**Case 1: Sowing the Seeds: A Case of Oligometastatic Anal Cancer 12 Years After Prostate Brachytherapy**

A 78-year-old man presented with rectal bleeding. Colonoscopy revealed a semicircumferential necrotic mass extending from the dentate proximally into the rectum, measuring 4 cm in length. Biopsy of the lesion was positive for poorly differentiated squamous cell carcinoma. Positron emission tomography−computed tomography revealed the anorectal mass with intense hypermetabolic activity, a 1.3-cm hypermetabolic left inguinal node, and a hypermetabolic lesion in the sacrum (Fig. 1). Sacral biopsy confirmed metastatic, poorly differentiated squamous cell cancer. The patient has a history of low-risk prostate cancer treated with low-dose-rate brachytherapy seed implant monotherapy (total dose, 144 Gy) in 2009.

Fig. 1: Axial images from the patient’s positron emission tomography−computed tomography scan depicting (A) the primary anal canal mass, (B) the left inguinal node metastasis, and (C) the sacral metastasis.

**Expert 1: Systemic Therapy, Then Locoregional Consolidation**

We suspect this is a new primary unrelated to prior radiation therapy (RT), a theory which would be supported if the pathologic specimen were found to be associated with human papillomavirus infection. For patients with oligometastatic anorectal squamous cell carcinoma, data suggest more favorable outcomes when treated with systemic therapy plus local therapy targeting the primary and metastatic sites compared with systemic therapy alone. However, the current scenario is complicated because the patient received prior prostate brachytherapy there-by exposing the anterior rectal wall adjacent to the prostate to radiation and, presumably, a small volume would have received prescription dose. In that context, considerably greater caution is warranted regarding the use of consolidative RT targeting the anorectum because the patient will be at risk of rectal injury, including bleeding, ulceration, perforation, or fistula, which could ultimately be highly morbid.

We favor initial treatment with systemic therapy for 2 to 3 months and assessment of response to determine whether the patient has biologically favorable disease, which supports an aggressive local treatment strategy. If the patient has stable or responsive disease (and specifically lack of further metastatic progression) and favored aggressive therapy after extensive shared decision making, we would treat with RT and concurrent chemotherapy. Positron emission/computed tomography and magnetic resonance imaging would assist with target delineation. Target volumes would include the elective low pelvis and inguinal nodes to 30 Gy, the gross anorectal primary plus 1 cm to 39 Gy, and the involved inguinal lymph node plus 1 cm and involved sacral segment to 45 Gy, using sequential boosts of each 1.5-Gy, twice-daily fractions.3 If the patient were to be risk averse, we would favor systemic therapy with reservation of RT for palliativeintent purposes.

**Expert 2: Warily Whacking the Weeds**

Patients with stage IV synchronous oligometastatic anal cancer who are treated with consolidative therapy have a considerable median overall survival (55 vs 17 months) and progression-free survival (16 vs 5 months) advantage compared with patients receiving chemotherapy alone. If local symptoms are manageable, this patient should receive 4 to 6 cycles of systemic therapy (carboplatin/paclitaxel) first. Although there is a risk of toxicity and late fistulation with pelvic irradiation after brachytherapy, symptoms from local progression of anal cancer are detrimental to quality of life due to worsening bleeding and pain. Therefore, since total consolidation can halt symptoms and yield long-term survival, this treatment can be offered after informed patient discussion.

A low dose per fraction should be used to limit late effects, which can include administering 3060 cGy in 17 fractions with intensity modulated radiation therapy to the tumor, anorectum, regional nodes, and involved sacrum with chemotherapy. A sequential boost to 5040 cGy to the gross disease (primary involved nodes, and sacrum) can be delivered depending on patient tolerance. Prior dosimetry can be fused if feasible, and attention to plan homogeneity at the rectal/prostatic interface with daily image guided radiation therapy is necessary. Although proton therapy may be considered given prior radiation, this treatment is unlikely to benefit since adequate coverage requires anterior rectal wall irradiation.

More than 90% of cases of anal cancer result from human papillomavirus infection. Although the status in unknown, there is no known association between anal squamous cell and brachytherapy. If human papillomavirus infection is negative and there is no immunosuppression history, a secondary neoplasm could be a possible result of prior brachytherapy.

**Expert 3: Prostrate After Prostate?**

For patients with metastatic anal cancer, we recommend starting with carboplatin/paclitaxel, up to 8 cycles, per the InterAACT trial. After chemotherapy, we would restage with positron emission tomography−computed tomography, and if the patient is responding to treatment, offer consolidation chemoradiation to the pelvis, including the sacral metastasis.

We would treat the pelvis, including elective lymph nodes (inguinal, external and internal iliac, presacral, and obturator), to 45 Gy, the fluorodeoxyglucose avid inguinal node to 50.4 Gy, and the primary tumor and sacral metastasis to 54 Gy in 30 fractions via a simultaneous integrated boost. With this plan, most of the previously irradiated anterior rectal wall would receive a total dose of 45 Gy in the elective volume, which we anticipate is a safe cumulative dose given the 13-year interval and that patients on the ASCENDE-RT trial received 46 Gy of external beam pelvic radiation therapy immediately followed by 115 Gy low dose rate brachytherapy. We would contour the urethra and avoid urethral hot spots to minimize risk of urethral-rectal fistula. We would favor treatment on a magnetic resonance imaging−guided linear accelerator for better organ-at-risk protection, including urethra visualization allowing for planning target volume margin reduction to 3 mm. We would plan for weekly adaptation, with additional adaptation on demand. We anticipate the primary tumor would shrink and move further away from the previously irradiated rectum; thus, replanning would allow further cooling of the area of reirradiation overlap. As for cancer etiology, it is certainly possible that the patient’s prior low dose rate brachytherapy contributed to his risk for anal squamous cell carcinoma, although dose fall-off from brachytherapy is sharp (>50% at 1 cm) and the patient fits the age demographic for non−HIV-associated anal squamous cell carcinoma.

**Expert 4: BID It to Win It**

For this oligometastatic anal squamous cell carcinoma, we would discuss definitive chemoradiation given the paucity of data supporting chemotherapy alone. The safety of pelvic reirradiation has been evaluated in a few prospective trials. Up-front surgical resection is a consideration but is less appropriate in the setting of metastatic anal cancer and inguinal node adenopathy. The patient’s desire for sphincter preservation should also be evaluated.

We would offer reirradiation with photons or proton therapy. The preferred regimen would be a total dose of 45 Gy in 1.5 Gy twice-daily fractions, followed by boost of 540 cGy in daily 1.8 Gy fractions to the sacral lesion and involved inguinal node. We would reduce the anterior extent of lower dose volume to include only a small portion of the prostate. To minimize the urethral dose, a foley catheter would be used at simulation, and the urethra would be contoured and identified as an organ at risk. The sacral metastasis can be treated concurrently and included in our higher dose target volumes, because the presacral space will be covered regardless and the additional toxicity is minimal.

The prior prostate brachytherapy primarily impacted the anterior rectal wall and prostatic urethra; as such, we would use bid fractionation and limit the total dose to the anal tumor. We would discuss the potential late effects, including proctitis and rectoprostatic fistula. Radiation-induced secondary malignancy is a possibility; however, further assessment of known risk factors for anal cancer, including sexual history and HIV and human papillomavirus status, would help determine the etiology of this anal cancer.

**Expert 5: New Growth After Planted Seeds, Treat With Rays**

Before Dr. Nigro’s excellent 1974 study changed the way that we treat anal canal squamous cell carcinoma, abdominopelvic resections were common but resulted in permanent colostomy for all patients.

So, in reality, the questions we are being asked here are the following:

1. Does the oligometastasis rule out the option of curative treatment?

2. Does the previous brachytherapy make this patient ineligible for an attempt at organ preservation?

Patients on the SABR-COMET trial (including those with colorectal cancer) had a 100% rate of local control when bone metastases were treated with hypofractionated radiation therapy. We would offer this patient curative treatment.

Increased risk of toxic effects with reirradiation leads to increased provider hesitancy to deliver such treatment. However, if intolerable rectal or anal-sphincter toxic effects should result from the reirradiation, this patient would undergo a surgery no worse than the primary surgery that would be planned. He loses nothing, rectum-wise, by trying radiation therapy.

We recommend simultaneous intensity modulated radiation therapy, per anal canal squamous cell treatment guidelines, and stereotactic body radiation therapy to his sacral metastasis, enabling careful control of the total dose to all genitourinary structures, incorporating our best knowledge of his previous brachytherapy dose. We would recommend that chemotherapy start after stereotactic body radiation therapy.

The Surveillance, Epidemiology and End Results Program study by Baxter et al tells us that the risk of rectal cancer increases after prostate radiation therapy, with a hazard ratio of 1.7, but only in irradiated sites. In this case, at least three-fourths of the tumor lies well outside the region exposed to any meaningful dose from prostate brachytherapy; thus, we consider a connection unlikely.

ChatGPT’s initial recommendation

**Expert 6: Multimodal Approach Involving Chemotherapy, Radiotherapy, and Possibly Immunotherapy**

For this patient with metastatic anal cancer, we propose a multimodal treatment approach, including chemotherapy, radiation therapy, and possibly immunotherapy. This recommendation takes into account the aggressive nature of the poorly differentiated squamous cell carcinoma, the presence of metastatic disease in the inguinal lymph node and sacrum, and the patient's age and history of prior radiation treatment.

1. Chemotherapy: The patient should receive systemic chemotherapy to address the metastatic disease. A widely used regimen for anal squamous cell carcinoma consists of a combination of 5-fluorouracil (5-FU) and cisplatin or carboplatin. Chemotherapy will help control the disease systemically and may enhance the efficacy of radiation therapy.
2. Radiation therapy: Concurrent chemoradiation is the standard approach for non-metastatic anal cancer. In this case, intensity-modulated radiation therapy (IMRT) is preferred for its ability to deliver precise radiation doses while sparing nearby healthy tissue and potentially reducing side effects. The radiation oncologist must carefully consider the patient's prior radiation exposure from prostate brachytherapy to avoid exceeding dose constraints for surrounding organs at risk. Target volumes should encompass the primary tumor, involved inguinal lymph node, and sacral metastasis.
3. Immunotherapy: Given the poorly differentiated nature of the tumor, the patient might benefit from immunotherapy, specifically PD-1 or PD-L1 inhibitors such as pembrolizumab or nivolumab. However, it is crucial to determine the patient's tumor PD-L1 status and discuss potential side effects before deciding on this approach.

A multidisciplinary team, including medical oncologists, radiation oncologists, and surgical oncologists, should evaluate the patient. Regular follow-ups and imaging should be conducted to assess treatment response and manage potential side effects.

It is vital to recognize that each patient's case is unique, and the final treatment plan should be individualized based on the patient's overall health, preferences, and potential side effects of the therapies. In some cases, palliative care may also be considered to manage symptoms and improve the quality of life.

ChatGPT’s revised recommendation after seeing other human experts’ recommendations

**Expert 7: Chemotherapy Followed by Consolidation Chemoradiation for Responsive Patients**

For patients with metastatic anal cancer, we recommend initiating treatment with up to 8 cycles of carboplatin/paclitaxel chemotherapy, as indicated by the InterAACT trial. Following chemotherapy, the patient should be restaged with positron emission tomography-computed tomography (PET-CT) to evaluate their response to treatment.

If the patient demonstrates a favorable response to chemotherapy (i.e., stable or responsive disease without further metastatic progression), we would proceed with consolidation chemoradiation targeting the pelvis, including the sacral metastasis. The chemoradiation plan would involve treating the pelvis, elective lymph nodes (inguinal, external and internal iliac, presacral, and obturator), to a dose of 45 Gy. Concurrently, a simultaneous integrated boost would be used to deliver 54 Gy in 30 fractions to the primary tumor and sacral metastasis.

With this approach, we anticipate that most of the previously irradiated anterior rectal wall would receive a total dose of 45 Gy in the elective volume, which is expected to be a safe cumulative dose given the 13-year interval since the patient's prostate brachytherapy. The urethra should be contoured to avoid hot spots and minimize the risk of urethral-rectal fistula.

We recommend using a magnetic resonance imaging (MRI)-guided linear accelerator for improved organ-at-risk protection and urethra visualization, allowing for planning target volume margin reduction to 3 mm. Weekly adaptation with additional adaptation on demand should be planned to account for tumor shrinkage and further protect the previously irradiated rectum.

While immunotherapy is not explicitly included in this recommendation, it can be considered as part of the treatment plan and discussed with the patient and the treatment team based on the patient's response to chemotherapy and other relevant factors.