**Case 14: Trim One’s (E)Wings—How Much is Enough?**

A 52-year-old woman presented with an enlarging firm perianal mass consistent with ischiorectal abscess. She underwent resection of a 5.5 × 3.5 × 3 cm mass abutting the external sphincter muscle. Final pathology was consistent with Ewing sarcoma (EWSR1-FLI1 fusion gene present) with positive margins and perineural invasion. Staging scans including computed tomography of the chest/abdomen/pelvis, and full-body positron emission tomography-computed tomography scan showed no evidence of metastatic disease.

She was started on systemic treatment with alternating cycles of vincristine, doxorubicin, and cyclophosphamide and ifosfamide and etoposide for total of 14 planned cycles (7 of vincristine, doxorubicin, and cyclophosphamide and 7 of ifosfamide and etoposide). Magnetic resonance imaging of the pelvis after cycle 2 of chemotherapy revealed no residual mass (Fig. 1). The patient was evaluated by colorectal surgery with recommendations for abdominal perineal resection and permanent colostomy and by radiation oncology with recommendations for definitive chemoradiation therapy.

Fig. 1: Magnetic resonance imaging after resection and 2 cycles of chemotherapy. (A) Postcontrast T1-weighted axial image with fat saturation. (B) T2-weighted axial image with fat saturation.

**Expert 1: Tipping the Scales Toward Single Modality**

Local control for Ewing sarcoma is typically planned as a single modality, surgery with planned negative margins or definitive chemoradiation therapy. Combined modality (surgery with pre- and/or postoperative radiation therapy) has not demonstrated significant benefit for local control or survival.

The modality of choice should be based on the likelihood of success (eg, the degree of confidence that a re-resection would provide the disease clearance of a traditional R0 resection), morbidity, and degree of disruption to systemic therapy, which we know is essential for both local control and overall outcomes. Owing to the lack of clinical equipoise to address the local control question in a prospective randomized fashion, we rely on retrospective analyses subject to selection bias, where traditionally surgery is favored for “expendable bones” and definitive radiation therapy is often the modality of choice for locally advanced tumors. These retrospective analyses incorporate patients treated with varied chemotherapy regimens, including less-intensive regimens, and it is known that local control can be influenced by the intensity of systemic therapy. Importantly, current data do not support using a different approach for extraskeletal Ewing sarcoma, for which a combined-modality soft tissue sarcoma approach should not be applied. We would consider the patient's non-oncologic positive margin surgery before chemotherapy to be analogous to a biopsy and would not use this to guide our recommendations. The role of perineural invasion on local control is not well described, and we would not adjust our local control planning. Considering all these factors, we would anticipate definitive chemoradiation therapy as the approach of choice.

**Expert 2: Tilting the Balance, and Gantry, Towards Preservation of Function**

Balancing Function Preservation and Local Control in Localized Ewing Sarcoma

Standard treatment for localized Ewing sarcoma includes chemotherapy and local therapy. Surgery and radiation therapy are effective local treatment options, but there has been no randomized trial comparing them. A pooled analysis of 1444 patients from Ewing sarcoma randomized trials found that the risk of local failure was higher for patients treated with radiation therapy, but all patients had similar event-free and overall survival. As discussed by the authors, this “reflects the relatively low contribution of local failure to overall disease failure in Ewing sarcoma” and validates radiation therapy as a reasonable alternative to morbid surgery. This study also found no benefit of surgery plus radiation therapy compared with either modality alone. Unless tumor shrinkage would allow for a less morbid surgery, teams should select one or the other. Clinical factors including patient age, expected margin status, and function preservation should be considered.

One consideration is that this is an extraosseous Ewing sarcoma. Although these tumors are less well studied than skeletal Ewing sarcoma, case series suggest that their behavior is similar, and the same concepts can likely be applied as with skeletal Ewing sarcomas.

Radiation therapy should be selected in this 52-year-old woman facing a permanent colostomy with surgery.

**Expert 3: Extraosseous, Always Personal**

Adult-onset extraosseus Ewing sarcoma diagnosed via non-oncologic resection is a challenging beginning to a disease with an already circuitous treatment paradigm. In cases of complete excision before induction chemotherapy, non–organ-enclosed tumors are considered appropriately removed only when a 2 cm margin is achieved.

Surgery (with or without radiation therapy) versus radiation as local control therapy is dictated by the feasibility of obtaining adequate margins and maintaining the patient’s functional integrity. No prospective, randomized study of surgery versus radiation exists. In review of the intergroup trials, however, the presumed blanket superiority of surgery over radiation may be questionable. Even when not controlling for disease site resectability, radiation therapy may be an equivalent option for some, if not all, patients with Ewing sarcoma in regard to local control3 and, in turn, comparable overall survival.

The options of radiation or surgery are typically reviewed among all treatment physicians, and if surgery is thought appropriate, it is offered. However, in applying the research data to specific patients with Ewing sarcoma, if radiation therapy is better able to minimize toxicity at a specific anatomic site where resection could be detrimental to the patient, it should be offered as a viable local control therapeutic option.

When reviewing treatment options, resuming consolidative chemotherapy should also be taken into account. Timely resumption of chemotherapy with less than 6 weeks between cycles should be built into local control management. The chemotherapy may be given concurrently with radiation therapy as primary local control therapy or administered with a radiation boost.

ChatGPT’s initial recommendation

**Expert 4: Combined Approach of Neoadjuvant Chemoradiation Therapy and Tailored Surgical Resection**

The management of adult-onset extraosseous Ewing sarcoma following a non-oncologic resection poses significant challenges in terms of balancing local control and preserving patient functionality. In light of the patient's perineural invasion and the perianal location of the primary lesion, a combined approach involving neoadjuvant chemoradiation therapy followed by definitive resection tailored to the patient's tumor response and preferences may be optimal for achieving local control while maintaining quality of life.

Neoadjuvant chemoradiation therapy can help reduce tumor size, increase the likelihood of achieving negative surgical margins, and potentially eradicate microscopic disease in the perineural tissues. This approach may also allow for a more conservative surgical approach if the tumor response is favorable, thus preserving the patient's anorectal function and avoiding the need for a permanent colostomy.

Following neoadjuvant chemoradiation therapy, the patient should be re-evaluated to determine the extent of tumor response and the most appropriate surgical approach. If there is a significant reduction in the tumor size and the risk of positive margins has decreased, a more conservative surgical approach, such as wide local excision, might be considered. However, if the tumor response is not as favorable or there is still a significant risk of positive margins, proceeding with an abdominoperineal resection (APR) and colostomy would be appropriate to ensure adequate local control.

In conclusion, for this particular case of adult-onset extraosseous Ewing sarcoma, a combined approach of neoadjuvant chemoradiation therapy followed by definitive resection tailored to the patient's tumor response and preferences may provide the most effective strategy for optimizing local control and preserving the patient's quality of life.

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

**Expert 5: Balancing Local Control and Function Preservation with Definitive Radiation Therapy in Adult-Onset Extraosseous Ewing Sarcoma**

Adult-onset extraosseous Ewing sarcoma diagnosed via non-oncologic resection presents a unique challenge within an already complex treatment paradigm. Local control therapy in Ewing sarcoma typically involves a choice between surgery (with or without radiation therapy) and radiation therapy alone, determined by factors such as the feasibility of obtaining adequate margins and preserving the patient's functional integrity. To date, no prospective, randomized study comparing surgery versus radiation therapy exists, and the presumed superiority of one modality over the other may be debatable in certain cases.

Given the patient's demonstrated positive response to the initial cycles of systemic chemotherapy, it is essential to continue with the planned 14 cycles for optimal systemic control. In terms of local control, definitive radiation therapy offers a reasonable alternative to more morbid surgical approaches, particularly in light of the tumor's perianal location and the associated risk of permanent colostomy. Radiation therapy can help achieve local control while preserving the patient's anorectal function and quality of life.

Our experience highlights the lack of clear evidence supporting additional benefits from combining surgery and radiation therapy compared to either modality alone. Therefore, it is appropriate to choose one modality based on factors such as tumor location, patient age, expected margin status, and the potential for function preservation.

As part of the multidisciplinary team, including the colorectal surgeon and the radiation oncologist, we should tailor the treatment plan according to the patient's response and preferences, carefully weighing the benefits and risks of each approach. In summary, my recommendation for this patient is to continue with the planned systemic chemotherapy and proceed with definitive radiation therapy as the primary local control strategy, aiming to preserve function and minimize morbidity.