan to the perianal primary site alone.

**Expert 1: The Goldilocks Spot for Radiation Therapy in Anorectal Melanoma: Yes to the Primary Site After Local Excision; No to the Groin**

Management of anorectal melanoma should be tailored to balance curative expectation against quality-of-life detriment, especially among patients with confirmed inguinal nodal metastases, a strong prognosticator of distant metastatic progression. Gross nodal involvement of the inguinal basin has historically been managed with lymphadenectomy given the lack of effective systemic therapy to control disease progression. Recent data have suggested that PD-1 blockade for mucosal melanoma results in response rates comparable to those observed for cutaneous melanoma.

If significant concern remained, we would recommend additional imaging with either magnetic resonance perfusion or positron emission tomography/magnetic resonance imaging to discern possible pseudoprogression (seen in approximately 20% of patients with low-grade glioma) from actual progression. Washington University reported their experience with patients with low-grade glioma with suspected progression, and 90% of suspicious findings ultimately were found to be pseudoprogression. Of the 10 patients in their cohort who ultimately underwent surgery for reresection for progression, 80% had treatment effect with no evidence of residual or recurrent tumor. In lieu of clear evidence of progression (eg, new symptoms or radiographic evidence of progression on serial imaging), we would be hesitant to pursue surgical intervention because this would likely be low yield and without clear benefit to the patient.

Therefore, in patients who are eligible for PD-1 blockade and able to adhere to close monitoring of gross disease, a trial of these agents in lieu of up-front inguinal lymphadenectomy is reasonable and offers the opportunity to control both nodal involvement and potential subclinical systemic disease. However, sphincter preservation is a critical therapeutic endpoint, and local therapy should be completed first.

Adjuvant radiation therapy improves local control rates (>80%) over those reported for wide local excision alone (historically 50%) and is a necessary part of both local disease control and quality of life for these patients (ie, colostomyfree survival). In a relatively large series published by Kelly et al, 0% of patients with nodal involvement at diagnosis were distant metastases free at 5 years. Therefore, I do not endorse a radiation therapy course to the groin to attempt to control gross nodal disease because the associated morbidity (eg, lymphedema, fibrosis) is not justified by curative expectation. My recommendation for this patient is postoperative irradiation to the primary site to 30 Gy in 5 fractions using volumetric modulated arc therapy, as was done.

**Expert 2: Comprehensive Approach to Anorectal Melanoma with Emphasis on Systemic Therapy**

For patients with anorectal melanoma and a positive inguinal lymph node after nononcologic transanal excision, we recommend a thorough approach that emphasizes systemic therapy while considering local control:

* Re-evaluation of the need for lymph node dissection: Since the patient presented with a single fluorodeoxyglucose (FDG)-avid inguinal lymph node, which is still stable after six months of immunotherapy, it is essential to re-evaluate the need for lymph node dissection. The decision should be based on a thorough assessment of the risks and benefits, taking into account the patient's age, comorbidities, and the potential impact on her quality of life. A multidisciplinary discussion involving the surgeon, medical oncologist, and radiation oncologist will help in determining the best course of action.
* Manage immunotherapy-related autoimmune encephalitis: Since the patient has developed immunotherapy-related autoimmune encephalitis, it is crucial to manage this side effect appropriately. This may include stopping the immunotherapy, administering corticosteroids, and/or other immunosuppressive agents. Close monitoring and follow-up are required to assess the patient's neurological status and manage potential long-term sequelae.
* Close surveillance and follow-up: Given the patient's age and the potential side effects of aggressive treatment, a close surveillance approach with regular follow-ups, imaging studies, and clinical examinations is recommended. This will enable the detection of any local recurrence or new metastatic disease at an early stage, allowing for timely intervention if necessary.

The rationale for this approach is to balance the need for local control and management of metastatic disease while minimizing treatment-related side effects and preserving the patient's quality of life. This patient's age, comorbidities, and the complexity of the disease presentation make it essential to weigh the risks and benefits of each therapeutic intervention carefully.

**Expert 3: Excise and Ionize**

Given the imperfect positive predictive value of positron emission tomography/computed tomography for malignant inguinal lymphadenopathy, we recommend excisional biopsy before adjuvant therapy. This provides diagnostic and staging information, and it renders the patient free of gross disease. We would not recommend further surgery for the primary site, considering the risk of sphincter compromise, nor a full inguinal dissection owing to the increased risk of lymphedema and absence of any proven benefit.

Once completed (and if node positive), we recommend adjuvant radiation therapy to both the primary site and limited draining lymphatics (mesorectal, presacral, internal/external iliac to sacroiliac joint and bilateral inguinals) using a dose-painted volumetric modulated arc therapy plan, with 25 Gy delivered to elective areas and 30 Gy to the postoperative primary site and excised groin lymph node bed over 2.5 weeks. Similar regimens have been shown as tolerable in the short-course rectal and anal melanoma literature.

Although immunotherapies are approved in the adjuvant setting for cutaneous melanomas, their efficacy in mucosal melanoma is unclear and would not replace radiation therapy in our view. Given the less favorable risk/benefit ratio, we recommend reserving immunotherapy for the salvage setting if distant metastasis occurs. Of note, this patient has a KIT mutated melanoma; therefore, a KIT inhibitor (such as imatinib) could be considered for metastatic progression, particularly if the patient has an exon 11 or 13 mutation.

In a disease with poor survival and high risk of distant metastasis, we prefer to remove gross disease, reduce the risk of locoregional morbid recurrence with radiation therapy,and reserve systemic therapy for progression.

**Expert 4: Defer Dissection: Radiation Therapy and Systemic Therapy**

Anorectal melanoma has a poor prognosis, with survival determined by distant disease. Thus, the decision as to how to integrate local management is challenging. As there are high rates of local recurrence after wide local excision with risk for locoregional symptoms, combined sphincter-sparing surgery followed by radiation therapy (RT) is a well-tolerated treatment option to provide local control.

In a patient who has received a transanal excision with positive margins, we would recommend re-excision, as negative surgical resection margins portend an improved prognosis. After maximum surgical resection, adjuvant radiation should be considered. At MD Anderson Cancer Center, local control was achieved in 82% of patients treated with hypofractionated RT of 30 Gy in 5 fractions after wide local excision, even with 17% of patients with positive tumor margins. Of note, some patients received a 1-fraction, 6-Gy boost to the tumor site, and a minority were treated with 25 Gy in 5 fractions. Treatment is well tolerated, with grade 2 diarrhea as the most common acute side effect.

With regard to lymph node (LN) treatment, we agree with deferring LN dissection, despite concerning inguinal lymphadenopathy and hypermetabolic activity, in favor of systemic therapy. Although inguinal LNs are at risk for involvement in anorectal mucosal melanoma, data suggest that LN involvement does not predict outcomes, and the role of sentinel LN biopsy is not clear.4 Omitting elective LN radiation in this case is reasonable because inclusion of inguinal LN basins in the radiation field has not been proven to improve outcomes and is associated with increased morbidity.1 We know that the majority of these patients have distant failure.5 Therefore, systemic therapy is critical in this patient population, and in lymph-node-positive patients, systemic therapy should be considered before radiation.

The role of immunotherapy relies on data derived from cutaneous melanoma. CheckMate 238 showed nivolumab improved recurrence-free survival over ipilimumab. Nivolumab plus ipilimumab is recommended for patients with stage IV cutaneous melanoma, regardless of mutation status after definitive treatment of all sites. Higher rates of grade ≥3 adverse events are expected with combination immunotherapy versus single-agent therapy, with the IMMUNED trial reporting that 22% of patients treated with ipilimumab and nivolumab for stage IV melanoma developed grade 3 or 4 autoimmune disorder. Thus, this patient’s immunotherapy- related autoimmune encephalitis can be expected and is likely unrelated to her radiation therapy. We generally recommend optimizing the timing of RT and immunotherapy to provide the greatest synergistic effect and minimize toxicity, and would consider immunotherapy before RT.

In summary, we treat patients with resected anorectal mucosal melanoma with 25 to 30 Gy in 5 fractions with consideration of a boost for gross residual disease, and the timing of RT is case specific and warrants multidisciplinary discussion.

**Expert 5: Balancing Local Control and Systemic Therapy in Anorectal Melanoma**

For patients presenting with anorectal melanoma and positive margins after a nononcologic transanal excision, we propose a comprehensive approach that balances local control and systemic therapy to optimize outcomes and preserve quality of life.

1. Re-excision for positive margins: Perform a re-excision to achieve better local control and an improved prognosis in the presence of positive surgical margins.
2. Adjuvant radiation therapy: Administer adjuvant radiation therapy to the primary site after maximum surgical resection to enhance local control rates.
3. Deferring lymph node dissection: Opt for systemic therapy in favor of lymph node dissection for the suspicious inguinal lymph node, given that nodal involvement doesn't significantly predict outcomes, and elective lymph node radiation hasn't been proven to improve outcomes.
4. Emphasizing systemic therapy: Acknowledge the importance of systemic therapy in patients with lymph-node-positive disease and consider the use of immunotherapy before radiation therapy, depending on the case specifics and following a multidisciplinary discussion.
5. Manage immunotherapy-related autoimmune encephalitis: Address and treat any treatment-related toxicities, including immunotherapy-related autoimmune encephalitis.
6. Close surveillance and follow-up: Monitor the patient's response to treatment and manage any treatment-related toxicities through regular follow-up appointments and surveillance.

This approach aims to address the challenges of anorectal melanoma management by prioritizing both local control and systemic therapy, ensuring the patient's quality of life is maintained throughout the treatment process.

**Expert 6: Locoregional-Directed Therapy Is Still a Cornerstone of Anorectal Melanoma Management**

Nodal involvement in anorectal melanoma is associated with worse outcome. Given that the inguinal basin is prone to false positives on imaging, confirming nodal status can inform adjuvant therapy. A limited nodal surgery may provide the necessary information without excessive toxicity in a case like this.

We would offer radiation therapy (RT) to the primary site before initiating systemic therapy, given the high risk of local recurrence (particularly with a positive margin) and goal of promoting sphincter preservation. An important note about RT planning with this regimen of 30 Gy in 5 fractions delivered twice weekly is that it was designed to have 30 Gy as an approximate “Dmax” such that the goal is coverage with the 90% isodose (27 Gy).

Our institution routinely treated anorectal melanoma patients with inguinal RT (regardless of nodal status) until 2003 but then stopped due to concerns regarding lymphedema. This change resulted in 3-year nodal control dropping from 82% to 54% (P = .0016; manuscript submitted). However, there was no effect on disease-free survival or melanoma-specific survival due to the competing risk of distant metastasis. For this reason, we do not routinely treat inguinal nodes, but a patient at high risk of nodal recurrence without high risk of toxicity (eg, with no/limited nodal surgery and high-risk nodal disease) may be considered for inguinal nodal RT. Although a subset could be cured with systemic therapy, the unfortunate reality is that for most mucosal melanoma patients this is not the case.