Effects of Neoadjuvant Chemotherapy on Image-Directed Planning of Surgical Resection for Distal Femoral Osteosarcoma

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Background: Standard therapy for localized osteosarcoma includes neoadjuvant chemotherapy preceding local control surgery, followed by adjuvant chemotherapy. When limb-salvage procedures were being developed, preoperative chemotherapy allowed a delay in definitive surgery to permit fabrication of custom endoprosthetic reconstruction implants. One rationale for its continuation as the care standard has been the perception that it renders surgery easier and safer. Our objective was to compare surgical procedures planned on the basis of magnetic resonance images (MRIs) of distal femoral osteosarcomas acquired before neoadjuvant chemotherapy with surgical procedures planned on the basis of MRIs acquired after neoadjuvant chemotherapy as a measure of the surgically critical anatomic effects of the chemotherapy.

Methods: Twenty-four consecutive patients with distal femoral osteosarcoma had available digital MRIs preceding and following neoadjuvant chemotherapy. Thorough questionnaires were used to catalogue surgically critical anatomic details of MRI-directed surgical planning. Four faculty musculoskeletal oncologic surgeons and two musculoskeletal radiologists evaluated the blinded and randomly ordered MRIs. Interrater and intrarater reliabilities were calculated with intraclass correlation coefficients. The Student t test and chi-square test were used to compare pre-chemotherapy and post-chemotherapy continuous and categorical variables on the questionnaire. Mixed-effect regression models were employed to compare surgical procedures planned on the basis of pre-chemotherapy MRIs and with those planned on the basis of post-chemotherapy MRIs.

Results: The blinded reviews generated strong intraclass correlation coefficients for both interrater (0.772) and mean intrarater (0.778) reliability. The MRI-planned resections for the majority of tumors changed meaningfully after chemotherapy, but in inconsistent directions. On the basis of mixed-effect regression modeling, it appeared that more amputations were planned on the basis of post-chemotherapy MRIs. No other parameters differed in a significant and clinically meaningful fashion. Surgeons demonstrated their expectation that neoadjuvant chemotherapy would improve resectability by planning more radical surgical procedures on the basis of scans that they predicted had been obtained pre-chemotherapy.

Conclusions: Surgeons can reliably record the anatomic details of a planned resection of an osteosarcoma. Such methods may be useful in future multi-institutional clinical trials or registries. The common belief that neoadjuvant chemotherapy increases the resectability of extremity osteosarcomas remains anecdotally based. Rigorous assessment of this phenomenon in larger cohorts and at other anatomic sites as well as re-evaluation of other arguments for neoadjuvant chemotherapy should be considered.

The standard of care for isolated extremity osteosarcoma in adolescents and young adults has changed very little in the last twenty years¹. Chemotherapeutic

regimens including doxorubicin, cisplatin, and high-dose methotrexate have predominated, and the timing of treatments has also changed very little. Most patients receive some

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portion of their chemotherapy prior to surgical local control (termed *neoadjuvant chemotherapy*) and then additional adjuvant chemotherapy following surgical resection. As so much of this care standard has been subjected to repeated evaluation in randomized controlled clinical trials¹, it may be assumed that the timing of treatments is similarly evidence-based. It is not.

The timing of treatments is instead rational, based on the following four considerations that led to its development and incorporation into common practice.

First, early in the days of limb salvage surgery, neoadjuvant chemotherapy was undertaken to delay definitive surgery to permit the fabrication of the custom endoprosthetic implants then used for limb salvage reconstructions.

Second, neoadjuvant chemotherapy permitted measurement of the treatment effect on the primary tumor² in the form of preoperative chemotherapy-induced tumor necrosis, thereby providing a surrogate measure of chemotherapeutic response and eradication of clinically undetectable microscopic metastatic disease.

Third, treating physicians thought that initiating systemic treatments quickly put priorities in proper philosophical order, with an upfront attack on the deadly presumed systemic disease, rather than an initial focus on the primary tumor and local control.

Fourth, surgeons preferred performing close-margin resections around tumors that had been largely treated already. Often-touted potentially advantageous treatment effects of neoadjuvant chemotherapy included tumor size reduction, clearing of peritumoral edema on magnetic resonance imaging (MRI) scans, development of a rind or pseudocapsule, and increased palpable firmness of the tumor.

The first rationale has largely disappeared now that modular implants and large regional and national allograft tissue repositories are available. The second rationale remains, but provides only prognostic information rather than treatment guidance, as changing protocols following a poor histological response (limited tumor necrosis) to preoperative chemotherapy does not improve prognosis³. In a Pediatric Oncology Group study beginning in the late 1980s, investigators attempted to provide evidence for the third rationale, but the study was closed after years of insufficient patient accrual⁴. The reason suspected for the poor enrollment was that many surgeons already believed too firmly in the fourth rationale to enroll their patients for possible randomization to the immediate-surgery arm when limb salvage was planned. Although they failed to reach significance, the published results trended toward improved survival in the immediate-surgery group⁴. This study's underpowered results did not slow the acceptance of neoadjuvant chemotherapy as the standard of care for patients with osteosarcoma.

Thus, even the lack of data for the third rationale is the result of the yet unstudied fourth rationale, that neoadjuvant chemotherapy makes local control surgery easier or safer. While a number of modalities have been tested with regard to their value in noninvasively measuring the treatment effect of neoadjuvant chemotherapy on the primary tumor prior to local

control surgery, no modality has been sufficiently successful at predicting the treatment effect to be widely adopted by sarcoma treatment centers⁵⁻¹⁴. While evaluation of changes between pre-chemotherapy and post-chemotherapy MRIs has not proven to accurately predict histologically confirmed treatment effects, these MRIs are still almost universally used by surgeons to plan local control resections¹⁵. Furthermore, MRI is the most accurate noninvasive means of staging the local bone and soft-tissue extent of sarcomas, including compartmental spread, neurovascular involvement, and intra-articular spread¹⁶⁻²².

We investigated the effect of neoadjuvant chemotherapy on MRI-based surgical planning for osteosarcoma. Even a tumor that has responded well to preoperative chemotherapy in terms of histological necrosis may have progressed with regard to surgically critical anatomy. This study was undertaken to evaluate the surgically important anatomic effects of neoadjuvant chemotherapy. Because the practice standard of neoadjuvant chemotherapy was deeply entrenched and we had no reason to believe that it was erroneous, we thought that it was both impractical and unethical to randomize patients to immediate surgery or neoadjuvant chemotherapy followed by surgery. Instead we chose to evaluate the practice in a pilot study using available data from existent MRIs. In order to measure surgically important anatomic changes on these MRIs, we developed a surgical planning questionnaire focused on the distal part of the femur, assessed its reliability across different surgeons, and tested it against a separate validation in the form of radiologists assessing the same MRIs with their own anatomic details questionnaire. With this tool, we could then safely ask our question: does neoadjuvant chemotherapy change the surgical resections planned by surgeons for distal femoral osteosarcomas?

Materials and Methods

Following institutional research ethics board approval, two prospectively collected sarcoma databases (from the pediatric and adult university sarcoma units) were searched to identify all patients treated for osteosarcoma of the distal part of the femur. Among these patients, only those with two or more pre-surgical MRI scans available in the electronic imaging system, including one pre-chemotherapy and one post-chemotherapy scan, were included. Health records were reviewed and patient age at diagnosis, sex, histological diagnosis and grade, dates of MRI scans, date of biopsy, date of surgery, preoperative chemotherapeutic regimen, surgical resection and reconstruction details, pathologic assessment of margins and response to chemotherapy, local recurrence, systemic recurrence, and duration of follow-up were collected. As the goal of the study was to aid with the decision to refer a patient for neoadjuvant chemotherapy, no patients were excluded because of slight variations in chemotherapy regimen, a subsequently noted poor response to chemotherapy, resultant amputation as local control, or local recurrence as evidence of failed local control. The goal was for the study population to have a typical distribution of initial presentations of distal femoral osteosarcoma.

The pre-chemotherapy and post-chemotherapy MRIs of each tumor were blinded with regard to patient identifiers and dates and then scrambled into an order that widely separated the two scans from any single patient in the list of scans to review. A series of T1-weighted, T2-weighted, and T1-weighted-post-gadolinium images was reviewed for each scan. A surgical planning questionnaire was generated; it noted all of the typical details of surgical planning, including the recommended overall procedure (hip disarticulation, transfemoral amputation, borderline limb salvage, or safe limb salvage), anticipated margins against major nerves and blood vessels, intended myectomies, bone resection levels, plans for

the extensor mechanism and knee joint, and soft-tissue-coverage needs. All participating surgeons reviewed this planning questionnaire form and agreed that it covered all of the essential elements of an osteosarcoma resection planned on the basis of MRI. Another questionnaire was developed by two musculoskeletal radiologists to record and measure all of the typical surgically critical anatomic details observable on MRI of the distal part of the femur.

Four faculty musculoskeletal oncologic surgeons reviewed the scans, and each filled out the surgical planning questionnaire for each MRI as if it was the preoperative MRI. The two musculoskeletal radiologists reviewed all of the scans together, in a similarly blinded fashion, and reached a consensus measurement for each parameter.

For details of the assessment of the reliability and validity of the questionnaire itself, see the Appendix.

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Statistical Methods

The surgeon and radiologist-designated parameters were compared between the pre-chemotherapy and post-chemotherapy scans by using the Student t test for continuous variables and the chi-square test for categorical variables, both in a paired fashion. As a result of the multiple comparisons, a p value of <0.0019 was considered significant (Bonferroni multiplier of twenty-seven).

To evaluate for more global changes between pre-chemotherapy and post-chemotherapy scans, mixed-effect regression models were used to assess the changes and account for the correlation between repeated measurements of patients²³. For this analysis, some of the data were simplified into dichotomous variables from more complex categorical variables. Hip disarticulation and transfemoral amputation designations were collapsed into a single amputation designation; safe and borderline limb-salvage designations were collapsed into a single limb salvage designation. All forms of extra-articular knee resection were

collapsed into one category as well. Expected margins were collapsed into positive-margin and negative-margin categories. The following variables were entered into the models: type of surgery (amputation or limb salvage); type of knee resection (intra-articular or extra-articular); expected margins (negative or positive) on the femoral/popliteal artery and vein; expected margins (negative or positive) on the sciatic, tibial, and common peroneal nerves; and resection length of the femur (in centimeters). The models were fitted with maximum likelihood for binary data²⁴ and restricted maximum likelihood for continuous data²⁵. P values of <0.05 were considered to indicate significance.

Results

The retrospective review of the prospectively collected sarcoma databases identified twenty-four consecutive patients treated for osteosarcoma of the distal part of the femur who met all of the inclusion criteria. Clinically, this group of patients with osteosarcoma had a typical distribution of demographic parameters, chemotherapeutic regimens, chemotherapeutic responses as measured by grading of necrosis on histological examination, and local control surgical procedures and outcomes (see Appendix). The forty-eight pre-neoadjuvant chemotherapy and post-neoadjuvant chemotherapy MRI scans were reviewed in a blinded fashion. The same imaging equipment was used to acquire both the pre-chemotherapy and the post-chemotherapy images of all but one patient. (See Appendix for a detailed assessment of provisional reliability and validity of the surgical and MRI assessment questionnaires.) Briefly, high interrater (intra-class correlation coefficient [ICC], 0.772) and intrarater (mean ICC, 0.778) reliability were noted among the four faculty surgeons who assessed the MRIs using the questionnaire. The radiologists' intrarater reliability was also strong (ICC, 0.941). The

Fig. 1
Change in mean surgery-type designation by the four faculty surgeons assessing the blinded pre-chemotherapy and post-chemotherapy MRIs. Surgery-type designations were converted to integers one through four and averaged for each case at each time point. While some remained unchanged, others changed following administration of neoadjuvant chemotherapy toward either more or less radical/risky resections. (Multiple parallel lines are drawn at slight vertical offsets when values overlap, such that a single line represents each case.)

Fig. 2

Surgery-type changes between pre-chemotherapy and post-chemotherapy MRIs did not strictly correlate with the histologically determined chemotherapeutic effect. The difference between pre-chemotherapy and post-chemotherapy surgery-type designations, converted to integers one through four and averaged for each time point, is represented on the vertical axis. A change of +1 represents a shift in the mean surgery-type designation to the next more ablative type, and a change of -1 represents a shift of one categorical type to the next less ablative type. While a cluster of histologically poor-response tumors also show the expected increase in ablative surgery type and another cluster of histologically good-response tumors show the expected decrease in surgery type, there are significant outliers of poor responders anatomically improving and good responders anatomically worsening.

MRI-planned surgical procedures also grossly correlated with the procedures that were actually performed. Both amputations and the single precarious (<1-mm) resection margin were predicted. Furthermore, cases for which surgeons predicted neurovascular margins of <1 cm on the basis of post-chemotherapy MRIs were noted to have margins of <1 cm on pathological evaluation.

The radiologists' interpretations (see Appendix) noted trends toward an increase in the percentage of fluid signal, indicating cystic or necrotic tissue, from 13.8 ± 18.1 (mean and standard deviation) on the pre-chemotherapy MRIs to 21.7 ± 19.3 on the post-chemotherapy MRIs ($p = 0.024$) and a decrease in the percentage of dense fibrous or osseous tissue signal from 82.5 ± 24.4 to 71.7 ± 21.8 ($p = 0.048$). While these p values were <0.05, they were considered nonsignificant because of the higher stringency necessary with multiple comparisons. (The Bonferroni multiplier-adjusted p value of significance was 0.0019.) The only other trend, with a p value of <0.2, was the distance between the distal extent of edema and the knee joint, which slightly increased by 0.4 cm ($p = 0.13$). Although the mean proximal length of femoral involvement, by either the tumor or edema, did not change significantly or even show a trend for change, the difference between the length of tumor involvement and the length of edema involvement narrowed slightly, reflecting the

fact that some cases had less intramedullary edema extending beyond the tumor following neoadjuvant chemotherapy, due either to a reduction in edema extent or to extension of tumor into what was previously considered edema. For every neurovascular structure that was assessed radiologically, encroachment of edema improved as often as, or more often than, it worsened, as demonstrated by a simple of count of cases with change. In direct contrast, encroachment of tumor worsened as often as, or more often than, it improved (see Appendix).

When we considered the surgical procedures planned by the surgeons on the basis of the MRIs (see Appendix), the only significant differences that we found were an increased number of en bloc resections of the proximal part of the tibia (seventeen compared with five; $p = 0.007$) and a lower percentage of cases in which the vastus intermedius muscle was planned to be resected (85% [still nearly all] compared with 94%; $p = 0.016$) based on post-chemotherapy images. There were changes in many parameters in many individual cases, but no others were directionally consistent to an extent that the differences were significant.

As a result of the modest sample size and the stringent α value necessary for multiple comparisons, the post-hoc power to detect any potentially significant change was approximately 50%. To increase the power to 90%, a secondary analysis was

Fig. 3

Surgeons expect chemotherapy to improve tumor resectability. Surgeons predicting whether a blinded MRI had been acquired before or after neoadjuvant chemotherapy tended to assume that scans from which they planned more radical surgical treatment (by numerical average) were obtained prior to neoadjuvant chemotherapy (overrepresented in categories to the left). MRIs depicting tumors estimated to be more easily resectable, whether actually acquired before or after neoadjuvant chemotherapy, were more frequently estimated to have been obtained after chemotherapy (categories to the right). (Cumulative rating designation diamonds are multiplied and offset horizontally such that each represents the number of predictions from a single MRI, without overlap.)

performed to consider every trend for which p was <0.2 . The trends favoring post-chemotherapy surgical plans included a smaller percentage of the short head of the biceps femoris muscle resected and fewer hamstring flaps for closure. The trends unfavorable to post-chemotherapy scans included more ablative articular resections; increased percentages of the rectus femoris, sartorius, semimembranosus, semitendinosus, and gracilis muscles resected; and more planned gastrocnemius flaps for closure. No expected neurovascular margins changed significantly, or even showed a trend for change, but all had a slight increase in the raw numbers of positive margins expected or structures sacrificed on the basis of the post-chemotherapy MRIs. Figure 1 demonstrates the directional changes of individual cases in terms of the surgery planned (hip disarticulation, transfemoral amputation, borderline limb salvage, or safe limb salvage).

In the mixed-effect regression models, only the type of surgery planned differed significantly between the pre-chemotherapy and post-chemotherapy scans ($p = 0.049$), with more amputations (three in total) planned on the basis of the post-chemotherapy scans. The type of knee resection planned on the basis of the post-chemotherapy MRIs (eight more extra-articular resections; $p = 0.069$) as well as the length of femoral resection planned (shorter by 0.8 cm; $p = 0.083$),

expected margins on the femoral/popliteal artery (four more sacrificed; $p = 0.82$) and vein (four more sacrificed; $p = 0.82$), and expected margins on the sciatic nerve (six more sacrificed; $p = 0.13$), tibial nerve (six more sacrificed; $p = 0.21$), and common peroneal nerve (six more sacrificed; $p = 0.13$) did not differ significantly from what was planned on the basis of the pre-chemotherapy scans.

The change in the type of surgery planned (safe limb salvage, borderline limb salvage, transfemoral amputation, or hip disarticulation) between the pre-chemotherapy and post-chemotherapy scans did not tightly correlate with the ultimate percentage of necrosis on histological examination (reflecting treatment effect) (Fig. 2). There were more dramatic improvements in the surgical plans for the patients whose tumor demonstrated a high percentage of necrosis. Tumors that prompted more aggressive post-chemotherapy surgical plans were found to have both high and low percentages of necrosis, but more were grouped among the poor histologic responders.

Effective blinding was confirmed by the finding that, when the faculty surgeons were asked to note whether the blinded scan being reviewed had likely been acquired pre-chemotherapy or post-chemotherapy, their prediction that a scan was a post-chemotherapy scan was correct (i.e., it was actually a post-chemotherapy scan) fifty-one times (of ninety-six opportunities) and their prediction that a

scan was a pre-chemotherapy scan was correct sixty-nine times (of ninety-six opportunities). Surgeons predicted that MRIs were pre-chemotherapy scans more frequently when they planned more ablative surgical procedures (Fig. 3).

Discussion

We found that surgical procedures planned on the basis of MRIs of distal femoral osteosarcomas acquired following neoadjuvant chemotherapy included slightly more amputations than did those planned on the basis of MRIs obtained prior to neoadjuvant chemotherapy. This increase in experienced surgeons preferring amputation post-chemotherapy could not be explained by significant differences in any other parameter measured, such as expected neurovascular margins. When the surgeons were asked to predict whether each scan had been acquired before or after chemotherapy, they confirmed both the success of the blinding and their bias that neoadjuvant chemotherapy should improve the resectability of a tumor. This bias was made apparent by the tendency of MRI scans prompting more aggressive surgery plans being predicted as being pre-chemotherapy scans with a strong consistency.

Given this bias, the lack of discernible improvement on final analysis of the surgical procedures planned on the basis of post-chemotherapy MRIs was surprising. The data we present in this report would argue that some of the thinking regarding the rationale for pursuing neoadjuvant timing of chemotherapy—that osteosarcomas are rendered more easily resectable—is anecdotally based. We found no evidence in this study of twenty-four serially collected cases to suggest that neoadjuvant timing of chemotherapy resulted in surgeons planning less radical resections of distal femoral osteosarcomas. The trends in these patients actually favored more conservative procedures when the operations were planned on the basis of pre-chemotherapy MRIs. This does not lead us to condemn neoadjuvant chemotherapy as detrimental with regard to surgically critical anatomy, but it does more firmly argue against its anatomic benefit in this group.

We did observe some likely sources of our own prior belief that neoadjuvant chemotherapy improves the resectability of osteosarcoma. Some tumors improved with regard to surgically critical anatomy during neoadjuvant chemotherapy; the improvement was dramatic in a few cases. Nullifying that observation across the entire study population were some tumors that worsened with regard to surgically critical anatomy during neoadjuvant chemotherapy, also a few dramatically. Unfortunately, the tumors that appeared to present the highest risk initially (i.e., those that would stand to benefit the most from even small anatomic improvements) were similarly bidirectional in their anatomic changes following neoadjuvant chemotherapy. A few tumors progressed from high-risk limb-salvage cases to those that most surgeons thought required amputations. When we merely counted the cases that improved or worsened between pre-chemotherapy and post-chemotherapy MRIs with regard to any specific neurovascular structure, we noted that more cases improved when radiologists measured edema encroachment and more

cases worsened when radiologists measured tumor encroachment. Notably, but not surprisingly, the surgeon-expected margins best matched the radiologists' measurement of tumor encroachment, not their measurement of edema encroachment. While surgeons may ignore edema when planning surgical margins, they certainly prefer to see less of it. The fact that edema frequently improves, without materially improving planned resection margins, may contribute to the established opinion that chemotherapy improves resectability.

The changes in the planned surgical procedures between the pre-chemotherapy and post-chemotherapy MRIs did not strictly correlate with the chemotherapeutic response as determined by the percentage of tumor necrosis found on histological examination. While more of the dramatic improvements in the planned surgical procedures were in the patients with a good necrosis response, one tumor with a good necrosis response worsened anatomically in terms of the resection planned. An anatomically larger tumor that is mostly necrotic histologically is not a novel finding to report. However, such cases confirm that MRI does not accurately predict histological response, as many others have also shown^{5-7,12,14}. Furthermore, they demonstrate that changes with regard to surgically critical anatomy indeed represent a distinct issue from percent tumor necrosis. This distinct issue of the surgically critical anatomic effects of neoadjuvant chemotherapy has received little if any specific attention in the literature prior to this study.

We are not advocating a change in the standard practice of providing neoadjuvant chemotherapy based on our study findings. There remain other aspects of the rationale for neoadjuvant chemotherapy that cannot be investigated by this study method. For example, it has been shown that a combination of negative margins and a high percentage of necrosis in the resected tumor are associated with the lowest rates of local recurrence²⁶. While the latter of these parameters may be a biological characteristic intrinsic to the tumor that might be applicable to neoadjuvant or adjuvant timing of chemotherapy, this has never been tested, to our knowledge, and could be tested only in a large randomized prospective trial powered to detect differences in the rates of local recurrence. Furthermore, an MRI-planned procedure is not an actual surgical procedure. The firmness, consistency, and palpable delineation of the margins of tumors may change dramatically during neoadjuvant chemotherapy. Any effects that such changes have on the ease and safety of surgical resection cannot be measured on MRIs. Finally, some surgeons may not use MRI to plan their resections, but depend more on these intraoperative findings to determine resection planes. The four faculty surgeons who participated in this study, who underwent fellowship training in four different nations and on three different continents, all use MRI extensively, but the findings of this study are less applicable to surgical practices in which MRI is not used to determine surgical planes.

While we cannot directly recommend any change in the standard of care on the basis of this study, we hope that it will prompt further study. Perhaps the effects of surgical timing on

actual rates of systemic and local control are worthy of another, more earnest attempt at investigation in a formal clinical trial. Furthermore, we assert, on the basis of this study, that the details of planned resections can be reliably recorded by surgeons. This suggests that even peer review of surgical strategies might be applied to characterize tumors with regard to surgically critical imaged anatomy when they are being managed in prospective clinical trials with surgery-related questions.

Appendix

(eA) Tables showing patient characteristics, results of the radiologists' evaluations, and planned surgical procedures; figures demonstrating the neurovascular expected-margin designations and proximal resection length designations by the radiologists and surgeons; and details of the assessment of the surgical and radiological MRI questionnaires are available with the online version of this article as a data supplement at jbjs.org. ■

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