ABSTRACT BOOK

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PAPER 1

Orthopedic Oncology and Preoperative Counseling: What Influences the Patient's Choice Between Limb Salvage and Amputation?

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Background
Orthopedic oncology represents a unique subset of orthopedic surgery, both in terms of diagnoses and treatment paradigms. The operative treatment of bone sarcomas is usually predicated on a decision between limb salvage and amputation. Decision-making has shifted from a paternalistic model to a shared decision between the physician and the patient, and the manner in which the relevant information is expressed to the patient may impact their decision choosing between limb salvage or amputation. This study sought to examine the effect of specific biases on patient decision making in the context of orthopedic oncology, namely the choice between amputation and limb salvage.

Questions/Purposes
Will the manner in which information is presented to a patient bias their decision regarding amputation versus limb salvage?

How will different types of bias affect patient decision making in orthopedic oncology?

At the time of decision-making, will a patient's personal background, demographics, or mental status affect their ultimate decision?

Patients and Methods
Institutional Review Board approval was granted. A scenario was designed in which information was presented to a simulated patient regarding the treatment of a bone sarcoma with either amputation or limb salvage. Further, specific iterations were designed to present this information in the context of different types of bias (framing bias, anchoring bias, affect bias, and bandwagon bias) according to the same methodology used by Bernstein et al (*J Am Acad Orthop Surg* 2016).

These scenarios were distributed using anonymous surveys, distributed by the Amazon MTurk platform, to potential participants, aged 18 years or older. Recruitment was geographically restricted to individuals in the United States, and was limited to individuals without a prior limb salvage or amputation surgery. Each respondent also completed questions regarding their demographics, knowledge of sarcoma/cancer, and their current mood.

Analysis of the data was performed using Stata/IC 14.2. Specifically, associations between the type of bias presented and the respondent's choice of limb salvage versus amputation were examined. Further, univariate and multivariate analyses were performed to evaluate a respondent's preference for limb salvage or amputation in the context of their supplied demographic and mood/mental status information (utilizing the PHQ9 and EQ5D questionnaires).

Results

Three hundred eighty-eight respondents completed the survey. The average patient age of 35.8 (range 20-78), with 56.5% identifying as male and 43.0% identifying as female, the remaining 0.5% identified as non-binary. In terms of education level achieved, 9.1% of respondents completed high school only, 44.1% obtained a bachelor's degree, 8.6% completed a Master's degree, and 1.0% obtained a Doctoral degree.

The following results were observed in the context of each of following biases. When amputation was framed as a means for avoiding functional loss (framing bias), 24.4% chose amputation. When limb salvage was framed as a means for function gain as compared to amputation, 9.1% of respondents chose amputation (p=0.003).

When given estimated surgical complications of limb salvage versus amputation, 23.3% of those surveyed chose amputation; however, once presented with a surgical complication unique to limb salvage (affect bias), 33.4% chose amputation (p= 0.1).

An open ended question was included in the survey that asked the maximal complication rate the respondent would accept for limb salvage surgery; this rate was 57.1% in this population. Once an estimated "acceptable" complication rate for limb salvage was presented to the respondent (anchoring bias), the average complication rate that was deemed acceptable by the respondent was reported at 59.8% (p=0.4).

Lastly, quoted complication rates for limb salvage and amputation were supplied; 22.5% of the respondents chose amputation in this context. However, when a qualifier was added that most patients choose to have an amputation (bandwagon bias), 28.0% chose amputation (p=0.4).

Univariate analysis revealed that the choice for limb salvage versus amputation (across all of the biases tested) was higher in those with a Hispanic ethnicity (OR 1.93), those employed in healthcare (OR 2.55), or those having a family member employed in healthcare (OR 1.97).

Conclusions

This study aimed to measure the effect that the intentional introduction of bias into the preoperative discussion regarding sarcoma surgery had on the patient's choice of limb salvage or

amputation. These designed scenarios (each of which tested a different bias) and their results do appear to illustrate that the manner in which information is presented to patient does have an effect on their choice for limb salvage or amputation. This information will help to further facilitate discussions on shared decision making in orthopedic oncology.

Level of Evidence: III

PAPER 2

Income and Gender Data in Orthopaedic Oncology: How do we Stack Up?

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Background:
While medical school gender ratios have reached close to 50:50 male to female representation, surgical subspecialties continue to have considerably more male than female surgeons. Previous studies utilizing public data have demonstrated discrepancy in male and female surgeon salaries. Data from these studies have largely been based upon a limited number of academic institutions. The objective of this study is to report stratified income and specialty data obtained from a large sample survey of AAOS members.

Questions:
1. Is there a wage gap between male and female orthopaedic surgeons?
2. How do hours worked, number of procedures performed, and years into career impact income?
3. How does orthopaedic oncology income data compare to the other subspecialties?

Methods:
Data was obtained as a part of the American Academy of Orthopaedic Surgeons (AAOS) 2014 Orthopaedic Surgeon Census Survey. Responses were received from 6,805 (24.26%) of those surveyed. The census form is a 19-question survey and includes information such as work status (full-time vs. part-time), gender, years in practice, practice type (private vs. academic), specialty area, hours per week worked, number of procedures per month performed, and gross income. The main outcome evaluated was gross income referring to total collections received for medical and professional services rendered. Statistical analysis was conducted by the AAOS Department of Research and Scientific Affairs.

Results:
Across all specialties, male surgeons surveyed reported higher mean annual income versus female colleagues ($802,474 vs. $560,618; p=0.016). Similar proportions of male and female surgeons reported working full-time (91.2% vs. 89.5%; p=0.325). More specifically, male and female surgeons reported working comparable mean hours per week (56.4 vs. 57.0). Among those working full-time, male surgeons reported higher income than their female colleagues ($857,654 vs. $594,538; *p*=0.015). A higher proportion of surveyed male surgeons reported working in private practice than female colleagues (63.5% vs. 40.4%; p<0.0001). Compared to female colleagues, male surgeons in private practice less than 10 years ($695,887 vs. $412,755;

p=0.073) and 11-20 years ($1,053,832 vs. $500,292; *p*=0.022) reported higher mean incomes. Interestingly, male surgeons reported a greater number of procedures per month than female surgeons (29.1 vs. 25.4; p<0.001). Among those that performed 26 or greater procedures per month, male and female surgeons reported comparable incomes ($949,508 vs. $872,903; (p=0.649). In 2014, the most common reported specialties among male surgeons were adult reconstruction (20%) and sports medicine (17%), while hand (24%) and pediatrics (18%) were most common among female surgeons. From 2008 to 2014, the distribution of surgeons in orthopaedic oncology increased from 1% to 2% for males and from 2% to 5% for females. Out of eleven reported subspecialties, orthopaedic oncologists report the fifth largest wage difference between male and female surgeons (53.7%; **Table 1**).

Conclusions:
Over the last decade, there has been a moderate increase in female representation in orthopaedic residency. Disparities within the field continue to exist, particularly regarding income. These discrepancies may be in part due to a larger proportion of female surgeons earlier in their careers, as well as female surgeons reporting a lower number of procedures performed per month, having lower representation in private practice settings, and a pursuing a different distribution of subspecialties. We are unable to conclude if these factors account entirely for the significant differences found in this study. Orthopaedic oncologists have increased in number nationally, with a faster rate of growth among female surgeons. If current trends are to continue, further studies are warranted to assess how to optimally engage outstanding prospective surgeons regardless of gender and to identify any potential bias that may contribute negatively to the career path of practicing females in orthopaedic surgery.

Table 1: Income data stratified by specialty

Specialty	Male Surgeon Income	Female Surgeon Income	Percent Difference	P-value
Shoulder & Elbow	$947,229	$384,444	84.5%	0.178
Spine	$943,515	$391,830	82.6%	0.291
Foot & Ankle	$815,006	$411,833	65.7%	0.183
Hand	$746,053	$399,253	60.6%	**0.004**
Oncology	$661,454	$381,095	53.7%	0.202
Trauma	$690,469	$424,319	47.7%	0.275
Total Joints	$950,116	$629,667	40.6%	0.760
Adult Knee	$831,151	$557,321	39.4%	0.473
Adult Hip	$627,152	$428,333	37.7%	0.407
Sports Medicine	$885,881	$1,297,926	37.7%	0.216
Pediatrics	$662,589	$482,500	31.5%	0.274

PAPER 3

Are Rural Osteosarcoma Patients at Risk for Worse Outcomes?

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Institution: University of Iowa

Background:
Osteosarcoma is a rare cancer that requires a multidisciplinary team for optimal management. There are potential barriers to access and timely presentation that may be unique and important to individuals that live at great distances from specialty treating centers. Prior studies have demonstrated that treating centers with higher volumes result in increased survival in extremity soft tissue sarcoma. It has also been found that patients with higher incidence cancers (breast, lung, colorectal) who had to travel more than 50 miles to a hospital had a more advanced stage at diagnosis, lower adherence to treatments, and worse prognoses. However, there is an undefined relationship between proximity to regional referral centers (distance, travel time, residence in a rural community) and the eventual oncologic outcomes after osteosarcoma treatment.

Purpose:
The purpose of this study was to investigate if patients who reside in rural counties, or at greater distances removed from comprehensive cancer centers, experience higher stage at presentation, larger tumors at presentation, or diminished overall survival.
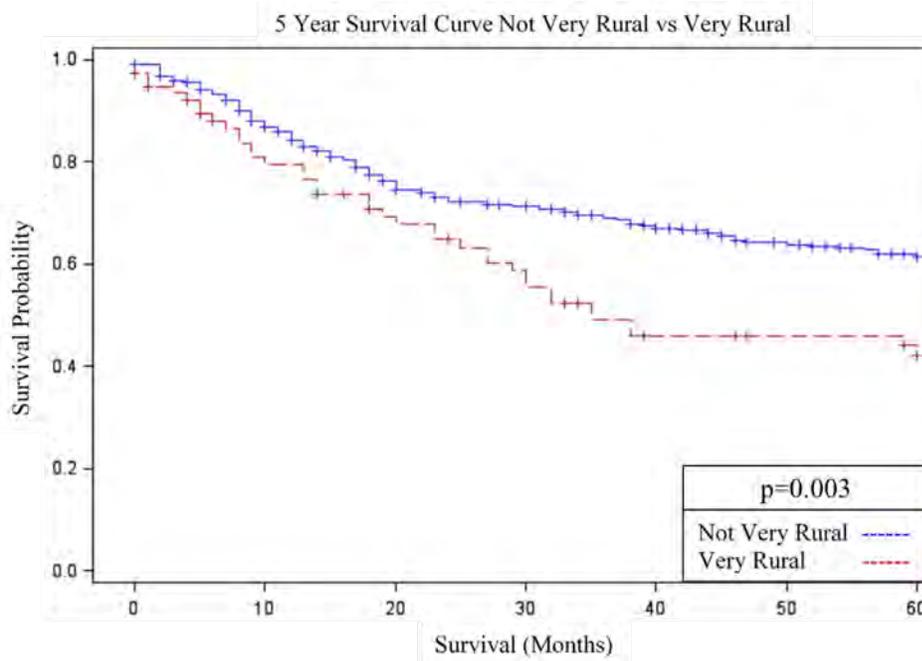
Methods:
We used the Surveillance, Epidemiology and End Results (SEER) Program Database as our data source. We included patients of all ages, race, and sex with high-grade osteosarcoma diagnosed from 1990-2014 residing Iowa, Utah, and New Mexico – the states in the SEER Program Database with population densities in the bottom half of the United Stated based on 2010 Census data. Our independent variables of interest were the distance or time required to travel from a patient's residence to a NIH-designated comprehensive cancer center. The cases were also grouped based on designation of counties using a Rural-Urban continuum code found within SEER*stat (version 8.3.4). Patients were compared as "urban" or "rural," and "very rural" compared to "not very rural" status. We considered a patient to be "very rural" if they resided in a rural county, and their county of residence was not adjacent to an urban county. A univariate analysis was done to see if the distance or time to a treating center affected the rate of presentation with metastatic disease or tumor size >8 cm. We then analyzed five-year survival rates via Kaplan-Meier survival curves based on a patient's rural status. A multivariate analysis was done utilizing cox regression to control for rural status, the presence of metastatic disease, and tumors >8 cm.

Results:

For the univariate analysis, there was increase in the rate of metastatic presentation for those who lived >2 hours versus <2 hours (28.1 and 18.4%, p = 0.021) to the nearest treatment center. We found patients in rural counties had a decreased five-year survival 50.3% [95% CI= 41.9-58.7%] versus 62.3% [95% CI=56.5-67.9], p=0.007. Patients considered very rural had a decreased survival rate 42.2% [95% CI=30.4-54.4] when compared to not very rural patients 61.5% [95% CI=56.4-66.6], p=0.003. Two cox regressions were used to assess mortality when controlling for metastasis, size, and a patient's rural status. In one analysis we used rural versus not rural and in the other we used very rural versus not very rural. In both cox regressions, metastasis was a risk factor for mortality when controlling for rural status and size of tumor with hazard ratios of 2.78 [95% CI=1.88-4.10] and 2.91 [95% CI=1.98-4.27]. Patients considered "very rural" demonstrated increased mortality when controlling for metastases and tumor size, hazard ratio 1.58 [95% CI=1.03-2.43].

Conclusions:

Distance and time to travel to the nearest comprehensive center showed a minimal effect on the size of the tumor or the presence of metastasis at presentation. In contrast, residence in a rural or very rural county demonstrated a greater association as a risk factor for mortality. When assessing mortality through multivariate analysis the presence of metastasis had the greatest negative predictive value, consistent with previous literature. Rural patients were not at a significantly higher risk of mortality when controlling for metastasis and tumor size, but very rural patients were at a higher risk. A patient's distance to travel to a treatment center may be less important for oncologic outcomes than a patient's potential access to care when living in a rural area. This possibly reflects logistical challenges resulting in diagnostic delays, missed appointments, fragmented systemic treatment, delayed recognition of complications, or treatment at a facility that has limited experience.

5 Year Survival Curve Not Very Rural vs Very Rural

p=0.003

Not Very Rural ------
Very Rural ------

Multivariate Cox Regression Analysis for Very Rural vs Not Very Rural Patients

Variable	Hazard Ratio (95% Confidence Interval)	P-Value
Metastatic		
Yes	2.78 (1.88-4.10)	<0.0001
No	Ref	
Rural Status		
Very Rural	1.58 (1.03-2.43)	0.0373
Not Very Rural	Ref	
Size		
>8 cm	1.113 (.784-1.58)	0.549
<8 cm	Ref	

PAPER 4

High Grade Intramedullary Osteosarcoma: Does Histologic Subtype Affect Outcome?

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Background:
Our understanding of osteosarcoma is limited by the rarity of this diagnosis, and the difficulty in obtaining large patient populations for evaluation and analysis. The association between tumor necrosis rate and survival is of particular interest, as it may help guide treatment recommendations and improve future outcomes. There are four major subtypes of high grade intramedullary osteosarcoma, and the question arises whether these subtypes exhibit a different response to standard chemotherapy, and thus have different oncologic outcomes.

Questions/Purpose:
1) Identify and expand upon the clinical characteristics of high-grade intramedullary osteosarcoma
2) Investigate the relationship between histologic subtype and response to therapy and outcomes
3) Report overall treatment outcomes in a large sub-group

Patients & Methods:
An IRB approved retrospective review was conducted of all patients with high-grade intramedullary osteosarcoma treated at our institution from 1989 to 2015. Descriptive statistics, survival analysis (overall, and recurrence-free survival) and Cox proportional hazards regression models were performed. All statistical analyses were performed using SPSS Version 24 for Windows.

Results:
430 patients were included. The major histologic subtypes evaluated were: osteoblastic (52%), chondroblastic (20%), fibroblastic (20%), and telangiectatic (8%). Median age at diagnosis was 17 years (range 4 to 86). 61% were male. The majority of the patients were Caucasian (53%) or Hispanic (32%). The most common site of disease was the femur (51%), followed by the tibia, humerus, and pelvis. Pathologic fracture was present at diagnosis in 66 patients (15%). 22% of patients had metastatic disease at the time of diagnosis. The vast majority underwent neo-adjuvant (96%), followed by adjuvant chemotherapy (93%). Negative surgical margins were obtained in 96% of patients. Open biopsy was obtained in 30 patients (7%). Neither type of biopsy (open or closed), nor the facility obtaining the biopsy (outside hospital versus our facility), was significantly associated with identifying the correct histologic subtype prior to surgery. Chondroblastic and telangiectatic subtypes were more commonly identified correctly at biopsy, compared to fibroblastic. The mean response to neoadjuvant therapy was 77%, with no significant difference among histologic subtypes. Mean overall survival for all patients was 6.7 years (range 1 month to 27 years), and recurrence free survival 2.2 years (range 1.6 months to 20 years). Metastatic disease at diagnosis, or recurrent disease, portended significantly worse survival ($p<0.01$), as did poor response to neoadjuvant chemotherapy ($p<0.01$). There was no significant association between histologic subtype and overall survival ($p = 0.09$).

Conclusions:
Overall survival for osteosarcoma is significantly impacted by metastatic disease at diagnosis and recurrence, as well as response (tumor necrosis) to neoadjuvant chemotherapy. Chondroblastic and telangiectatic subtypes are more commonly identified correctly with biopsy than fibroblastic. Although no statistically significant association was found between histologic subtype and necrosis or survival, future therapies may alter this relationship and continued research is warranted.

PAPER 5

ONCOLOGIC OUTCOME IN PATIENTS WITH OSTEOSARCOMA OF THE EXTREMITIES AND PATHOLOGIC FRACTURES: THE EFFECT OF MICRO RNA PROFILES

Authors: Santiago A. Lozano Calderón MD, PhD; Cassandra Garbutt, MS; Jason Kim, BS; Ivan Chebib, MD; Vikram Deshpande, MD; Petur Nielsen, MD; Dimitris Spentzos, MD.

BACKGROUND: In the past, pathologic fractures were considered a contraindication for limb salvage surgery. With the advent of chemotherapy and new techniques in surgical resection and limb reconstruction, limb salvage in this setting became more prevalent. Research assessing the oncologic outcome in this subset of patients when comparing to patients without fracture is controversial. Some argue that the local hematoma, spilling of tumor and subsequent tumor bed contamination after a pathologic fracture are responsible of higher local recurrence rates and higher risk of distant metastasis and low survival. Others argue that the worse prognosis is because of a more aggressive biology in this tumors with the pathologic fracture being just another manifestation of biologic aggressiveness. Recent literature reviews and attempts of meta-analyses in patients with osteosarcoma of the extremities with pathologic fractures suggest no difference in local recurrence but higher rates of metastases and lower survival. Currently, there is no literature evaluating differences in patients with osteosarcoma in terms of biological behavior when a fracture is present or not.

Micro-RNA are small, non-coding RNA molecules that play a key role in gene regulatory expression at the post translational level. Recent publications have shown differences in terms of micro RNA profiles when comparing patients with worse prognosis than others or with different responses to therapeutic interventions in the setting of Colon cancer and Lung cancer. Some micro-RNA molecules have been proved to be markers of poor oncologic outcome in patients with osteosarcoma. No analysis of micro-RNA profiles in osteosarcoma patients with pathologic fractures has been reported to date.

QUESTIONS: 1) What are the differences between the patients with osteosarcomas of the extremities that have sustained pathologic fractures vs. those that did not in terms of micro-RNA profiles? 2) is there any correlation or higher prevalence of micro-RNA markers of poor prognosis in patients with pathologic fractures secondary to osteosarcoma of the extremities?
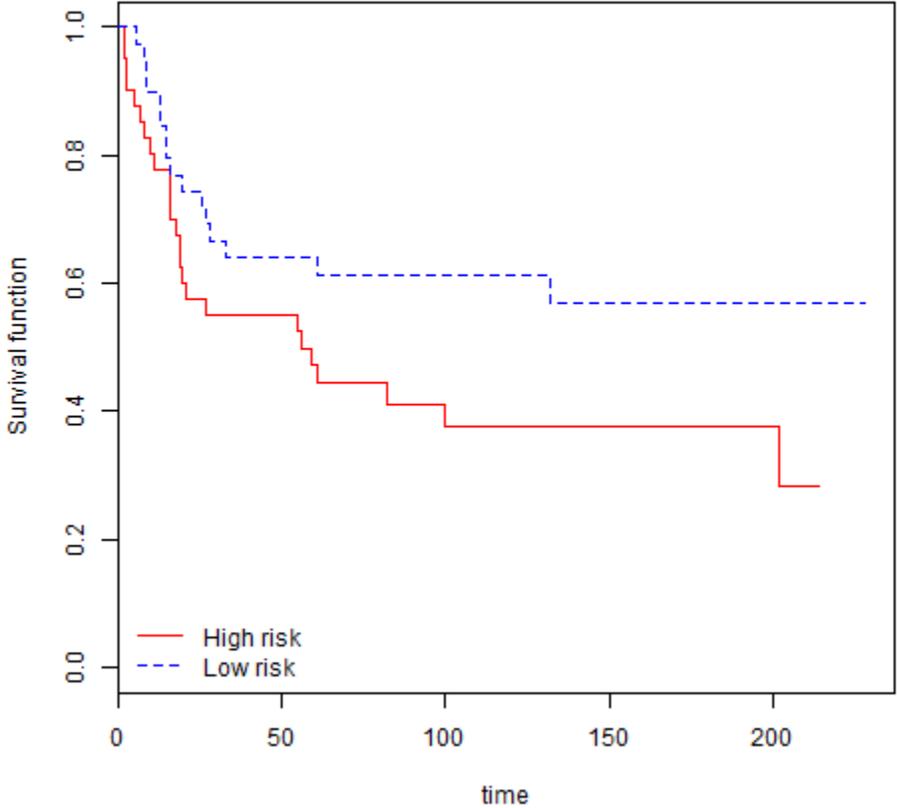
MATERIALS AND METHODS: Eighty samples of patients with high grade osteosarcomas of the extremities where submitted to RNA isolation and micro-RNA sequencing in the context of an simultaneously ongoing project for osteosarcoma genomic profiling at our institution. Data from this ongoing work was used to perform correlative analysis within the pathologic fracture study. Processing and normalization were done per standard methods for the Illumina HiSeq sequencing platform and count data analysis. Fourteen of these samples had a pathologic fracture at presentation or through preoperative treatment with chemotherapy. Differences between the pathologic fracture and the non-fracture groups were evaluated using standard methods of differential expression for count data and were largely consistent using two different algorithms (edgeR and DESeq). Top markers from the differential expression analysis were also utilized in exploratory analysis for predicting long term patient outcomes via Supervised Principal Components Survival Analysis as well as cluster based unsupervised grouping. Additionally we compared the "fracture" and "non-fracture" groups with respect micro-RNA markers previously demonstrated to be prognostic of outcome in publications by members of our group. Additonally, histological samples are being analyzed by specimen type, size of tumor, confirmation of OS, subtype of osteosarcoma, grade (reclassified based on WHO and CAP criteria), % necrosis, mitotic activity, vascular invasion, tumor-associated lymphocytes, presence/abscence of anaplasia, presence/abscence of osteoclast-type giant cells, type of bone and soft tissue infiltration, margin status, joint involvement and margin status.

RESULTS: mIR 155-5p was significantly more down regulated in patients with pathologic fractures. This is a marker of local aggressiveness in our cohort and in previously published research. Down regulation of miR 155-5p decreases cell apoptosis and cell death. miR 455-3p is significantly down regulated in patients with pathologic fractures. This marker is also down regulated in patients with pathologic fractures with osteoporosis. miR 214-3p is significantly down regulated in patients with pathologic fractures in osteosarcoma. Top markers from the pathologic fracture associated signature can be used in a model to predict metastasis and survival but not local recurrence. The microRNA profiles of the patients with facture also differential expression of miRNA markers previously shown to be prognostic of outcome in independent published studies.

CONCLUSION: Pathologic fractures in osteosarcoma appear to be associated to low survival and higher risk of metastasis. The pathologic fracture may be a manifestation of the more aggressive biology of this subtype of osteosarcoma patients and not necessarily the cause of a worse outcome. Micro-RNA profiling demonstrated differences between both groups and a higher prevalence of micro-RNA markers of worse clinical outcome in patients with pathologic fractures in the setting of osteosarcoma of the extremities. Future research will focus on in situ hybridization to identify the location of these micro-RNAs at the cellular or stromal level. These micro-RNAs circulate in blood and might become future markers to identify patients at risk of fracture or with a possible worse oncological outcome.

miRNAs		Difference in Gene Expression	P_Value	FDR
hsa-miR-155-5p	Down- Regulated in patients presenting with a fracture at diagnosis	0.361132458	< 1e-4	0.0091
hsa-miR-210-3p		0.39680442	2.00E-04	0.0168
hsa-miR-214-3p		0.515698588	8.00E-04	0.0369
hsa-miR-23b-5p		0.356210019	2.00E-04	0.0162
hsa-miR-24-3p		0.537896311	< 1e-4	0.0042
hsa-miR-379-3p		0.269975426	0.0035	0.0906
hsa-miR-455-3p		0.2914661	< 1e-4	0.0014
hsa-miR-494-3p		0.270612428	0.0012	0.0462
hsa-miR-106a-5p	Up- Regulated in patients presenting with a fracture at diagnosis	5.013784541	< 1e-4	0.0014
hsa-miR-1246		17.92498492	< 1e-4	< 1e-4
hsa-miR-20b-5p		4.703712883	< 1e-4	0.0048
hsa-miR-2115-3p		5.665879817	0.0014	0.0507
hsa-miR-2115-5p		6.960543691	1.00E-04	0.01

hsa-miR-223-3p		9.229803925	< 1e-4	< 1e-4
hsa-miR-363-3p		4.546952711	< 1e-4	0.0017
hsa-miR-4772-3p		4.725935698	0.0034	0.0906

Log rank p=0.07
Permutation p=0/09

Figure 1A

Recurrence free survival prediction with three prognostic fracture markers, miR-210-3p, miR-24-3p, miR-2115-3p
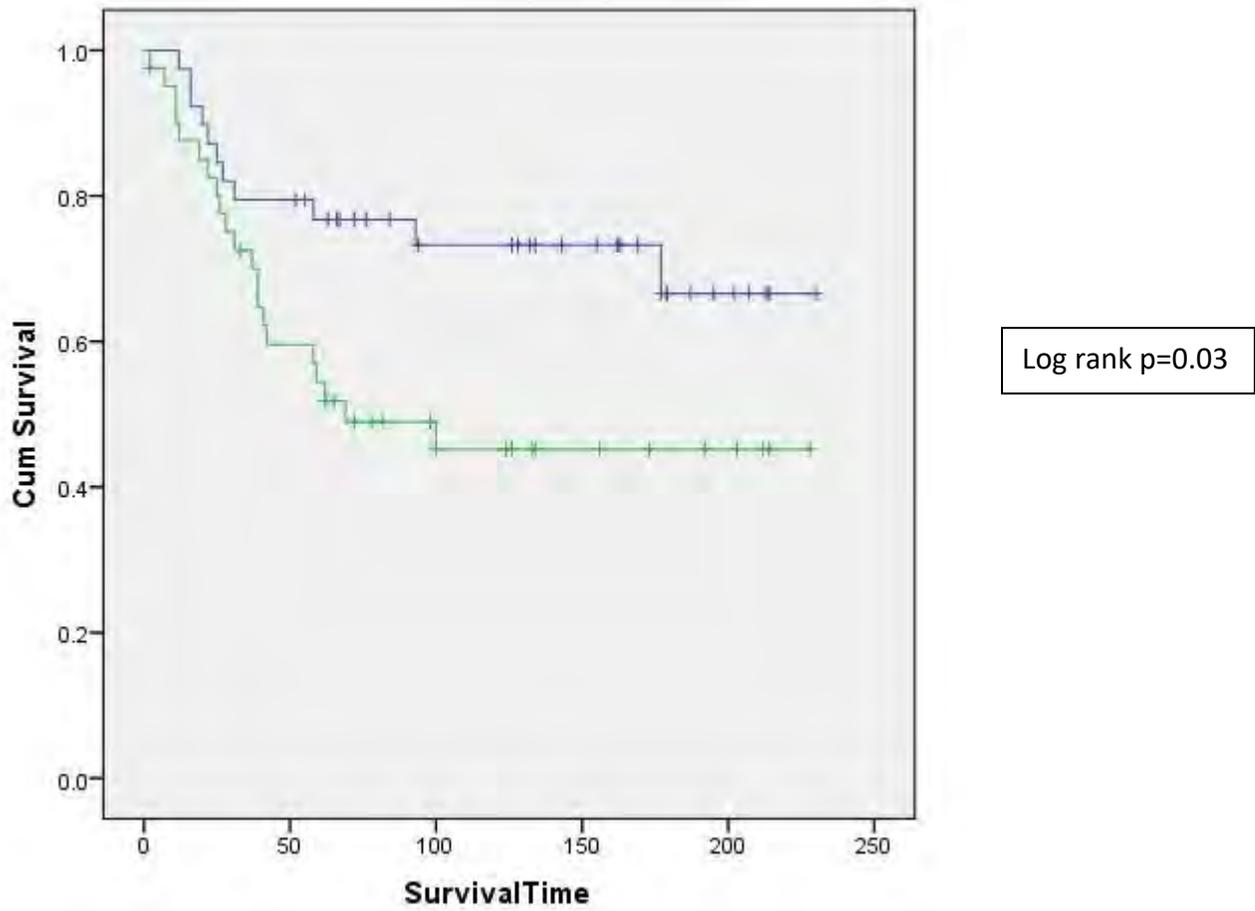
Log rank p=0.03

Figure 1B
 Overall survival prediction with three top prognostic fracture markers, miR-210-3p, -miR-24-3p, miR-2115-3p

PAPER 6

Limb-Salvage Surgery is Associated with Better Long-term Overall Survival Compared to Amputation for Osteosarcoma of the Extremity

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Introduction: Osteosarcoma accounts for the majority of deaths from bone tumors, which are the third most-common cause of cancer-related death in children and young adults. Conventional treatment involves wide surgical resection, with increasing use of limb-salvage techniques over amputation.

Questions/purposes: In the present study, we created propensity score matched cohorts from a large multicenter database to compare long-term survival for patients with osteosarcoma after limb-salvage surgery or amputation. Secondary purposes were to identify factors associated with survival, and to control for such variables in comparing limb-salvage surgery versus amputation.

Methods: We reviewed all osteosarcoma patients between 2004-2014 in the National Cancer Data Base, a robust national database of cancer patients maintained by the American College of Surgeons that captures 70% of new cancer diagnoses in the United States. We identified a total of 2227 patients with osteosarcoma of the extremity and extracted information regarding patient demographics (age, sex, race, Charlson/Deyo comorbidity, socioeconomic status, primary payer), tumor attributes (size, metastasis, grade, location, histology), and treatment (limb-salvage surgery, amputation, surgical margins, and adjuvant radiation and chemotherapy). A multivariate Cox proportional hazards model was first constructed to evaluate significant predictors of long-term survival. To better control for treatment bias between amputation and limb salvage surgery, patients were matched 1:1 using propensity scores with a nearest-neighbor algorithm. A Kaplan-Meier survival analysis was then performed on the matched cohorts.

Results: On multivariate Cox-regression analysis, independent factors prognostic for increased mortality included older age (Hazard Ratio [HR]=1.025, 95% Confidence Interval [CI] 1.02-1.03), increased tumor size ([HR]=1.002, [CI]=1.001-1.003), higher grade ([HR]=1.267, [CI]=1.131-1.418), metastatic disease ([HR]=3.216, [CI]=2.691-3.844), positive surgical margins ([HR]=1.479, [CI]=1.116-1.959), use of chemotherapy ([HR]=1.382, [CI]=1.057-1.806), and amputation ([HR]=1.319, [CI]=1.110-1.567). Independent factors for decreased mortality were female gender ([HR]=0.792, [CI]=0.677-0.926) and higher socioeconomic status ([HR]=0.898,

[CI]=0.835-0.966). Propensity score matching resulted in two cohorts (limb salvage and amputation) with 473 patients each and negligible differences in demographic, tumor, and treatment characteristics (Table 1). Median follow-up was 44 months in the limb-salvage group and 40 months in the amputation group. The 5 and 10-year survival rates for the limb-salvage group were 67.1% and 59.3%, respectively, compared to 56.2% and 45.6% for the amputation group. For the entire period, limb salvage was associated with better overall survival compared to amputation (Fig 1, p = 0.001)
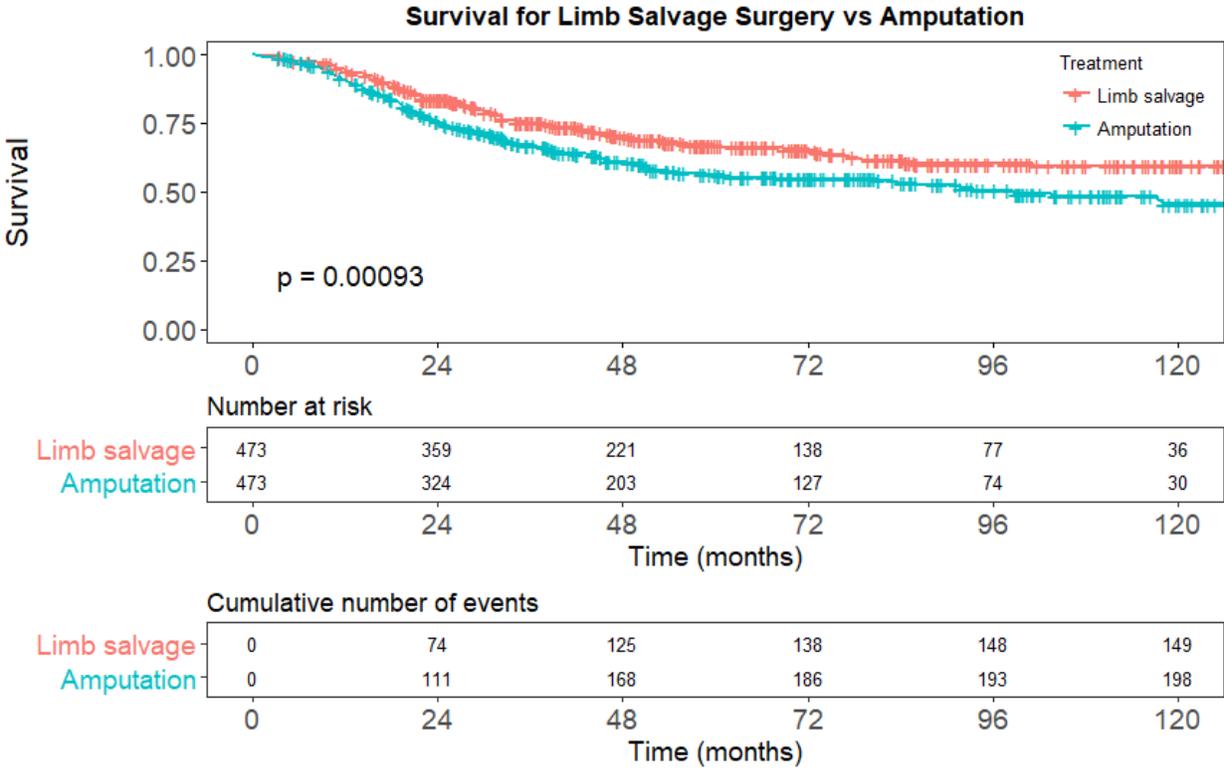
Discussion: The present study found that both in multivariate Cox regression and propensity score matched cohorts, limb-salvage surgery was associated with better overall survival than amputation for the treatment of extremity osteosarcoma. Our results provide further evidence that limb-salvage surgery does not negatively impact overall survival and may instead confer a protective effect in this large patient cohort. Overall, these findings support the continued use of limb-salvage techniques for osteosarcoma patients.

Table 1. Limb salvage versus amputation cohorts, pre and post-propensity score match.

	Unmatched (complete dataset)			Matched (1:1)		
	Limb salvage	Amputation	P-value	Limb salvage	Amputation	P-value
Age (SD)	25.3 (17.3)	30.5 (20.8)	<0.001	29.5 (20.1)	30.5 (20.8)	0.424
Gender			0.029			0.739
Male	975 (55.6%)	290 (61.3%)		284 (60.0%)	290 (61.3%)	
Female	779 (44.4%)	183 (38.7%)		189 (40.0%)	183 (38.7%)	
Race			0.973			0.632
White	1321 (75.3%)	354 (74.8%)		346 (73.2%)	354 (74.8%)	
Black	289 (16.5%)	80 (16.9%)		91 (19.2%)	80 (16.9%)	
Other	144 (8.2%)	39 (8.2%)		36 (7.6%)	39 (8.2%)	
SES Composite			<0.001			0.148
1	317 (18.1%)	97 (20.5%)		121 (25.6%)	97 (20.5%)	
2	434 (24.7%)	136 (28.8%)		120 (25.4%)	136 (28.8%)	
3	463 (26.4%)	141 (29.8%)		123 (26.0%)	141 (29.8%)	
4	540 (30.8%)	99 (20.9%)		109 (23.0%)	99 (20.9%)	
Insurance			<0.001			0.361
Private	1166 (66.5%)	263 (55.6%)		288 (60.9%)	263 (55.6%)	
Medicaid	380 (21.7%)	121 (25.6%)		99 (20.9%)	121 (25.6%)	
Medicare	104 (5.9%)	51 (10.8%)		52 (11.0%)	51 (10.8%)	
Other government	35 (2.0%)	10 (2.1%)		6 (1.3%)	10 (2.1%)	
No insurance	69 (3.9%)	28 (5.9%)		28 (5.9%)	28 (5.9%)	
Charlson/Deyo			0.18			0.993
0	1601 (91.3%)	425 (89.9%)		424 (89.6%)	425 (89.9%)	
1	137 (7.8%)	39 (8.2%)		40 (8.5%)	39 (8.2%)	
≥ 2	16 (0.9%)	9 (1.9%)		9 (1.9%)	9 (1.9%)	
Tumor site			<0.001			0.753
Upper limb	311 (17.7%)	50 (10.6%)		47 (9.9%)	50 (10.6%)	
Lower limb	1428 (81.4%)	415 (87.7%)		415 (87.7%)	415 (87.7%)	
Limb or joint, NOS	15 (0.9%)	8 (1.7%)		11 (2.3%)	8 (1.7%)	
Grade			0.001			0.238
1	124 (7.1%)	11 (2.3%)		19 (4.0%)	11 (2.3%)	
2	130 (7.4%)	27 (5.7%)		21 (4.4%)	27 (5.7%)	
3	868 (49.5%)	258 (54.5%)		240 (50.7%)	258 (54.5%)	
4	632 (36.0%)	177 (37.4%)		193 (40.8%)	177 (37.4%)	
Metastasis			0.112			1
No	1548 (88.3%)	404 (85.4%)		405 (85.6%)	404 (85.4%)	
Yes	206 (11.7%)	69 (14.6%)		68 (14.4%)	69 (14.6%)	
Tumor size (cm, SD)	10.1 (6.4)	11.8 (7.8)	<0.001	11.6 (8.6)	11.8 (7.8)	0.709
Histology			0.01			0.423
Osteosarcoma, NOS	1054 (60.1%)	317 (67.0%)		336 (71.0%)	317 (67.0%)	
Chondroblastic	222 (12.7%)	57 (12.1%)		54 (11.4%)	57 (12.1%)	
Fibroblastic	114 (6.5%)	36 (7.6%)		29 (6.1%)	36 (7.6%)	
Telangiectatic	52 (3.0%)	14 (3.0%)		17 (3.6%)	14 (3.0%)	

Paget's	4 (0.2%)	3 (0.6%)	2 (0.4%)	3 (0.6%)
Small cell	8 (0.5%)	3 (0.6%)	0 (0.0%)	3 (0.6%)
Central	107 (6.1%)	20 (4.2%)	17 (3.6%)	20 (4.2%)
Well differentiated	3 (0.2%)	0 (0.0%)	N/A	N/A
Parosteal	133 (7.6%)	17 (3.6%)	13 (2.7%)	17 (3.6%)
Periosteal	37 (2.1%)	3 (0.6%)	5 (1.1%)	3 (0.6%)
High grade surface	20 (1.1%)	3 (0.6%)	0 (0.0%)	3 (0.6%)
Surgical margins			<0.001	1
No	1625 (92.6%)	460 (97.3%)	459 (97.0%)	460 (97.3%)
Yes	129 (7.4%)	13 (2.7%)	14 (3.0%)	13 (2.7%)
Radiation			0.058	0.449
No	1702 (97.0%)	467 (98.7%)	463 (97.9%)	467 (98.7%)
Yes	52 (3.0%)	6 (1.3%)	10 (2.1%)	6 (1.3%)
Chemotherapy			0.796	0.395
No	249 (14.2%)	70 (14.8%)	60 (12.7%)	70 (14.8%)
Yes	1505 (85.8%)	403 (85.2%)	413 (87.3%)	403 (85.2%)

Fig 1. Kaplan-Meier survival analysis for limb-salvage versus amputation.

PAPER 7

Biomechanical "Scratch Fit" -Achieving Adequate Operative Press Fit Fixation with Distal Femoral Oncologic Implants

AUTHORS
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BACKGROUND

Complications for oncologic implants of the distal femur involve primarily aseptic loosening of the stem fixation or deep implant infections. Implant loosening with cemented implants have been documented in multiple series to be approximately 20-30 % at 10 years of follow-up. Subsequent uncemented distal femoral implants have had a lower incidence of aseptic loosening but have challenges with the intra-operative assessment of the adequacy of stem fixation within the femoral canal.

PURPOSE AND RESEARCH QUESTIONS

Our biomechanical study was intended to resolve the adequacy of oncologic implant press-fit stem fixation within the reamed canal of the distal femur for the uncemented Stryker GMRS oncologic distal femoral implant.

#1 Does the initial stem engagement (i.e., "Scratch Fit") into the femoral canal using a standardized force (50 N) predict the adequacy of stem fixation within the femoral canal?

#2 Is there a difference in the uncemented stem fixation within the femur for different diameters (13, 14, and 15 mm) of the Stryker GMRS uncemented press-fit stems (Stryker Orthopaedics; Mahwah, New Jersey)?

PATIENTS AND METHODS:

Twelve unpaired fresh frozen cadaveric femoral specimens were obtained (via LifeNet Health) and handled per CDC biohazard guidelines during specimen preparation and testing. Mean age was 61.0 ± 10.6 years with ages ranging from 46 to 75 years. The specimens were thawed and inspected for bony defects and the distal end cut at 13 cm to emulate a distal femoral resection. The proximal femur was cut at the proximal lesser trochanter to allow potting with perpendicular screw fixation and poly-methylmethacrylate potting of the specimen.

Before femoral reaming, the mid/distal femoral shaft diameter was measured to assess both the outer and intramedullary diameters on AP and lateral x-rays. Femoral reaming was carried out to a diameter that was 0.5 mm smaller than the measured intramedullary diameter. GMRS stems were initially placed ,after reaming the femur, into the distal femoral canal with firm hand pressure applied to a spring-based insertion tool positioned over the standard Stryker insertion tool and calibrated to apply a standard force of 50 N(11.2 lbs) .Initial stem placement resulted in a stem that was only partially implanted into the femur with a resulting variable distance (defined

as "Scratch Fit") between the stem collar and the cut surface of the femoral shaft. That "Scratch Fit" distance was measured before impacting the stem into the canal with a standard orthopaedic mallet until the stem collar was seated flush with the cut femoral surface.

Stem torsional testing to failure was performed on a multi-axis biomechanical test frame in conjunction with a 3-D motion-capture system (Vicon Motion Systems, Model MX13, Lake Forest, CA). Axial torsion was applied to the stems at a controlled angular displacement rate (0.5 deg/sec) with the potted end of the femur fixed to the base. A six-axis load cell (Omega 160, ATI Industrial Automation; Apex, NC) sampled at 100 Hz recorded the applied torque. Kinematics of both the implant and distal femur were captured using the Vicon system which tracked reflective infrared targets at a 60 Hz sampling rate. To simulate body weight, each femur was preloaded with 700 N of compression via a pneumatic cylinder just prior to torsional testing to failure.

Standard Vicon analysis software was used to process acquired kinematic data with the remaining data analysis performed in Matlab. Peak torsional moment at failure was compare to "Scratch Fit" to address the research questions posed.

RESULTS:

Scratch fit distances ranged from 7-46 mm with a mean of 29.1 +/- 12.7 mm. Peak torques ranged from 11.5 to 57.5 Nm with a mean of 33.6 +/- 17.0 Nm. Fig 1 shows peak (max.) torque plotted against scratch fit for all stems/specimens with good correlation ($r^2=0.6404$). When separated by stem diameters, Fig 2 shows strong correlations between peak torque and scratch fit.

DISCUSSION AND CONCLUSIONS

While there are at least three metrics that affect uncemented stem implant placement and stability (i.e., femoral canal size, femoral reaming, and implant type/size (diameter), there appears to be some correlation between initial stem placement (i.e., "Scratch Fit") after femoral reaming to implant torsional (rotational) stability; this correlation is even stronger when controlling for stem diameter. This suggests that use of a standardized force to measure "Scratch Fit", and greater initial "Scratch Fit" length may provide stronger press-fit stem fixation and an improved operative standard for making intra-operative decisions for these particular patients.
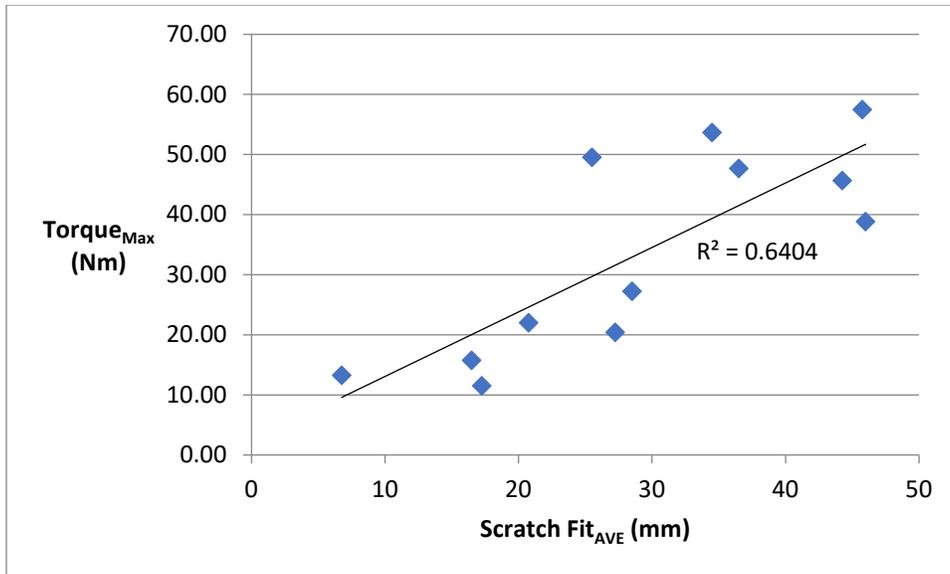
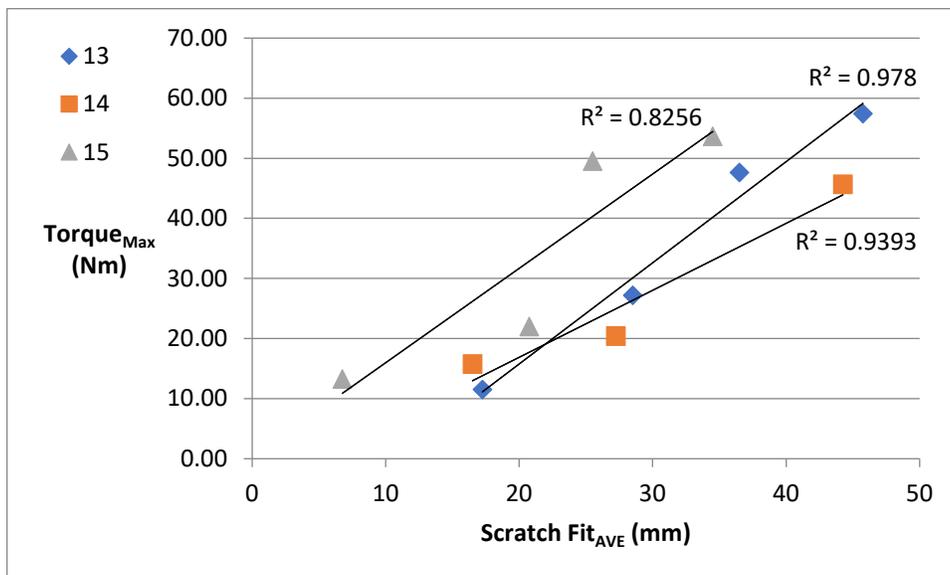**Figure 1.** Peak Torque vs. Scratch Fit (all stems).

Figure 2. Peak Torque vs. Scratch Fit separated by stem size.

PAPER 8

Press Fit vs Cemented Femoral Stems in Arthroplasty for Oncologic Indications

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Background: Limb salvage has largely replaced amputation in the treatment of primary bone tumors and encompasses multiple reconstructive modalities. Post-resection THA/TKA has additional considerations compared to its non-oncologic counterparts including integrity of the native bone (particularly in patients receiving adjuvant therapy), and greater demand for stability and longevity given a younger patient population. Studies have shown varied success in arthroplasty with both cemented and press fit stems. Currently there is no consensus regarding which method is superior. The cemented stem provides immediate, stable fixation that is not affected by adjuvant chemotherapy or radiation but carries a known risk of aseptic loosening. Press fit stems allow for ingrowth of native bone, hypothetically creating a long-lasting, durable reconstruction, which is particularly appealing in younger, more active patients. However, inadequate osteointegration and stress shielding may lead to need for revision. Previous studies have looked at aspects of surgical technique and the components themselves as potential predictors of failure in these implants. Cement mantle width and canal fill ratio are classically discussed as predictors of outcome, yet some studies have shown no clinical significance associated with these parameters. Based on these varied findings, there remains a need for analysis of which components, surgical techniques, or patient factors contribute to failure, and how this should influence choice of reconstruction modality in a given patient.

Questions: 1) Does the rate of failure differ between cemented and press fit femoral stems in arthroplasty for oncologic indications? 2) What are the predictors of failure in cemented and press fit femoral stems?

Patients and Methods: We retrospectively identified all patients treated between 1990-2015 with resection of primary bone tumor and subsequent arthroplasty with either a cemented or press fit femoral stem. Patients were excluded if they had previous reconstruction at the site, the implant was placed in allograft rather than native bone, or if inadequate imaging was available for analysis. Demographics, treatment, and follow up data were collected (Table 1). Eighty-one patients (31 male, 50 female) were included; the median age at date of surgery was 54 years. For image analysis, post-operative AP radiographs were measured using the PACS system. In press

fit stems, the width of the canal, stem, and diaphysis were measured at the base, middle, and distal end of the stem. In cemented stems, the stem, diaphysis, and width of the cement mantle were measured at the base, middle, and distal end of the stem. To determine the stem to canal ratio, stem to diaphyseal ratio, and cement mantle width, measurements at the base, mid, and distal sites were averaged. Failure was defined as any event that led to revision of the implant (fracture, hardware failure, loosening, dislocation, mechanical failure, infection). All data was analyzed using STATA 14.0 (Statacorp LP, College Station, TX, USA). The Mann-Whitney test was used for continuous variables and Fisher's exact test for categorical variables. Factors that reached significance, defined as $p < 0.05$, were then analyzed via logistic regression to determine an odds ratio.

Results: There was no significant difference in overall failure rates between patients with a press fit stem versus cemented stem (p=0.783) (Table 2). The median stem to canal ratio in press fit implants was 0.91 (IQR 0.88-0.94) and 0.72 (0.63-0.76) in cemented, and median cement mantle width was 2.75 mm (IQR 2.0-3.5). Neither stem to canal ratio, stem to diaphyseal ratio, nor cement mantle width were associated with a higher rate of implant failure in press fit or cemented stems, respectively. BMI was associated with an increased risk of failure in press fit stems (OR 1.25, 95% CI 1.05 -1.50), and age was inversely related to increased risk of failure in cemented stems (OR 0.92, 95% CI 0.87-0.97).

Conclusions: The all-cause failure rate was not significantly different in arthroplasty with press fit versus cemented femoral stems, suggesting that both are appropriate methods of post-resection reconstruction and can be selected according to relevant patient factors. Age was inversely associated with failure in cemented stem, indicating that press fit is the more appropriate option for younger, active patients. However, the stability of a cemented stem may improve durability and survival in patients with higher BMI.
There were several limitations to this study, including its retrospective nature and limited sample size. Additionally, surgical procedures were performed by multiple surgeons within our institution using several implant systems. Despite the limitations, these preliminary results provide direction for further investigation.

Level of Evidence: III

Table 1. Baseline Characteristics

Variable	Press Fit	Cemented
	Median (IQR)	*Median (IQR)*
Age (years)	51 (37-57)	60 (48-72)
BMI (kg/m^2)	26.5 (23.3-29.3)	29.9 (24.3-32.6)
Stem:canal	0.91 (0.88-0.94)	0.72 (0.63-0.76)
Stem:diaphysis	0.51 (0.46-0.53)	0.43 (0.39-0.46)
Cement Mantle (mm)	---	2.75 (2-3.5)
	n (%)	*n (%)*
Gender		
Female	23 (68)	27 (57)
Male	11 (32)	20 (43)
Smoker	10 (29)	7 (15)
Diabetes Mellitus	3 (9)	7 (15)
Site		
Proximal femur	15 (44)	28 (60)
Distal femur	19 (56)	19 (40)
Chemotherapy	11 (32)	21 (45)
Radiation	13 (38)	16 (34)
Infection	4 (12)	8 (17)
All cause failure	8 (24)	9 (19)

Table 2. Bivariate analysis of predictors of failure

Variable	Press Fit	Cemented
	p-value	*p-value*
Age	0.16	**<0.001**
BMI	**0.02**	0.94
Site	1	0.13
Smoker	0.67	0.32
Diabetes	1	0.611
Chemotherapy	1	0.48
Radiation	1	0.70
Stem:canal	0.61	0.30
Stem:diaphysis	0.79	0.21
Cement mantle	----	0.49
	OR (95%CI)	*OR (95%CI)*
Age	----	0.92 (0.87-0.97)
BMI	1.25 (1.05-1.50)	---

PAPER 9

Distal Femoral Compressive Osseointegration Endoprostheses: A Minimum Ten-Year Follow-Up Study with Functional Results

Authors: Kara Tanaka[1], Adrianna Carrasco[2], Richard O'Donnell[2], Rosanna Wustrack[2]
[1]School of Medicine, University of California, San Francisco, [2]Orthopaedic Surgical Oncology, Department of Orthopaedic Surgery, University of California, San Francisco

Background: Compressive osseointegration endoprostheses show long-term survival promise for tumor-based reconstructions. Early studies showed equivalent survivorship to traditional cemented-stem endoprostheses, however, there are no reports of performance at or beyond minimum 10-year follow-up. Patient perception of function and health status has yet to accompany the clinical and surgical outcomes.

Questions/Purpose: What is the spindle survival rate of Compress® endoprosthesis implanted in the distal femur at 10-year follow-up? What is the rate of unplanned surgical revision for these devices? How do patients rate their functional outcomes and perception of health?

Patients and Methods:
Retrospective study with additional patient-reported functional and health status outcomes.

Fifty-three patients with oncologic indications underwent distal femoral reconstruction with Compress® (Compress Compliant Pre-stress Device, Biomet Inc, Warsaw, IN, USA) endoprostheses between 1998 and 2007 by a single orthopaedic surgeon. Inclusion criteria was primary or secondary oncologic indication for distal femoral limb salvage and reconstruction to Compress® device **[FIGURE 1]**. Patients were followed on annual basis or until death from disease or removal of endoprosthesis (mean, 104 months; median 124 months; range 7-208 months). We assessed clinical and radiographic records for Compress® spindle survival and any unplanned surgical intervention.
We employed Kaplan-Meier log-rank technique to determine the spindle survivorship rate and spindle retention rate. Patients completed questionnaires addressing function (TESS) and health status (EQ-5D-3L). Patients excluded from TESS and EQ-5D-3L surveys if they no longer retained their endoprosthesis due to infection and subsequent above-the-knee amputation, or if they died due to progressive disease prior to 10-year follow-up.

Results: We found Compress® spindle survivorship of 88.9% (CI 75-95.3%) at 10-year follow-up and 88.9% (CI 75-95.3%) at 15-year follow-up **[FIGURE 2]**. Median spindle survival was 105.4 months, range 7.7-208.5 months. Five patients had spindle failure requiring removal and reconstruction to a second endoprosthesis. Ten patients died due to disease, ten were lost to follow-up, and five incurred infection and subsequent above-the-knee amputation. Twenty-eight patients maintained a functional Compress® beyond ten years. Unplanned surgical revision rate was 40%, with all patients returned to good functional status. Participating patients reported their

function at 0.831 (TESS) and state of health at 83 +/- 13.7 for self-assessment and at 0.800 +/- 0.131 when weighted for US populations (EQ-5D-3L).

Conclusion: The survival rate of distal femoral compressive devices in this cohort is 88.9% (CI 75-95.3%) at 10 years, suggesting that Compress® reconstruction continues to be an appropriate and optimal choice for oncologic tumor resection. These survival results show continued equivalent long-term survivorship with traditional cemented-stem endoprostheses. Patients with greater than 15-year follow-up had no additional failures between 10 and 15 years, suggesting stable osseointegration and hypertrophy at the bone-implant interface. Patient-reported outcomes at 10-year follow-up demonstrated good function and state of health.

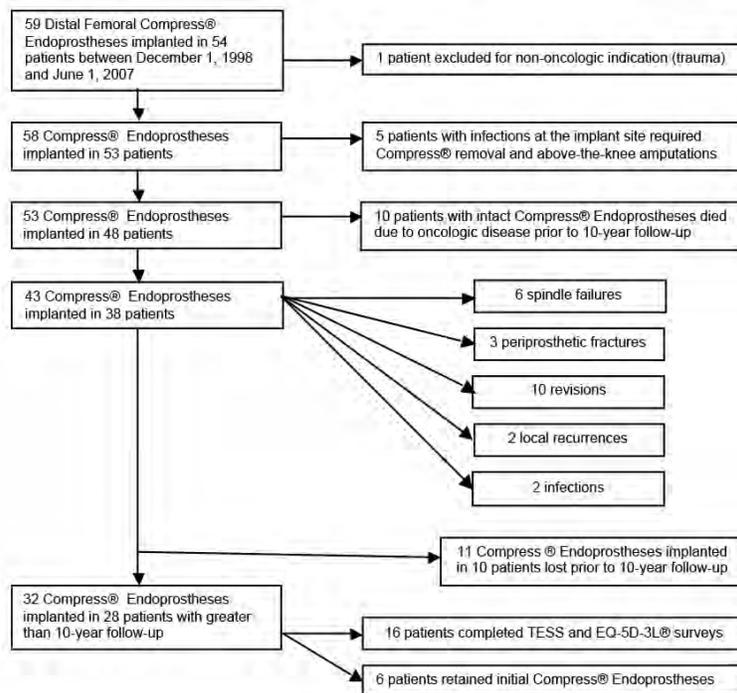Level of evidence: Level IV, therapeutic study.

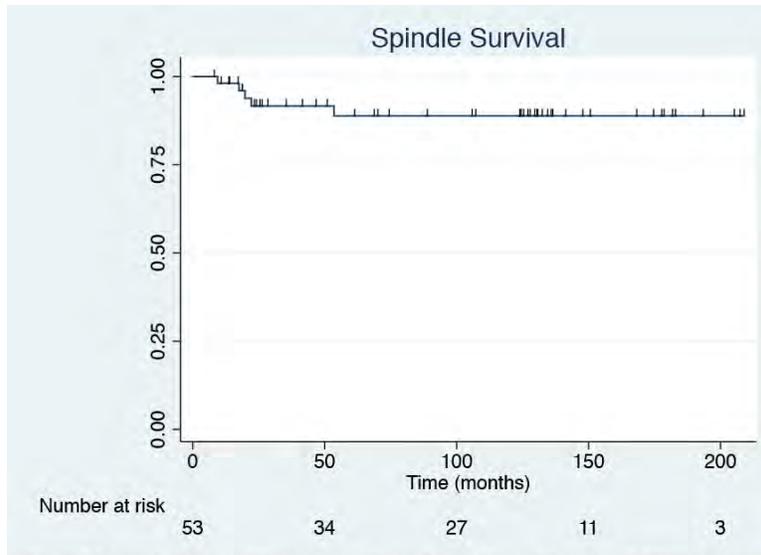Figure 1: Patient inclusion/exclusion criteria and adverse events

Figure 2: Kaplan-Meier survival curve for spindle survival. Median spindle survival was 105.4 months, range 7.7-208.5 months. 10-year survival 88.9% CI 75-95.3%. Censoring lines are when patients died due to progressive disease, were lost to follow-up, or had permanent removal of a Compress® device.

PAPER 10

Outcomes of Expandable Prostheses for Primary Bone Malignancies in Skeletally Immature Patients: A Meta-Analysis

Authors: Daniel A. Portney, BS, Andrew S. Bi, BS, Robert A. Christian, MD, Terrance D. Peabody, MD

Institution: Northwestern University Feinberg School of Medicine, Department of Orthopaedics
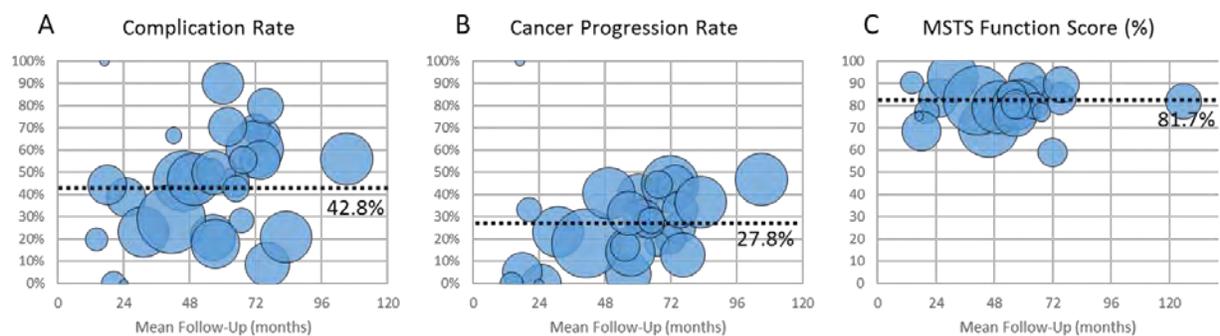
Background: Osteosarcoma and other primary malignancies of bones are commonly diagnosed in skeletally immature patients as the peak incidence occurs in the second decade of life. Historically, primary bone malignancies of the extremities were treated with amputation, though in the last 50 years, limb-sparing surgery has proven to be effective and is now the standard of care. For pre-adolescents and adolescents with remaining growth potential, expandable prostheses have become a preferred option to preserve function and cosmesis. Expandable prostheses have evolved from original models in the 1970s that required minimally invasive procedures for expansion to newer models that can be expanded non-invasively. Current literature features many small case-series with a wide range of complication rates. As a result, it is difficult for surgeons to estimate outcomes following limb-sparing reconstruction with expandable prostheses and communicate these outcomes to their patients.

Purpose: This study aims to provide an updated estimate for the complication rates, oncologic progression, and functional outcomes in patients who undergo limb-sparing surgery for primary bone malignancies. Furthermore, we pose the following questions: 1) Do non-invasive expandable prosthetics have better outcomes than minimally-invasive prosthetics? 2) Can we identify subsets of individuals who have significantly better outcomes when individual patient data is pooled together?

Methods: We conducted a systematic review according to PRISMA guidelines to identify publications on PubMed with patients with primary bone malignancies that underwent limb-sparing reconstruction with expandable prostheses. We narrowed our range to articles published in 1997 to present written in English and excluded review papers and studies that had the potential for repeated patients with other studies. We included 32 studies, all of which were case-series or retrospective studies. Twenty-three of the 32 studies provided individual patient demographic and outcomes data. Overall, this included 611 total patients, and 340 patients with individual patient data. The primary outcomes studied were complication rate, rate of oncologic progression, and MSTS functional score. Secondary outcomes included the complication rate by type (classification in Table footnote), number of lengthening procedures, mean amount lengthened, and the prevalence of a limb-length deformity.

Results: Thirty of the 32 studies reported complication rates, and the weighted mean complication rate was 42.8%. Twenty-eight studies reported oncologic outcomes, with a weighted mean rate of cancer progression of 27.8%. Twenty-three studies reported MSTS function scores with a weighted mean of 81.7%. Minimally-invasive and non-invasive prostheses had a similar overall complication rate (43.4% vs. 50.0% respectively, p=0.258), but they had significantly different frequencies of each type of complications. Minimally invasive prostheses have a higher rate of soft-tissue complications (11.2% vs. 2.7%, p=0.005) and non-invasive prostheses had higher rates of structural complications including peri-prosthetic fractures and device failures (27.4% vs. 16.8%, p=0.030). Non-invasive prostheses had an insignificantly lower infection rate (11.6% vs. 19.6%). Complication rates were higher in patients with follow-up greater than 6 years (61.2%) than in those with 3-6 years of follow-up (40.0%) and less than 3 years of follow-up (37.7%) (p=0.001), and this difference was true for mechanical complications (p<0.01). Amputations were higher in patients with less than three years of follow-up (p=0.005), this cohort included patients with amputations because of local tumor spread. MSTS functional outcome scores were not significantly related to age at surgery (p=0.437) or prosthesis type (p=0.449).

Conclusions: This series provides clinicians with pooled summary data to guide clinical decisions regarding the functional outcomes and complication risk associated with the use of expandable prostheses in skeletally immature patients. All of the data comes from previous literature and is pooled from retrospective series, thus the accuracy is dependent on the accuracy of the individual reports. Despite these limitations, this series represents the largest summary of outcomes after limb-sparing reconstruction with expandable prostheses to date. This analysis can assist surgeons to better understand outcomes and educate their patients and their families regarding limb-sparing reconstruction with expandable prostheses for primary bone malignancies.

Figure 1. Scatter plots for each included study's complication rate, cancer progression rate (death or tumor progression), and reported MSTS function score as a function of each study's mean follow-up period. The size of the bubble relates to the number of patients in each study and the black dotted line indicates the weighted average for each metric. Panel A shows the rate of having any reported complication (ie. infection, aseptic loosening, structural failure and peri-prosthetic fracture, and amputation/disarticulation). 30/32 of the studies with 586 patients reported clear rates of complications. Panel B shows the rate of death or tumor progression (by metastasis, active disease, or local spread). 28/32 of the studies with 532 patients reported clear rates of disease progression. Panel C shows the average reported MSTS function score as a percentage, raw scores (out of 30) were converted to percentages. 23/32 of the studies with 400 patients reported numerical MSTS scores.

Table I. Complication rates by patient cohort

	Subtotal (n)	All Complications	Complication Types		Complication Subtypes[a]				
			Mechanical	Non-Mechanical	Type I	Type II	Type III	Type IV	Type V
Total	296	45.9%	34.8%	19.6%	6.8%	13.2%	22.0%	15.2%	7.1%
Age									
<8	45	51.1%	46.7%	13.3%	11.1%	17.8%	33.3%	11.1%	4.4%
8-10	82	51.2%	40.2%	23.2%	7.3%	17.1%	22.0%	19.5%	7.3%
10-12	78	43.6%	28.2%	24.4%	7.7%	9.0%	20.5%	19.2%	5.1%
>12	91	40.7%	29.7%	15.4%	3.3%	11.0%	17.6%	9.9%	9.9%
p-value[b]		0.457	0.093	0.269	0.357	0.320	0.211	0.192	0.727
Prosthesis									
Minimally-Invasive	143	43.4%	33.6%	23.1%	11.2%	15.4%	16.8%	19.6%	7.7%
Non-Invasive	146	50.0%	37.0%	17.1%	2.7%	11.6%	27.4%	11.6%	6.8%
p-value[b]		0.258	**0.026**	0.206	**0.005**	0.352	**0.030**	0.063	0.783
Tumor Location									
Knee	191	47.6%	36.1%	20.9%	9.4%	12.6%	20.9%	16.2%	6.8%
Hip	23	52.2%	39.1%	34.8%	8.7%	17.4%	39.1%	30.4%	13.0%
Total Femur	35	48.6%	34.3%	20.0%	0.0%	20.0%	17.1%	14.3%	8.6%
p-value[b]		0.918	0.932	0.303	N/A	0.452	0.104	0.207	0.553
Follow-Up									
<36 months	138	37.7%	20.3%	19.6%	2.2%	5.8%	14.5%	10.9%	12.3%
36-72 months	60	40.0%	33.3%	11.7%	8.3%	11.7%	20.0%	10.0%	3.3%
>72 months	98	61.2%	56.1%	24.5%	12.2%	24.5%	33.7%	24.5%	2.0%
p-value[b]		**0.001**	**<0.00001**	0.143	**0.009**	**0.0001**	**0.002**	**0.007**	**0.005**

a: Type I includes soft-tissue complications, Type II includes aseptic loosening, Type III includes peri-prosthetic fractures and device lengthening failures, Type IV includes infections, Type V includes amputations

b: chi-square goodness of fit test within groups

PAPER 11

Long Term Outcomes of Total Humeral Replacement for Primary Bone Tumors in 18 Patients

Authors: Nicholas N. Bernthal MD, Zachary D.C. Burke MD, Alexander Upfill-Brown MSc, Richard Hwang, Francis Horniceck MD, Jeffrey J. Eckardt MD

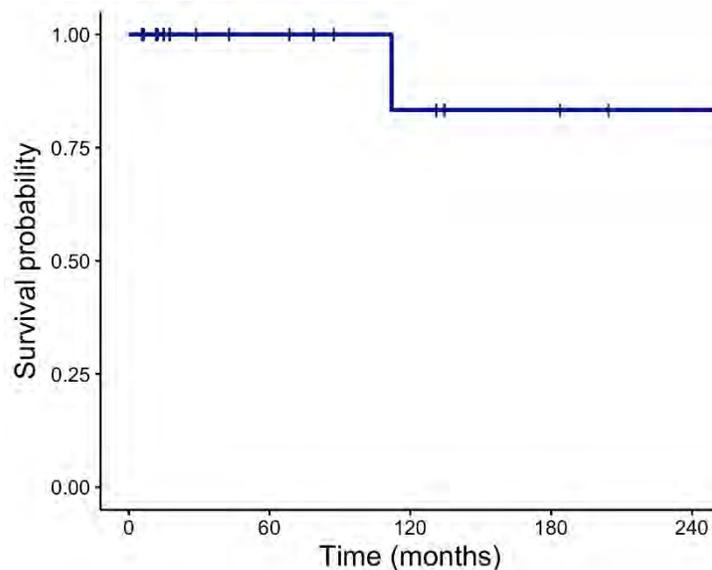Department of Orthopaedic Surgery, University of California Los Angeles, Los Angeles, CA

Background: The proximal humerus is amongst the most common locations of primary bone sarcoma, but tumors requiring total humeral replacement (THR) are rare, representing < 2% of endoprosthetic reconsuctions. As with proximal humeral resection, THR is complicated by instability of the poly-axial glenohumeral joint, whereas the common complication of aseptic loosening that is inherent in endoprosthetic reconstruction is not a significant concern. Data describing the outcomes, survivorship, and complication of THR are limited. Soft-tissue failure at the shoulder and mechanical failure of the ulnar stem are the most frequently documented mechanical complications. Nerve palsy has also been documented as a common complication. There is a paucity of data on long-term survivorship and outcomes for THR with only two series reporting 10-year survival.

Questions/Purposes: We aim to examine the long-term survivorship, outcomes, and modes of failure of total humeral endoprosthetic replacement. Specifically, we seek to answer the following questions: (1) What is the mechanical survivorship of this technique? (2) What are the rates of shoulder instability, ulnar component failure, and radial nerve palsy? (3) Does THR results in acceptable functional outcomes for patients as measured by MSTS score?

Patients and Methods: This is a retrospective review of a prospectively collected endoprosthesis database consisting of 512 consecutive endoprosthetic reconstructions performed for oncologic diagnoses at a single-center between 1980 and 2018. We identified 17 patients with 20 THR implants. Sixteen endoprosthesis were implanted following primary resection of tumor (8 osteosarcoma, 1 metastatic osteosarcoma, 3 Ewing's sarcoma, 2 chondrosarcoma, 1 malignant fibrous histiocytoma, 1 multiple myeloma). The remaining 5 were implanted as revision prostheses. Twelve patients were alive at recent follow-up; 15 patients had a minimum of 1 year follow up. Thirteen patients had MSTS scores available, 12 of which had a minimum of 1 year follow up. Eleven patients had sufficient data for complete analysis of radial nerve palsy and shoulder instability. Outcomes evaluated were implant survival, revision surgery categorized according to the Henderson Failure Mode Classification, complications, and functional outcomes. Bushing changes expansion related revisions were not considered failures. Analyses were repeated for THR revisions. Prosthesis survival is analyzed at 5-year, 10-year and 15-years using Kaplan-Meier analysis.

Results: The median follow-up for surviving patients was 123 months (25th-75th percentile, 15 to 204 months) and 43 months (25th-75th percentile, 15 to 131 months) for all patients analyzed. A total of 2 prostheses required revision for mechanical failure, both for soft-tissue failure resulting in symptomatic shoulder dislocation. Both mechanical failure and all-cause survival at 5, 10, and 15 years were 100%, 83% and 83%, respectively (Figure 1). Mean MSTS score for the upper extremity was 70% (range 34-100%). There were no cases of ulnar component failure, and three of eleven analyzed patients (27%) experienced symptomatic shoulder instability, two of which required revision. There were no cases of nerve palsy. One patient underwent revision of expandable prostheses due to lack of further expansion, and one underwent a procedure for augmentation of collapsed expansion mechanism. One patient underwent radial heal excision for symptomatic elbow instability. There was one wound dehiscence that was taken to the operating room for debridement at 1 month in an irradiated patient. There were no infections.

Conclusions: Total humerus endoprosthetic replacement is a reasonable reconstruction option for patients who require complete excision of the humerus for malignant bone tumors. THR offers limited but satisfactory functional outcomes with low failure and complication rates. In our study, survivorship is comparable to previous series. Soft tissue failure at the shoulder necessitating revision was the only mode of failure (Henderson I) in this series. Previous series have cited periprosthetic infection as the most common cause of all cause failure, but no infections were documented in this series. There were no nerve palsies or failures of the ulnar component as have been documented previously. Despite expected range of motion and strength limitations, total humeral reconstruction offers preservation of upper extremity function with a low rate of complications and failure.

Figure 1 - Kaplan-Meier survival curves for failure of total humerus endoprostheses.

PAPER 12

Long Term (> 15 year) Outcomes of Custom Cross-Pin Fixation of Tumor Endoprostheses Stems

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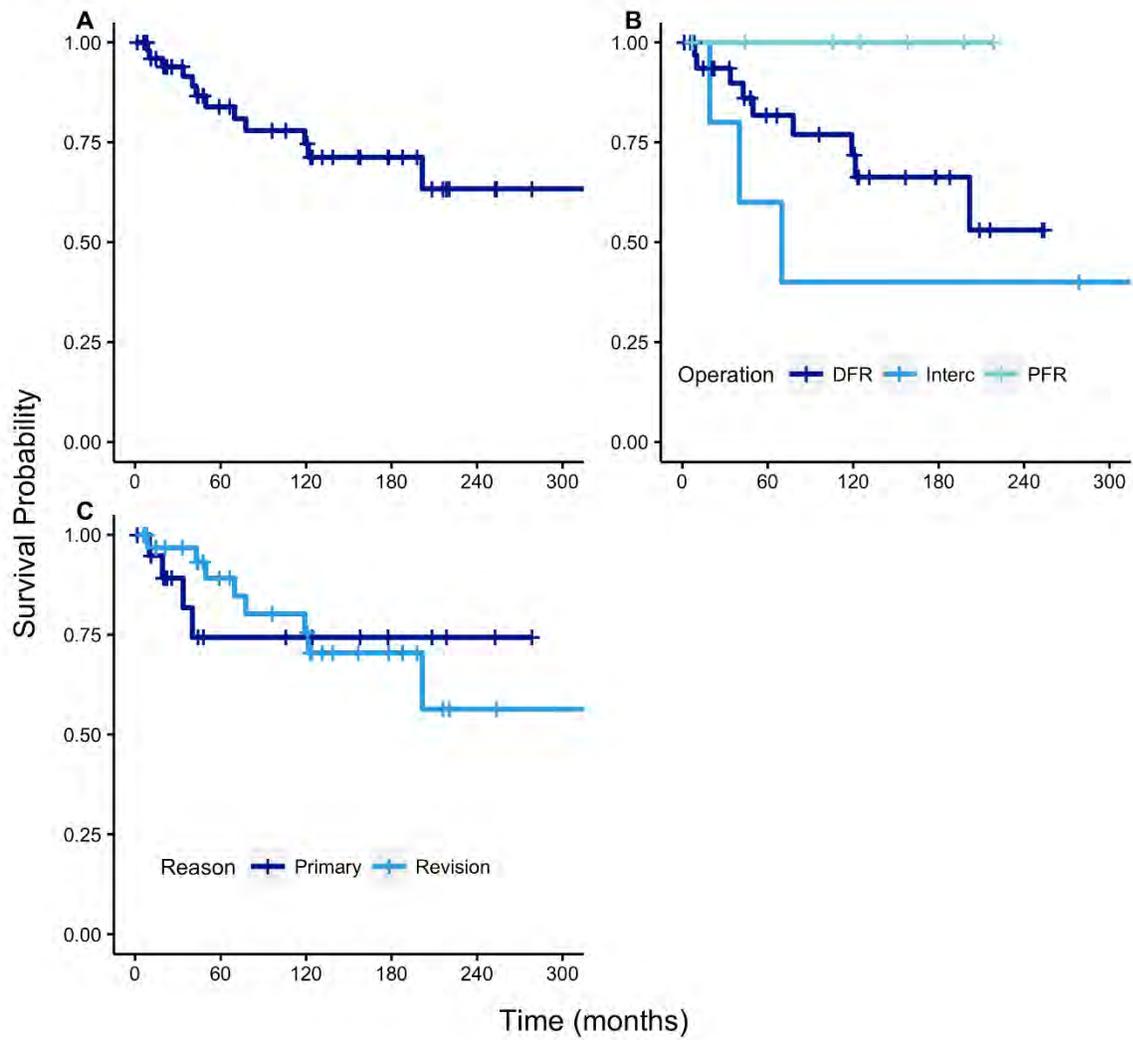
Background: Aseptic loosening due to rotational stress is a major cause of failure in cemented endoprosthetic reconstructions, particularly in large resections or revisions with short residual segments of bone requiring short intramedullary stems. Reconstructive techniques developed specifically for short segment fixation have been proposed, including extra-cortical plates and compressive osseointegration. Existing series demonstrate 8-14% mechanical failure rate at short-to-intermediate term follow-up using these techniques. We have previously reported on a custom cross-pin fixation technique that creates a bone-cement-prosthesis composite to resist rotatory stress with no cases of aseptic loosening in 24 endoprosthesis at mean 57 month follow up. Here we present the long-term outcomes and mechanical survivorship of this construct.

Questions/Purposes: We aim to examine the long-term survivorship, outcomes, and modes of failure of a custom cross-pin fixation technique for endoprosthetic reconstruction for primary bone tumors. Specifically, we seek to answer the following questions: (1) what is the mechanical survivorship of this technique? (2) Does location of reconstruction impact mechanical survivorship? (3) How does survivorship differ between primary and revision reconstructions?

Patients and Methods: This is a retrospective review of our endoprosthesis database consisting of 512 consecutive cemented endoprosthetic reconstructions performed for oncologic diagnoses at a single-center between 1980 and 2016. We identified 51 patients with 56 endoprosthetic implants with cross-pin fixation between August 1985 and November 2009. Twenty-one endoprosthesis were implanted following primary resection of tumor (9 osteosarcoma, 6 Ewing's sarcoma, 5 chondrosarcoma, 1 spindle-cell sarcoma), with the remaining 35 implanted as revision prostheses (21 for aseptic loosening, 6 structural failure, 6 infection, 2 soft tissue failure). Prosthesis locations included distal femoral (36), proximal femoral (7), intercalary (6; 5 femoral, 1 tibial), proximal humeral (3), proximal tibial (3), and distal humeral (1). Bushing changes, cross-pin changes, and planned expansions of growing implants were excluded. Outcomes evaluated were implant survival, revision surgery categorized according to the Henderson Failure Mode Classification, complications, and functional outcomes. Analyses were repeated for subsequent APT component revisions. Prosthesis survival is analyzed at 5-year, 10-year and 15-years using Kaplan-Meier analysis.

Results: Median follow-up period was 132 months (25th-75th percentile, 44 to 189 months). A total of 22 stems required revision: 8 for infection, 7 for structural failure, 5 for aseptic loosening and 2 for tumor progression. Of those stems requiring revision for aseptic loosening, two were in the same patient with a primary femoral intercalary endoprosthesis with proximal loosening. Mechanical survivorship at 5, 10, and 15 years was 84%, 75% and 71% respectively (Figure 1A). All cause survivorship at 5, 10, and 15 years was 72%, 64% and 51%, respectively. Mechanical failure varied by location, with no mechanical failures detected of PFR constructs. Femoral intercalary survivorship was 60%, 40% and 40% at 5, 10, and 15 years respectively (Figure 1B). There was not a substantial difference in survival between primary and revision reconstructions with survival at 5, 10, and 15 years of 74% for primary and 89%, 76% and 71% for revisions (Figure 1C).

Conclusions: The rate of mechanical survivorship (84% at 5 years) in our series is similar to those reported for other methods of reconstruction for short diaphyseal segments such as compressive osseointegration and extra-cortical plating. The mechanical failure rate differed by location with no failures of proximal femoral constructs and 40% survival of femoral intercalary constructs at 10 years. There were no differences in mechanical failure between primary and revision constructs. However, when primary constructs failed, they did so in the first five years with no failures after that time in contrast to revisions. Overall, custom cross-pin fixation remains a viable option for challenging endoprosthetic reconstruction of short metaphyseal segments with an acceptable rate of mechanical failure at long term follow up.

Figure 1 - Kaplan-Meier survival curves for mechanical failure of endoprosthetic stems with cross pins. (A) Mechanical failure for all endoprosthesis, (B) by type of reconstruction for three most common operations, (C) by indication, either primary resection or revision.

PAPER 13

Patient-Specific 3D Printed Implant Design for Pediatric Orthopaedic Oncology Reconstruction

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Background: Due to the limitation of available implant hardware, current standards of care for pediatric orthopaedic oncology reconstruction following bone resection often remove nearby articular joints. Additive manufacturing, also known as 3D printing, enables rapid, cost-effective production of custom implants that can be designed with porous features unattainable with traditional manufacturing methods. Furthermore, 3D printed constructs can be articular-sparing to preserve native, healthy anatomy.
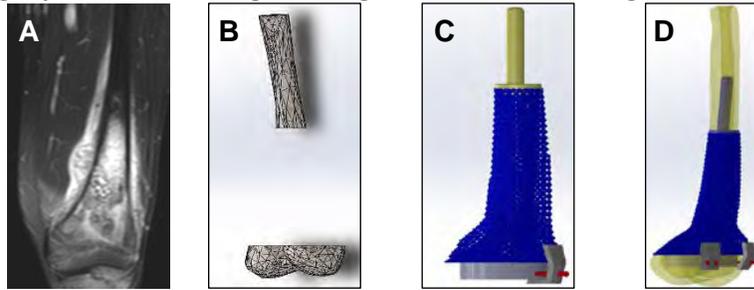
Purpose: *In this retrospective IRB-approved (IRB #00005099) study, we design pediatric patient-specific implants to be manufactured via 3D metal printing based on medical imaging data for proximal humerus, proximal tibia and distal femur osteosarcomas.*

Methods: Pediatric oncology patients were identified using the Penn State i2b2 database. Cases involving the proximal tibia, distal femur, and proximal humerus were selected and MRI data were obtained. Bones were reconstructed (Mimics, Materialise) and rendered as solid models (SOLIDWORKS, Dassault Systèmes). Virtual resection surgery was performed with guidance from an orthopaedic musculoskeletal oncology surgeon. Implants were designed to fill post-surgical defects and lattice structures were designed (Element Pro, nTopology) for each implant. Specific attention was given to fixation points between implant and bone during the design for 3D printing workflow using biocompatible titanium alloy (Ti-6Al-4V). Validation of the proposed 3D printed implants are on-going with emphasis on mechanical fatigue strength through finite element analysis (ABAQUS/CAE, Dassault Systèmes) as well as mechanical testing.

Results: Novel articular and growth plate-sparing implant designs were developed as alternatives to joint sacrificing endoprosthetic reconstruction following tumor resection. The proximal tibia and distal femur implants shown in **Fig. 1** combine a non-stochastic lattice structure to fill the region of resected bone, a stem for stabilization and fixation, and a boss for screw fixation to the

spared articular surface. The resulting designs are being 3D printed at University Park and their mechanical integrity assessed through testing at Penn State College of Medicine.
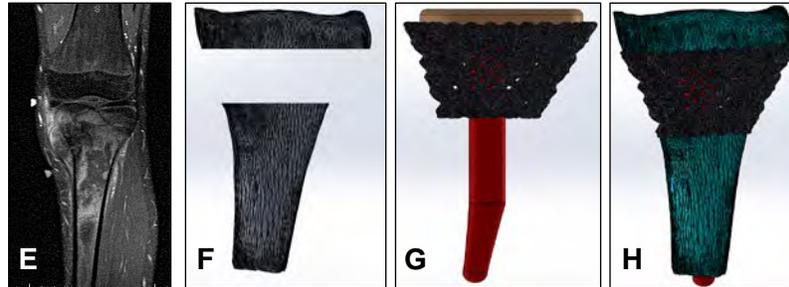
Case 1: 13 y.o. with left distal femur osteosarcoma

Case 2: 17 y.o. with left proximal tibia osteosarcoma

Figure 1. Design workflow for custom implant design for distal femur and proximal tibia osteosarcomas. Patient imaging data (A, E) is reconstructed into a solid model with virtual tumor removal (B, F) and an implant is designed to fill the bone defect (C, G). Implant fit is then assessed (D, H).

Conclusion: Three unique custom implants have been designed for different applications in joint-sparing tumor removal surgery in different anatomical regions. Custom implant design, taking advantage of unique capabilities of 3D printing, can match defect geometry, improve implant fixation, and provide porous scaffolds that enable bone integration while supporting physiological loads and restoring function.

PAPER 14

OUR EXPERIENCE WITH 3-D PREOPERATIVE PLANNING, STEREOLITHOGRAPHIC MODELS AND CUSTOM-MADE IMPLANTS IN A UNIVERSITY HOSPITAL IN A DEVELOPING COUNTRY

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BACKGROUND
In the setting of complex oncologic surgery where the main goal is to achieve adequate surgical margins, precision turns to be a main feature and every tool available that helps to achieve it should be taken into account. Recent studies have shown the benefits of computer assisted surgery and 3-D preoperative planning. Furthermore, the use of stereolithographic models, including surgical cutting guides, has also been reported with promising results in the field of maxillofacial surgery. Having this information into account and in the pursue of a more accurate method that could add precision to our procedures, preserving bone stock and reducing surgical times while making the surgery more secure, we developed a 3D planification Unit in our institution. The Unit is composed of Orthopedic Oncologists, bioengineers and radiologists.

QUESTIONS/PURPOSES
1) Is there a place for 3-D preoperative planning, stereolithographic models and surgical cutting guides in orthopedic oncology?
2) The aim of this paper is to show our experience, so far, with the use of virtual 3-D preoperative planification, stereolithographic models and surgical cutting guides, and custom-made implants in the ambit of a University Hospital in a developing country.

PATIENT AND METHODS
In this paper we describe in detail the process of virtual 3-D preoperative planification, the development of stereolithographic models and the arguments we used in order to decide whether or not to use computer assisted navigation systems for each of our cases. Moreover, we discuss the benefits we found when using this method, but even more important, we discuss the pitfalls during our learning curve, and how we managed to build the 3-D planification Unit in a country with scarce resources.

RESULTS

We performed a total of 32 surgical procedures, all with the use of virtual 3-D preoperative planification. In 29 cases the surgery was carried out with the help of stereolithographic models designed during the preoperative planification process and 3-D printed. In 26 cases we used 3-D printed surgical cutting guides in order to gain precision when performing osteotomies for bone resection at the patient's site. In 16 cases we also used similar 3-D printed surgical cutting guides for the osteotomy at the allograft's site. When doing so, both surgical cuts were meticulously planned in order to perfectly match both pieces. Furthermore, a computer assisted navigation system was used in 9 cases to guide us during the surgical procedure. In 5 cases a custom-made implant was used. Four other cases were discussed in order to perform a 3-D planning but we decided that those cases were not adequate for the method.

CONCLUSION

The development of a 3-D planification Unit has resulted in several benefits for our team. The fact of each member having a strict role during planification has organized the preoperative process. The surgeons are now more confident when facing complex surgeries. Overall, we believe this methodology added several benefits for our team and for the patients. Nevertheless, future studies should be carried out in order to show whether or not these appreciations are in fact real and cost effective.

#	Age	Location	Gender	Diagnosis	3-D Planning	SLG Models	Surgical guides	CA-N
1	18	Humerus	M	GCT-B	Yes	Yes	Yes	No
2	33	Humerus	F	Fibrous Dysplasia	Yes	Yes	Yes	No
3	21	Distal Femur	F	GCT-B	Yes	Yes	Yes	No
4	36	Tibia	M	GCT-B	Yes	Yes	Yes	No
5	30	Proximal Femur	F	GCT-B	Yes	Yes	Yes	No
6	42	Proximal Femur	M	Chondrosarcoma	Yes	Yes	Yes	No
7	27	Pelvis	F	Chondrosarcoma	Yes	Yes	Yes	Yes
8	60	Pelvis	F	Chondrosarcoma	Yes	Yes	Yes	Yes
9	21	Tibia	M	GCT-B	Yes	Yes	Yes	No
10	38	Fibula	F	Osteosarcoma	Yes	Yes	Yes	No
11	36	Knee	M	Pseudarthrosis	Yes	Yes	Yes	No
12	36	Knee	M	Pseudarthrosis	Yes	Yes	Yes	No
13	18	Pelvis	M	Ewing Sarcoma	Yes	Yes	No	Yes
14	51	Scapula	F	Chondrosarcoma	Yes	Yes	Yes	Yes
15	52	Scapula	F	Chondrosarcoma	Yes	Yes	No	Yes
16	45	Humerus	F	Osteosarcoma	Yes	Yes	No	No
17	35	Humerus	F	Chondrosarcoma	Yes	Yes	Yes	No
18	34	Proximal Femur	F	Fibrous Dysplasia	Yes	Yes	Yes	No
19	53	Tibia	M	Chondrosarcoma	Yes	Yes	Yes	No

20	50	Distal Femur	F	GCT-B	Yes	Yes	Yes	No
21	32	Tibia	M	GCT-B	Yes	Yes	Yes	No
22	7	Femur	F	Ewing Sarcoma	Yes	Yes	Yes	No
23	19	Tibia	F	Osteosarcoma	Yes	Yes	Yes	No
24	31	Tibia	F	GCT-B	Yes	Yes	Yes	No
25	30	Pelvis	M	Osteochondroma	Yes	Yes	Yes	No
26	60	Tibia	M	Adamantinoma	Yes	Yes	Yes	No
27	41	Distal Femur	M	GCT-B	Yes	Yes	Yes	No
28	53	Pelvis	F	Chondrosarcoma	Yes	No	No	Yes
29	56	Sacro	F	Chondrosarcoma	Yes	No	No	Yes
30	58	Sacro	F	Chordoma	Yes	No	No	Yes
31	26	Pelvis	M	Ewing Sarcoma	Yes	Yes	Yes	Yes
32	19	Tibia	M	Chondromyxoid fibroma	Yes	Yes	Yes	No

Table 1. GCT-B: Giant Cell Tumor of Bone; SLG Models: Stereolithographic Models; CA-N: Computer Assisted Navigation.

PAPER 15

Dynamic Prediction For Patients With High-Grade Extremity Soft Tissue Sarcoma

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Objective. Increasing interest lies in the personalised prediction of disease progression for soft tissue sarcoma patients. Currently, available prediction models are limited to predictions from the time of diagnosis or surgery. However, updated patient information during follow-up may change a patient's prognosis, which is not accounted for in these models. The concept of dynamic prediction allows to include updated information as well as model time-varying covariate effects to make the prediction of overall survival at different times during follow-up. This information can be used to provide better-individualised treatment options that depend on the dynamic assessment of a patient's prognosis.

Background.

Purposes

Patients and Methods. Information from 2232 patients with high-grade extremity soft tissue sarcoma who underwent surgery at 14 specialised sarcoma centres, was used to develop a dynamic prediction model with primary endpoint overall survival.
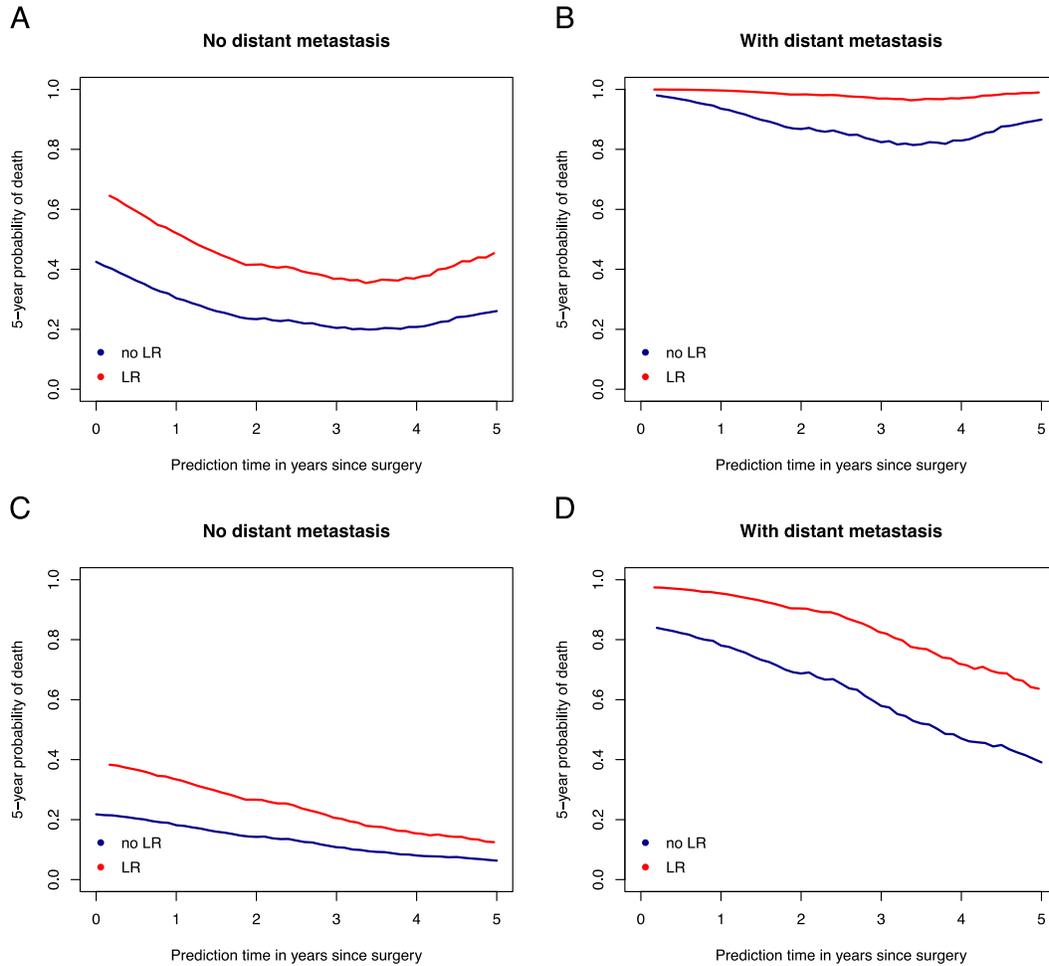
To estimate a patient's probability of surviving an additional 5 years from a particular prediction time point a proportional landmark supermodel was used. Landmark models are able to make predictions from a particular time, by using all (updated) information of patients still alive and in follow-up at that time.

Results. Surgical margin and tumour histology have a time-varying effect on overall survival. The effect of margin is strongest shortly after surgery and fades slightly over time. The occurrence of local recurrence and distant metastasis during follow-up have a strong effect on overall survival and they must be accounted for to make updated predictions. See two examples in figure 1.

Conclusions. The presence of time-varying effects for some prognostic factors as well as the effect of the time-dependent variables local recurrence and distant metastasis on survival suggest the inadequacy of baseline models for predictions during follow-up. To the best of authors' knowledge, this is the first dynamic prediction model in this field. The model will be made freely available through the PERSARC *after surgery* mobile app.

: synthesis of literature and findings, limitations, clinical relevance

Fig.1 The 5-year probability of death estimates for patients with different characteristics and at different stages of disease progression.

Blue: without local recurrence (LR); **red**: with LR.

(Upper row): fictive 61-year-old with a 9 cm deep myxofibrosarcoma, that was resected with free margin without adjuvant radiotherapy. (A) without distant metastasis (DM) at time of prediction (t_p). (B) diagnosed with DM before time of prediction (t_p).

(Lower row): fictive 45-year-old with a superficial located synovial sarcoma, that was resected with a free margin with adjuvant radiotherapy. (C) without DM at time of prediction (t_p). (D) diagnosed with DM before time of prediction (t_p).

PAPER 16

Cement spacers for intercalary reconstructions

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Background:

Improvement in oncological outcomes and prolonged survival of bone tumor patients necessitates durable reconstructions. Elaborate techniques with long surgical times and costly implants have become the standard of care. However, in patients with poor prognosis, simpler reconstruction method with shorter surgical time, less complications, and lower cost are welcome. Cement spacers are routinely used in two-stage revision operations. They have never been studied as definite reconstruction option. We performed this study to evaluate the durability, complications rates and need for revision of these spacers used as a definite intercalary reconstruction in bone tumor patients.

Purpose/Questions:

1) can intercalary cement spacers serve as a definitive reconstruction technique that allows for full weight bearing?
2) does this method decrease early complication rates, therefore facilitating adjuvant treatments?
3) is there a need to revise this reconstruction with a more durable one because of related late complications?

Patients and methods:

This is a retrospective case-series study. We reviewed our institutional data form 2007 to 2017 and included patients who received intercalary cement spacer reconstructions of a weight bearing bone. Patients with cement spacers of the pelvis, articulating spacers, knee arthrodesis or spacers of short bones were not included.
Total of 15 patients (7 male and 8 female), with a mean age of 54 years (range, 20 to 79) were included in the study. Eight patients with the diagnosis of a primary bone sarcoma were treated with wide margins intercalary resection, 5 patients with metastatic bone disease were treated with an intralesional surgery, and revision surgery for an infected intercalary allograft was done in 2 patients

Reconstruction was done for intercalary bone defects in the femur (mean length, 161 cm; range, 110 to 240 cm) in 12 patients, in the humerus (mean length, 98 cm; range, 65 to 130 cm) in 3 patients. The mean follow-up was 32 months (range, 2-135 months); last clinical visit, death or revision of the spacer was considered the end-point of follow-up. Complications, reoperations and function, as evaluated with the MSTS score, were recorded.

Results:

At the mean follow-up of 57 months (range, 11 to 120), 6 patients were alive with their intercalary cement spacers in place. All were weight-bearing with only 2 patients requiring assistive device. The mean MSTS score for these patients was 81% (range,50% to 97%). Four patients died from the disease with their spacers in place without any complications at mean follow-up of 14 months (range, 2 to 30). Two patients experienced mechanical failure of their spacers at 3 and 17 months postoperatively. Both had intramedullary nail as a sole form of fixation in femoral location. Length of the reconstructed defect was 180 and 240cm. Both patients were revised to an allograft with good results. Two patients were converted to a biological reconstruction with a vascularized fibula at 19 and 26 months postoperatively, because of disease remission and improved prognosis. One patient experienced a local recurrence and was treated with hip disarticulation. No patient experienced an infection complication during the period of this study. The mean surgical time was 175 minutes (97 minutes for plate osteosynthesis,190 minutes when intramedullary nail was used and 240 when combination of both was used).

1) Cement spacer is suitable form of reconstruction for selected group of patients and allows for a full weight bearing.
2) This form of reconstruction both decreased surgical time and early complication rate. There were no infections and only one patient (7%) required a revision surgery in the first year postoperatively.
3) There is no indication for preventive revision of this reconstruction as the long term results are encouraging with only two patients (13%) suffering a mechanical failure

Conclusions:

Cement spacer may be used as a definitive reconstruction option for patients with intercalary bone defects with low complications rates and good function. Zero infection rate in our series, makes this an appealing option for patients, whose prognosis is dependent on swift continuation of adjuvant therapy. This method does not compromise conversion to a more elaborate reconstruction in the future if needed. Surgical time and complications are lower when the spacer is stabilized to the native bone with plate and screws. Sole intramedullary nail in the femoral location appears insufficient and prone to mechanical failure.
This is a small sample, retrospective study with an obvious bias towards older patients and patients with short life expectancy and low functional demands.

PAPER 17

Short- and intermediate term function after distraction osteogenesis for bone reconstruction of osseous tumors in the upper and lower extremity

Background
Surgical resection with wide margins is a critical step in achieving local control for the majority of bone sarcomas. Limb salvage surgery has been shown to be comparable to amputation to achieve oncological goals as long as negative margins can be attained. Techniques of bone regeneration are currently used to manage large and massive bone defects in trauma, infection and congenital deformities, and less commonly used for oncological osseous defects. The method of reconstructive surgery is influenced by many factors: the location of the tumor, the size of the defect, the preference of the patient and surgeon, the involvement of the articular surface, the prognosis, and the response to chemotherapy. The inhibitory effect of chemotherapy, especially in multi-agent protocols, has not been sufficiently studied previously.

Questions
Is distraction osteogenesis (DO) safe and effective for the early and late reconstruction of bone defects in the upper and lower extremity during concomitant delivery of chemotherapy? What are the short- and midterm functional outcomes in oncology patients treated with DO? What is the rate of complications with this technique?

Methods
We evaluated 44 patients who underwent DO reconstruction of the upper and lower extremity between 08/2014 and 03/2018. Indications were primary and revision reconstructions for osseous malignant neoplasms, including secondary discrepancy or deformity. The method of DO included single and double level bone transport via internal or external fixation. 31 (70%) patients completed treatment with DO using an external fixator, 12 (30%) using an internal device. Adjuvant and neoadjuvant chemotherapy, radiation dose and timing, total defect size, and complications were reviewed for all eligible patients. Functional and emotional outcomes were assessed using the MSTS score.

Results
In 40 (91%) cases, the defect was in the lower extremity (femur= 25 cases, tibia= 15 cases). All surgical margins were free of tumor. 41 (93%) patients underwent reconstruction because of primary neoplasms involving bone and 3 (7%) patients because of bone metastases. The median total defect size in tumor patients was 14.25 cm (range 9-25 cm). 17 (39%) patients received chemotherapy prior to DO, 15 (34%) patients during the reconstruction surgery; 4 (9%) patients received radiation therapy before surgery. The rate of major complications was 52%. Median follow-up time was 18 months (range 0.1-39.75). Median MSTS score at the last follow-up visit was 19 (range 6-30). 16 (36%) patients needed unplanned revision surgery. Patients with MSTS

score >15 had less revision surgeries; however, there is no significant relationship between revision surgery and MSTS score (p 0.739). Patients with a defect greater than 15cm had a significantly higher risk of developing minor or major complications (p 0.039). Presence or absence of chemotherapy, the use of internal or external fixation or joint fusion did not have a significant effect on functional outcome or postoperative complications.

Conclusion

We postulate that the use of DO is safe for the primary and secondary reconstruction of malignant bone neoplasms. It is also an effective technique to regenerate bone during systemic chemotherapy. Despite high complication rate, DO is an effective method for reconstructing even large bony defects and yields good, sustainable functional results.

Figures

Patient 1 ; intraoperative imaging

Patient 1 ; 3 years after surgery

References

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PAPER 18

Long-Term Follow-up of Massive Allograft Reconstructions. What we Expected after Ten Years of Surgery

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Background: Massive bone allografts have been used for limb salvage of bone tumor resections as an alternative to endoprostheses, however, they have different outcomes and risks. Allografts have been associated with considerable rates of infection, fracture and nonunion. Although several studies on massive allograft reconstructions for bone tumors reported that most complications occur in the first years following surgery and after that, allografts become relatively stable and reliable, there is no solid evidence concerning complications after long-term outcomes. The purposes of this study were (1) to analyze the survival of the allografts in a group of patients treated for bone tumors located in the lower limb with a minimum of ten years of followup; (2) to analyze risk factors for allograft survival such as age, sex, affected bone, type of reconstruction, type of tumor (malignant or benign), type of failure, and use of chemotherapy; and (3) to determine which complications we should expected after 10 years of followup.

Methods: We retrospectively analyzed the records of patients treated with massive bone allografts (intercalary and osteoarticular) for a benign or malignant bone tumor in the femur and tibia between 1986 and 2007. During this period, 198 patients were treated with massive allografts in long bones of the lower extremity (132 femurs and 66 tibias) after resection of a primary bone tumor, which included 120 osteoarticular, and 78 segmental intercalary allografts. Minimum followup was 10 years unless death occurred earlier (mean 192 months; range, 1-370 months), and no patient was lost to followup. The mean age was 22 years, and 105 were males and 93 females. Predominant diagnoses were osteosarcoma (n=125, 63%), giant cell tumor of bone (n=27, 14%) and Ewing's sarcoma (n=19, 10%). Chemotherapy was given to 146 patients

(74%). The selected variables were analyzed using multivariate logistic regression to identify risk factors for failure.

Results: Patient survival was 85,4 at 5 years (95%CI 80,4-90,3), 84,3 at 10 years (95% CI 79,3-89,4), and 82,8 at 20 years (95% CI 77,4-88,3). At a mean follow-up of 192 months, 31% of the reconstructions failed (62 of 198), 7 of these 62 (4%) failures occurred after 10 years of the initial reconstruction. The risk of allograft failure (Fig. 1) was 36% at 5 years (95%CI 30-43), 40% at 10 years (95% CI 33- 47), and 44% at 20 years (95% CI 37-51). Predominant reasons for failure were fracture (n=26, 13%), infection (n=21, 11%) and tumor recurrence (n=13, 7%). We found higher risk of failure in ostearticular tibia allografts when we compared against osteoarticular femur allografts (p = 0.01) (Fig. 2) or tibia intercalary allografts (p = 0.02) (Fig. 3). Regarding failures, fractures were more significantly frequent in femur (p < 0.01) infections were significantly more frequent in tibia (p < 0.000001) and local recurrence were higher in tibia but not significantly (p < 0.053) (Fig. 4). When we analyzed time of failure, 20 of 21 infections occurred in the first three years after surgery, while only 8 of 26 fractures occurred in the same period. Seven reconstructions (five osteoarticular and two intercalary) failed after more than ten years of follow-up; reasons for late failure were fractures in 4, infection in one, instability in one and second tumor in one.

Conclusions: We find in this study that the risk of allograft failure was 40% at 10 years that increases to 44% at 20 years, mainly due to fractures of the allograft. We found higher rate of failures in the proximal tibia osteoarticular allografts. Regarding causes of failures fracture was more frequent in femur allografts and infection more frequent in tibia allografts.
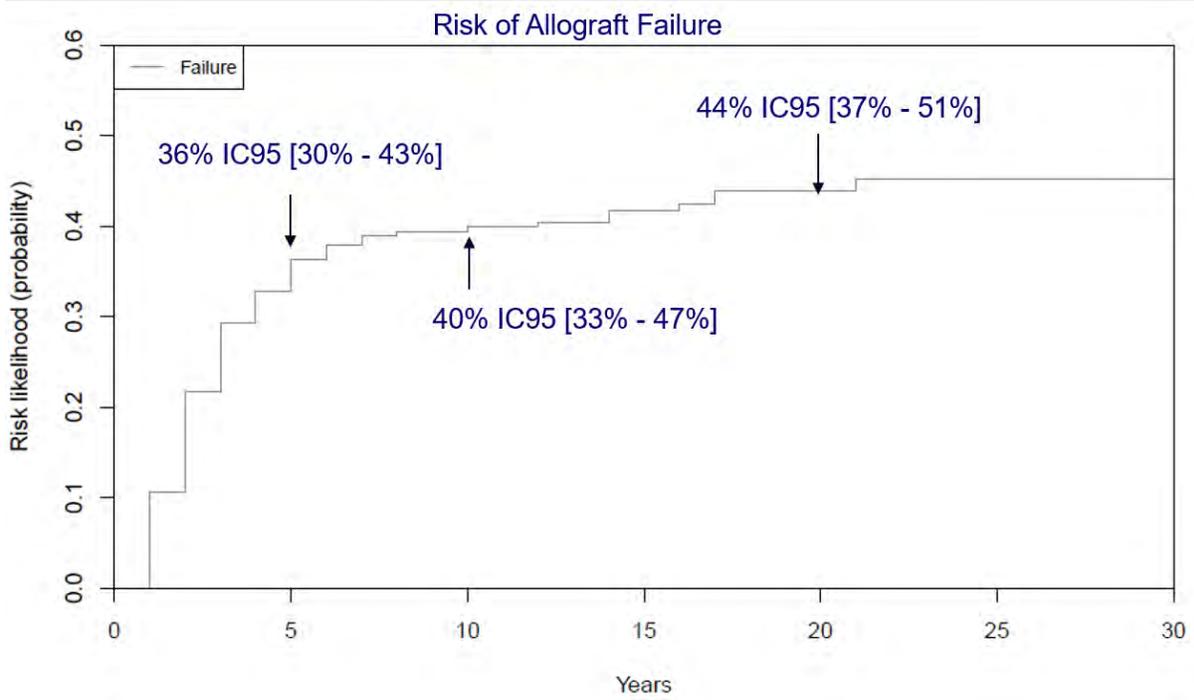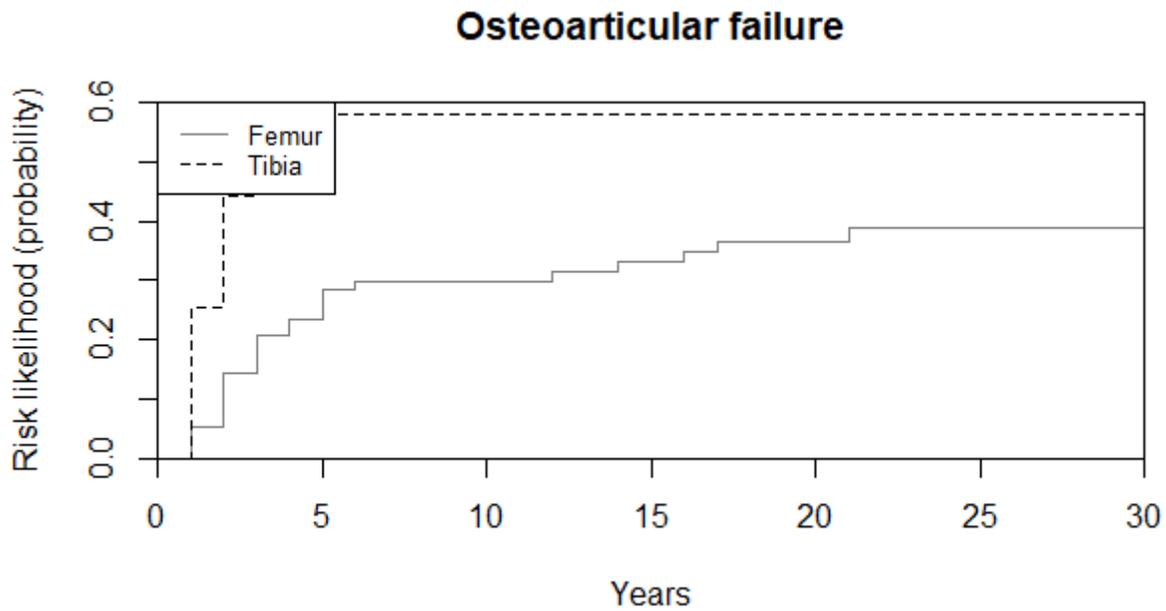
Figure1

Risk of Allograft Failure
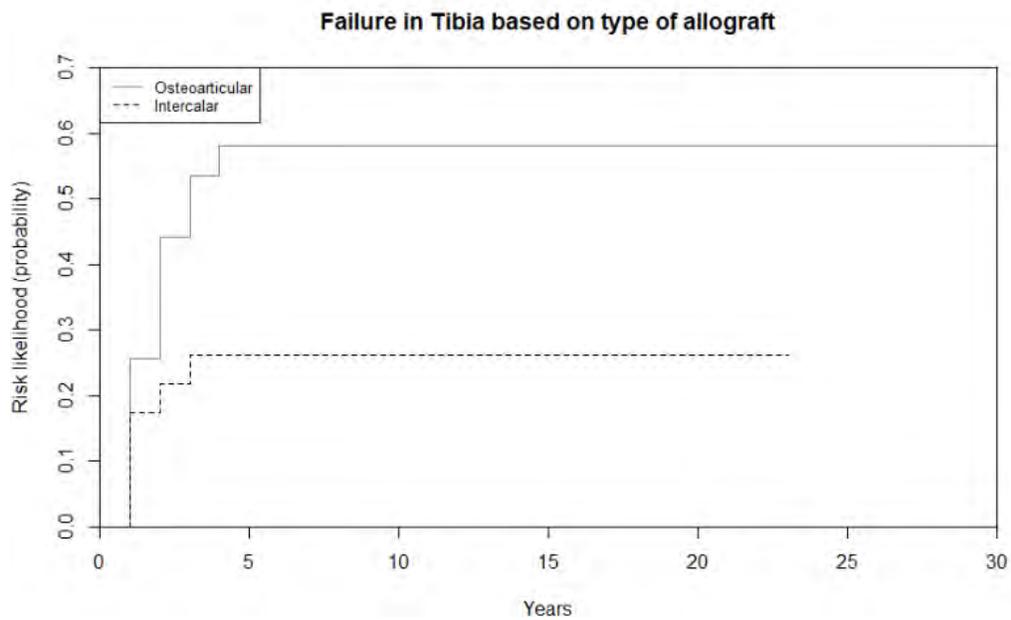
44% IC95 [37% - 51%]

36% IC95 [30% - 43%]

40% IC95 [33% - 47%]

Figure 2

Osteoarticular failure

Figure 3

Failure in Tibia based on type of allograft

Legend:
— Osteoarticular
--- Intercalar

Y-axis: Risk likelihood (probability)
X-axis: Years

Figure 4

Fracture, infection and recurrence

Legend:
Femur recurrence 5%
Tibia recurrence 12% p < 0.053
Femur fracture 18%
Tibia fracture 5% p < 0.01
Femur infection 4%
Tibia infection 24% p < 0.000001

Tibia Infection
Femur Fracture
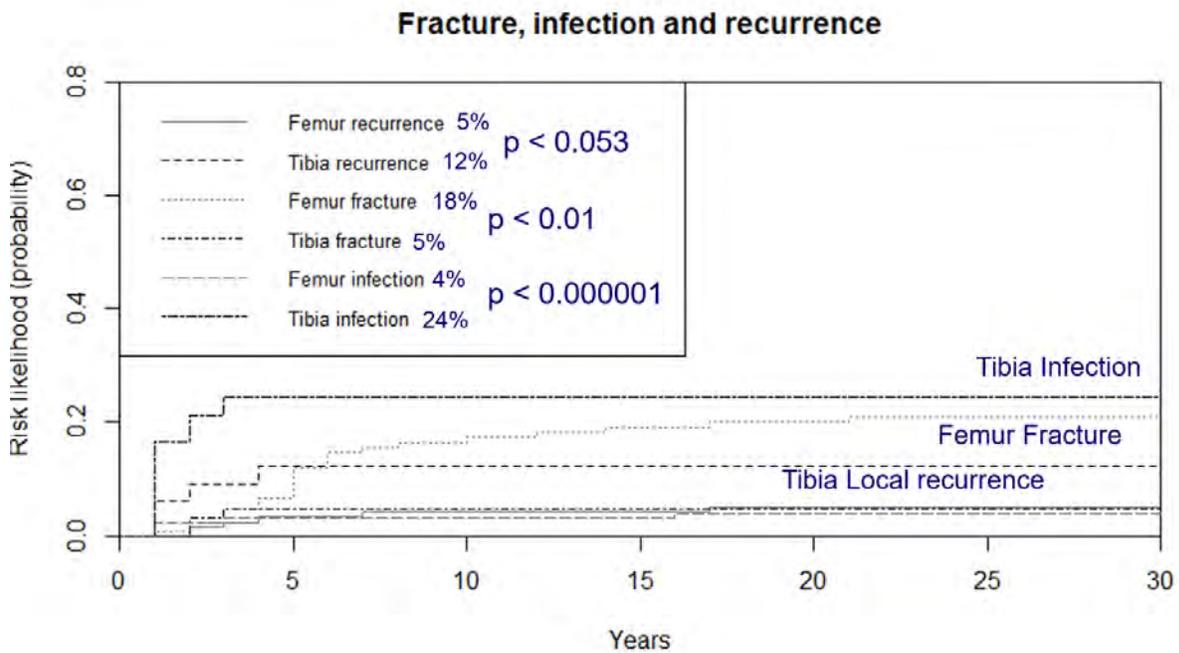Tibia Local recurrence

Y-axis: Risk likelihood (probability)
X-axis: Years

PAPER 19

Long Term Outcomes of Telescope Allograft Technique for Diaphyseal Reconstruction in Limb Salvage Surgery

Authors:
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Institution:

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Background:
Loosening and progressive bone loss remain major problems that compromise endoprosthetic survival and complicating revision surgery. A short residual segment of bone makes prosthetic fixation difficult and may require sacrifice of the nearby joint. Allograft-prosthesis composite (APC) potentially increases bone stock and adds an extra biological construct; however, risk of complications like nonunion, allograft resorption and fractures are high. In 2009, the use of intussuscepting massive allograft for preservation of residual bone was described to overcome the potential drawbacks of end-to-end apposition by offering longer allograft-host interface and larger contact surface area.

Purposes:
We analyzed prospectively collected data from our institution to address the following questions: (1) Is the telescope allograft technique effective in preserving the adjacent at-risk joint in patients with severe femoral or humeral bone loss in the setting of primary or revision tumor surgery? (2) What are the long-term outcome of reconstructions with the telescope allograft technique including 10-year survivorship; and (3) assess short- and long-term complications of this procedure.

Methods:
Twenty-four patients underwent a total of 31 telescope procedures (11 males and 13 females). The median age at the time of surgery was 32 years (range: 4-56). Median follow-up was 9 years (range: 2-17.3). Allograft failure was defined as graft removal due to non-union, fracture, loosening, or hardware failure. Twenty-three patients had a history of primary bone tumor, with diagnoses of osteosarcoma (n=14), chondrosarcoma (n=3), Ewing sarcoma (n=3), giant cell tumor (n=2), and malignant fibrous histiocytoma (n=1), and one patient had failed proximal and distal femoral megaprostheses for a non-oncologic condition. Three patients had 3 telescope procedures in the humerus while 21 patients had 28 telescope procedures in the femur. The telescope technique was the primary reconstruction in 9 patients and was used for revision surgery in 15. In 19 of the 24 cases, APC was used while 5 patients underwent allograft

reconstruction and internal fixation. The allograft/bone defect length ratio and the allograft/host overlap length were recorded. ANOVA was used to assess statistical significance ($p<0.05$).

Results:

1) The at-risk adjacent joint was preserved in 18 of 19 patients (95%) with APC using the telescope technique, avoiding a total femur or total humerus arthroplasty. Deep infection caused failure in one case, requiring further surgery and ultimately to conversion to total femur replacement.

2) Overall survivorship of allografts was 75% at 5 years and 68% at 10 years, and the mean time to allograft failure was 4 years (range: 0.5-12.5 years). Overall survivorship of APC was 58% at 5 years and 52% at 10 years. The median MSTS score of the entire cohort was 24 (range: 14-29). All patients were ambulatory at the last follow-up visit and the median time to full weightbearing in the femoral reconstruction group was 4 months (range: 2-20 months). Median time to allograft incorporation was 8 months (range: 3-23 months). Mean allograft survival was 82 months for primary reconstruction and 65 months in revision cases ($p=0.3$). Mean allograft survival was 65 months in the distal femoral replacement group and 42 months in the proximal femoral replacement group ($p=0.4$). Sixty-five percent of the resected bone segment length was successfully reconstituted by allografts in the whole cohort, representing 83% in the primary reconstruction group and 57% in the revision group ($p=0.007$). Mean allograft/host bone overlap in survived allograft group was 5.2 cm (95% CI: 3.8-6.6) versus a mean of 3.8 cm (95% CI: 2.7-5.1) in the failed allograft group ($p=0.3$).

3) Complications included infection in 3 patients (13%), allograft fracture in 5 (21%), non-union in 3 (13%), hardware failure/revision in 7 (29%), and heterotopic ossification in 2 (8%).

Conclusions:

The telescope allograft technique in this cohort had satisfactory 10-year survivorship (68%). Primary reconstruction, distal femoral replacement, and allograft/host bone overlap of ≥5 cm were associated with prolonged allograft survival with the use of the telescope technique. Surgical revision of failed megaprostheses was technically more challenging than primary reconstruction with respect to bone stock reconstitution; however, use of the telescope allograft technique was effective in preserving the adjacent joint despite severe bone deficiency.

Case 1: A 7-year-old female who received a distal femoral replacement for osteogenic sarcoma presented with aseptic loosening 1 year after surgery.

(A-C) Preoperative radiographs. **(D)** Immediate postoperative radiograph after first allograft telescope procedure; **(E)** radiograph taken 1 year later, showing allograft resorption. **(F)** Postoperative radiographs taken immediately after a second allograft telescope procedure. **(G, H)** Radiographs 7 years after surgery showing full allograft incorporation and successful extension of the prosthesis.

Case 2: A 31-year-old male who presented 18 years after proximal femoral replacement for osteogenic sarcoma with dislocation, infection, and severe shortening. He was treated with staged revision and re-implantation.

(A, B) Preoperative radiographs. **(C-E)** 6-month postoperative radiographs after re-implantation with APC telescope technique. **(F)** 5-year postoperative radiograph showing full incorporation.

PAPER 20

Sarcopenia is associated with increased mortality and complications following limb-sparing reconstruction for sarcoma of the extremities.

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Background: Sarcopenia is an age- or disease-related condition of decreased skeletal muscle mass and functional strength, and is associated with increased complications and mortality in carcinoma patients. Previous literature evaluating patients with soft tissue sarcoma reported no relationship between sarcopenia and survival, however there is a paucity of literature evaluating sarcoma patients. Sarcopenia may be a useful and objective screening tool to identify sarcoma patients at increased risk of postoperative complications and mortality.

Questions/purposes: We examined the prognostic impact of skeletal muscle mass and density, e.g. sarcopenia, as well as patient-, tumor-, and treatment-related factors on postoperative outcomes following excision and limb reconstruction for sarcoma of the extremities.

Patients and Methods: We performed a retrospective, single-center review of 148 patients treated with surgical excision and limb reconstruction for sarcoma of the extremities from October 2010 to January 2017. Cross-sectional psoas area was measured from a preoperative axial computed tomography scan at the level of the L3 pedicle. Sarcopenia was assessed as Psoas Index (PI) <5.45 cm^2/m^2 for men and <3.85 cm^2/m^2 for women. Logistic regression was used to assess the association between postoperative complications or mortality with patient demographics, PI, tumor grade, stage, and adjuvant therapy.

Results: Primary sarcoma was diagnosed in 133 patients, recurrent sarcoma in 7, and metastatic sarcoma in 8. There were 101 cases of soft tissue tumors and 47 cases of primary bone tumors. Sarcopenia was present in 41 patients prior to treatment. Neoadjuvant therapies were given in 93 patients (62.8%) and adjuvant therapies were given in 74 patients (50%). Seventy eight patients experienced complications (52.7%) and 20 patients died. Presence of sarcopenia (OR 6.6, ref=no sarcopenia, $p=0.0002$) and metastatic disease (OR 18.9, ref=primary tumor, $p=0.0004$) was associated with a significantly greater odds of mortality. Patients with sarcopenia compared to patients without had 2.5 times greater odds of postoperative complications ($p=0.0205$). Age was the strongest predictor of wound complications, with a 3% increase in odds for wound complication for each 1 year increase in age (OR 1.03).

Conclusions: Sarcopenia is an independent risk factor for postoperative complication and mortality following sarcoma excision and limb reconstruction. Skeletal muscle mass may be an objective screening measure to identify patients at risk for poor outcomes. Prospective studies are needed to better define screening criteria and identify interventions to mitigate, in part, the increased risk of complication and mortality associated with sarcopenia.

PAPER 21

Tranexamic Acid Use in Cancer Patients Undergoing Wide Resection and Endoprosthetic Reconstruction – A Retrospective Review

Investigators:
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Abstract:
Resection of bony tumors and endoprosthetic reconstruction presents a significant risk of perioperative blood loss, often requiring transfusion. As transfusions are known to have inherent risks, a goal of therapy is to therefore minimize perioperative blood loss. Tranexamic acid (TXA) is an antifibrinolytic agent commonly used to reduce blood loss in orthopedic procedures, most often arthroplasty. The safety, even in patients with significant comorbidities, and efficacy of TXA use in joint arthroplasty is well documented in the literature. It has not only been shown to decrease perioperative blood loss and transfusion rates, but also to decrease postoperative hospital stay and increase patient satisfaction. There is, however, a dearth of literature exploring the safety and efficacy of TXA use in musculoskeletal oncology patients. As a result, no standard of care regarding the use of TXA exists within the musculoskeletal oncology community and its utilization varies from surgeon to surgeon.

The aim of this retrospective comparative study was to explore the effects of topical TXA use on perioperative blood loss, blood transfusion rates, DVT occurrence, and postoperative hospital stay in patients undergoing wide resection of malignant bone tumors and endoprosthetic reconstruction.

A total of 111 patients who underwent wide resection of a malignant bone tumor and endoprosthetic resection between 1/1/2013 and 1/1/2018 at a single academic medical center were included in the study; 33 patients in the TXA group and 78 patients in the non-TXA group. All patients in the TXA group received 1g topical TXA diluted into 100 mL normal saline and administered into the wound bed prior to closure. The Hemoglobin Balance method was used to calculate perioperative blood loss. All patients were started on chemical prophylaxis postoperative day one and continued for a minimum of twenty-eight days. Patients were followed for a total of six weeks to determine incidence of acute postoperative DVT. Analysis of patient specific factors identified no significant differences between the TXA and non-TXA groups with regards to age, sex, BMI, tobacco use, diabetes, diagnosis, preoperative hemoglobin, or preoperative hematocrit. Surgery specific analysis for proximal femur replacement (PFR), distal femur replacement (DFR), hemiarthroplasty, and proximal tibia replacement (PTR) procedures was conducted.

Patients in the TXA group experienced a significant reduction in calculated mean blood loss at 24, 48, and 72 hours postoperatively, with a 558 mL reduction in calculated mean blood loss at the 72 hour mark (p=0.0007). Surgery specific analysis further demonstrated significant reductions in calculated mean blood loss at 24, 48, and 72 hours postoperatively with TXA use in PFR and DFR patients. A 794 mL, or 38%, reduction in 72-hour calculated mean blood loss was observed in the PFR group (p=0.006), while a 561 mL, or 28%, reduction was observed in the DFR group (p=0.02). hemiarthroplasty and PTR patients in the TXA group also experienced a reduction in their postoperative blood loss, however these findings did not reach statistical significance. Furthermore, PFR patients in the TXA group experienced a 0.76 units PRBC per patient reduction in three-day postoperative blood transfusion rate (p=0.01), and left the hospital 2.3 days earlier on average than their non-TXA counterparts (p=0.0006). DFR, hemiarthroplasty, and PTR patients in the TXA group also left the hospital earlier on average than their non-TXA counterparts, but these findings did not reach statistical significance. No significant difference in postoperative transfusion rate was observed between TXA and non-TXA patients who underwent DFR, hemiarthroplasty, or PTR. No increase in acute DVT occurrence rate was found with TXA use. Two (6.1%) patients in the TXA group, and 3 (3.8%) patients in the non-TXA group experienced an acute postoperative DVT (p=0.61). No patients experienced a pulmonary embolism.

This study is, to the best of our knowledge, the first English-language study to examine the use of TXA in musculoskeletal oncology patients undergoing wide resection of a malignant bony tumor and endoprosthetic reconstruction. Despite the weaknesses inherent to the present study, it provides initial data to support the efficacy and safety of topical TXA use in this patient population. Further large-scale studies should be undertaken to fully explore the efficacy and safety of TXA in these patients with the aim of establishing a new standard of care for the use of TXA in the musculoskeletal oncology community.

PAPER 22

IVC Filter Placement in 286 Patients with Malignant Disease: Benefits Continue to Outweigh Risks

Authors:
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Kathleen Beebe, M.D., Francis Patterson M.D., Joseph Benevenia M.D.

Background:
Patients with malignant disease who are undergoing orthopaedic procedures are at increased risk of venous thromboembolism (VTE), which can lead to fatal pulmonary embolism (PE). Pharmacologic anticoagulation can be an effective measure to prevent VTE after orthopaedic surgery, but can pose an increased bleeding risk to patients with malignancy. Particularly in orthopaedic oncology patients with post-resection dead space and indwelling drains, increased bleeding may contribute to higher rates of wound complications (i.e. hematoma, etc.) Additionally, patients on chemotherapy and various other medical treatments may be contraindicated to receive certain types of chemical VTEs prophylaxis. In addition to mechanical prophylaxis, inferior vena cava (IVC) filters may be an effective method to prevent fatal PE in musculoskeletal oncology patients undergoing orthopaedic procedures.

Questions/Purposes:
We asked the following questions:
1. What was the rate of VTE and PE in orthopaedic oncology patients with IVC filters?
2. Does risk of VTE and PE differ by anatomic location?
3. What was the rate of complications related to IVC filter placement?
4. What was the rate of wound complications requiring return trip to the OR?

Patients and Methods:
A retrospective chart review was performed in patients surgically treated at our institution for oncologic disease who had IVC filter placement from 2007-2018. Records, including all duplex ultrasounds and chest CT reports, were reviewed for clinical reports of acute DVT or PE. Demographic information included patient age, sex, histologic diagnosis, history of DVT or PE, and anatomic location. Type of type of surgery, anatomic region, and development of wound complications requiring return to OR within 30 days of the index procedure were reviewed and analyzed. IVC filter information including access point for insertion, filter retrieval, duration of filter use, and any complications associated with the filter requiring additional interventions were reviewed. Patients with benign conditions, tumors of the spine, or previous DVT or PE were excluded from analysis. Chi-squared analysis of categorical variables was performed using GraphPad prism. Odds ratios were generated using the Baptista-Pike method. Significance was set at $p<0.05$.

Results:
From 2007-2018, 286 patients (134 males, 152 females) received IVC filters. Mean age was 61.0±15.9 years old. Mean follow-up was 19.7±27.7 months. Diagnoses included primary sarcoma (121), metastatic disease (125), and myeloma/lymphoma/leukemia (40). Osseous management was performed in 238 (83.2%) patients, while soft-tissue management was performed in 48 (17.8%) patients. Anatomic locations included femur (168), pelvis (35), tibia (18), humerus (15), calcaneus (1), and scapula (1). Soft-tissue locations included thigh (46), buttocks (1), and calf (1). IVC filter placement occurred at the left (94) or right (142) common femoral vein in 82.5% of cases. Three (1.1%) filter-placement complications have occurred: one patient with IVC filter prong protrusion repaired during nephrectomy, one patient with hepatocellular carcinoma who experienced a retroperitoneal bleed following filter placement, and one patient with occlusion of filter by tumor thrombus requiring retrieval by vascular surgery. Nineteen (6.6%) filters have been removed after insertion at a mean of 4.1±3.2 months post-placement. Two filters underwent attempted but unsuccessful retrieval – both patients have remained complication-free. Twenty-seven (9.4%) patients required I&D within 30 days of surgery. Ten (3.5%) patients suffered DVT postoperatively. Two (0.7%) patients with diffuse pulmonary metastasis and hemorrhage were diagnosed with concordant suspected small vessel pulmonary embolism. At latest follow-up, no patient died of an acute fatal pulmonary embolism. DVT occurred most commonly after surgery at the femur (4.2%), but no significant differences were found by anatomic region (p=0.462). Risk of DVT was comparable following surgery at the upper versus lower extremity (3.3% vs. 0.0%; p=0.459), with endoprosthesis versus ORIF (5.2% vs. 0.0%; p=0.056), or with soft tissue versus bone involvement (4.2% vs. 2.8%; p=0.620). Requirement for I&D within 30 days of index procedure was higher following soft-tissue versus osseous surgery (18.8% vs. 7.6%; OR 2.8; p=0.016) and after treatment at the thigh and pelvis versus other anatomic locations (19.8% vs. 5.4%; OR 4.3; p=0.001), but comparable following endoprosthesis vs. ORIF (7.4% vs. 2.9%; p=0.203). No patients with upper extremity surgery required I&D.

Conclusions:
Patients with treatment of disease at the femur had the highest rate of DVT, while patients with treatment of disease at the thigh and pelvis were at greatest risk for requiring I&D within 30 days of surgery. These risks are worthy of consideration when deciding upon prophylactic IVC filter placement. Following treatment of malignant disease at the bone or soft-tissues, IVC filter placement was consistent with a 99.3% prevention rate of pulmonary embolism and a 1.1% filter-related complication rate. No patient in this series suffered an acute, fatal pulmonary embolism.

PAPER 23

Polyethylene Wear in Distal Femur Replacement in Oncology Patients

Authors:
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Background:
Endoprosthetic distal femur replacements are usually used in oncologic patients where the bone resection required to remove the tumor along with the associated soft tissue resection precludes the use of standard knee arthroplasties. Wear of the polyethylene parts continues to be a hazard for the long term success of distal femur replacements in oncologic patients.

Questions/Purpose:
In this study we asked: (1) What is the incidence of topside polyethylene wear in distal femur replacement in oncologic patients before 2000? (2) What is the incidence after 2000? And we hypothesized that between both groups, old vs. new polyethylene parts, there is no difference in wear incidence.

Methods
This is a single center, observational retrospective cohort three-arm study. We reviewed our surgical database and identified all the patients with limb salvage surgery utilizing a distal femoral replacement, with a press-fit implant or a Compress® Compliant Pre-Stress implant, all the implants were from the same manufacturer. All operations were performed at a tertiary center between August 1993 and December 2015. Follow up was for a minimum of 12 months or until revision surgery was performed. There was no selection bias. Operative reports, clinic notes and radiographs were analyzed. Patients were divided in 3 arms; group one with patients with a press-fit implant before the year 2000, a second group with the same implant done from 2000 to 2015 and group three with patients who had a Compress® implant. In the first two groups all patients received a Finn/OSS Knee prosthesis from Biomet (Warsaw, IN). We used either the chi-square test or Fisher's exact test for categorical variables. For the survival analysis we used the Kaplan Meier test. All tests were deemed significant at the 0.05 level.

Results
After the exclusion criteria, 224 patients were in included in the study. The male to female ratio was 49.6% to 50.4%. The mean age was 32 years old (range 9-83). The most common diagnoses were osteosarcoma (67.0%) and chondrosarcoma (11.2%). More than half of the patients

underwent a revision of the implant (56.7%). The general mean time for the revision was of 85 months (Range 9-198).

Of all the patients who had a revision 34.6% showed polyethylene wear signs on the topside of the polyethylene part, 19.6% of them had symptoms of polyethylene wear and that was the indication for the surgery. In 8.7% wear of the tibial bearing part was an incidental finding. Nineteen patients who had a revision presented polyethylene wear on the first group (50.0%), nine on the second (27.3%) and sixteen on the third one (28.6%). Those differences were statistically significant, showing the old polyethylene had more wear when compared to the new version of it (p<0.001).

The incidence of polyethylene wear was of 28.8% in the group with the old polyethylene parts, 16.4% on the press fit with the new poly group and 15.5% on the Compress® one. The difference was statistically significant when comparing the older polyethylene versus the newer version (p=0.04). All groups had a higher percentage of females with polyethylene wear, but that was only significant for groups one and three (p<0.001 and p=0.02 respectively).

A survivorship analysis of the polyethylene in three groups with a Kaplan Meier test was performed. For the first group the 5-year survival was of 90.2% and at 10 years of 42.8%. In the second group the 5 and 10-year survival was 90.5% and 80.4% respectively. And for the last group we found a 95.4% survival for the 5-year period and 81.7% at 10 years. The difference was statistically significant (p=0.026).

Conclusion
Oncologic patients are in general younger and more active than the patients necessitating joint replacements, as such they may have many years to live ahead and it would beneficial to reduce the number of revisions needed throughout their lifetime. Newer polyethylene parts have a lower incidence of wear when compared to older ones. They also have longer survival times, showing a 91-95% survival rate at 10 years.

PAPER 24

Outcomes of Free Vascularized Fibular Grafts for the Treatment of Radiation-Induced Femoral Nonunions

Authors: Meagan E. Tibbo, Matthew T. Houdek, Karim Bakri, S. Andrew Sems, Steven L. Moran

Background: Nonunion is a common complication following a fracture in the setting of previous radiotherapy; however, currently there is a paucity of data describing the optimal treatment for these nonunions. Free vascularized fibular grafts (FVFG) have been used successfully in the treatment of large segmental bone defects in the axial and appendicular skeleton; however, their efficacy with respect to treatment of radiated nonunions is limited or comes from small series or cohorts combining multiple fracture sites.

Questions/Purposes: The purpose of the study was to assess the 1) union rate, 2) clinical outcomes, and 3) complications following FVFG for radiation-induced femoral fracture nonunions.

Patients/Methods: We identified 24 patients who underwent FVFG for the treatment of radiation-induced femoral fracture nonunion between 1991 and 2015. There were 11 males and 13 females, with a mean age of 59 years (range, 29 – 78) and a mean follow-up duration of 5 years (range 1-15 years). Three patients had a history of diabetes mellitus and three were current tobacco users at the time of FVFG. No patient was receiving chemotherapy during recovery from FVFG. Oncologic diagnoses included unspecified soft tissue sarcomas (n = 5), undifferentiated pleomorphic sarcoma (UPS) (n = 3), myxofibrosarcoma (n = 3), liposarcoma (n = 2), Ewing's sarcoma (n = 2), lymphoma (n = 2), hemangiopericytoma, leiomyosarcoma, multiple myeloma, myxoid chondrosarcoma, myxoid liposarcoma, neurofibrosarcoma, and renal cell carcinoma.

Mean total radiation dose was 56.3 Gy (range, 39 – 72.5 Gy), given at a mean of 10 (range 2-24) years prior to FVFG. The average FVFG length was 16.4 cm. In addition to FVFG, 13 patients underwent simultaneous autogenous iliac crest bone grafting, 9 had other cancellous autografting, 1 received cancellous allograft, and 3 were treated with synthetic graft products. The FVFG was fixed as an onlay graft using lag screws in all cases; additional fixation was obtained with an intramedullary nail (n = 19), dynamic compression plate (n = 2), blade plate (n = 2), or lateral locking plate (n = 1).

Results: Nineteen (79%) fractures went on to union at a mean of 13 (range, 5– 28) months. Musculoskeletal Tumor Society scores improved from 22% preoperatively to 77% at latest follow-up (p < 0.0001). Among the 5 fractures that failed to unite, 2 were converted to proximal femoral replacements (PFRs), 2 remained stable pseudarthroses, and 1 was converted to a total hip arthroplasty. A 6th case did unite initially; however, subsequent failure lead to PFR. Patients who failed had a significantly shorter time interval between their radiotherapy and FVFG (3 vs 12 years, *P*=0.008). Seven patients (29%) required a second operative grafting. There were 5 additional complications including 3 infections, 1 wound dehiscence, and one screw fracture. No patient required amputation.

Conclusions: Free vascularized fibular grafts are a reliable treatment option for radiation-induced pathologic femoral fracture nonunions, providing a union rate of 79% and an improvement in functional outcome.

PAPER 25

Effect of Perioperative Radiation Therapy on Outcomes of Vascularized Fibular Graft Reconstruction of Long Bones

Authors:
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Background/Purpose:
Vascularized fibular graft (VFG), with its inherent blood supply, may be used as a biological option to reconstruct long bones following bone and soft tissue tumor resections, and it can enhance union rate when combined with allografts. In patients with bone and soft tissue tumors, radiation therapy (RT) is sometimes needed as an adjuvant therapy for local control. Early RT complications include wound dehiscence, hematoma formation, and infection. Long-term complications include neurological dysfunction, soft tissue fibrosis, skin scarring, pathological fracture, and non-union, as well as the most serious complication, radiation-induced sarcoma. It is well known that radiation weakens bone and can substantially compromise fracture healing rates.

We retrospectively analyzed our institutional experience with the use of VFG to assess: (1) the effect of short-term perioperative radiation therapy on VFG union rate; (2) the correlation between onset and dose of RT with time to union of VFG; and (3) the rate of complications and revision surgeries in such patients.

Methods:
We searched our institutional surgical database to identify oncologic patients who received vascularized fibular grafts between 1986 and 2014 in conjunction with intercalary prosthesis, allograft, and/or internal fixation. From the initial group of 109 patients, we excluded patients who had VFG for management of complications induced by prior long-term RT (n=13) and patients with insufficient follow-up and/or missing medical records (n=8). Of the remaining 88 patients, 74 had received no radiation therapy (NRT) and 14 had short-term perioperative RT, including 8 with preoperative RT (median RT-to-surgery interval: 1.8 months) and 5 with postoperative RT (median surgery-to-RT interval: 6 months). We matched the 14 RT cases with 27 cases selected from the NRT group based on age, tumor location, and VFG reconstruction technique. Mean age was 24 years (range: 7-58) and median follow-up was 70 months (range: 26-298). Primary histologic diagnoses were osteogenic sarcoma (n=13), Ewing sarcoma (n=10), chondrosarcoma (n=9), adamantinoma (n=3), soft tissue sarcoma (n=3), and others (n=3). The tumor location was
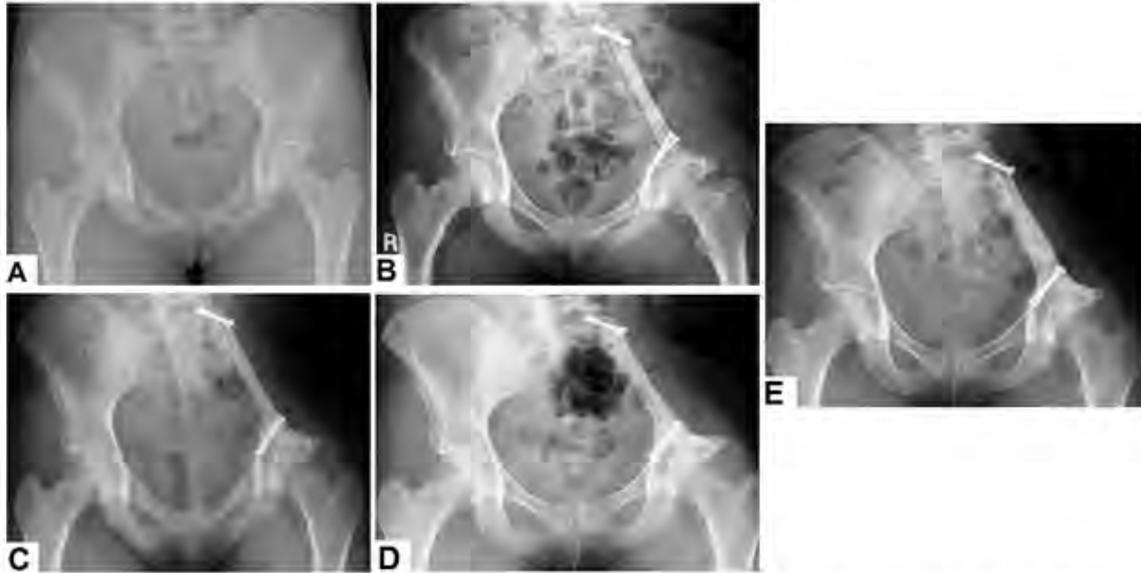
in the humerus (n=15), femur (n=6), forearm (n=9), tibia (n=9), and the sacroiliac joint (n=2). VFG was used as a sole construct in 33 patients (80%), and it was used with prosthesis or allograft in 8 patients (20%). The median radiation dose was 4500 cGy (range: 800-5580). Autogenous iliac graft and/or allograft cancellous bone chips were used in 15 patients (37%). ANOVA, chi-square, and linear regression tests were used to assess statistical significance ($P<0.05$).

Results:
1) 38 flaps (93%) survived through the last follow-up, only 1 patient in the NRT group underwent above elbow amputation 30 months after surgery for local recurrence in the forearm. Median MSTS score in the whole cohort was 24 (range: 15-30). Radiological union was achieved in 12 (86%) of 14 patients in RT group versus 24 (89%) of 27 patients in the NRT group ($P=0.99$). Mean time to union was 12.5 months (95%CI: 7-18) in RT group versus 12.8 months (95%CI: 10-16) in NRT group ($P=0.9$). VFG hypertrophy was seen in 5 of 14 (36%) patients in the RT group and in 13 of 27 (48%) in the NRT group ($P=0.5$).
2) There was no correlation between dose of RT and VFG union time ($R^2=0.003$, $P=0.9$). Also, there was no correlation between the RT-Surgery time interval and union time ($R^2=0.05$, $P=0.5$).
3) Postoperative complications included infection in 1 (7%) of 14 patients in the RT group and 3 (11%) of 27 in the NRT group. There was non-union in 2 of 14 (14%) in the RT group and 3 (11%) of 27 in the NRT group, and hardware failure occurred in 4 (29%) of 14 in the RT group and 4/27 (15%) in NRT group. Five patients in the RT group needed revision surgery; revision procedures included hardware revision and bone grafting for non-union in the femur and subsequent excision for local recurrence (n=1), external fixator frame placement in the tibia for established non-union 8 months after VFG (n=1), wound debridement and latissimus dorsi flap for wound necrosis (n=1), and hardware removal in 2 patients, 1 of whom also had graft fracture at the distal osteosynthesis site in the humerus.

Conclusions:
Radiation therapy is known to have serious effects on bone quality and healing potential; however, short-interval perioperative RT in our cohort had no significant effects on VFG union rate or time as compared to matched cases who did not receive RT. Additionally, we found no associations between RT dose or surgery-RT interval and VFG union time. Use of VFG in our cohort was associated with excellent postoperative function and low complication rate.

Case 1: A 16-year-old female patient presented with residual chondrosarcoma after resection in an outside institute with adjuvant radiation therapy with a total dose of 3400 cGy.
(A) Initial presenting radiograph. **(B)** Immediate postoperative radiograph after radical resection and double-barreled VFG reconstruction 2 months after last RT session. **(C)** 7-month postoperative radiograph showing early proximal osteosynthesis site union. **(D)** 12-month postoperative radiograph showing complete union at both osteosynthesis sites. **(E)** Last follow-up radiograph, 4 years after surgery, showing graft hypertrophy and full incorporation with pelvic bone, MSTS score 28.

PAPER 26

Early Outcomes of Osseointegrated Implants in Transhumeral and Transfemoral Amputations

Authors:
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Background:
The majority of individuals using traditional socket-based prostheses after combat-related upper or lower-limb amputations can experience difficulties such as skin ulceration, local pain, decreased functionality, and general discomfort at the junction of the residual limb and prosthetic device. Osseointegration combines a bone-anchored prosthesis with a transdermal component designed to mitigate socket-related complications and promote increased prosthetic use in patients with upper and/or lower extremity amputations. As with any transdermal system, infectious complications can occur. With this in mind, we sought to report the early results and complications associated with the Osseointegrated Prosthesis for the Rehabilitation of Amputees (OPRA) implant system in both transhumeral and transfemoral amputations.

Questions/Purposes:
1. To evaluate the frequency and severity of surgical, medical, and mechanical complications related
　　to the use of OPRA in patients with transhumeral and transfemoral amputations
2. To evaluate "before and after" changes in functional ability and pain using a variety of measures

Patients and Methods:
We are conducting two prospective studies in patients with transhumeral and transfemoral amputations under an FDA Early Feasibility Study and Humanitarian Device Exemptions, respectively. Eligible individuals included those age 22-65 with combat-related transhumeral or transfemoral amputations and reported difficulty using a traditional socket suspension mechanism. Exclusion criteria include active infection, poorly controlled diabetes, severe peripheral vascular disease, current tobacco use, and inability to comply with the rehabilitation protocol. Surgery is performed in two stages separated by three months. The first stage consists

of insertion of an implant (fixture), while the second stage incorporates a skin-penetrating device (abutment) that serves as the attachment to the prosthesis after gradual load-bearing. All patients undergo pre-operative range of motion testing and Patient-Reported Outcomes Measurement System (PROMIS) domains (pain interference, pain behavior, and upper/lower extremity function as appropriate), and visual analog pain scale questionnaires. In addition, transfemoral amputees complete the Questionnaire for Persons with a Transfemoral Amputation, Orthotic Prosthetics User's Survey score, and transhumeral amputees complete the Disabilities of the Shoulder and Hand, PROMIS domains (pain interference, pain behavior, and physical function). Assessments are conducted at baseline, then 3, 6, 12, and 24 months after stage-2 surgery.

Results:
Three transhumeral amputation patients have undergone both stages of the procedure, completed graduated load-bearing rehabilitation, and have increased their prosthetic wear time by an average of 72% at 12 months post stage 2 surgery. Patient reported questionnaires also demonstrate a trend towards decreased pain and increased functionality. Ipsilateral shoulder range of motion in forward flexion, extension, abduction, internal and external rotation have increased in all patients. There were no surgical, medical, or mechanical complications, and fixtures remain intact radiographically without evidence of loosening, stress shielding, or clinical infection.

To date, seven transfemoral amputation patients have received a total of 11 implants (four bilateral). Four patients have completed stage 2 and three patients have completed stage 1 of the procedure. One patient developed a soft tissue infection not involving the implant or bone seven weeks post-op from stage 2 surgery and was treated with focal debridement and oral antibiotics without issue. Another patient required incision and drainage with retention of implant components. All implants have been retained without any evidence of mechanical or infectious complications. Data generated from questionnaires and biomechanics are forthcoming following evaluation three-months postoperatively.

Conclusions:
Osseointegrated devices have demonstrated early promising results for both transhumeral and transfemoral amputees with low rates of implant-related and soft tissue infections and encouraging functional results. Although these studies are still in the early stages, we have found the OPRA implant system to be feasible with an acceptable rate of early complications, which is lower than that previously described. We plan to accrue more patients and continue follow-up for two years postoperatively to determine whether the OPRA system is safe, durable, and effective in improving pain and functional ability in this challenging patient population

PAPER 27

Socioeconomic Factors Affecting Outcomes of Surgical Treatment of Bone and Soft Tissue Sarcomas: A SEER Database Study

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Background:
A number of population-based studies have been published in the oncologic literature recently highlighting the effect of socioeconomic disparities on outcomes in patients with numerous forms of cancer. Two highly publicized studies in the journal Cancer analyzed data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database to investigate whether socioeconomic factors have an impact on outcomes. One of these studies collected data from more than 13,600 adult patients who had glioblastoma multiforme, and found that an uninsured patient was 14% more likely to have a shorter survival time (and 26% more likely to have a larger tumor at time of diagnosis) as compared to a patient with private insurance.[1] A similar study of more than 10,200 adults who were diagnosed with testicular cancer showed that uninsured patients were 26% more likely to be diagnosed with metastatic disease, and 62% more likely in Medicaid patients, compared to those with private insurance.[2] Many of these research questions have yet to be answered in patients with primary bone and soft tissue sarcomas.

Questions/Purposes:
1. For patients in the SEER database with primary cancers of bone / soft tissue sarcomas in the extremities, what is the relationship between insurance status and the prevalence of distant metastases?
2. For patients in the SEER database with primary cancers of bone / soft tissue sarcomas in the extremities, what is the relationship between insurance status and the rate of indication for limb salvage surgery versus amputation?
3. For patients in the SEER database with primary cancers of bone / soft tissue sarcomas in the extremities, what is the relationship between insurance status and survival time in months?

Patients and Methods:
The Surveillance, Epidemiology and End Results database was used to identify 4,144 patients who were diagnosed and treated for primary bone tumors between 2007 and 2014. Additionally, 7,508 patients who were diagnosed and treated for soft tissues sarcoma in the extremity between 2007 and 2014 were included in the analysis. Patients were categorized into one of three

insurance groups: insured with private insurance (non-Medicaid insurance), insured with Medicaid, and uninsured. Patients without information available regarding insurance status were excluded. The association between insurance status and survival was assessed using Cox proportional hazards regression that adjusted for patient age, sex, race, ethnicity, extent of disease (lymph node and metastatic involvement), tumor grade, tumor size, histology and primary site of the tumor.

Results:

For primary bone sarcomas, 3,098 (74.8%) were insured with non-Medicaid insurance, 884 (21.3%) were insured with Medicaid, and 162 (3.9%) were uninsured. As compared to those insured with non-Medicaid insurance, the Medicaid patients were more likely to be a minority, younger, and unmarried. Medicaid patients were 79% more likely to present with distant metastasis to the lung at the time of diagnosis (relative risk ratio [RRR] 1.79; 95% confidence interval [95% CI], 1.32 – 2.42) and were 75% more likely to receive amputation surgery (RRR 1.75, 95% CI 1.44 – 2.12) than their non-Medicaid counterparts. In a Cox regression multivariate analysis, Medicaid patients had reduced disease-specific survival compared with non-Medicaid insured patients (hazard ratio [HR] 1.34, 95% CI 1.09 – 1.64).

For extremity soft tissue sarcomas, among the 7,508 patients included in the analysis, 6,292 (83.80%) had non-Medicaid insurance, 904 (12.04%) had Medicaid insurance, and 312 (4.16%) were uninsured. Medicaid-insured patients were more likely to be a minority, female, and unmarried compared to those with non-Medicaid insurance. Medicaid patients were more than twice as likely to present with metastasis at the time of diagnosis (RRR 2.44; 95% CI, 1.92 – 3.08). Lymph node involvement was also elevated in this group (RRR, 2.75 95% CI 1.98 – 3.84). Medicaid patients received fewer limb-salvage surgeries than non-Medicaid patients (RRR, 0.43 95% CI 0.34 – 0.54). In a Cox regression multivariate analysis, Medicaid patients had reduced disease-specific survival compared with privately insured patients (HR 1.22; 95% CI 1.02-1.46), however uninsured patients displayed the greatest reduction in disease-specific survival (HR 1.69; 95% CI 1.27 – 2.26).

Conclusions:

Socioeconomic disparities as manifested by differences in insurance were correlated with a significantly increased risk of metastasis at time of diagnosis, reduced likelihood of being indicated for limb salvage procedures, and reduced disease-specific survival in both bone and soft tissue tumors. These findings hold true even when accounting for demographic variables, tumor grade, and stage. Further study is warranted into the mechanism by which poorer socioeconomic status translates into worsened outcomes, but it is clear that socioeconomic disparities serve as a poor prognostic indicator for bone and soft tissue sarcomas alike.

Figure 1. Kaplan-Meier Survival Estimates for Primary Bone Tumors as a Function of Insurance Status
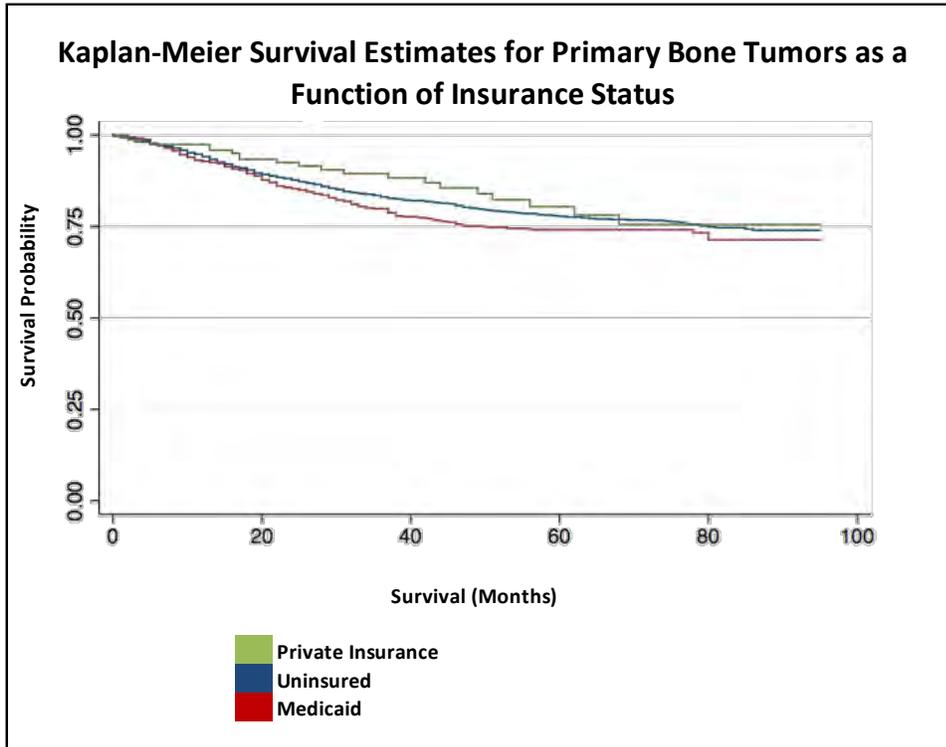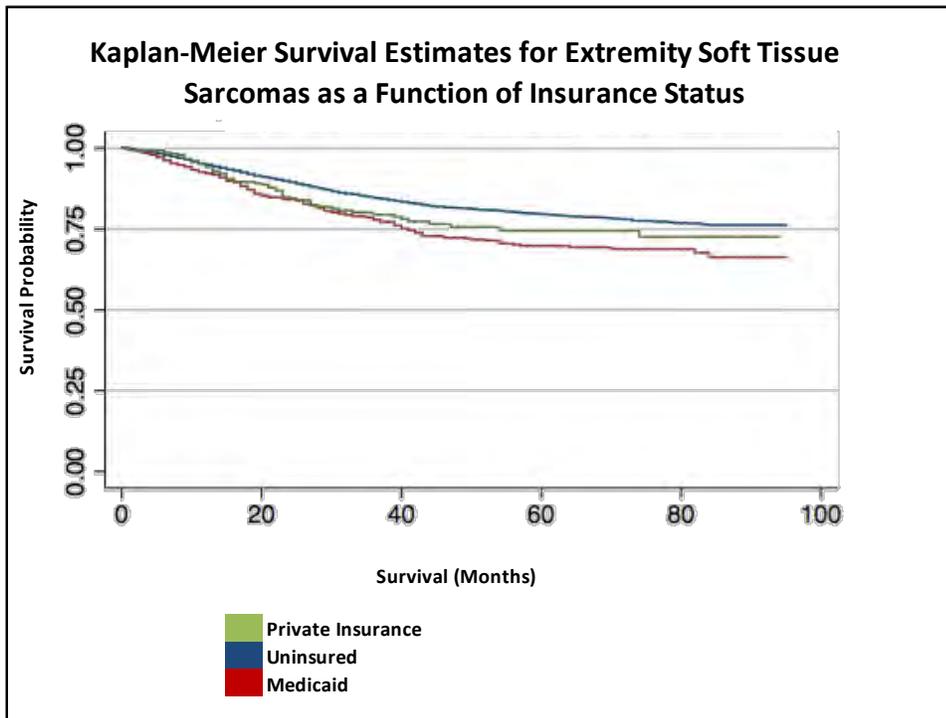

Figure 2. Kaplan-Meier Survival Estimates for Extremity Soft Tissue Sarcomas as a Function of Insurance Status

References:

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2. Markt SC, Lago-Hernandez CA, Miller RE, et al. Insurance status and disparities in disease presentation, treatment, and outcomes for men with germ cell tumors. *Cancer*. 2016;122(20):3127-3135. doi:10.1002/cncr.30159

PAPER 28

Host Immune Response in Undifferentiated Pleomorphic Sarcoma – A 10-year Retrospective Analysis

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Background:

Undifferentiated pleomorphic sarcoma (UPS) is an aggressive soft-tissue sarcoma (STS) characterized by high rates of local and metastatic recurrence. Due to the paucity of therapeutic options, advanced disease remains lethal in a large majority of patients. The slow and inefficient development of new effective therapies for patients is due to the unique heterogeneity and rare biology that underlies STS. Prior studies have shown that STS use multiple mechanisms to suppress immune responses directed at the tumor microenvironment, providing a protective niche to promote tumor growth. Thus, an improved understanding of how the tumor microenvironment modulates UPS progression may enhance our ability to predict therapeutic responses and improve outcomes.

Questions/Purposes:

Which patient characteristics and clinicopathologic parameters correlate with improved survival in UPS patients? What is the host immune response observed in UPS tumors? Do the presence or absence of specific tumor infiltrating lymphocytes (TILs) influence disease progression or survival?

Patients and Methods:

Thirty-six clinically annotated UPS patients collected over 10 years at a single institution with minimum five-year follow-up and available tumor specimens were including in this retrospective study. A univariate cox regression analysis was used to determine clinicopathologic factors associated with overall survival (OS) and disease-free survival (DFS). Using primary tumor specimens, we performed a targeted immunohistochemical analysis of the UPS microenvironment. We quantified expression of lymphocyte markers (CD8, CD20, CD68) and immune checkpoint protein (PD-L1) in all 36 UPS tumors using automated image analysis. The median percentage of positive cells for each subpopulation was used to define high expression vs. low expression. The Kaplan-Meier method was used to analyze OS and DFS; the association of specific TILs with OS and DFS was analyzed using the Log Rank Test.
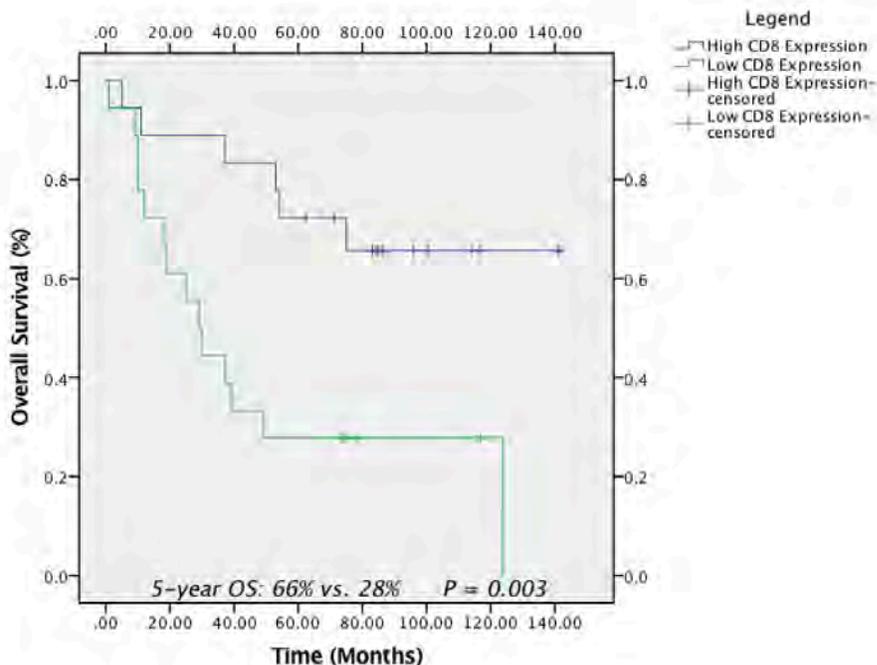
Results:

Factors that correlated with improved overall survival in our UPS cohort included localized disease (p=0.015), and use of intraoperative radiation therapy (IORT) or adjuvant radiation therapy (p=0.01). There was also a trend toward worse survival with tumors greater than 5 cm at diagnosis (p=0.09). Our immunohistochemical analysis revealed the presence of TILs (CD8, CD20, CD68) and expression of immune checkpoint protein (PD-L1) in UPS tumors. Patients with a greater population of CD8+ TILs had a 5-year OS of 66% compared to those with lower levels of 28% (p=0.003, Figure 1). CD8+ T-cell expression in UPS tumors inversely correlated with local recurrence (p=0.04), suggesting CD8+ T-cell mediated immune surveillance. Interestingly, we also observed an increase in metastatic events in patients whose tumors harbored low CD8 expression compared to high CD8 expression (59% vs. 41%).

Conclusions:

Through our quantitative immunohistochemical (IHC) analysis of immune cell subsets in UPS tumors, we identified improved survival in patients with increased infiltration of CD8+ T-Cells. Our study demonstrates that patients with low levels of CD8+ TILs are at increased risk of local (and potentially metastatic) recurrence. These findings underscore the importance of immune mediated tumor surveillance in UPS. Our results are consistent with other non-mesenchymal tumors and provide clinical and biological rationale to further investigate STS to identify subtype specific prognostic biomarkers that can potentially influence the development of novel therapeutic strategies. Recent advancements in systemic immunotherapy further highlight the immunogenicity of UPS tumors and demonstrate the clinical impact of targeting the tumor microenvironment to improve outcomes for UPS patients.

Figures:

Figure 1. Cytotoxic T cell tumor infiltration as a positive prognostic indicator in UPS patients.

PAPER 29

The Role of Radiation Therapy and Margin Width in Localized Soft Tissue Sarcomas

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Type of study: Therapeutic Study
Level of evidence: III

Background: Soft tissue sarcomas (STS) are often treated with multimodality therapy including wide local excision, radiation +/- chemotherapy. Multiple studies have demonstrated that positive margins result in increased local recurrence rates. Controversy exists in the literature regarding what constitutes an adequate margin. Additionally, the role of radiation therapy (RT) in decreasing the width of a wide resection is unclear.

Questions/Purposes: The aim of this study is to 1) assess if the width of a surgical margin on wide local excision in localized STS impacts local recurrence, and 2) assess if RT can decrease the margin width necessary to minimize local recurrence.

Patients and Methods: From 2000-2016, patients with stage I-III primary extremity and truncal/abdominal wall STS who underwent wide local excision with pre-operative, post-operative, or no RT were identified using the US Sarcoma Collaborative database (multi-center, prospectively collected retrospective database). Patients were stratified by margin status (positive, ≤1mm, or >1mm). Crude local control incidence was assessed and compared amongst treatment groups (pre-operative, post-operative, or no RT). Kaplan-Meier analysis was performed to assess local-recurrence free-survival and Fisher's exact test was performed to assess treatments associated with local recurrence.

Results: A total of 514 patients were identified. Median follow-up was 1.3 years. Median age at diagnosis was 58 years. The LR in patients with positive margins was 9% (13/144), ≤1mm margins was 4.2% (2/47), and 9.3% in patients with >1 mm margin (30/323) (p=0.315).

The local recurrence incidence for patients that received no RT was 11.2% versus 1.7% in those that received any form of RT (pre-operative or post-operative) (p=0.02).

For patients with positive margins, the local recurrence rate was 11.1% (12/65), 0% (0/7), and 10.6% (1/24) (p=0.176) in the no RT, pre-operative RT, and post-operative RT groups, respectively. In the ≤1mm group, the local recurrence rate was 5.7% (2/35), 0% (0/4), 0% (0/7) (p>0.99) in the no RT, pre-operative RT, and post-operative RT groups, respectively. Lastly, in the > 1mm group, the local recurrence rate was 10.2% (28/272), 0% (0/18), and 3.7% (2/127) (p=0.10) in the no RT, pre-operative RT, and post-operative RT groups, respectively.

Conclusions: RT appears to be the most important associated factor with reduced LR in this cohort. Width of margin did not impact LR, and there is no significance of positive, ≤1mm, or>1 mm margins predicting LR rates. The results of this study suggest that even in those patients with microscopically positive margins, RT can decrease the LR rate to similar rates as a negative margin. Despite such findings, determination of an appropriate resection margin remains difficult to determine. Patients should be discussed at an institutional multidisciplinary tumor board and treatment options should be tailored to patient clinical and demographic characteristics.

	Positive			≤1mm			>1mm		
RT	**None**	**Pre-op only**	**Post-op only**	**None**	**Pre-op only**	**Post-op only**	**None**	**Pre-op only**	**Post-op only**
# Patients	108	7	24	35	4	7	272	18	27
Median Tumor Size	4.3 cm	6.5 cm	5.5 cm	4.3 cm	6.3 cm	3.3 cm	3 cm	4.5 cm	3.7 cm
Local Recurrence	11.10% (12/65)	0% (0/7)	10.60% (1/24)	5.70% (2/35)	0% (0/4)	0% (0/7)	10.20% (28/272)	0% (0/18)	3.70% (2/127)

Table 1: Margin status with corresponding width and clinical demographics

PAPER 30

ONCOLOGIC AND CLINICAL OUTCOMES OF LIMB SPARING SURGERY IN SOFT TISSUE SARCOMA AT MEDIAN AND LONG TERM FOLLOWUP

Author

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Introduction

Soft tissue sarcomas (STS) are a malignant tumors that origins from mesenchymal and connective tissue. More than 50 histological subtypes of STS had been described and they represent approximately 1% of all adult cancers. It can develop at any age and in any anatomical region of the body. According to the current literature, survival is between 60 and 70%. Surgery with free margins is the treatment of choice but with respect to adjuvant the results are controversial.

Questions/purposes

The objective of our study was evaluated the outcomes of limb sparing surgery in patients with STS and analyzed: 1) oncologic outcomes; 2) prognostic factor; 3) functional results; 4) non oncologic complications.

Methods

We retrospectively reviewed a group of patients with soft tissue sarcoma that were treated with limb sparing surgery at a single institution between 2004 and 2012. A total of 400 soft tissue extremity sarcoma were treated at our institution and 328 patients finally matched the inclusion criterias (diagnosis of a primary soft tissue sarcoma treated with limb salvage surgery and a

minimum of 5 year follow-up or patients alive) were included for analysis. The mean follow-up of the series was 85 months (range: 60-180) and the median age was 45 years (range 2-80). The primary site of tumor location were the lower extremity (242/328, 74%). 220 patients received adjuvant radiotherapy and 81 patients received adjuvant chemotherapy. Patients were divided in two groups for the analysis: Group 1: high grade STS and Group 2: low grade STS.

The functional evaluation of the patients was performed with the use of the revised 30-point functional classification system established by the International Society of Limb Salvage and the Musculoskeletal Tumour Society and active range of movement was evaluated in the last follow-up. We analyzed survival according to the Kaplan-Meier method with 95% confidence intervals (CI), comparing survival between groups using the log-rank test. OS was defined as the time interval from the date of diagnosis to the date of death from any cause or to the date of the last follow-up. EFS was defined as the time from diagnosis to either the date of the last follow-up, death, local or distant recurrence. Statistical significance was set at a p-value ≤ 0.05. The statistical significance of the differences was evaluated with the criterion of $p < 0.05$.

Results

Oncologic results:

One year overall survival (1yOS) of the series was 96 % (95% CI: 81-89) and 5 years overall survival (5yOS) was 67% (95% CI: 64-75). Five year local recurrence free survival (5yLRFS) was 74% (95% CI:68-78) and 5 year metastasis free survival (5yMFS) was 71,6 (95% CI:68-78)

Group 1 (high grade STS): 1yOS was 96 % (95% CI:92-98) and 5yOS was 61% (95% CI: 55-68). 5yLRFS was 69% (IC95% 63/76) and 5yMFS was 63% (IC95% 56/68)

Group 2 (low grade STS): 1yOS was 98 % (95% CI: 95-100) and 5yOS was 87 % (95% CI: 80-93). 5yLRFS was 84 %(95% CI:75-90) and 5yMFS was 84% (95% CI:89/98)

Prognostic factors

Neoadjuvant radiotherapy had been a positive prognosis factor for local recurrence in high grade sarcomas (p=0.032) but it was not significant in terms of metastasis development (p=0.41). Neoadjuvant chemotherapy had not demonstrated to reduce the local recurrence rate (p=0.14) or survival prognosis (p=0.29) for high grade soft tissue sarcomas. 8,5% patients had amputation.

Functional results:

Group 1: Mean MSTS was 26 (range: 23-29) and the median time for returning to patients' habitual activity was 8 months (range:6-16)

Group 2: Mean MSTS was 28 (range: 26-30) and he median time for returning to patients' habitual activity was 4 months (range:2-6)

Non oncologic complications

18% (60/328) of the series presented with a non-oncological complication. Deep infection and surgical wound dehiscence had been the most prevalent (35/60) and most of them occurred in the group that received neoadjuvant radiotherapy. Limb salvage surgery was possible for 92% of the series at last follow up.

Conclusions

Five year overall survival for extremities soft tissue sarcomas is 67% and significantly affected by grade (61% vs 87%). For high grade soft tissue sarcomas, neoadjuvant radiotherapy seems to reduce the risk of local recurrence but increase non oncological complications.

KEYWORDS: Soft tissue sarcoma; adjuvant radiotherapy; neoadjuvant chemotherapy; limb sparing surgery

PAPER 31

Development of a Prognostic Nomogram to Predict for Post-operative Surgical Site Infection in Localized Soft Tissue Sarcomas of the Extremity

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Background: Post-operative surgical site infections (SSI) pose a challenging complication in patients with localized extremity soft tissue sarcomas (STS). Estimation of an individual's risk for SSI may allow for proactive management in the perioperative setting. There are several risk factors known to be associated with post-operative SSI in STS, but there is no individualized predictive model for this cohort. A nomogram is a useful tool for predicting survival outcomes in sarcoma patients, however, there is no such tool to predict for post-operative SSI in localized STS patients.

Questions/Purposes: The goal of this study is to 1) assess risk factors associated with post-operative SSI in patients with localized STS of the extremity using multi-centric data and 2) create a predictive nomogram that will assess an individual's risk of developing SSI after STS resection.

Patients and Methods: Patients undergoing limb-salvage resection for localized primary or recurrent extremity STS between January 2000 and April 2016 at participating US Sarcoma Collaborative institutions were identified. SSI were defined SSI as either a superficial wound not requiring drainage or a deep wound with drainage due to dehiscence or intentional opening of the wound within 120 days post-operatively. Patients who had missing SSI status or died without SSI before 120 days were excluded. Sixteen variables were selected a priori as potential factors for SSI: age, gender, BMI, diabetes, smoking, chronic steroid use, albumin, extremity location, tumor category, tumor size, tumor depth, neoadjuvant and adjuvant chemotherapy, neoadjuvant and adjuvant radiation, and functional status.

Univariate analysis was performed using Fisher's exact tests for categorical and Wilcoxon rank-sum tests for continuous predictors. Multiple logistic regression was used to train the prediction model used to create the nomogram. The first 2/3 of each dataset (N = 1112, surgery dates January 2000- December 2010) was used to train the logistic regression model, which was tested on the remaining 1/3 of the dataset (N = 557, surgery dates December 2010-April 2016). Recursive Feature Elimination was used during cross validation to select variables for the final model. Prediction performance of the datasets was evaluated using the receiver operating curve, area under the curve, and calibration plot. All statistical analyses were performed using R, version 3.4.4.

Results: 1740 patients underwent resection for their localized primary or recurrent STS. After missing values were eliminated, 1669 patients with SSI were evaluated. Median age was 59 years old and median tumor size was 8.5 cm. Median BMI was 27.6. The SSI incidence was 13%
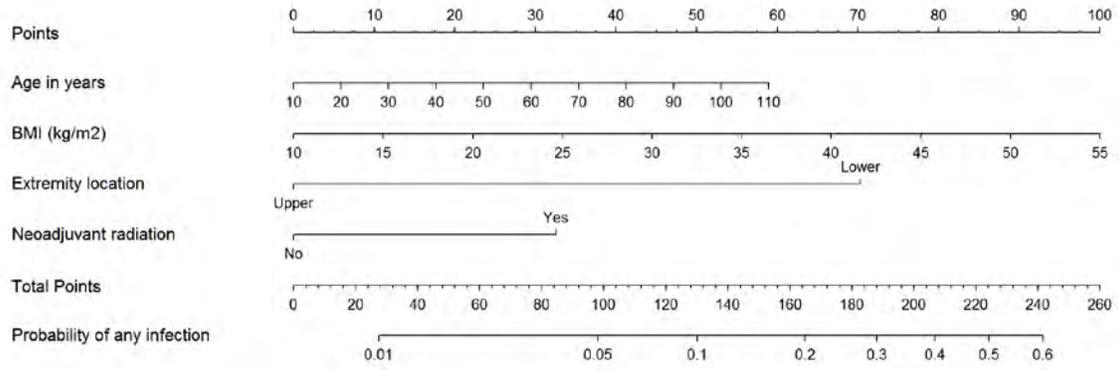
(219/1669). Results of the UVA are located in Table 1. On MVA, increasing age (OR 1.02, 95% CI 1.00-1.03, p=0.008); BMI (OR 1.05, 95% CI 1.02-1.09, p=0.004); lower extremity location (OR 5.62, 95% CI 2.87-12.69, p<0.001) and neoadjuvant radiation (OR 2.16, 95% CI 1.47-3.16, p<0.001) were associated with SSI. Results were incorporated into a predictive nomogram for SSI (Figure 1). The resultant nomogram was internally validated by the methods described.

Conclusions: SSI after STS resection is a frequent, relevant complication. Age, BMI, tumor location, and timing of radiation are all associated factors of SSI risk. A validated nomogram has been established based on these factors that can provide individual prediction of SSI for patients with resected STS of the extremity. This prognostic model may help clinicians counsel patients regarding these risk factors and allow for surgeons to optimize perioperative management in patients at high risk for post-operative SSI.

Table 1: Factors Associated with Post-operative Surgical Site Infection on Univariate Analysis

Variable	p-value
Gender	> 0.999
Age	0.033
BMI	0.002
Diabetes	0.017
Smoking History	0.316
Albumin (g/dL)	<0.01
Chronic Steroids	> 0.999
Primary vs Recurrent Tumor	0.003
Extremity Location	<0.01
Depth of Tumor	0.183
Tumor Size (cm)	<0.01
Neoadjuvant Chemotherapy	0.340
Adjuvant Chemotherapy	0.842
Neoadjuvant Radiotherapy	<0.001
Adjuvant Radiotherapy	0.001
Functional status	0.017

Figure 1: Nomogram for Post-operative Sugical Site Infection

PAPER 32

Designing a rational follow-up schedule for soft tissue sarcoma

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Background: Local recurrence or development of pulmonary metastasis following resection of extremity soft tissue sarcoma (STS) necessitates close follow-up surveillance. Many different follow-up protocols have been proposed for these patients, however, there is limited evidence to support the use of one specific schedule over another.

Purpose: The objective of this study was to determine the frequency and timing of local recurrence and metastasis following resection of extremity STS, and apply these findings to design a rational follow-up schedule.

Methods: Utilizing a prospective database, a retrospective single center review was performed on all patients with minimum 2 year follow-up who had surgically resected localized extremity STS. Low grade liposarcoma and dermatofibrosarcoma protuberans were excluded. The standard follow-up protocol at the study center included a chest x-ray and physical exam every 3 months for 2 years, then every 6 months until 5 years and yearly until 10 years for intermediate and high grade tumors. For low grade tumors it was every 6 months until 5 years. Any questionable findings on chest imaging or physical exam warranted cross-sectional imaging to confirm the diagnosis of metastasis or local recurrence. Kaplan-Meier curves were calculated based on histologic grade (low, intermediate, high), tumor size (greater than or less than 5cm), and the event rate for local recurrence and metastatic disease was calculated on an annual basis for 10 years. Based on the yearly event rate for each grade of tumor stratified by size, a rational follow-up protocol was established. An event rate greater than 0.1 per year (i.e. >10% chance of developing metastasis) was used to define patients who would require a follow-up every 3 months. An event rate of 0.025-0.1 would necessitate follow-up every 6 months, an event rate of 0.025-0.01 would suggest a follow-up on a yearly basis, and patients with an event rate of less than 0.01 events would require no further follow-up.

Results: A total of 230 (121 small, 109 large) low grade, 626 (244 small, 382 large) intermediate grade and 960 (261 small and 699 large) high grade extremity STS patients were reviewed. At the conclusion of the study 1115 were alive with no evidence of disease, 92 were alive with evidence of disease, 450 had died of disease, and 160 had died of other causes.

There were 121 small low grade tumors with 8 metastatic events (6.6%) and 5 local recurrences (4.1%). There were 244 small intermediate grade tumors with 31 metastatic events (12.7%) and 18 local recurrences (7.4%). There were 261 small high grade tumors with 53 metastatic events (20.3%) and 28 local recurrences (10.7%).

There were 109 large low grade tumors with 20 metastatic events (18.3%) and 8 local recurrences (7.3%). There were 382 large intermediate grade tumors with 112 metastatic events (29.3%) and 27 local recurrences (7.1%). There were 699 large high grade tumors with 359 metastatic events (51.4%) and 66 local recurrences (9.4%).
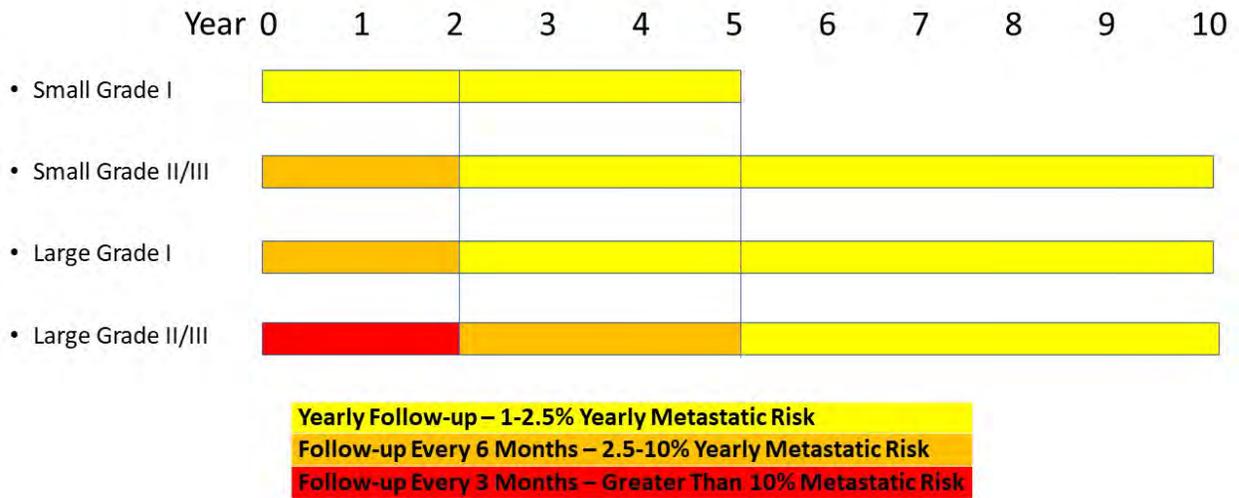
The event rate of development of metastasis was greater than that of local recurrence at all time points. Therefore the event rate for metastatic spread was used to develop the protocol. For the development of a clinically applicable algorithm, consolidation of the tumor groups was performed. High grade and intermediate grade tumors both met the highest threshold event rate in the first 2 years and they were grouped together due to similar proposed follow-up schedules. This left four remaining groups necessitating a follow-up protocol (Table 1). Based on the results, for small low grade tumors we propose a yearly follow-up with chest imaging and physical exam for 5 years. Large low grade tumors and small intermediate/high grade tumors can be followed with the same suggested protocol: every 6 months for 2 years then yearly to 10 years. Large intermediate and high grade tumors should be seen every 3 months for 2 years, every 6 months for years 3-5, then yearly until 10 years (Figure 1).

Conclusion: Based on the results of this study, we can recommend 3 distinct follow-up protocols based on tumor grade and size that are easy to apply clinically. These results can streamline patient care by providing optimal follow-up while minimizing resource utilization. In comparison to the ESMO guidelines for follow-up, our protocol proposes less frequent follow-ups for large low grade tumors and for small tumors regardless of grade, but a similar follow-up for large high grade tumors. Follow-up for extremity STS should be tailored to the risk of recurrence or development of metastatic disease and using this proposed schedule, overutilization of medical resources and patient anxiety can be reduced.

Table 1: Event Rate Based on Size and Grade

	0-1 years	1-2 years	2-5 years	5-10 years
Small Low Grade	1.7%	0%	1.1%	0.6%
Small Int/high Grade	6%	3.4%	1.6%	0.9%
Large Low Grade	6.4%	2.9%	1.3%	1.2%
Large Int/high Grade	26%	11%	2.8%	1.1%

Figure 1: Proposed Follow-up Protocol

PAPER 33

One Year Results of the IlluminOss Lightfix Trial Indicate Durable Improvements in Pain and Function After Treatment of Humeral Metastatic Disease

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Background: We previously reported preliminary thirty day results of the IlluminOss Lightfix Trial in 2016. During the interim, the IlluminOss System (IS) has been approved for treatment of metastatic disease affecting the humerus, which can be a particularly challenging problem. Poor bone quality and extensive, sometimes progressive, bone loss can limit the success or even feasibility of internal fixation of impending and actual pathological fractures. The IlluminOss System (IS, IlluminOss Medical, Inc., East Providence, RI) was developed to address this unmet need for a better means of fixation and to avoid damage to the rotator cuff as occurs with conventional nails.

IS is a minimally invasive delivery and stabilization technique. An incision is made over the greater tuberosity to insert a polyethylene (Dacron) balloon which is then filled with a liquid biocompatible monomeric, thereby conforming to the medullary canal, providing stable internal fixation once polymerization with light delivered by a fiberoptic cable has been achieved. The polymer can be drilled allowing for additional hardware (screws, plates) if necessary to further stabilize the bone. The location of supplemental hardware is not pre-determined by the device configuration.

Questions/Purposes: The primary objective of the IlluminOss Lightfix Trial is to evaluate ninety day safety and performance data of the IS and to evaluate changes in pain and function for the purpose of US FDA marketing clearance. In addition, patients were followed for one full year to gain insight into the long term performance of the device and clinical outcomes. Our questions and purpose were as follows:
(1) Does stabilization of the humerus with IS affected by metastatic disease reduce pain?
(2) Does stabilization of the humerus with IS affected by metastatic disease increase functional status?
(3) Describe the clinical and radiographic safety success.

Patients and Methods: The study design is a prospective, multi-center, open label study with an accrual goal of 80 adults, suffering from pain due to single impending or actual pathological fractures of the humerus secondary to metastatic malignancy. Enrollment started April 2015 and was completed in June 2016.
Inclusion Criteria
1. VAS Pain Score > 60mm on 100mm scale.
Impending Fracture-Specific Inclusion Criteria
2. Mirels' Score ≥ 8.
3. Destruction of cortical bone > 50%.

Clinical and radiographic follow-up evaluations were scheduled for 7, 30, 90, 180, and 360 days post-index procedure with Visual Analogue Scale (VAS) and MSTS function instruments.
Primary endpoints:
Safety Success (defined as no serious device related complication, additional surgical interventions (revisions, supplements, fixations, or removals), device fracture, migration, mal-alignment, or loss of reduction or fixation).
Reduction in VAS Pain Score of 54 and improvement in normalized MSTS function of 23 (both > 80% of historical controls) over 90 days relative to pre-treatment baseline (1-4).
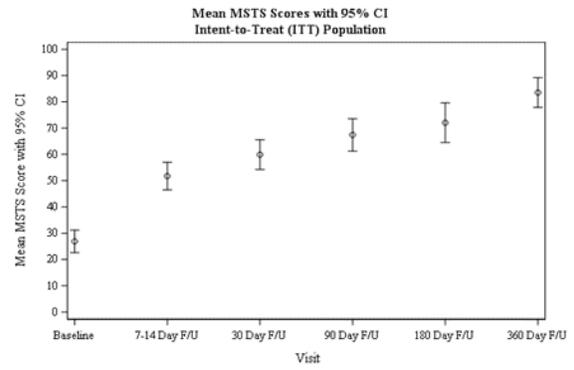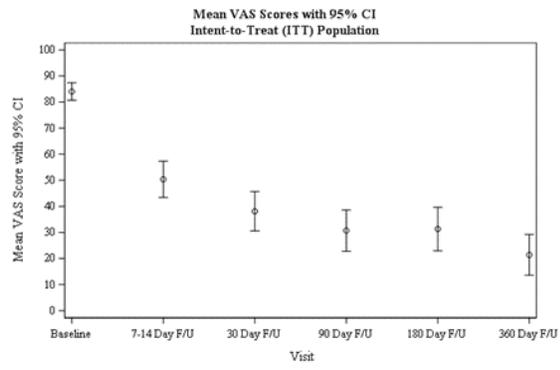*Statistical methods*: The number and percentage of patients achieving the Safety Success endpoint at days 7, 30, 90 and 360. Mean changes in VAS and MSTS scores from baseline to day 90 will be compared relative to reference values (54 and 23 respectively). All patients with at least day 7 follow-up were included in the primary analysis through the use of a mixed model for repeated measures (MMRM), significance set at $p < 0.05$.

Results: Eighty-one patients were enrolled from 13 centers. Complete data were available for seventy-six.
Average age 65 (36-89); 54% male, 46% female; myeloma 24%, breast 18%, lung 18%, renal cell 16%, other 24%. 58% had fractures and 42% impending fractures. 57% were proximal, 36% diaphyseal, 7% distal. Average procedure time was one hour and 34 minutes from incision to closure (0:39 – 4:22). There was no ancillary hardware used in 72%, supplemental screws were used in 22%, plate and screws were used in 6%. Thirty-five patients were alive at 1 year.

Between baseline and 30, 90 and 360 days after surgery, VAS pain scores (0-100) decreased from 84 to 38, 31, and 23 ($p < 0.001$), which did not meet the noninferiority criteria of 54 at 90 days. Normalized MSTS function scores (0-100) increased from 27 to 59, 67, and 82 ($p < 0.001$), which did meet the noninferiority criteria of 23 at 90 days. Twelve implants fractured. The clinical and radiographic success rate at one year was 83%.

Conclusions: Enrollment into the largest prospective, industry sponsored clinical trial in metastatic fractures has been completed and FDA approval has been granted for IS. Stabilization was achieved using a single incision in the majority of patients. Pain and function continued to improve for most patients during one year of follow-up.

Mean VAS Scores with 95% CI
Intent-to-Treat (ITT) Population

Mean MSTS Scores with 95% CI
Intent-to-Treat (ITT) Population

PAPER 34

Comparison Of Photodynamic Stabilization, Intramedullary Nail, And Cemented Plate For Pathologic Humerus Fractures

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Background: Approximately 350,000 people each year in the United States have a skeletal metastasis, most commonly to the femur followed by the humerus. This pain and loss of arm function tremendously reduces quality of life for people who on average have approximately one year to live. Current treatment usually features cemented plate fixation (CPF) which is susceptible to failure if tumors progress, or titanium intramedullary nail (IMN) which is more durable but causes significant rotator cuff damage. Both options tend to delay radiation therapy (XRT) for at least a couple weeks until wounds heal. Photodynamic stabilization (PDS) – an intramedullary stabilization system featuring a Dacron catheter filled with a dental polymer-type liquid, hardened in situ upon exposure to visible light via an embedded coil – can impart a stabile extremity with a wound-free pathology site suitable for immediate XRT, which may offer a useful alternative to IMN and CPF for pathologic humerus fractures.

Questions/Purposes: 1) Is PDS a reliable technique? 2) Is PDS adequately durable for pathologic bone stabilization? 3) Can PDS reduce surgical time, blood loss, inpatient stay, and permit quicker XRT? 4) What other benefits, complications, and solutions are associated with PDS?

Patients and Methods: As part of a nonblinded multicenter prospective trial our hospital recruited 20 consecutive pathologic humerus fractures (19 patients) between July 2015 and June 2016 for PDS surgery. Retrospective review identified 60 nailed fractures (58 patients) and 18 plated fractures (17 patients) from January 2010 to June 2015. Patients were seen two weeks, three months, then annually after surgery.

Results: Demographics among cohorts were comparable. PDS patients had shorter operative time than IMN and CPF (58.4 vs 78.9 vs 129.6 minutes; p<.001) with the majority under one hour, less estimated blood loss, higher rate of XRT within 24 hours (47% vs 0% vs 0%; p<.001), and shorter hospital stay (2.5 vs 3.7 vs 6.6 days; p=.012) with 53% discharged within one day. Survival at 90 days and one year did not achieve statistical difference. Hardware failure was more common in PDS (20%) and CPF (17%) than IMN (0%; p=.002) but reoperation rate was not statistically different (15% PDS vs 17% CPF vs 7% IMN; p=.323). PDS failure did not complicate conversion to IMN or hemiarthroplasty (Figure 1).

Conclusions: This is the first study evaluating PDS for pathologic fractures, and the first human study of PDS in the United States for any use. PDS proved to be a reliable technique as only one patient experienced intra-operative difficulty; this was likely due to inadequate polymer injection and was immediately remediated with IMN treatment. PDS seems durable enough for most patients and comparable to CPF; if tumors progress or bone does not unite hardware failure may occur which can be managed by routine salvage options. PDS patients usually have faster surgery (usually under one hour), with less blood loss (usually scant), a shorter hospital stay (usually discharged within one day), and quicker XRT (usually same or next day). PDS showed the ability to obviate preoperative embolization for vascular tumors, and when hardware fails the implant removal is swift with routine tools. Further investigation is merited to help clarify whether rapid treatment, discharge, and XRT is routinely achievable and perhaps clarify risk factors of implant failure and improve patient selection criteria. It may be possible to change pathologic humerus fracture care from a minimum two or three day experience (embolization, followed by stabilization, followed by pain control and delayed XRT) into an outpatient stabilization (embolization skipped and pain better controlled) and immediately post operation and discharge home, which not only allows patients swifter resumption of systemic care but also would cost less and require fewer resources.

Figure 1: PDS failure converted to hemiarthroplasty.
Radiographs of a 66 year old male with primary renal cell cancer. (A) Proximal humerus pathologic fracture. (B) IO fixation. (C) Local progression eight months later led to IO failure. (D) Converted to hemiarthroplasty.

PAPER 35

Oncologic Advantages Using Carbon Fiber Implants

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INSTITUITON:
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BACKGROUND:
Standard materials for prophylactic stabilization of bone or reconstruction of bony defects in the oncologic patient affords excellent biomechanical advantages however are radio-opaque, making radiographic follow up difficult if not impossible. Carbon-fiber-reinforced polyetheretherketone (CFR-PEEK) implants offer several potential advantages in the field of musculoskeletal oncology due to their radiolucent properties. Biomechanical properties, durability, and ease of use allows for these implants to be used with regularity in the treatment of impending or pathological fractures with the additional benefit of improved capabilities in oncologic surveillance in terms of healing and tumor monitoring using all radiographic modalities.

QUESTIONS/PURPOSE:

1. Through a retrospective review, are we able to achieve bony stability in the oncologic situation using carbon fiber implants?

2. Does the use of Carbon Fiber enhance our ability to monitor the patient for healing and local recurrence?

3. Does the carbon fiber implant adversely interfere with achieving stability or monitoring of the patient?

MATERIALS AND METHODS:
One hundred and thirty-eight patients with impending or pathological fractures underwent stabilization using carbon fiber plates or nails (CarboFix™). Clinical and radiographic evaluations were performed with a mean follow up of 28 months. Diagnoses included both benign and malignant bone tumors as well as metastatic disease to bone. The surgical techniques, including methodology of interlocking screws through an invisible implant are discussed. Mechanical stability, durability, patient and implant outcomes, as well as monitoring modalities are discussed. Additionally, the implant design and clinical implications of an invisible nail is reported. Radiographic assessment was performed by an MSK radiologist

and the treating surgeon (HGR). Evaluation of graft incorporation, fracture healing, tumor recurrence, and maintenance of stability was assessed. The biomechanical evaluation of the carbon fiber implants is also addressed.

RESULTS:

Successful stabilization was achieved in all patients. Surgical time ranged from 18 - 118 minutes with fluoroscopy time averaging slightly less than two minutes. The surgical technique did not differ between the use of metallic implants and carbon fiber implants. There were no intra-operative or peri-operative complications. EBL ranged from 25 –150 cc and hospital length of stay ranged from 1 – 3 days. 89% of pathological fractures demonstrated early signs of healing by six weeks and union (enough to allow full weight bearing) by 12 weeks. There was one instance of hardware failure at insertion of nail and four cases of implant removal due to pain at site of implant. Postoperative radiographs enabled the visualization of the fracture or tumor site far more clearly due to the invisibility of the implant. There were no adverse effects due to the carbon fiber implant in terms of tumor surveillance or evaluation of bone healing. Evaluation of the tumor field was far easier and more inclusive than metal implants and the use of CT or MRI did not produce significant artifact. Assessment of fracture healing and graft incorporation was likewise improved when compared with metal implants. Oncologic monitoring of the patient through all radiographic modalities were unencumbered with the carbon fiber implants.
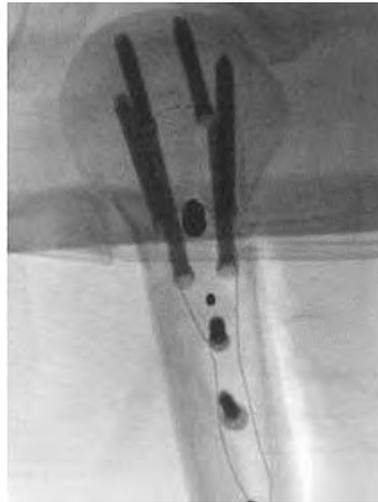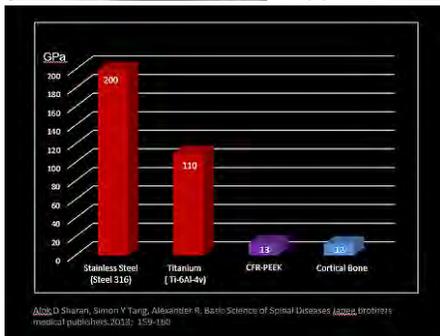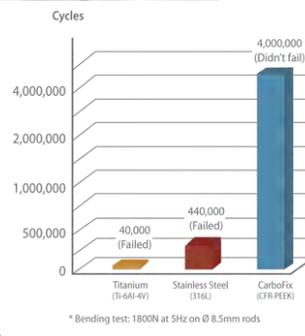

FIGURE 1.

FIGURE 2.

FIGURE 3.

FIGURE 4.

CONCLUSIONS:

The surgical and medical management of patients treated with carbon fiber fixation devices for impending or pathological fractures was very similar to the management of patients treated with metallic implants. The benefits however are quite significant in that the invisibility allows the clinician to more clearly monitor the most important area of concern, that being the fracture site, or impending fracture site for evidence of healing and local recurrence of disease. The carbon fiber implant is MRI and CT compatible and mechanically equivalent to similar implants of metallic design. The lower modulus of elasticity better matches that of bone. The fatigue strength is greater than metal implants of similar size. The use of carbon fiber implants in the patients with metastatic and primary neoplasia of bone plays an improved role in our ability to monitor and therefore care for these patients.

PAPER 36

Prophylactic Stabilization of Metastatic Femoral Lesions Has a Survival Benefit Compared to Pathologic Femur Fracture Fixation: Nationwide Analysis in the VA Healthcare System

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Background:
The skeletal system is one of the most common sites of metastatic disease (1, 2). It is estimated that over 1.6 million new cancers were diagnosed in 2016 in the United States and more than 250,000 patients are living with metastatic bone disease (3). The femur is the most common site of metastatic disease and pathologic fracture in the appendicular skeleton (2, 4, 5). Providing quality care for metastatic bone disease is an increasing challenge for the healthcare community, including orthopaedic surgeons.

Questions remain about the magnitude of benefit of prophylactic stabilization, limited in part by the small samples of prior research. Databases large enough to capture a large, geographically diverse population are generally administrative in nature, lack the depth of data required to compare differences in population comorbidities and do not follow patients long enough to determine survival differences (6-8). VA databases provide a unique opportunity to investigate longitudinal outcomes in the largest integrated healthcare system in the United States.

Question: Is prophylactic fixation of metastatic lesions of the femur associated with improved survival?

Patients and Methods:

This retrospective cohort study utilized a large nationwide clinically-integrated relational database. All patient records between Sept. 30, 2010 to October 1, 2015 within the VA Informatics and Computing Infrastructure Corporate Data Warehouse (VINCI CDW) were queried using the CPT codes 27187 (prophylactic treatment femoral neck and proximal femur) and 27495 (prophylactic treatment femur). This defined the prophylactic stabilization population (PSP). The pathologic fracture fixation (PFF) group was defined by the ICD-9 codes 733.14 (pathologic fracture neck of femur), 733.15 (pathologic fracture other part of femur) or 733.10 (pathologic fracture unspecified site) combined with a CPT code of 27245 (open treatment

femur/hip with nail), 27244 (open treatment femur/hip with plate), 27507 (open treatment femoral shaft fracture with plate) or 27506 (open treatment femoral shaft with nail).

Patient specific variables were obtained from the database were age, gender, cancer diagnosis, date of death or last follow-up, and comorbidites. Gagne comorbidity scores were calculated (9, 10).

The primary end point of the analysis was overall survival. Univariate survival was estimated by the method of Kaplan and Meier, with between group differences compared using the log-rank test. Covariate data was used to create a Cox proportional hazards model and adjust for confounders. The final multivariate model was created using a backward procedure using the Akaiki information criterion for variable selection.

Results:

Of 950 identified patients, 362 (38%) received prophylactic femoral stabilization and 588 (62%) underwent pathologic femur fracture fixation. The cohort was overwhelmingly male (95%). The mean age of the PSP was 67 versus 69 in the PFF (p=0.010). The prophylactic stabilization group had improved unadjusted survival at every time point from 3 months to 5 years following their index surgery. Figure 1 is the Kaplan-Meier Curve for unadjusted survival by metastatic lesion treatment type, demonstrating improved survival following prophylactic stabilization (p=0.018).
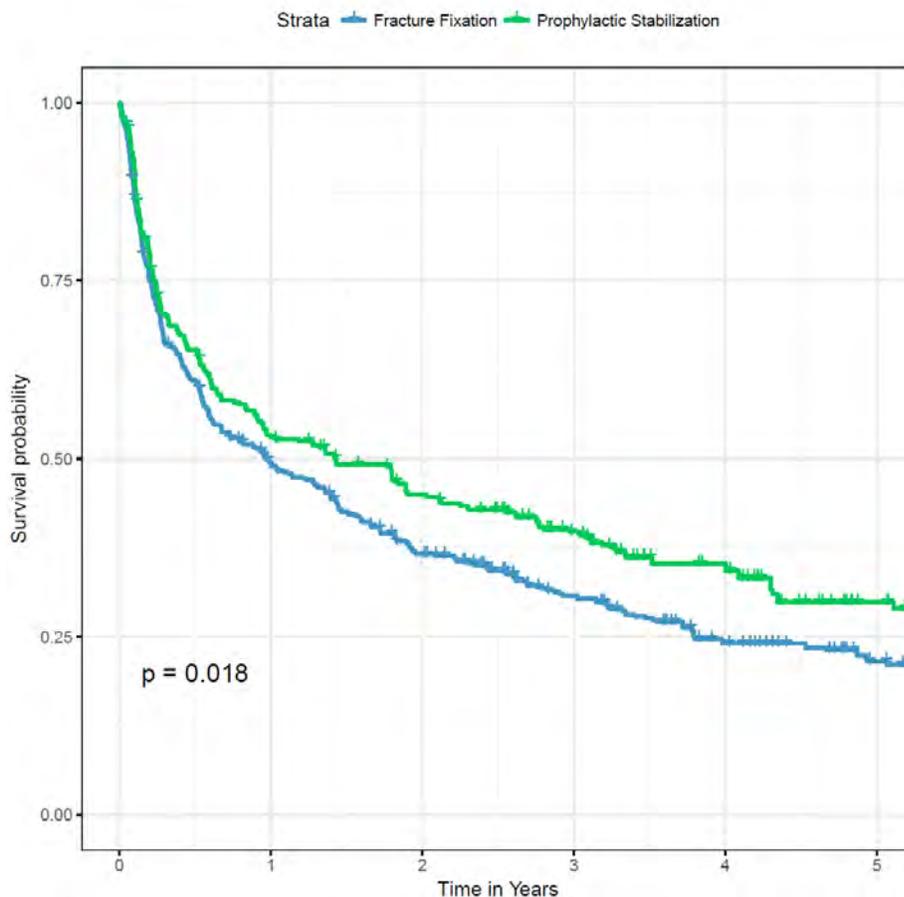
The univariate hazard ratio (HR) for risk was significantly lower for the prophylactic stabilization group (0.82, p=0.01). In the final multivariate model, which included Gagne comorbidity score and primary cancer diagnoses, the risk of death remained significantly lower for the prophylactic stabilization group (HR 0.75, p=0.002; Table 1).

Discussion and Conclusion:

In a nationwide analysis of mortality in 362 patients treated with prophylactic stabilization of femoral metastatic lesions and 588 patients who underwent fixation of pathologic femoral fractures, prophylactic treatment was associated with improved overall survival. This finding remained significant after adjusting for comorbidities and specific cancer diagnoses.

This study supports prophylactic stabilization as currently performed in a large US health system. While the nationwide analysis bolsters external generalizability, details of indication were not investigated and this population has a low representation of women. Limitations also include retrospective issues, including unaccounted for selection bias such as overall malignancy burden, and the potential for coding errors that is common to all database studies. These results provide a rational for prospective efforts to assess whether actively identifying lesions at risk and intervening pre-fracture improves outcomes.

Table I. Association of Patient Age and Comorbidities with Risk of Death Following Prophylactic Femur Stabilization Versus Pathologic Fracture Fixation		
Variable	**Hazard Ratio**	**P Value**
Univariate Model		
Prophylactic Stabilization	0.82	0.01
Pathologic Fracture Fixation	Ref	
Multivariate Model		<0.001
Treatment of Metastatic Lesion		
Prophylactic Stabilization	0.75	0.002
Pathologic Fracture Fixation	Ref	
Gagne Comorbidity Score	4.0	<0.001
Site		
Hematologic	Ref	
Kidney	3.0	<0.001
Liver	6.6	<0.001
Lung	4.2	<0.001
Prostate	1.8	<0.001

Figure 1: Kaplan-Meier plot of overall survival in patients with metastatic bone disease treated with prophylactic femoral stabilization vs fixation of completed femur fractures.

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PAPER 37

Thirty-Day Readmission, Reoperation and Mortality in Surgical Management of Metastatic Bone Disease: An Analysis of the National Surgical Quality Improvement Program

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Background: Metastatic bone disease is a significant cause of morbidity and mortality, often presenting with debilitating pain or pathologic fracture. Surgical intervention to prophylactically stabilize or repair a pathologic fracture may reduce pain and preserve limb function. However, because surgery for metastatic disease is not curative, risks and benefits must be carefully considered. Previous studies are limited by small data sets due to the rare incidence of these procedures. Additional research is needed to evaluate outcomes and risk factors so that physicians can identify patients who are most likely to benefit from surgical intervention. The American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP) prospectively collects perioperative data from more than 600 hospitals in the United States. ACS-NSQIP has been used to evaluate outcomes after metastatic spine tumor surgery (1). To our knowledge, no ACS-NSQIP studies have evaluated outcomes in surgical management of metastatic disease of the femur and humerus.

Purpose: The aim of this study is to use a large national registry to elucidate the incidence and timing of readmission, reoperation, and mortality in the first 30 days following surgical treatment of metastatic bone tumors of the femur and humerus.

Patients and Methods: We performed a retrospective review of patients in ACS-NSQIP who underwent surgery between 2011 and 2015. Patients were identified using CPT and ICD-9 codes related to metastatic tumors of the femur or humerus. CPT codes included prophylactic stabilization, radical resection of tumor, open reduction internal fixation (ORIF), or any arthroplasty procedure. ICD-9 codes included secondary malignant neoplasm of bone, the primary cancer diagnosis (breast, prostate, lung, kidney, thyroid, lymphoma, or multiple myeloma), or pathologic fracture accompanied by "disseminated cancer" designation in the ACS-NSQIP. Patient demographics, preoperative labs, and comorbidities were extracted. Timing and incidence of readmission, reoperation, and mortality within the first 30 days after surgery were evaluated using summary statistics. Readmissions and reoperations that were related to the original procedure were designated as such in the ACS-NSQIP. P-values were determined using Mann-Whitney U-test for continuous variables.

Results: 879 patients with appropriate CPT and ICD-9 codes were identified. 194 (22.1%) had a metastatic tumor of the humerus and 685 (77.9%) had a metastatic tumor of the femur. The average time from hospital admission to the OR was 2.5 days, and the average length of stay was 8.7 days. The mean duration of surgery was 124.8 minutes (SD = 76.7). 126 patients (14.3%) underwent radical resection of tumor, 222 (25.3%) received prophylactic stabilization, 383 (43.6%) underwent an arthroplasty procedure, and 270 (30.7%) underwent ORIF. The 30-day mortality rate was 11.1% with an average time from operation to death of 17.8 days (SD = 8.6). Overall 30-day readmission rate was 12.6% with average time to readmission of 16.8 days (SD = 7.2). Related readmission rate was 5.6% with an average time to readmission of 16.8 days (SD = 6.4). Overall 30-day reoperation rate was 4.0% with an average time to reoperation of 14.7 days (SD = 7.7). Related reoperation rate was 2.2% with an average time to reoperation of 15.8 days (SD = 7.5). No differences were seen between the femur and humerus groups with respect to mortality, related reoperation, or related readmission (Table 1).

Conclusions: Surgical management of metastatic tumors of the femur and humerus carries substantial risks of mortality, readmission, and reoperation in the first 30 days after surgery. Our data suggests that mortality rates may in fact be higher than previously reported (2). Further study is needed to identify specific patient factors that increase the risk of post-operative complications and mortality. Limitations in our dataset include lack of oncology-specific data points such as tumor size and location, extent of metastatic disease, and treatment details. Despite these limitations, the ACS-NSQIP database provides an exciting opportunity to evaluate orthopedic oncologic surgery outcomes in a large patient population.

Table 1: Outcomes from metastatic tumor surgery in humerus vs femur

	Humerus	Femur	P-value
Mortality	9.3%	11.7%	.35
Related Reoperation	2.1%	2.2%	1.0
Related Readmission	4.1%	6.0%	.32

References:

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PAPER 38

Prophylactic vs. Post-Fracture Stabilization for Neoplastic Lesions of the Long Bones: A Comparison of 30 Day Post-Operative Outcomes

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Introduction: Pathologic fractures are a negative prognostic factor, associated with an increased risk of morbidity and mortality in patients with neoplastic lesions of long bones. It has been theorized that this association may be partially explained by the dissemination of malignant cells after pathologic fractures as well as the functional impairment and immobility associated with the pain. Such findings highlight the possible role for prophylactic fixation in decreasing complications and potentially improving survival in this patient population.

Multiple methods have been described to predict the risk of pathologic fracture in osseous metastases. A study by Riestevski et al found that amongst patients that required treatment for a completed pathological fracture, 60% missed the opportunity for prophylactic stabilization. Another equally important determinant of treatment, however, is the risk of complications amongst patients undergoing post-fracture stabilization and those undergoing it prophylactically. Ultimately, the goal for many of these patients is for pain control, maintenance of function, and maximizing quality of life with their family.

Although some studies demonstrated improved survival in patients who received prophylactic vs post-fracture stabilization for neoplastic disease of the long bones, there is a paucity of the literature when it comes to differences in short term outcomes. Given the importance of short term outcomes such as postoperative complications and length of hospital stay on patients' wellbeing and counseling, as well as the appropriation of healthcare resources, a direct comparison between these two patient groups is of paramount importance. The aims of this study are to compare patients receiving prophylactic stabilization for neoplastic disease of the long bones to those undergoing post-fracture stabilization of a pathologic fracture in terms of: 30-day major medical complications, 30-day reoperations, non-routine discharge, and the total length of hospital stay.

Methods: The American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) database was queried for records of patients diagnosed with neoplastic disease (ICD 9: 140X-239X. ICD 10 C00X-D49X) and metastatic neoplasms to the bones (ICD 9: 198.5. ICD 10: C79.51. Patients with a diagnosis of pathologic fracture (ICD 9: 733.1. ICD 10: M84.45) with concomitant disseminated cancer, were on radiotherapy, or chemotherapy (NSQIP variables) were also included. Patients were categorized as either undergoing prophylactic fixation for impending pathologic fracture (n=461) or open treatment for completed pathologic fracture (n=856). The

groups were compared with respect to several potential confounders using Student t, Kruskill-Wallis, and χ2 tests. Logistic and Poisson regression models (inclusion threshold of P < .1) were used to assess the associations of prophylactic vs post-fracture stabilization with outcomes. The alpha level was set at 0.05.

Results: Of the 1,416 patients who met our inclusion criteria, 1317 had complete data and were included in the analysis. Of those, 31% (461) were in the prophylactic stabilization group. Patients in the fracture stabilization group were slightly older on average (65.9 vs 62.6, p <0.01), with a higher BMI (28.2 vs 27.4, p=0.05). Gender, smoking status, and ASA class were not different between the groups (p>0.05). Of the several comorbidities assessed, the only significant difference was a higher proportion of post-fracture stabilizations noted to have disseminated cancer in the database (90.2 vs 80.5, p=0.02). Operative time was similar between the groups (p=0.89). The proportion of patients who experienced a major medical complication within 30 days was significantly higher in the fracture group (15.8% vs. 9.8%, p<0.01). On univariate analysis, patients in the fracture group had a significantly higher proportion of death (10.3% vs. 6.1%, p=0.01). Patients in the fracture group also had a significantly longer length of hospital stay after surgery (8.2% vs. 6.9%, p<0.01), and a higher proportion were discharged to a facility other than home (44% vs. 25.3%, p<0.01). Both groups demonstrated a similar 30-day reoperation rate (p>0.05). After controlling for potential cofounders, prophylactic fixation was associated with a lower risk for major medical complications (OR=0.64; 95%CI: 0.45-0.93; p=0.02), discharge to a location other than home (OR=0.48; 95%CI 0.36-0.63; p<0.01), and lower risk of a longer length of hospital stay (IRR=0.86; 95%CI 0.74-0.96; p=0.01) on multivariable analysis.

Conclusion: Despite similar baseline characteristics, prophylactic stabilization of neoplastic lesions of bone is associated with lower risk of major post-operative complications within 30 days, decreased hospital length of stay, and lower risk of discharge to a facility other than home, when compared to completed pathologic fractures. As such, early diagnosis and surgical management of bone lesions at risk for pathologic fracture may help improve early postoperative morbidity and mortality, while decreasing healthcare utilization and maximizing time at home.

Table 1

Baseline Patient Characteristics and Surgical Factors: prophylactic fixation of impending pathologic fracture vs. open treatment for completed fracture, American College of Surgeons National Surgical Quality Improvement Program Database,(2006-2016)

Variable	n (%)		P Value
	Prophylactic (n=461)	Completed (n = 856)	
Age (y)	62.6 ± 13.8*	65.9 ± 12.6*	**<0.01**
Female sex	260 (56.4)	484 (56.5)	0.96
Body mass index (kg/m²)	28.2 ± 7.0*	27.4 ± 6.6*	**0.05**
ASA class			0.24
I	3 (0.7)	3 (0.4)	
II	76 (16.5)	120 (14.0)	
III	299 (64.9)	538 (62.9)	
IV	82 (17.8)	193 (22.6)	

	1 (0.2)	1 (0.1)	
V			
Comorbidities			
Ascites	3 (0.7)	9 (1.1)	0.47
Bleeding disorder	40 (8.7)	84 (9.8)	0.50
Chronic steroid use	73 (15.8)	130 (15.2)	0.76
Congestive heart failure	5 (1.1)	14 (1.1)	0.95
COPD	37 (8.0)	78 (9.1)	0.50
Current smoking	97 (21.0)	175 (20.4)	0.80
Diabetes mellitus	73 (15.8)	148 (17.3)	0.50
Dialysis	3 (0.7)	13 (1.52)	0.17
Hypertension	228 (49.5)	460 (53.7)	0.14
Renal failure	0 (0.0)	1 (0.1)	0.46
Disseminated cancer	371 (80.5)	772 (90.2)	**<0.01**
Surgical factors			
Operative time (min)	96.3 ± 50.0	95.9 ± 54.1	0.88
Preoperative transfusion	30 (6.5)	52 (6.1)	0.76

Table 2

Univariate Comparison of Outcomes: prophylactic fixation of impending pathologic fracture vs. open treatment for completed fracture, American College of Surgeons National Surgical Quality Improvement Program Database, (2006-2016).

Variable	n (%)		*P* Value
	Impending (n=461)	Completed (n = 856)	
Length of hospital stay	6.9 ± 8.1 *	8.2 ± 9.0 *	**<0.01**
Discharge to facility other than home†	99 (25.3)	318 (43.7)	**0.01**
Unplanned reoperation†	5 (1.4)	21 (3.1)	0.08
Any major complication	45 (9.8)	135 (15.8)	**<0.01**
Cardiac arrest	0 (0)	4 (0.5)	0.14
Cerebrovascular accident	2 (0.4)	5 (0.6)	0.72
Death	28 (6.1)	88 (10.3)	**0.01**
Myocardial infarction	2 (0.4)	4 (0.5)	0.93
Pneumonia	11 (2.3)	28 (3.3)	0.37
Pulmonary embolism	4 (0.87)	16 (1.9)	0.16
Reintubation	3 (0.7)	9 (1.1)	0.47
Sepsis	3 (0.7)	13 (1.5)	0.17
Septic shock	2 (0.4)	4 (0.5)	0.93
Ventilator dependence	1 (0.2)	5 (0.6)	0.35

*Data presented as mean ± standard deviation.

†Data on disposition status and unplanned reoperation were available for 1,317 and 1,037 patients, respectively

PAPER 39

Hybrid Surgery-Radiosurgery Therapy For Metastatic Epidural Spinal Cord Compression (Mescc): A Comparison of 30 Day Post-Operative Outcomes

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Purpose: Patient-reported outcomes (PRO) represent an important measure of cancer therapy effect. For patients with metastatic epidural spinal cord compression (MESCC), hybrid therapy using separation surgery and stereotactic radiosurgery (SRS) preserves neurologic function and provides tumor control. There is currently a paucity of data reporting PRO after such combined modality therapy for MESCC. Delineation of hybrid surgery-radiosurgery therapy effect on PRO validates the hybrid approach as an effective therapy resulting in meaningful symptom relief.

Patients and Methods: Brief Pain Inventory (BPI) and MD Anderson Symptom Inventory – Spine Tumor (MDASI-SP), PROs validated in the cancer population, were prospectively collected. Patients with MESCC who underwent separation surgery followed by SRS were included. Separation surgery included a posterolateral approach without extensive cytoreductive tumor excision. A median post-operative radiosurgery dose of 2700 cGy was delivered. The change in PRO three months after the hybrid therapy represented the primary study outcome. Pre- and post-operative evaluations were analyzed using the Wilcoxon signed-rank test for matched pairs.

Results: One hundred and eleven patients were included. Hybrid therapy resulted in a significant reduction in the BPI items "worst" and "right now" pain (P<0.0001), and in all BPI constructs (severity, interference with daily activities, and Pain Experience, P<0.001). The MDASI-SP demonstrated reduction in spine specific pain severity and interference with general activity (P<0.001), along with decreased symptom interference (P<0.001).

Conclusions: Validated PRO instruments showed that in patients with MESCC, hybrid separation surgery-radiosurgery therapy results in a significant decrease in pain severity and symptom interference. These prospective data confirm the benefit of hybrid therapy for treatment of MESCC and should facilitate referral of patients with MESCC for surgical evaluation.

PAPER 40

The Treatment of Metastatic Spine Disease in Patients without Definitive Operative Indications: Radiation Therapy vs. Surgical Decompression and Corpectomy for Neurologically Intact Patients with Epidural Spinal Cord Compression and Indeterminate SINS

Authors:

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Background

The management of metastatic spine disease (MSD) has evolved and there is now a greater spectrum in the clinical presentation of these patients. Numerous studies have concluded that surgical intervention may be indicated for progressive neurologic compromise or spinal instability, however, many patients do not have such definitive presentations. The Spinal Instability Neoplastic Score (SINS) was developed to provide guidance on when to surgically treat spinal instability, although many patients fall within the indeterminate category (SINS 7-12). Additionally, many of these patients present with epidural spinal cord compression (ESCC) before the onset of neurological compromise. Given the inherent risks of surgery in patients with neoplastic disease, significant benefit should be expected when pursuing surgical treatment. External beam radiation therapy (EBRT) remains a treatment option to avoid the risks associated with surgery in the right clinical scenario. The purpose of this study was to compare length of survival (LOS) and length of ambulatory ability (LOA) in patients without strict operative indications based on spinal instability or neurological compromise undergoing surgical and non-surgical treatment modalities.

Questions/Purposes

(1) For patients with indeterminate SINS (7-12) and ESCC without neurological compromise, is there a survival and ambulatory benefit to surgery + EBRT vs. EBRT alone?
(2) Among patients in the surgically treated cohort, does complete corpectomy and tumor resection confer a survival and ambulatory benefit when compared to decompression alone?

Patients and Methods

We queried our institution's medical record from 2012-2016 for patients treated for spinal metastatic disease and retrospectively reviewed their SINS, degree of ESCC, and neurological status. Inclusion criteria included no neurological deficits, SINS 7-12, and at least grade 1 ESCC.

All patients had the ability to ambulate prior to surgery. The cohort was stratified by treatment approach: either external beam radiation alone (EBRT) or surgery + EBRT (S+E). The surgical cohort was further stratified by surgical procedure: decompression alone or corpectomy and tumor resection. Demographic, clinical, and outcomes data were compared using Chi Squared tests and ANOVA. Kaplan-Meier analysis with the log rank test was used to assess differences in LOS and LOA.
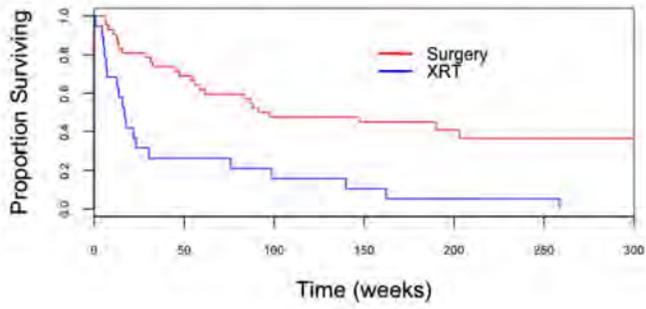
Results

61 patients were included in our analysis (EBRT n=19; S+E n=42). Amongst the surgical cohort, 11 patients underwent decompression alone, while 31 patients underwent corpectomy and tumor resection. The average SINS of S+E group (SINS 9.4) was statistically greater than the EBRT group (SINS 8.6) (p<0.001). There was no significant difference between the grade of ESCC between the two groups (p=0.06). The average Tokuhashi score of S+E group (Tokuhashi 10.7) was significantly greater than the EBRT group (Tokuhashi 9.1) (p=0.002). In univariate analysis, the S+E group had improved LOS (p<0.001, figure 1) and LOA (p<0.001). At one year, 66.6% of those treated surgically were still ambulating, compared to just 26.3% for patients treated with EBRT.

   Of those patients treated surgically, there was no significant differences amongst each group in Tokuhashi score (p=0.266), ESCC grade (p=0.309), or primary cancer type (p=0.419). When comparing length of survival and length of ambulation, there was no significant difference between patients receiving decompression alone and those who underwent corpectomy and tumor resection (LOS p=0.919, LOA p=0.977) (figure 2).
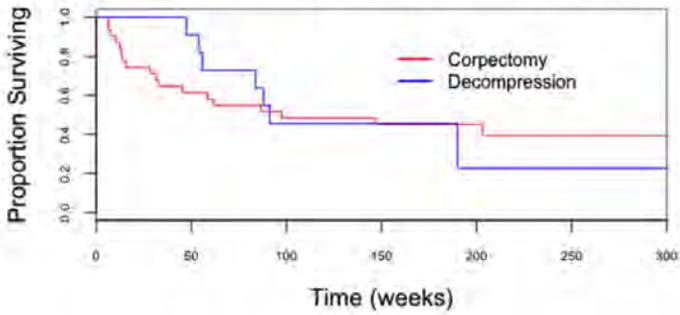
Conclusions

The optimal treatment of MSD patients without definitive surgical indications, such as indeterminate spinal instability (SINS 7-12) and ESCC without neurological compromise, remains unclear. In our institution's cohort, although a small sample size, there was a significant survival and ambulatory benefit to surgical treatment compared to EBRT. Furthermore, more complex surgery, such as corpectomy and tumor resection did not provide increased LOS or LOA when compared to less invasive, decompressive techniques. Although larger patient cohorts and prospective studies are required to validate our findings, this initial investigation may indicate that less invasive, decompressive surgical treatment provides survival and ambulatory benefit to MSD patients with previously indeterminate indications for surgery.

Kaplan-Meier Curve of Survival by Treatment Approach in Patients with Spinal Metasteses undergoing Depcompression

Kaplan-Meier Curve of Survival by Decompression v. Corpectomy in Patients with Spinal Metasteses

PAPER 41

Variation In The Administration and Reporting Of The MSTS Score: Evidence For The Need Of Standardized Outcome Measurement Guidelines

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Background: The Musculoskeletal Tumor Society (MSTS) score has been widely used to assess functional outcomes of patients with extremity tumors requiring surgical intervention. The 1993 version was designed as a hybrid tool with the patient reporting his/her emotional acceptance of the functional outcome and the provider completing the remaining items (at the point of care). Variations in the tool utilization may contribute to the poor reliability of the MSTS score. The purpose of this study is to 1) review the literature to identify variations in MSTS score reporting and 2) evaluate differences between reporting MSTS scores at multiple, standardized time points versus reporting MSTS scores at "last follow up" for the same patient sample.
Methods: 1) A literature review of 301 English articles reporting MSTS functional outcome scores published between 1946-2016 was performed. Data collected included the range of follow-up endpoints, the frequency of assessments over time, the form of statistics reported (group mean, median, standard deviation, range), and indication whether the patient reported his/her emotional acceptance. 2) Point of care MSTS UE and the MSTS LE scores for two orthopaedic surgical populations (Open Reduction Internal Fixation and Endoprosthesis) were collected at standardized perioperative time points.
Results: <u>Literature review</u>: The MSTS score was reported at "last follow-up" for ninety percent of the 301 articles reviewed (Table 1). Eighty percent reported the range of "last follow-up". Thirty-six percent of these reported variation in patients' post-operative visit times ranging from 37 to 99 months.

Table 1

MSTS Functional Score Reporting Pattern	Number (of 301)	Percentage
Single point in time	263	87
Multiple points during follow-up	24	8
Collected pre-op	5	2
Reported MSTS only at final follow-up	271	90
Reported the range of final follow-up	242	80
Mean Follow-up	130	43
Median Follow-up	91	30
Standard Deviation reported (or able to calculate from table provided)	134	45
Range of MSTS score reported (or table of values)	188	62
Mean of MSTS score (or table of values)	297	99
Median of MSTS score (or table of values)	108	36

Table provided of each MSTS score	72	24
No scores reported: only general descriptors	78	26
1993 version, but used only Excellent, Good, Fair, Poor to describe results	34	11
1987 version	39	13
1993 version	189	63
Used both 1987 and 1993 versions of MSTS	4	1

Eighty seven percent of the publications reported a single patient assessment with the MSTS score. Forty three percent reported the MSTS scores as a mean score and less than 9% of the articles reported the actual standard deviation with the mean. Twenty-six percent of the publications reported no MSTS scores at all (only descriptive words), and of those, the definition of score ranges for those descriptive terms was not provided.

Point of Care MSTS UE and LE

PAPER 42

An Evaluation of PROMIS Health Domains in Sarcoma Patients Compared to the United States Population

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Background:
Healthcare providers historically have focused on physician-directed scoring systems and survival statistics to determine the "success" in treating various conditions, cancer included. The error in this strategy comes in failing to realize that how a physician and patient define success may be widely different. The Patient Reported Outcomes Measurement Information System (PROMIS) is a new patient-reported scoring system that was developed under the National Institute of Health (NIH) and is being widely adopted. It has the advantage over previous outcome measurement systems in that it is completely patient-reported and has the ability to convert raw scores to T-scores in order to compare these values across medical conditions. In this way we can now compare our sarcoma patients to those with more common ailments or even the general United States (US) Population. This system will afford us a better understanding of what constitutes a successful outcome from the patient perspective and allow us to provide care more in line with their goals and desires.

Questions/Purpose: (2-4)
We utilized the PROMIS system to evaluate health domains of patients who had a diagnosis of non-metastatic sarcoma and had previously undergone surgical resection. We aimed to compare these values to that of the US population in order to identify differences. Additionally, we separated the sarcoma cohort into early (< 2years) and late (>2 years) groups based on the time from their last surgical procedure in order to determine if the differences that were found were maintained over time.

Patients and Methods:
PROMIS measures were obtained on all clinic patients beginning September 1st, 2016. After Institutional Board Review (IRB) approval we queried the data from September 1st through December 31st, 2016. Six hundred and four patients completed the PROMIS questionnaire. We excluded all patients with benign disease, those with metastatic disease, and those who had yet to undergo an operation. This left 134 patients in the final cohort with a diagnosis of non-metastatic sarcoma who had already undergone a resection. These patients were then further divided into an early group and a late group as defined by less than or more than two years from the last surgical date.

Demographic data, pathologic diagnoses, and operative reports were obtained from chart review. The PROMIS 43 profile, which collects short form data for seven health domains, was used. These domains include physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate (in social activities), and pain interference. If patients completed more than one evaluation during the study period then the latest questionnaire was used. The raw scores were converted to T-scores in order to allow comparisons to the United States general population. In the PROMIS system the US general population is given a T-score of 50 with a standard deviation of 10. If a patient has a T-score below 50 they have less of the tested domain. Conversely, if a patient's score is above 50 then the opposite is true.

Results:
There was no difference in the gender, location, average age of the patients, or history of inadvertent resection between the early and late sarcoma cohorts (**Figure 1**). We also found no significant difference in the average pain scores between these groups.

	Early (N=73)	Late (N=65)	Total (N=138)	P-Value
Sex				
Female	33	28	61	
Male	40	37	77	0.803
Upper Extremity				
Yes	17	10	27	
No	56	55	111	0.246
Prior Resection				
Yes	11	6	17	
No	62	59	121	0.301
Age (Mean +/- SD in months)	59.8 +/- 17.6	54.7 +/- 19.4		0.112
Time from surgery to survey (Mean +/- SD in	11 +/- 7	72 +/- 58		<0.001
Limb Salvage				
Yes	57	57	114	0.139
No	16	8	24	
Average Pain Score (Mean	3.63	4.12		0.28

Figure 1: Patient Demographics

When comparing PROMIS health domains we noted several significant differences (**Figure 2**). The physical function score in the early cohort was significantly reduced when compared to the US general population. This score remained significantly lower than the US population in the late cohort as well. Additionally, we found a significant reduction in the depression T-scores in both the early and late cohorts when compared to the US general population.

Early versus Late Follow-up		Mean	SD	U.S. General	SD	P-Value
Physical Function T-Score	Early	42	11	50	10	<0.001
	Late	44	10			<0.001
Anxiety T-Score	Early	50	9	50	10	0.567
	Late	49	10			0.309
Depression T-Score	Early	46	9	50	10	<0.001
	Late	45	9			<0.001
Fatigue T-Score	Early	48	11	50	10	0.062
	Late	48	12			0.182
Sleep Disturbance T-Score	Early	48	9	50	10	0.082
	Late	48	11			0.169
Ability to Participate T-Score	Early	48	12	50	10	0.208
	Late	51	11			0.245
Pain Interference T-Score	Early	53	11	50	10	0.085
	Late	53	11			0.059

Figure 2: PROMIS values

We were unable to find a significant difference in the anxiety, fatigue, sleep disturbance, ability to participate, or pain interference scores in either the early or late sarcoma cohorts when compared to the US population.

Conclusions:

Both the early and late sarcoma cohorts report lower physical function scores when compared to the US general population. In spite of this limitation they also report lower depression scores, indicating that these patients suffer less from depression than the United States general population. These results appear to be independent from the proximity of the surgical resection and are important in order to better understand our patients and to assist with our future patient counseling.

PAPER 43

PROMIS May Be A Superior Measure of Patient Reported Outcomes in Musculoskeletal Oncology Patients

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Background:
Patient reported outcomes (PROs) are increasingly being used in musculoskeletal oncology to follow patients' post-operative course and identify areas of improvement. The MSTS and TESS scores are well studied in musculoskeletal oncology, however the newer Patient Reported Outcomes Measurement Information System (PROMIS) has not been fully evaluated with regards to this population. Orthopaedic oncology patients are often affected by multisystem disease and often have lower baseline function and more chronic pain. As a result, utilizing an adaptive, computerized outcomes measure may be especially useful in this group.

Purpose:
The purpose of this study is 1) to compare the patient reported outcomes scores of the MSTS, TESS and PROMIS - physical function (PF), pain interference (PI), and depression assessment (DA) domains, and 2) to determine the floor and ceiling effects of MSTS, TESS, and PROMIS in our study population.

Methods:
350 patients were identified as having undergone orthopeadic surgery for either benign or malignant musculoskeletal neoplasms or metastatic disease requiring surgical intervention. Patients completed the MSTS, TESS and PROMIS (physical function, pain interference, and depression assessment) questionnaires. 95 patients were excluded due to incomplete data sets. The Shapiro-Wilk test was used to determine distributions of PROs. Spearman correlation coefficients were used to describe the associations between the PROMIS PF, PI, DA and other

PROs. Statistical significance was set at p < 0.05. The strength of the correlations between the PROMIS PF Computer Adaptive Testing (CAT) and the other patient-reported outcome measures were classified as high (≥0.7), high-moderate (0.61 to 0.69), moderate (0.4 to 0.6), moderate-weak (0.31 to 0.39), or weak (≤0.3). Convergent validity was tested by assessing the correlation between the PROMIS PF, PI and DA categories, and legacy instruments (MSTS and TESS scores). An a priori power analysis was conducted for a 2-sided test with alpha level of 0.05. Ceiling effects were measured by calculating the percentage of respondents who obtained the highest possible score on a given patient-reported outcome measure, and floor effects were measured by calculating the percentage of respondents achieving the lowest score. A percentage of ≥15% was designated as a significant ceiling or floor effect

Results:
The PROMIS PF and PI were highly correlated with the MSTS and TESS (P <0.0001) and there was a moderate correlation with PROMIS DA, MSTS and TESS (P<0.0001). No test was found to display a significant ceiling or floor effect in this population. The MSTS score displayed 12.55% of patients reporting the maximum score. Similarly, 10.98% of patients scored the maximum TESS score. These findings suggest both the MSTS and TESS scores approach decreased sensitivity in patients scoring highly due to this reduced variance. We did not observe this type of skewed distribution with any PROMIS CATs (PF, PI or DA).

Conclusion:
The PROMIS physical function and pain interference computerized adaptive testing are useful patient reported outcomes tools with regards to musculoskeletal oncology patients. The PROMIS PF and PI are highly correlative with MSTS and TESS scores, which are commonly used to assess PROs in this unique patient population. No statistically significant ceiling or floor effects were seen in any test, although our findings suggest both the MSTS and TESS scores approach decreased sensitivity in patients scoring highly due to this reduced variance. Further research is needed to validate this measure in musculoskeletal oncology patients.

PAPER 44

Accelerometer-based measurement of balance and gait after treatment for lower extremity musculoskeletal cancer in the clinic: A feasibility and validity study

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Background: Major surgery for lower extremity musculoskeletal cancer can severely impair balance and gait. Furthermore impaired balance and gait lead to reduced mobility, lack of confidence, and loss of adaptive mechanisms to maintain the body in space, and falls. Yet balance and gait assessments are not part of routine clinical practice. Small inexpensive portable accelerometers may be useful in bridging this gap.

Questions/purposes: The aim of this study was therefore to develop, validate and assess the feasibility and acceptability of accelerometer-based assessments of balance and gait assessment in this patient group.

Methods: This was a prospective cross-sectional study of patients treated for lower extremity musculoskeletal tumours. Balance and gait were quantified using a tri-axial accelerometer (Axivity, AX3) placed on the lower back (L5 level). Patients performed standard activities including standing with eyes open and fast walking. Summary measures of balance; (area (ellipsis), magnitude (RMS), jerkiness (jerk), frequency (f95) of postural sway), and gait (temporal outcomes, step length and step velocity) were derived from raw accelerometer data

using validated algorithms in MATLAB® (R2012a) program. Outcomes were compared to control groups to establish discriminant validity. This was performed using Independent t-tests or Mann-Whitney U tests. Balance and gait outcomes were compared to existing outcome measures [disability scale (Toronto Extremity Salvage Score (TESS)), impairment scale (Musculoskeletal Tumour Rating System (MSTS)) and quality of life scale (Quality of life-Cancer survivors (QoL-CS)) to establish convergent validity. This was performed using regression models to assess the influence of balance and gait measures on existing scales and vice-versa.

Results: Of 40 patients recruited, data from 34 adults of mean age 43 (19-89) years were analysed. Patients were treated for tumours in the femur (19), pelvis/hip (3), tibia (9), or ankle/foot (3). 27 had limb sparing surgery (LSS) and 7 amputation (AMP). Balance and gait assessments were acceptable, comfortable, feasible to obtain, and valid in these patients. Patients presented with a significantly higher area (ellipsis) (Figure 1), magnitude (RMS) and jerkiness (jerk) of postural sway than controls ($p<0.05$). Furthermore, patients walked with a significantly higher step time, stance time, swing time; reduced step length and step velocity (Figure 1) compared to controls ($p<0.05$). Whilst, MSTS was a significant predictor of balance and gait, balance (RMS_AP) and total gait time negatively predict TESS and QoL ($p<0.05$) (Table 1).

Conclusion: This study supports the feasibility and validity of using a tri-axial accelerometer to quantify balance and gait in the clinic in patients treated for lower extremity musculoskeletal cancer. Balance and gait are significantly affected after treatment. Poor balance and gait outcomes are significantly associated with reduced activity levels and a worsened QoL. This is important clinical information to guide rehabilitation strategies.

PAPER 45

A markerless motion capture to quantify functional outcomes using a depth-sensor after treatment for lower extremity sarcomas in the clinic: A feasibility and validity study

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Background: Physical limitations are widely reported after treatments for sarcomas, yet rapid quantitative functional assessments are lacking. Costly and cumbersome systems pose a barrier to clinical translation.

Questions/purpose: The aim of this study was therefore to assess the feasibility and validity of a single portable inexpensive markerless motion capture sensor (Microsoft Kinect) for rapid functional outcome assessments in the clinic after treatments for lower extremity sarcomas.
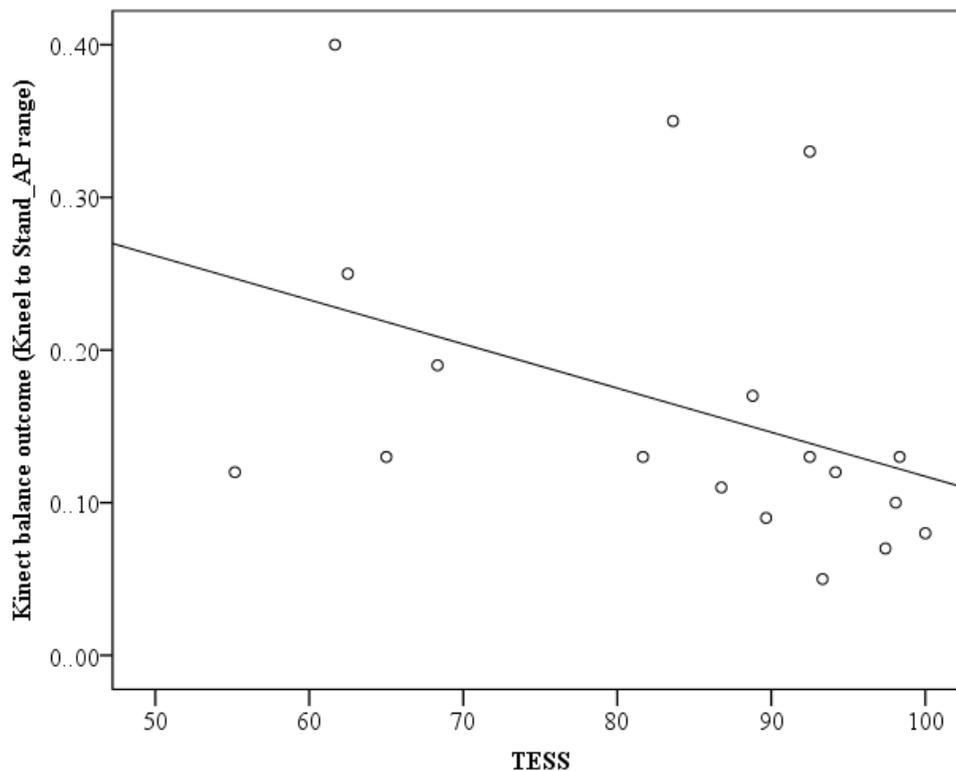
Methods: This was a prospective cross-sectional study of patients treated for lower extremity sarcomas. Motion capture of three standard activities; single-leg stance, stand to kneel/kneel to stand and normal pace walks were quantified using Kinect. Summary Kinect measures of balance [anterior-posterior (AP) and medio-lateral (ML) range during single-leg stance and AP, lateral range and movement velocity during kneeling] and gait [step length and velocity] were derived. Kinect measures were compared to existing measures [disability scale (Toronto Extremity Salvage Score (TESS)) and impairment scale (Musculoskeletal Tumour Rating System (MSTS)] to establish convergent validity. Spearman's rho correlations were calculated to examine relationships between Kinect measures and existing scales.

Results: 34 adult datasets of mean age 43 (19-89) years were analysed. Patients were treated for tumours in the femur (19), pelvis/hip (3), tibia (9), or ankle/foot (3). 27 had limb sparing surgery (LSS) and 7 amputation (AMP). Motion capture using Kinect were well tolerated and produced clinically useful data with face validity. There were significant correlations between (i) MSTS and balance ($p=0.007^*$, $r=-0.567$), movement velocity ($p=0.020^*$, $r=0.502$) and gait ($p=0.022^*$, $r=-0.416$); and (ii) between TESS and balance ($p=0.015^*$, $r=-0.564$) (Figure 1) and movement velocity ($p=0.021^*$, $r=-0.541$).

Conclusion:

This study supports the feasibility and validity of using a single depth-sensor to quantify clinic-based physical functioning in the clinic in patients treated for lower extremity sarcomas. Structural/functional impairments are significantly associated with poor balance and gait, which in turn are associated with higher disability. This is important clinical information to guide rehabilitation strategies.

Figure 1: Relationship between Kinect balance outcome and established measure TESS ($p<0.015^*$, $r=-0.564$) [Poor dynamic balance during kneeling (increased Kneel to Stand_AP range) is associated with high levels of disability (low TESS scores)]

PAPER 46

Patient specific 3D cutting guides provide similar cut accuracy and superior far-side cut penetration accuracy compared with computer navigation or freehand technique in an idealized sawbones pelvic resection model

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Background: Wide margin pelvic resections about the sacroiliac (SI) joint are amongst the most challenging procedures in musculoskeletal oncology. Mastery of three dimensional anatomy and leveraging of current technology may improve both accuracy and inadvertent damage to pelvic structures. Several options are available to optimize these parameters including standard freehand method, computerized navigation, or patient-specific cutting guides.

Questions/Purposes: Amongst freehand, navigation, or patient specific cutting guide techniques, which achieves the greatest accuracy of planned cut? Which achieves the least damage to pelvic viscera and critical neurovascular structures beyond the cutting margins? Can each technique be generalized to fellowship-trained orthopedic oncologists?

Patients and Methods: We used an idealized male pelvis sawbones model and asked four fellowship-trained musculoskeletal oncologists to perform a perfect cut in the plane of the SI joint. Four surgeons used 11 specimens to perform 22 separate cuts (8 navigation via O-arm/Stealth (Medtronic, Memphis, TN), 8 patient specific 3D-printed cutting guide (BodyCad, Montreal, CA), and 6 freehand) based on a priori power analysis. Cut penetration to pelvic viscera was measured using low density sawbones foam. Penetration into the foam and cut deviation from an idealized model was quantified using high resolution optical scanning. Differences between groups were analyzed using one way analysis of variance statistical methodology.

Results: Freehand technique resulted in mean 67% +/- 21% cut accuracy to within 5 mm of the idealized resection margin, whereas the navigation technique resulted in 71% +/- 21% and patient specific guide technique 86% +/- 10% (p=0.099). When accuracy threshold was reduced to +/- 2mm, the results were 26% +/- 16%, 33% +/- 16%, and 48% +/- 14% (p=0.038). Pelvic soft tissue damage was estimated using a low, medium, or high depth penetration scale based on quantified optical scanning. 17% of freehand technique demonstrated the lowest penetration damage with no foam scoring or indentation, whereas navigation demonstrated 38% low grade penetration and patient specific guide demonstrated 75% low grade penetration (p<0.001). There

were no differences detected in these outcomes based on years into practice (range 1- 6) of the operating surgeon.

Conclusions: No clear standard of care technique has emerged for complex three dimensional pelvic resections, but our idealized sawbones model suggests that patient specific cutting guides provide similar or superior cut accuracy and the best avoidance of far-side cut penetration and inadvertent injury to soft tissue structures. Additionally, they are technically straightforward to use and require no capital expenditure. Thus, patient specific cutting guides such may provide high value to the orthopedic oncologist and represent a promising simplification of intraoperative technology.

PAPER 47

Hip Joint Reconstruction is not necessary following Periacetabular Resection for Sarcoma

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Background: Periacetabular resections are among the most challenging of orthopaedic oncologic procedures. These operations frequently result in massive bone and soft tissue defects. One of the goals of oncologic surgery is to maintain function, and after a large pelvic resection restoring function is extremely challenging. Recently there has been a trend to leave the hip joint flail and forego a formal anatomic reconstruction due to purported shorter operative time, lower complication rates and similar function compared to hip joint reconstruction.

Purpose: The purpose of this study was to compare function and complication rates between reconstructed and non-reconstructed hips after large periacetabular resections for sarcoma.

Methods: We retrospectively reviewed 50 patients from a single centre between 1989 and 2014 who underwent a modified internal hemipelvectomy involving at minimum all of zone 2. The primary outcome measures were the Toronto extremity salvage score (TESS), the Musculoskeletal Tumor Society scoring system 1993 (MSTS 93), number of additional operations following the index surgery to manage complications and if the original hip joint reconstruction remained functional and in-situ at last follow-up.

Results: A total of 16 patients underwent periacetabular resection without reconstruction (mean follow-up 48 months, range 4-176), 19 were treated with a bulk allograft-prosthetic composite reconstruction (mean follow-up 123 months, range 2-324), and 15 patients received a saddle type prosthesis (mean follow-up 92 months, range 4-208). There were no significant differences in functional outcomes between the groups at mean follow-up of 90 months. The TESS score was 71.5, 65.4 and 64.3 for flail, allograft and saddle reconstructions respectively (p=0.391), and the MSTS score was 63.3, 46.5 and 63 (p=0.323). Of the flail patients, 15/16 had their 'reconstructions' intact at last follow-up, one conversion to external hemipelvectomy. In the allograft group only 6/19 patients retained their original reconstructions, three conversions to external hemipelvectomy. In the saddle group 10/15 patients had their original reconstructions in-situ with no conversions to external hemipelvectomy. The median number of additional operative procedures to manage complications was zero for the flail group (Range 0-22), three for the allograft group (Range 0-9) and zero for the saddle group (Range 0-8) (p=0.017 between flail and allograft, p=0.922 between flail and saddle).

Conclusion: In this series of large pelvic resections, periacetabular reconstruction provided no functional benefit but allograft reconstruction significantly increased the risk of post-operative complications requiring additional surgery. Though it may seem counter-intuitive that leaving a patient with a flail hip could result in a functional outcome similar to anatomic hip joint repair, the theoretical advantage of reconstruction may be offset by extensive resection of the periarticular musculature. Significant abductor dysfunction with a reconstructed hip may be just as dysfunctional as the leg length discrepancy resulting from a flail hip. Furthermore, medialization of the residual proximal femur in flail cases may help to offset some of the loss of abductor function. These factors, when combined with a higher rate of complications in the reconstruction group, may help to explain our findings. The results of this study support leaving the hip flail following periacetabular resection of large pelvic bone sarcomas.

PAPER 48

Comparison of Reconstruction versus No Reconstruction Following Acetabular Resection for Pelvic Chondrosarcoma

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Background: Limb salvage procedures have become the treatment of choice for most pelvic chondrosarcomas. Following resection of the acetabulum reconstruction of the hip joint can be complex and associated with a high rate of complications. Due to the high rate of complications and reported acceptable functional outcome without reconstruction, some treating surgeons choose not to perform a reconstruction; however there are few studies comparing the outcome of acetabular reconstruction versus no reconstruction.

Purpose: The aim of this study was to combine patients from two tertiary sarcoma centers with experience treating pelvic chondrosarcoma to compare the outcome of acetabular reconstruction versus no reconstruction in terms of patient function and complications.

Methods: Of 135 cases of surgically treated chondrosarcoma of the pelvis at our institution between 1996-2015, 74 (67%) involved the acetabulum, however 15 were treated with a hindquarter amputation and removed from the cohort. The remaining cohort (n=59, 54%) consisted of 39 males and 20 females; with a mean age at surgery of 52 (range 24-81) years and a mean follow-up of 9 (range 2-20) years. The most common tumor Grade was II (n=38, 64%) and a negative margin was achieved in 50 (85%) of patients, with the most common resection being an Enneking and Dunham Type 2/3 (n=28, 47%). Thirty-four (58%) patients underwent an acetabular reconstruction, most commonly a complex total hip arthroplasty (n=13, 38%) or a saddle prosthesis (n=13, 38%). Twenty-five (42%) patients were not reconstructed.

Results: When comparing groups, there was no difference in the mean age (P=0.47), proportion of males (P=0.10), mean tumor volume (P=0.76), proportion of high grade tumors (P=1.0), and number of positive margins (P=0.71). Likewise there was no difference in the type of resection performed (Table 1).

Following the procedure, 54 (92%) patients were ambulating; of these 16 (27%) were ambulating without gait aids. There was no difference in the proportion of patients ambulating following a reconstruction versus no reconstruction (P=0.64). Likewise there no difference in the proportion

of patients ambulating without the use of gait aids between groups (P=1.0). At the patients most recent follow-up the mean MSTS93 score was 58% (range 20-100%). There was no difference in the mean MSTS score between patients who were reconstructed versus those who were not (57% vs. 58%, P=0.92). When comparing the different techniques of reconstruction, there was no significant difference (P=0.13) comparing the mean MSTS93 for THA (65%) vs allograft (60%) vs. a saddle (47%), however patients with a THA had a significantly higher mean MSTS93 score compared to a saddle (65% vs. 47%, P=0.04).

Complications were common following the procedure, with 43 (73%) patients sustaining at least one postoperative complication. Patients undergoing a reconstruction were more likely to sustain a complication, (85% vs. 58%, P=0.03). There was no difference in the rates of wound complications (P=1.0) or deep infection (P=0.29), however patients undergoing a reconstruction were more likely to have a postoperative fracture of the ilium (P=0.01). One patient who was initially not reconstructed was converted to a complex total hip arthroplasty due to a painful pseudoarthrosis. Likewise one patient in the no reconstruction group underwent an external hemipelvectomy due to an external iliac artery rupture.

There was no difference in the 10-year overall survival (50% vs. 57%, P=0.70), local recurrence (70% vs. 77%, P=0.68) and metastatic disease (57% vs. 60%, P=0.86) between patients who underwent a reconstruction and those who did not.

Conclusion: Reconstruction following resection of the acetabulum is technically demanding. For certain patients reconstruction may provide some benefit, however the results of this study indicate there is no difference in functional outcome, ambulatory ability or disease free survival between patients who underwent a reconstruction and those who did not; however patients undergoing a reconstruction were at significantly increased risk of postoperative complications.

Table 1: Comparison of Patients Undergoing Reconstruction versus no Reconstruction Following Acetabular Resection for Chondrosarcoma of the Pelvis

	Reconstruction (n=33)	No Reconstruction (n=26)	P Value
Mean Age ± SD	51±14	54±13	0.47
Males	25 (75%)	14 (54%)	0.10
High Grade Tumors	7 (21%)	6 (23%)	1.0
Mean Tumor Volume ± SD	647±1,390 cm^3	747±888 cm^3	0.76
Positive Margin	6 (18%)	3 (12%)	0.71
Resection Type			
Type 2	4 (12%)	1 (4%)	0.37
Type 1, 2	1 (3%)	3 (12%)	0.31
Type 2, 3	16 (48%)	13 (50%)	1.0
Type 1, 2, 3, 4	4 (12%)	3 (12%)	1.0
Type 1, 2, 3	8 (24%)	6 (23%)	1.0
Type of Reconstruction			
Complex Total Hip	13 (39%)	n/a	n/a
Allograft Prosthetic Composite	7 (22%)	n/a	n/a
Saddle Prosthesis	13 (39%)	n/a	n/a
Functional Outcome of Surgery			

Mean MSTS 93	57±23	58±20	0.92
Ambulatory	31 (94%)	23 (88%)	0.64
Independent Ambulatory	9 (27%)	7 (27%)	1.0
Complications			
Any Complication	28 (85%)	15 (58%)	0.03
Wound Complications	14 (42%)	12 (46%)	1.0
Postoperative Infection	15 (45%)	8 (31%)	0.29
Ilium Fracture	7 (21%)	0 (0%)	0.01

PAPER 49

What is The Risk of Mortality following Local Chordoma Recurrence?

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Background: Sacrococcygeal chordomas have historically been treated surgically, with or without additional radiotherapy. However, even with negative margins and adjunctive therapies, there remains a high risk of local recurrence. Although essential for counseling, decision-making, and prognostication, the mortality risk of patients experiencing recurrence remains poorly described.

Questions:
  1) *What is the expected mortality of patients undergoing resection of a primary sacrococcygeal chordoma following local recurrence?*
  2) *How does the life expectancy of patients experiencing a local recurrence compare to patients without recurrence?*
  3) *What is the relationship between patient age, local recurrence, and mortality?*

Patients and Methods: 193 patients from four tertiary sarcoma centers undergoing resection of primary sacrococcygeal chordomas from 1990 to 2015 were reviewed. Mean patient age was 59 (range 13-88), with 124 males and 69 females and 89 patients received adjunctive pre- or postoperative radiotherapy. Patients were followed for a mean of 7 years (range 1 to 25). Cumulative incidence functions and competing risks regression for death due to disease and non-disease mortality were employed to analyze mortality trends following local disease recurrence.
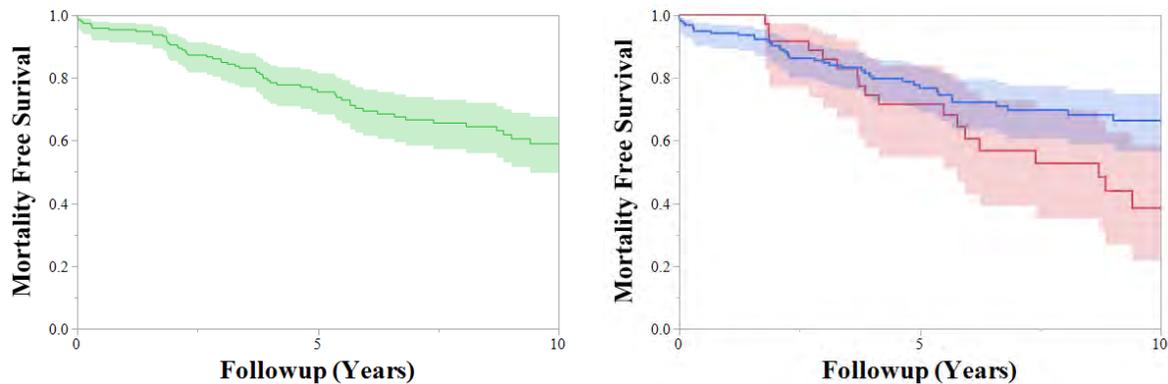
Results:
  1) *What is the expected mortality of patients undergoing resection of a primary sacrococcygeal chordoma following local recurrence?*
    Overall 2-, 5- and 10-Year survival for all 193 patients was 91%, 76%, and 59%, respectively (Figure 1A). During the course of follow-up, 36 patients (19%) experienced a local recurrence. Patients with local recurrence demonstrated 92% 2-Year survival, 72% 5-Year survival and 39% 10-Year survival (Figure 1B).

  2) *How does the life expectancy of patients experiencing a local recurrence compare to patients without recurrence?*
    Patients with local recurrence demonstrated statistically comparable (p = 0.10) survival to

those who did not experience local recurrence. However, a trend towards lower survival was noted over time for patients experiencing local recurrence, with 5% lower 5-Year survival and 38% lower 10-Year survival in the local recurrence free group (Figure 1B).
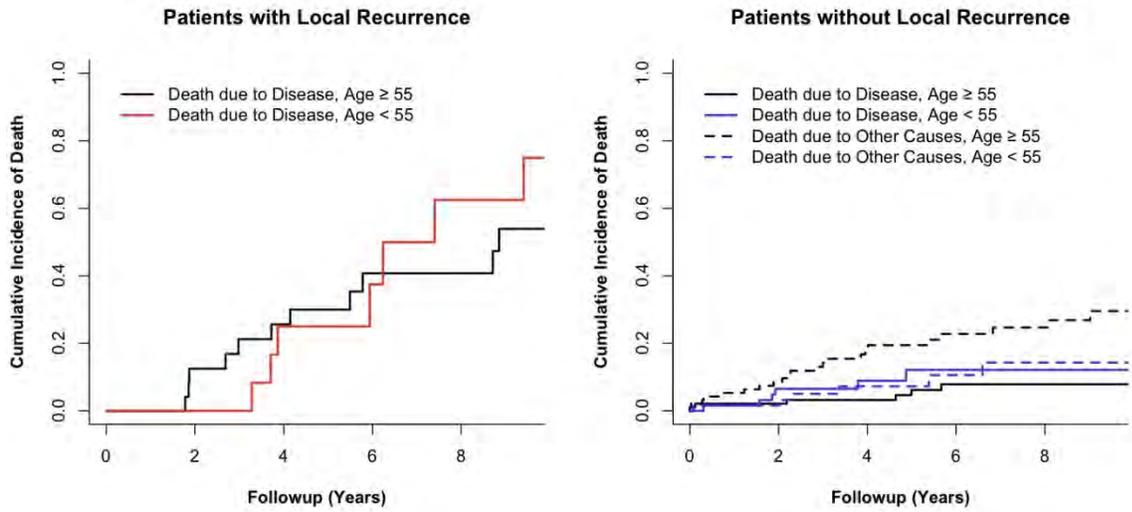
3) *What is the relationship between patient age, local recurrence, and mortality?*
All patients experiencing local recurrence and subsequent mortality experienced morality due to disease. For patients with local recurrence, age less than 55 years conferred similar mortality rates (2 Years: 0%, 5 Years: 25%, 10 Years: 75%) compared to patients $\geq$ 55 years (2 Years: 13%, 5 Years: 30%, 10 Years: 54%) (p = 0.82, Figure 2A). Amongst patients without local recurrence, patients under 55 years of age had similar risk of death due to disease compared to patients $\geq$ 55 years (8% at 10 years, p = 0.24). In contrast, patients $\geq$55 were 2.1-fold more likely to experience death due to other causes (30% at 10 years) than patients under 55 (14% at 10 years, p = 0.01, Figure 2B).

Conclusions: Patients with local recurrence following resection of a primary sacrococcygeal chordoma trended towards 38% higher 10 year mortality than those without recurrence. Mortality risk over time is similar in the setting of local recurrence, whether patients are young (< 55 years) or older ($\geq$ 55 years). For older patients without recurrence, death due to non-disease causes occurs over 2-fold more commonly than death due to disease, and should be taken into account during patient counselling and decision making.

Figure 1A-B: A) Overall mortality free survival for all patients undergoing resection of primary sacrococcygeal chordoma (Green). B) Mortality free survival for patients experiencing local recurrence (Red) and those without local recurrence (Blue).

Figure 2: Cumulative incidence of death due to disease and death due to other causes by patient age for A) Patients with local recurrence, and B) Patients without local recurrence.

PAPER 50

Factors Associated with 5-Year Survival in Chordomas: A National Cancer Database Study

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Background:
Chordomas are rare neoplasms that arise along the axial skeleton from persistent notochordal elements. Ideally, chordomas are managed with wide surgical resection; however, the location of these tumors makes it difficult to achieve negative margins and adjunct radiotherapy is commonly utilized. The paucity of these tumors makes it difficult to perform large reviews, and determinants of survival remain unclear. We investigated the largest registry of primary bone tumors, the national cancer database (NCDB), to investigate current treatment trends for chordomas and determine prognostic factors for survival. Our hypothesis was that surgical resection in addition to radiotherapy would be associated with improved survival.

Purpose(s):
1. To identify survival determinants for axial chordomas
2. To identify current treatment trends for chordomas, and the 5-year survival rates between different treatment modalities

Method:
We retrospectively reviewed 1456 patients in the NCDB from 2004-2015 with a histologic diagnosis of chordoma. Multivariate analysis was performed to determine survival determinants. The study variables included age, gender, race, insurance status, annual income, comorbidity index, high versus low volume surgical center, location of tumor, tumor grade, tumor size, surgical margin, radiation therapy. The Kaplan-Meier (KM) method with statistical comparisons based on the log-rank test was used to assess survival rates between individual variables.

Results:
The cohort included 1456 patients; including chordomas of the sacrum (n=563), the mobile spine (n=362), and the skull base (n=531). The overall 5-year survival rate was 75.7%. Skull base chordomas had a 5-year survival of 83.9%, which was significantly improved over chordomas of the sacrum (71.7%, p<0.001) and mobile spine (69.8%, p<0.001). Multivariate analysis

demonstrated significantly improved 5-year survival with age <65 years, income above national average, private health insurance, comorbidity index <2, histologic low-grade tumor, tumor size <5cm, location of tumor, surgical resection, and negative surgical margins. Radiotherapy was not associated with improved 5-year survival in the multivariable analysis.

Treatment of the chordomas included surgery alone (n=616), surgery and radiotherapy (n=526), and radiotherapy alone (n=115). The 5-year survival rates of surgery alone (79.9%) and surgery and radiotherapy (82.3%) were significantly improved over radiotherapy alone (36.5%, p<0.001). However, the difference between surgery alone and surgery plus radiotherapy did not reach statistical significance. Following surgical resection, achieving a negative margin was associated with improved 5-year survival compared to having a positive margin (84.8% v. 76.4%, p=0.005). Adjunct radiotherapy did not statistically improve survival in patients with a positive surgical margin, compared to no radiation (77.9% v. 73%, p=0.198).

Conclusion:

This study is the largest powered study investigating survival determinants in patients with axial chordomas. Surgical resection with a negative surgical margin provides the greatest 5-year survival rate in chordomas. Radiotherapy was not associated with improved survival in the multivariable analysis. Younger age, private health insurance, increased income, fewer medical co-morbidities, low grade tumors, tumor size < 5cm, skull base chordomas, and achieving negative surgical margins were significant factors for improved 5-year survival.
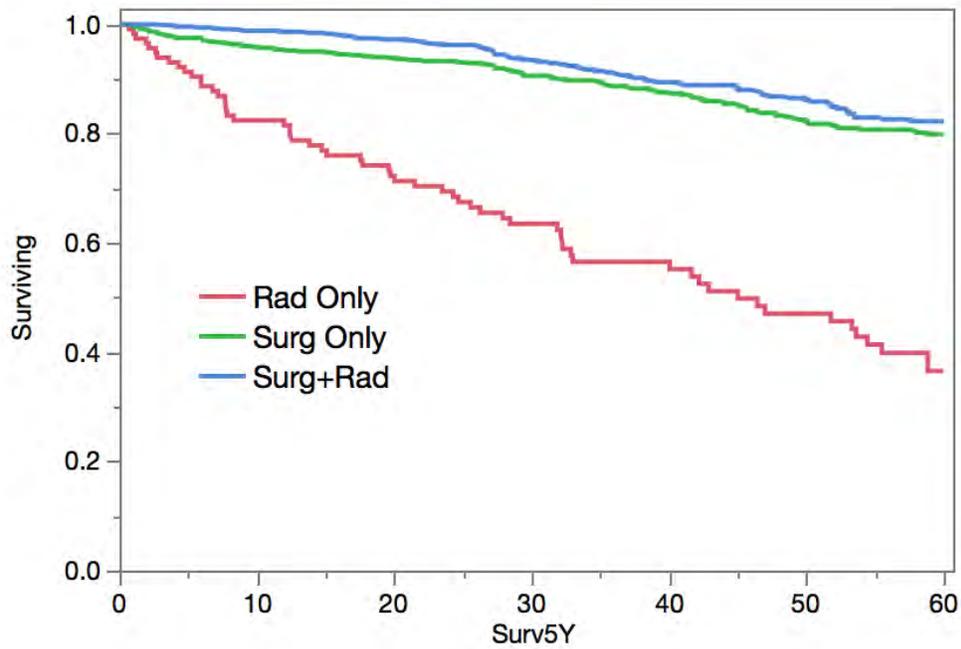
Table 1. Independent predictors of mortality in multivariate proportional hazards analysis

Variable	HR	Lower 95%	Upper 95%	P value
Patient variables				
Age (years) (Ref=0-45)	Ref			
45-65	1.37	0.97	1.94	0.07
>65	3.17	2.08	4.86	**<0.001***
Female sex (Ref=Male)	0.93	0.75	1.15	0.50
Hispanic (Ref=Non-Hispanic)	1.27	0.80	2.00	0.306
Race (Ref=Caucasian)				
African-American	0.83	0.49	1.41	0.50
Asian	0.81	0.48	1.39	0.45
Comorbidity Score >1 (Ref=0-1)	1.79	1.12	2.85	**<0.013***
Insurance (Ref=Private Insurance)				
Medicare	1.29	0.92	1.82	0.13
Medicaid	2.28	1.45	3.59	**<0.001***
No insurance	1.94	1.03	3.68	**<0.04***
Income below median ($48,000)	1.34	1.05	1.70	**0.01***
Tumor and treatment variables				
Grade (Ref=Low grade)				
Intermediate grade	0.75	0.37	1.54	0.44
High grade	2.29	1.26	4.17	**0.007***

Size of tumor (Ref <5cm)	1.78	1.33	2.39	**<0.001***
Surgery (Ref=No surgery)				
All types	0.45	0.32	0.60	**<0.001***
Local resection	0.48	0.34	0.67	**<0.001***
Radical resection	0.42	0.30	0.60	**<0.001***
Surgical margins positive	1.51	1.09	2.10	**0.014***
Radiation use	1.00	0.64	1.56	0.98
Location spine (Ref sacrum)	1.38	1.05	1.82	**0.019***

HR = hazard ratio; * indicates statistical significance ($\alpha = 0.05$)

Figure 1: Kaplan Meier Curve of Survival Based on Treatment Type

PAPER 51

Non-Surgical Outcomes In Multiple Myeloma Peri-Acetabulum Lesions

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Background: Multiple myeloma is a malignancy of the hematologic system very commonly affecting the skeletal system, with the incidence of periacetabular and pelvic involvement around 6% (1,2). Primarily managed with chemotherapy, novel agents have been used to improve the life span of patients with myeloma. Surgical methods can be used to address these pathologic lesions when symptomatic. The modified Harrington technique, is a commonly used method of successfully operatively treating painful metastatic lesions of the weight bearing acetabulum (3). Peri-acetabular reconstructions have high complication rates and are demanding procedures. Non-operative treatment with protected weight bearing and chemotherapeutic treatment of the underlying disease is another option for these symptomatic peri-acetabular lesions, little is known about non-operative treatment of these lesions.

Questions/Purposes: 1. Can multiple myeloma patients be non-operatively treated successfully for lytic lesions of the acetabulum in the weight bearing dome 2. For treated patients, determine the symptom (pain) duration, the healing time, period of protected weight bearing, chemotherapy regimen utilized and myeloma subtype.

Patients and Methods: Between 2006 and 2017, 7 patients with the mean age of 62 years (45 to 78) at presentation were treated non-operatively for weight bearing multiple myeloma lesions of the acetabulum. A retrospective review of all treated patients was performed, we excluded both operatively treated lesions of the acetabulum as well as interventional radiology cementoplasty treatment. Only patients with biopsy proven multiple myeloma were considered for this study. All patients had lesions in the weight bearing dome of the acetabulum and were symptomatic

Results: Average patient age at diagnosis of multiple myeloma with biopsy was 62.1 years. Our patient demographics were 2 Black patients (29%), 1 Hispanic patient (14%), and 4 White patients (57%). There were 3 female patient (43%), and 4 male patients (57%). The average acetabular lesions were 6.5 cm in the largest measured diameter on advanced imaging. The average symptom duration for 6 of the patients whose symptoms resolved with chemotherapy was 6.4 months. Eighty five percent (6/7) of the patients had complete resolution of the pain. One patient had some persistent pain, but it appeared to be secondary to arthritic changes in the hip. The average length of protected weight bearing was 4.5 months. For resolution of the acetabular lesions, 4 patients had complete resolution radiographically, whereas 3 of the patients had significant but incomplete resolution radiographically. Two patients were newly diagnosed with multiple myeloma at presentation, whereas 5 patients were referred with the diagnosis already established. Six patients were treated with VTD-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) chemotherapy protocol and 1 with a VTDA (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin) protocol.

Six patients (86%) had IgG Kappa light chain and 1 patient (14%) had IgG Lambda multiple myeloma subtype. None of the patients with acetabular lesions were treated with radiation. Conclusions: Whereas a few studies have looked at surgical treatment of peri-acetabular multiple myeloma lesions including large peri-acetabular reconstructions and percutaneous acetabuloplasty/cementoplasty, no studies have evaluated the non-operative treatment of these periacetabular lesions (3,4,5). In conclusion non operative treatment of multiple myeloma lesions in the weight bearing surface of the acetabulum is a very viable option with average protecting weight bearing of 4.5 months. This option avoids all the risks associated with surgical reconstruction.

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Invited Speaker Presentations

Paper 52

Degree of Osteosarcoma Differentiation Influences Tumour Response to BMP-2 Signalling

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Background: Impaired bone healing biology secondary to soft tissue deficits and cytotoxic chemotherapy contribute to non-union, fracture, infection and revision surgery following structural allograft reconstructions in osteosarcoma (OS) patients. Approved bone healing augments such as bone morphogenetic protein-2 (rhBMP-2) have great potential to improve osteosynthesis and mitigate these complications. rhBMP-2 use in sarcoma surgery is limited, however, due to theoretical concerns of pro-oncogenic signalling within the tumour resection bed. To the contrary, multiple recent pre-clinical studies demonstrate that BMP-2 may actually induce OS differentiation and limit tumour growth. Further pre-clinical studies evaluating the oncogenic influences of BMP-2 in osteosarcoma are needed.

Aim 1: To evaluate how BMP-2 signalling affects OS cell proliferation and metastasis both *in vitro* and within an active tumor bed.
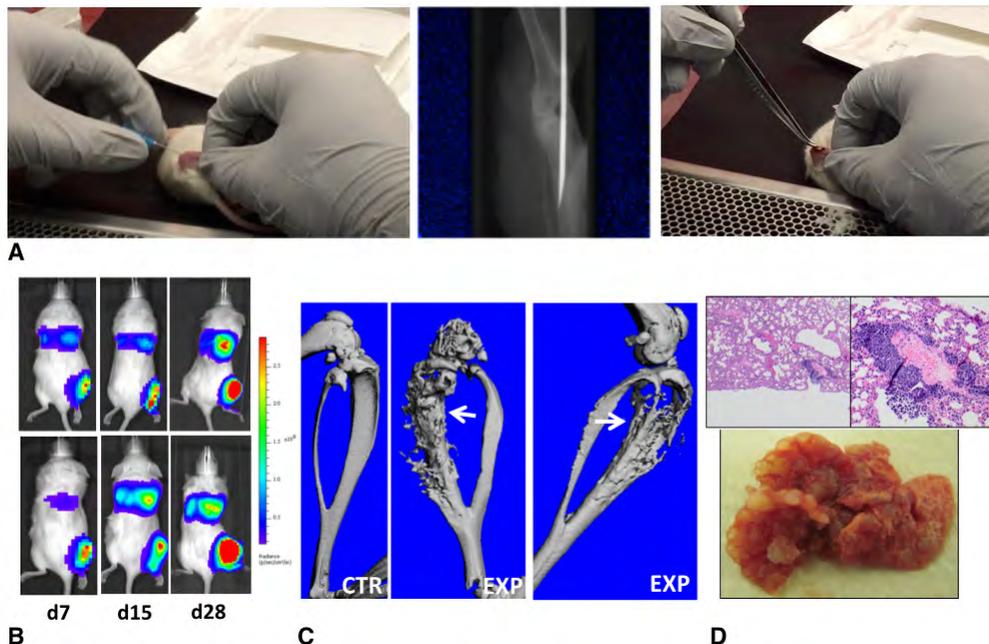
Aim 2: To delineate if tumor response to BMP-2 signalling is dependent on the degree of OS cell line differentiation.

Methods: An intratibial xenograft murine model of OS was utilized (Figure 1). A well differentiated OS cell line (SaOS-2) and a poorly differentiated OS cell line (143b) were assessed for proliferative capacity *in vitro* and *in vivo*. *In vitro* proliferation was assessed in the presence and absence of osteogenic differentiation media (ODM). OS cells were injected into the intramedullary proximal tibia of immunocompromised (NOD-SCID) mice, and a weight adjusted dose of rhBMP-2 was delivered to the active tumour bed on an absorbable collagen sponge (ACS) (Figure 1A). In separate experiments, 143b and SaOS-2 cells were also engineered to over-express BMP-2 to facilitate both *in vitro* and *in vivo* assessment of elevated BMP-2 signalling. Local tumour growth and metastases were assessed using weekly bioluminescence imaging (BLI) for 4-6 weeks (Figure 1B). At the experimental end point we assessed radiographic tumour burden using *ex-vivo* micro-CT (Figure 1C), as well as tibial and pulmonary gross and histologic pathology (Figure 1D).

Results: OS developed in 100% (21/21) of mice injected with 143b cells, and 74% (17/23) of mice injected with SaOS-2 cells. A diagnosis of OS was confirmed on histology. rhBMP-2
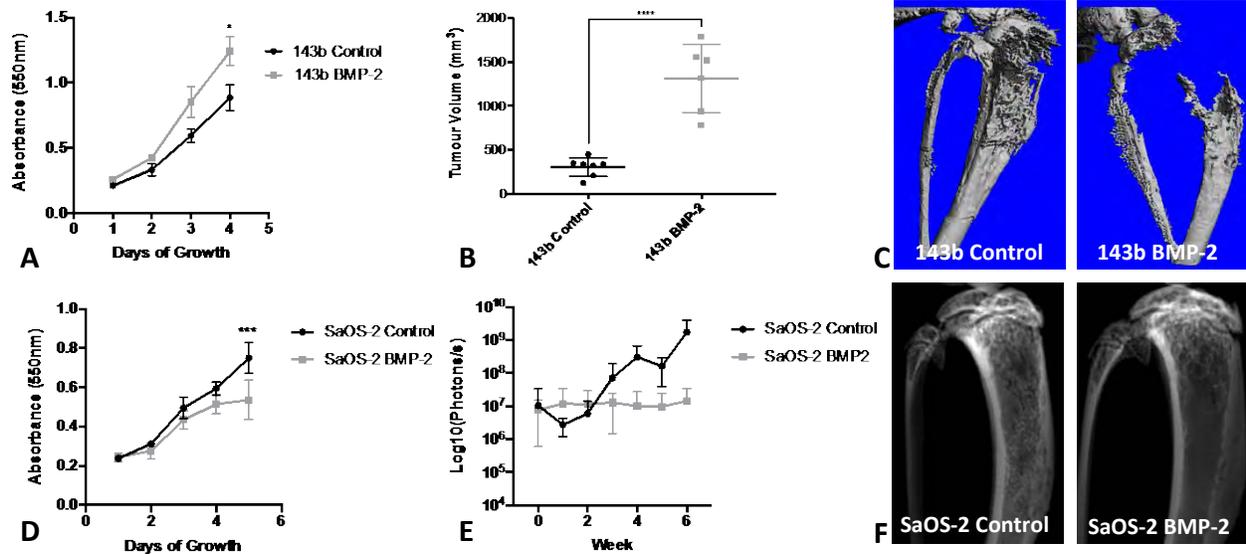
significantly potentiated local tumour growth in poorly differentiated OS (143b) tumours as assessed by tumour volume (p < 0.001). BMP-2 over-expression in 143b cells resulted in increased cellular proliferation *in vitro* (p = 0.014) (Figure 2A); an effect that was lost when grown in ODM (p = 0.65). Furthermore, in 143b tumours BMP-2 significantly increased tumour volume (p = 0.001) (Figure 2B) and enhanced osteolysis detected on micro-CT (Figure 2C) but did not affect rates of lung metastasis (67% vs. 71%, BMP-2 vs. Control). rhBMP-2/ACS application to mice harbouring well-differentiated OS (SaOS-2) tumours did not effectively alter tumour growth (p = 0.7). However, when grown in ODM, BMP-2 over-expression reduced SaOS-2 *in vitro* proliferation (p < 0.001) (Figure 2D). BMP-2 over-expression also reduced *in vivo* SaOS-2 tumour burden (p < 0.001) (Figure 2E) and decreased tumour-associated matrix deposition (Figure 2F) as assessed by bone mineral density (BMD, p = 0.034) and trabeculation (Tb.N, p = 0.019), but did not affect rates of lung metastasis (0% vs. 0%).

Conclusions: Using an intratibial murine model of OS we have assessed the impact of both endogenous and exogenous BMP-2 delivery to an active tumour bed. Our results suggest a differential impact of BMP-2 signalling on OS tumour biology, whereby BMP-2 signalling incites a proliferative effect on poorly differentiated OS cells but reduces proliferative capacity in a well-differentiated OS cell line. This dichotomous effect may be partially mediated by the osteoblastic differentiation of OS tumours, and the inherent ability for OS cells to undergo BMP-2 mediated terminal differentiation. These results do not support the clinical application of BMP-2 in OS limb salvage surgery due to the potential for stimulating growth of poorly differentiated OS cells within the tumour bed. rhBMP-2 is a pro-inflammatory growth factor; therefore, additional studies designed to assess the effects of BMP-2 in an immune-competent mouse model are currently ongoing. Furthermore, as BMP-2 led to a decreased tumour burden in a more differentiated OS model, further investigation into how BMP-2 can be coupled with other established OS differentiation therapies is warranted.

Figure 1. Experimental overview

(A) Osteosarcoma cell lines are injected in the proximal tibia. rhBMP-2 soaked absorbable collagen sponge is surgically implanted around the tibia after cell line injection. In separate experiments, Osteosarcoma cells engineered to over-express BMP-2 are injected into the proximal tibia. (B) Weekly bioluminescent imaging is used to monitor intra-osseous tumour growth and lung metastases. (C) Ex vivo microCT is used to visualize and quantify tumour-associated matrix deposition and osteolysis. (D) Lung metastases are assessed microscopically under low power and on gross examination of lung tissue.

Figure 2. BMP-2 signalling promotes 143b tumour burden, while limiting SaOS-2 proliferation. 143b cells over-expressing BMP-2 have increased cell viability during proliferation (A), increased tumour volume at 4 weeks (B), and increased tumour-associated osteolysis (C). BMP-2 over-expression in SaOS-2 resulted in a reduction of cell viability during proliferation when stimulated by osteogenic differentiation media (D), a reduction in *in vivo* proliferation (as assessed by tibial photon counts, E) and a reduction in tumour-associated matrix deposition (F).

Paper 53

Nanopiece Delivery of Nucleotide Therapeutics Inhibits Chondrosarcoma Progression

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Background: Chondrosarcoma remains the only primary bone cancer without an effective systemic treatment. Conventional cytotoxic chemotherapy is not effective, and patients typically succumb to pulmonary metastases. Another approach for systemic treatment is targeted therapeutics, which have yet to be fully developed. A promising translational approach is manipulation of misexpressed microRNAs. MicroRNAs are short, endogenous, non-coding RNAs that negatively regulate gene expression by promoting mRNA degradation or by translational repression through complementarity with sequences in the 3' UTR. In cancer, microRNAs can function analogous to tumor suppressors or as oncogenes (oncomiRs) when over- or underexpressed, the net effect dependent on the target genes. In prior work we identified miR-181a as an oncomiR in chondrosarcoma, that in turn upregulates VEGF and MMP expression and chemokine receptor (CXCR4) signaling. Systemic delivery of microRNAs and anti-miRNA oligonucleotides (AMOs) remains an unsolved problem. In order to translate our findings into a potential treatment, we have developed a Nanopiece (NP) platform that can be used to deliver nucleotide based therapeutics. Nanopieces are nanorods composed of biomimetic rosette nanotubes and nucleic acid therapeutics.

Questions/Purposes: Our purposes were to determine 1) if NP can deliver nucleotide sequences intracellularly to human tumor cells in vitro and in vivo, and 2) if NP carrying AMOs administered systemically inhibit expression of oncogenic microRNA, and thereby inhibit tumor progression in a murine tumor model.

Methods: Xenograft tumors in nude mice were generated with 1×10^6 CS-1 cells (a gift from Dr. Francis Hornicek). The Janus base nanotubes were dissolved in water and nanoparticles (NP) were generated by sonicating a mixture of AMO and nanotubes. Mice were treated with seven IV injections of NP$^{antimiR-181a}$ or NP$^{antimiR-control}$ over a three-week period starting two weeks after implantation of chondrosarcoma cells. Mice were evaluated with in vivo bioimaging (Florescence Molecular Tomography) for tumor angiogenesis and MMP activity. Tumors and lungs were harvested at 6 weeks or sooner if required by our IACUC protocol as determined by veterinary staff, who were blinded to treatment group. Total RNA and protein were extracted from tumors for qRT-PCR and ELISA analysis of key signaling molecules. Tumor size and

weight were measured and lung metastatic burden was quantified using microscopy. Data were analyzed with the Student's t-test or one-way ANOVA, followed by the Student's t-test with Bonferroni correction for individual comparisons. The null hypothesis of no difference was rejected at a significance level of 5%. Generalized linear models were used to compare bioimaging, tumor weight, and lung metastatic burden. The Wilcoxon weighted chi-square test was used to compare Kaplan-Meier survival functions of times-to-event outcomes.

Results: To determine whether NP can deliver nucleotide sequences intracellularly in vivo, a molecular beacon for GAPDH alone or carried by NP was administered by tail vein injection to mice bearing xenograft tumors. The molecular beacon only fluoresces after binding the intracellular target mRNA (GAPDH). Tumor fluorescence was only observed when the NP^{mbGAPDH} was used, indicating NP can deliver nucleotide sequences intracellularly. When xenograft tumors were directly injected with NP$^{anti-miR-181a}$ miR-181a expression was reduced to 52% of control. In mice treated with 7 doses of NP$^{anti-miR-181a}$ miR-181a was reduced to 46% of control in the xenograft tumor ($p<0.01$). In prior work, we found that RGS16 is a direct target of miR-181a, and that diminished expression of RGS16 enhances CXCR4 signaling, which culminates in MMP1 and VEGF expression. In these treated mice, RGS16 mRNA expression was restored ($p<0.01$), MMP1 mRNA expression decreased ($p<0.04$) and both MMP1 and VEGF protein content decreased ($p<0.01$; $p<0.03$). Florescence Molecular Tomography *in vivo* imaging indicates decreased MMP activity in the tumors ($p<0.02$); angiogenesis was not significantly affected. Tumor weight was reduced by 25% ($p<0.04$). There was a reduction in the ratio of lung sections with tumor that approached statistical significance ($p<0.06$), and survival as measured by days to forced euthanasia was increased ($p=0.05$). Taken together, the results indicate that the systemic delivery of NP$^{anti-miR-181a}$ inhibited tumor progression.

Conclusions: These data support that miR-181a is a therapeutic target in chondrosarcoma and that Janus base nanopieces may be developed for a clinically relevant nucleotide delivery platform for cancer treatment.

Paper 54

Mithramycin A Inhibits Proliferation and Radiosensitizes EWS:Fli1^{+} Ewing Sarcoma

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Introduction: Ewing sarcoma (EWS) is the second most common bone tumor that typically occurs in adolescents and young adults. The fusion oncogene EWS:Fli1 results from reciprocal chromosomal translocation (11; 22)(q24; q12) joining the *EWSR1 gene* on chromosome 22 to the Friend leukemia virus integration site1 (Fli1*)* gene on chromosome 11, and is present in more than 85% of EWS cases. Mithramycin A (MithA) is a DNA binding RNA synthesis inhibitor that blocks the EWS:Fli1-mediated transcription of pro-survival and DNA damage repair genes. Thus, we hypothesized that combing MithA with ionizing radiation could radiosensitize EWS cells and increase cytotoxicity.

Objective: To evaluate the potency of MithA against seven EWS cell lines, and to determine whether MithA could radiosensitize EWS cells in vitro.

Methods: Seven EWS cell lines were obtained from Children's Oncology Group (TC-71, CHLA25) or American Type Culture Collection (A673, RD-ES, SK-ES-1, Hs822.T Hs863.T. Dose-response cell viability assays were conducted across a range of MithA (500 to 0.12 nM) dilutions. Effects on cell viability were performed to determine IC50 values. Radiosensitivity in the presence or absence of MithA was determined by clonogenic survival assays following exposure to 225kVp x-rays at 1.2Gy/min. Cells were pre-treated with IC50 doses of MithA or vehicle for one hour prior to exposure to 0,1,2,4,6, or 8Gy radiation. Western blotting was performed with RIPA lysates to compare levels of several phosphoproteins associated with DNA damage response, including pATM, pH2AX, p-p53, pBRCA1 and pChk2.

Results: MithA effectively suppressed the growth of EWS:Fli1^{+} tumor cells at the average of half maximal inhibitory concentration (IC_{50}) of 13nM. Whereas cell lines lacking this fusion oncogene with average IC_{50} of 343nM. Furthermore, when combined with ionizing radiation, MithA showed a significant radiosensitizing effect. Mechanistic experiments suggested that MithA achieves radiosensitization by inhibiting DNA repair and/or blocking cell cycle arrest and may lead to tumor cell death by mitotic catastrophe instead of an apoptotic mechanism.

Conclusions and Discussion: We have found that MithA selectively inhibited growth of EWS:Fli1$^+$ tumor cells relative to fusion negative cells. Also, MithA enhanced radiation-induced DNA damage in EWS:Fli1$^+$ cells, demonstrating synergistic radiosensitization. Finally, MithA suppressed survival mechanisms (DNA repair and cell cycle arrest) induced by DNA damage, suggesting the potential for complementary action with other DNA-damage-inducing agents used in treating EWS.

Paper 55

Demonstrating Osteoinductivity in a Decellularized Xenograft Bone Substitute

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Background: Management of large bone defects resulting from tumor resection remains a major clinical challenge to musculoskeletal orthopaedic oncologists. Autologous bone grafting is the gold standard treatment; however, due to morbidity and limited supply, alternatives have been used. Allograft is a commonly employed alternative; however, due to the risk of disease transmission tissue engineering substitutes have garnered increased attention. The ideal properties for any bone graft include osteoinductivity, osteogenicity, and osteoconductivity. The most elusive of these properties is osteoinductivity, which is defined as the ability to stimulate primitive cells to develop into a bone forming lineage.

Questions/Purpose:
1) Demonstrate osteoinductive potential of a porcine bone scaffold after undergoing a novel decellularization and oxidation process *in vitro*.
2) Prove osteoinductive properties of a porcine bone scaffold after undergoing a decellularization and oxidation process *in vivo*.
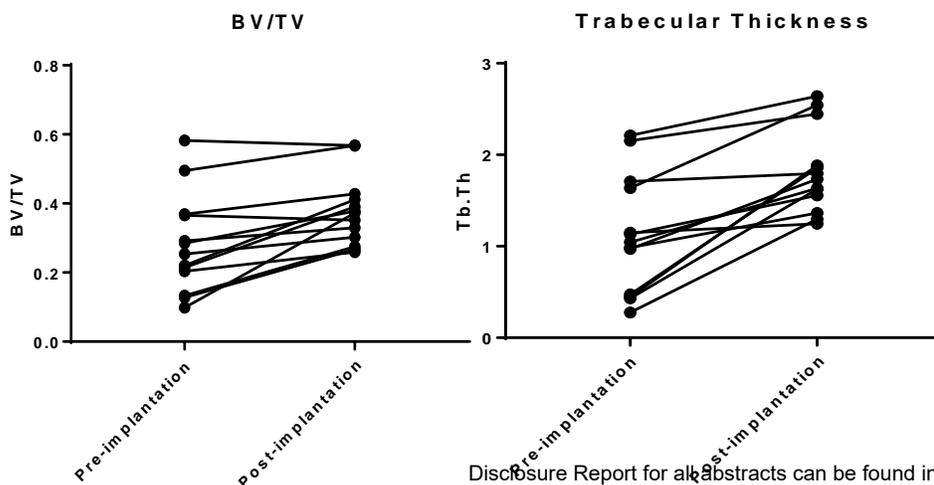
Patients and Methods: Undifferentiated cells (c2c12 pre-osteoblasts) were seeded onto the XG for 15 days and then analyzed with confocal microscopy and scanning electron micrographs at serial time points. For comparison against a similar commercial standard, cells were also seeded on cancellous demineralized bone matrix (DBM). DNA quantification was performed on a sub-set of the seeded XG to identify alkaline phosphatase (ALPh) enzyme activity and real time polymerase chain reaction (rt-PCR) to measure gene expression of markers of early osteogenic differentiation (RunX2, ALPh, and Collagen 1). Next a second line of undifferentiated cells (MC3T3 pre-osteoblasts) were seeded and incubated on the XG for 7 days and compared to a control monolayer for gene expression of different osteoblast markers using quantitative PCR (ALPh, and bone morphogenetic protein (BMP)-7). To demonstrate cell viability and osteoinductivity *in-vivo,* the XG with and without MC3T3 cells were subcutaneously implanted in Black-6 mice for 4 weeks. The XG underwent micro-computerized-tomography (microCT) scanning before implantation. Upon explantation the XG were analyzed for gene expression of

osteoblast markers (ALPh, receptor activator of nuclear factor κ B ligand (RANK-L), BMP-2, and BMP-7) or microCT scanned to assess new bone formation and subsequent histological assessment with Russel-Movat Pentachrome staining and immunohistochemical (IHC) staining for antibodies against osteopontin (OPN) and ALPh to identify active bone remodeling. Multiple group comparisons were performed using one way ANOVA, t-tests were performed on independent means when comparing two groups, and paired t-tests were used when comparing paired groups. Statistical significance was determined when α error was less than 0.05.
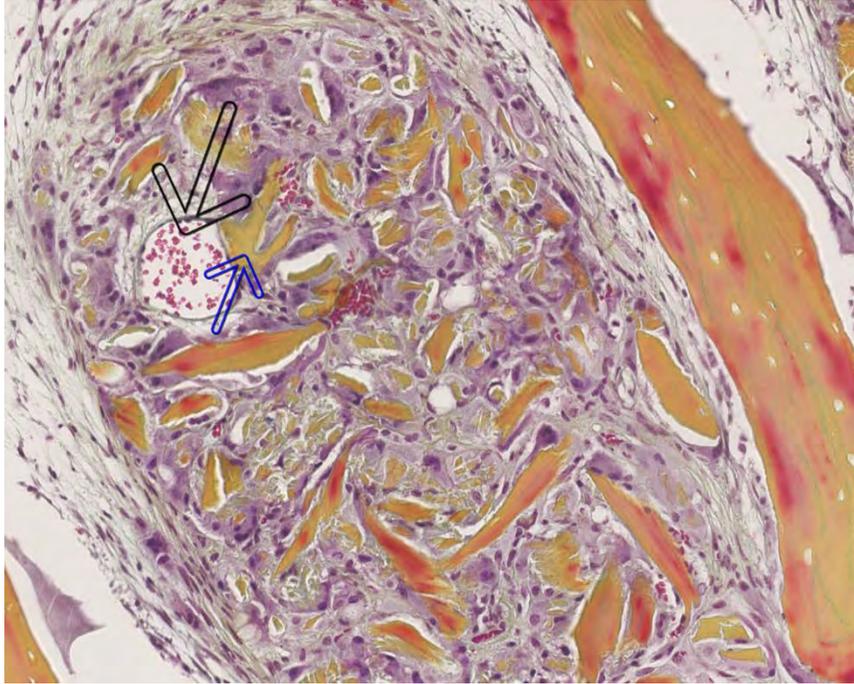
Results: The c2c12 pre-osteoblasts seeded onto the scaffold for 15 days proliferated and deposited extracellular matrix components identified on imaging. Molecular studies showed that seeded cells had significant increases in ALPh enzyme activity at day 7 and 15 ($p<0.0001$). Furthermore, collagen 1, ALPh and Runx2 expression increased with cell incubation time and peaked at day 7 on both bone XG and DBM matrices. The XG pre-seeded with MC3T3 cells *in vitro* demonstrated expression of ALPh significantly greater compared to a monolayer ($p=0.0021$); however, bone BMP-7 was not. *In vivo* expression of ALPh, BMP-7, and BMP-2 was increased within the pre-seeded XG; however only ALPL was significant ($p=0.0009$). Furthermore, RANK-L gene expression was equal between the two groups. MicroCT data demonstrated a greater increase in change in bone volume:total volume (BV/TV) and trabecular thickness (TbTh) in the pre-seeded XG; however, only TbTh reached significance ($p=0.03$). Paired t-tests showed significantly increased BV/TV ($p=0.0013$) and TbTh ($p=0.0002$) after explantation in both groups indicating new bone formation, regardless of cell seeding (Figure 2). Pentachrome staining demonstrated vascular infiltration and new bone formation (Figure 2). Furthermore, IHC analysis of these XG demonstrated positive staining for osteopontin and ALPh.

Conclusion: Osteoinductive potential was demonstrated in a xenograft bone scaffold after undergoing a novel decellularization and oxidation process *in vitro* and these properties were confirmed with *in vivo* experiments demonstrating new bone formation. Previous literature in this area has identified one of the pitfalls for tissue engineered bone replacements is the inability to vascularize, integrate and undergo remodeling; therefore, we believe this construct has potential clinical implications due to the demonstrated vascularization and new bone formation. Further research must be performed using this construct within a defect model to assess osteointegration and overall bone remodeling.

Figure 1: Bone volume and trabecular thickness both increase between pre-implantation and explantation signifying new bone formation within the xenograft.

Figure 2: Pentachrome staining demonstrating new vessel formation (black arrow) and new bone formation (blue arrow)

Paper 56

Clinically relevant tumor-initiating cells in patient-derived xenograft (PDX) models of bone cancers

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Background: Most cancer research to date has relied on *in vitro* and *in vivo* model systems that are inefficient and are frequently unsuccessful in attempts to translate findings to the clinic. Historically, it has been difficult to characterize metastasis *in vivo*, as culture cell line-derived animal models recapitulate neither the original tumor heterogeneity nor the specific metastasis patterns of the disease. Moreover, a significant hurdle in the treatment of metastatic bone disease is that the development of therapeutic agents is often based on targets identified primary cancers. *Hypothesis:* Tissue heterogeneity and increased genomic instability confer metastatic advantage to certain clones during oncogenesis; the tumor microenvironment also plays a crucial role. We hypothesize that failure of targeted therapies and emergence of therapy-resistant clones is dependent on cancer type and are also specific to metastatic sites, possibly in a patient-specific fashion. Here, we describe our novel approaches to developing patient-derived xenograft (PDX) models from human specimens of bone metastases and rare bone cancers and our use of these models to recapitulate the tumor microenvironment and patterns of metastasis. We have also isolated and characterized tumor initiating cells (TICs), tumor exosomes, tumor stromal cells, and TIC spheroids, with the aim of developing them as tools for future study of metastatic bone disease.

Methods: We generated PDX models using freshly resected specimens from prostate, breast, and kidney cancer patients with bone metastases, as well as rare tumors of mesenchymal cell origin such as osteosarcoma, Ewing sarcoma, and uveal melanomas. PDXs were generated by transplanting freshly resected tumor tissues in the flanks of immunocompromised mice. The resulting tumors were harvested, dissociated in collagenase Type A, and later characterized via stem cell antibody-binding, evaluated via spheroid-forming ability *in vitro*, used in generating additional PDXs through injection at orthotopic sites, and used for screening small-molecule inhibitors as described previously (Rajasekhar et al., 2011; Bakhoum et al., 2018). Tumor stromal cells were also isolated and characterized for molecular crosstalks with TICs (Sansone et al., 2016, 2017). Through collaboration with nanotechnology experts, we developed precisely targetable nanoparticles (Shamay et al, 2018). Exosomes were isolated from fresh human tumor tissue specimens that were minced and incubated for overnight explant culture in antibiotic-

supplemented RPMI. The media was collected and centrifuged to remove cellular debris, followed by serial centrifugation and ultracentrifugation to form the exosome-containing pellet. The pellet was resuspended for BCA protein quantification and Nanosight microscopic visualization. Exosomes were analyzed via mass spectrometry as described (Hoshino et al., 2015). Secondary metastases in the PDX models were localized by luciferase activity imaging of lentiviral vector-expressing fluorescent marker-luciferase fusion protein. Osteosarcoma metastases were radiolabeled and imaged via PET scans following tail-vein injections of [^{89}Zr]-DFO-Pritumumab, a monoclonal antibody that targets vimentin expressed on mesenchymal tumors. The metastatic tumors could be clearly visualized at 24h post-administration and tumor signal relative to background increased with time.

Results: We have successfully developed PDX models and isolated TICs from prostate and breast cancer bone metastases, as well as Ewing sarcoma. TICs were confirmed by their ability to form self-renewing spheres in vitro and tumor initiation ability *in vivo*, which are the functional characteristics of TICs. We found these cells are enriched with the expression of known cancer stem cell markers, such as TRA-160, Sox9, and EpCAM in epithelial-tumor-derived TICs, such as from prostate cancer, and CD44, CD99, and others in mesenchymal-derived TICs, such as from Ewing sarcoma. In osteosarcoma PDX models, we successfully recapitulated metastasis to lung and visualized localization of the metastatic tumors to the lung. In addition, we observed the enhanced metastatic ability of PDXs generated in humanized mice with immunocompromised control mice. Using mass spectrometry, we profiled the exosomes for specific markers. Exosomal integrins α6β4 and α6β1 were associated with lung metastasis, while exosomal integrin αvβ5 was linked to liver metastasis. We also completed a preliminary immunoprofiling data analysis of patient bone tumors and tumors from the PDXs.

Conclusions: Our generation and study of PDX models offer novel avenues to identify TICs, their functional mechanisms, and crosstalks with stroma for clonal evolution during metastasis. Our TICs derived from orthotopic models will be valuable assets to develop organ-specific targetable nanoparticles in a humanized environment. Exosome profiling data can help predict future metastatic sites in patients. The tumor stroma offers an invaluable opportunity to understand the role and targetable functions of patient specific tumor microenvironments. These models will be useful to optimize nanotechnology for targeted delivery of functional therapeutics to stroma and/or the TICs. The abovementioned spheroid assays can be exploited to develop novel compound screening strategies.

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Paper 57

Precision medicine: big data analysis of breast cancer gene expression to predict metastasis to bone

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Background: Metastatic growth of breast cancer frequently occurs in bone, and the more than 200 bones serve as the largest reservoir of advanced cancers in humans. Skeletal metastases, which have a significant osteolytic component, cause pain, pathologic fractures, hypercalcemia, and neurologic deficits. Although skeletal metastases are known to have devastating effects, the molecular mechanisms underlying aggressive bone destruction and tumor metastasis to bone are poorly understood. It is still unclear why only certain patients develop skeletal metastasis. The purpose of this study is to identify genes that control cancer-induced destruction of bone and those that increase the metastatic potential of cancer cells for use in the prediction of skeletal metastasis and idenfication of new therapeutic targets. These genes will be identified through xenograft model studies, as well as analysis of clinical and gene expression datasets.

Questions/Purposes: Why do breast cancers exhibit preferential metastasis to bone? What factors induce osteolytic characteristics in breast cancer metastases to bone?

Materials and Methods:

1. *Aggressive bone destruction model*: To identify the genes involved in aggressive bone destruction, we injected 4 different human breast cancer cell lines (MCF7, MDA-MB157, MBA-MB231, and HCC1806) and human mammary epithelial cells (hMEC) into the breast and tibiae regions of nude mice. At 4 weeks, we measured tumor size and bone destruction using radiographs.

2. *Patient and gene expression data*: All clinical information and gene expression data were retrieved from the GEO database (http://www.ncbi.nlm.nih.gov/geo) and Array express (https://www.ebi.ac.uk/arrayexpress). Raw data were preprocessed using Robust Multi-array Average for normalization. E-MTAB-783 was used to investigate the differential expression of genes from cell lines that displayed non-aggressive and aggressive bone destruction. GSE2043

(n=284) was used as the training data set. GSE2603 (n=82) and E-MTAB-365 (n=115) were used as validation data sets.

3. *Development of the aggressive bone destruction signature*: The supervised method was used to identify the differential expression of genes from cell lines that displayed non-aggressive and aggressive bone destruction with the significant level of the univariate t-test set to less than 0.01. These genes were used to develop a classifier for predicting bone metastasis using BRB-ArrayTools with the leave-one-out cross-validation method (LOOCV).

4. *Validation of the prognostic signature*: Validation of the gene signature was accomplished using an independent dataset containing clinical outcomes and gene profiles. The compound covariate predictor was utilized as a class prediction algorithm. Kaplan-Meier survival analyses, Chi-square and log-rank tests were used to evaluate predicted metastatic risks for two subgroups of patients.

5. *Pathway and transcription factor analysis*: Pathway and transcription factor enrichment analyses were carried out using Metacore (https://portal.genego.com). The *p* value <0.05 was used to identify significant pathways and transcription factors.

6. *Human Pathological Specimens*: We examined whether transcription factors controlling the genes of interest were present in breast cancer cells (N=12) from pathological fracture sites.

Results: We found that MDA-MB231 and HCC1806 cells showed aggressive bone destruction and increased tumor size at 4 weeks in the xenograft model. However, no tumor growth in bone was observed in hMEC, MCF7, or MDA-MB157 cells (Fig. 1A). Forty-four probesets of 40 genes found to be significantly different between cell lines with non-aggressive bone destruction and those with aggressive bone destruction were identified (Fig. 1B). The gene signatures developed from these 40 genes is predictive of bone metastasis-free survival in both the training dataset (*p*=0.006, Fig. 1D) and validation datasets (*p*=0.036, Fig. 1E). Transcription factor analysis revealed that the 40-gene signature is significantly affected by CREB, c-Myc, Sp1, Oct-3/4, ESR1, and RelA. Most importantly, 4 weeks after inoculation with MDA231 cells, levels of CREB, the transcription factor most significantly impacting the 40-gene signature, dramatically increased in cancer cells in the tibia, compared to those in the breast. In addition, IHC analysis showed that CREB was expressed only in aggressive breast cancer cells in the tibia, but not in normal breast tissue, tibial tissue, or breast cancer cells in breast tissue of nude mice. In human metastatic breast cancer tissue, CREB was overexpressed, and no CREB staining was observed in cancer-free human bone.

Conclusions: We have demonstrated that the metastasic gene signature identified in this study is a useful tool to predict the bone metastatic outcome, suggesting the general utility of this classifier in an era of precision medicine. We recommend the use of this gene signature as a molecular diagnostic test to assess the risk of metastasis to bone in breast cancer patients. In addition, the 40 genes identified through this study can be analyzed to identify new therapeutic targets for preventing skeletal metastasis and improving clinical outcomes.
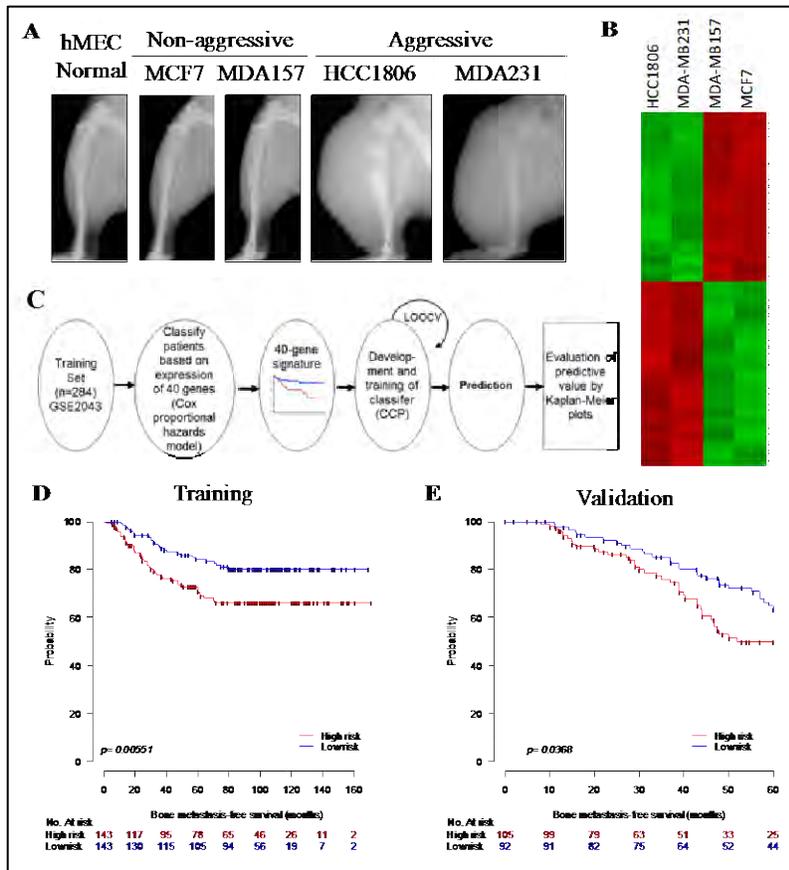
Figure 1: Development of the aggressive bone destruction gene signature of various breast cancers. (A) Radiographs of nude mouse tibia 4 weeks after injection with hMEC or breast cancer cell lines (N=3). (B) Heat map of genes with significantly different expressions between aggressive bone destruction cell lines (MDA MB 231 and HCC1806) and non-aggressive bone destruction cell lines (MCF7 and MDA MB 157). Genes were selected based on the two-sample t-test with an adjusted p-value (FDR) cutoff of 0.01. (C) Schematic overview of the strategy was used to develop the prediction model and evaluation of predicted outcomes in independent datasets by the 40-gene signature. (D) Kaplan-Meier plots for bone metastasis-free survival of two risk groups in the training dataset. (E) Validation datasets were classified by the 40-gene signature into low and high risk and evaluated by Kaplan-Meier analyses. The *p* values were computed by a log-rank test.

Paper 58

Defining optimal administration time and tissue contrast ratios required for margin assessment in soft-tissue sarcomas using an EGFR-targeting fluorescence probe

Authors:
Eric Henderson, MD; Brent Bates, MSc; Jason Gunn, BS; Keith Paulsen, PhD; Brian Pogue, PhD; and Kimberley Samkoe, PhD

Introduction and Purposes:
Successful sarcoma treatment generally requires wide local tumor excision. Current operative techniques for sarcoma resection—reliance on pre-surgical imaging and visual/tactile cues—are unchanged over decades and often unsuccessful at achieving clear tumor margins. Targeting agents utilizing near-infrared (NIR) fluorescence have gained momentum for identifying tumor tissue during surgical guidance. Our group has performed preclinical testing in a rodent sarcoma xenograft model to determine optimal administration and tissue contrast ratios in anticipation of an epidermal growth factor receptor (EGFR)-targeting NIR fluorophore (ABY-029), which was approved by the FDA as an exploratory Investigational New Drug (eIND 122681). Here, we describe our preclinical work preparatory to a first-in-human, Phase 0 trial of ABY-029.

Methods:
Gelatin tissue phantoms were created using a variety of intralipid (scattering medium; 0.5 and 1%) and blood (absorption medium; 0, 0.5, 1, and 2%) to mimic the physical and optical properties of sarcomas and the normal tissues generally surrounding the tumor (muscle, fat, connective tissue). These phantoms were used to study required Tumor-to-Background Ratios (TBR) of tumor-mimicking inclusions in varying sizes and depths in normal tissue mediums. Determining the optimal time point for surgery after administration of intravenous ABY-029 to achieve TBR > 2 was undertaken in a panel of sarcoma xenograft tumors (SK-NEP-1, SW-982, MG-63, VA-ES-BJ, and SK-L-MS1) with known, varying EGFR expression. ABY-029 uptake and distribution in the xenograft tumors and normal mouse tissues monitored for up to 24 hours post-administration.

Results:
We determined that inclusions as deep as 3 cm could be detected using broad-field fluorescence imaging when the tissue background recapitulated that of normal connective tissue. The ability to excise a tumor with 1 cm margins was assessed using large tissue phantoms with a sarcoma mimicking inclusion and varying levels of fluorescence in the surrounding phantom to achieve TBRs of 1, 2, 3, 5, and 10. In this blinded-surgeon study, removal of phantom material to attain negative tumor margins was successful for TBR >3. It was found that a suitable TBR was

achieved between the sarcoma tumors and normal background tissues at time points greater than 2 hours, however, highest TBRs were encountered 4-8 hours after injection.

Conclusions:
We were able to perform successful wide-local excision of tissue-simulating phantom tumors using fluorescence guidance alone with a TBR ≥2. We obtained TBRs ≥2 in all sarcoma xenografts when fluorescence imaging was performed >2 hours after ABY-029 administration. Based on these successes, we will proceed with a Phase 0, first-in-human trial of ABY-029 to assess binding success in EGFR+ soft-tissue sarcomas.

PAPER 59

Risk factors in Tenosynovial Giant Cell Tumours, evaluated in 17 international sarcoma centers

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Objective
Tenosynovial Giant Cell Tumour(TGCT), previously Pigmented Villonodular Synovitis(PVNS), is a rare, locally aggressive neoplasm. Two types are distinguished: localized- and diffuse-TGCT. A multicenter-pooled database of individual patient data is essential to evaluate risk factors for recurrent disease.

Study design
Individual patient data from 17 sarcoma centers are the base of this international multicenter retrospective cohort study with histologically proven TGCT of large joints, between 1990-2016.

Methods
Out of 1156 collected cases, 875(522 female, median age at operation 36(range 6-89)years) are included with complete information. Median follow-up is 47.2(95%CI 43.0-52.2)months. 329 of 534 affected knees are diffuse-type, 72% primarily treated with open resection; 196 localized-type, 82% primarily treated with open resection.

Results
Total number of first recurrence is 381(44%). Number of recurrences in the knee, are for diffuse-type 222(58%) and localized-type 30(8%). Mean time from primary surgery to operation for local recurrence is 36.2(95%CI 32.9-39.5) months. At final follow-up 630(72%) patients show no evidence of disease (173 alive with disease, 8 death of other disease, 64 lost). 5-year recurrence free survival of all TGCT-patients is 51%(95%CI 47-55), in diffuse-type 41%(95%CI36-46); localized-type 75%(95%CI 68-82).
In univariate analyses, recurrences occurred significantly more frequent in diffuse-TGCT(p<0.001), male patients(p=0.04), the knee(p=0.01), arthroscopic-resection(p<0.001) and in recurrent patients(p<0.001). A significant higher risk(p<0.01) for recurrence in multivariate analyses was calculated in diffuse-type HR2.75(95%CI1.66-4.55), arthroscopic resection HR2.86(95%CI1.56-5.26) and recurrent patients HR2.42(95%CI1.46-4.03).

Conclusions
Risk factors of first local recurrence in TGCT are diffuse-type after arthroscopic resection and after previous tumour-surgeries.

Relevance for MSTS
Identification of risk factors for recurrent disease is necessary to define eligible patients for (new) systemic and (neo)adjuvant treatment possibilities in TGCT.

Keywords
Tenosynovial Giant Cell Tumor, TGCT, Pigmented Villonodular Synovitis, PVNS, risk factors, international multicentre study, EMSOS+ study

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Table 1: **Univariate analysis** of clinical, pathologic and treatment variable for progression free survival in patients with TGCT
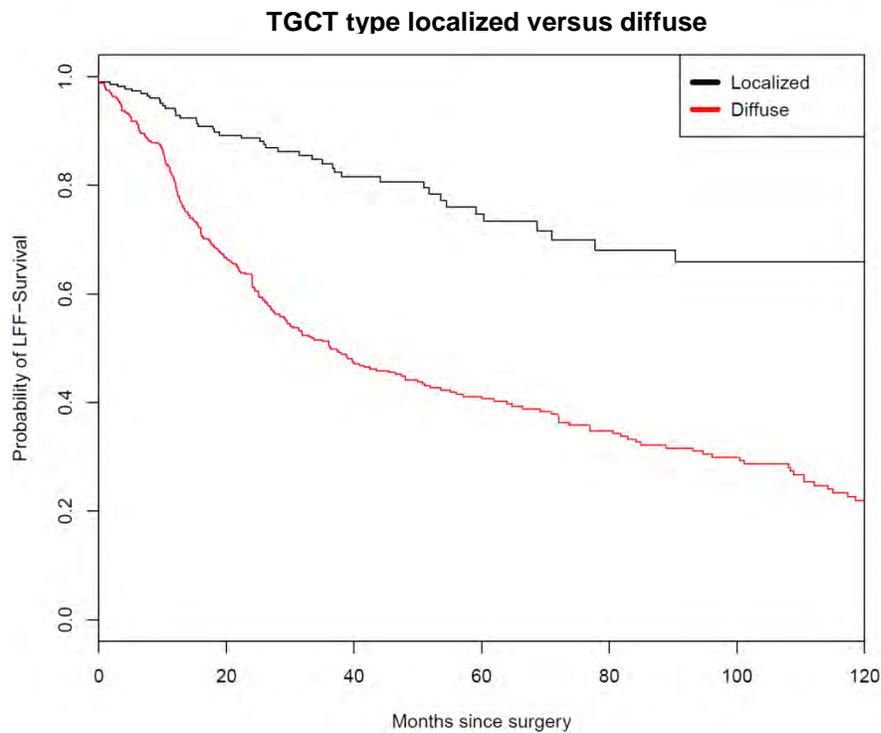
		Pts no	PFS5	95%CI	P
Overall		875	51	47-55	
Type	Localized	307	75	68-82	**<0.001**
	Diffuse	549	41	36-46	
Age	<18	63	45	32-64	0.40
	18-65	782	51	47-55	
	>65	30	65	47-89	
Gender	Male	353	46	40-53	**0.04**
	Female	522	54	49-60	
Joint	Knee	534	46	41-52	**0.01**
	Hip	66	51	40-67	
	Ankle	137	62	52-73	
	Other	137	57	48-69	
Size	≤2cm	60	56	39-80	**0.01**
(451 pts)	2-5cm	149	75	66-85	
	≥5cm	242	59	52-67	
Bone involve.	No	404	55	50-62	0.66
	Yes	136	56	47-66	
Surgical tech.	Arthroscopy	133	21	14-31	**<0.001**
	Open	666	60	55-64	
Admission	Primary	648	64	59-69	**<0.001**
	Recurrent	206	25	19-32	

Pts no = number of patients, PFS5 = Progression Free Survival at 5 year, P = p-value.
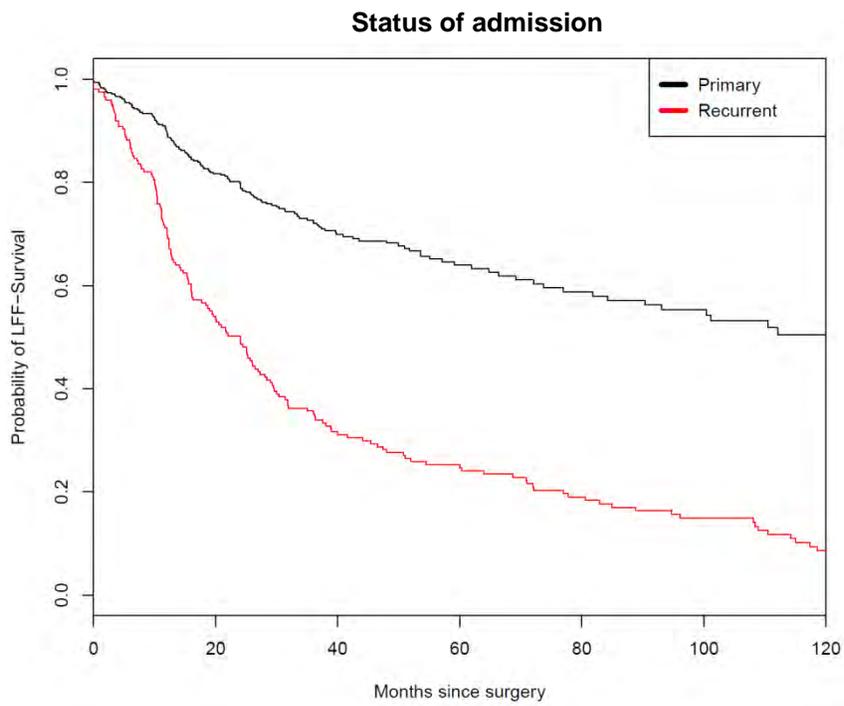
Table 2: **Multivariate analysis** of clinical, pathologic and treatment variable for progression free survival in patients with TGCT, using significant variables from univariate analysis and covariates without multiple missing values (size).

		HR	95%CI	P
Type	Localized	1		
	Diffuse	2.75	1.66-4.55	**<0.01**
Gender	Male	1		
	Female	0.77	0.52-1.13	0.18
Joint	Knee	1		
	Hip	1.10	0.60-2.00	0.76
	Ankle	0.76	0.43-1.34	0.34
	Other	0.56	0.28-1.11	0.10
Surgical tech.	Arthroscopy	1		
	Open	0.35	0.19-0.64	**<0.01**
Admission	Primary	1		
	Recurrent	2.42	1.46-4.03	**<0.01**

HR = Hazard ratio, P = p-value.

Figure 1: Progression free survival localized- versus diffuse-type.

Status of admission

Figure 2: Kaplan Meier primary- versus recurrent patients.
LFFS = Local Failure Free Survival.

PAPER 60

Occupational Injuries Among Orthopaedic Oncology Surgeons

Authors: Abdulrahman Alaseem, Krista Goulding, Robert Turcotte, Nathalie Ste-Marie, Mohammad Mesfer Alzahrani, Saad Al-Qahtani

Background:
Orthopaedic oncology is a demanding subspecialty that deals with complicated cancer patients and involves complex surgical procedures. Physical and psychological stressors may place surgeons at a higher risk for work-related occupational injuries and ultimately affect the delivery of care.

Purpose:
The purpose of this study was to assess the prevalence and characteristics of occupational injuries among orthopaedic oncology surgeons.

Method:
A modified version of the physical discomfort web-based survey was developed to assess occupational injury among orthopaedic oncology surgeon members of the Musculoskeletal Tumor Society (MSTS), the Canadian (CANOOS) and European Musculoskeletal Oncology Societies (EMSOS). The cross-sectional survey queried musculoskeletal complaints by region, psychological disturbances, as well as treatment and required time off work. Sixty-seven surgeons responded.

Results:
The overall prevalence of occupational injury among orthopedic oncologists was 56 of 67 surgeons, or 84% (musculoskeletal 76%; psychological 50%; and both 43%). The most prevalent musculoskeletal diagnoses were low back pain (39%), lumbar disk herniation (16%), tendinitis (15%), lateral epicondylitis (13%) osteoarthritis and varicose vein (10% each). Overall, 46% required surgery and 31% required time off work. Psychological disorders were reported by 33 respondents overall; the most prevalent were burnout (27%), anxiety and insomnia (20% each) and depression (11%). Older age (OR=2.66, 95%CI: 1.34, 5.29, p=<0.01) and more years in practice (OR=2.97, 95%CI: 1.42, 6.22, P=<0.01) were independently associated with time required off work.

Conclusion:
Orthopaedic oncologists report a high prevalence of occupational injury. Low back injury and burnout are the most commonly reported work-related disorders. Strategies optimizing the operative environment and preventative measures for work-related stress should be the focus of future initiatives.

PAPER 61

The Role of Denosumab in Joint Preservation for Patients with Giant Cell Tumour of Bone: Not a Magic Bullet?

Authors: David L Perrin, Julia D Visgauss, David A Wilson, Anthony M Griffin, Peter C Ferguson, Jay S Wunder

Purpose: The standard treatment for giant cell tumor of bone (GCTB), a locally aggressive osteolytic condition, remains extended intralesional curettage. Local recurrence continues to be a challenging dilemma for the orthopaedic oncologist treating GCTB, despite the use of surgical adjuvants. We previously reported the local recurrence rate for GCTB following extensive intralesional curettage at our institution to be 12-14%. Denosumab is a monoclonal antibody that competitively inhibits RANK ligand, interrupting the osteoclastic activating pathway responsible for the extensive osteolysis seen in GCTB. Initially Denosumab was suggested for management for unresectable GCTB; however recent interest has led to its increased use as neoadjuvant therapy for operable disease. In this setting, the goal of treatment is to facilitate joint salvage procedures via consolidation of periarticular and subchondral bone in otherwise difficult to resect tumors, as well as to decrease recurrence rates. We previously reported early results in a series of 20 consecutive patients with high risk GCTB treated with neoadjuvant Denosumab, with a local recurrence rate of 15% at a mean of 16 months. The goal of this study was to present updated mid-term follow-up results and to determine if the initial favourable results of Denosumab treatment were sustained.

Methods: Data was collected from our institute's prospectively collected bone tumour registry. All patients with GCTB considered 'high risk' for unsuccessful joint salvage, due to minimal residual periarticular bone, large soft tissue mass or pathologic fracture, were treated with both neoadjuvant Denosumab and extended intralesional curettage were included. Data including anatomical lesion site, surgical reconstruction method, local recurrence and development of metastasis during follow-up were analyzed.

Results: Twenty-five patients with high risk periarticular GCTB were treated with neoadjuvant Denosumab followed by surgical resection with extended curettage between January 2012 and March 2016. The mean average time to follow-up was 33.7 months. 48% of patients were female and the mean average patient age was 33.8 years. The tumour occurred most commonly around the knee in 17/25 cases (68%). The joint was successfully salvaged in 24/25 patients. One patient required a knee replacement due to a displaced intra-articular fracture associated with arthritis. Local recurrence developed in 7/25 patients (28%). One patient developed lung metastases which have been successfully controlled with Denosumab.

Conclusion: Although the early results of a clinical trial of neoadjuvant treatment of GCTB with Denosumab were optimistic, further follow-up demonstrated a higher than expected rate of local recurrence at 28%. While Denosumab leads to an increase in osseous consolidation which facilitates joint preserving surgery, the multi-loculated nature of the new bone matrix may trap stromal tumor cells thereby causing difficulty to determine the true margins of the tumor during intralesional curettage. Although Denosumab continues to have a role in maintenance therapy for patients with unresectable GCTB, its neo-adjuvant usage should be considered with caution in light of these results.

PAPER 62

Oncologic and Functional Outcomes after Treatment for Desmoid Fibromatosis of the Extremities

Authors: Erik Newman, MD[1]; Jonathan Lans, MD[1]; Jason Kim, BS[1]; Marco Ferrone, MD[2]; John Ready, MD[2]; Joseph Schwab, MD[1]; Kevin Raskin, MD[1]; Santiago Lozano Calderon, MD PhD[1]

Institutions: Departments of Orthopaedic Surgery, Massachusetts General Hospital[1] and Brigham & Women's Hospital[2]

Introduction: Desmoid fibromatosis of the extremities is a challenging clinical entity. The ideal treatment strategy has not been elucidated, and the impact of treatment on symptoms and function is not well understood.

Questions: We set out to identify tumor- and treatment-specific variables associated with event-free survival (EFS) in patients with primary and recurrent desmoid tumors of the extremities. Utilizing patient-report survey instruments, we also sought to describe these patients' symptomatic and functional outcomes.

Methods: Patients treated for desmoid fibromatosis of the upper and lower extremities (excluding tumors of the hands and feet) between 1991 and 2017 at two cancer centers were reviewed; those with oncologic follow-up of at least 6 months were included and were contacted for administration of 2 validated self-report instruments (PROMIS Physical Function and Upper Extremity short forms) and a questionnaire, unique to this study, that asked patients to assess their symptomatic and functional outcomes. Episodes of treatment for recurrent tumors were analyzed in a pooled fashion, wherein treatment episodes for patients with multiple recurrences were included separately as independent events. EFS was defined as time to treatment failure (disease recurrence or clinically-significant progression).

      Bivariate EFS analyses were performed for patients with primary and recurrent tumors, with the following variables: treatment group (local therapy, LT; systemic therapy, ST; local plus systemic therapy, L+ST); age at treatment; tumor volume, girdle location (axilla or buttock / pelvis), depth, and nerve involvement; margin status; and receipt of radiation therapy. Treatment group, and other covariates with p-values <0.1 in bivariate analyses, were included in multivariate Cox proportional hazards models.

      Patient self-report data were analyzed with descriptive statistics. PROMIS function scores (Physical Function or Upper Extremity, as appropriate) were compared with non-parametric testing with respect patient- and treatment-specific variables.

Results: Data were analyzed for 96 patients with sufficient follow-up, including 62 primary tumors, 103 discrete episodes of treatment for recurrence, and 40 patients who completed survey
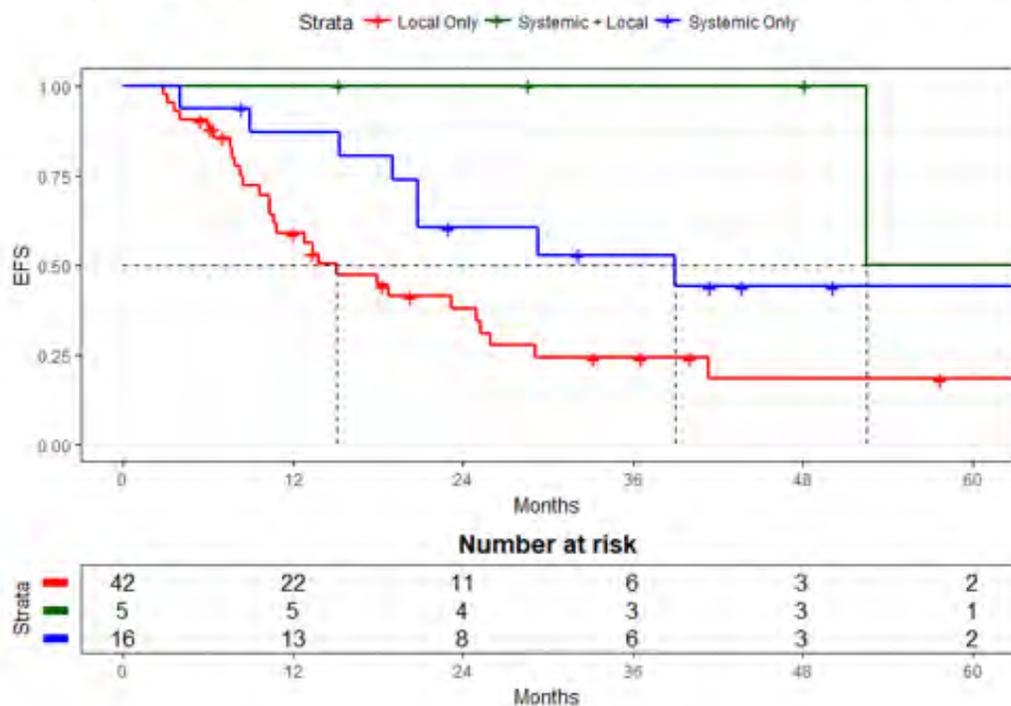
instruments, at median follow-ups of 63, 60, and 116 months, respectively. The 5-year EFS for treatment of primary tumors was 18% after LT, 44% after ST, and 50% after L+ST (Fig. 1). In the primary tumor multivariate analysis, only girdle location was a significant predictor of treatment failure (HR 2.51, 95% CI 1.22-5.16, p = 0.012), though there was a trend towards improved EFS after L+ST (adjusted HR 0.18, 95% CI 0.02-1.37, p = 0.097). When analyzing outcomes for treatment of recurrence, EFS was also lowest following LT (LT, 55%; L+ST, 65%; ST, 69% at 5 years), though not significantly so. Only tumor volume ≥ 100cm^3 was significantly associated with worse outcomes in the recurrence multivariate model (HR 3.39, 95% CI 1.54-7.44, p = 0.0024). Nearly 70% of recurrence treatment episodes occurred within 5 years of initial diagnosis and nearly 90% occurred within 10 years of diagnosis.

Analysis of questionnaire data suggested that most patients would choose to undergo treatment again, including 83%, 69%, and 59% who would again opt for surgery, chemotherapy, or radiation therapy, respectively. However, only 48% and 52% of surveyed patients felt that treatment resulted in any improvement in pre-diagnosis pain and overall symptoms, respectively; only 23% reported improvement in pre-diagnosis numbness or tingling; and only 40% and 48% felt that treatment improved their overall quality of life and physical function, respectively. Mean PROMIS function scores were significantly lower among patients who underwent more than one resection (39 vs. 51, p = 0.0065) and among those who received *both* surgery and radiation at any point (38.5 vs. 47, p = 0.0096) (Table 1).

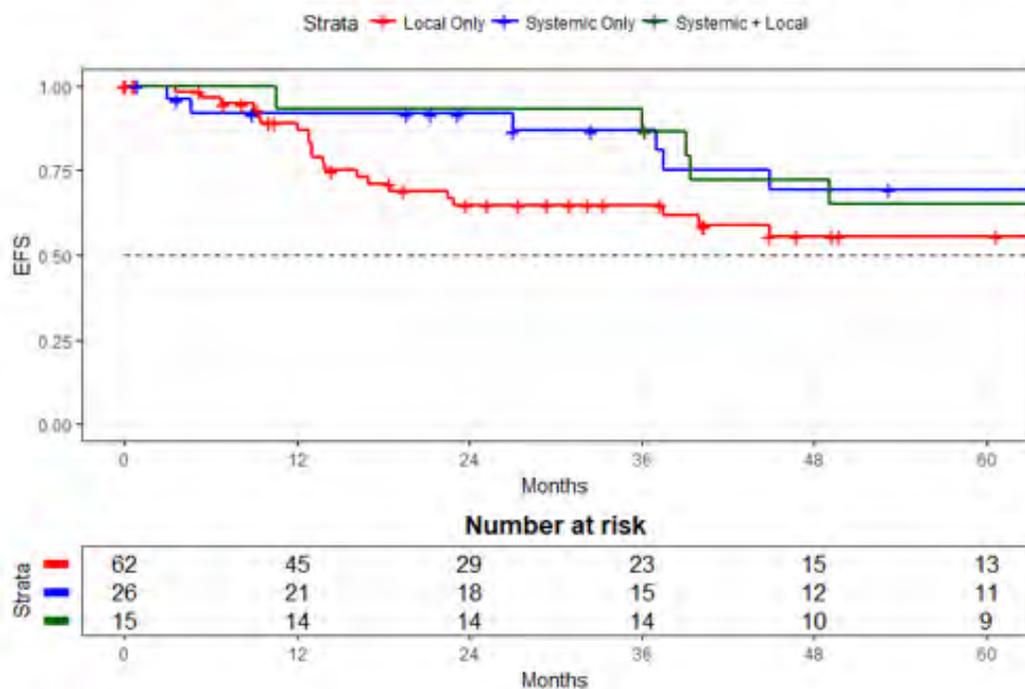**Conclusions:** Recurrence rates are high after treatment for desmoid fibromatosis. Axillary and buttock / pelvic primary tumors and large (≥ 100cm^3) recurrent tumors were significantly associated with worse event-free survival; there was a trend towards improved outcome after local plus systemic treatment for primary tumors. Per patient-report data, the impact of treatment on symptoms and quality of life was fair at best, and PROMIS data suggested that more aggressive local treatment was associated with worse functional outcomes. It may be the case that desmoid tumors "burn out," regardless of treatment modality, within 5-10 years of diagnosis. The goal of treatment should be to shepherd patients through this period with a focus on maximizing symptom management and minimizing morbidity.

Figure 1.

Event-Free Survival after Treatment for Primary Tumors by Treatment Group

Strata + Local Only + Systemic + Local + Systemic Only

Event-Free Survival after Treatment for Recurrence by Treatment Group (Pooled Treatment Episodes)

Strata + Local Only + Systemic Only + Systemic + Local

Table 1. PROMIS Outcomes Data according to Patient- and Treatment-Specific Variables

	n (patients with available survey data)	PROMIS function metric score†	p-value*
Age at diagnosis (years)			0.18
<35	19	45.6	
≥35	21	41.0	
Location - girdle			0.85
Non-girdle	28	43.1	
Girdle (axilla or pelvis/buttock)	12	43.5	
Location - upper extremity			0.060
Lower extremity	20	46.4	
Upper extremity	20	40.0	
Tumor volume††**			0.45
<100 cm³	17	46.5	
≥100 cm³	20	42.6	
Nerve involvement††**			0.20
No	24	45.8	
Yes	13	41.1	
Tumor depth††			0.056
Superficial to fascia	7	51.3	
Deep to fascia	33	41.5	
Total # desmoid resections			**0.0065**
0	3	46.9	
1	11	52.1	
≥2	26	39.0	
Treatment with both radiation and surgery at any point			**0.0096**
No	21	47.4	
Yes	19	38.5	
Disease status at final follow-up			0.86
No evidence of disease	26	43.1	
Disease stability	11	42.7	
Disease progression	3	45.9	

†The PROMIS Physical Function SF 10a was utilized for patients with lower extremity tumors and the PROMIS Upper Extremity SF v2.0 7a was utilized for patients with upper extremity tumors. PROMIS instruments are calibrated such that a score of 50 corresponds to the mean for the general population, with a standard deviation of 10; higher scores correlate with improved function.
*p-values calculated with non-parametric tests (Wilcoxon rank-sum or Kruskal-Wallis, as appropriate).
††Tumor volume, depth, and nerve involvement at time of presentation to our institutions.
**Tumor volume and nerve involvement data unavailable for 3 patients each.

PAPER 63

Cost Analysis for Patients Treated for Bone and Soft Tissue Sarcomas: Index Admissions and Readmissions

Authors
Gabriel S. Makar BS, Karina W. Lo BS, Christina J. Gutowski MD MPH, John Gaughan MS PhD MBA, Tae Won B. Kim, MD

Background
Patients treated for bone and soft tissue sarcomas by orthopaedic oncologists are associated with increased risk of medical and surgical complications. However, reimbursements for their care remain relatively low. The expected cost of a single episode of care for a patient with a bone and soft tissue sarcoma is not well-defined in the literature, whereas the arthroplasty literature has established the mean cost of a primary joint replacement to be $$56,000 - $60,000 A better understanding of the costs exerted by orthopaedic oncology patients on the healthcare system can facilitate a more appropriate reimbursement strategy.

Questions/Purposes
The purposes of this paper were to (1) calculate the mean cost of an index admission in patients surgically treated for a bone or soft tissue sarcoma, (2) calculate the mean cost of planned and unplanned readmissions, and (3) identify risk factors associated with admission and readmission costs.

Methods
A retrospective review was conducted of patients treated for a bone or soft tissue sarcoma at a single, tertiary-level hospital between January 2012 and December 2016. An index admission was defined as radical resection or wide excision of the tumor, with or without reconstruction. If a patient had an admission for either one of the two procedures outside the 90-day readmission window, the admission was considered a new, distinct index admission. A planned readmission was defined as those readmissions which were pre-planned for a medical or surgical reason such as chemotherapy. An unplanned readmission was defined as those which were unexpected medical or surgical complications. Univariate and multivariate regression analysis was used to analyze demographic information, oncologic data, comorbidities, and admission/readmission details to identify factors associated with cost of index admissions and readmissions. Lastly, analysis of how much individual factor contributed to the overall cost was performed.

Results
232 distinct index admissions from 173 patients occurred. 27% (62) and 73% (170) of admissions were for bone and soft tissue sarcomas respectively. 145 readmissions, both planned and unplanned, occurred in 108 patients. 29% (42) and 71% (103) of readmissions occurred in patients with bone and soft tissue sarcomas respectively.

The mean cost of an index admission for bone sarcomas was $123,943 (range $379-$560,792), and soft tissue sarcoma was $49,588 (range $537-$442,608). This increased cost of $74,355 was statistically significant (p<0.001). The mean cost of a planned and unplanned readmission within 90 days after treatment for a bone sarcoma was $20,084 (range $399-$8,252) and $87,650 (range $8,092-$354,768) respectively (p<0.02). Comparatively, the mean cost of a planned and unplanned readmission after treatment for a soft tissue sarcoma was $28,364 (range $1,429-$189,294) and $73,448 (range $5,293-$502,267) respectively (p<0.02).

On multivariate regression analysis, factors associated with an increased cost of the index admission were treatment of bone sarcomas, number of days in the ICU and hospital length of stay (Table 1). 19/173 patients (11%) had an ICU stay, with a mean of 3.8 days (range 1-9 days). Each day in the ICU increased the cost by $6,147. The average length of stay in the hospital for all patients was 4.2 days (range 1-41 days). Each day in the hospital was associated with a $7,550 increase in cost. Risk factors associated with higher cost in readmissions were those that were unplanned and patients who had unplanned surgeries.

Conclusion
Compared to available arthroplasty literature, the cost of an inpatient admission for a patient treated for a bone sarcoma nearly doubles that of a total joint replacement patient. Treatment for a soft tissue sarcoma is not as costly as a bone sarcoma, but cost nearly as that of a total joint arthroplasty. Overall, orthopaedic oncology patients represent a high-risk population that place a considerable economic burden on the healthcare system. In light of these findings, the authors suggest re-evaluation of the reimbursements for the treatment of bone and soft tissue sarcomas.

Table 1. Factors Associated with Increased Index Admissions Costs after Multivariate Analysis		
Variable	**Critical Value**	**P-Value**
Bone Tumor	3.21	0.0017
ICU* Days	3.18	0.0018
Length of Stay	15.57	<0.0001

ICU* - Intensive Care Unit;

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Oncology patients are high cost outliers in bundled payments for total joint replacement

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Background:
On April 1, 2016, the Centers for Medicare and Medicaid Services (CMS) began its first mandatory bundled payment program, Comprehensive Care for Joint Replacement (CJR) model in place of the prior fee-for-service model.[1–4] Under this bundled payment model, hospitals are held financially accountable for the quality and cost of a 90 day episode of care.

Although bundled payments models have been shown to reduce health care costs, this new bundled payment model does not account for the patient's socioeconomic status or diagnosis.[4–7] The majority of elective hip and knee arthroplasty is performed for degenerative osteoarthritis (OA) in relatively healthy, active patients. However, arthroplasty procedures are also done in patients with primary or metastatic tumors around the hip or knee, who are complex, non-optimized patients. Oncology patients often require longer operations and modular endoprostheses for reconstruction. These patients are more likely to experience postoperative complications, and longer lengths of inpatient and post-acute care hospital stays. Under the CJR model, hospitals are reimbursed using very broad procedural designations, not for what or whom they are treating.

The focus of current bundled payment literature has been on cost reduction in post-acute care, and has not addressed factors associated with increased total episode costs as it relates to the Medicare beneficiary, including the influence of specific diagnostic categories.

Purpose:
The purpose of this study is to determine whether patients enrolled in the CJR bundle undergoing total joint replacement for primary bone tumors or metastatic disease incur higher hospital costs than patients with primary osteoarthritis.

Patients and methods:
A retrospective review was performed on all patients enrolled in the CJR bundled payments system from April 1, 2016 to December 31, 2017 at a single academic medical center. All patients enrolled had both Medicare A and B as their primary payor and were discharged under Medicare Severity-Diagnosis Related Group (MS-DRG) 470 (major joint replacement) or 469 (major joint replacement with major complications or comorbidities).

Patient information and data related to hospital stays was abstracted from chart review. Data related to the hospital course was provided by our hospital's financial services department including length of stay, day of discharge, discharge destination, and total hospital costs.

To determine whether tumor patients had higher total hospital costs, this group was compared to patients diagnosed with primary osteoarthritis using a two-tailed t test. To adjust for known or suspected moderators of total hospital costs, we then performed a multiple linear regression with significant variables identified in bivariate models.
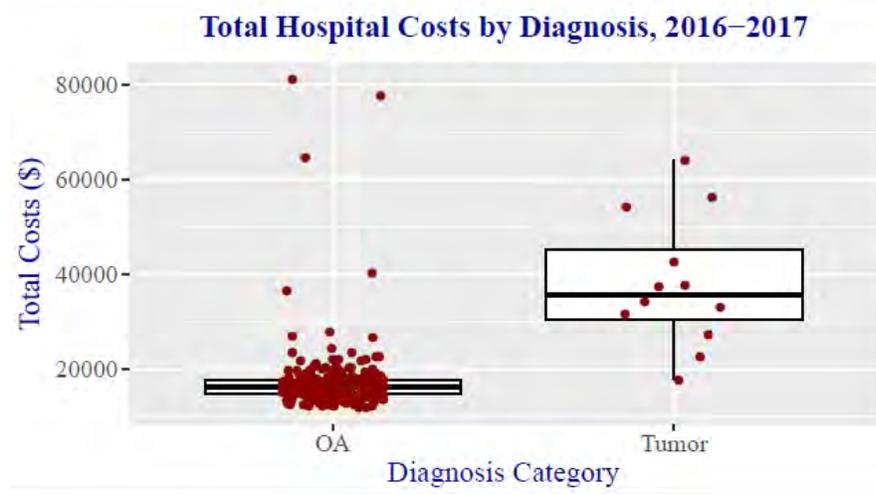
Results:

303 patients met inclusion criteria. Of these, 12 had undergone a joint replacement for primary or metastatic tumor, and 291 for osteoarthritis. Tumor and OA patients differed with respect to age (76 vs 70.7, p=0.03) but not gender (0.4 vs 0.4, p=1.00). Length of stay was greater in the tumor group (6.6 vs. 2.1 days, p=<0.0001). In bivariate models, age and gender were not associated with increased hospital costs (p=0.50 and p=0.13, respectively). A greater percentage of tumor patients were discharged to a SNF (67% vs 29%, p=0.008). Overall, discharging a patient to a skilled nursing facility was associated with higher costs ($2616, p=0.01), as was each additional day in the hospital ($4000, p<0.0001).

The mean tumor patient had $38,017 in hospital costs compared to $16,970 in the OA group, a statistically significant difference of over 200 percent (Figure 1) (p<0.0001).

Multivariate regression yielded a model with two significant predictors: length of stay and tumor. Even after controlling for length of stay, treatment for a primary or metastatic tumor remained a significant predictor of hospital costs ($5681, p=0.02).

Figure 1. Total hospital charges by diagnosis in patients enrolled in the CJR bundle

Conclusion:

Patients with primary tumors or metastatic disease enrolled in the CJR bundled payment model incur significantly higher costs than patients who receive joint replacements for primary osteoarthritis. This study has important implications for health policy. The purpose of the CJR bundled payments system is to reduce the cost curve for common procedures like total joint arthroplasty and thus decrease Medicare expenditures in this category. Unfortunately, our study provides evidence that tumor patients far exceed the hospital costs of patients with osteoarthritis.

This reality creates a financial disincentive to hospitals who provide this necessary and complex service to orthopaedic oncology patients. Given that costs associated with these patients exceed the CJR reimbursement by an insurmountable margin, our recommendation is that oncology patients be excluded from the CJR bundle in the future.

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PAPER 65

Analysis of principles inspiring design of 3D printed prostheses in two referral centers

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Background. Three-dimensional (3D) printing is an emerging technology used in numerous medical field in the last decades. Reconstruction of large bone defects after tumor resections or complex revision surgeries is challenging especially in specific sites where modular prostheses are not available. The possibility to realize custom-made 3D printed prostheses improves their application in surgical field despite the complications rate, gaining a lot of attention for potential benefits.

Questions/Purposes. We asked: (1) What are the emerging indications and designs of 3D-printed prostheses for complex bone reconstructions? (2) What complications occur with the use of custom implants considering site? (3) What are the oncologic and functional outcomes of these patients at mid-term follow-up?

Patients and Methods. We performed a retrospective chart review of every patient in whom a custom-made 3D printed prosthesis was used to reconstruct a bone defect after resection for a bone tumor or challenging revision surgery from 2014 to 2017 in two referral centers of orthopedic oncology. We included patients with a minimum follow-up of 12 months. Forty-one patients (17 men [41%]) with a mean age of 55 years (range, 10-78 years) were included. During the period under study, our general indications for using these implants were reconstructions of bone defects, in absence of available modular prostheses, in which the principal alternative treatment included the use of massive allograft. Nine were non-oncologic patients, whereas in the remaining cases chondrosarcoma was the predominant diagnosis (n=17 [41%]); eight patients (19%) had osteosarcoma, three (7%) had Ewing's sarcoma, two (5%) had osseous metastases of a distant carcinoma, one had multiple myeloma, and one had recurrent giant cell tumor. Custom-made 3D printed prostheses were used in pelvis (34), forearm (2), scapula (2), distal tibia (1), calcaneus (1) and femoral diaphysis (1). The reconstruction included articular replacement in 13 cases (32%) whereas a combined spinopelvic implant has been used in two cases.

Results. Overall complication rate was 36.5% (15/41 cases). Six patients (15%) had postoperative wound dehiscence requiring surgical debridement, whereas other four cases (10%) were successfully treated with surgery, flap and antibiotic therapy due to deep infection, maintaining their implants. One patient reported a periprosthetic fracture and four (12.5% [4/32 cases]) had

local recurrence. The implant survival to major complications was 70% at 2 years f-up. In the oncologic group, 28 patients (87%) were disease-free (one after treatment of LR and one after lung metastasectomy), whereas one was alive with disease (3%) and three died with disease (9%) at last follow-up. Mean MSTS functional outcome score at follow-up was 70% (range, 36%-93%), with a full weight bearing at an average time of 73 days from surgery of lower limbs.

Conclusions. At mid-term follow-up, the custom-made 3D printed prostheses demonstrated a still high complication rate when used to reconstruct bone defects after large surgical resections. Infection and wound healing problems are relatively common after these complex reconstructions, especially in pelvic reconstructions. We believe these 3D-printed prostheses are useful reconstructive options after tumor resections or failed prior implants. We will continue to follow our patients over the longer term to ascertain the role of this implant in these settings; however, larger studies will need to confirm indications and control for prognostic factors.

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Revisiting the Role of Radiation Therapy in Chondrosarcoma: A National Cancer Database Study

Authors

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Background

Although chondrosarcomas (CS) are historically radioresistant, given their hypoxic environment and genetic makeup, advancements in radiotherapy have brought attention to its use in these patients. These advancements have allowed for higher doses, more precise delivery, and higher energy particles, all of which help deliver a more potent dose directly to tumor tissue. Given the rarity of these tumors and historical radioresistance, there are limited studies of large cohorts to assess the effect of radiotherapy on survival outcomes in chondrosarcoma patients. Using the largest registry of primary bone tumors, the National Cancer Database (NCDB), we sought to better characterize the use of radiotherapy in CS patients.

Questions/Purposes

(1) Which chondrosarcoma patients are receiving radiotherapy?
(2) Amongst those patients, in a multivariable analysis, is there a survival benefit related to radiotherapy dose or modality, comparing conventional external beam radiation therapy (EBRT) and non-conventional radiation therapy?

Patients and Methods

We retrospectively analyzed patients in the NCDB from 2004-2015 and included those with a histologic diagnosis of chondrosarcoma, who underwent radiotherapy, with a reported dose and delivery modality. Delivery modalities included conventional EBRT, and stereotactic radiosurgery (SRS), proton-beam therapy (PBT), conformal radiation therapy (CRT), and intensity modulated radiation therapy (IMRT), which were all categorized as non-conventional. Demographic, clinical, and outcomes data was compiled and presented utilizing descriptive statistics. The Kaplan-Meier (KM) method with statistical comparisons based on the log-rank test was used to identify which individual variables related to dosage and delivery modality were associated with improved 5-year survival rates. Multivariate proportional hazards analyses were performed to determine independent predictors of survival while controlling for basic demographic, tumor, and treatment factors.

Results

A total of 5,552 patients with a histologic diagnosis of chondrosarcoma were identified, 685 of which received radiation therapy (12.6%). Comparing patients receiving RT to those who did not receive RT, the RT group were more likely to be high or intermediate grade (73% vs 56%,

p<0.001) and have positive margins after surgical resection (43.2% vs 11.6%, p<0.001). 376 patients (54.9%) received conventional ERBT and 309 (45.1%) patients received non-conventional radiation therapy modalities, such as SRS, PBT, IMRT, and CRT. The 5-year survival rates of those receiving high-dose EBRT (>50gy) was 59.0%, significantly higher than the 32.5% survival rate of low-dose EBRT (<50gy) (p<0.001, figure 1). Similar significance was found when comparing high and low doses of nonconventional RT (77.6% vs 62.6%, p=0.001). When comparing conventional EBRT to non-conventional RT modalities, regardless of dose, there was a significant improvement in overall 5-year survival rates of nonconventional modalities (72.8% vs. 48.1%, p<0.001, figure 2), including an improved 5-year survival rate amongst the low-dose cohort (62.5% vs. 36.6%, p<0.001).

In a multivariate proportional hazards analysis controlling for various patient, tumor, and treatment variables, including RT dose and modality, both low-dose RT and conventional EBRT were independently associated with significantly increased mortality (low- vs. high-dose RT HR 1.31 (1.00-1.72), p=0.0495, conventional EBRT vs. non-conventional modalities HR 1.53 (1.18-1.99), p=0.002). After stratifying by tumor site, the most significant survival benefit of radiotherapy was in pelvis CS. In the pelvis, low-dose RT was also associated with worse survival compared to high-dose RT (HR 2.36 (1.40-3.99), p=0.0014). Similarly, conventional modalities were associated with worse survival in the pelvis, (HR 1.65 (1.01-2.71), p=0.046).

Conclusions
Wide resection remains the standard definitive treatment of chondrosarcoma, however, adjuvant therapy is sometimes required despite the radioresistance of chondrosarcoma. Based on our review of the NCDB, patients with high-grade lesions and positive margins after surgical resection, as commonly seen in pelvis CS, may require adjuvant radiotherapy. High-dose, non-conventional RT provides a significant survival benefit compared to alternatives, however further, prospective studies are needed to validate these findings and investigate local recurrence rates.
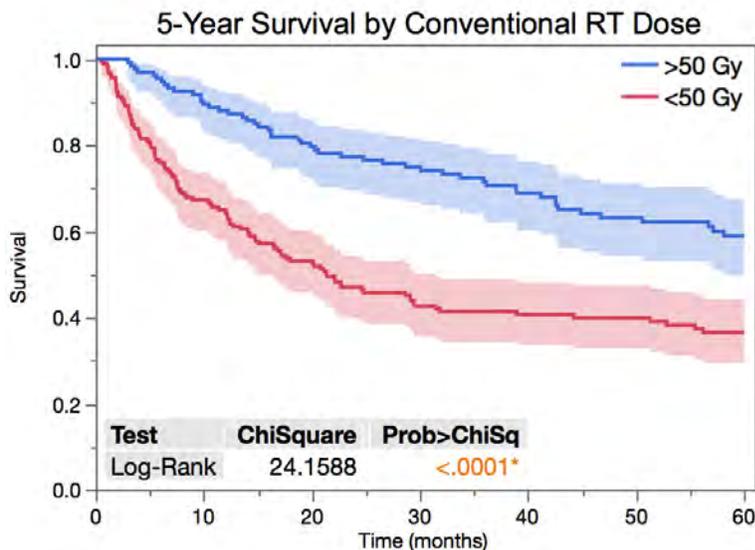
Figure 1

Figure 2

5-Year Survival by RT Modality