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Upfront surgical resection for primary bone tumors: rationale and potential benefits

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Abstract

Local control for the treatment of primary bone tumors is generally delayed following neoadjuvant chemotherapy. This was born out of the historical need to manufacture custom implants when performing limb-salvage resection. There is increasing reason to reconsider the timing of local control in the setting of primary bone tumors. In this report, we describe two cases in which upfront surgery was utilized and review rationale, prior literature, and potential benefits of this approach.

Keywords: Upfront surgery, Primary bone tumor, Rhabdomyosarcoma, Undifferentiated pleomorphic sarcoma

Introduction

Primary bone tumors, such as osteosarcoma and Ewing's sarcoma, are traditionally treated with neoadjuvant chemotherapy followed by surgical resection and subsequent adjuvant chemotherapy (Rosen et al., 1979). The rationale to postpone local control was born out of necessity. Once limb-salvage surgery became oncologically acceptable, megaprostheses were used to reconstruct skeletal defects following tumor extirpation. Historically, these implants were custom made and required a few months' time for their design and manufacture. Despite the subsequent development of off-the-shelf modular prosthetic systems, the practice has persisted to date. This has been attributed to several other factors, including the ability to evaluate tumor response to chemotherapy, the early systemic treatment of micro-metastatic disease, as well as the ability to develop a rapport with patients and their family prior to undertaking a life-altering surgery.

Despite this prescribed approach, the need to postpone local control is substantially diminishing. Many implants no longer require custom fabrication. The importance and impact of tumor necrosis on treatment is currently unclear, and first line therapy is generally considered the most effective approach at this junction (Bacci et al., 2003).

In some cases, upfront surgery may even offer tangible benefits. For example, there are rare primary bone tumors, which do not neatly fit within the histologic classification schema and which pose real diagnostic challenges. In such instances, sample error must be considered and larger, sometimes much larger, biopsies are needed to arrive at a diagnosis. Knowing this, upfront surgery may be preferred, in that it offers the entire lesion for histopathologic analysis and increases the confidence in any subsequent treatment recommendation. In addition, there are a number of theoretical benefits that may merit consideration as well.

In this report, we present two cases in which upfront surgery was utilized. One patient was ultimately diagnosed with a pleomorphic rhabdomyosarcoma of bone (PRMS-B) and another patient with an undifferentiated pleomorphic sarcoma of bone (UPS-B). Both patients presented as diagnostic dilemmas and were indicated for upfront local control to aid in both the diagnosis as well as their subsequent management.

Case presentations

Patient 1

A 39-year-old male presented in May 2017 with several months of right knee pain. On exam he was tender to palpation at the proximal medial tibia and exhibited soft-tissue fullness in the area of concern. The patient

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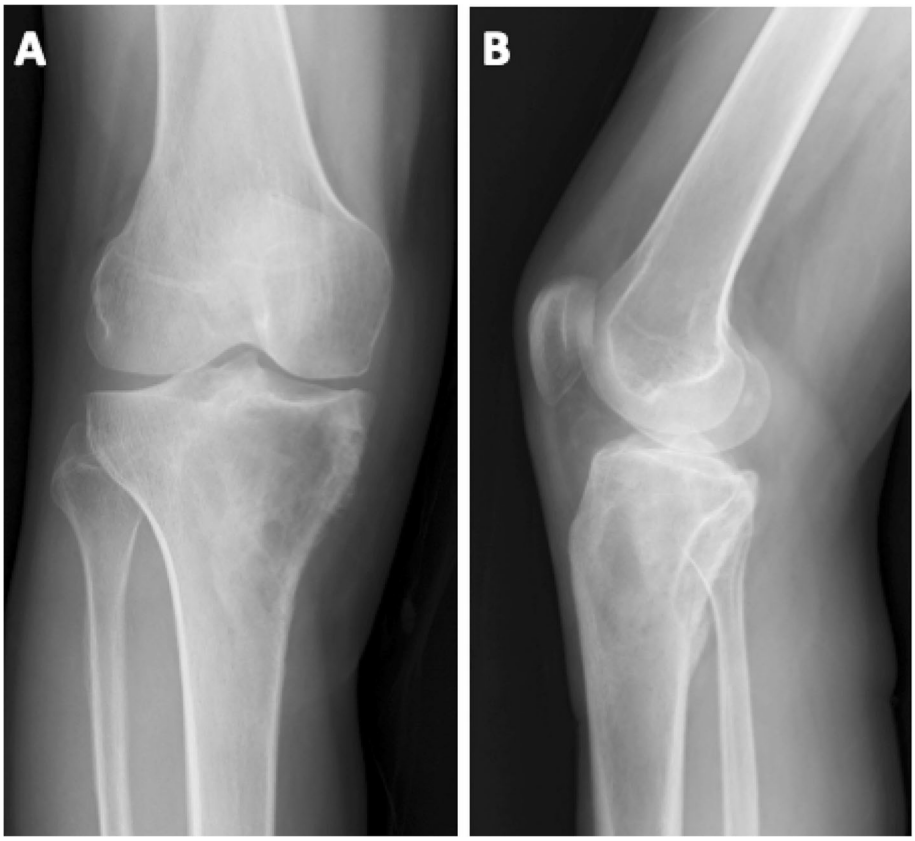

Fig. 1 **a** Anteroposterior and **b** lateral radiographs of the right knee in a 39 year-old male showing an eccentric lytic lesion in the proximal tibia with associated periosteal reaction

retained full active range of motion of the knee and was neurovascularly intact.

A right knee radiograph demonstrated an eccentric, primarily lytic lesion at the proximal medial tibial epiphysis with cortical irregularity (Fig. 1). Magnetic resonance imaging demonstrated a sharply marginated marrow-replacing lesion extending distally from the articular surface and measuring approximately 11 cm in its longest dimension (Fig. 2). The lesion appeared dark on T1-weighted MRI sequences. On T2-weighted MRI sequences the lesion appeared heterogeneous in signal intensity. Post-contrast imaging revealed avid peripheral enhancement with central non-enhancement. Cortical thinning, bone destruction and a soft-tissue component were readily apparent. The patient underwent a chest CT and PET scan for further staging workup, both of which failed to demonstrate overt metastatic disease.

His case was presented to the institutional multidisciplinary orthopedic oncology tumor board and recommendations were to proceed with an open biopsy of the proximal tibia, which ensued uneventfully. Biopsy results demonstrated the tumor to be composed of undifferentiated round, epitheliod, spindled and pleomorphic cells with rhabdomyoblastic differentiation. Immunohistochemistry revealed positive staining for desmin (Fig. 3), indicative of muscle differentiation, as well as CD99, CD68 and focally positive for Myo-D1. Staining was negative for EMA, CD34, SMA, S100 and WT-1. The differential diagnosis included a dedifferentiated chondrosarcoma versus a primary rhabdomyosarcoma of bone.

His case was again presented at the institutional multidisciplinary tumor board. Given the diagnostic uncertainty recommendations were to proceed with wide resection and reconstruction, deferring systemic therapy for the time.

Following resection, histologic evaluation supported the diagnosis of a primary pleomorphic rhabdomyosarcoma of bone (PRMS-B). Thereafter, he was indicated for systemic chemotherapy. At his most recent follow-up at 2 years post-operatively, he presented with recurrent pain in the knee. An infectious workup was negative, however radiographs and MRI revealed signs of component loosening. He underwent a revision procedure and has been doing well since, with no evidence of local recurrence or metastatic disease.

Patient 2

A 52-year-old female presented in September 2017 for evaluation of a left distal femur bone lesion. Her history

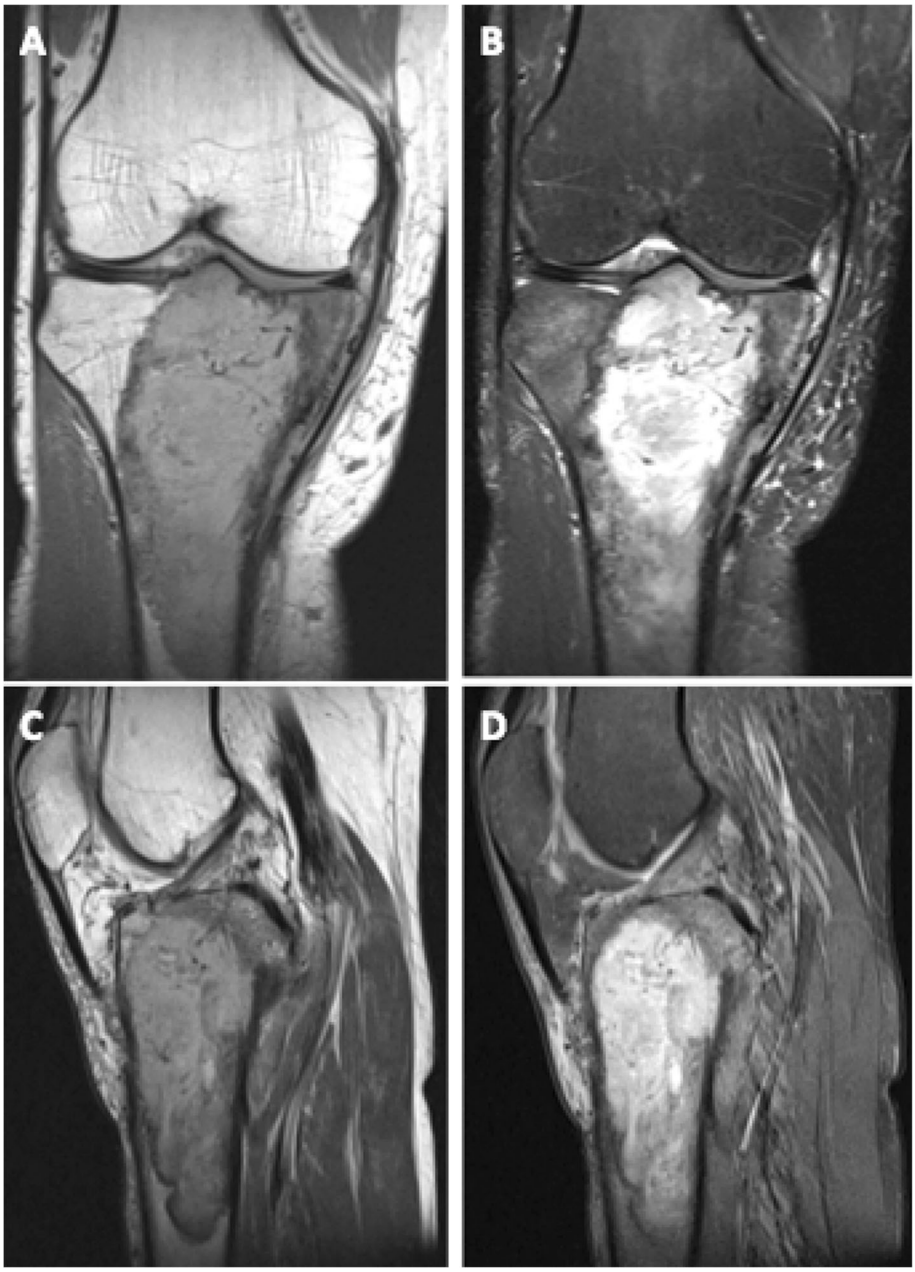

Fig. 2 **a** Coronal Proton Density **b** Coronal T2-weighted fat-suppression **c** Sagittal proton density **d** Sagittal T2 -weighted fat-suppression magnetic resonance images of a right knee in a 39 year-old male demonstrating a well-circumscribed marrow-replacing lesion within the proximal tibia that extends from the articular surface distally. An associated periosteal reaction is evident as well as cortical thinning and destruction. There is also a soft-tissue component to the mass that extends anteromedially

was notable for a prior diagnosis of a benign bone lesion treated in the same location approximately 11 years earlier for which she underwent curettage and bone grafting abroad.

The patient developed recurring left knee pain, including rest pain, which began several months prior to her presentation. On exam, she exhibited a well-healed lateral surgical scar over the distal femur. She was exquisitely tender to palpation over the lateral femoral condyle and had a mild effusion. She tolerated active and passive flexion from 0 to 90 degrees, thereafter limited by pain. She was neurovascularly intact distally.

Plain radiographs demonstrated a mixed sclerotic and lucent lesion within the lateral femoral condyle (Fig. 4). Magnetic resonance imaging revealed a large mass replacing the entirety of the lateral femoral condyle, crossing midline and encroaching upon the medial femoral condyle (Fig. 5). The lesion was dark on T1-

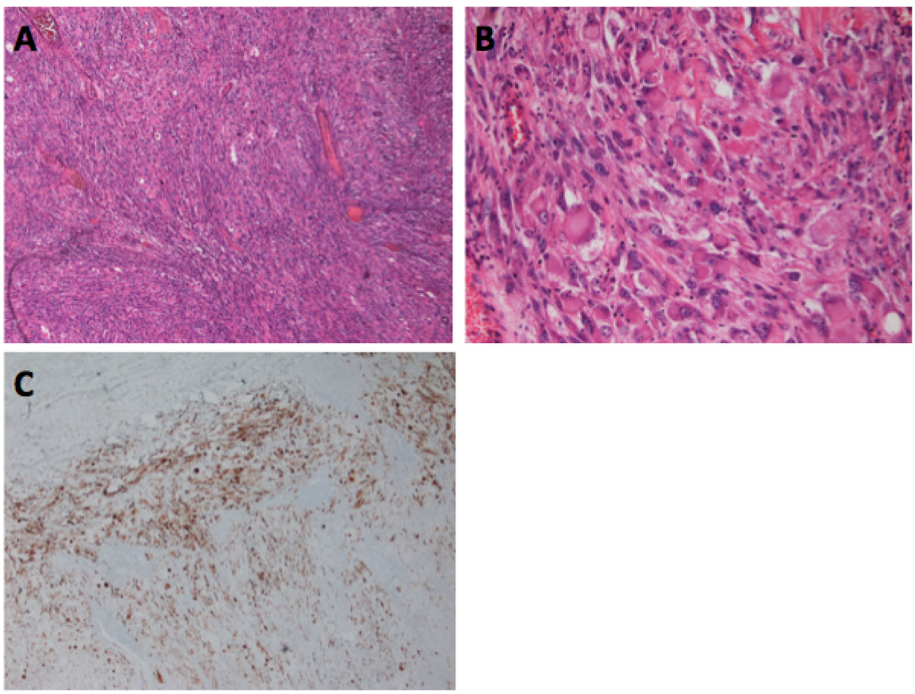

Fig. 3 **a** Photomicrograph demonstrating hypercellularity (× 10, H&E) **b** Photomicrograph demonstrating rhabdomyoblasts with pleomorphic nuclei (× 40, H&E) **c** Immunohistochemical staining positive for desmin, indicative of muscle differentiation

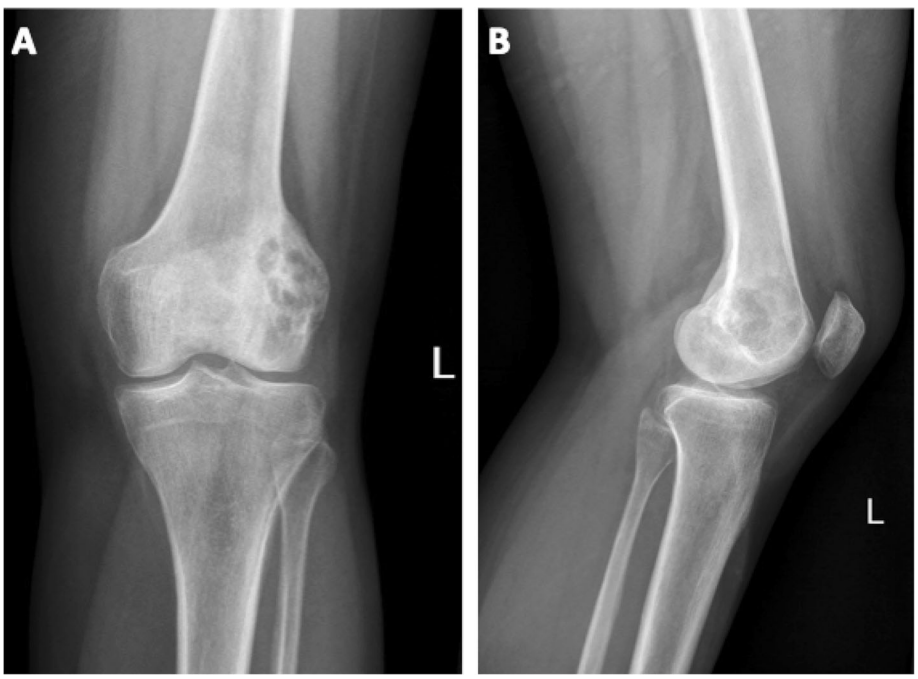

Fig. 4 **a** Anteroposterior and **b** lateral radiographs of the left knee in a 52 year old female showing a mixed sclerotic and lucent lesion within the lateral femoral condyle

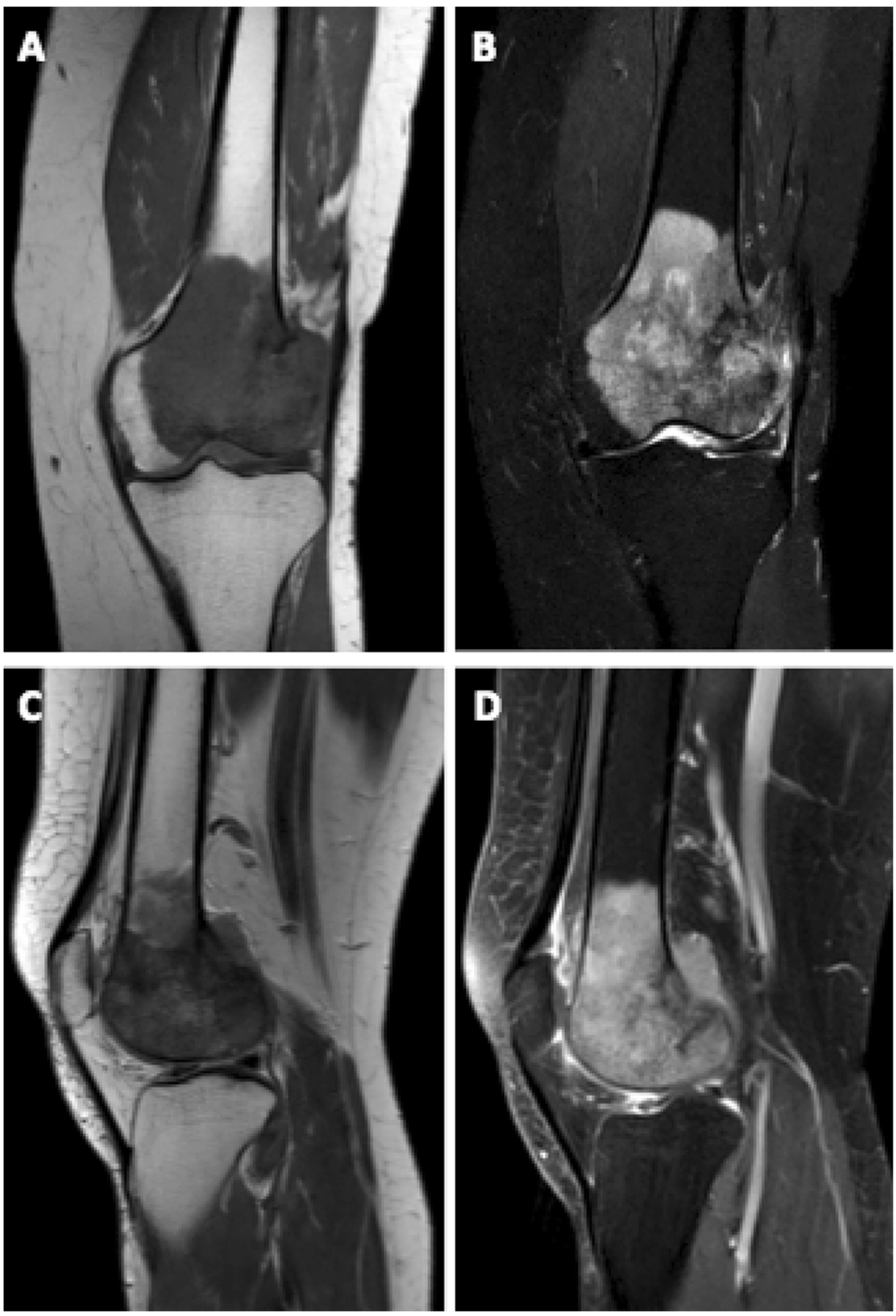

Fig. 5 **a** Coronal T1 **b** Coronal T2 **c** Sagittal T1 **d** Sagittal T1 fat-suppression C+ magnetic resonance images of a left knee in a 52 year old female. A large mass within the lateral femoral condyle that crosses the midline to involve the medial femoral condyle is demonstrated. There is soft tissue extension at the lateral femoral condyle with large areas of enhancing tumor within the soft tissue. Furthermore, areas of markedly low T1 and T2 signal in the lateral femoral condyle validate history of prior curettage and packing in the area

weighted images and bright on T2-weighted images. Post-contrast fat suppressed T1-weighted images demonstrated central non-enhancement with extensive enhancement in the remainder of the tumor. Comparison of advanced imaging confirmed interval enlargement relative to prior imaging obtained a few months earlier. Further imaging was obtained including a bone-scan, chest CT, and PET scan all of which failed to demonstrate metastatic disease.

Her case was presented to the institutional multidisciplinary orthopedic oncology tumor board and recommendations were to proceed with an open biopsy of

the distal femur. Histologic findings were most supportive of a high-grade spindle cell tumor compatible with undifferentiated pleomorphic sarcoma of bone (Fig. 6). Her case was again discussed and given the unusual presentation and progression of her tumor, upfront surgery was recommended to ensure proper diagnosis and to guide subsequent recommendations. She underwent wide excision and reconstruction uneventfully.

Final pathology confirmed the initial diagnosis of undifferentiated pleomorphic sarcoma of bone and she was subsequently started on systemic therapy in accordance with the EUROBOSS protocol. The patient completed several cycles of treatment, but was unable to tolerate the associated toxicities and elected thereafter to discontinue further treatment. At 15 months post-operatively, she presented with complaints of global discomfort in the left knee. Initial concerns for septic loosening were ruled out after joint aspiration was negative for infection. A revision procedure was done to replace the loose femoral component and to resurface the patella which exhibited moderate wear. Early results have been excellent, with pain relief and improved function. She remains well with no evidence of local recurrence or metastatic disease.

Discussion

Prior to the widespread adoption of treating primary bone tumors with neo-adjuvant chemotherapy followed by surgical resection and adjuvant therapy, the timing of surgery has not been extensively investigated or discussed. Today, custom prostheses are readily available for use almost immediately and are rarely a reason for delay of local control. Furthermore, recent EURAMOS-1 results have shown that the ability to improve osteosarcoma outcomes by the addition of cytotoxic agents has not born out (Bielack et al., 2015; Marina et al., 2016; Whelan et al., 2015). As such, the utility of and need for tumor necrosis may be less relevant than previously thought and perhaps timing of surgery in select scenarios should be reconsidered.

In this report, upfront surgery was used to affirm the diagnosis and ensure appropriate therapy. While use of neoadjuvant chemotherapy is widely agreed upon, its earlier purpose and rationale often no longer applies, particularly within the context of osteosarcoma (Bacci et al., 2003). Furthermore, despite the historical evolution of delayed local control, upfront surgical resection offers a number of theoretical advantages.

Firstly, approximately 20 % of patients with primary bone tumors present with truly localized disease; that is

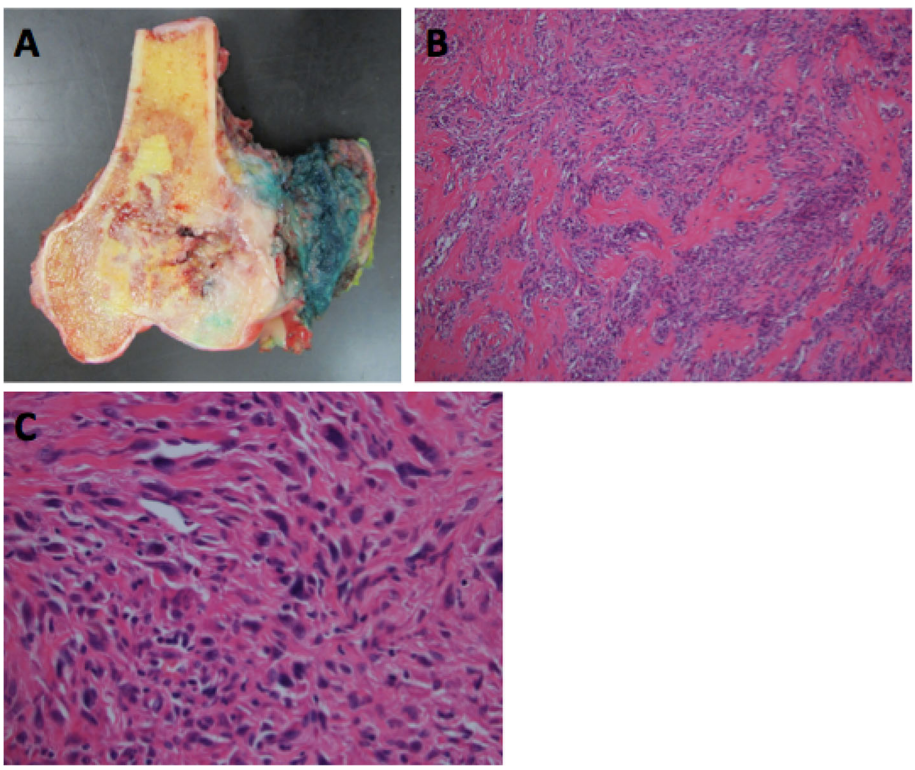

Fig. 6 **a** Clinical photograph of resected tumor **b** Photomicrograph demonstrating hypercellularity and fibrous stroma (× 10, H&E) **c** Photomicrograph demonstrating spindle shaped, pleomorphic nuclei (× 40, H&E)

without disseminated micro-metastatic disease. Some of these patients will ultimately fail first-line chemotherapy, relapse, or otherwise exhibit a chemo-resistant tumor. In theory, upfront surgery offers these patients a cure.

Secondly, while oncologic outcomes remain paramount, functional outcomes need to be considered as well. Patients, relatives and surgeons are increasingly expecting more of the limb-salvage surgery and its subsequent reconstruction. Currently, patients who undergo surgery do so in a substantially deconditioned state. They oftentimes maintain non-weight bearing precautions, use crutches or other assistive devices and minimize any meaningful activity for the approximate 10-week period preceding local control. Additionally, they undergo treatment with cytotoxic chemotherapy and in turn, oftentimes remain sedentary for long periods of time during which they lose muscle mass. Their nutritional intake suffers and they often develop abnormal gait patterns. Upfront surgery, which would subject patients to surgery at a time of peak health, may result in preserved conditioning and muscle mass, and should allow for faster rehabilitation. In the absence of cytotoxic chemotherapy, healing may be more reliable and rapid. The need for assistive devices and weight bearing precautions would be minimized. In theory, all of these advantages should culminate in improved functional outcomes.

Thirdly, it remains critically important that adequate tumor samples be obtained and banked for basic and translational research. While small biopsies can be cultured, expanded, and even passaged within preclinical models, these techniques have inherent limitations. Some researchers feel that as these tumors are artificially stressed and manipulated, they evolve and mutate further, drifting substantially from their initial tumor biology. Upfront surgery offers the opportunity to secure bulk primary tumor for research, which hopefully results in improved tumorigenic understanding. At this point, it seems that only through deliberate efforts to bolster and support translational research that rationally designed therapeutics and incrementally improved outcomes can be realized.

Upfront surgery is hardly a new concept and to date, it has been explored or adopted in a number of preclinical and clinical settings. Bell et al. utilized a murine osteosarcoma model to evaluate the impact of surgical timing with respect to chemotherapy. The authors characterized mean survival, incidence of lung metastases and systemic relapse between four groups. They compared the effects of surgery alone, surgery plus preoperative chemotherapy, surgery plus post-operative chemotherapy, and surgery plus peri-operative chemotherapy. They found no significant differences between the pre-operative and post-operative chemotherapy groups in all categories (Bell et al., 1988). Goorin et al. randomly assigned 100 patients with non-metastatic osteosarcoma to receive either immediate surgery with post-operative chemotherapy or delayed surgery following neoadjuvant chemotherapy. They found that at five years, the projected event-free survival (EFS) was 69% +/− 8% in the immediate surgery and 61% +/− 8% in the delayed surgery group ($p = 0.8$). They concluded that neoadjuvant chemotherapy and subsequent or delayed local control did not offer a clear advantage over upfront local control with respect to EFS (Goorin et al., 2003). Meyers et al. also found that in 279 patients with untreated localized osteosarcoma, disease-free survival was not affected by use of preoperative chemotherapy versus immediate surgery (Meyers et al., 1992). Taken together, upfront surgery seems to be, at a minimum, oncologically equivalent to delayed surgery.

Pleomorphic rhabdomyosarcoma (PRMS) is a soft-tissue tumor that affects the head and neck, genitourinary system and the extremities. These tumors are histologically defined by dedifferentiated round to spindle shaped cells with dense eosinophilic staining. This heterogeneous population of cells makes diagnosis a challenge, often requiring the use of immunohistochemistry (IHC). The presence of pleomorphic rhabdomyoblasts as well as positive IHC staining for at least one muscle-specific marker is diagnostic of PRMS (Dagher & Helman, 1999; Fletcher et al., 2006; Furlong et al., 2001; Keyhani & Booher, 1968).

It is exceptionally rare for PRMS to present as a primary bone tumor. To our knowledge, there are only 11 previously reported cases of primary rhabdomyosarcoma of bone (RMS-B) (Table 1), only two of which were diagnosed as PRMS-B (Balogh et al., 2016; Bressner et al., 2016; Hakozaki et al., 2008; Hsueh et al., 1986; Kumar et al., 2011; Lamovec et al., 1994; Lucas et al., 1996; Oda et al., 1993; Pasquel et al., 1976; Thomas et al., 2002; Wang et al., 2000). In all cases, the primary lesion originated within bone and extended into the surrounding soft tissue. Treatment strategies varied among reports, though a combination of surgery, chemotherapy and/or radiotherapy were utilized. No general consensus exists in terms of surgical timing. Admittedly, the paucity of reported cases makes it difficult to draw robust conclusions; however, reported clinical outcomes vary and do not seem to be dependent upon treatment approach.

Undifferentiated pleomorphic sarcoma (UPS), previously referred to as malignant fibrous histiocytoma (MFH), is a recognized rare primary bone tumor which shares many features of osteosarcoma but lacks obvious histologic evidence of malignant bone formation. It is generally grouped and treated as an osteosarcoma. It is defined on histology by a fibrous stroma with a mixture of spindle cells, giant cells, and histiocyte-like cells (McCarthy et al., 1979; Widemann & Italiano, 2018). Given the cytologic and nuclear

Table 1 Reported cases of rhabdomyosarcoma of bone in the literature including treatment and outcomes

Author	Year	Cases	Age/ Sex	Location	Diagnosis	Treatment	Outcome
Lamovec et al	1994	1	31/ M	Tibia, proximal	Pleomorphic rhabdomyosarcoma of bone	Above knee amputation with postoperative chemotherapy	Died of Metastatic disease at 3 years 4 months
Hsueh et al	1986	1	11/ M	Femur, distal	Embryonal rhabdomyosarcoma of bone	Hip disarticulation, adjuvant chemotherapy	Lung metastases - lost to follow-up
Pasquel et al	1976	1	13/F	Femur, diaphysis	Embryonal rhabdomyosarcoma of bone	Initially refused radical surgery – radiotherapy and chemotherapy with no improvement, coxofemoral disarticulation	Lung metastases
Thomas et al	2002	1	22/ M	Humerus, proximal	Embryonal rhabdomyosarcoma of bone	Neoadjuvant chemotherapy with forequarter amputation	Lost to follow-up, died 11 months post-operatively
Lucas et al	1996	1	7/F	Femur, diaphysis	Embryonal rhabdomyosarcoma of bone	Neoadjuvant chemotherapy, above knee amputation, postop radiation	No signs of local recurrence/metastasis 7 months post op
Oda et al	1993	1	32/ M	Ilium, wing	Embryonal rhabdomyosarcoma of bone	Hemipelvectomy with adjuvant chemotherapy	No signs of local recurrence/metastasis 4 years post op
Balogh et al	2016	2	17/ M 9/M	Pelvis, diffusely Pelvis, diffusely	Alveolar rhabdomyosarcoma of bone in both cases	Chemotherapy alone	Died at 7 months Died at 30 months
Hakozaki et al	2007	1	16/F	Sacrum	Embryonal rhabdomyosarcoma of bone	Chemotherapy and radiation	Died at 17 months
Wang et al	1999	1	45/ M	Femur, proximal	Pleomorphic rhabdomyosarcoma of bone	Neoadjuvant chemotherapy, limb salvage surgery, adjuvant chemotherapy	No signs of local recurrence/metastasis 4 years post op
Bressner et al	2016	1	34/ M	Femur, distal	Pleomorphic rhabdomyosarcoma of bone	Neoadjuvant chemotherapy (presumed Ewing), rotationplasty, adjuvant chemotherapy	Died at 8 months
This Study	2019	1	39/ M	Femur, distal	Pleomorphic rhabdomyosarcoma of bone	Limb salvage surgery with adjuvant chemotherapy	No signs of local recurrence 2 years postop

pleomorphism that is seen after extensive sampling and use of various diagnostic techniques, UPS is a diagnosis of exclusion (Fletcher et al., 2006).

UPS seldom presents as a primary bone tumor, however review of the literature reveals several cases describing their radiographic and histologic features (Gustafson, 1994; Kumar et al., 1990; Little & McCarthy, 1993). Treatment of UPS-B involves surgical resection, chemotherapy and/or radiation, a well-established protocol for soft tissue sarcomas (Bielack et al., 1999; Natarajan et al., 2007; Sun et al., 2017). Huvos et al. reported on 130 patients diagnosed with UPS of bone (UPS-B). All of their patients underwent surgical resection; however 66 patients were treated before 1974, when modern chemotherapy was not available at the institution. They found no significant difference in survival estimates between the pre- and post-1974 treatment groups (Huvos et al., 1985). Picci et al. reviewed 51 patients with UPS-B who were treated using standardized osteosarcoma protocols with neo-adjuvant chemotherapy, surgical resection and adjuvant chemotherapy. They found that the histologic response to neo-adjuvant chemotherapy was in many cases poor, and that a clear improvement in overall survival was not proven (Picci et al., 1997). Weiner et al. and Ozkurt et al. supported these claims, using upfront surgical resection and adjuvant chemotherapy to achieve long-term disease free survival in 3 and 14 patients with UPS-B respectively. (Ozkurt et al., 2016; Weiner et al., 1983).

Although immediate surgical resection of primary bone tumors is not currently standard of care, it does offer potential advantages. Admittedly, instances remain where it may not be the appropriate approach. For example, the tremendous soft-tissue extension of a Ewing sarcoma typically noted at presentation can recede substantially following induction chemotherapy, in turn, aiding surgical resection. In other instances, custom implants such as growing prostheses are indicated. Induction chemotherapy provides treatment during the manufacturing process, which has historically been the rationale for preoperative chemotherapy.

In summary, the previous 3 decades have demonstrated stagnant outcomes for primary bone tumors, particularly for osteosarcoma and novel or "unconventional" approaches should be strongly considered. While upfront surgery may impose a few logistical challenges on surgical schedule and surgical coordination, these can largely be met. Both preclinical and clinical data seems to support that this approach is, at a minimum, oncologically non-inferior and there are a number of theoretical and real advantages both for the patient and for the field. The two rare primary bone tumors presented in this report both obviated the need for upfront surgery given their diagnostic ambiguity and treatment challenges. Admittedly, it is difficult to extrapolate experiences with rare primary bone tumors to more commonly encountered tumors such as osteosarcoma and Ewing's sarcoma in order to make treatment recommendations. However, they may serve as examples in which upfront surgery should be considered, and may offer broader relevance and unrealized potential. Further investigations will need to be conducted in the future to determine whether a shift in the standard treatment approach for primary bone tumors should be made. That said, careful selection and patient-specific considerations are both essential and should be weighed in the context of a multi-disciplinary team that understands the inherent challenges and benefits of each approach.

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Authors' contributions
DG, BH, RY and AC were all directly involved in the care of both patients. YZ, AS, DG, BH, RY and AC were all major contributors in writing the manuscript. JT was involved in obtaining IRB study approval. All authors read and approved the final manuscript.

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The Albert Einstein College of Medicine Institutional Review Board reviewed this case report study and have approved it for publication [IRB # 2018–8768].

Consent for publication
all necessary consents were obtained.

Competing interests
The author(s) declare no competing interests.

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