**Case 7: Mending the Rent: Knife Versus Rays Versus Syringe**

A 60-year-old woman with hypertension presented with postmenopausal bleeding, pain in lower abdomen, and urinary incontinence of 1-month duration. Obstetric (P2L2) and menopausal history were unremarkable. Clinical examination revealed a firm growth involving the cervix and anterior vaginal wall up to the introitus with bilateral medial parametrial involvement. Foul-smelling vaginal discharge was noted. Cervical biopsy revealed poorly differentiated squamous cell carcinoma. Staging magnetic resonance imaging (Fig. 1a) revealed a cervix lesion (8.0 × 4.3 × 4.0 cm) involving the anterior/posterior cervical lips and extending superiorly to the lower uterine corpus and inferiorly to the proximal two-thirds of the vagina with parametrial extension, involvement of the posterior bladder wall, and enlarged pelvic/paraortic nodes. Positron emission tomography-computed tomography (Fig. 1b) showed a metabolically active soft tissue cervical mass (4.5 × 5.0 × 6.9 cm; SUVmax, 12.9) involving the lower uterine body, left parametrium, upper vagina, posterior urinary bladder, and anterior rectal wall with enlarged pelvic/paraortic nodes. Cystoscopy revealed bladder-trigone indentation by cervical growth, and biopsy was suggestive of bladder involvement. The patient received extended-field radiation therapy with concurrent weekly cisplatin to a dose of 45 Gy in 25 fractions to the whole pelvis and paraortic region with simultaneous integrated boost to a dose of 55 Gy in 25 fractions to gross nodes. Magnetic resonance imaging of the pelvis (after chemoradiation) (Fig. 2) showed partial regression of the cervical mass (2.9 Antero-posterior × 3.6 Transverse × 2.2 Craniocaudal cm) involving the posterior lip/upper vagina, bilateral parametrium, and posterior urinary bladder wall with sloughing off in the midline upper vaginal region causing direct communication between the vagina and urinary bladder lumen with complete regression of lymph nodes.

Fig. 1: (a) Axial and sagittal T2 imaging shows a cervix mass abutting the posterior urinary bladder wall with fat-plane loss. (b) Positron emission tomography/computed tomography showed metabolically active locally advanced cervical carcinoma.

Fig. 2: Post-Chemoradiation Imaging: Sagittal T2 imaging shows a small focal collection abutting the bladder wall, with loss of fat planes. Corresponding post-contrast images show a fistulous tract.

**Expert 1: Combination of Knife and Syringe**

This patient has a locally advanced, poorly differentiated squamous cell carcinoma of the cervix with bladder involvement and metastatic lymph nodes. The patient has already received extended-field radiation therapy with concurrent weekly cisplatin to a dose of 45 Gy in 25 fractions to the whole pelvis and para-aortic region with simultaneous integrated boost to a dose of 55 Gy in 25 fractions to gross nodes. Post-treatment imaging showed partial regression of the cervical mass and complete regression of lymph nodes, but a fistulous tract between the vagina and urinary bladder has developed.

Considering the treatment response and the presence of a fistula, our most favored therapeutic approach for this patient would be a combination of salvage surgery and adjuvant therapy. The specific recommendations are as follows:

* Salvage surgery: Given the remaining cervical mass and the fistula, we would recommend a radical hysterectomy with bilateral salpingo-oophorectomy, partial vaginectomy, and partial cystectomy, along with repair of the fistulous tract. This surgery aims to remove the remaining tumor and address the fistula.
* Adjuvant therapy: After the surgery, we would recommend adjuvant chemotherapy, preferably with a combination of cisplatin and paclitaxel or carboplatin and paclitaxel, depending on the patient's tolerance and previous response to cisplatin. This adjuvant therapy is intended to target any residual microscopic disease and decrease the risk of recurrence.

The patient has already received a course of chemoradiation with partial tumor response, but the fistula complicates the situation and can severely affect the patient's quality of life. Salvage surgery offers a chance to remove the remaining tumor, repair the fistula, and potentially improve the patient's quality of life. Adjuvant chemotherapy will help address any residual disease and reduce the risk of recurrence.

**Expert 2: Mend and Cure with Surgery**

In stage IVA cervical cancer, both primary pelvic exenteration and chemoradiation have almost equal oncologic outcomes. However, exenteration is not usually done because of quality-of-life issues compared with chemoradiation. 1 In this woman, after pelvic radiation with concurrent chemotherapy, there is significant residual disease and a vesicovaginal fistula (VVF) owing to breakdown of cancer-bearing tissues, albeit in response to treatment.

Brachytherapy is not recommended in patients who develop VVF and have residual disease.2 VVF after chemoradiation is due to endarteritis. Flaps to close the fistula have higher failure rates compared with unirradiated tissue. Hence, in this woman with residual disease in cervix, vagina, and bladder with a VVF, diversion surgery (preferably anterior en bloc resection [anterior pelvic exenteration])3 is preferrable. The intent of treatment will still be curative at this point.

The role of chemotherapy will depend on surgical margins. If positive, platinum-based chemotherapy may be indicated. Palliative chemotherapy without resection or urinary diversion will lead to ascending infections and poor tolerance. If she is not fit for exenteration, urinary diversion will be needed.

**Expert 3: Rays Over Knife**

For stage IVA cervical cancer, the gold standard is concurrent chemoradiation followed by image-guided brachytherapy, including in the presence of a fistula which is not a contraindication for brachytherapy. Given the presence of vesicovaginal fistula, this patient should undergo placement of bilateral percutaneous nephrostomy tubes prior to treatment.

We would proceed with perineal interstitial HDR brachytherapy in order to cover the residual disease.1 A preplanning magnetic resonance imaging (MRI) with vaginal gel and an MRI or computed tomography (CT) with cylinder in place can be performed to guide needle position and depth. Intraoperatively, the uterine cavity is dilated to allow tandem insertion under transabdominal ultrasound guidance. A cylinder with perineal template and interstitial catheters are placed under ultrasound guidance with particular attention to anterior bladder coverage. The ultrasound can be placed in the vagina first for anterior needle placement. The ultrasound can be utilized transrectally for the paravaginal/parametrial needles. After applicator placement, the patient ideally would undergo MRI-simulation. If MRI-simulation is not available, we recommend fusion of CT simulation with pretreatment MRI with cylinder in place. The high-risk clinical target volume will include the gross disease (vagina, parametria and bladder), entire cervix, and gray areas on T2W MRI. A dose of least 85 Gy equivalent dose in 2 Gy fractions to high risk clinical target volume D90 (minimum dose covering 90% of the volume) should be delivered with D98 to the gross tumor volume of 95 Gy equivalent dose in 2 Gy fractions.

If bladder involvement cannot be covered appropriately with definitive doses (even if a reimplant were to be attempted), we recommend aborting the procedure and referring the patient for salvage pelvic exenteration which is the gold standard for persistent and recurrent disease after definitive chemoradiation. Chemotherapy in lieu of exenteration can be considered in the palliative setting after exhaustion of all curative approaches. We would also consider enrolling the patient on a clinical trial.

**Expert 4: Image-Guided Brachytherapy with Nephrostomy Tube Placement for Symptom Management**

The patient described presents a complex case of stage IVA cervical cancer with residual disease and vesicovaginal fistula following chemoradiation. Our recommendation is as follows:

* Complete definitive radiation therapy using perineal interstitial HDR brachytherapy to cover the residual disease, ensuring appropriate coverage of the tumor and adjacent tissues.
* Prioritize symptom management by placing bilateral percutaneous nephrostomy tubes before initiating brachytherapy to alleviate urinary symptoms related to the vesicovaginal fistula.
* Closely monitor the patient's response to brachytherapy, evaluating her need for additional treatment, such as salvage surgery or systemic therapy, depending on her response and overall health.

This recommendation focuses on providing the standard treatment for stage IVA cervical cancer, which is concurrent chemoradiation followed by image-guided brachytherapy, while also addressing the unique challenges posed by the vesicovaginal fistula in this patient. The multidisciplinary team should evaluate the patient, taking her preferences, overall health, and potential benefits and risks of each treatment modality into account. The goal is to develop a personalized plan that optimally balances the potential for disease control with the patient's quality of life.

**Expert 5: Combination of Knife and Rays with MRI-Guided Ablative Brachytherapy**

The authors describe a complex case of locally advanced cervix cancer. Imaging and examination were concerning for extensive disease with involvement of bladder and anterior rectal wall along with pelvic and para-aortic lymph nodes. For this reason, the patient was treated with definitive chemoradiation (external beam radiation therapy, EBRT) to the pelvic and para-aortic region with simultaneous integrated boost to the involved nodes. Positron emission tomography/computed tomography (CT) and magnetic resonance imaging (MRI) after EBRT showed good imaging response with residual disease in cervix with vesicovaginal fistula and regression of all enlarged nodes.

Patients with such advanced locoregional disease are at high risk for both local and distant disease progression after completion of definitive therapy. EMBRACE-I results published in 2021 give us insight on outcomes for IVA cervical cancer patients treated with definitive chemoradiation with MRI-based brachytherapy boost in the modern era. In this study, 2.5% (34 patients) enrolled had IVA disease and had a 5-year pelvic control rate of 81%. These patients were at elevated risk of developing fistula and ureteral strictures (18.6% [n = 6]; 21.3% [n = 23], respectively). Similarly in another series of CT-based interstitial brachytherapy, 8 patients had stage IVA disease with crude local control and vesicovaginal fistula being 62.5 % and 12.5% respectively. Furthermore, patients with IVA disease, are at elevated risk for developing distant disease, also with the EMBRACE series showing 5-year disease-free survival and overall survival of 47% and 52%, respectively.2 Also, in patients with para-aortic nodal disease at presentation like the case here there is increased rate of distant disease, which adversely impacts their outcomes with 5 year disease-free survival and overall survival in the range of 25% to 50%.

Based on this information, we recommend the patient complete her definitive radiation with image-based brachytherapy preferably with MRI guidance as there would be better lineation of target volume in the setting of fistula and residual disease seen on imaging. We would recommend brachytherapy boost with the hybrid applicator with vaginal cap to cover vaginal disease and template to cover parametrial disease to deliver EQD2 dose of 85 to 90 Gy to HRCTV (to include the entire cervix and adjacent residual disease including gray zones) and D98 of >95 Gy to residual GTV seen on MRI.

Because this patient has developed vesicovaginal fistula on treatment, we favor bilateral nephrostomy now to divert urine to help with symptoms caused by constant leakage. About 12 to 16 weeks after completion of brachytherapy would perform positron emission tomography/CT along with MRI imaging with functional sequences to assess for locoregional response and any new distant metastases. Should the patient have evidence of complete response on pelvic examination and imaging, we would then favor replacement of bilateral nephrostomy urinary diversion

with ileal conduit as more definitive treatment to manage symptoms from fistula. These vesicovaginal fistulas are unlikely to heal and very hard to repair even after complete regression of disease. Should the patient have biopsy proven persistent disease at 12 to 16 weeks then an informed risks and benefits discussion should occur with the patient for palliative systemic treatment or salvage exenteration. She should understand that despite aggressive surgical salvage with associated morbidities, she is at elevated risk of failing distantly due to extent of nodal disease at presentation.