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The Evolving Concept of Margins in Musculoskeletal Oncology

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The surgical margin in musculoskeletal oncology is a complex idea that has evolved over time owing to improved adjuvant treatment and a better understanding of the biology of sarcomas. The historical surgical concepts of “wide” or “2 cm” margins are no longer appropriate. Today's musculoskeletal oncologist must balance the aggressivity of the surgical resection against the morbidity associated with that resection. Presented herein are both an introduction and an advanced look into the status and data supporting the concept of the surgical margin in musculoskeletal oncology.

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Introduction

The surgical margin is a keystone in cancer care. It refers to the amount of normal, noncancerous tissue removed during surgical excision of a tumor. The concept of the surgical margin is something that is all too apparent to a patient with cancer, given the frequent assumption linking local and distant control. Questions such as “Doctor, did you get it all?” are commonplace for the surgical oncologist. These questions, although important, place the emphasis not on the overall cancer care of an individual patient but only on the surgical excision, a step in a patient's individual cancer care. The surgical margin however is more complex than this simplistic appreciation, especially for sarcoma care, and is something that has evolved over time. It represents an entity that the treatment team needs to closely understand as the relationships between surgical margin, local recurrence, and metastasis are important for patient care.

Sarcomas are a heterogeneous group of malignant tumors of connective tissue that represent one of the rarest forms of human cancer. Although rare, there are more than 14,000 new sarcomas diagnosed each year in the United States alone. Treatment for sarcomas revolves around surgical removal. Although adjuvants like radiation or chemotherapy have

evolved over time to assist with the local and systemic treatment of sarcomas, surgery remains the foundation of sarcoma care, making the surgical margin of the utmost importance.

The goal of surgical treatment in musculoskeletal oncology is a “negative” margin. A negative-margin excision is one where the entire tumor has been removed with a “cuff” of normal surrounding tissue. If one were to imagine a tumor as the fruit of an orange, this “cuff” of normal tissue could be explained as the orange's rind—which encases the tumor completely. The question then becomes, how thick does this normal “cuff” of tissue need to be to minimize recurrence while minimizing patient morbidity? This simple question is the one that has been debated extensively within the musculoskeletal oncology community and does not have an easy answer, as not all margins should be considered equal in their risk to the patient.

The Evolving Concept of Margins Over Time

The initial description of the sarcoma surgical margin by Enneking^{1,2} used nomenclature like intralesional, marginal, wide, or radical to describe soft tissue sarcoma margins. These terms are still used today. The key difference between then and now, as it relates to the surgical margin, is the development of good adjuvant therapy, which can be used to enhance surgical margins.

To best understand this nomenclature regarding sarcoma surgical margins, one must understand sarcoma growth. Local

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growth in sarcomas occurs in a radial fashion, compressing the surrounding tissue at the host-tumor junction, forming a “pseudocapsule” around the tumor. The pseudocapsule however is not a true barrier to tumor extension, as viable tumor cells are frequently found within and beyond the pseudocapsule.³ The Enneking description of the surgical margin accounts for this simple fact when considering the margin. As such, an intralesional margin is one where the surgeon cuts into the tumor during removal. This assumes that viable tumor has been left in the patient. One could consider an incisional biopsy as an intralesional margin. A marginal margin is one where tumor removal is accomplished by dissection along the pseudocapsule. Given the potential for viable tumor within or beyond the pseudocapsule, a marginal margin may be supplemented with adjuvant therapy, pending the level of risk. For a wide surgical margin, a cuff of normal tissue separates the surgical plane from the tumor (much like the orange’s rind). The wider the surgical margin, the greater the chance that all foci of local disease are removed. A radical margin is one where the entire involved compartment is removed (eg, removal of the entire femur for a distal femoral tumor or removal of the entire quadriceps compartment for a soft tissue sarcoma that developed in the vastus medialis).

As the Enneking classification of surgical margins was developed concurrent with advances in reliable adjuvant therapy, the concept of the sarcoma surgical margin has evolved over time.⁴⁻⁶ On resection, tumors are superficially “inked” by pathologists to best assess the surgical margin. The ink allows the pathologist to microscopically determine whether tumor extends to the surgical margin (ink) or whether some normal tissue exists between cancer and the surgical margin’s ink (positive vs negative margin). Historically, this ink would allow the pathologist to measure the width of the surgical margin and help predict risk, assuming the larger the margin, the greater the chance that all local cancer foci are removed. Nowadays, rather than quantify a distance (2 cm vs 2 mm) of margin between tumor and pathologist’s ink, many surgeons look for either a positive or negative margin, assuming that adjuvant therapy has treated the extra foci of disease. Such close negative margins preserve critical structures (bone, major vessels, or nerve) and decrease the morbidity of the surgical resection.⁷⁻¹⁰

One close negative margin does not equal another. Certain tissues are better or worse in their ability to prevent sarcoma spread.^{11,12} As such, a 1-mm surgical margin of fat carries much more risk to the patient than the same margin of fascia, as fascia serves as a very good boundary to tumor spread. Ideally, sarcomas would only occur in easily resectable locations, distant from critical structures, with good boundaries to tumor spread. Unfortunately this is not the case. For these reasons, adjuvant therapy and a mastery of musculoskeletal anatomy allow the treating surgeon to plan the surgical margin in such a way to remove the tumor but spare critical structures and minimize morbidity.

Negative margins are required in sarcoma care. The size of the margin however must be weighed with the associated morbidity of that margin. One may assume that the larger the margin, the better the cancer outcome for the patient.

However, amputation does not appear to improve survival rates in sarcoma.¹³ In a similar fashion, soft tissue sarcomas that occur adjacent to critical structures (bone, major vessel, or major nerve) have similar rates of outcome irrespective of whether these critical structures are resected or preserved with a microscopically close negative margin.⁴ When considering the increased patient morbidity associated with amputation or resection of a critical structure (bone, major vessel, or major nerve) against similar cancer outcome measures, many surgeons attempt limb- or critical structure–salvage surgical options.^{7-10,14,15}

The Effect of Adjuvant Therapy on the Sarcoma Margin

Adjuvant chemotherapy and radiation therapy have been crucial to the evolution of the sarcoma surgical margin.¹⁶⁻¹⁹ Although these adjuvants will likely never supplant surgical excision, over time they have allowed the surgeon to remove less normal tissue, perform less morbid procedures, and maximize patient function.

The advent of a successful chemotherapy protocol for osteogenic sarcomas was the single biggest contribution to improve long-term patient survival.²⁰ Before chemotherapy, a diagnosis of osteogenic sarcoma was associated with poorer than a 20% 5-year survival even after amputation. This was owing to unappreciated microscopic pulmonary metastatic disease, previously left untreated before chemotherapy. At present, chemotherapy coupled with limb-salvage surgery offers greater than a 60% 5-year survival for most patients with osteogenic sarcoma.²¹ Although the chemotherapy has improved survival for bone sarcomas, limb-salvage surgery with a negative surgical margin is accepted as standard of care. Positive margins in bone sarcomas are particularly worrisome and should be avoided as most data suggest that these patients tend to do poorly regarding overall survival.²²⁻²⁴

Soft tissue sarcoma chemotherapy however is a controversial topic for both local control and overall survival.²⁵ As survival rates in patients with soft tissue sarcoma have not improved over the past 20 years, many look toward improved chemotherapeutics as the key to improved long-term survival in soft tissue sarcoma.²⁶ It is not known whether the limited success of chemotherapy in soft tissue sarcoma is owing to the vast heterogeneity of soft tissue sarcomas, circulating tumor-derived stem cells, or some biologic attributes that are not fully understood. Nevertheless, chemotherapy as it relates to survival rates in soft tissue sarcoma continues to be controversial.

Equally controversial is the role of chemotherapy to the surgical margin in soft tissue sarcomas.²⁶ In soft tissue sarcoma, the surgical margin is directly related to the rate of local recurrence. Wide negative surgical margins alone afford greater than 70% 5-year local control rates in soft tissue sarcomas.⁵ Although the association between local recurrence and overall survival is another very controversial topic in soft tissue sarcoma, most agree that local recurrence is somehow related to overall survival.²⁷ To this point, efforts to minimize rates of

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