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CORR Insights®: Survival, Recurrence, and Function After Epiphyseal Preservation and Allograft Reconstruction in Osteosarcoma of the Knee

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Where Are We Now?

The combination of multidrug chemotherapy and limb-salvage surgery has been the

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treatment of choice for high-grade osteosarcoma for almost three decades. Unanimous consensus exists upon the ominous significance of local recurrence following limb preserving surgery after preoperative chemotherapy in patients presenting with localized disease [3, 17]. Although surgical margin and histological response to preoperative chemotherapy are well documented as the main risk factors in this setting [16], our understanding of the pathogenesis and impact on survival of this complex problem is largely incomplete. There are three fundamental issues, inherently related, that affect local recurrence and have important implications regarding whether the technological and surgical advances reported by Aponte-Tinao and colleagues [2] should be employed:

Surgical management, imaging and staging, as the rationale framework to plan the extent of surgery and type of margin, and the response to chemotherapy.

With respect to surgery, local recurrence in the presence of positive margin is perhaps straightforward; however, its occurrence following a negative margin remains unclear. In my experience, undetected intraoperative tumor contamination may occur as a consequence of specimen manipulation. In fact, subtle crack and hemorrhage in areas of cortical destruction or periosteal stripping extending from the osteotomy to the neoplasm or its proximity may remain unrecognized during either surgery or pathologic assessment of surgical margin. There is no consensus on an absolute value that represents a “safe” margin, neither in bone nor in soft tissue, where majority of local recurrences are located. This reflects a lack of surgical studies systematically addressing the width, quality and location of surgical margin in respect to the onset of local recurrence. We do not

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fully understand the importance of peritumoral changes visible on MRI as intraosseous edema and extending sometimes for several centimeters from the tumor border, which often normalizes nearly completely during preoperative chemotherapy. In particular, we do not know whether scattered tumor cells may be present in the marrow spaces of this reactive zone, or even in normal-looking bone, and account perhaps for subsequent recurrence in spite of a negative histologic margin on frozen section and definitive pathologic assessment. Skip metastasis is a well-known phenomenon in osteosarcoma characterized by tumor deposit(s) separate from the primary lesion within the same compartment, associated with much higher risk of local and distant relapse [9]. However, also the presence of scattered tumor cells at some distance from the primary mass may result from tumor self-seeding by circulating cancer cells and appears to be a theoretically plausible mechanism for tumor recurrence despite complete tumor excision, even in the absence of an obvious skip lesion [14]. Regardless, local recurrence despite a negative surgical margin conceptually challenges our understanding of the problem. Indeed, the current staging systems and margin classifications do not explain the phenomenon of local recurrence in this setting [7, 8, 18], and we ultimately have to assume the presence of

undetected tumor cells distant from the tumor.

In respect to pathologic response to preoperative chemotherapy, this remains the most powerful treatment-related prognostic information [4, 10, 15]. However, it is typically available only a week after surgery and preoperative evaluation thus hinges on clinical and radiographic assessment. While reduction of pain and swelling is the most common scenario, the predictive value of MRI and ^{18}F -FDG PET imaging for assessment of chemotherapy response has not fully translated into surgical decision-making. Although correlated with histological necrosis in the primary tumor site, the relationship of the imaging results with necrosis is not strong enough and it lacks the anatomic resolution to identify residual viable disease and to direct surgery [6, 12]. Preoperative evaluation for extent of surgery and selection of appropriate margin remains an inexact science that integrates imaging study results and clinical experience.

Last, we do not know the answer to a key question of the problem, which is whether local recurrence is the direct cause of subsequent systemic relapse, or it is just associated with it as local manifestation of cancer progression; perhaps both instances are possible, implying that different mechanisms are in play depending upon the timing of both local and distant relapse. Local

recurrence is the first sign of recurrent disease in approximately half of the cases, whereas it follows or presents synchronously with distant metastases in the remaining patients [1, 3]. While isolated local recurrence after inadequate surgery presumably “permits” metastatic relapse, at least in some of the patients, its occurrence after a negative margin and in association with or shortly after distant metastasis suggests they both are signs of biologic aggressiveness.

Where Do We Need to Go?

Understanding local recurrence in high-grade osteosarcoma is central to the purpose of successful limb salvage and systemic treatment, no matter if we consider recurrent tumor cause or local epiphenomenon of cancer progression. Aponte-Tinao et al. have analyzed their experience with intercalary epiphyseal-sparing surgery around the knee, a technique devised to preserve the native joint in order to maximize limb function and durability, in a selected group of 35 patients with favorable clinical-radiographic profile of response to chemotherapy [2]. Rationale for maintaining the native joint it is not only improved functionality, as the result of preserved proprioception and adequate range of motion, but also to obviate long-term

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prosthetic failure. In this respect, successful host-allograft union is the trade-off to prosthetic fixation.

They have reported excellent overall survival (86% at 5 and 10 years), epiphyseal preservation (86%, 26 of 30 long-term survivors), and function (mean MSTS score: 26 points) at long-term followup. Some of the technical problems of diaphyseal and metadiaphyseal reconstruction, such as coronal, sagittal, and rotational malalignment, were not addressed; future studies should try to do this. They have experienced 54% complications requiring further surgery (19 patients) and, of particular relevance, 9% local recurrence rate (three patients). The high frequency of local recurrence in a selected population of more than 80% “good responders” (29 of 35), as opposed to reported larger series of 45% to 55% “good responders” [4, 10, 15], highlights the risks possibly related with narrow margins. In fact, although a minimum negative margin of 10 mm was obtained in all patients, margin width was not stratified and correlated with local recurrence. Despite overall responsive clinical features, six of the 35 patients demonstrated less than 90% tumor necrosis on pathologic assessment of the specimen. The incidence of local recurrence with less than 90% necrosis was 17% (one of six), more than two times higher if compared to 7% (two of 29) with 90% or more necrosis,

although this was not reported or statistically elaborated by the authors. The relatively small patient population, limited analysis of margins and the retrospective nature of the study prevent from further inference and speculation; all of these represent potential areas of opportunity for future research. However, even much larger, cooperative retrospective studies are unlikely to provide homogeneous data and definitive answers to the problem [1]. Prospective cooperative collection of homogeneous data related to the known risk factors, and including disease course after relapse and updated followup, should be pursued. Integration with state-of-art dynamic and functional imaging is necessary to maximize cancer detection and define potential and limitations of “personalized” treatment in this setting. As local recurrence is associated with distant relapse in vast majority of patients, new agents and systemic strategies are necessary to improve success rate in poor responders and relapsed patients in general.

How Do We Get There?

Detailed specimen review, prospective systematic collection of comprehensive data on surgical margin, including type of tissue, width and relationship with tumor spatial geometry, and cross-check analysis with contemporary functional

imaging is necessary to understand the intimate relationship between margin and tumor response to chemotherapy. Meanwhile, clinical practice should be optimized to prevent local recurrence. The role of MRI and ^{18}F -FDG PET imaging in predicting response needs to be integrated with clinical information and fully exploited preoperatively, with the dual goal of early identification of unsatisfactory response and consideration of alternative strategy when available, and of avoiding “narrow” margins in poor responders. Refinement of current staging systems and margins assessment is dependent upon advances in cancer detection and the capability to identify smaller tumor deposits, just as in the past when CT first, and subsequently MRI, improved conventional radiography in clinical decision making. Newer generation technologies using molecular and particle-based agents, also known as “theranostics” (a term that blends the ideas of therapeutics and diagnostics), and other fluorescence-based imaging systems have been developed for image-guided procedures [13]. Recent FDA-approved silica nanoparticle is a cancer-targeting dual modality platform combining PET and optical imaging approaches, designed to translate preoperative PET imaging findings to the intraoperative setting using a high-resolution fluorescent camera system for real-time visualization of fluorescent tumor deposits in melanoma patients [5].

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In analogy, innovative imaging approaches are required to probe osteosarcoma; basic and clinical research may lead to development of multimodal nanoparticles or other agents for selective tumor targeting at and may provide an insight into the mechanisms related to cancer progression and distant spread. Prospective cooperation of the scientific community should be pursued and implemented in order to define novel treatment approaches for patients with relapsed disease. Emerging strategies are currently focusing on immunomodulation, targeting of the tumor microenvironment, membrane tyrosine kinase receptor inhibitors, intracellular signaling inhibitors, antifolates, and targets of genomic instability [11]. As many of these agents will prove ineffective in clinical trials, persistence and dedication are required to aim at a moving target.

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