2016 MSTS Annual Meeting

Final Program

October 5-7, 2016
Renaissance Hotel
Detroit, MI

Michael P. Mott, MD, Program Chair
Theodore W. Parsons, III, MD, FACS , President

Educational Goals and Objectives

At the conclusion of this CME activity, the attendee should be able to:
Recognize the new options for limb salvage surgery for patients with malignant bone and soft tissue tumors; complications, treatments and pitfalls.
Update on recent progress in basic and transitional research as it relates to diagnosis and/or prognosis of the orthopaedic oncologic patient.
Identify new approaches for targeted therapies to treat patients with primary or metastatic bone or soft tissue tumors.
Understand the role/importance of collaborative registries and/or research in both malignant and benign bone and soft tissue tumors.
Update knowledge of bone and soft tissue tumors and tumor-like conditions based upon clinical, radiologic and pathologic information.
Update on understanding of quality of life issue/quality of life issues in the longstanding survivors of extremity sarcoma.

Wednesday, October 5, 2016	
10:00 AM - 2:00 PM	Executive Committee Meeting
1:00 PM - 5:30 PM	Registration
1:00 PM - 5:00 PM	Poster Exhibit Set-up
1:00PM - 5:00 PM	Technical Exhibit Set-up
3:00 PM - 6:00 PM	MSTS Coding Course
6:00 PM - 8:00 PM	Welcome Reception
Thursday, October 6, 2016	
5:30 AM - 5:30 PM	Registration
6:00 AM - 7:00 AM	MSTS 5K Fun Run along the River Walk
7:00 AM - 8:30	Breakfast
7:20 AM - 7:40 AM	Product Theater - BoneSupport
7:00 AM - 5:30 PM	Poster/Technical Exhibits
10:00 AM - 10:20 AM	Product Theater - Exactech, Inc.

1:50 PM - 2:45 PM	MSTS Business Meeting - open to MSTS members only		
2:55 PM - 3:15 PM	Product Theater - Onkos Surgical		
2:45 PM - 3:30 PM	Poster Viewing		
5:20 PM - 6:00 PM	MSTS Committee Members Meet & Greet		
7:45 AM	Welcome		Michael P. Mott, MD and Theodore W. Parsons, III, MD, FACS
Session I: Soft Tissue Sarcomas			
Moderators: David M. King, MD and Megan E. Anderson, MD			
8:00 AM - 8:07 AM	Paper 1	Six-Week Interval Between Preoperative Radiation And Surgery Is Associated With Fewer Major Wound Complications In Soft Tissue Sarcoma	Christopher Collier, MD
8:07 AM - 8:14 AM	Paper 2	Cost Effectiveness Analysis Of Neoadjuvant Versus Adjuvant Radiotherapy Treatment For Soft Tissue Sarcoma Of The Lower Extremities	Megan Crosmer
8:14 AM - 8:21 AM	Paper 3	Post-Operative Day 1 Fasting Blood Glucose May Predict For Wound Complications In Patients With Soft Tissue Sarcomas Treated With Preoperative Radiotherapy	Meena Bedi, MD
8:21 AM -8:28 AM	Paper 4	What Are The Results Of Surgical Treatment Of Postoperative Wound Complications In Soft Tissue Sarcoma? A Retrospective, Multi-Center Case Series	Benjamin J. Miller, MD, MS
8:28 AM - 8:35 AM	Paper 5	The Utility Of Plain Radiographic Surveillance For Detecting Local Recurrences Of Extremity Soft-Tissue Sarcomas	Robert J. Wilson, MD
8:35 AM - 9:00 AM		Moderated Discussion	
Session II: Soft Tissue Sarcomas			
Moderators: Ginger E. Holt, MD and Dieter Lindskog, MD			
9:00 AM - 9:07 AM	Paper 6	What Margin Classification System Best Discriminates The Risk Of Local Recurrence After Soft Tissue Sarcoma Resection?	Kenneth Gundle

9:07 AM - 9:14 AM	Paper 7	How Should We Resect An Infiltrative Soft Tissue Sarcoma? -Comparison With Radiological And Histological Infiltration	Shintaro Iwata, MD
9:14 AM - 9:21 AM	Paper 8	Five-Aminolevulinic Acid Photodynamic Therapy For Myxofibrosarcoma	Shachar Kenan, MD
9:21 AM - 9:28 AM	Paper 9	Coupling Tumor Detection And Cancer Treatment: The Use Of Fluorescent-Labeled Cetuximab For Image-Guided Soft Tissue Sarcoma Surgery	Nicole Kellan Behnke, MD
9:28 AM - 9:35 AM	Paper 10	The Role Of Chemotherapy And Radiation In Soft Tissue Osteosarcoma	Marilyn Heng, MD, FRCSC
9:35 AM - 10:00 AM		Moderated Discussion	
10:00 AM - 10:20 AM		Product Theater - Exactech, Inc.	
10:00 AM - 10:30 AM	Break		
Session III: Collaborative/Intergroup Studies			
Moderators: Lawrence R. Menedez, MD and Wakenda K. Tyler, MD			
10:30 AM - 10:38 AM	Paper 11	Ten Years Of Cases From Recently Trained Tumor Fellows: An Analysis Of The ABOS Part Ii Database	Benjamin J. Miller, MD, MS
10:38 AM - 10:46 AM	Paper 12	A Qualitative Study To Determine Barriers And Facilitators Encountered In Collaborative Prospective Research In Orthopaedic Oncology	Marilyn Swinton, MSc
10:46 AM - 10:54 AM	Paper 13	Illuminoss Lightfix Trial: A Prospective, Multi-Center Study Of The Illuminoss System For The Treatment Of Impending And Actual Pathological Fractures In The Humerus From Metastatic Bone Disease	Richard A. Terek, MD, FACS
10:54 AM - 11:15 AM		Moderated Discussion	
11:152 AM - 11:23 AM	Paper 14	Treatment Of Metastatic Lesions Of The Femoral Head And Neck: A Survey Of The Members Of The Musculoskeletal Tumor Society	Taylor Reif, MD

11:23 AM - 11:31 AM	Paper 15	Predictors Of Surgical Site Infection And Implant Failure Secondary To Infection In Proximal, Distal And Total Femur Replacement In Patients Treated For Musculoskeletal Tumors	Daniel Driscoll, BA
10:31 AM - 11:38 AM	Paper 16	The Prophylactic Antibiotic Regimens In Tumor Surgery (Parity) Multicenter Randomized Controlled Trial: International Expansion Of The Collaborative Network	Michelle Ghert, MD for PARITY Investigators
11:38 AM - 12:00 PM		Moderated Discussion	
12:00 PM - 1:00 PM	Lunch		
Session IV: Pelvic and Axial			
Moderators: Kevin A. Raskin, MD and Cynthia M. Kelly, MD			
1:00 PM - 1:07 PM	Paper 17	A Modified Tomita Saw Technique In Patients Undergoing En Bloc Spondylectomy For Spinal Tumors: Surgical Technique And Results	Akash A. Shah
1:07 PM - 1:14 PM	Paper 18	Computer Assisted Planning And Patient Specific Instruments Improves Accuracy Of Pelvic Bone Tumor Resection: A Cadaveric Study	Roberto Velez, PHD, MD
1:14 PM - 1:21 PM	Paper 19	Can Aortic Balloon Occlusion Reduce Blood Loss In Sacral Tumor Resections When The Lower Lumbar Spine Is Involved?	Yidan Zhang, MD
1:21 PM -1:28 PM	Paper 20	Outcome and Complications Following Free Fibula Reconstruction for Oncologic Defects Of the Spine and Pelvis	Matthew T. Houdek, MD
1:28 PM - 1:35 PM	Paper 21	A Systematic Review Of Surgical Outcomes After Limb-Sparing Resection And Reconstruction For Pelvic Sarcoma	Robert J. Wilson, MD
1:35 PM -1:50 PM		Moderated Discussion	
1:50 PM - 2:45 PM		MSTS Business Meeting - MSTS Members Only	

2:30 PM - 3:30 PM		Break	
2:55 PM - 3:15 PM		Product Theater - Onkos Surgical	
2:45 PM - 3:30 PM		Poster Viewing & Question Session	
Session V: Basic Science			
Moderators: Francis Y0ung Lee, MD, PhD. and Amalia M. DeComas, MD			
3:30 PM - 3:37 PM	Paper 22	Indocyanine Green Dye Angiography Quantifies Primary And Metastatic Osteosarcoma Tumor Burden In An Immunocompetent Mouse Model	Mitchell Fourman, MD
3:37 PM - 3:44 PM	Paper 23	A Non-Immunogenic Method For Transfecting Osteosarcoma Cells With The Luciferase Reporter	Brock A. Lindsey, MD
3:44 PM - 3:51 PM	Paper 24	Validation Of A Rat Model For Analyzing MiRNA In Chrondrosarcoma	Timothy J. Evans, MD, MS
3:51 PM - 3:58 PM	Paper 25	Atrx Mutation In Canine And Human Osteosarcoma: In Vitro Exploration Of A Novel Therapeutic Approach	Suzanne Bartholf DeWitt, DVM
3:58 PM - 4:05 PM	Paper 26	The Role Of Osteoblasts In The Osteolytic Bone Metastasis Of Renal Cell Carcinoma	Robert J. Satcher, Jr., MD
4:05 PM - 4:12 PM	Paper 27	Reduction In Functional And Material Bone Strength Following Radiation Therapy	Timothy Damron, MD
4:12 PM - 4:30 PM		Moderated Discussion	
Session VI: Quality of Life/ Miscellaneous			
Moderators: David D. Greenberg, MD and Emily E. Cormody, MD			
4:30 PM - 4:37 PM	Paper 28	Predictive Analytics To Determine Functional Outcome Trajectories In Orthopaedic Oncology	Theresa Nalty, PhD, PT, NCS
4:37 PM - 4:44 PM	Paper 29	Long-Term (> 15 Year) Outcomes Of Cement In Cement Technique For Revision Endoprosthesis Surgery	Nicholas M. Bernthal, MD
4:44 PM - 4:51 PM	Paper 30	Lessons And Advice From Our Patients: A Report On A Focus Group Of Sarcoma Survivors	Benjamin J. Miller, MD, MS
4:51 PM - 4:58 PM	Paper 31	Predictors Of Venous Thromboembolism In Patients With Primary Sarcoma Of Bone	Courtney L. Kaiser ,BA

4:58 PM - 5:05 PM	Paper 32	Are Perioperative Allogeneic Blood Transfusions Associated With 90-Days Infection After Operative Treatment For Bone Metastases?	Nuno Rui Cools Paulino Pereira, MD
5:05 PM - 5:20 PM		Moderated Discussion	
5:20 PM		Meeting Adjourns	
5:20 PM - 6:00 PM		MSTS Committee Meet & Greet	
	Social Event - Strolling Dinner at Henry Ford Museum		
	6:15 PM & 6:30 PM	Buses Depart from Marriott Renaissance Center Hotel - two departure times	
	8:30 PM - 10:00 PM	Buses Return to the Marriott Renaissance Center Hotel - Every 30 minutes beginning at 8:30 PM	
Friday, October 7, 2016			
7:00 AM- 8:30 AM	Breakfast		
6:00 AM - 8:30 AM	Registration		
7:30 AM - 7:50 AM	Product Theater - Onkos Surgical		
7:00 AM - 1:00 PM	Poster/Technical Exhibits		
8:00 AM - 9:00 AM	President's Lecture - Kaled M. Alektiar, MD		
Session VII: Pediatric/ Miscellaneous			
Moderators: Joel I. Sorger, MD and Parker Gibbs, Jr., MD			
9:00 AM - 9:07 AM	Paper 33	Cost-Utility Of Osteoarticular Allograft Vs. Endoprosthetic Reconstruction For Primary Bone Sarcoma Of The Knee: A Markov Analysis	Robert J. Wilson, MD
9:07 AM - 9:14 AM	Paper 34	Long Term Results Of Oncologic Implants For Limb Salvage Of Malignant Bone Tumors In Children	Ernest (Chappie) Conrad, MD
9:14 AM - 9:21 AM	Paper 35	Does Surgery Or Radiation Provide The Best Overall Survival In Ewing'S Sarcoma? A Review Of The National Cancer Data Base	Benjamin J. Miller, MD, MS

9:21 AM - 9:28 AM	Paper 36	Limb Length Discrepancy In Skeletally Immature Patients With Sarcomas About The Knee: Risks And Results Of Limb Salvage Reconstruction	Brooke Crawford
9:28 AM - 9:35 AM	Paper 37	Imaging Or Pathology – What Is The Greatest Predictor For Local Recurrence In Pediatric Osseous Sarcomas?	Ernest (Chappie) Conrad, MD
9:35 AM - 10:00 AM		Moderator Discussion	
10:00 AM - 10:20 AM		Product Theater	
10:00 AM - 10:20 AM		Break	
Session VIII: Benign/ Miscellaneous			
Moderators: Scott D. Weiner, MD and Adam S. Levin, MD			
10:30 AM - 10:37 AM	Paper 38	Good Functional Status Following Claviculectomy Without Reconstruction or Benign And Malignant Tumors	Lisa Kafchinski, MD
10:37 AM - 10:44 AM	Paper 39	Virtual Analysis And Planning Of Tumor Resections And Reconstructions. Pearls, Pitfalls And Lessons Learned	Werner Hettwer
10:44 AM - 10:51 AM	Paper 40	Factors Affecting Nonunion Of Allograft-Host Junctions In Intercalary Reconstructions Of The Femur And Tibia – A Novel Classification For Allograft Union Prognosis	Jose Ignacio Albergo, MD
10:51 AM - 10:58 AM	Paper 41	Well-Differentiated Lipoma-Like Liposarcoma: Time To Excise This Term?	Anna Cohen Rosenblum, MD
10:58 AM - 11:05 AM	Paper 42	Preliminary Results On The International Multicenter Retrospective Tenosynovial Giant Cell Tumor Study	Monique Mastboom
11:05 AM - 11:20 AM		Moderated Discussion	
Session IX: Metastatic			
Moderators: Joel Mayerson, MD and Lee R. Leddy, MD			
11:20 AM - 11:27 AM	Paper 43	Better Outcomes Following Prophylactic Surgery For Patients With Bone Metastases To The Proximal Femur Than Pathologic Fracture At Presentation	Ben Deheshi, MD, MSC, FRCS C
11:27 AM - 11:34 AM	Paper 44	Outcomes Following Surgical Management Of Metastatic Long Bone Disease	Anas Nooh, MBBS, MSC

11:34 AM - 11:41 AM	Paper 45	Effectiveness Of Constrained Liner Use During Harrington Hip Reconstruction In Oncology Patients	Deren Bagsby, MD
11:41 AM - 11: 55 AM		Moderated Discussion	
11:55 AM - 12:02 PM	Paper 46	Quality Of Life, Pain Interference, Anxiety, And Depression In Patients With Metastatic Bone Disease	Nuno Rui Cools Paulimo Pereira, MD
12:20 PM - 12:09 PM	Paper 47	The Burden Of Metastatic Disease Of The Femur On The Medicare System	David W. Hennessy, MD
12:09 PM - 12:16 PM	Paper 48	Variation In Management Of Metastatic Humeral Fractures	Bianca Verbeek, MD
12:16 PM - 12:30 PM		Moderated Discussion	
12:30 PM - 1:00 PM	Discussant: Best Paper Award		
12:30 PM - 1:00 PM	Discussant: Best Poster Award		
1:00 PM	*Meeting Adjourns*		

Thank you for attending the 2016 MSTS Annual Meeting. Contact info@msts.org if you have any questions or additional comments you wish to share.

PAPER 1

Six-Week Interval Between Preoperative Radiation and Surgery is Associated with Fewer Major Wound Complications in Soft Tissue Sarcoma

Authors: Christopher D. Collier, MD; Charles A. Su, MD, PhD; Michael S. Reich, MD; Leigh-Anne Tu, MD; Patrick J. Getty, MD

Institutions: Case Western Reserve University/University Hospitals Case Medical Center, Cleveland, OH

Background: Management of soft tissue sarcoma routinely requires surgery combined with radiation therapy. Patients treated with preoperative radiation (preRT), compared to postoperative radiation, have a lower rate of long-term joint fibrosis and a higher rate of major wound complications (MWCs), reported to range from 27.5-35% resulting in significant morbidity. Prior studies indicate that surgery is typically performed three to six weeks after the last dose of preRT. However, the optimal preRT-surgery interval and its association with MWCs is unknown.

Questions/purposes: The primary purpose of this study was to determine whether an increase in the preRT-surgery interval decreases the rate of MWCs after resection of soft tissue sarcoma. Secondary purposes were to determine the variables associated with MWCs and to assess long-term outcomes in this cohort.

Methods: Using an institutional musculoskeletal oncologic database, 161 patients who underwent resection of a soft tissue sarcoma by a single surgeon were identified from 2004-2013. The standard practice at our institution is a five to six week preRT-surgery interval. Study methodology was modeled after the National Cancer Institute of Canada randomized trial (O'Sullivan, Lancet, 2002). Patients were included if they had wide local excision of an extremity or trunk soft tissue sarcoma after preRT. Patients were excluded if they did not receive preRT (N=88), received their last dose of preRT greater than three months before surgery (N=8), had open wound at the time of surgery (N=6), underwent amputation (N=4), or had less than one month of follow-up (N=1). The 54 remaining patients were included in this retrospective chart review with a primary endpoint of MWCs, defined as a secondary operation, invasive procedure, wound packing, or readmission for wound care. Secondary outcomes of local recurrence-free, disease-free and overall survival were assessed. Average follow-up was 1,178 ± 902 days (median: 970, range: 43 – 3,376). Variables were analyzed for an association with MWCs as indicated. Statistical significance was set at $p < 0.05$.

Results: The preRT-surgery interval in this population 45.6 ± 12.1 days (Table 1). Major wound complications occurred in 14.8% (N=8). The majority of wound complications (87.5%) occurred within two months of surgery (Figure 1A). Patients excluded from the overall analysis for open wounds at the time of surgery went on to have a significantly higher number of MWCs (66.7%, $p = 0.011$), demonstrating the unique risks inherent to this group.

Descriptive statistics and univariate analysis investigated the relationship between 25 variables of interest and MWCs (Table 1). Tumor size on gross pathology was found to have a statistically significant association with MWCs ($p = 0.032$). Several variables showed a trend towards increased MWCs, including: increased preoperative tumor size on MRI ($p = 0.051$), peripheral vascular disease ($p = 0.054$), neurovascular involvement ($p = 0.130$), increased age ($p = 0.157$), high grade ($p = 0.176$), and localization to the medial compartment of the thigh ($p = 0.185$).

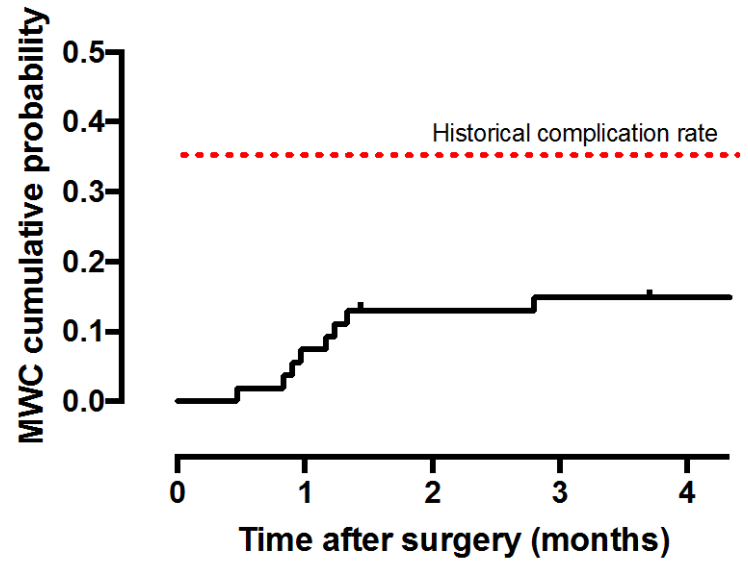
Two-year and five-year local recurrence-free survival was 85.1% (95% CI: 71.1 – 92.7%) at both time points as no local recurrence occurred after two years. Two-year and five-year disease-free survival was 58.3% (95% CI: 41.0 – 72.2%) and 52.1% (95% CI: 34.9 – 66.8%), respectively. Two-year and five-year overall survival was 77.2% (95% CI: 63.3 – 86.4%) and 54.4% (95% CI: 39.0–67.0%), respectively (Figure 1B).

Conclusions: This study presents one of the longest reported preRT-surgery intervals for soft tissue sarcoma at approximately six weeks. Major wound complications in this population occurred at a rate of 14.8%, which is lower than the reported range of 27.5-35%, and is similar to rates seen after postoperative radiation alone at 17%. Univariate analysis for association with MWCs and survival analysis demonstrated trends consistent with prior reports. This study was limited by its retrospective design, small sample size, and the lack of a short preRT-surgery interval group. Ongoing work has identified this short interval control group and data collection is now underway. This will allow us to directly compare short versus long preRT-surgery intervals and improve our power to detect additional risk factors for MWCs. In summary, the optimum preRT-surgery interval in soft tissue sarcoma has yet to be defined; however, this study supports the exploration of a longer interval to reduce major wound complications and their associated morbidity.

Table 1. Descriptive statistics and univariate analysis for major wound complications.

Variable	No (N = 46)	Yes (N = 8)	Total (N = 54)	p value
Age at surgery				0.157[+]
Number	46	8	54	
Median	57.8	71.6	60.5	
Mean (SD)	58.7 (17.5)	65.8 (16.5)	59.8 (17.4)	
Range	21.2 – 97.1	29.0 – 78.9	21.2 – 97.1	
Gender				0.248[*]
Female	17 (37.0%)	5 (62.5%)	22 (40.7%)	
Male	29 (63.0%)	3 (37.5%)	32 (59.3%)	
Lower extremity				0.667[*]
No	11 (23.9%)	1 (12.5%)	12 (22.2%)	
Yes	35 (76.1%)	7 (87.5%)	42 (77.8%)	
Proximal lower extremity	30 (65.2%)	6 (75.0%)	36 (66.7%)	
Distal lower extremity	5 (10.9%)	1 (12.5%)	6 (11.1%)	
Tumor size on gross pathology (cm)				0.032[+]
Number	46	7	53	
Median	9.5	15.0	10.0	
Mean (SD)	10.6 (5.9)	15.3 (4.1)	11.2 (5.9)	
Range	2.2 – 27.0	10.0 – 23.0	2.2 – 27.0	
Preoperative tumor size (cm on MRI)				0.051[+]
Number	44	7	51	
Median	9.9	14.0	10.1	
Mean (SD)	10.3 (5.1)	13.7 (2.9)	10.8 (5.0)	
Range	2.2 – 25.6	9.0 – 18.1	2.2 – 25.6	
Peripheral vascular disease				0.054[*]
No	45 (97.8%)	6 (75.0%)	51 (94.4%)	
Yes	1 (2.17%)	2 (25.0%)	3 (5.6%)	
Neurovascular involvement[b]				0.130[*]
No	38 (86.4%)	5 (62.5%)	43 (79.6%)	
Yes	6 (13.64%)	3 (37.5%)	9 (20.4%)	
High grade (FNCLCC 3)				0.176[*]
No	12 (26.1%)	0 (0.0%)	12 (22.2%)	
Yes	34 (73.9%)	8 (100.0%)	42 (77.8%)	
Medial compartment of the thigh[a]				0.185[*]
No	27 (58.7%)	4 (50.0%)	31 (57.4%)	
Yes	3 (6.5%)	2 (25.0%)	5 (9.3%)	
Radiation-surgery interval (days)				0.793[+]
Number	40	6	46	
Median	43	43	43	
Mean (SD)	44.8 (10.2)	51.3 (28.7)	45.6 (12.1)	
Range	30 – 82	26 – 79	26 – 82	

Multiple additional variables investigated by univariate analysis for relationship with major wound complications were found to have $p > 0.2$, including: diabetes, smoking status, thyroid disease, distal lower extremity compartments, prior surgical excision, tumor depth on preoperative MRI, AJCC staging, intraoperative radiation, postoperative radiation, chemotherapy, flap coverage, reconstructive service involvement, surgical margins, body mass index, and tumor distance from skin. [+] Mann Whitney U test; [*] Fisher's Exact test; [a] compared to tumors in proximal lower extremity subset; [b] neurovascular involvement defined as loss of fat plane or encasement on MRI.



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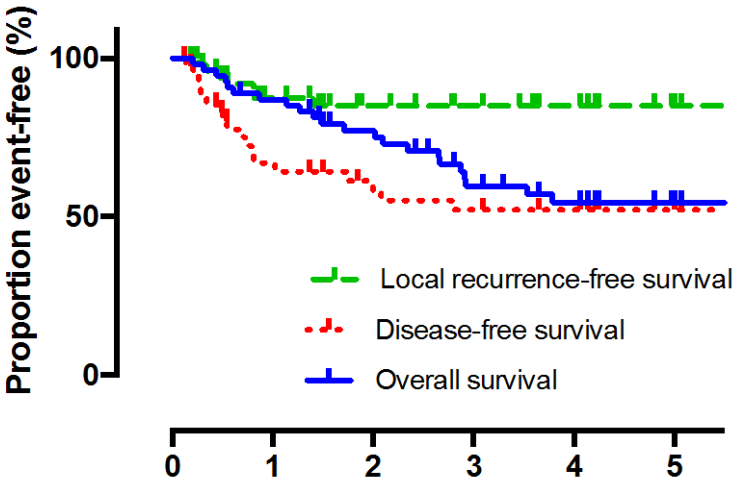

Patients at risk						
Local Recurrence-free survival	54	39	29	25	21	14
Disease-free survival	43	26	20	18	16	10
Overall survival	54	47	38	27	21	15

B

Fig. 1A-B Cumulative probability estimate of major wound complication (MWC) in patients after surgery is shown in (**A**). Historical complication rate (red dashed line) is shown for comparison and represents a MWC rate of 35% at four months as previously described for preoperative radiation therapy (O'Sullivan, Lancet, 2002). Kaplan-Meier curves for local recurrence, disease-free survival, and overall survival are shown in (**B**). Patients with pre-operative metastatic disease were excluded from disease-free survival calculations.

PAPER 2

Cost Effectiveness Analysis of Neoadjuvant versus Adjuvant Radiotherapy Treatment for Soft Tissue Sarcoma of the Lower Extremities

Authors: Megan Crosmer, MD, Perez Agaba, BS, Howard Levinson, MD, Richard Mather III, MD, MBA, William Eward, DVM, MD, and Brian Brigman, MD

Institution: Duke University Hospital

Background: Soft tissue sarcomas (STS) are rare, malignant soft tissue tumors that are commonly found in the extremities. Extremity STS are treated with wide local excision and either neoadjuvant or adjuvant radiotherapy. Neoadjuvant and adjuvant radiotherapy provide equivalent outcomes in terms of local control and overall survival; however, neoadjuvant radiotherapy is associated with increased rates of wound complications while adjuvant radiotherapy is associated with increased risks of fibrosis and lymphedema.

Purpose: The purpose of this study was to compare economic costs and quality of life associated with the adverse events of neoadjuvant versus adjuvant radiotherapy to determine the most cost effective treatment option.

Methods: A Markov decision model was constructed for a cost-utility analysis comparing neo- to adjuvant radiotherapy for extremity soft tissue sarcoma. Outcome probabilities of fibrosis, lymphedema, and wound healing complications were derived from the literature for both neoadjuvant and adjuvant radiotherapy. Costs of treatment for wound complications, lymphedema, and fibrosis were derived from the Medicare database. Utilities were measured in the form of quality-adjusted life years (QALYs) and were derived from the literature.

Results: The cost of treatments for wound complications, lymphedema, and fibrosis were $7,109.15 for neoadjuvant therapy versus $2,496.56 for adjuvant radiotherapy. Neoadjuvant and adjuvant radiotherapy produced 3.21 and 3.08 QALYs respectively. The incremental cost effectiveness ratio for neoadjuvant therapy was $35,214, which is below willingness to pay. Holding all other variables constant, adjuvant XRT is preferred if the rate of fibrosis is less than 43.8% or if the risk of wound complication is less than 2.4%. Neoadjuvant XRT is preferred if the rate of fibrosis is below 35.9% or if the rate of wound complication is less than 45%. Neoadjuvant XRT is also preferred if the cost of a secondary procedure for wound complication is less than $36,319 or if the rate of a secondary procedure for wound infection is less than 87.6%. At a fibrosis utility of 0.706 the impact of the complications from the treatment approach are balanced.

Conclusion: In patients receiving radiotherapy for extremity STS, neoadjuvant radiotherapy is more costly in terms of treatments for adverse events (wound complications, lymphedema, and fibrosis) than adjuvant radiotherapy. Patients who receive neoadjuvant radiotherapy, however, have improved quality of life as compared to patients receiving adjuvant radiotherapy. As long as willingness to pay

exceeds $35,000, neoadjuvant radiotherapy is the preferred cost effective treatment. Individual risks and costs should be taken into account, however, to determine the best treatment for each patient.

PAPER 3

Post-operative Day 1 Fasting Blood Glucose May Predict for Wound Complications in Patients with Soft Tissue Sarcomas Treated with Pre-operative Radiotherapy

Authors: Meena Bedi, MD[1]; David M. King, MD[2]; Carlos Mendez, MD[3]; Barbara Slawski, MD[3]; John Charlson, MD[4]; Donald Hackbarth, MD[2]; and John C. Neilson, MD[2]

Institution: Departments of Radiation Oncology[1], Orthopaedic Surgery[2], Internal Medicine[3], and Medical Oncology[4] at the Medical College of Wisconsin

Background: Uncontrolled blood glucose impacts key phases of the wound healing process. Post-operative glycemic control with blood sugars ≥200 mg/dL has been shown to increase the risk of wound complications (WCs) in diabetic and non-diabetic patients undergoing non-oncologic surgeries. Various factors have demonstrated to predict for post-operative WCs in soft tissue sarcomas (STS), however, the effect of post-operative blood glucose on this outcome remains to be determined.

Questions/Purposes: The goal of this study is to 1) evaluate if post-operative fasting blood glucose influences the development of WCs, 2) determine a blood glucose level cutoff that may predict for increased risk of WCs and 3) evaluate if diabetic patients have higher post-operative blood glucose correlating to increased risk of WCs.

Patients and Methods: From 2000-2015, 191 patients with stage I-III STS of the extremity and chest-wall were treated with pre-operative radiation +/- chemotherapy followed by limb-sparing resection. Patient, demographic, treatment, post-operative variables, and wound outcomes were retrospectively reviewed. Patients excluded from the study were <18 years old, had STS of locations other than the extremity or chest-wall, recurrent or bone sarcomas, and follow-up < 6 months. Fasting blood glucose was recorded on post-operative day (POD) 1 and 2. WCs were defined as those requiring operation, prolonged wound care or antibiotics after definitive surgery. Predictors for WC were evaluated using fisher exact test for univariate analysis (UVA) and logistic regression for multivariate analysis (MVA). Receiver operative curve (ROC) analysis was used to assess the fasting blood glucose level that best predicted for post-operative WCs.

Results: Median follow-up was 3.6 years. Median pre-operative radiation dose was 50 Gy. Sixty-nine (36%) patients underwent neoadjuvant chemotherapy. Thirty-two (17%) received intra-operative steroids. Twenty-two (11.5%) patients had diabetes. The overall WC rate was 29%. Predictors for WC are located in Table 1.

On UVA, proximal lower extremity tumors ($p<0.0001$) and elevated POD 1 fasting glucose ($p<0.0001$) were associated with an increased rate of post-operative WCs. Median POD 1 fasting blood glucose in patients with and without WCs was 158 mg/dL and 111 mg/dL, respectively. POD 2 fasting blood glucose did not predict for post-operative WCs ($p= 0.93$).

On MVA, lower extremity STS (p=0.002, OR 6.4, 95% CI 1.9762 to 20.8482) and elevated POD 1 fasting blood sugars (p<0.0001, OR 1.1, 95% CI 1.0468 to 1.1114) led to increased WCs post-operatively.

ROC analysis revealed that POD 1 blood sugars of >127 mg/dL predicted for post-operative WCs, with a sensitivity of 89% (AUC 0.898, p<0.0001). In patients with a POD 1 fasting blood sugars of >127 mg/dL, the WC rate was 62% versus 5% in patients with POD 1 fasting blood sugars of ≤127 mg/dL (p<0.0001). In patients with POD 1 fasting blood sugars of ≥200 mg/dL, the WC rate was 88% versus 23% in patients with POD 1 fasting blood sugars of <200 mg/dL (p<0.0001).

Median POD 1 fasting blood glucose in patients without diabetes was 118 mg/dL and 153 mg/dL in patients with diabetes (p=0.02). Diabetes did not predict for post-operative WCs on UVA or MVA. Of the patients with diabetes, 9 (41%) had WCs. All 9 patients with WCs had POD 1 fasting blood sugars of >127. Of the patients without diabetes, 45 (27%) had WCs. Of those, 40 (89%) had POD 1 fasting blood sugars of >127 mg/dL.

Conclusions: POD 1 fasting blood glucose in STS is correlated with increased post-operative WCs. Although diabetics had higher POD 1 blood glucose, diabetes was not predictive of WCs A fasting blood glucose of >127 mg/dL on POD 1 may lead to an increased risk of WCs in both diabetic and non-diabetic patients, suggesting the critical time in wound healing is within the initial 24 hour post-operative period. Strict glucose control may be warranted in patients who receive pre-operative radiotherapy and are inherently at an increased risk of post-operative WCs.

Variable	P-value
Age	0.6
Performance Status	0.1
Diabetes	0.2
Cardiovascular Disease	0.3
BMI	0.2
Smoking	0.6
Tumor Location	p<0.0001
Tumor Size	0.1
Neoadjuvant Chemotherapy	0.6
Flap Reconstruction	0.4
Intra-operative Steroid Use	0.07
POD 1 Fasting Blood Glucose	p<0.0001
POD 2 Fasting Blood Glucose	0.9

Table 1: Predictors for Post-operative Wound Complications

PAPER 4

What are the results of surgical treatment of postoperative wound complications in soft tissue sarcoma? A retrospective, multi-center case series

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Institutions: Work performed at the University of Iowa Department of Orthopaedics and Rehabilitation, Iowa City, IA

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Background: Non-oncologic complications, such as infection, wound dehiscence, and seroma formation, are common following resection of a soft tissue sarcoma. Although there are a number of studies illustrating the incidence of and risk factors for postoperative wound complications, we are unaware of any investigation that identifies the surgical treatment and eventual outcome of these complications.

Questions/Purposes: The purposes of this study were 1) to identify the time to complication, treatment employed, and eventual outcome of wound complications and 2) to identify risk factors that may predispose patients to failure in complication management.

Patients and Methods: This was a multi-institutional, retrospective, consecutive case series of patient data from December 1, 2009 to November 30, 2014. We included all patients treated with a primary closure of a limb sparing resection of a soft tissue sarcoma of the pelvis or extremity who developed a non-oncologic wound complication requiring operative intervention. We excluded patients who were treated with a soft tissue reconstruction (free flap, fasciocutaneous rotational flap, or skin graft) at the time of tumor resection, infections present at time of resection, or use of a prosthesis or allograft. Participants were all fellowship-trained orthopaedic oncologists, and submitted de-identified patient data through the Research Electronic Data Capture (REDCap) into a central repository managed by the primary research team.

We recorded patient (age, sex, body mass index, Age-Adjusted Charlson Comorbidity Index Score), tumor (histology, size, grade, location, depth, primary or recurrent), and treatment (chemotherapy, radiation) factors. The primary outcomes were a healed wound at the end of treatment and the total

number of procedures required to address the complication. We performed a descriptive analysis to report the time to surgical treatment, modalities of surgical treatment, and final wound status. Bivariate methods (chi-square and Fisher's exact testing) were used to investigate clinical associations that resulted in failure of wound healing or requirement of multiple unplanned procedures.

Results: There were 61 patients from 11 institutions included in the analysis. The median of age of the cohort was 67 years old (range 14-96 years old) with a median length of follow-up of 13.3 months (range 0.4-65.8 months). Thirty-two patients were treated with preoperative radiation and 11 were treated with perioperative chemotherapy. The median time from surgery to the initial recognition of a complication was 22 days (range 0-173 days), with 51 patients (84%) presenting in the first 6 weeks postoperatively, and the median time from recognition of complication to surgery was 5 days (range 0-219 days). The complications treated included infection (32), wound dehiscence/necrosis (23), and seroma/hematoma (6). The definitive procedures included primary closure (44), healing by secondary intention (9), muscle flap (6), and skin graft (2). No patient was treated with an amputation to manage the wound complication. Six patients (10%) had a wound requiring continued dressing changes after the treatment of dehiscence/necrosis (3) or infection (3). Twelve patients (20%) required at least one (range 1-4) additional unplanned procedure to address an infection (10) or seroma (2). Eight patients had a planned two-stage procedure (six for infection and two for dehiscence/necrosis), all but one of whose wounds healed without further complication. In a bivariate analysis, we found patients with an infection were at increased risk of requiring multiple unplanned procedures (p=0.024) (Table 1).

Conclusions: Limb sparing resection of a soft tissue sarcoma is known to be at high risk of postoperative wound complications. We found that 84% of these complications were identified in the first 6 weeks after surgical resection. One third of patients with a postoperative infection required additional unplanned procedures to adequately deal with the complication. In these patients, the treating surgeon may consider a planned two-stage procedure as part of the initial treatment for infection management. Patients may be counseled that a postoperative wound complication is rarely a devastating event, and resulted in a healed wound in 90% of cases and retention of the affected limb.

Table 1. Bivariate analysis of risk factors for non-healed wounds or multiple unplanned surgical procedures.

Risk factor	One or multiple planned	Multiple unplanned	p value	Healed	Not healed	p value
Patient age						
≥65	28	5	0.335	28	5	0.205
<65	21	7		27	1	
BMI						
≥30	23	4	0.522	25	2	0.685
<30	26	8		30	4	
Location						
Proximal thigh	11	4	0.467	12	3	0.152
Other	38	8		43	3	
Size						
≥10 cm	24	5	0.649	25	4	0.411
<10 cm	25	7		30	2	
Depth						
Deep	39	11	0.438	46	4	0.294
Superficial	10	1		9	2	
Radiation						
Preop	27	6	0.751	29	4	0.678
Not preop	22	6		26	2	
Delay in treatment						
>2 weeks	11	2	1.000	12	1	1.000
≤2 weeks	38	10		43	5	
Cause						
Infection	22	10	0.004	29	3	0.836
Dehiscence	23	0		20	3	
Seroma	4	2		6	0	

PAPER 5

The Utility of Plain Radiographic Surveillance for Detecting Local Recurrences of Extremity Soft-Tissue Sarcomas

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Institutions: Study Performed at Vanderbilt University Medical Center, Department of Orthopaedics and Rehabilitation, Nashville, TN, USA.

Background: Imaging surveillance with plain radiography is frequently performed following soft tissue sarcoma (STS) resection to help detect local tumor recurrences. Recent literature has questioned the utility of plain radiography in detecting local recurrences following the treatment of genitourinary, pulmonary, and breast cancers. However, the utility of plain radiographs in identifying locally recurrent lesions has not been assessed following extremity STS resection.

Questions/Purposes: The purpose of this study was to (1) identify the rate of local recurrence following extremity STS resection at a high-volume STS center, (2) examine the mechanisms by which local recurrences are identified, and (3) assess the utility of surveillance plain radiographs for the detection of local recurrence following extremity STS resection.

Patients and Methods: A consecutive series of patients undergoing STS resection between January 2008 and December 2015 was created using International Classification of Diseases (ICD) 9/10 coding. Inclusion criteria consisted of: (1) patients at least 18 years of age, (2) pathology-verified STS, and (3) upper or lower extremity location defined as distal to the inguinal ligament in the lower extremity and lateral to the chest wall in the upper extremity. Retrospective chart review was performed to collect a variety of demographic, comorbidity, and perioperative variables. The histological type and grades of each tumor were identified. The local recurrence of a STS following the initial resection was confirmed with pathology. Surveillance at our institution is pursued according to National Comprehensive Cancer Network guidelines in conjunction with x-ray imaging of the tumor site. All follow up plain radiographic image interpretations by both treating surgeons and radiologists were recorded and the mechanism by which recurrent lesions were detected was confirmed. Mechanisms included magnetic resonance imaging (MRI), positron emission tomography (PET), identification of a mass by the patient prompting a subsequent clinic visit and detection during physical exam by the treating surgeon.

Results: 463 patients met inclusion criteria, with a mean age of 57.8 years. 28 (6.0%) experienced a local recurrence. The mean time between resection and local recurrence was 4.24 years. 18 (64.3%) locally recurrent tumors were classified as high or intermediate grade. The histologic subtypes most frequently associated with recurrence were undifferentiated pleomorphic sarcoma, liposarcoma, and myxofibrosarcoma. Of the patients with local recurrence, lesions were identified via: physical exam in clinic (10), patient self-exam (8), MRI (7), PET imaging (2), and plain radiographs (1). Fourteen of the 28 patients with local recurrence underwent plain radiographic surveillance, with initial detection of local recurrence in one patient (7.1%). The lone patient was

undergoing serial plain radiographs for a radiation-induced pathologic femur fracture adjacent to the resection bed. New femoral bone lysis adjacent to the resection bed prompted advanced imaging and needle biopsy.

Conclusions: The utility of plain radiographic surveillance for detecting local recurrences of extremity STS is questionable. The most common mechanism for detecting local recurrence was a physical exam performed by the treating surgeon in clinic. The monetary, time, and radiation costs associated with plain radiographic surveillance may be better allocated for alternative uses such as more frequent clinical examination or MRI surveillance.

Level of Evidence: III

PAPER 6

What margin classification system best discriminates the risk of local recurrence after soft tissue sarcoma resection?

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Level of Evidence: Prognostic Level 2

Background: The surgical margin after soft tissue sarcoma (STS) resection is an established predictor of local recurrence (LR). However, studies vary in how they report surgical margins and the relative merits of various classification systems are unknown. Agreement on STS resection margin reporting may facilitate communication and research.

Question/Purpose: The purpose was to compare commonly utilized margin classification systems based on their ability to discriminate the risk of LR among classification groups. The primary outcome was the cumulative probability of local recurrence with death as a competing risk.

Method: We retrospectively reviewed a prospectively collected STS database at a single tertiary center following research ethics board approval. STS treated surgically between 1989 and 2014 were eligible. Exclusion criteria were tumors of the abdominal cavity or retroperitoneum, and patients with dermatofibrosarcoma protuberans, well-differentiated liposarcoma or metastases at presentation.

Four margin classification systems were compared:

1. The R-classification system, where R0 is a negative margin (no tumor cells at inked margin of resection specimen), R1 is a positive microscopic margin defined by tumor cells at the inked margin, and R2 is a gross positive margin.
2. The International Union against Cancer (UICC) system, which differs from the R-classification as follows: R0 represents no tumor cells within 1mm of the inked specimen border, and R1 resection is defined as any microscopic tumor cells within 1mm of the inked specimen margin, while R2 remains a gross positive margin.
3. A gross positive versus gross negative only system.
4. A margin context classification, for which positive margins are separated into three categories: planned close but ultimately positive at a critical structure such as a major nerve, vessel, or bone; positive margin after whoops re-excision; and inadvertent positive margins.

Fine and Gray competing risk regression model assessed each level from the four margin classification systems, with a Wald test for overall significance of each system.

Results: A total of 2,217 STS patients were eligible, of whom 44% were female, follow-up averaged 65 months (95%CI 63-68 months) and the average age was 56 (95%CI 55-57). The majority of tumors were deep (68%) and high grade (54%), with an average maximum diameter of 8.3 cm (95%CI 8-8.6). The use of adjuvant radiation was common (61%).

The R-classification demonstrated a significant difference in the cumulative probability of LR among its three tiers ($p<0.001$ by Wald test; Fine and Gray subdistribution hazard between each R-level $p<0.001$). At 5 and 10 years, the LR rate was significantly different between resections deemed R0 (5yr: 6%[5-7]; 10yr: 8%[7-9]) and R1 (5yr: 17%[12-21]; 10yr: 21%[16-26]). R2 resections had elevated rates of LR (5yr: 38%[20-57]; 10yr: 44%[23-64]) but with wider confidence intervals due to a low rate of occurrence (1%, 26/2217).

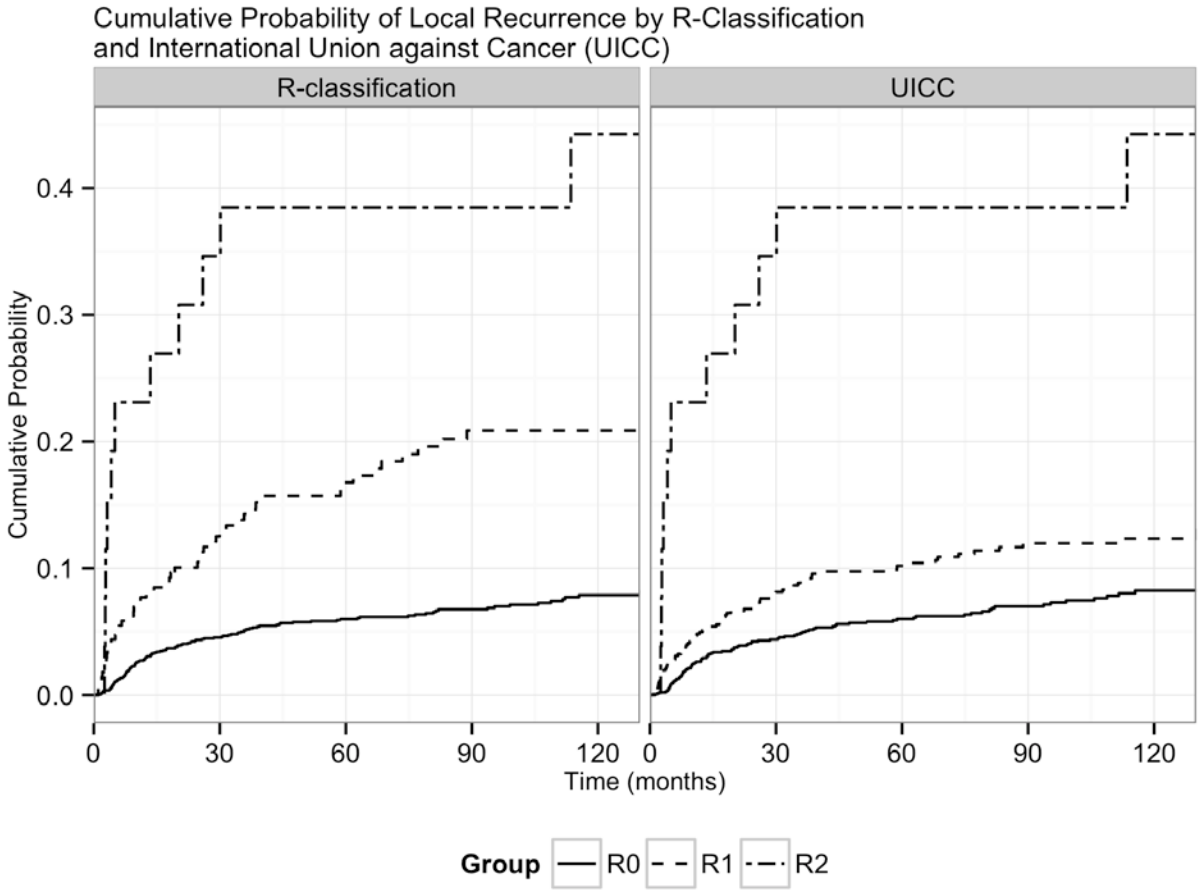
The UICC system classified less resections as R0 (1450 vs 1894) and more as R1 (721 vs 277) than the R-classification system ($p<0.001$). This resulted in a relatively lower cumulative probability of LR in the R1 group without changing LR rates for R0 resections: at 5 years the LR rate was 6% (95%CI 5-7) for R0 and 10% (7-13) for R1, and at 10 years R0 was 8%(7-10) with R1 being 12%(10-15). R2 LR rates were equivalent to the R-classification. While the Wald test for the UICC system was significant overall ($p<0.001$), this was due to the higher LR rate in R2 resections; the Fine and Gray subdistribution hazard showed no significant difference between R0 and R1 resections ($p=0.07$)

By gross margins alone, negative margins had 5 and 10-year cumulative LR probability of 7.5%(6-9) and 9.6%(8-11) with gross positive rates similar to the R-classification and UICC (Wald test $p<0.001$).

The margin context classification also had a significant difference in the cumulative probability of LR among its tiers ($p<0.001$ by Wald test). This system was able to stratify positive margins into lower and higher risk categories: planned close but ultimately positive margins on critical structures were not significantly different than negative margins (5-year cumulative probability of LR, 10%[5-17] vs 6%[5-7], Fine and Gray subdistribution hazard $p=0.6$), but inadvertent positive margins had significantly higher probability of LR (5yr: 28%[19-37], Fine and Gray subdistribution hazard $p<0.001$).

Conclusions: In a retrospective analysis of 2,217 STS patients, the R-classification system that defines an R1 margin as microscopic tumor at the inked border was beneficial, as it was able to identify distinct risk stratifications for LR. The UICC system narrowed the difference in probability of LR between R1 and R0 resections (Figure), suggesting that less than a 1mm margin may be adequate with adjuvant radiation. Only assessing gross margins results in an estimation of LR weighted towards the risk for microscopically negative margin resections due to their preponderance in the sample (86%), and the rarity of grossly positive margins (1%) limits the discriminative value of this classification scheme. Subdividing positive margins by their context provides additional significant stratification benefits that may aid in surgical planning, patient education and postoperative monitoring.

Considering margins microscopically less than 1 mm to be R1 hindered estimation of LR risk and did not significantly lower the cumulative probability for patients with an R0 plus 1 mm margin. If confirmed in other series, these results suggest studies of STS should report margins using the R-classification as well as the margin context classification.


Cumulative Probability of Local Recurrence by R-Classification
and International Union against Cancer (UICC)
R-classification
UICC
Cumulative Probability
0.0
0.1
0.2
0.3
0.4
0
30
60
90
120
Time (months)
Group
R0
R1
R2

PAPER 7

How Should We Resect an Infiltrative Soft Tissue Sarcoma? -Comparison with Radiological and Histological Infiltration

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Institution: Chiba Cancer Center

Introduction: Tumor infiltration, frequently observed in spindle cell sarcomas of soft tissue, is often associated with an inadequate surgical margin and results in failure of local control. However, not enough information concerning the tumor infiltration of soft tissue sarcoma has been provided till now. The purpose of this study is to clarify 1) which subtype of soft tissue sarcoma have an infiltration property, 2) whether radiological tumor infiltration in soft tissue sarcomas correlates with histological infiltration, and 3) whether tumor resections with infiltration-free margins improve their outcome.

Methods: We retrospectively reviewed 145 patients diagnosed with soft tissue sarcoma who underwent initial definitive surgery at our hospital between 2006 and 2014. Radiological infiltration (R-inf) was defined as a high-intensity tail-like extension along the fascial plane observed in either STIR or gadolinium-enhanced fat-suppressed (GdFS) MRI. Histological infiltration (H-inf) was also defined as the infiltrative growth of the atypical tumor cells along the fascial plane. Each distance was measured by radiologist, musculoskeletal tumor surgeon, and pathologists. Correlation between R-inf and H-inf was analyzed using the Pearson's correlation coefficient. Local control rate (LCR) and overall survival (OAS) were analyzed using the Kaplan–Meier method, and the association of potential prognostic factors with LCR and OAS were analyzed using the log-rank test and the Cox proportional hazards regression model. [Results] H-inf was observed in 58 (40%) patients and was frequently observed in myxofibrosarcoma (72%), undifferentiated pleomorphic sarcoma (52%), leiomyosarcoma (33%), and malignant peripheral nerve sheath tumor (33%), although rare in myxoid (6%) and dedifferentiated (10%) liposarcoma. R-inf was observed in 59 (41%) patients, showing significant correlation with H-inf ($P < 0.0001$). Comparing distances of these two factors, R-inf obtained by GdFS MRI images ($R^2 = 0.41$) showed a stronger correlation to the H-inf than that

obtained by STIR image (R^2 = 0.09). Twelve (8%) patients demonstrated local failure, and five-year OAS and LCR were 76% and 89%, respectively. Univariate analysis with 5-year LCR demonstrated that a positive margin with not only tumor mass but also infiltrative tumor cells was a significant prognostic factor compared with a wide margin (P = 0.0015).

Conclusion: Tumor infiltration is common in myxofibrosarcoma and undifferentiated pleomorphic sarcoma. R-inf as assessed by GdFS MRI images highly correlated with H-inf. Our results suggest that wide resection with an infiltration-free margin would improve local control of these sarcomas. Taken together, we should excise myxofibrosarcoma or undifferentiated pleomorphic sarcoma beyond their radiological infiltrations detected by GdFS MRI image.

PAPER 8

Five-Aminolevulinic Acid Photodynamic Therapy for Myxofibrosarcoma

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Background: Five-aminolevulinic acid (5-ALA), an endogenous intermediary involved in the heme biosynthesis pathway, is a known compound used in photodynamic therapy (PDT) to treat various malignancies. 5-ALA is preferentially converted to protoporphyrin IX (PpIX) within the mitochondria of malignant cells, where it functions as a potent photosensitizer, capable of oxidative damage and cell death when exposed to light of sufficient energy and wavelength. Although its use for tumors of the brain, skin, bladder, cervix and colon has been described extensively, its use with soft tissue sarcomas is poorly documented. The purpose of this study was to analyze the selective cytotoxic effects of 5-ALA on myxofibrosarcoma cells versus control non-malignant cells using flow cytometry.

Questions/Purposes:

1) Does 5-ALA exposure lead to myxofibrosarcoma cell death?
2) Are normal non-malignant cells protected from the cytotoxic effects of 5-ALA?
3) Can 5-ALA safely be used in photodynamic therapy to treat soft tissue sarcomas?

Methods: 10,000 myxofibrosarcoma (MUG-myx1) cells and adipose derived stromal (ADS) cells were treated with 5-ALA at a concentration of 500µg/mL for either one or three hours with subsequent washout exchange to a 5-ALA free medium. Experimental conditions were set so that 5-ALA was administered in saturation conditions, allowing for maximal uptake by both cell lines. Flow cytometry (BD Fortessa) was performed either twenty minutes or one hour after medium exchange. There were three resulting groups per cell line- Group 1: one hour of 5-ALA exposure analyzed twenty minutes post exchange. Group 2: three hours of 5-ALA exposure analyzed twenty minutes post exchange. Group 3: three hours of 5-ALA exposure analyzed one hour post exchange.

Results: Both the ADS and MUG-myx1 cell lines displayed two isolated peaks of fluorescence for each group. The lower peak represents either necrotic cells or cells which have not responded to 5-ALA. The higher peak represents 5-ALA responsive, viable cells. The first group had an ADS low peak of 34.2 intensity units and a high peak of 1,889 intensity units. At this same time point, the MUG-myx1 peaks were similar to the ADS peaks, although slightly higher, at 42.5 and 2,198 intensity units, respectively. The distribution of cells was similar in both groups, with about 10% of cells representing the low peak and 90% of cells representing the high peak.

The MUG-myx1 cell distribution changed for the 2nd and 3rd groups, with low peak distributions rising from 10.8% to 25.4% and 40.4%, respectively and high peak distributions decreasing from 89.2% to 74.6% and 59.6%, respectively. This was unlike the ADS cell line where the cell distribution remained unchanged regardless of length of exposure to 5-ALA or time after medium exchange.

Conclusions: The results of this study demonstrate the powerful, selective and time dependent cytotoxic effects of 5-ALA photodynamic therapy (PDT) against myxofibrosarcoma cells. Interestingly, 5-ALA

continued to destroy myxofibrosarcoma cells well after medium exchange, while sparing ADS cells. These findings are most likely attributable to intracellular accumulation of the photosensitizer PpIX within malignant cells, as a consequence of impaired 5-ALA metabolism.

5-ALA driven PDT offers many advantages over traditional chemotherapeutic agents, including lack of immunosuppression, a favorable side effect profile and reduced long term morbidity. Additionally, 5-ALA has been used for “tumor paint” to selectively induce fluorescence of malignant cells allowing for tumor margin assessment during resection. 5-ALA, with its two pronged applications of selective tumor identification and kill has the potential of transforming our surgical and medical approach to treating soft tissue sarcomas.

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Fig. 1: Group 1- Flow Cytometry Fluorescence Intensity, 20 Minutes after Medium Exchange with 1 Hour 5-ALA exposure

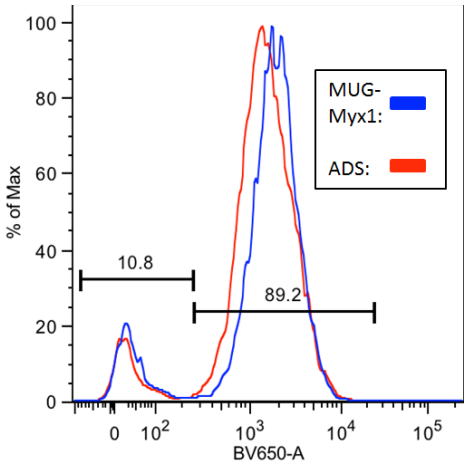


Fig. 2: Group 2- Flow Cytometry Fluorescence Intensity, 20 Minutes after Medium Exchange with 3 Hour 5-ALA exposure

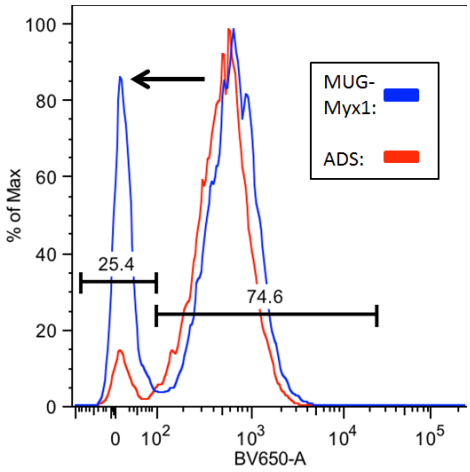
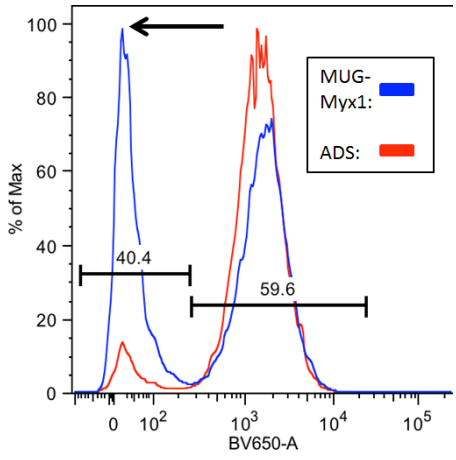


Fig. 3: Group 3- Flow Cytometry Fluorescence Intensity, 1 Hour after Medium Exchange with 3 Hour 5-ALA exposure



PAPER 9

Coupling tumor detection and cancer treatment: The use of fluorescent-labeled Cetuximab for image-guided soft tissue sarcoma surgery.

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Institution: University of Alabama at Birmingham

BACKGROUND: Soft tissue sarcomas (STS) are a histologically heterogeneous group of solid malignancies that share a common mesenchymal tissue origin, most often occur in the extremities and whose treatment typically includes limb-sparing resection with wide negative margins, often involving a circumferential 2cm of healthy surrounding tissue. Tumors of this type can grow greater than 30cm in size and involve critical anatomic structures, which make accurate assessment of margin status challenging. Fluorescence-guided surgical resection is a new technique used to delineate tumor margins in the intraoperative setting, with preclinical studies demonstrating improved oncologic outcomes in multiple tissue types when cancer-specific imaging probes are used to guide resection. Recent literature describes the use of cathepsin protease activated imaging probes selective for STS, but there have been no studies evaluating the use of disease-specific chemotherapeutic agents conjugated to imaging probes. This is a novel strategy that not only may achieve highly tumor-specific imaging used as an intraoperative tool for margin assessment, but also can possibly couple this tool simultaneously to a patient's pre-existing chemotherapeutic treatment regime. This translational strategy has the potential to both improve patient morbidity by decreasing unnecessary healthy tissue resection and improve oncologic outcomes by reducing margin-positive resections.

The overexpression of epidermal growth factor receptor (EGFR) in multiple histologic subtypes of STS provides a potential target for fluorescence-guided surgery by exploiting the chemotherapeutic treatment strategy of blocking disease-specific biologic receptors. Recent studies demonstrate the safety and utility of fluorescently labeled cetuximab, an FDA-approved, anti-EGFR antibody, for intraoperative margin assessment in head and neck cancer, and our aim was to evaluate its potential for STS. The use of a labeled chemotherapeutic agent, which is independently known to be efficacious in select sarcoma subtypes, has significant and unique translational potential for both simultaneous detection and treatment of tumor.

SPECIFIC AIMS: Our goal was to identify an ideal imaging probe for fluorescence-guided soft tissue sarcoma surgery, by evaluating the STS-targeting specificity of two chemotherapeutic-probe conjugates, and comparing them to the cathepsin-activated imaging probes recently reported in the literature. Our hypothesis was that the drug-probe conjugates would successfully target STS in vivo and produce superior tumor specificity with better signal-to-noise ratios than the cathepsin-activated probes. We also aimed to determine the smallest amount of tumor detectable by our imaging probe conjugate.

METHODS: This was a preclinical feasibility study. Athymic nude mice bearing subcutaneous HT1080 fibrosarcoma tumors were injected with one of five imaging probes: IRDye800CW fluorescent probe conjugated to either cetuximab (anti-EGFR) or DC101 (anti VEGFR2), IRDye800CW conjugated to an isotype control (IgG), or a cathepsin-activated

imaging probe (IntegriSense 750 and Prosense 750). Fluorescence imaging was performed daily with both open- and closed-field systems. Tumor-to-background ratios (TBR), signal washout times and normalized tumor signal averages were evaluated for each of the five imaging probes. Additionally, on day 9, smallest resectable game evaluation was performed, with 1mg tumor samples, examining the cetuximab-probe conjugate's sensitivity for detecting the minimal residual disease in the post-resection tumor bed as compared to the IgG control.

RESULTS: At day 9- post systemic injection, the TBR of the cetuximab-IRDye800CW group (11.1) was significantly greater than the Integrisense750 group (6.88, p=0.005), the IgG-IRDye800CW control group (4.44, p=0.00005), the Prosense750 group (2.35, p=0.00009), and the DC101-IRDye800CW group (1.87, p=0.00003). During in vivo imaging, cetuximab-IRDye800CW significantly outperformed all other agents by several folds of contrast enhancement when measured with normalized tumor signal averages. From the smallest resectable game evaluation, the cetuximab-IRDye800CW probe was able to detect a $1mm^3$ fragment of tumor with robust fluorescence.

CONCLUSIONS: This feasibility study demonstrates the superiority of cetuximab-IRDye800CW for providing disease-specific contrast in a subcutaneous animal model of STS, suggesting utility for in-vivo surgical imaging and margin assessment. The novel strategy of coupling the improved margin-negative surgical resection techniques with ongoing established chemotherapy has considerable translational significance and is an avenue for potential exploration with other drugs used to treat STS.

PAPER 10

The Role of Chemotherapy and Radiation in Soft Tissue Osteosarcoma

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Background: The role of chemotherapy (CT) in primary bone osteosarcoma and the role of radiotherapy (RT) in soft tissue sarcoma are each well defined. However, soft tissue osteosarcoma (STO) is a rare entity for which there lacks consensus on the role of similar adjuvant treatments.

Questions and Purpose

1) Describe the surgical and disease related outcomes in the largest series reported to date of soft tissue osteosarcoma.
2) Investigate if there is an association between the use of adjuvant therapies, such as chemotherapy and radiation therapy, and outcomes such as disease recurrence and survival.

Methods: A retrospective review of the sarcoma databases of 16 international institutions identified all adult patients aged 18 years or older treated for soft tissue osteosarcoma from 1971 to 2015. Patient and tumour characteristics, treatment, and outcome with respect to complications, recurrence, and overall survival were reviewed. Chi-square tests and multiple logistic regression were used to analyze for associations with outcomes of recurrence. Survival analysis with Kaplan-Meier, log rank tests, and Cox proportional hazards regression was performed.

Results: 330 adult patients with STO were identified and had a median age of 59 years (range 19 - 88 yrs) and 187 (57%) were male. The majority of patients presented with deep (n=270, 82%) and localized disease (n=285, 86%).

320 patients (97%) underwent surgical resection of their tumour – 28 were treated with amputation (9%) and 292 received limb-salvage surgery (88%). Adjuvant treatment with either chemotherapy or radiation was given to 222 patients (67%) as follows. CT alone, 94 (29%); RT alone, 61 (18%), CT+RT, 67 (20%). Eighty-five (26%) experienced a complication following treatment, mainly wound or infection-related.

Of the 280 patients who presented with only localized disease and underwent definitive surgical treatment, recurrences were as follows: local only, 30 (10.7%); distant only, 90 (32.1%); local+distant, 36 (12.6%).

Median time to recurrence was 7.9 months (range 1 to 166 months). Multiple logistic regression controlling for radiation treatment, chemotherapy, margin status, depth and size of tumour revealed margin status (Micro + OR 3.9 (95%CI 1.49-9.73), p=0.004, and Gross + OR 14.4 (95%CI 3.79 – 70.7), p<0.001) and radiation treatment (OR 0.45 (95% CI 0.21-0.91), p=0.03) to be independently associated with local recurrence. The use of chemotherapy was not independently associated with distant recurrence (p=0.34); only depth (OR 2.58 (95%CI 1.18 – 6.13), p=0.02) and tumour size (OR 1.07 (95%CI 1.03 – 1.12), p=0.001) were significant risk factors for distant recurrence.

Overall cause-specific survival at 5 years was 58% (95% CI 52-64%). 5-year survival was 64% (95%CI 58-70%) and 7% (95%CI 1-40%) for patients presenting with localized and metastatic disease, respectively.

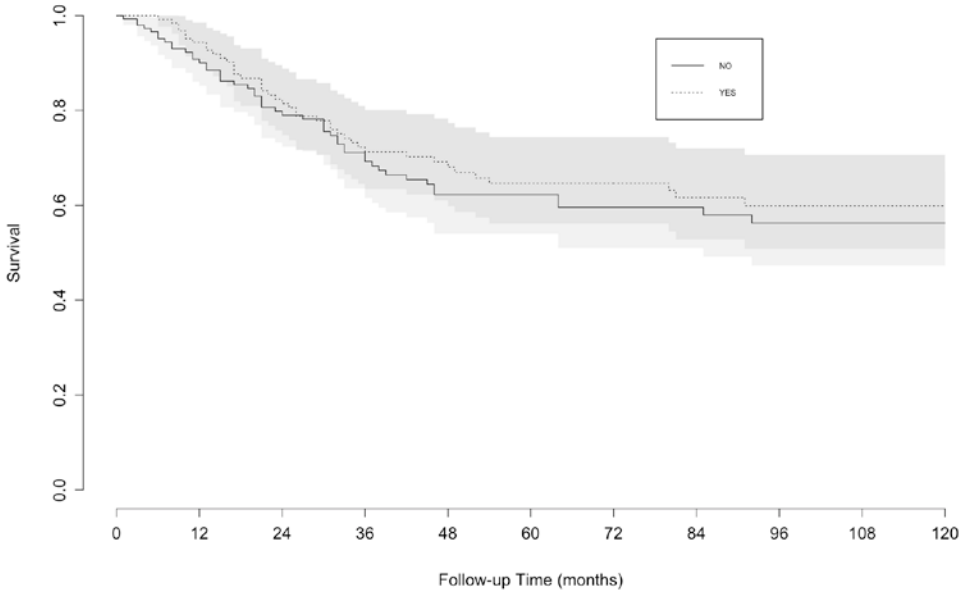
For patients presenting with localized disease and undergoing definitive surgery (n=280), there was no significant difference in cause-specific survival with respect to the addition of chemotherapy (p=0.36), radiation therapy (p=0.09) or both adjuvants together (p=0.25) to the treatment paradigm.

Using cox proportional hazards regression analysis, and controlling for age, sex, type of surgery, depth of tumour, maximal diameter of tumour, margin status, radiation treatment and chemotherapy, only age (HR 1.02 (95%CI 1.00-1.04), p=0.02), deep tumours (HR 4.87 (95%CI 1.93-12.3), p<0.001), and maximal diameter (HR 1.02 (95%CI 1.01-1.02), p<0.001) were significant independent predictors of mortality due to soft tissue osteosarcoma.

Conclusions: This is the largest series of STO to date wherein we report a favorable outcome for patients with localized disease. Our results suggest that soft tissue osteosarcoma seems to behave more like a soft tissue sarcoma than a conventional bone osteosarcoma. While the use of radiation treatment was significantly associated with decreased local recurrence, chemotherapy was not associated with differential survival in patients presenting with localized disease and thus should only be considered with careful multi-disciplinary discussion.

Figures:

Survival Based on Chemotherapy



Local Recurrence Based on Radiation Therapy

PAPER 11

Ten Years of Cases From Recently Trained Tumor Fellows: An Analysis of the ABOS Part II Database

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Background*:* Fellowship training at the conclusion of residency is common. While national trends indicate that fellowship trained surgeons are more frequently performing cases within their defined subspecialties, this may not be the case for recently trained tumor fellows.

Questions/Purposes*:* Determine (1) the number of examinees who self-reported tumor fellowship training over the last decade; (2) the number and proportion of tumor, trauma, adult reconstruction, and other procedures performed by tumor trained fellows; and (3) changes in the proportion of procedures performed by tumor trained fellows.

Methods: The American Board of Orthopaedic Surgery (ABOS) Part II database was used to identify examinees who reported tumor fellowship training between 2004 and 2013. All submitted procedures were broadly categorized as "tumor," "trauma," "adult reconstruction," or "other". Annual procedure volumes were calculated and univariate analysis allowed comparison of categorized procedures over the duration of the study.

Results: The median annual number of candidates reporting tumor fellowship training was 12.5 (range 7-16). A total of 14,718 procedures were performed, 32.6% of which were categorized as tumor procedures. Overall, only 36.4% of candidates reported tumor procedures making up >50% of their case volume. Between 2004-5 and 2012-13, the proportion of tumor procedures decreased (45.4% vs. 36.4%; $p<0.001$), while the number of adult reconstruction procedures increased (8.8% vs. 18.8%; $p<0.001$)(Figure 1).

Conclusions: Between 2004 and 2013, only one-third of recently trained tumor fellows had practices with tumor procedures accounting for >50% of their total case volume. This information should be of interest to current trainees interested in orthopaedic oncology fellowship training as well as orthopaedic oncology educators.

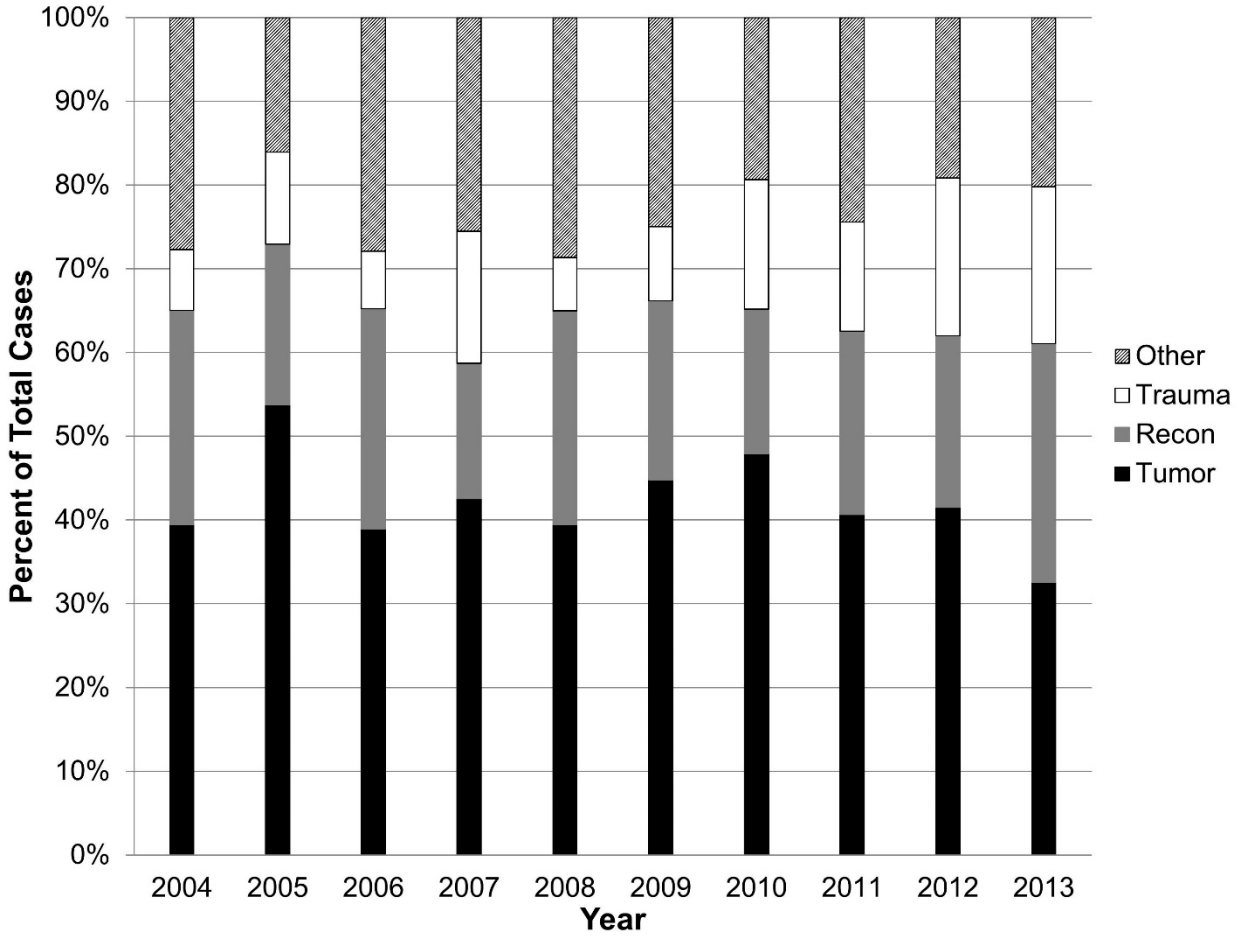

Fig. 1. This graph displays the proportion of tumor, recon (adult reconstruction), trauma, and other procedures performed by examinees who reported a history of orthopaedic oncology fellowship training between 2004 and 2013.

PAPER 12

A Qualitative Study to Determine Barriers and Facilitators Encountered in Collaborative Prospective Research in Orthopaedic Oncology

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BACKGROUND: Due to the rarity of bone and soft-tissue malignancies, multi-center prospective collaboration is essential for broadly meaningful research and evidence-based advances in patient care. The objective of this study was to identify barriers and facilitators encountered in large-scale collaborative research in orthopaedic oncology by orthopaedic surgeons involved or interested in prospective multi-center collaboration.

METHODS: All surgeons who are involved in or have expressed interest in the ongoing Prophylactic Antibiotic Regimens in Tumor Surgery (PARITY) trial were invited via email to participate in an in-person focus group to discuss barriers and facilitators encountered in collaborative research in orthopaedic oncology. The resulting focus group discussion was digitally recorded, transcribed verbatim and anonymized. The focus group transcript was coded using conventional content analysis and a qualitative descriptive approach – an analytic approach which aims to organize the data with little theoretical interpretation in the language of the participants. We chose Qualitative Description because it allows the

findings to be represented and organized in a manner that will facilitate knowledge translation in the orthopaedic oncology community for future scientific endeavors.

RESULTS: The 13 orthopaedic surgeons who participated in the in-person focus group discussion represented orthopaedic oncology practices from 7 different countries (Argentina, Brazil, Italy, Spain, Denmark, United States and Canada). Four categories and associated themes emerged from the discussion: (1) The Need for Collaboration in the Field of Orthopaedic Oncology due to the rare incidence of disease and the need for higher level evidence to guide treatment; (2) Motivational Factors for Participating in Collaborative Research including establishing proof of principle, learning opportunity, sense of community and answering a relevant research question; (3) Facilitators for Participating in Collaborative Research including leadership, institutional facilitators, authorship, trial set-up, trial momentum and Methods Centre support; and (4) Barriers to Participating in Collaborative Research including institutional barriers, personal level barriers, protocol barriers, paperwork, translation and lack of funding.

CONCLUSIONS: Orthopaedic surgeons involved in an ongoing international RCT were motivated by many factors to participate in the trial and described many barriers to and facilitators for their participation. There was a collective sense of fatigue experienced in overcoming barriers to participating in collaborative research which was mirrored by a strong collective sense of the importance of, and need for collaborative research in the field of orthopaedic oncology. Overall, the experiences were felt to be important and educational first steps to move forward collaborative studies in the field of orthopaedic oncology, and the knowledge gained from this study will guide future study design and large-scale collaborative research development in the field of orthopaedic oncology.

PAPER 13

IlluminOss Lightfix Trial: A Prospective, Multi-Center Study of the IlluminOss System for the Treatment of Impending and Actual Pathological Fractures in the Humerus from Metastatic Bone Disease

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Background: Surgical treatment of metastatic disease affecting the humerus 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.

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 safety and performance data of the IS. Results from this study will be used to confirm clinically and statistically significant reductions in pain and improvements in function for the purpose of US FDA marketing clearance.

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%.

Actual Fracture-Specific Inclusion Criteria
4. Fracture is closed, Gustilo Type I or IIA.

General Exclusion Criteria
1. Primary tumor at site.
2. Concomitant traumatic fracture at any other location that would preclude ability to assess pain in humerus.
3. Infections that could involve the device implant site.
4. Allergy to implant materials.

Impending Fracture-Specific Exclusion Criteria
5. Mirels' Score < 8.
6. Destruction of cortical bone < 50%.
7. Prior surgery and/or prior fracture of affected site.
8. Any articular component to impending fracture.

Actual Fracture-Specific Exclusion Criteria
9. Open fractures with severe contamination.
10. Extremely comminuted fractures where insufficient holding power of the balloon on the intramedullary canal is probable.
11. Delivery sheath is unable to cross fracture site after proper fracture reduction
12. Intramedullary canal smaller than the diameter of the sheath.

Clinical and radiographic follow-up evaluations are scheduled for 7, 30, 90, 180, and 360 days post-index procedure.

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 MSTS function of 7 (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 will be reported cumulatively for 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 7 respectively). All patients with at least day 7 follow-up will be 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. Baseline data is available on 77. 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%. 90 day follow up data is available for 39 patients, 13 of whom died. Preliminary Safety Success was 94%. There were five device fractures, all in patients with actual fractures with primary renal cell carcinoma or myeloma.

Data monitoring, collection and analysis are ongoing. Results will be updated prior to the annual meeting.

Conclusions: Enrollment into the largest prospective, industry sponsored clinical trial in metastatic fractures has been completed, the purpose of which is to obtain FDA approval for a new device for fixation of the humerus affected by metastatic disease. Stabilization was achieved using a single incision in the majority of patients. Five of 81 devices fractured. Clinical outcomes data collection is ongoing.

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2. Kim JH et al. Minimally invasive surgery of humeral metastasis using flexible nails and cement in high-risk patients with advanced cancer. Surgical Oncology. 2011;20(1):e32-e37.
3. Pretell J et al. Treatment of pathological humeral shaft fractures with intramedullary nailing. A retrospective study. Int Orthop. 2010;34(4):559-563.
4. Deschamps F et al. Percutaneous stabilization of impending pathological fracture of the proximal femur. Cardiovasc Intervent Radiol. 2012;35(6):1427-1432.

PAPER 14

Treatment of Metastatic Lesions of the Femoral Head and Neck: A Survey of the Members of the Musculoskeletal Tumor Society

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Background: Metastatic disease involving the femoral head and neck is often treated with a hemiarthroplasty or total hip arthroplasty (THA) to prevent pathologic fracture. There are no outcome studies to support one option over the other in the oncologic literature. This investigation seeks to identify the current practices of orthopedic oncologists with regard to implant choices when treating metastatic lesions of the femoral head and neck. We hope to use this information to identify areas of substantial disagreement that could be addressed by a prospective multi-institutional clinical trial.

Questions:

1. Do orthopaedic oncologists treat metastatic lesions of the femoral head and neck with hemiarthroplasty or THA?
2. Does the choice of treatment depend on patient variables including age, extent of metastasis, and histologic subtype of the primary cancer?
3. Does the choice of treatment depend on completion of an arthroplasty fellowship, or active elective arthroplasty practice?
4. When hemiarthroplasty is chosen, is monopolar or bipolar head reconstruction preferred?

Methods: This investigation was designed as an online survey of the members of the Musculoskeletal Tumor Society (MSTS). The investigation was reviewed by our Institutional Review Board and deemed exempt. The Research and Executive Committees of the MSTS each reviewed and approved the content. The survey contained surgeon demographic questions and 7 clinical vignettes with identical imaging of a pathologic lesion of the femoral head and neck (Table 1). The primary outcome measured was decision to treat the lesion with hemiarthroplasty or THA. Secondary outcomes measured were the reason for each treatment decision (using a ranked Likert scale) and the use of monopolar or bipolar hemiarthroplasty. Member responses were analyzed by age of the respondent, whether the respondent had completed an adult reconstruction fellowship, and whether the respondent had an elective adult arthroplasty practice. Pairwise Kappa statistics were used to determine the inter-observer reliability on primary treatment decision of hemiarthroplasty compared to THA.

Results: A total of 93 (30.0%) members of the MSTS completed the survey. The reconstructive option chosen by the respondents varied by the clinical presentation. Overall the responses in the cases of younger patients with only skeletal metastatic disease and a favorable histologic subtype (cases 1, 2 and 4) indicated a lack of agreement between treatment with THA or hemiarthroplasty, with 40.9%, 52.7% and 32.3% of respondents choosing THA, respectively (Tables 1 and 2). Kappa analysis indicated that for respondents choosing a THA for case one, there was substantial inter-observer agreement for choosing a THA cases 2 and 4. On a rank scale, decreased risk of dislocation

was identified by respondents as the most important reason for choosing hemiarthroplasty, while improved pain and functional outcome was most important for THA. Completion of an arthroplasty fellowship or maintaining an elective arthroplasty practice was rarely a significant predictor of treatment decision (Table 2). When a hemiarthroplasty was chosen, most respondents reported using bipolar rather than monopolar heads (57.9%-79.5%).

Conclusion: When treating metastatic lesions of the femoral head and neck for impending pathologic fracture orthopaedic oncologists do not agree on reconstructing with THA versus hemiarthroplasty for patients with younger age, bone only disease and favorable histology. Furthermore, in the cases of hemiarthroplasty, there is a lack of practice regularity as to the type of head utilized. This investigation indicates the need for a prospective study to evaluate patient outcomes following reconstruction of metastatic defects of the femoral head and neck in order to determine the optimal treatment method for these patients.

Table 1: Description of clinical vignettes presented to respondents

			Metastases				
Vignette	Age	Histology	Solitary Bone	Multiple Bone	Bone and Visceral	Plan for Radiation	Kappa vs 1
1	68	Breast	x			x	n/a
2	55	Breast	x			x	0.72
3	80	Breast	x			x	0.36
4	68	Breast		x		x	0.77
5	68	Breast			x	x	0.44
6	68	Lung	x			x	0.49
7	68	Lung			x	x	0.15

Table 2: Percentage of respondents choosing THA over hemiarthroplasty for reconstruction

Vignette	n =	1	2	3	4	5	6	7
Overall	93	40.9	52.7	17.2	32.3	18.3	20.4	5.38
Age								
30-39	32	43.8	62.5	12.5	28.1	12.5	15.6	6.3
40-49	23	34.8	34.8	8.7	30.4	13.0	13.0	4.3
50-59	21	33.3	42.9	14.3	28.6	19.0	19.0	0.0
60-69	12	66.7	75.0	58.3	58.3	50.0	50.0	16.7
70+	5	20	60.0	0.0	20.0	0.0	20.0	0.0
	p=	0.30	0.21	**0.01**	0.39	**0.07**	0.13	0.37
Fellowship								
Arthroplasty	9	44.4	66.7	44.4	44.4	33.3	33.3	11.1
None/Non-arthroplasty	84	40.5	51.2	14.3	31.0	16.7	19.0	4.8
	p=	0.99	0.49	**0.04**	0.46	0.36	0.38	0.41
Elective Practice								
Arthroplasty Practice	45	48.9	55.6	24.4	37.8	24.4	26.7	11.1
None/Non-arthroplasty	48	33.3	50.0	10.4	27.1	12.5	14.6	0.0
	p=	0.13	0.59	0.07	0.27	0.14	0.15	**0.02**

PAPER 15

Predictors of Surgical Site Infection and Implant Failure Secondary to Infection in Proximal, Distal and Total Femur Replacement in Patients Treated For Musculoskeletal Tumors

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Background: Primary and metastatic bone tumors frequently occur in the femur. Metallic endoprostheses are becoming the most common reconstruction modality used for treatment of these tumors. Although significant progress has been made in implant technology, rates of surgical site infection (SSI) and failures of these devices secondary to infection remain high in comparison to other arthroplasty procedures. Few studies have focused specifically on the identification of predictors of SSI and implant failure due to infection of proximal, distal and total femoral replacements in oncologic treatment.

Questions/Purposes: We aimed to retrospectively identify the predictors of (1) SSI and (2) implant failure due to infection in proximal, distal and total femur replacement in patients treated with radical resection and endoprosthetic reconstruction of malignant and/or locally aggressive benign musculoskeletal tumors.

Patients and Methods: This is a retrospective survey of patients treated for a malignant bone tumor or a locally aggressive benign bone tumor with a proximal, distal or total femur replacement at a large, urban adult hospital from 1992 to 2015. Patients were identified using a database search and data was collected from electronic medical records. 177 candidates were available for review. Outcome parameters were (1) SSI and (2) implant failure due to infection. For SSI evaluation, patients were included if they had a SSI one year from surgery or if they had at least one year of follow up. For evaluation of implant failure, patients were included if they had a documented implant failure or at least one year of follow-up. Because exclusion criteria differed for our two outcomes, two different cohorts were created. Twenty-two patients were excluded from the SSI cohort due to lack of follow-up and 12 patients were excluded from the implant failure cohort due to lack of follow-up. Two patients were excluded from both cohorts because of treatment for non-oncologic reasons. 163 patients [69 males (42.33%), median age 51 (IQR 37-61)] were included in the implant failure cohort. 153 patients [65 males (43.05%), median age 51 (IQR 36-61)] were included in the SSI cohort. All SSIs were confirmed by clinical presentation and positive culture. Implant failure was defined as an implant requiring complete revision of the endoprosthesis, unplanned revision of a failed portion of the endoprosthesis, fixation of a periprosthetic fracture, soft-tissue reconstruction to restore joint stability, endoprosthetic removal without subsequent reconstruction, or amputation. For SSI predictors, bivariate analysis was performed

using binary logistic regression analyses for each variable. Significant bivariate predictors were used to create a multivariable logistic regression. For implant survival predictors, log-rank test of equality across strata was performed for each categorical variable and a bivariate Cox-proportional hazard regression was performed for each continuous variable. Significant predictors were entered into a multivariate Cox proportional hazards model. All factors that maintained a p-value of <0.08 were then entered into a backward elimination stepwise regression to test independence.

Results: Of the 153 patients in the SSI cohort, 20 patients (13.25%) experienced SSI while 131 (86.75%) did not (Table 1). Two variables, hematoma formation (p=0.05) and wound dehiscence (p=0.009) were significant bivariate predictors of SSI. Wound dehiscence maintained significance (p= 0.02, OR=9.86, 95%CI=1.43-68.06) in multivariate analysis.

Of the 163 patients in the implant failure cohort, implant failure due to infection occurred in 10 patients (6.13%; Table 2) while 23 patients (14.11%) experienced failure due to aseptic loosening, 9 (5.52%) due to soft tissue failure, 17 (10.43%) due to structural failure and 3 (1.84%) due to tumor progression. Median implant survival was 3.67 years (IQR 1.67-6.51). Of the 10 patients who had implant failure secondary to infection, 4 (40%) previously experienced SSI. Postoperative hematoma formation (p<0.001), previous SSI (p=0.002), preoperative albumin level (p=0.032), infection at another site on date of surgery (p=0.033), and wound dehiscence (p=0.0495) reached significance in bivariate analysis of implant failure due to infection. After stepwise regression with multivariate Cox proportional hazards modeling, hematoma formation was a significant independent predictor of implant failure due to infection (HR=30.03, 95%CI=4.95-182.09, p<0.001).

Conclusions: Our patient population had similar rates of both SSI and implant failure secondary to infection compared with previous studies of oncologic procedures. Our finding that aseptic loosening was the most common cause of implant failure differs from some previous studies that have found infection to be a leading cause of implant failure. Our data suggest that strict intraoperative hemostasis is warranted to reduce implant failure due to infection while aggressive management of wound dehiscence is warranted to reduce SSI. Our study is limited by its retrospective nature and our combination of different types of femoral replacement.

Level of evidence: III

Table 1. Comparison of no surgical site infection and surgical site infection groups

	No SSI n = 131	SSI n = 20	
	median (IQR)	median (IQR)	*p*-value
Age (years)	51 (35-61)	50 (37-69.5)	0.652
BMI (kg/m^2; n =133)	27.5 (24.1-32.8)	26.76 (24-30.4)	0.3531
Charslon Comorbidity Index	2 (2-6)	4.5 (2-6)	0.315
No. of preceding procedures	1 (1-2)	1 (1-3)	0.624
Preoperative Albumin (mg/dL; n = 104)	4.4 (4-4.65)	4 (3.6-4.6)	0.131
Preoperative WBC (10^9/L; n = 144)	7.55 (6-8.9)	6.7 (5.8-8.45)	0.444
Pre-operative hospital stay (day)	0 (0-1)	0 (0-0.5)	0.938
Procedure duration (minutes)	185 (152-245)	148 (127.5-240.5)	0.137
Length of resection (cm; n = 92)	15.25 (12-20)	12 (10.5-20)	0.67
Transfusion (units pRBC; n = 149)	0 (0-2)	0 (0-1)	0.804
	n (%)	*n (%)*	
Male	55 (41.98%)	10 (50%)	0.331
History of smoking (n = 150)	27 (20.61%)	4 (20%)	0.585
ACS wound category (n = 150)			0.501
1	125 (96.15%)	20 (100%)	
2, 3, or 4	5 (3.85%)	0 (0%)	
Replacement location			
Proximal replacement	43 (32.82%)	6 (30%)	0.55
Distal replacement	68 (51.91%)	9 (45%)	
Total replacement	20 (15.27%)	5 (25%)	
Infection at other site on day of surgery	6 (4.58%)	0 (0%)	0.437
Hip region affected	59 (45/04%)	12 (60%)	0.157
Flap/skin graft used	5 (3.82%)	1 (5%)	0.58
Hair removal (n = 130)	35 (31.25%)	3 (15%)	0.238
Drain use	118 (90.77%)	18 (90%)	0.586
Vacuum assisted closure	7 (5.34%)	1 (5%)	0.714
Revision of prior surgery	57 (43.51%)	12 (60%)	0.128
Press fit used	30 (22.90%)	5 (5%)	0.515
Malignant disease	111 (84.73%)	15 (75%)	0.215
Neoadjuvant chemotherapy (n = 115)	19 (18.27%)	4 (36.4%)	0.151
Neoadjuvant radiotherapy (n = 115)	20 (19.23%)	3 (27.3%)	0.382
Metastasis	37 (28.24%)	8 (40%)	0.207
Hematoma	**2 (1.53%)**	**2 (10%)**	**0.078**
Wound dehiscence	**2 (1.53%)**	**3 (15%)**	**0.015**

Note: P-values for Fisher's exact test for nominal variables, Mann/Whitney test for continuous variables.

Bolded p-values significant (p<0.05)

For variables with missing data, n is listed

Table 2. Comparison of implant failure due to infection and no implant failure due to infection groups

	No failure due to infection n = 153	Failure due to infection n = 10	
	median (IQR)	median (IQR)	*P value*
Age (years)	52 (37-61)	43.5 (38-59)	0.6985
BMI (kg/m^2; n =125)	27.55 (24.3-32.8)	26.98 (24.91-32.6)	0.97
Charslon Comorbidity Index	3 (2-6)	4 (2-6)	0.9771
No. of preceding procedures at site	1 (1-2)	1 (1-3)	0.9885
Preoperative Albumin (g/dL; n = 111)	4.4 (4-4.6)	3.85 (2.95-4.65)	0.1961
Preoperative WBC (10^9/L; n = 154)	7.5 (5.95-8.75)	7 (6.4-10)	0.646
Pre-operative hospital stay (days)	0 (0-0.5)	0 (0-1)	0.9786
Procedure duration (minutes; n =142)	184 (141-246)	174 (164.5-217.5)	0.8249
Length of resection (cm; n= 102)	15.75 (12-20)	15 (9.25-27.5)	0.7169
Blood transfusion (units pRBC)	0 (0-1)	0 (0-2)	0.6132
	n (%)	*n (%)*	
Male	62 (40.52%)	7 (70%)	0.098
History of smoking	30 (19.61%)	3 (30%)	0.328
ACS wound category (n = 152)			
1	148 (97.37)	9 (90%)	0.276
2, 3, or 4	4 (2.63%)	1 (10%)	
Replacement location			
Proximal replacement	50 (32.68%)	3 (30%)	0.452
Distal replacement	80 (52.29%)	4 (40%)	
Total replacement	23 (15.03%)	3 (30%)	
Infection at other site on day of surgery	**4 (2.61%)**	**2 (20%)**	**0.045**
Hip region affected	71 (46.41%)	5 (50%)	0.539
Flap/skin graft used	6 (3.92%)	0 (0%)	0.68
Hair removal (n=132)	37 (28.03%)	4 (40%)	0.175
Drain use	139 (91.45%)	9 (90%)	0.606
Vacuum assisted closure	8 (5.23%)	0 (0%)	0.596
Revision of prior surgery	73 (47.71%)	4 (40%)	0.444
Press fit used	39 (25.49%)	2 (20%)	0.518
Malignant disease	127 (83.01%)	7 (70%)	0.253
Neoadjuvant chemotherapy (n = 115)	62 (40.52%)	2 (20%)	0.535
Neoadjuvant radiotherapy (n = 115)	23 (20%)	1 (10%)	0.513
Metastasis	44 (28.76%)	3 (30%)	0.591
Hematoma	**2 (1.31%)**	**2 (20%)**	**0.019**
Wound dehiscence	5 (3.27%)	1 (10%)	0.32
Previous surgical site infection (SSI)	**14 (9.15%)**	**4 (40%)**	**0.015**

Note: P-values calculated with Fisher's exact test for nominal variables, Mann/Whitney test for continuous variables.

Bolded p-values significant (p<0.05)

For variables with missing data, n is listed

PAPER 16

The Prophylactic Antibiotic Regimens in Tumor Surgery (PARITY) multicenter randomized controlled trial: International expansion of the collaborative network

Author: Michelle Ghert for The PARITY Investigators

Institution: McMaster University

Background:
PARITY is an international multi-center randomized controlled trial in which patients with a bone tumor of the lower extremity undergoing endoprosthetic reconstruction are randomized to one of two study arms: 1 day of post-operative antibiotics, or 5 days of postoperative antibiotics. The study opened to pilot phase enrolment in 2013. The following is an update of the trial progress with a focus on enrolment and international expansion.

Methods:
PARITY patients are randomized by the pharmacy team at each site through an online randomization program (www.randomize.net). The remaining study participants (patients, surgeons, nurses, study personnel) are blinded to treatment allocation. The primary outcome is surgical site infection and outcomes assessment is adjudicated by the PARITY Adjudication Committee through an online secure platform (Global Adjudicator™). Data is monitored for patient safety by an independent Data Safety and Monitoring Committee. Data quality is screened at regular intervals to maintain high standards of data quality. A total of 37 sites across 7 countries and 5 continents have opened for enrolment in the PARITY trial.

Results:
At the time of abstract submission, a total of 158 patients have been randomized across sites in the United States, Canada, Argentina, Brazil, South Africa, Spain and Australia. Sites currently in the active start-up phase (contract negotiations and ethics applications) represent the United States, the Netherlands, Israel, Denmark, Germany, France and India. The PARITY Pilot was published in September 2015 and the Canadian Institutes of Health Research and the Canadian Cancer Society have awarded funding for the definitive phase of PARITY. Data from the pilot study confirms feasibility in enrolment, follow-up and data quality. The regulatory complexities of opening the study in Europe were overcome in early 2016 and the first European patient was enrolled in Spain in February 2016.

Conclusion:
Challenges of multi-center collaboration have been overcome by strong investigator and research personnel support at each site in facilitating contract negotiations, trouble-shooting ethics applications, translating study material into different languages, managing variances in available antibiotics and working with national regulatory requirements. Despite the momentum of the PARITY trial, the pace of enrolment indicates that a larger collaborative network will be crucial for reaching the enrolment target of 600 patients. All MSTS Members are invited to participate.

PAPER 17

A Modified Tomita Saw Technique in Patients Undergoing En Bloc Spondylectomy for Spinal Tumors: Surgical Technique and Results

Authors: Akash A. Shah, MD, Nuno R. Paulino Pereira, MD, Francis J. Hornicek, MD, Joseph H. Schwab, MD

Institution: Department of Orthopaedic Surgery, Massachusetts General Hospital, Boston, MA

Background: Achieving negative tumor margins has long been a challenge in the surgical management of spinal tumors, as the anatomical proximity of the tumor to major neurovascular structures often makes en bloc resection technically difficult. However, total en bloc spondylectomy (TES) has been shown to improve local control and survival, as opposed to curettage and piecemeal resection. Tomita et al. reported the TES with a Tomita thread-wire saw in 1994; this technique relies on a single posterior approach, consisting of an en bloc laminectomy with a subsequent en bloc corpectomy via a thread-wire saw, which is operated in an anterior-posterior direction. Alarmed by the risk of damaging the spinal cord when sawing through the vertebral body, our group of orthopaedic oncologists has employed a modified approach. After an en bloc laminectomy and posterior stabilization during a first posterior stage, the Tomita saw is passed around the vertebral body – we maneuver the saw between the thecal sac and vertebral body. In a second anterior stage, the surgeon uses the Tomita saw to resect the tumor in an anterolateral direction, sparing the spinal cord and major vessels from potential injury.

Purpose: We feel that this modified staged approach may result in better oncologic resection margins while reducing the risk of damage to critical neurovascular structures; however, two-staged procedures may introduce increased risk of blood loss, higher infection rates, and other complications. Thus, we aim to describe this new surgical technique in greater detail, assess intra-operative and post-operative complications, and assess surgical outcomes.

Patients and Methods: This is a retrospective analysis of 33 patients who underwent a modified Tomita saw spondylectomy for a spinal tumor at a single tertiary-care institution from the years 2000-2016. We identified eligible patients from our oncological database by searching for certain phrases in operation reports that indicate spondylectomy using the modified Tomita saw procedure, and extracted all relevant clinical and operative data. We graded complications based on the Clavien-Dindo classification of surgical complications.

Results: The median age of our 33 patients was 58 years, and 19 (58%) were male. The most common primary tumor type was chordoma (58%), followed by chondrosarcoma (24%). Most tumors were located in the lumbar spine (60%), and most TES spanned 1 vertebral level (58%). Negative oncologic margins were achieved in all patients. With respect to intra-operative complications, dural tears were encountered in 11 (33%) patients and significant bleeding occurred in 2 (6.0%) cases. There was no spinal cord injury. The most common post-operative complications were grades II (15%) and IIIb (15%) in the Clavien-Dindo classification of surgical complications, with the majority of patients (55%) suffering from grade I complications. Importantly, there were no deaths within the hospital admission among patients who underwent the modified Tomita saw procedure. Furthermore, we observed 100% survival in the 26 patients with at least 1 year of follow-up, 100% survival in the 9 patients with at least 3 years of follow-up, and 100% survival in the 2 patients with at least 5 years of follow-up.

Conclusions: This modified Tomita saw procedure represents a potentially safer technique for spinal tumor resection than the traditional TES approach. We think that the combination of passing the saws ventral to the spinal cord in the first posterior stage, and sawing in an anterolateral direction in the second anterior stage of the procedure protects the spinal cord from injury; indeed, no patient in this analysis suffered spinal cord injury. The majority of patients suffer only mild complications with 0 deaths observed within the hospital admission, suggesting that the two-staged approach does not introduce significant risk to the post-operative course. Notably, negative oncologic margins were achieved in every patient and 100% survival was observed after 1, 3, and 5 years in patients with appropriate follow-up. These encouraging results – observed regardless of primary tumor type – demonstrate the excellent safety and outcome profile of the modified Tomita saw technique.

Table 1. Baseline Characteristics	n = 33	
	Median (IQR)	
Age (years)	58	(33 - 64)
	Number (%)	
Sex		
Male	19	(58)
Female	14	(42)
Primary tumor type		
Chordoma	19	(58)
Chondrosarcoma	9	(24)
Metastasis†	3	(9.0)
Ewing's sarcoma	1	(3.0)
Solitary fibrous tumor	1	(3.0)
Location of tumor		
Lumbar spine	20	(60)
Thoracic spine	12	(36)
Thoracolumbar spine	1	(3.0)
Number of resected vertebral levels		
1	19	(58)
2	6	(18)
3	7	(21)
4	1	(3.0)

IQR = Interquartile Range.

† Metastatic tumors included: leiomyosarcoma (n=1), mixed germ cell tumor (n=1), and pleomorphic sarcoma (n=1).

Table 2. Outcomes and Complications	n = 33	
	Number (%)	
Negative oncologic margins	33	(100)
Intra-operative complications		
Dural tear	11	(33)
Significant bleeding	2	(6.0)
Spinal cord injury	0	(0.0)
Post-operative complications†		
II	5	(15)
IIIa	3	(9.1)
IIIb	5	(15)
IVa	1	(3.0)
IVb	1	(3.0)
V	0	(0.0)
	Rate (%)	
Survival‡		
1 year	26/26	(100)
3 years	9/9	(100)
5 years	2/2	(100)

† Clavien-Dindo classification of surgical complications, including only grade II or higher and excluding blood transfusions. Grade II: complication requiring pharmacological treatment with medications other than antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physical therapy; Grade III: complication requiring surgical, endoscopic, or radiologic intervention (a) without general anesthesia (b) with general anesthesia; Grade IV: life-threatening complication with (a) single organ dysfunction (including dialysis) (b) multi-organ dysfunction; Grade V: death.

‡ Of the 26 patients >1 year out from surgery, 0 were lost to follow-up. Of the 10 patients >3 years out from surgery, 1 was lost to follow-up. Of the 3 patients >5 years out from surgery, 1 was lost to follow-up.

PAPER 18

Computer assisted planning and patient specific instruments improve accuracy of pelvic bone tumor resection: A cadaveric study.

Authors:
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Institutions:
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2. Fundación Vall d´Hebron Institut de Recerca VHIR, Barcelona, Spain

Background: Tumor resection within the pelvis is challenging due to the complex bone geometry and the proximity of organs, nerves and vessels. Preoperative planning and its precise execution is crucial to obtain wide margins and avoid unnecessary tissue resection or iatrogenic lesions. Local recurrence is directly related to inappropriate margins. Recently, computer assisted preoperative planning and patient specific instruments (PSIs) have been developed for improving surgical resection accuracy.

Questions/Purposes: The aims of this experimental study were to assess the accuracy of PSIs versus a standard manual technique and the precision of computer assisted planning and PSI guided osteotomy workflow in pelvic tumoral resection.

Materials and Methods: In an experimental cadaveric study computer tomography scans were obtained from 5 female cadaveric pelvises. Using Mimics ® software, segmentation was performed to create a 3d pelvic bone model for each pelvis. Then with the 3-matic® software 5 pelvic osteotomies were designed, one sacroiliac, one biplanar supraacetabular, 2 parallel iliopubic, and one ischial. On the right hemipelvis, angles and distances of the planes from key anatomic references were recorded. These preoperative guidelines were printed for the right hemipelvis osteotomies. On the left hemipelvis, using the 3-matic® software, patient specific instruments (PSI) were designed to guide standard oscillating saw osteotomies (Figure 1). These guides were then manufactured through 3d printing. The osteotomies were performed using standard manual technique on the right hemipelvises and using the PSIs on the left hemipelvises (Figure 1). CT scans were obtained from the resected specimens. Postresection CT scans were quantitatively analyzed to determine the accuracy of the resections compared to the preoperative plan, which included measuring the maximum linear deviation and the angular pitch and roll deviation of the osteotomies from the preoperative planned planes. Statistical analysis was performed using SPSS (SPSS 20.0 Student Version for Windows). Descriptive statistics were used to present the results. Quantitative variables were compared using the parametric t-student test and the non-parametric Mann-Whitney U-test considering a p value of < 0.05. A box plot graphs were used to summarise the distribution of our sample.

Results: Compared with the manual technique, the patient specific instrument guided osteotomies resulted in a mean improvement of 9,6 mm ($p < 0,008$) in the sacroiliac osteotomies, 6,2 mm ($p < 0,008$) and 5,8 mm ($p < 0,032$) in the biplanar supraacetabular osteotomies, 3mm ($p < 0,016$) in the ischial osteotomies, and 2,2 mm ($p < 0,032$) and 2,6 ($p < 0,008$) in the parallel iliopubic osteotomies with a mean linear deviation of 4,9 mm ($p < 0,001$) for all the osteotomies (Chart). Fifty-three percent of the standard

technique osteotomies (n=16) had a linear deviation greater than 5mm and 27% (n = 8) greater than 10mm whilst with the PSIs there were 10% (n = 3) and 0 % (n = 0) respectively. We observed a mean of 7,06º ($p < 0,001$) improvement in pitch and mean of 2,94º ($p < 0,001$) improvement in roll for the angular deviation from the preoperative planned planes.

Conclusions: There are no previous reports in the literature evaluating the precision of PSIs in pelvic tumor surgery. Our study has several limitations. In a clinical setting the soft tissue tumor mass can impede or limit the application of PSIs. Nerves and vessels are also present in the surgical field which can both alter the results from incorrect placement or from iatrogenic damage. Only two surgeons performed all the osteotomies, and although the results seem clear and promising larger clinical studies with multiple surgeons should be performed to validate these results. Computer assisted planning and patient specific instruments improve accuracy of pelvic bone tumor resection when compared to standard manual techniques in an experimental study.

Level of Evidence V: Cadaveric Study

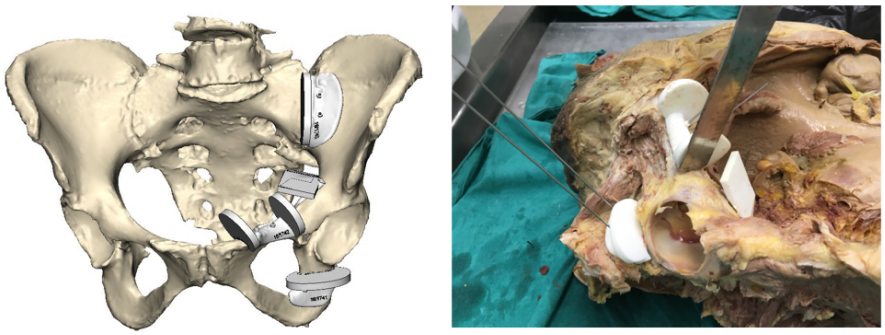
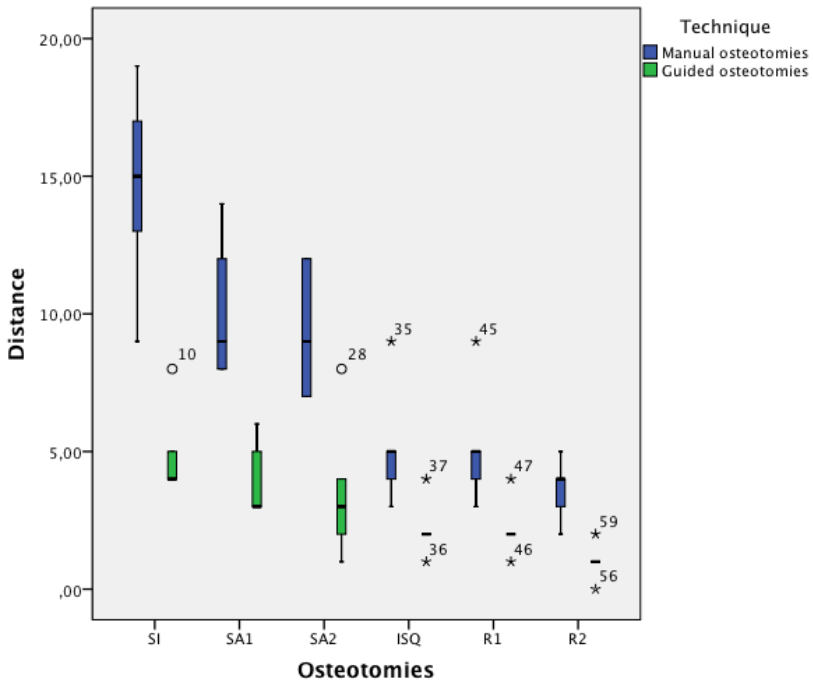


Figure 1. Left: Designed PSIs in 3D pelvic bone model. Right: Iliopubic osteotomy guided with PSI.



PAPER 19

Can Aortic Balloon Occlusion Reduce Blood Loss in Sacral Tumor Resections When the Lower Lumbar Spine is Involved?

Authors: Yidan Zhang, MD, Wei Guo, MD, PhD, Shidong Wang, Nikolas Zaphiros

Institutions: Musculoskeletal Tumor Center, Peking University; and People's Hospital, Beijing, China.

Background:
Although orthopedic surgeons have successfully used aortic balloons to reduce blood loss during sacral tumor resections, it has not been validated in more massive sacral tumors involving the lower lumbar spine. It is also unknown what precautions should be taken to avoid balloon-related complications under these circumstances.

Questions/Purposes:
We asked: (1) Can aortic balloon occlusion reduce blood loss in sacral tumor resections when the lower lumbar spine is involved? (2) Does the aortic balloon help decrease the operating time and shorten the length of stay in hospital? (3) What balloon-related complications are commonly seen and distinct from those whose lumbar spine is not involved?

Patients and Methods:
Between 2004 and 2015, 56 patients were diagnosed with sacral tumors involving the lower lumbar spine (L4, L5) at our institute. During that time, 30 of the patients received aortic balloon occlusion therapy while 26 of the patients did not. The criterion on whether or not to use aortic balloon occlusion was largely dependent on the surgeons' preference. For instance, some surgeons limited the use of the aortic balloon only for patients younger than 70 years of age, while others avoided using the balloon out of cautiousness for severe complications. The balloon was introduced percutaneously via femoral artery through a catheter and placed caudal to the level of the renal artery bifurcation. We compared intraoperative blood loss, transfusion volume, operating time, postoperative wound drainage and length of stay in the hospital between the two groups using independent t-test and Mann-Whitney-Wilcoxon test. All the patients were followed up for at least 6 months for balloon-related complications.

Results:

Intraoperative blood loss and transfusion volume was determined to be significantly less in patients treated with the balloon ($p<0.05$). Length of stay in the hospital was also shorter compared to the non-balloon group ($p<0.05$). Moreover, the total operating time, which included the radiographic intervention, was not prolonged in the balloon group. However, the balloon group tended to have more wound drainage within the 12 h after the operation, which was not significant ($p>0.05$). Major balloon-related complications included acute renal failure, temporary renal insufficiency and lower limb ischemia and femoral artery dissection requiring direct arterial intervention. Minor balloon-related complications included local hematoma and temporary femoral artery spasm, which could be reversed by removal of the sheath. Delayed wound bleeding requiring surgical exploration or immediate embolization were seen in both groups. There was no significant causality directly or potentially related to the balloon-related complications.

Conclusions:

Our results show that placement of the balloon at a certain level just caudal to the renal artery bifurcation, can reduce intraoperative blood loss and transfusion in sacral tumor resections even when the lower lumbar spine is involved. The indication for aortic balloon occlusion therapy may potentially be extended to the solitary lower lumbar tumors. Balloon-related complications are common. Most of the complications were not deadly and reversible by corresponding treatments. Acute renal failure, temporary renal insufficiency were complications I had never seen when the lower spine was not involved. The limitations of this study include its retrospective fashion and small number of cases. A randomized controlled trial is a better way to elucidate the therapeutic effect.

Figures and Tables:

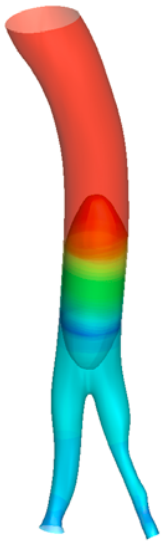


Fig.1 A pressure cloud chart of the aortic balloon placing at the level between renal artery bifurcation and iliac artery bifurcation.

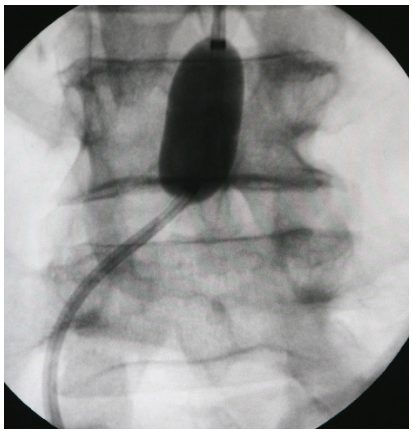


Fig.2 An X-Ray image of an inflated balloon placing at L3 vertebral level.

PAPER 20

Title: Outcome and Complications Following Free Fibula Reconstruction for Oncologic Defects of the Spine and Pelvis

Authors: Matthew T. Houdek, MD, Karim Bakri, MD, Franklin H. Sim, MD, Peter S. Rose, MD, Steven L. Moran, MD

Institution: Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN

Background: Following tumor resection of the axial skeleton and pelvis, reconstructive surgeons are often left with large composite bone and soft tissue defects in a physiological poor host. Vascularized bone transfer, namely free fibula transfer, can be used in order to supplement stability to the spine and pelvis in the setting of large osseous defects. In the extremities the use of these flaps has been reliable, however, due to the various host factors the use of vascularized bone transfer has associated with a high complication rate in the setting of oncological reconstruction. Currently there is a paucity of data on the use of these flaps in the axial skeleton and pelvis, with historically a high rate of failure without vascularized bone transfer.

Purpose: The aim of this study was to review our institution's experience with the use of vascularized fibula reconstruction following an oncological resection in the axial skeleton and pelvis affecting 1) overall survivorship, 2) disease specific survival, both local recurrence and distant disease, 3) union of the fibula 4) postoperative complications and 5) patient function.

Methods: We retrospectively reviewed the records of 25 cases of vascularized fibula transfer performed to reconstruct a bony defect following an oncological resection of the spine, sacrum or pelvis from 2000 and 2014. Pertinent demographics as well as information regarding the surgical procedure and disease status at latest follow-up were reviewed. Disease free survival and overall survival were estimated using Kaplan Meier method. The cohort consisted of 14 males and 11 females; with a mean age at surgery of 38 years (14-68 yrs) and a mean follow-up of 5 yrs (range 1-14 yrs). The most common pathology was osteosarcoma (n=5) and chondrosarcoma (n=5).

The vascularized fibula was performed for sacropelvic reconstruction following total sacrectomy (n=6), multilevel vertebrectomy (lumbar, n=2, thoracic, n=3), external hemipelvectomy and sacrectomy (n=4), hemisacrectomy (n=4), internal hemipelvectomy and hemisacrectomy (n=3), and internal hemipelvectomy (n=3). Two fibulas were used in the reconstruction in 8 patients.

Results: The overall 2-, 5-, and 10-year survival was 73%, 53%, and 35%. In regards to disease specific survival, the overall 2-, 5-, and 10-year survival was 76%, 66% and 44%. No analyzed factor was associated with a worse disease specific survival (Table 2). Disease recurrence occurred in 7 patients (local only, n=2, distant, n=3, local and distant, n=2), leading to death in 5 patients.

In regards to union of the fibula graft, 4 patients expired prior to graft healing. Of the patients alive at final follow-up, the fibula graft failed in 4 patients. Although not significant, there were no cases of failure when a double rod construct was used compared the 4 failures where a single rod construct was used (P=0.26). One patient underwent an additional autologous bone grafting procedure. The mean time to union was 8 months (range 4-13 months) with an overall union rate of 76%.

Complications were common following this procedure, with 19 (72%) patients sustaining at least 1 postoperative complication. Complications included infection (n=6), wound dehiscence/delayed healing (n=6), hardware failure (n=3), dural leak (n=2), small bowel obstruction due to herniation through the posterior abdominal wall (n=2), fibula graft fracture (n=2), pedicle thrombosis (n=1), ischemic optic neuritis (n=1), and femoral nerve palsy (n=1). One patient had a failed condominant muscle flap failure, leading to an extended external hemipelvectomy due to infection and exposed surgical hardware. One patient sustained a rupture of the pedicle to the vascularized fibula from the iliac vessels, leading to death. There were no reported donor site complications.

Following the procedure the mean MSTS functional score was 16 (range 4-26). Thirteen patients were ambulating following the procedure.

Conclusion: The free-fibula is considered the work horse vascularized bone graft for extremity reconstruction, however data on the use of the vascularized fibula in the axial skeleton and pelvis is limited. The results of this study show the fibula can supplement reconstruction and fusion, with graft union in a majority of patients. Complications were high following the procedure and likely related to the physiological poor host and size and complexity of the surgery. Currently we advocate for the use of a double rod construction, as this could potential reduce rates of failure.

Table 1: Demographics of Patients Undergoing Vascularized Fibular Reconstruction of a Spinopelvic Defect

All Patients	
Males	14
Females	11
Mean age	38 years (range 14-68)
Mean Fibular Length	11 cm (range 7-18 cm)
Chemotherapy During Recovery Period	11
Radiation to Area	11
High Grade Tumors (Grade III or IV)	19
Pathology	
Osteosarcoma	5
Chondrosarcoma	5
Pleomorphic Sarcoma	3
Ewing Sarcoma	2
Chordoma	1
Post Radiation Osteosarcoma	2
Rectal Carcinoma	2
Benign Nerve Sheath Tumor	1
Myeloma	1
Myxopapillary Ependymoma	1
Angiosarcoma	1
Malignant Germ Cell Tumor	1

Table 2: Factors Associated with Development of Disease Recurrence and Overall Survival

Patient Factors	**Disease Specific Survival Hazard Ratio (95% CI)**	***P* Value**	**Overall Survival Hazard Ratio (95% CI)**	***P Value***
Age				
≤ 40 Years	1.28 (0.27-6.63)	0.74	1.91 (0.49-9.32)	0.35
> 40 Years	0.77 (0.15-3.59)	0.74	0.52 (0.10-2.03)	0.35
Male Gender	1.55 (0.33-7.96)	0.56	2.34 (0.60-11.29)	0.22
High Grade Tumor	2.06 (0.32-39.69)	0.47	3.43 (0.61-64.19)	0.18
Tumor Recurrence	-	-	2.29 (0.59-9.39)	0.22

PAPER 21

A Systematic Review of Surgical Outcomes after Limb-Sparing Resection and Reconstruction for Pelvic Sarcoma

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Institution: Investigation performed at Vanderbilt University Medical Center

Background: Limb-sparing resection and reconstruction for pelvic sarcomas in multiple small studies has been fraught with complications, reoperations and impaired patient function. However, the non-oncologic complication and reoperation rates and functional outcomes for patients have never been rigorously synthesized.

Purpose: A systematic review was undertaken to more accurately determine the non-oncologic complication and reoperation rates and functional outcomes for patients after pelvic sarcoma resection and reconstruction.

Methods: The review was performed in accordance with PRISMA guidelines. PubMed and Cochrane database searches of English-only studies using the terms Pelvis AND Sarcoma and Pelvis AND Sarcoma AND Surgery were performed. Study inclusion criteria: 10 or more patients enrolled, at least 12 months of follow-up, utilized validated functional outcome measure(s), and the majority of the resections were for primary bone sarcoma.

Results: 2,350 studies were reviewed, of which 22 level IV studies with a total of 801 patients met inclusion criteria. Reconstructive techniques varied widely and included allografts, allograft-prosthesis composites, saddle prostheses, custom endoprostheses and irradiated autografts. Pooled averages showed an average 5-year survival of 55%. The average local recurrence rate was 18.3%. The average non-oncologic complication rate was 49%. The average non-oncologic reoperation rate was 37%. The average Musculoskeletal Tumor Society Score was 65%.

Conclusion: The non-oncologic complication and reoperation rates for pelvic reconstructions are remarkably high and 5-year survival is poor. Functional outcomes are acceptable but may not be significantly better than an equivalent resection without reconstruction. Consideration should be given to forgoing pelvic reconstruction especially in patients with poor prognosis. Further studies comparing non-oncologic complication rates, reoperation rates, and functional outcomes in patients with equivalent resections treated with or without reconstruction are needed to further elucidate the utility of pelvic reconstruction.

Level of Evidence: III

PAPER 22

Indocyanine Green Dye Angiography Quantifies Primary and Metastatic Osteosarcoma Tumor Burden in an Immunocompetent Mouse Model

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Background: The 5-year survival rate of osteosarcoma (OS) with metastases at the time of diagnosis has been found to be as low as 15-30%. This figure has largely remained stagnant over the past few decades. A challenge in the development of novel chemotherapies lies in our inconsistent ability to quantify the primary and metastatic OS burden in immunocompetent *in vivo* models. Indocyanine green (ICG) is an FDA-approved near-infrared dye that binds tightly to plasma albumin and provides an accurate representation of intravascular flow. In areas of vascular interruption, such as a burn or malignancy, ICG reliably extravasates. No quantitative or prognostic studies of ICG fluorescence of primary or metastatic OS have been previously performed.

Purposes: Here we validated ICG both histologically and clinically as a rapid and novel tool for quantifying primary and metastatic OS burden. We also established a relationship between primary and metastatic OS fluorescence that can serve as the basis for the evaluation of novel chemotherapies.

Methods: Forty 4-6 week-old female Balb/c mice received injections of 0 (control), 100K, 250K, 500K, 750K, and 1 million K7M2 OS cells into their left hindlimbs. Amputations were performed 4 weeks after injection, followed by euthanasia and *ex vivo* lung harvest at 10 weeks. Twenty-four hours after ICG was retro-orbitally injected, fluorescence imaging with SPY-Elite (Novadaq, Bonita Springs, FL, USA) was performed immediately prior to amputation (Figure 1A) and euthanasia (Figure 1B). Quantification was performed with SPY-Q software (Novadaq) and NIH ImageJ (Bethesda, MD, USA). All tumors were measured using computed tomography (FIDEX, Animage, Pleasanton, CA, USA), and primary and metastatic tumor samples were cryosectioned for near-infrared microscopy. Statistical analysis was performed using Prism 7.0 (GraphPad, LaJolla, CA, USA).

Results: Clinical tumor growth was observed in 30 animals (75% growth rate). Significantly ($p < .05$) increased hindlimb fluorescence was observed in animals that developed clinical tumors (3.5 SD 2.3) compared to those without palpable tumors (.71 SD .38). All hindlimbs with clinical tumors had an average normalized hindlimb fluorescence above 1 normalized arbitrary perfusion unit (apu). A linear relationship ($r^2 = .81$) was observed between hindlimb fluorescence and lung fluorescence (interpreted as metastatic burden). This relationship was not observed when computed tomography was analyzed, and was independent of the number of cells injected. ICG was histologically localized to the OS stroma within both primary tumor (Figure 2) and lung samples.

Conclusions: ICG Angiography appears to be a rapid, high resolution technique for characterizing OS in our preclinical model. ICG was found to have a high specificity to tumor stroma, a low false positive rate and illustrate a clear relationship between primary and metastatic disease burden not seen using radiographic measurements alone. This model will be used as the basis for our pre-clinical studies.

Figure 1: Indocyanine green fluorescence of OS primary tumor (A) and lung metastases (B)

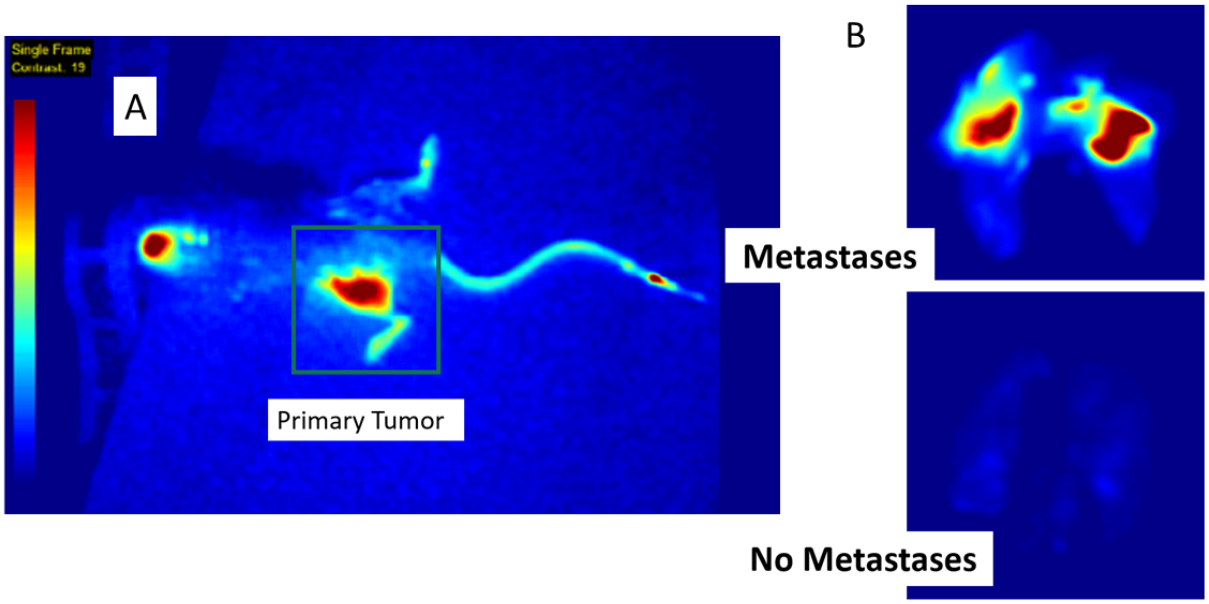
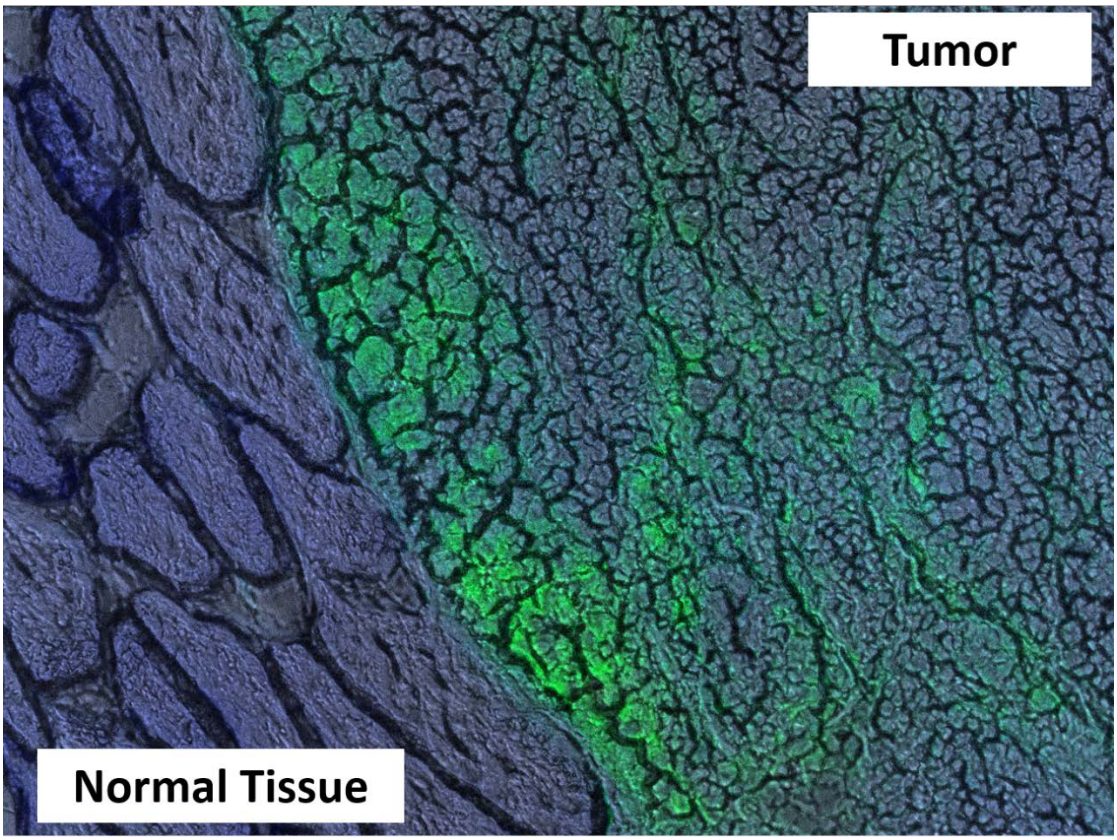


Figure 2: Histologic localization of ICG (green) to the tumor stroma, with no signal detected within the surrounding muscle



PAPER 23

A Non-Immunogenic Method for Transfecting Osteosarcoma Cells with the Luciferase Reporter

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Abstract Number: XXXXXXX

BACKGROUND: Bioluminescent cell lines for the modeling of osteosarcoma have been developed and shown success in tracking metastases *in-vivo*, but commonly use adenoviral vectors to transfect the native cell line with bioluminescent reporters. Adenovirus has known immunogenic properties, and its use might confound preclinical trials aimed at evaluating novel immunotherapies for osteosarcoma.

PURPOSE: The purpose of this study was to establish a novel method for the transfection of the K7M2 cell line with the luciferase reporter, confirm that its luminescent properties are stably transferred to multiple generations, and establish that it retains its highly metastatic nature.

METHODS: The ViaFect transfection reagent and pGL4.51 plasmid vector were used transfect the K7M2 osteosarcoma cells with the luciferase reporter. Non-transfected cells were then killed with selective medium containing Geneticin-418. The resultant cell line was propagated using standard methods. $4.5x10^5$ transfected K7M2 cells were added to a 12 well plate, and imaged 24 hours using Luciferin substrate and the *In-Vivo* Imaging System (IVIS). Imaging was completed weekly for a total of 12 weeks. Cells were used to create orthotopic primary tumors in BALB/c mice, and the presence of pulmonary metastatic disease was assessed using micro CT, MRI, and IVIS. IVIS was performed weekly for approximately 14 weeks. Primary tumor histology of transfected and non-transfected tumors was obtained and compared.

RESULTS: There were no significant differences in radiance of the transfected cells at baseline and at 12 weeks ($3.93x10^6$ p/sec/cm^2 versus $9.71x10^6$ p/sec/cm^2). Linear regression modeling did not reveal significant differences in radiance of the transfected cells over time (R^2=0.019, p=0.65). Orthotopic inoculation of cells in mice successfully induced metastatic disease as evidenced by MRI and micro CT. IVIS revealed large metastatic lesions beginning at 10 weeks (figure 1). Primary tumors were detectable on IVIS from baseline and throughout the study. No differences in histology between cell types was observed.

CONCLUSIONS: The present study describes a novel method for transfecting K7M2 cells with the bioluminescent luciferase reporter. The results confirm the bioluminescent properties of the cells and

indicate that this luminescence is retained over a period of 12 weeks. Use of these transfected cells in-vivo demonstrated rapid tumor progression and metastatic disease that did not differ from its non-transfected counterpart. This method of transfection should be considered in preclinical models of osteosarcoma aiming to evaluate immunotherapies, as it is less likely to be immunogenic.

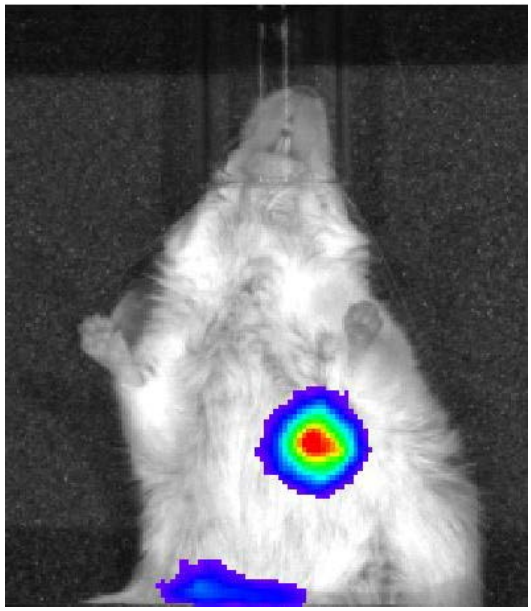

Figure 1: K7M2 metastatic lesion in a mouse as detected by IVIS. A primary tumor was created with orthotopic inoculation of K7M2 cells transfected with a bioluminescent reporter.

PAPER 24

Validation of a Rat Model for Analyzing MiRNA in Chrondrosarcoma

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Introduction/Purpose: Scientific models to study the genetic background of rare sarcomas could prove invaluable but require scientific corroboration. This study was undertaken to validate the use of a rat model for studying miRNA function in the development of chondrosarcoma.

Methods: In order to validate this model, we compared the expression of miRNAs in the rat chondrosarcoma relative to normal rat cartilage with miRNA expression in human chondrosarcoma relative to normal human cartilage. 20 healthy Sprague-Dawley rats were sacrificed, sterna and rib cartilage were collected, RNA extracted and 233 miRNAs analyzed. The expression of these miRNAs was then compared to their expression in the Swarm rat chondrosarcoma (SRC) model as well as their expression in normal human tissue and human chondrosarcoma. We then used interclass correlation coefficients to determine the similarity amongst these different tissue types.

Results: The analysis was carried out on a total of 233 matched miRNA. Interclass correlation coefficient (ICC2) was applied to the data in whole between the rat and human miRNA. For normal human vs normal rat cartilage the ICC was 0.84 (95% CI: 0.82-0.87). The ICC for chondrosarcoma in human vs rat tissue was 0.70 (95% CI: 0.65-0.74). A Pearson correlation coefficient was also applied to each individual miRNA. The correlation coefficient for human vs rat chondrosarcoma involving rat tissue from SRC samples prior to implantation was calculated to be 0.174 (p: 0.55). The correlation coefficient for human vs rat chondrosarcoma for those tissue samples isolated after harvesting the tissue from the Swarm rats was 0.168 (p: 0.09).

Conclusion: Our findings suggest that human and rat normal cartilage as well as chondrosarcoma genetics are sufficiently similar for use of rat models to study chondrosarcoma (ICC values >0.70). Our data also reveals similarities between specific miRNA, especially those with the most similar fold-change (miR26b, 126, 1456, 195, 320).

PAPER 25

ATRX Mutation in Canine and Human Osteosarcoma: *In Vitro* Exploration of A Novel Therapeutic Approach

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Background: Osteosarcoma (OS) is the most common primary bone cancer, with a poor prognosis that has not improved in several decades(1). Unlike human OS, which is uncommon, there are more than 15,000 new cases of canine osteosarcoma each year(2, 3). Naturally occurring cancers in dogs can serve as unique models of human disease because they represent biologically-complex conditions in a way that is not possible with genetically-engineered animal models. Spontaneous canine OS arises in the presence of an intact immune system, has an identical anatomic presentation, and has similar patterns of metastasis, recurrence, and resistance to therapy as human OS(3). The relatively high frequency of canine OS, the similarities to the human disease, and the lethality it causes render canine OS an ideal "model" for human OS.

Recent studies have identified frequent loss-of-function mutations in ATRX in gliomas, neuroblastomas, and soft tissue sarcomas(4, 5). ATRX plays a role in numerous biological functions including chromatin remodeling, X chromosome inactivation, and DNA methylation, and multiple studies have shown that these mutations shift cancer cells toward the alternative lengthening of telomeres pathway for telomere maintenance(6), thereby sensitizing these cells to ATR inhibitors.

We hypothesized that mutations in ATRX would render OS cells susceptible to ATR inhibition, a therapy which has not been utilized for OS.

Questions/Purposes: The purpose of this study was to assess and manipulate ATRX in canine and human OS cell lines to understand the role of ATRX in OS pathogenesis and to investigate ATR inhibition as a novel therapy for ATRX-mutated OS.

Patients and Methods: Three canine OS cell lines (Abrams, Moresco, and D17) and four human OS cell lines (143B, MG63, SAOS2, and U-2 OS) were grown in culture, and ATRX expression was assessed. Knockdowns were performed using two independent siRNAs targeting either human or dog ATRX. Colony forming assays were performed by plating 100 cells per well in 6-well format in triplicate and counting colonies after two weeks. Side population cells were stained with Hoechst and analyzed by flow cytometry.

We obtained the ATR inhibitor, AZD6738, from Astra Zeneca, and tested the cell viability of human 143B cell lines and canine Abrams cell lines with or without siRNA knockdown or CRISPR/Cas9 knockout of ATRX and treatment with AZD6738.

Results: ATRX protein was confirmed to be intact in all but the SAOS-2 and U-2OS lines. ATRX knockdown reduced the colony forming capacity of OS cells and the number of side population cells enriched for tumor initiating cells. siRNA-mediated knockdown of ATRX in conjunction with 1μM

AZD6738 treatment resulted in a significant reduction of viable cells, supporting our hypothesis. Knockdown of ATRX alone had no effect on Abrams (canine) or 143B (human) OS cells.

Conclusions: ATRX mutation renders OS cells more sensitive to ATR-inhibitors, a therapy that has not been previously investigated in OS. This finding will now be explored in mouse models of OS and xenografts of human and canine OS tumors.

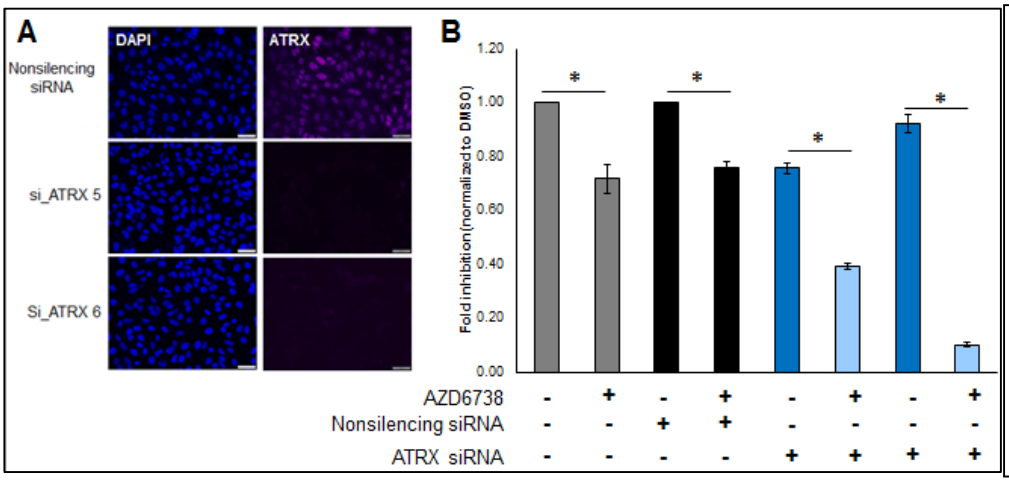

Figure: Loss of ATRX sensitizes OS cells to ATR inhibition. **A.** RNAi-mediated silencing of ATRX protein in human OS 143B cells using two independent siRNAs. **B.** Human OS 143B cells were counted using the Cell Titer Glo assay following siRNA knockdown of ATRX alone or in combination with the novel ATR inhibitor AZD6738. Silencing of ATRX sensitized 143B cells to AZD6738.

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PAPER 26

Role of osteoblasts in the osteolytic bone metastasis of renal cell carcinoma

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Background: Bone metastasis from renal cell carcinoma (RCC) has a unique osteolytic phenotype that is resistant to pharmaceutical treatment. After forming, there is a high incidence of pathologic fractures and subsequent disease progression. Understanding the molecular mechanisms involved will identify strategies for treating bone metastases more efficaciously. Osteolysis is produced by interactions in the bone microenvironment, which includes both osteoblasts and osteoclasts. Tumor cells from RCC have previously been thought to constitutively activate osteoclasts (**Figure 1A**). However, evidence for RANKL expression in RCC *bone metastases* has been difficult to demonstrate either in patients or *in vitro*. Moreover, the frequently observed resistance to treatments based solely on inhibiting RANKL mediated osteolysis indicates that additional mechanisms are at work. An alternative and unexplored possibility for producing osteolysis in bone metastasis from renal cell carcinoma is osteoblast inhibition. Our studies have shown that an osteolytic metastatic clear cell RCC cell line, 786-O Bo, secretes BIGH3, a protein that inhibits osteoblast differentiation. Thus, we hypothesize that osteoblast inhibition in the bone microenvironment is responsible for tilting the normal balance towards bone resorption (**Figure 1B**).

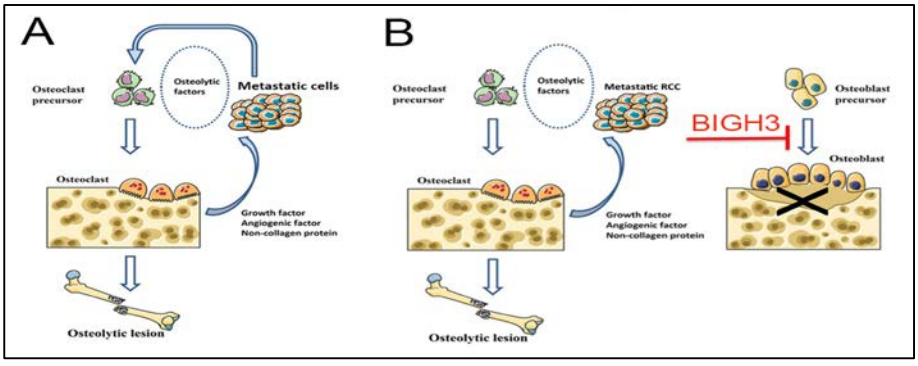

Fig 1. Proposed mechanisms of bone metastasis. A. Constitutive activation of osteoclasts. B. Inhibition of osteoblasts by metastatic RCC secreted factors, including BIGH3.

Questions/Purposes:

1. Determine whether factors secreted by bone metastatic RCC (BIGH3, etc) suppress bone formation through inhibition of osteoblasts in vitro.
2. Determine whether osteolysis is inhibited in vivo using BIGH3 knockdown cell lines.

Methods: In order to study the possibility of osteoblast inhibition, we used a SCID mouse xenograft model and in vitro co-culture studies with osteoblast cell lines (primary mouse calvarial osteoblasts). We first isolated a clear cell RCC cell line, 786-O Bo that homes to bone and creates osteolytic metastasis. BIGH3 was then knocked down in 786-O Bo cell lines using shRNA. These cells were then evaluated for ability to form osteolytic metastases via injection in SCID mice femora.

Results: Control 786-O Bo cells that were injected directly into SCID mice femora created osteolytic bone metastasis that were evident after 4 weeks. Conditioned medium from 786-O Bo cells, as well as purified BIGH3, had similar inhibitory effects on differentiation and mineralization in cultured osteoblast cell lines. 786-O Bo cell lines with BIGH3 knocked down produced bone metastases with less osteolysis compared with controls (**Figure 2**).

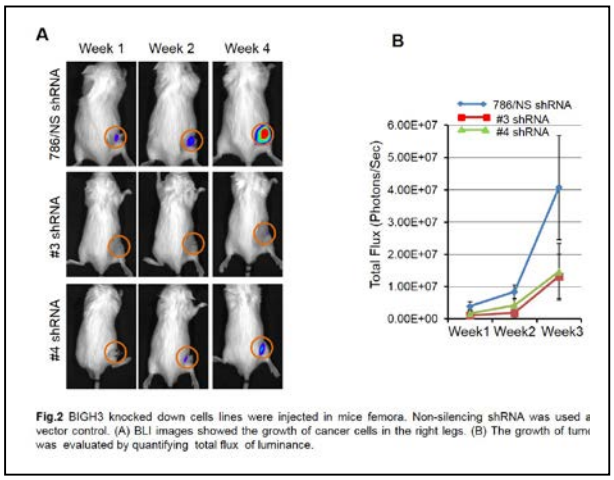

Fig.2 BIGH3 knocked down cells lines were injected in mice femora. Non-silencing shRNA was used a vector control. (A) BLI images showed the growth of cancer cells in the right legs. (B) The growth of tum was evaluated by quantifying total flux of luminance.

Conclusions: BIGH3 inhibits osteoblast differentiation and bone formation in vitro. BIGH3 inhibition via knockdown reduces osteolytic bone metastasis formation in SCID mice. Taken together, this evidence supports an alternative possibility that centers on osteoblast inhibition (rather than osteoclast activation) for producing osteolytic bone metastases in renal cell carcinoma. Osteoblasts appear to be inhibited by factors secreted by invading RCC cells. Whether these factors affect osteoclasts, osteocytes, or have an autocrine effect on metastatic cells, is unknown and will be the focus of future work.

Disclosure Report for all abstracts can be found in the Final Program Book

PAPER 27

Reduction in Functional and Material Bone Strength Following Radiation Therapy

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Background: Post-radiotherapy fragility fractures are a frequent complication of oncologic care. Clinically, these fractures are difficult to predict and there does not appear to be a relationship between bone density and fracture risk for this population. Irradiated bone is sometimes described as embrittled and animal model work has indirectly associated radiation therapy with weaker bones.

Purpose: The goal of this study was to quantify post-irradiation changes in bone quantity and quality, and identify how these factors contribute to loss of functional bone strength. To do this we used a mouse model of unilateral hindlimb irradiation and quantified changes to morphology and biomechanics of the mid-diaphysis of the femur. A secondary goal was to determine if single limb radiation had deleterious effects on the contralateral limb (abscopal effects).

Methods: Female BALB/CJ mice aged twelve weeks (Jackson Labs, Bar Harbor, ME) were anesthetized and exposed to either 1) unilateral hindlimb irradiation (4 consecutive daily fractions of 5 Gy each, 225 kV and 17 mA) or 2) sham irradiation (anesthesia but no irradiation). Mice were euthanized and femurs harvested four days prior to the first radiation dose, and at 0, 4, 8, 12, and 26 weeks post-RTx (n=9-13/group/time point). Three femur groups were collected: The irradiated femurs (*RTx group*), the non-irradiated contralateral femurs from the RTx group (*Contralateral group*), and femurs from the sham group (*Sham group*). The femurs were imaged by micro-computed tomography for quantification of bone mineral density and diaphyseal cross-sectional morphology (cortical area, endosteal (marrow space) area, total area (bone+marrow), and cortical wall thickness). Following this, the mechanical strength of the femurs was assessed using three-point bend loading to failure. Femurs were placed in the testing fixture (8 mm support span), and loaded in the posterior-anterior plane? at a rate of 1 mm per minute with simultaneous image capture. Outcome measures included functional bending strength and flexural (material) strength. Flexural strength was determined by calculating the highest tensile stress on the periosteal surface of the mid-diaphysis at peak load. Bending strength was normalized to mouse body weight to account for potential change in mass due to irradiation.

Results: Radiation significantly reduced the diaphyseal cortical bone mineral density (BMD) (**Figure 1A**) at later time points (4-26 weeks vs. shams). The contralateral non-irradiated limb showed a distinct reduction in BMD compared to the sham group, suggesting that limited field irradiation may systemically reduce BMD in mice. Similar results were found for cortical cross sectional area (**Figure 1B**) and wall thickness (**Figure 1C**). Material strength (**Figure 2A**) was reduced for the RTx versus contralateral limb for 2-8 week time points. The sham group had higher strength compared to the RTx and contralateral groups at 12 weeks, but at 26 weeks material strength was not different between the groups. RTx reduced functional bending strength (**Figure 2B**) compared to the contralateral limb (2-26 weeks) and this did not recover. The contalateral limbs had an intermediate loss of functional strength compared to sham femurs.

Conclusions: The results from this study show that radiation therapy can cause a reduction in the quantity and density of bone in the mid diaphysis, and that this bone tissue is weaker (lower bone quality). Functionally, this results in bones with diminished bending strength (~20%), suggesting that these bones may be more likely to suffer a fracture. There were also substantial abscopal effects, with the contralateral limb demonstrating diminished strength, density and size compared to the sham limbs. Clinical BMD assessment of RTx sites [Dhakal, Int J Rad Onc, 2011] did not show a difference from internal non-RTx/contralateral sites, but patients may have lost bone in the contralateral limb also, so may have lower BMD and higher fracture risk compared to population controls.

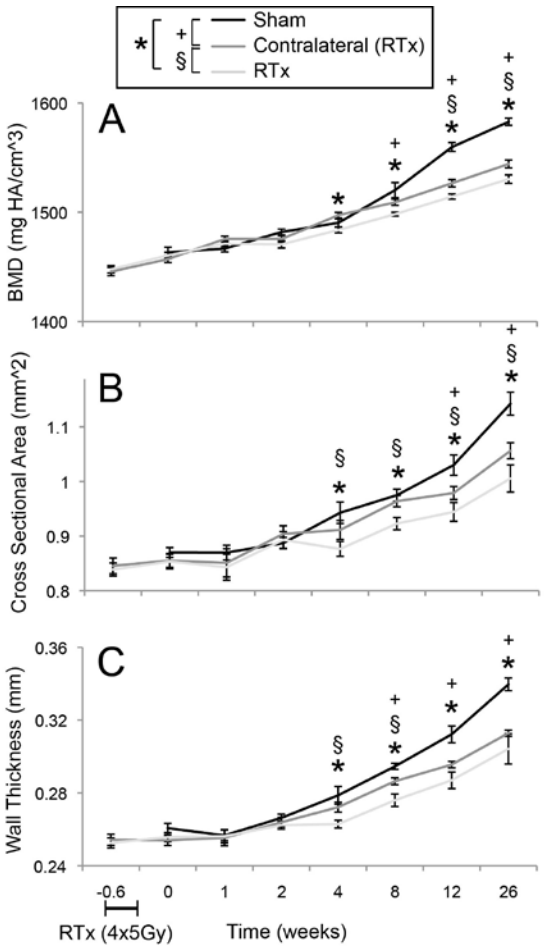

Figure 1: Bone mineral density (A), diaphyseal cross sectional area (B), and cortical wall thickness (C) as a function of time for the three treatment groups. Statistical comparisons (symbols) shown at $p<0.05$.

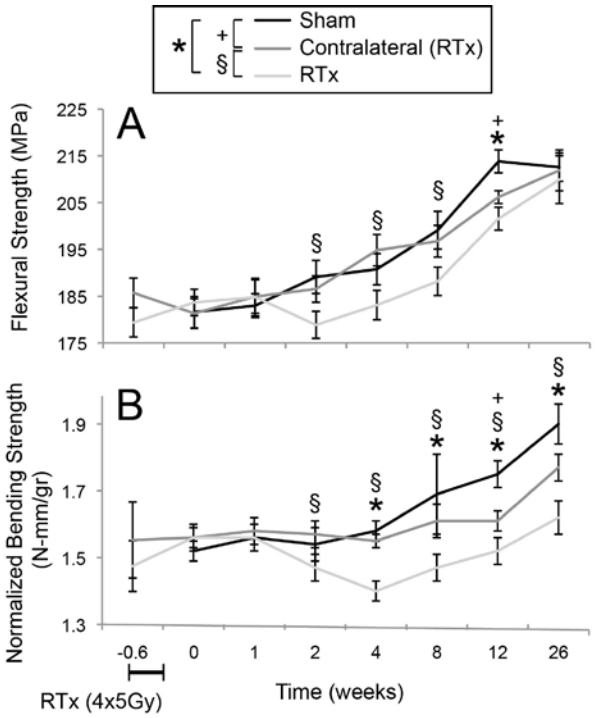

Figure 2: Flexural strength (A) and bending strength normalized to mouse body mass (B) as a function of time for the three treatment groups. Statistical comparisons (symbols) shown at $p<0.05$.

PAPER 28

Predictive analytics to determine functional outcome trajectories in orthopaedic oncology

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Purpose: To determine which patient-specific factors assessed pre-operatively are predictive of post-operative patient-reported outcomes.

Question:

1) Can the pre-operative (baseline) Karnofsky score be used to predict a patient's post-operative recovery over the course of a year as reflected by the PROMIS Global Health tool?

Method: Thirty one patients with two or more PROMIS Global Health (GH) Outcome scores were selected for this analysis .The Karnofsky Performance Score (KPS) at pre-surgical baseline (*M*=65.48, *SD*=19.81) ranged from 20% (very sick; hospital admission necessary) to 90% (able to carry on normal activity with minimal signs or symptoms). In our sample the ECOG and Karnofsky were highly correlated (r=.91). The baseline pre-operative score for the Karnofsky was completed on all 31 patients of which 14 patients had a score of 60% or less (equivalent to ECOG scores of 2, 3, 4, or 5). The Karnofsky was chosen for this study due to the directionality of the score (higher is better) to stay in line with the directionality of the PROMIS Global Health score.

In this sample all patients were asked to complete the PROMIS GH tool pre-operatively and at post-operative months 3, 6, and 12. In addition, patients with metastatic disease were scheduled for two additional assessments at post-operative weeks 2 and 6. The PROMIS algorithms generates two T-scores from the GH tool representing items of a Physical construct and a Mental construct. The Physical Function T-score from the PROMIS GH tool was plotted over time for each individual. In order to compare patients trajectory (given the varied time points of assessment and patient's missed follow-up visits), the trajectories for each individual were calculated with a linear regression to arrive at the individual's trajectory (slope) and calculated intercept (baseline) given the actual GH T-scores over time. In order to generate a binary outcome for the next stage of the analysis, the slope representing the trajectory over time for the PROMIS GH T-score for each patient was used to code that individual as "better" (positive slope) or "worse" (negative slope). In a few instances, patients had a true fluctuation in their recovery, but the overall linear slope was zero. In order to code as "better or worse" the actual trajectory was reviewed.

Logistic Regression models (SPSS 22.0) were built with the outcome (Better or Worse) predicted by up to 3 variables (in adherence to the 10:1 observation-to-predictor ratio). Variables utilized in model testing included the location of the surgery, the severity of the tumor burden, the age of the patient, the sex of the patient, the Karnofsky score (either dichotomized at 70 or using the actual score), the intercept

(calculated baseline) of the PROMIS GH Physical construct, or the slope of the mental construct from the PROMIS GH T-score.

Results: Variables were screened for multicollinearity and no exclusions were necessary. The model with the PROMIS GH Physical component intercept and the pre-operative Karnofsky score correctly classified 80% of the patients who were coded as "worse" (negative post-operative recovery slope) and 58% of the patients who were "better" and was statistically reliable in distinguishing between the two groups ($X^2(2)=6.93$, $p<.05$). This model accounted for 66% of the variability of the Karnofsky. Residuals were analyzed for Cook's distance, deviance, and leverage. No cases were identified as outliers or exerting influence over the model. Adding a third variable such as age, gender, tumor burden, region of surgery, or aspects of the PROMIS GH Mental construct did not improve the model fit.

The results from this two predictor model were utilized in a predictive equation of outcome ("better" or "worse"). This equation was validated using the model's constant (2.052) and the weights for the pre-operative Karnofsky (.050) and the Promis GH Phys T score calculated intercept (-.141) and the average standardized residuals to represent individual variability. To assess the predictive model with only baseline data, the actual baseline (pre-operative or 2 week post-operative) score for each patient's PROMIS GH Physical T-score and the baseline pre-operative Karnofsky score were entered. Only one patient (0.03% of our sample) actually got worse, when the model predicted the patient would get better after surgery.

Conclusions: The Karnofsky pre-operative score can be used in conjunction with the patient-reported PROMIS Global Health T-score to provide an accurate probability of the recovery trajectory over the course of the first post-operative year. Additional work using a larger sample size will determine which additional factors may improve the predictive power of the model. Future aims will include the development of powerful predictive models to assess a patient's probability of experiencing a poor outcome and to identify modifiable factors that may be addressed in order to decrease the chance of a patient experiencing such an outcome.

Tumor Burden	Karnofsky Performance Score		Region					Total
			Spine	Pelvis	Sacrum	UE	LE	
Mets	severity	Worse 60% KPS or less	1		1	2	2	10
		Better 70-100% KPS	2		0	4	4	9
No Mets	severity	Worse 60% KPS or less		0	1	4	4	5
		Better 70-100% KPS		1	0	3	3	7

PAPER 29

Long-term (> 15 year) Outcomes of Cement in Cement Technique for Revision Endoprosthesis Surgery

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Background: Cemented endoprosthetic reconstruction after resection of primary bone sarcomas has been a standard-of-care option for more than three decades. With increased patient survival and prosthesis utilization, the incidence of failed endoprostheses requiring revision surgery has increased. Revision of cemented endoprotheses by cementing into the previously existing cement mantle is technically demanding. Stress shielding, cement extrusion, and subsequent fixation in previously cemented bone create considerable challenges for revision.

Purpose: We aim to examine the clinical outcomes of revision cemented endoprostheses using the cement in cement (CiC) technique. We also aim to examine the clinical outcomes of subsequent revisions of cemented endoprostheses using the CiC technique.

Patients and Methods: This is a retrospective review of our endoprosthesis database consisting of 512 consecutive cemented endoprosthetic reconstructions performed for oncologic diagnoses between 1980 and 2014. 54 of 512 (10.5%) of these were revised at the cement-implant interface with a CiC technique. Bushing changes, revisions for adjacent joint pathology, revisions to total femur endoprostheses, and planned expansions of growing implants were excluded. Outcomes evaluated were prosthesis survival, further revision surgery categorized according to the Henderson Failure Mode Classification, complications, and functional outcomes. Analyses were repeated for subsequent CiC revisions.

Results: Fifty-four patients (10.5%) underwent initial CiC revision of their primary endoprosthesis (mean 10.2 years post-op) for aseptic loosening (29), structural failures (20), and infection (5). Five-, 10-, and 15-year Kaplan-Meier survival of initial revision implants were 73%, 51%, and 34%, respectively. 15-year survival of initial CiC revision of distal femur replacement was 32%, proximal femur replacement was 62%, and proximal tibia replacement was 0%. Mean MSTS Score was 27 in this cohort. Thirty-four of 54 patients (69%) required a subsequent revision (mean 8.9 years post-op) for aseptic loosening (15), structural failure (15), infection (5), and tumor progression (2), whereas three of 54 (6%) required amputation. Five-, 10-, and 15-

year Kaplan-Meier survival of subsequent revision implants were 65%, 58%, and 44%, respectively.

Conclusion: At long term follow up, endoprostheses revised with the CiC technique showed consistent 15-year survival from initial (34%) to subsequent (44%) revision. Additionally, survival rates were influenced by location of replacement. Outcome scores were high in this cohort. Despite a relatively high failure rate, these results are encouraging and demonstrate that this repeatable technique is a reasonable solution to a challenging problem.

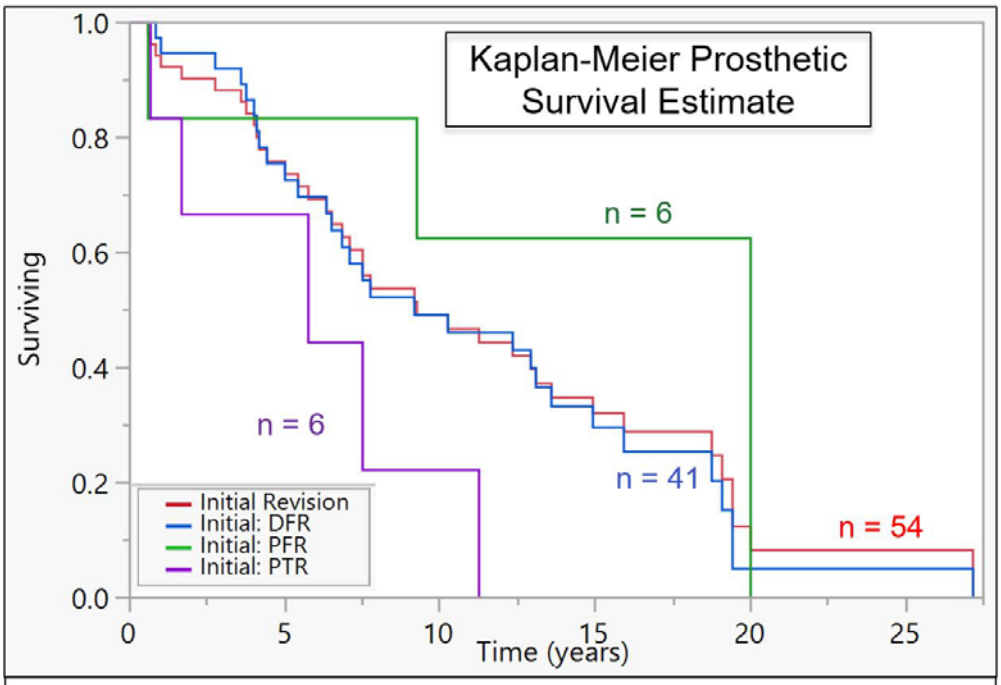

Figure 1. Kaplan-Meier survival estimate of endoprosthetic reconstructions. Initial revision = first revision after index procedure. DFR = distal femur replacement. PFR = proximal femur replacement. PTR = proximal tibia replacement.

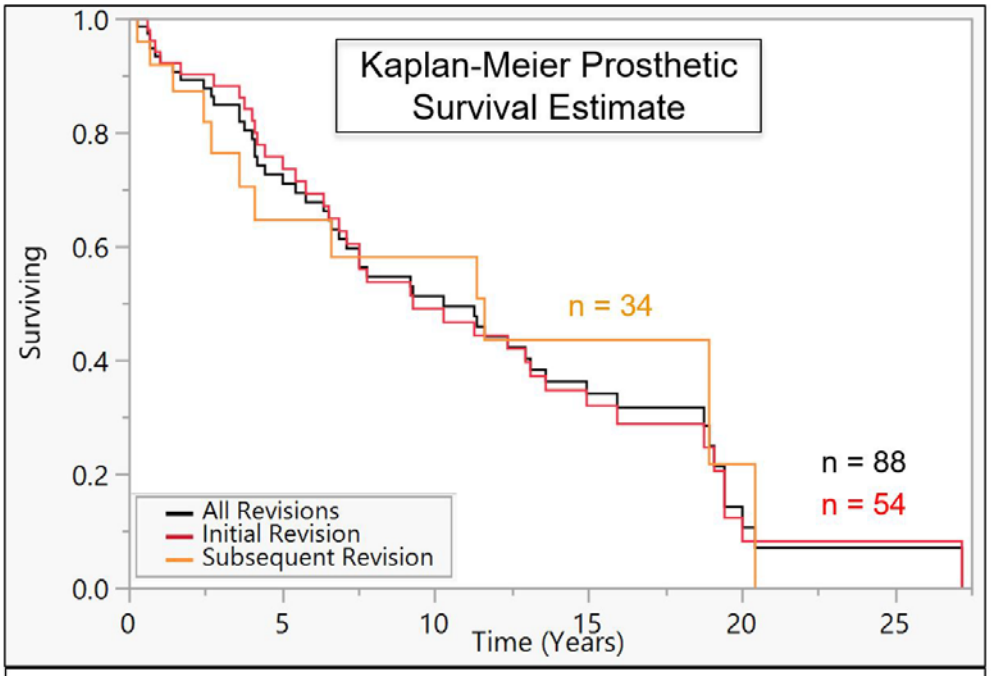

Figure 2. Kaplan-Meier survival estimate of endoprosthetic reconstructions. Initial revision is first revision after index procedure. Subsequent revision is second revision after index procedure.

PAPER 30

Lessons and advice from our patients: a report on a focus group of sarcoma survivors

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Background: Sarcomas are a rare, heterogenous group of malignancies often requiring extensive surgery, chemotherapy, and radiation. These dramatic and life-altering interventions can have lasting impact on the function and quality-of-life of sarcoma patients. There remains little in the available literature regarding the unique perspectives and needs of patients facing a sarcoma diagnosis and subsequent recovery from treatment. In order to gain a more patient-oriented perspective on this topic, we performed a qualitative study utilizing focus groups of sarcoma survivors.

Questions/Purposes: We were primarily interested in what information (e.g. basic cancer information, survival statistics, plan of care, long-term function) was most important, as well as the main sources used to obtain the information. Second, we queried how patients coped with various physical and psychological issues that arose during and after treatment. Lastly, we elicited advice on what the care team could do differently to improve patient understanding and the overall experience.

Methods: The format chosen was a qualitative, focus group research method. Focus groups are ideal for in-depth exploration of a topic about which little is known and are increasingly popular to explore health-related behaviors, beliefs, or feelings. The Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist was used as a guide to ensure an appropriate methodology and study design. We identified a purposive sample of English-speaking potential participants ≥18 years of age with a diagnosis of a sarcoma treated by a single surgeon between 2011 and 2015 (n=217). After recruitment by mail, three focus groups of 4-9 participants (20 total) were moderated by the orthopaedic tumor service nurse practitioner and audio/video recorded for transcription purposes (Table 1). No other members of the care team were present during the focus groups. The transcripts were analyzed by the research team and a non-affiliated third party in the Social Science Research Center to identify common themes.

Results: We were able to categorize the primary themes into four major categories: 1) Information about diagnosis and treatment, 2) Relationship with the care team, 3) Social support, and 4) Restoration to "normal." A summary of the primary discussion points is presented in Table 2.

Conclusions: Although existing literature can be found regarding cancer patient perspectives in general, knowledge regarding specific needs of sarcoma patients in particular is limited. In order to provide optimal care, sarcoma providers should understand the unique issues and challenges encountered by our patients. Given the inherent qualitative nature of this study, we cannot quantify results or generalize these themes to all sarcoma patients; however, we did identify common themes that can serve as a guide for future research endeavors and program improvements.

Table 1. Demographic breakdown of the cohort

Characteristic	Number
Age (years)	
Average (range)	51 (22-79)
Sex	
Male	11
Female	9
Location	
Upper extremity	4
Lower extremity	15
Pelvis	1
Type	
Bone	7
Soft Tissue	13
Histology	
Undifferentiated pleomorphic sarcoma	4
Myxofibrosarcoma	4
Chondrosarcoma	5
Osteosarcoma	2
Leiomyosarcoma	2
Malignant peripheral nerve sheath tumor	1
Fibromyxosarcoma	1
Synovial sarcoma	1
Grade	
1	7
2	2
3	11
Stage	
Localized	17
Metastatic	3
Adjuvant treatment	
Chemotherapy	4
Preoperative radiation	6
None	10
Surgery	
Resection only	15
Curettage, cementation, and fixation	2
Distal femur prosthesis	2
Acetabular reconstruction	1
Time since surgery (years)	
Average (range)	2.2 (0.6-4.8)

Table 2. Lessons and advice from the focus group

Theme	Lessons	Advice
Information about diagnosis and treatment	• Information-seeking behavior was highly individual • Although the internet was utilized, the oncology care team is the primary source of information • Younger patients were more likely to use internet-based resources and social media • Genetic component and familial risk was a common concern • Functional limitations were more significant than anticipated	• Desire for survival statistics is variable, with many patients expressing a desire not to know • The need for specific information (survival estimates, housing options during treatment, financial support, coping strategies) should be revisited at different time points during treatment and recovery, as opposed to only at the initial diagnosis and planning stage
Relationship with care team	• Trust in oncology providers was very important – many were disillusioned due to delays in diagnosis • Physical access to care team was important and was a perceived barrier for those located remotely from the treating institution • Patients were surprised and frustrated that their primary care providers did not know the details of their diagnosis and treatment	• Local access would be beneficial (e.g. outreach clinics, telemedicine) • Patients desire improved communication between specialists and primary care physicians during and after treatment
Social support	• Family and friends provided most of the physical care and logistical support, but could also be a source of stress and anxiety • Discussion with both sarcoma and non-sarcoma cancer survivors was helpful • Social media was a good source of support for many	• Access to a social worker to help navigate the non-medical aspects of treatment would alleviate stress • A social media forum of sarcoma patients (e.g. a closed Facebook page) would be well received
Restoration to “normal”	• Was a very emotional and passionate topic • Frustration that physical therapy was not focused on reaching a pre-treatment level of activity • Expectations for recovery differed widely, with some anticipating return to a high level of function • Psychosocial challenges during and after treatment were often more significant than physical challenges	• Recovery should be expected to be slow, with “good” and “bad” days • Physical therapy is important and should be tailored to the individual • A distress screening tool at various time points during and after treatment may help identify those in need of additional psychosocial support

PAPER 31

PREDICTORS OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH PRIMARY SARCOMA OF BONE

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BACKGROUND: Venous thromboembolism (VTE) is known to be independently associated with both orthopaedic surgery and malignancy. Patients undergoing surgery for musculoskeletal malignancies are at an increased risk for thromboembolic events. The literature reports incidence of VTE in this patient population to be between 0.6-14.8%. Although VTE can lead to serious morbidity and mortality, prophylactic anticoagulation may cause bleeding and wound complications, particularly in patients undergoing radiation and removal of large volumes of tissue. It is therefore essential to understand the factors that place patients at higher risk for VTE. Furthermore, where prophylaxis is indicated, there is no consensus about the most effective regimens. Two sets of guidelines are commonly used: The American Academy of Orthopaedics (AAOS) and the American College of Chest Surgeons (ACCS). The AAOS recommends aspirin (ASA) or warfarin, while the ACCS recommends a regimen of low-molecular-weight heparin (LMWH), heparin, or warfarin.

PURPOSES: 1) Analyze the rate of venous thromboembolic events in patients surgically treated for primary bone sarcoma; 2) Identify risk factors for venous thromboembolism; 3) Assess efficacy of prophylactic agents in VTE prevention.

PATIENTS AND METHODS: 379 patients with primary bone sarcoma were identified from our institution's orthopaedic oncology database from 1990-2015 (175 females, 204 males, median age at diagnosis 42 years). Patients were excluded if they were under 18 years or had less than 90 days of post-operative follow-up. Occurrence of thromboembolic event was defined as radiographically confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE) within 90 days of the index surgery. Patient and treatment characteristics were compared across patients with and without a thromboembolic event. All data was analyzed using STATA 13.1 (Statacorp LP, College Station, TX, USA). The Mann-Whitney test was used for continuous variables and Fisher's exact test for categorical variables. Statistical significance was held at $p<0.05$ throughout. Bivariate logistic regression was performed to determine a crude odds ratio with a confidence interval of 95% for factors showing significant association with VTE. Multiple imputation was carried out to correct for missing data in the variables that reached significance. All factors that maintained a p-value of <0.08 and were non-collinear were then entered into a backward elimination stepwise regression to test independence and calculate an adjusted odds ratio.

RESULTS: 21 patients (5.5%) had a clinically symptomatic, radiographically confirmed VTE within 90 days of index surgery (12 DVT, 9 PE). 57% of patients with an event were male. There were no fatal VTEs.

Of the 33 variables tested for an association with VTE, 7 reached statistical significance in bivariate analysis (Table 1). Through multiple logistic regression, higher preoperative white blood cell count and post-operative wound complications were found to be independent risk factors for VTE (Table 2).

74% of patients received chemical prophylaxis. Of the 100 patients who did not receive prophylaxis, 2 had a VTE. Overall, warfarin was the most commonly used chemoprophylactic agent (33%), followed by LMWH (23%), and ASA (6%). Since the early 2000's there has been a severe decrease in use of warfarin and a corresponding increase in LMWH. 12% of patients were treated with a regimen of multiple chemoprophylactic agents. The risk of wound complications increased significantly in patients who received chemical prophylaxis (OR 2.21, 95% CI 1.00-4.87).

CONCLUSIONS: Our patient population had a relatively low rate of VTE (5.5%) compared to the literature. Increased preoperative white blood cell count was found to be an independently associated risk factor for development of VTE, as was post-operative wound complication. However, wound complications are managed with bed rest, which may be the underlying cause of these VTEs. Additionally, patients who received chemical prophylaxis had significantly more wound complications. None of the prophylactic agents were significantly associated with a decreased risk of VTE and the risk actually increased for patients who were on multi-agent regimens. Our results indicate that chemical prophylaxis may in fact be contributing to the development of post-surgical wound complications which in turn increases risk of venous thromboembolic events.

The limitations of this study include its retrospective nature and incomplete availability of clinical information for some patients. The relatively small number of outcomes restricted our statistical analysis and we were unable to control for all potential confounders. Despite these limitations, the results presented here provide the clinician with valuable data to consider when assessing a patient's risk for VTE and also highlight the need for prospective studies exploring when and which prophylactic agents should be used for the prevention of VTE in orthopaedic oncology patients.

Level of Evidence: III

Disclosure Report for all abstracts can be found in the Final Program Book

Table 1. Patient and treatment characteristics for VTE and No VTE groups (n=379)

Variable	No VTE (n=358)	VTE (n=21)	
	Median (Interquartile range)	**Median (Interquartile range)**	**p value**
Age (years)	42 (27-55)	37 (24-52)	0.611
BMI (kg/m²)†	25.3 (22.4-29.2)	28.4 (25.1-32.8)	0.216
Preoperative white blood cell count (1000/mm3)†	6.5 (5.2-8.4)	9 (7.0-11.4)	**0.005**
Preoperative platelet count (1000/mm3)†	259 (202-340)	300.5 (248-358)	0.064
Preoperative hemoglobin (g/dl)†	12.6 (10.8-13.9)	11.8 (10.6-13.6)	0.252
Preoperative albumin (g/dl)†	4.3 (3.9-4.6)	4.1 (3.6-4.3)	0.113
Preoperative partial thromboplastin time (sec)†	26.8 (24.8-28.8)	24 (22.8-26.65)	**0.004**
Largest tumor dimension (cm)†	8 (5.4-11)	9.6 (5.5-12.3)	0.294
Duration of surgery (min)†	292 (181.0-411.5)	314 (206-387)	0.592
Total estimated blood loss during surgery (mL)†	350 (200 - 500)	1000 (600 - 1700)	**0.016**
Postoperative white blood cell count (1000/mm3)†	9.8 (7.9-12.2)	10 (8.35-14.25)	0.317
	Number (%)	**Number (%)**	
Sex			
Men	191 (53.4)	13 (61.9)	0.505
Women	167 (46.7)	8 (38.1)	
Site of tumor			
Hip/pelvis (including thigh)	126 (35.2)	13 (61.9)	
Knee	85 (23.7)	3 (14.3)	
Distal to knee	37 (10.3)	2 (9.5)	0.094
Upper Extremity	56 (15.6)	0 (0)	
Spine	23 (6.42)	2 (9.52)	
Other	31 (8.7)	1 (4.76)	
Histology			
Osteosarcoma	196 (54.8)	11 (52.4)	
Chondrosarcoma	120 (33.5)	6 (28.6)	
Ewing's Sarcoma	17 (4.8)	2 (9.5)	0.55
Malignant Fibrous Histiocytoma	13 (3.63)	1 (4.8)	
Fibrosarcoma	11 (3.1)	1 (4.8)	
Other	1 (0.3)	0 (0)	
Tumor grade			
1/3	78 (21.79	3 (14.3)	0.74
2/3	136 (38.0)	8 (38.1)	
3/3	144 (40.2)	10 (47.6)	
Tumor invading vasculature†	44 (12.9)	6 (28.6)	0.053
Smoking Status†			
Never smoked	180 (60.6)	9 (56.3)	0.762
Quit	71 (23.9)	5(31.3)	
Current Smoker	46 (15.5)	2 (12.5)	
Diabetes	20 (5.6)	1 (4.8)	1
History of cancer	39 (10.9)	1 (4.8)	0.712
History of VTE	15 (4.2)	2 (9.5)	0.241
Pathologic fracture	41 (11.5)	4 (19.1)	0.295
Intraoperative tourniquet use	58 (16.2)	2 (9.5)	0.55
Blood transfusion†	217 (62.2)	15 (71.4)	0.49
Flap reconstruction	57 (15.9)	1 (4.8)	0.222
Skin graft	17 (4.8)	1 (4.8)	1
Positive surgical margins†	74 (21.7)	7 (33.3)	0.277
Adjuvant chemotherapy	190 (53.1)	14 (66.7)	0.265
Adjuvant radiotherapy	82 (22.9)	5 (23.8)	1
Postoperative infection	33 (9.2)	6 (28.6)	**0.014**
Postoperative wound complications	44 (12.3)	9 (42.9)	**0.001**
Additional surgery	8 (38.9)	67 (18.7)	**0.045**
Chemoprophylactic Agent			
None	98 (27.4)	2 (9.5)	
ASA	21 (5.9)	1 (4.8)	
LMWH	80 (22.4)	7 (33.3)	**0.012**
Warfarin	122 (34.1)	4 (19.1)	
Multiple agents	37 (10.3)	7 (33.3)	

***Bold** indicates significance (P value less than 0.05). g/dL = gram per deciliter, mL = milliliter, BMI = Body Mass Index, Kg/m2 = kilogram per square metre*

Mann-Whitney U test used for continuous variables, Fisher's exact test used for categorical variables

† BMI available in 209 patients, preoperative white blood cell count in 279 patients, preoperative platelet count in 275 patients, preoperative hemoglobin in 275 patients, preoperative albumin in 128 patients, preoperative partial thromboplastin time in 243

patients, largest tumor dimension in 321 patients, duration of surgery in 241 patients, total estimated blood loss in 309 patients, postoperative white blood cell count in 343 patients, tumor invading vasculature in 363 patients, smoking status in 313 patients, blood transfusion in 370 patients, positive surgical margins in 362 patients

Table 2. Factors associated with VTE

	Crude OR (95% CI)	p-value*	Adjusted OR (95% CI)	p-value*
Preoperative white blood cell count†	1.14 (1.01-1.29)	***0.029***	1.15 (1.01-1.31)	***0.029***
Total estimated blood loss during surgery†	1.00 (0.99-1.00)	*0.055*		
Preoperative partial thromboplastin time†	0.87 (0.74-1.00)	*0.057*		
Postoperative infection*	3.94 (1.43-10.84)	***0.008***		
Postoperative wound complications	5.35 (2.13-13.43)	***<0.001***	5.30 (2.07-13.55)	***<0.001***
Additional Surgery	2.67 (1.07-6.71)	***0.036***		
Chemoprophylactic Agent				
None	1 (ref)			
ASA	2.33 (0.2-26.94)	*0.497*		
LMWH	4.29 (0.87-21.21)	*0.074*		
Warfarin	1.61 (0.288-8.95)	*0.589*		
Multi	9.27 (1.84-46.67)	***0.007***		

Variables with a p-value <0.08 entered in multiple logistic regression model

† Multiply imputed data set was generated to account for missing data points

* Due to collinearity with postoperative wound complications, postoperative infection was not entered into the multivariate analysis model

* Logistic regression test

PAPER 32

Are Perioperative Allogeneic Blood Transfusions Associated With 90-days Infection After Operative Treatment For Bone Metastases?

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Background: Transfusion rates are high in patients undergoing surgery for musculoskeletal tumors. There is mounting evidence that exposure to allogeneic blood transfusions deregulate the immune system, making patients more prone to develop infections. It remains unclear whether this association holds for patients undergoing surgery for bone metastatic lesions.

Questions/Purposes: We assessed whether allogeneic blood transfusions were associated with infection –within 90 days– after surgery for bone metastatic disease. Furthermore, we assessed other risk factors associated with infection.

Patients and methods: We included 1266 patients, aged 18 years or older, who had surgery for a bone metastatic lesion between 2002 and 2013 at one of two affiliated tertiary care hospitals. Our primary outcome was postoperative infection within 90 days after surgery. Blood transfusions within 7 days before and after surgery were considered to be perioperative. We used bivariate and multivariate logistic regression to assess whether blood transfusion was associated with infection.

Results: Two hundred seventy-two patients (21%) developed an infection (Table 1); infections occurred in 23% (178/774) of the patients who were exposed to at least one perioperative blood transfusion, and in 19% (94/492) of the patients without exposure to allogeneic blood transfusion.
We found no independent association between exposure to blood transfusion and infection (Odds Ratio [OR] 1.02, 95% Confidence Interval [CI]: 0.76 – 1.37, p = 0.889), nor a dose-response relationship (OR 1.02, 95% CI: 0.98 – 1.07, p = 0.245). Older age (OR 1.01, 95% CI: 1.00 – 1.02, p = 0.035), a higher modified Charlson comorbidity index (OR 1.13, 95% CI: 1.05 – 1.22, p = 0.002), surgery to the axial skeleton (OR 1.89, 95% CI: 1.42 – 2.51, p < 0.001), and previous radiotherapy (OR 1.45, 95% CI 1.07 – 1.96, p = 0.015) were independently associated with infection (Table 2).

Conclusions: There was no association between allogeneic blood transfusion and infection. We found other risk factors that should be taken into consideration when deciding to operate.

Level of Evidence: Level 2, retrospective study

Table 1. Infection types and number of infection types

Infection variable	No Transfusion Group (n = 492)		Transfusion Group (n = 774)		All patients (n = 1266)	
	Number (%)		**Number (%)**		**Number (%)**	
Type of infection						
Pneumonia	41	(8.3)	81	(10)	122	(10)
Urinary tract infection	32	(6.5)	68	(8.8)	100	(7.9)
Surgical site infection	21	(4.3)	48	(6.2)	69	(5.5)
Sepsis	19	(3.9)	46	(5.9)	65	(5.1)
Central venous line infection	1	(0.2)	3	(0.4)	4	(0.3)
Endocarditis	4	(0.8)	0	(0)	4	(0.3)
Meningitis	0	(0)	1	(0.1)	1	(0.1)
Number of 90-day infections*						
0 infections	398	(81)	596	(77)	994	(79)
1 infection	76	(15)	124	(16)	200	(16)
2 infections	13	(2.6)	41	(5.3)	54	(4.3)
3 infections	4	(0.8)	11	(1.4)	15	(1.2)
4 infections	1	(0.2)	2	(0.3)	3	(0.3)

** Different types of infections. If one type of infection (e.g. pneumonia) occurred twice within 90 days, this was counted as 1 infection*

Table 2. Multivariate logistic regression assessing whether there is an association between exposure to blood transfusion and infection, whether there is an association between the number of units transfused and infection, and other risk factors for infection. (n = 1266) †

	Blood transfusion (exposure versus no exposure)			Blood transfusion (dose dependent)		
	Odds Ratio (95%CI)	**Standard Error**	**p value**	**Odds Ratio (95%CI)**	**Standard Error**	**p value**
Blood transfusion* (exposure vs. no exposure)	1.02 (0.76 - 1.37)	0.16	*0.889*	-	-	-
Blood transfusion per dose* (per unit transfused)	-	-	-	1.02 (0.98 - 1.07)	0.02	*0.245*
Age in years	1.01 (1.00 - 1.02)	0.01	***0.035***	1.01 (1.00 - 1.02)	0.01	***0.037***
Modified Charlson Comorbidity Index	1.13 (1.05 - 1.22)	0.04	***0.002***	1.13 (1.05 - 1.22)	0.04	***0.002***
Location of lesion treated for						
Appendicular skeleton	*Reference value*			*Reference value*		
Axial skeleton	1.89 (1.42 - 2.51)	0.27	***< 0.001***	1.82 (1.37 - 2.44)	0.27	***< 0.001***
Pathologic fracture	1.21 (0.91 - 1.61)	0.18	*0.196*	1.20 (0.90 - 1.59)	0.17	*0.217*
Previous local radiotherapy	1.45 (1.07 - 1.96)	0.01	***0.015***	1.45 (1.08 - 1.96)	0.01	***0.015***

Bold indicates significance (P value less than 0.05).

** Allogeneic blood transfusion within 7 days prior until 7 days after surgery.*

† After multiple imputation to estimate missing values (40 imputations)

PAPER 33

Cost-Utility of Osteoarticular Allograft vs. Endoprosthetic Reconstruction for Primary Bone Sarcoma of the Knee: A Markov Analysis.

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Background: The most cost-effective reconstruction option after resection of primary bone sarcoma is unknown. The goal of this study was to compare the cost effectiveness of osteoarticular allograft to endoprosthetic reconstruction and primary bone sarcoma resection of the proximal tibia or distal femur.

Methods: A Markov decision model was used. Revision and complication rates were taken from existing outcome studies of allograft and endoprosthetic reconstructions. Direct costs, in 2015 U.S. dollars, were calculated from Medicare reimbursement, Medicare diagnosis related group rates and implant and allograft prices. Health-state utilities were derived from the Health Utilities Index 3 survey for patients with limb-salvage surgery after Osteosarcoma resection with additional assumptions. Incremental cost-effectiveness ratios were used to compare the two reconstructive options with less than $100,000 per quality-adjusted life year (QALY) considered cost-effective. One-way sensitivity analyses were performed to compare the two reconstructive options.

Results: Osteoarticular allografts, with a direct cost of $33,693.27, were the favored strategy with a cost per QALY of $2,153.68 in comparison with a direct endoprosthesis cost of $52,241.81. One-way sensitivity analysis revealed if allografts cost over $38,333 or endoprostheses were less than $47,000, endoprosthetic reconstruction was the favored strategy. Endoprosthetic reconstruction was favored if the allograft complication rate was higher than 10% or the allograft revision rate was higher than 24%. A company-provided discounted endoprosthesis price of $35,659.81, when compared to the full allograft price of $33,693.27, was equally cost-effective to allografts with a cost per QALY of $4,997.52.

Conclusions: Osteoarticular allografts are more cost-effective than endoprosthetic reconstructions of the distal femur or proximal tibia after primary bone sarcoma resection. However, price discounted endoprosthetic reconstruction could make the two strategies equally cost-effective.

Level of Evidence: III

Disclosure Report for all abstracts can be found in the Final Program Book

PAPER 34

Long Term Results of Oncologic Implants for Limb Salvage of Malignant Bone Tumors in Children

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Background: Despite significant clinical success, modular oncologic implants have demonstrated significant 5 and 10 year failure rates.

Questions/Purpose: The purpose of this study was to describe our experience with revision and infection rates for oncologic implants after osseous resection in children.

Material and Methods: We retrospectively reviewed implant and sarcoma registries. Between 1990-2016, 105 pediatric patients presented to our multidisciplinary sarcoma service for limb salvage surgery and were reconstructed with a cemented or uncemented oncologic implant. Inclusion criteria were under age 21 years, follow-up of at least 12 months and a malignant bone tumor located in the long bones and pelvis. 95 patients were included in the final analysis. Functional outcome was assessed using the Musculoskeletal Tumor Society rating system, in addition to TESS and step counter activity monitors.

Results: Average age at diagnosis was 13.71 years (range, 4.18-20.5 years). The tumor sites included: 50 distal femur, 22 proximal tibia, 6 proximal femur, 10 proximal humerus, 1 distal humerus, 1 total femur, 5 pelvis. Of the 72 implants about the knee; 42 utilized a cemented, 29 utilized an uncemented stem. Stem revision procedures including aseptic loosening, septic loosening or stem fracture occurred in 45.2% (19/42) of cemented stems and in 34.5% (10/29) of uncemented stems. Aseptic loosening occurred in 21.4% (9/42) of cemented and 10.3% (3/29) of uncemented implants. The other implant revisions including soft tissue procedures, patellar and mobile bearing revisions occurred in 9.5% (4/42) of cemented stems and in 6.9% (2/29) of uncemented stems. Overall incidence of revision surgery was 36.6% (26/71). Growing

implants were placed in patients with second staged revision procedures for mature implants. 13.7% (13/95) patients had deep implant infection and revision procedure and there was no significant difference in the incidence of cemented and uncemented implants. Overall 12.6% (12/95) patients required multiple revision procedures. 10 patients underwent amputation as a result of persistent infection or local recurrence. In the surviving patients, the mean MSTS score at long-term followup was 22.7 (10 to 29). Mean length of follow-up was 77.8 months.

Conclusion: Functional recovery after oncologic limb salvage resection for pediatric osseous sarcoma is good. Long term results are however compromised by a significant incidence of implant infections (13.9%) and revision procedures (36.6%) which occurred primarily in cemented stems for septic (12.2%) and aseptic (21.4%) loosening. Overall stem revision procedures occurred in 45.2%. Uncemented stem fixation appears to have lower incidence of aseptic loosening compared to the cemented stems. For that reason uncemented stems might represent a better alternative in younger patients. Efforts should be directed toward lowering the incidence of implant infections in all patients.

	Cemented (N=42)	Uncemented (N=29)
Revisions	17/42 (40.5 %)	9/29 (31.0%)
Sepsis/Deep Infection	5/41 (12.2%)	4/28 (14.2%)
Aseptic Loosening	9/42 (21.4 %)	3/29 (10.3%)

Overall Survival	**Cemented**		**Uncemented**
5 years	72%	5 years	53%
10 years	59%	8 years	44%
Survival to Aseptic Revision	**Cemented**		**Uncemented**
5 years	83%	5 years	79%
10 years	74%	8 years	69%
Survival to Septic Loosening/Deep Infection	**Cemented**		**Uncemented**
5 years	83%	5 years	94%
10 years	64%	8 years	(94%)

PAPER 35

Does surgery or radiation provide the best overall survival in Ewing's sarcoma? A review of the National Cancer Data Base

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Institution: University of Iowa Department of Orthopaedics and Rehabilitation

Background: Ewing's sarcoma is a common primary malignancy of bone, most often presenting in adolescents and young adults. While there is agreement that optimal management should include multi-agent chemotherapy, there is continuing debate regarding the ideal modality for local control, namely radiation alone, surgery alone, or surgery and radiation. Ewing's sarcoma is unique among bone sarcoma as it is radiosensitive, and treatment of the primary tumor with radiation alone may provide adequate local control and overall survival while retaining a higher level of function than would be possible after a large surgical resection and reconstruction. The National Cancer Data Base (NCDB) is a collaboration between the American College of Surgeons Commission on Cancer and the American Cancer Society and collects treatment and outcomes data from 1,500 hospitals, representing 70% of all new cancer diagnoses in the United States. This data source has not been previously utilized to investigate the overall survival by treatment in Ewing's sarcoma.

Questions/Purposes: Our goal was to use the NCDB to answer the following questions: 1) What patient, tumor, and treatment characteristics predict diminished overall survival? 2) Does the method of local control impact overall survival? 3) In patients treated with surgery, does the addition of radiation provide a survival benefit?

Patients and Methods: We identified 1,031 patients younger than 40 years of age with a diagnosis of high-grade Ewing's sarcoma of bone in the axial or appendicular skeleton. We excluded patients who did not receive multiagent chemotherapy, had a diagnosis of more than one malignancy, did not have diagnostic confirmation in the database, or had unknown vital status. Our variables of interest included patient (age, sex, race, population density of residence, distance to treating center, socioeconomic status), tumor (size, stage, site), and treatment (surgery and/or radiation, margins) factors. We performed a Kaplan-Meier survival analysis at 2, 5, and 10 years with a log-rank test to determine univariate measures of association. Factors with a level of significance of $p<0.1$ at the 5-year time point were included in a multivariate Cox proportional hazards model.

Results: In the univariate analysis, we found decreased survival at 5 years in patients with metastatic disease (40% vs 73%, $p<0.001$), age ≥18 years (55% vs 73%, $p<0.001$), size >8 cm (59% vs 75%, $p<0.001$), axial site (61% vs 71%, $p=0.002$), male sex (63% vs 72%, $p=0.013$), and treatment with radiation alone (52% with radiation alone, 65% with surgery and radiation, 77% with surgery, $p<0.001$). These variables were included in the multivariate analysis, which revealed diminished 5-year survival for patients with metastatic disease (Hazard Ratio [HR]=2.41, 95% Confidence Interval [CI] 1.87-3.09), treatment with radiation alone (HR=2.09, 95% CI 1.56-2.80 compared to surgery alone), age ≥18 years (HR=1.91, 95% CI 1.52-2.40), tumor size >8 cm (HR 1.50, 95% CI 1.18-1.92), and male sex (HR=1.33, 95% CI 1.04-1.70) while controlling for tumor site. For only patients who were treated with surgery with or without radiation (n=687), a multivariate analysis revealed decreased survival at 5 years for metastatic disease (HR=2.30, 95% CI 1.55-3.42), age ≥18 years (HR=2.11, 95% CI 1.53-2.91), and positive margins (HR=1.60, 95% CI 1.05-2.45) while controlling for sex, site, size, and treatment. Surgery alone was consistently the

method of local control that resulted in the highest survival; the addition of radiation after surgery in non-metastatic patients with axial tumors or positive surgical margins may be beneficial (Fig. 1).

Conclusions: In a multivariate Cox proportional hazards model, we found treatment in patients with radiation alone resulted in diminished overall survival, even when controlling for age, sex, metastatic disease, tumor site, and tumor size. Although treatment with surgery alone resulted in the best overall survival, the addition of radiation after resection in axial tumors or positive surgical margins may provide some benefit to overall survival. The results of this investigation provide support to the approach of surgical resection with negative margins when possible. Future work should focus on the role of surgical resection with planned positive margins and radiation in tumors where traditional curative surgical techniques would result in excessive morbidity.

Level of Evidence: Level III, retrospective comparative study

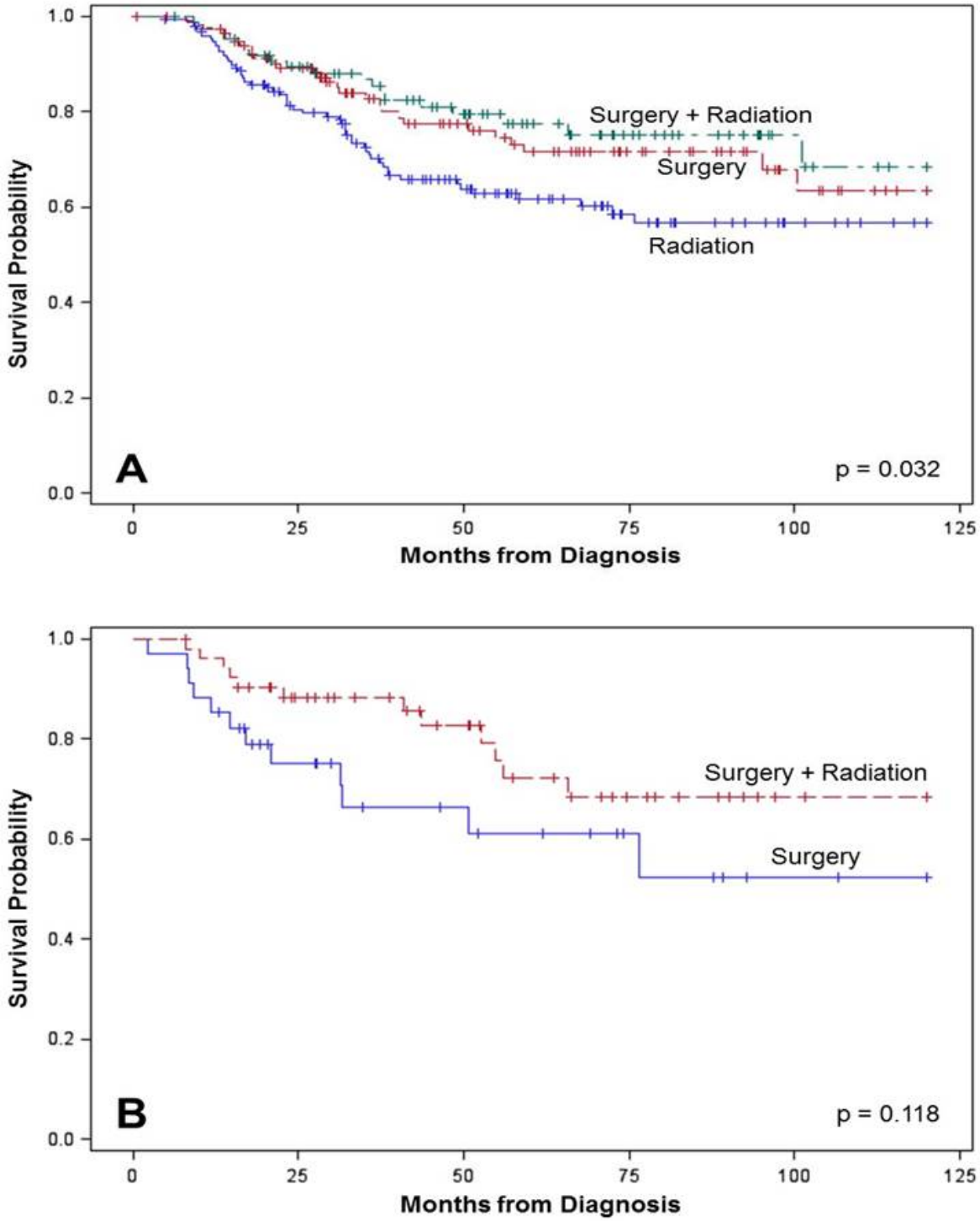

Figure 1. 10-year Kaplan-Meier curves for non-metastatic patients with axial tumors (A) and positive margins (B).

PAPER 36

Limb Length Discrepancy in Skeletally Immature Patients with Sarcomas about the Knee: Risks and Results of Limb Salvage Reconstruction

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Background: In the pediatric population, sarcomas tend to occur around the knee most frequently, with distal femur and proximal tibia locations accounting for 50% of osteosarcomas. In light of better long-term survival, final length of the affected limb – especially in sarcomas about the knee – has become an important consideration when choosing which salvage reconstruction is most appropriate.

Purpose: At our institutions, we use a general algorithm to select salvage procedures based on a patient's expected remaining growth. This study reviews a cohort of patients that were treated based on this method to evaluate their leg length discrepancies post treatment.

Methods: Forty-seven patients from January 1, 2000 to November 15, 2015 were identified with primary bone sarcomas about the knee (femoral to tibial diaphysis). Patients were 12 years old or younger at time of diagnosis, with the average age being 9.6 years. Five patients had tumors of the diaphysis, 28 had distal femoral tumors, and 15 had proximal tibial tumors; one patient had both proximal tibial and distal femoral involvement. Using our algorithm, salvage options were osteoarticular allograft (19 patients, average age at time of surgery 10.7 years), intercalary allograft – physeal sparing (8 patients, average age 8 years) and physeal sacrificing (7 patients, average age 11.3 years), hinged total knee arthroplasty – expandable (11 patients, average age 8.1 years) and static (2 patients, average age 10 years) and allograft-prosthetic composite, which was not used as a primary treatment in this cohort.

Results: In total, 28 patients had measurable leg length discrepancies, with 20 of those requiring treatment. Patients who developed limb length discrepancies were younger across all treatment groups except the physeal sacrificing intercalary allograft group. Overall, average initial leg length discrepancy was 2.9cm (range 0.5-7.3cm), with final discrepancy 2.15cm (range 0.8-5.5cm). Of the osteoarticular allograft group, eight patients (42%) had discrepancies, and all of these required treatment; the average age at presentation was 10.5 years, and initial versus final leg length discrepancy was 3.6cm to 2.2cm. Of those with physeal sparing intercalary allografts, six patients (75%) had discrepancies, but only two required equaling procedures; their average age was 7.33 years at presentation, and initial discrepancy

compared to final was 2.9cm to 2.2cm. In the physeal sacrificing group, four patients (57%) developed discrepancies; three required treatment. Average age in this group was 11.5 years and intial compared to final measurements were 3.2 to 2.4cm. Nine patients (69%) treated with tumor prostheses had leg length discrepancies, seven required treatment. Average age at presentation was 7.66 years, and initial/final discrepancies were 2cm to 1.8cm. In the prosthesis group, two patients had static implants and neither developed leg length differences. Eleven patients had expandable prosthesis, and ten (90.9%) developed a discrepancy, seven were treated for it. Average age was 7.9 years and initial to final measurements were 2.0 to 1.8cm.

Conclusion: Given the literature on adult limb length discrepancies showing increased energy expenditure and muscle work with discrepancies 2cm and above, and based on the results demonstrated here, we feel this algorithm helps surgeons choose the appropriate limb salvage procedure in patients with significant growth remaining.

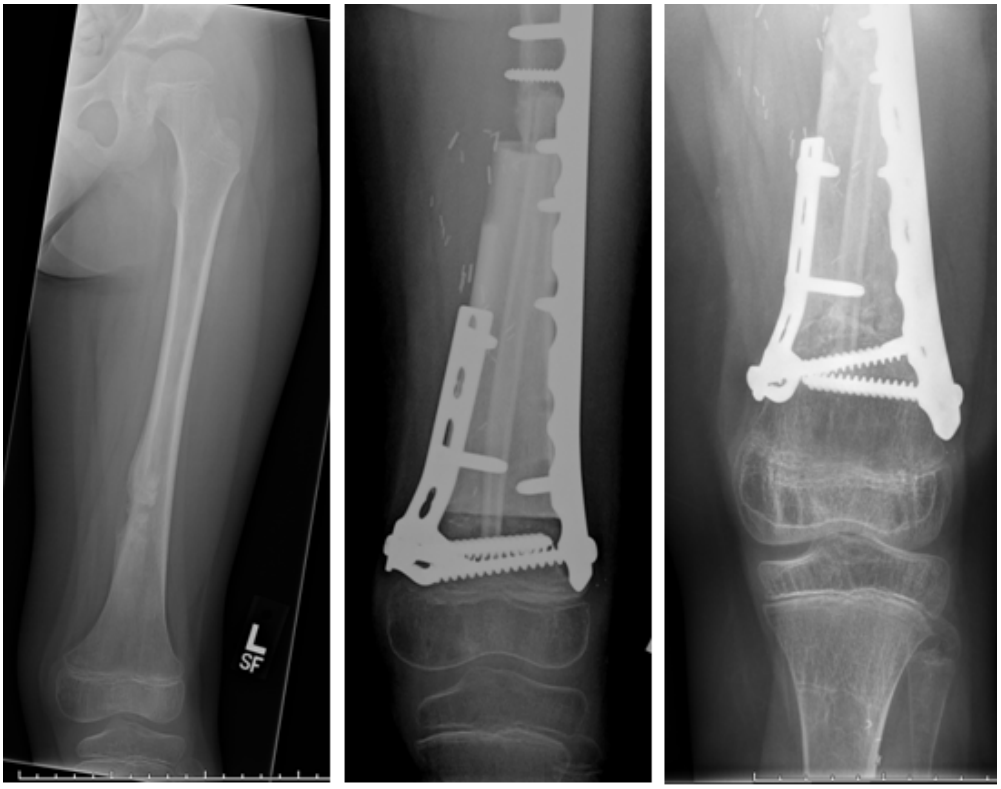
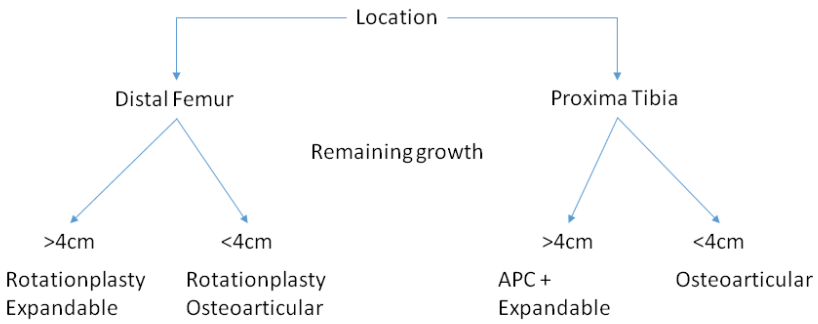


Figure 1. Diaphyseal-metaphyseal junction osteosarcoma, treated with a physeal-sparing intercalary allograft. The figure on the right shows continued growth of the distal femoral physis over time.

Treatment algorithm for bone sarcoma in pediatric knee



PAPER 37

Imaging or Pathology – What is the Greatest Predictor for Local Recurrence in Pediatric Osseous Sarcomas?

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Institution: Seattle Children's Hospital, Seattle, WA USA

Background: Guidelines for acceptable surgical margins for osseous sarcomas remain poorly defined by current published criteria.

Question/Purpose: Our goal was to review pathology results after pediatric limb salvage procedures and assess size of the estimated surgical margin (mm), necrosis %, and tumor margin contamination. The ability of preoperative imaging to predict the final surgical margins and patient clinical outcomes associated these procedures were also analyzed.

Methods: This study reviewed cases involving pediatric limb salvage surgery of the distal femur or proximal tibia for diagnoses of Osteosarcoma or Ewing's sarcoma treated with current COG protocols between 2009 and 2015. Patients were excluded if they had insufficient clinical follow-up, inadequate imaging or pathologic reports, or were treated with an amputation. The final cohort consisted of 40 patients that had at least twelve months of follow-up. MRI imaging, PET imaging, and pathology records were retrospectively reviewed for the assessment of tumor size, pre- and post-chemotherapy MRI tumor margins, and tumor margins documented by final pathology. Final pathology tumor margin measurements (Figure 1) were compared with preoperative MRI predicted margins. Overall histologic tumor necrosis and patient disease status regarding local recurrence or metastases was also documented.

Results: Our review evaluated 40 patients treated with limb salvage resection and reconstruction with either an allograft or oncologic implant. The average age was of this cohort was 12.5 (2.7-22.3) years with a mean follow-up of 53.6 (12.0-133.8) months. Average tumor size was 80.8 (21.0-200.0) mm with a mean post-chemotherapy SUV ratio (PET2/PET1) of 0.38 (0.8-0.94).

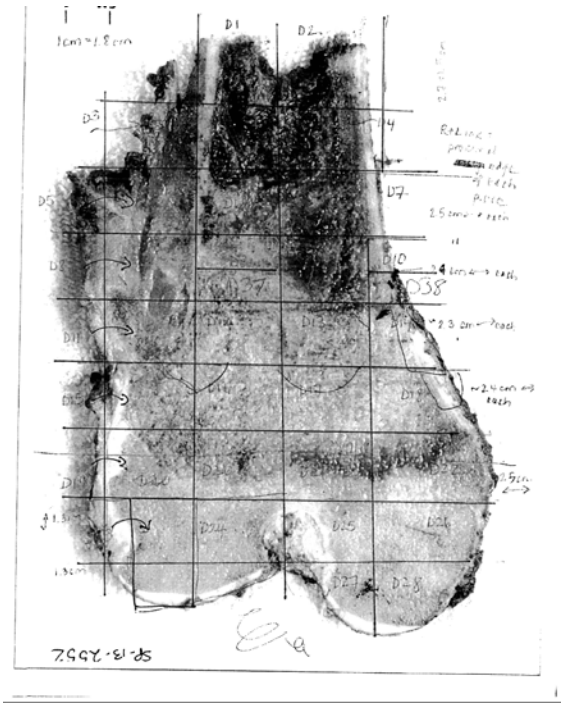
Patient tumor mass shrinkage (of the inflammatory) zone following chemotherapy occurred in 65% (26/40) of patients. Average overall tumor necrosis was 76.34% (0-100). Final average osseous tumor pathologic margins were 9.96 mm, while preoperative (post-chemotherapy) MRI predicted margins averaged 10.52 mm. Contaminated margins were present in 17.5% (7/40) patients.

5 (12.5%) patients in the overall cohort suffered a local recurrence and only 2 of 7 (28.5%) patients with a contaminated margin suffered a local recurrence. All patients who suffered a local recurrence (or metastasis) had a poor histologic response (<90% necrosis) on final pathology, P=0.049. The majority of contaminated surgical margins occurred at the soft tissue margins rather than at a bony margin. Final pathologic margins were best described with specimen photographs (Fig 1).

Conclusion: Preoperative MRI imaging predicted the final pathologic tumor margins within 5mm for 86% of patients with close margins (≤2cm). Close or contaminated margins did not yield a greater likelihood for local recurrence in our patient cohort, but all patients who suffered local recurrence showed poor tumor response to preoperative chemotherapy (<90% necrosis). Preoperative SUV ratios less than 0.5 were predictive of poor histologic response on final pathology, but did not appear to predict local recurrence.

Preoperative MRI imaging appeared to accurately predict final pathologic tumor margins and pathologic necrosis predicted the likelihood of local recurrence better than preoperative PET imaging. A greater appreciation of these imaging modalities should assist with preoperative planning and joint or physis sparing procedures in children.

Figure 1: Pathology diagram of a distal femur osteosarcoma resection specimen



Paper 38

Good Functional Status Following Claviculectomy Without Reconstruction For Benign And Malignant Tumors

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Institution: University Musculoskeletal Oncology Unit, Mount Sinai Hospital, Department of Surgery, University of Toronto, Ontario, Canada

Background: Partial or total claviculectomy may be necessary for the treatment of primary tumors of the clavicle and shoulder girdle, or for management of metastatic disease in these locations. Reports of poor functional outcomes and high complication rates following claviculectomy with reconstruction exist in the literature.

Purpose: The goal of this study was to evaluate functional status and complications after partial or total clavicle resection without reconstruction.

Patients and Methods: A retrospective review of our prospectively collected database identified 24 patients who underwent either partial or total claviculectomy for bone or soft tissue tumors involving the clavicle between 1991 and 2014. Functional status was assessed using the Toronto Extremity Salvage Score (TESS) and Musculoskeletal Tumor Society (MSTS) scoring systems. Oncologic outcomes, surgical complications and type of soft tissue reconstruction for wound coverage were also analyzed.

Results: Seventeen women and seven men were included in our study group. The mean age was 44 years (range 16-85) and the most common diagnoses were osteosarcoma (6), soft tissue sarcomas (6), and chondrosarcoma (2). Ten patients (42%) had concomitant soft tissue reconstruction procedures, including eight local rotational flaps and two free flaps. Three of the 24 patients experienced a complication requiring further surgery: two for infection and one for revision of a free flap micro-vascular anastomosis. At a median follow-up of 71.6 months, 15 patients were alive without evidence of disease, two patients were alive with evidence of disease, three patients had died of disease, and four patients had died of other causes. Local tumor recurrence occurred in one patient. The mean MSTS-93 score was 84 (range 63-93) and the mean TESS score was 86.5 (range 74-92). Fifteen patients had a total claviculectomy and nine patients had partial claviculectomy. There was no difference in functional outcome scores for partial or total claviculectomy.

Conclusion: Partial or total claviculectomy, without reconstruction, for treatment of tumors of the clavicle and shoulder girdle region is associated with high functional outcomes and low complication rates.

PAPER 39

Virtual Analysis and Planning of Tumor Resections and Reconstructions. Pearls, Pitfalls and Lessons Learned

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Background: In certain situations, complex local anatomy and limitations of surgical exposure can make adequate bone tumor resection and reconstruction very challenging. During recent years, we have increasingly adopted current technological advances permitting precise virtual planning and pre-operative production of patient-specific resection guides, allografts and implants.

Purpose: To review our early clinical experience and accuracy achieved with entirely virtually planned single stage tumor resection/reconstructions.

Methods: We report 3 cases of bone tumors (one periacetabular chondrosarcoma, one periacetabular solitary metastatic renal cell carcinoma and one recurrent adamantinoma of the tibia) in which both, resection and reconstruction were based entirely on pre-operative virtual analysis and planning. All resections were accomplished with specifically designed, pre-operatively manufactured resection guides. Immediate subsequent defect reconstruction was either performed with a precisely matching allograft (n=1) or composite implant (n=2) consisting of a defect specific titanium scaffold and multiple integrated fixation features to provide for optimal immediate stability as well as subsequent opportunity for ingrowth into the residual bone. We reviewed the sequence of all procedural steps as well as the accuracy of each osteotomy plane (n=11) by direct intra-operative measurement, post-operative margin status and virtual comparison of pre- and post-operative CT scans.

Results: Intra-operative application/assembly of the resection guides could be accomplished with relative ease in all cases, permitting quick and efficient reproduction of the planned osteotomies (n=11) with a high degree of accuracy (maximum resection-implant gap of 0-3mm). Histologically all resection margins were negative as planned except in one case where the os pubis resection was extended due to intraoperative concern. All implants could be placed as planned, with post-operative imaging demonstrating satisfactory implant position. Virtual analysis of post-operative CT scans showed minimal deviation of final implant position from the pre-operative plan.

Conclusion: Reliable, accurate placement of resection planes and their optimal alignment with respect to tumor extent and desired preservation of unaffected bone is the most challenging and time consuming step during the analysis and planning phase. However it is also the crucial step with regard to subsequent design and production of clinically and oncologically meaningful case-specific resection guides and implants. If these prerequisites are met, this technology can afford high intraoperative accuracy, contribute to increased intra-operative surgeon confidence and decreased operative time.

PAPER 40

Factors affecting nonunion of allograft-host junctions in intercalary reconstructions of the femur and tibia – A novel classification for allograft union prognosis

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Background: Nonunion of allograft-host junctions results from a complex interplay between biological and mechanical factors, and its treatment tends to be problematic. To date, solid evidence on risk factors for nonunion after intercalary allograft reconstructions is lacking. Moreover, to our knowledge, it has never been thoroughly evaluated if contact at the junction results in a decreased likelihood of nonunion.

Questions/Purposes:
(1) What is the incidence of nonunion in intercalary allograft-host junctions in reconstructions of the femur or tibia after resection of a primary bone tumor?
(2) What are the risk factors for nonunion, and does contact at the allograft-host junction result in a decreased likelihood of nonunion?

Patients and Methods: We present a retrospective case series of all patients with a primary bone tumor of the femur or tibia in whom an allograft was used to reconstruct an intercalary (whole-circumference) osseous defect, in two tertiary referral centers of orthopaedic oncology. From center one, patients who had their operations between 1989 and 2012 were included. From center two, patients who had their operations between 2008 and 2012 were included because before that time, there were no digital radiographs available. A prerequisite for inclusion was the availability of conventional radiographs in the anteroposterior and lateral direction taken in the first 30 days after surgery, because these radiographs were used to assess the degree of contact at the allograft-host junction. To minimize bias with regard to the influence of contact at the junction, we chose to only include transverse one-plane osteotomies in patients in whom one or more plates were used (either plates alone, or in combination with an intramedullary nail); whenever technically feasible, this was the preferred method for cutting and fixation of allografts in both centers.

The degree of contact was classified into grades 1, 2A, 2B, and 3. Grade 1 was defined as full contact over the entire length of the osteotomy in both directions; no radiolucent line was

visible. Grade 2 was defined as partial contact and was further divided into grades 2A (≥50% contact) and 2B (<50% contact). Grade 3 was defined as a lack of cortical contact; a radiolucent line was visible over the entire length of the osteotomy (figure 1). All osteotomies were independently assessed and graded by two reviewers who had not been involved in the care of the patients. In case of disagreement, a meeting was arranged between the reviewers to reach consensus. The occurrence and time to complications were subsequently determined. Nonunion was defined as the lack of consolidation in at least two of the four cortices (anteroposterior and lateral radiographs) at 12 months. Moreover, the junction was considered to be a nonunion if any additional operation had been performed to achieve union or because of problems with the fixation within 12 months after the index procedure – regardless of the eventual outcome.

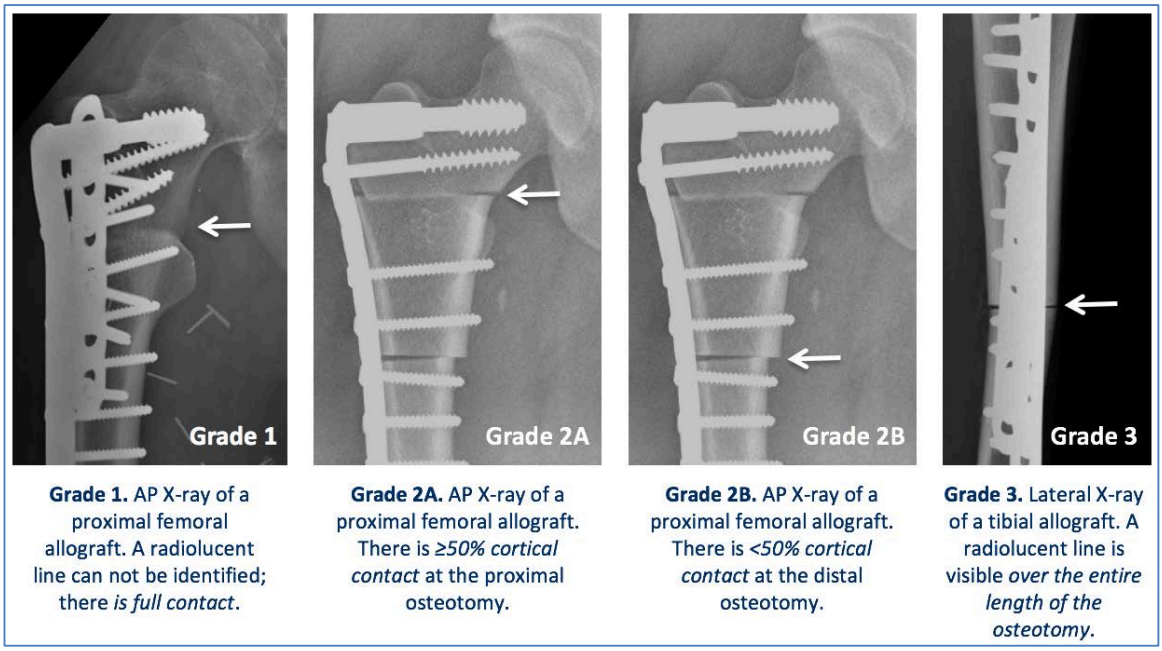
Results: We included 96 osteotomies (61 femoral [64%] and 35 tibial [37%]) from 57 patients (34 males, 60%) with a median age of 17 years (2-71). Median follow-up was 8.6 years (95%CI, 6.1-11.2). Predominant diagnoses were osteosarcoma (n=26, 46%), adamantinoma, and Ewing sarcoma (both; n=9, 16%). Fifty-six osteotomies (58%) were subjected to (neo)adjuvant chemotherapy, two (2%) to radiotherapy, and two (2%) to both. Osteosynthesis was performed with single (n=53, 55%) or double plating (n=39, 41%), or a plate combined with a nail (n=4, 4%). Sixty-five osteotomies (68%) were diaphyseal, 31 (32%%) were meta-epiphyseal.

Twenty-three osteotomies (24%) were classified as grade 1, 29 (30%) as grade 2a, 28 (29%) as grade 2b and 16 (17%) as grade 3. Kappa-coefficient for inter-rater reliability was 0.749 ('substantial'). Nonunion occurred in none of the grade 1, 2/29 (7%) grade 2A, 5/28 (18%) grade 2B, and 8/16 (50%) grade 3 osteotomies (p=0.017, table 1). Nonunion risk was higher for diaphyseal (12/65, 19%) than for meta-epiphyseal junctions (3/31, 10%) (p=0.268). Osteotomies that were subjected to chemotherapy had a nonunion risk (10/58, 17%) that was comparable to those that were not (5/38, 13%) (p=0.590). Nonunion was less frequent in osteotomies in patients aged ≤16 years (3/41, 7%) than in older patients (12/55, 22%) (p=0.053).

Conclusions: Contact at the junction was the most important risk factor for nonunion. Patient age and osteotomy level also appeared to influence the risk of developing nonunion. Our novel classification system demonstrated strong correlation with clinical outcome and a good inter-rater reliability. In order to reduce nonunion rates and thereby improve outcomes of allograft reconstructions, care should be taken to obtain rigid fixation with firm contact at the junction.

Level of evidence
Therapeutic studies, level IV.

Figure 1.



Grade 1. AP X-ray of a proximal femoral allograft. A radiolucent line can not be identified; there *is full contact*.

Grade 2A. AP X-ray of a proximal femoral allograft. There is *≥50% cortical contact* at the proximal osteotomy.

Grade 2B. AP X-ray of a proximal femoral allograft. There is *<50% cortical contact* at the distal osteotomy.

Grade 3. Lateral X-ray of a tibial allograft. A radiolucent line is visible *over the entire length of the osteotomy*.

Table 1.

Grade	Total N (%)	Nonunion N (%)
1	23 (24)	- (-)
2A	29 (30)	2 (7)
2B	28 (29)	5 (18)
3	16 (17)	8 (50)

PAPER 41

Well-Differentiated Lipoma-Like Liposarcoma: Time to Excise This Term?

Authors: Anna Cohen-Rosenblum MD, MSc, Ryan Durfee MD, Arun Aneja MD, Rex Haydon MD, PhD, Terrance Peabody MD, Michael Simon MD.

Institution: University of Chicago

Background: The appropriate terminology for tumors of the extremities with well-differentiated mature adipocytes and focal nuclear atypia has been debated for the past 50 years. While some authors use the term "well-differentiated lipoma-like liposarcoma" (WDLL), others prefer "atypical lipomatous tumor" (ALT) since these tumors generally do not dedifferentiate or metastasize (as opposed to tumors with similar histology occurring in the retroperitoneum).

Questions/Purposes: 1) To review the extant literature regarding these tumors for incidence of recurrence, dedifferentiation, metastasis, and tumor-related death. 2) To examine similar data for these tumors from our institution. 3) To determine an appropriate term for these tumors given the available outcomes data.

Patients and Methods: This is a retrospective chart review of all patients with a diagnosis of ALT or WDLL of the extremity over a 30-year period recorded in our orthopaedic oncology and pathology databases. Inclusion criteria were age over 18 at time of diagnosis and at least 2 years of orthopaedic oncology clinic follow-up. Patients were evaluated for any recurrence, dedifferentiation, metastasis or tumor-related death. In addition, a systematic review was performed of the extant literature regarding these tumors.

Results: From our institution, we found 23 patients with diagnoses of ALT or WDLL that met these criteria, including 13 males and 10 females. Mean follow-up time was 6.3 years, with a range from 2 to 21 years. 6 patients had local recurrences (26%), and there were no instances of dedifferentiation, metastasis or tumor-related death. One patient who had a recurrence was also found to have new pulmonary nodules; these were excised and found to be non-metastatic granulomatous tissue. Our systematic review of 11 studies from 1979-2015 pooled with the data from our institution found 427 total patients with these diagnoses, and included 81 recurrences (22%), 15 instances of dedifferentiation (3.5%), 1 instance of metastasis (0.2%) and 0 tumor-related deaths.

Conclusions: Due to the relatively benign behavior of these well-differentiated lipomatous tumors of the extremity (approximately 1/5 chance of recurrence but a very low likelihood of dedifferentiation, metastasis and/or tumor-related death), we propose that they are most appropriately referred to as "atypical lipomatous tumors". The term "well-differentiated lipoma-like liposarcoma" is not only cumbersome but potentially misleading to patients and surgeons due to its inclusion of "liposarcoma", and may lead to unnecessarily aggressive treatment.

Paper 42

Preliminary results on the international multicenter retrospective Tenosynovial Giant Cell Tumour Study

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Introduction: Tenosynovial Giant Cell Tumour(TGCT), previously named Pigmented Villonodular Synovitis(PVNS), is a rare, locally aggressive neoplasm. The lesion can either present as a single nodule(nodular-type), or as multiple nodules(diffuse-type) along a synovial layer or tendon sheath. Current literature primarily consists of several relatively small cohort studies containing generally inhomogeneous data. A multicenter-pooled database of individual patient data is therefore essential in order to evaluate current treatment protocols and their clinical results, as well as risk factors for progressive disease and local recurrence. Our goal is to set up a retrospective multicenter cohort with histologically proven TGCT, treated between 1990 and 2014 with a minimum follow-up of two years.

Methods: (Un)published data of individual patients from five tertiary orthopedic oncology centers are the base of this international multicenter database. 407 (239 female, median age at operation 34.7years) cases with TGCT are included: 190 of 276 affected knee-joints are diffuse-type, 86% of these primarily treated with open-resection; 86 nodular-type, 85% primarily treated with arthroscopic-resection. 131 other joints are affected of which 84(64%) are diffuse-type. TGCT of fingers and toes are excluded.
The median follow-up time overall is 6.39(95%CI 5.19-7.59) years.
To assess the effect of risk factors on first recurrence, a multivariate cox-regression model with risk factors: gender(male/female), age at first operation(years), surgical treatment(arthroscopic/open), affected joint(knee/other) and TGCT-type(diffuse/nodular) is estimated. The results are reported as hazard ratios(HR) and their corresponding 95% confidence intervals(95%CI). Local recurrence free survival at 2-and 5-years is calculated from the time of first surgical resection to first recurrence.

Results: Total number of first recurrence is 157(39%); located about the knee, diffuse-type 103(54%) and nodular-type 13(15%); other affected joints, diffuse-type 30(35%) and nodular 7(15%). Mean time to local recurrence is 11.68(95%CI 9.57-13.80) years.
The HR for gender(0=male), age at operation, surgical treatment(0=open-resection), joint(0=knee) and TGCT-type(0=diffuse) is 1.43(95%CI 1.04-1.96), 0.99(95%CI 0.98-1.00), 1.07(95%CI 0.83-1.37), 1.39(95%CI 0.96-2.00) and 2.40(95%CI 1.64-3.52) respectively. Recurrences occurred significantly more frequent in male patients (p=0.018) and in diffuse-type(p=0.0001).

The median time to recurrence; in male is 5.16 (95%CI 3.10-7.20) years and in female 16.05(95%CI 4.82-27.36) years (p=0.017); after arthroscopy 5.00(95%CI 2.36-7.64) years and after open-resection 10.56(95%CI 7.52-13.53) years (p=0.089).
Local recurrence free survival at 2-and 5-years is 0.74(95%CI 0.69-0.80) and 0.59(95%CI 0.54-0.65) respectively. At final follow-up 343 patients(84%) show no evidence of disease (49 alive with disease, 5 death of other disease, 10 lost).

Conclusion: Preliminary results on the international multicenter TGCT database show a high risk of first local recurrence, especially with diffuse-type. Nodular-types recur less, but still remarkably often. Interestingly recurrences are diagnosed significant earlier in men. To prolong time to recurrence, open resection is advocated, especially in young patients with TGCT about the knee and in diffuse or recurrent cases.

Further investigation of risk factors for recurrence of TGCT is essential for proper treatment planning in an era of new systemic and (neo)adjuvant treatment possibilities. In order to get more reliable information about this orphan disease and expose possible risk factors for local recurrence, multidisciplinary but foremost international multicenter collaboration is of utmost importance.

PAPER 43

Better Outcomes Following Prophylactic Surgery for Patients With Bone Metastases to the Proximal Femur Than Pathologic Fracture at Presentation

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Background: Current evidence suggests prophylactic surgery is preferable to stabilization following pathologic fracture for patients with metastatic bone lesions at risk of fracture. Reduced morbidity and impact on functional outcomes, shorter operative times, and an expedited recovery are quoted as reasons to identify and treat patients with high-risk lesions in a prophylactic fashion.

Questions/Purposes: This study aims to strengthen the argument that prophylactic fixation is preferable to stabilization by comparing patient outcomes between prophylactic surgical intervention versus surgery following pathologic fracture.

Patients and Methods: A team of orthopedic surgeons and trainees retrospectively reviewed the electronic medical records and imaging studies of 125 patients who underwent surgical intervention for proximal femoral metastatic bone lesions at a Canadian center. We compared surgical procedure types and outcomes between the two groups, prophylactic (32 patients) versus pathologic fracture (93 patients). Outcome data included surgical complications, re-operation rates, tumor progression, and peri-operative cardio-pulmonary complications. Fisher's Exact test was used for statistical comparison of the variables between the two groups.

Results: There were significantly more arthroplasty procedures, relative to intramedullary fixation, performed in the fracture group (47/93, 50.5%) than the prophylactic group (9/32, 28.1%) (p=0.0147). The rate of surgical complications was lower in the prophylactic group (1/32, 3.1%) than the fracture group (12/93, 12.9%), but did not reach statistical significance (p=0.0871). However, there were no re-operations in the prophylactic group relative to 5/93 (5.4%) reoperations in the fracture group. There was no significant difference in tumor progression between the two groups. There was a higher rate of peri-operative cardio-pulmonary complications in the fracture group (19/93, 20.4%) than the prophylactic group (3/32, 9.4%), but did not reach statistical significance (p=0.0843).

Conclusions: Our data support early identification of patients with bone metastases at increased risk of pathologic fracture for prophylactic fixation to minimize the risk of surgical and cardio-pulmonary complications and reoperation. We also found that patients presenting with pathologic fractures of the proximal femur are more likely to be treated with arthroplasty whereas patients in the prophylactic group are more likely to be managed successfully with intramedullary fixation with no re-operations necessary in our series. Although there was a trend for better outcomes following prophylactic surgery, larger collaborative studies are indicated to confirm these findings.

PAPER 44

Outcomes Following Surgical Management of Metastatic Long Bone Disease

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Background: Bone metastases represent the most frequent cause of cancer-related pain. It has been estimated that 1 in 5 affected patients are symptomatic, placing a large burden on patients' health-related quality of life and the healthcare system. Although most bony metastatic lesions can be managed non-operatively, surgical management remains the standard of care for patients with severe pain, impending or established pathological fractures. Surgical management is felt to be indicated in patients with an expected survival over 4 to 6 weeks. Studies have demonstrated functional improvement post-operatively as early as six weeks, but little data exists on exact timing of these improvements post-operatively.

Question/Purpose: In this study, we sought to examine: (1) whether patients' functional outcome, pain and quality of life improved following surgery for long bone metastases and how these improvements occurred over time; (2) the overall and 30-day rate of rate of complications; and, (3) the oncologic outcomes including local disease progression.

Patients and Methods: A multicenter, prospective study was conducted between 2008 and 2016 to examine the improvement in function and quality of life following surgery for patients with long bone metastases. A total of 187 patients were enrolled in the study, with full post-operative data available for 139 patients. The Musculoskeletal Tumour Society (MSTS) 1993 functional score, the Toronto Extremity Salvage Score (TESS), the Brief Pain Inventory (BPI) form, and the Quality Of Life During Serious Illness (QOLLTI-P) form were administered preoperatively and post-operatively at 2, 6, 12, 26 and 52 weeks. The majority of patients (69.8%) had lower limb lesions while 30.2% had upper limb tumours. Pathological fractures were present in 47 (33.8%) patients. The median Mirel's score for those who underwent prophylactic surgery was 10 (7-12). Fifty-four (38.9%) patients were treated with intramedullary nailing, 48 (34.5%) patients underwent endoprosthetic replacement, 31 (22.3%) had plate osteosynthesis, 4 (2.9%) underwent curettage only, and 2 (1.4%) were managed with allograft reconstruction. Eighty-five (61.2%) patients had postoperative radiotherapy, 17 (12.2%) had preoperative radiotherapy and 6 (4.3%) had pre-and postoperative radiotherapy. Thirty-seven (26.6%) patients completed the 52-week follow-up. Analysis of variance followed by post hoc analysis was conducted to test for significance between pre- and post-operative scores. A p-value of less than 0.05 was considered statistically significant.

Results: MSTS 1993 scores demonstrated a statistically significant improvement at 2 weeks (62.2±20.4%) when compared to the preoperative scores (42.3±24.4%) (95% CI=15.5-31.4, P<0.001). Likewise, significant improvement was observed at 6, 12, 26 and 52 weeks when compared to the preoperative scores (p<0.001). There was no difference in TESS scores at 2 weeks post-operative compared to pre-operative, however, there was a significant difference at 6,12,26 and 52 weeks when compared to the preoperative scores (P<0.001). With regard to pain relief, the BPI scores demonstrated a reduction in pain scores at 2, 6, 12, 26 as well as 52 weeks when compared to the preoperative scores (P<0.001). There was no difference in quality of life as measured by the QOLLTI-P score. The overall rate of complications was 41%, with 57 complications reported in 47 patients. The 30-day rate of systemic complications was 13.7%, with only one early death. Local disease progression occurred in 16 patients (11.5%). Fixation failure and infection occurred in 2.9% and 4.3%, respectively.

Conclusion: Surgical management of metastatic long bone disease improves patients' functional outcome and pain scores as measured by the MSTS, TESS and BPI scores. These improvements were significant as early as 2 weeks post-operatively for MSTS and BPI. We did not find a difference in quality of life in this cohort. These results suggest that surgical management is beneficial in patients with metastatic bony disease with expected short-term survival.

Level of Evidence: II

PAPER 45

Effectiveness of Constrained Liner Use in Harrington Hip Reconstruction in Oncology Patients

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INTRODUCTION: Patients with destructive bone lesions secondary to metastatic disease are often at high risk for fracture, with the hip being a common site of occurrence. Surgical management of acetabular disease with prosthetic replacement allows early mobilization, however in patients with extensive destruction of bone, secure fixation and reinforcement of this anatomic site can be challenging. In 1981, Harrington et al first described a technique for reconstructing acetabular diseased bone and tumor tissue with methylmethacrylate supplemented by metal pin fixation (cement-rebar construct), to allow total hip reconstruction. This combination provides adequate structural capacity to permit immediate weight bearing, however it is not without associated morbidity. Bernthal et al described a 9.6% rate of prostheses failure, most commonly from loosening and dislocation, while Ho et al demonstrated a 10.5% rate of dislocation. In fact, all reviewed published reports utilizing this technique describe dislocations. We believe that initial use of constrained liners would help alleviate dislocation risk, without jeopardizing component loosening or excessive polyethylene wear in this patient population.

QUESTIONS/PURPOSE:
Does initial constrained liner use reduce post-operative dislocation rate?
Does this increase loosening, radiographically or clinically?
Does this increase perioperative complications?
Does radiation treatment have an effect on component fixation?

METHODS: Sixty-eight patients who underwent Harrington hip replacements for metastatic cancer from 8/2005 to 3/2016 at our musculoskeletal oncology referral center were identified in a surgical database. All patients had a constrained acetabular liners implanted as part of their index procedure. Electronic medical records and radiographs were reviewed, specifically looking at peri-operative complication rates, as well as loosening and dislocation during follow-up. Given that all patients had constrained liner implantation, there was no comparable control. We conducted a literature search of published studies from 1995 to 2015 involving Harrington (cement-rebar) acetabular reconstruction for oncologic and metabolic patients.

RESULTS: In our study population, metastatic carcinoma was the most prevalent diagnosis, occurring in 39 (57%) patients. Non-metastatic disease was seen in 17 (25.0%) patients. Harrington class II acetabular destruction was seen in 21 patients (30.8%) and class III destruction in 47 (69.2%). Eleven patients (16.1%) received radiation perioperatively. Intra-operative time averaged 153.2±39.2 minutes, with an average blood loss of 323.2±258.6 mL.

Twenty-four (35.3%) patients died during follow up, at an average age of 59.1±17.0 years. At an average of 6.2±10.8 month follow up (range 1 to 50 months), we found no incidents of post-operative dislocation. No patients had component failure requiring revision or evidence of loosening on x-ray. Neither of these complications was influenced by perioperative radiation treatment. In our study, five patients (7.3%) had a post-operative complication, including prominent hardware requiring removal (2 patients, 2.9%), fall with wound dehiscence (1 patient, 1.5%), pathologic peri-prosthetic femur fracture (1 patient, 1.5%), and superficial infection requiring irrigation and debridement (1 patient, 1.5%). No patients died of complications related to the surgery. Review of the literature demonstrated 9 historical control papers, comprising a total of 387 patients. They demonstrated 37 patients (9.5%) with dislocations and 17 patients (4.4%) requiring revisions for component loosening. Numerous post- operative complications were also reported including: deep infection (17 patients, 4.39%), pulmonary embolism (3 patients, 0.7%), myocardial infarction (4 patients, 1.0%), and death (12 patients, 3.1%).

DISCUSSION AND CONCLUSION: The modified cement-screw rebar technique has demonstrated good durability as a reconstructive option in metastatic acetabular disease, though one major complication is dislocation. Based on our review of the literature, dislocation occurs in approximately 9.5%. Dislocation treatment includes attempts of closed reduction but often necessitates component revision. Revision surgery to correct hip instability in the setting of cemented implants in these patients is technically demanding and adds an unnecessary burden of additional surgery on patients with a typically shortened lifespan due to terminal disease. Even modest reduction in complications during the limited lifespan of oncologic patients can have dramatic positive effects on quality of life in patients with an oncologic burden. Initial use of a constrained liner provides significantly increased stability to the hip joint. Component loosening is unlikely due to the limited lifespan and reduced physical demands of this patient population. This study demonstrates that initial use of a constrained liner can alleviate the morbidity associated with post-operative dislocations without increasing risk of perioperative complications, such as component loosening.

PAPER 46

Quality Of Life, Pain Interference, Anxiety, And Depression In Patients With Metastatic Bone Disease

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Background: Maintaining or even improving quality of life (QOL) is a key aspect when treating patients with bone metastatic disease. It would be helpful for the decision-making process to understand which patients are at risk for worse QOL, pain, anxiety, and depression.

Questions/Purposes: The aims of this study were to (1) assess what factors are independently associated with QOL, pain interference, anxiety, and depression in patients with metastatic bone disease, and (2) to compare patient reported outcomes of patients with metastatic bone disease with general US population values.

Patients and methods: We included 202 adult patients with bone metastases from solid tumors, lymphoma, and myeloma who completed the EuroQOL 5 Dimension (EQ-5D), PROMIS Pain Interference, PROMIS Anxiety, and PROMIS Depression questionnaires between 2011 and 2015 as part of a quality improvement program. The primary outcomes were QOL, pain interference, anxiety, and depression. We assessed what factors were independently associated with each outcome measure using stepwise backward multivariable linear regression analysis. We used the one sample signed rank test to assess whether scores differed from US population averages (0.85 for the EQ-5D, 50 for the PROMIS questionnaires).

Results: The median EQ-5D score was 0.68 (Interquartile Range [IQR] 0.40 – 0.81), the median PROMIS Pain Interference score was 65 (IQR 56 – 70), the median PROMIS Anxiety score was 53 (IQR 39 – 61), and the median PROMIS Depression score was 48 (IQR 38 – 57).
Younger age (β regression coefficient [β] 0.003; 95% Confidence Interval [CI] 0.0001, 0.007; p = 0.041), smoking (β -0.12; 95% CI -0.22, -0.01; p = 0.026), having a pathologic fracture (β -0.10; 95% CI -0.18, -0.02; p = 0.012), and being unemployed (β -0.09; 95% CI -0.17, -0.02; p = 0.017) were independently associated with worse QOL. Current smoking status was the only factor independently associated with more pain interference (β 6.03; 95% CI 1.59, 10.5; p = 0.008). A primary tumor type with relatively poor prognosis (β 3.79; 95% CI 0.37, 7.21; p = 0.030), and having a pathologic fracture (β 6.31; 95% CI 2.54, 7.21; p = 0.001) were associated with more anxiety. Being single (β 5.85; 95% CI 0.83, 10.9; p = 0.023), and having a pathologic fracture (β 4.40; 95% CI 0.80, 8.01; p = 0.017) were associated with more depression (Table 1).

Quality of life scores ($p < 0.001$), pain interference scores ($p < 0.001$), and anxiety scores ($p = 0.011$) were significantly worse for patients with bone metastases when compared with general US population values, whereas depression scores were comparable ($p = 0.171$) (Table 2).

Conclusions: We identified risk factors independently associated with patient reported outcomes in patients with bone metastatic disease: younger age, current smoking status, pathologic fracture, and being unemployed were associated with worse quality of life; current smoking status was associated with more pain interference; a primary tumor type with poor prognosis and a pathologic fracture were associated with more anxiety; being single, and having a pathologic fracture were associated with more depression. These patients reported lower QOL, more pain interference, and more anxiety when compared with general US population values – their depression scores were comparable. These findings could be used to assist physicians in their clinical decision-making process, and to direct treatment strategies for specific groups of patients.

Level of evidence: Level 2, Lesser quality prospective study

Table 1. Multivariable linear regression analysis, assessing factors independently associated with patient reported outcomes.

Explanatory variables per questionnaire	β regression coefficient (95% CI)	Standard error	*p*-value
EQ-5D Index			
Age (in years)	0.003 (0.0001, 0.007)	0.001	***0.041***
Smoking status*			
Never smoker	*reference*		
Former smoker†	-0.05 (-0.13, 0.03)	0.04	*0.252*
Current smoker	-1.12 (-0.22, -0.01)	0.05	***0.026***
Pathologic fracture			
No	*reference*		
Yes	-0.10 (-0.18, -0.02)	0.04	***0.012***
Employment status*			
Employed	*reference*		
Unemployed	-0.09 (-0.17, -0.02)	0.04	***0.017***
PROMIS Pain Interference			
Smoking status*			
Never smoker	*reference*		
Former smoker†	3.05 (-0.37, 6.46)	1.72	*0.080*
Current smoker	6.03 (1.59, 10.5)	2.25	***0.008***
PROMIS Anxiety			
Primary tumor type‡			
Good prognosis	*reference*		
Poor prognosis	3.79 (0.37, 7.21)	1.73	***0.030***
Pathologic fracture			
No	*reference*		
Yes	6.31 (2.54, 7.21)	1.90	***0.001***
PROMIS Depression			
Marital status*			
Married/living with partner	*reference*		
Separated/divorced/widowed	0.53 (-3.97, 5.02)	2.27	*0.817*
Single	5.85 (0.83, 10.9)	2.54	***0.023***
Pathologic fracture			
No	*reference*		
Yes	4.40 (0.80, 8.01)	1.82	***0.017***

***Bold** indicates significance (two-tailed p-value below 0.05); adjusted R squared values for the multivariate analyses were 0.0586 for the EQ5D, 0.0407 for the PROMIS Pain Interference, 0.0902 for the PROMIS Anxiety, and 0.0632 for the PROMIS Depression.*

** Marital status was available in 200 cases (99%).*

† Quit at least one year ago.

‡ Primary tumor type with good prognosis includes breast, kidney, prostate, thyroid, myeloma and lymphoma, and with poor prognosis includes all other tumor types.

EQ-5D = EuroQol 5 Dimension Questionnaire; PROMIS = Patient-Reported Outcomes Measurement Information System.

Table 2. Patient reported outcomes for patients with bone metastases, and comparison with general population values.

	n (%)	Median (Interquartile Range)	General Population Value	*p*-value
EQ-5D Index	202 (100)	0.68 (0.40 - 0.81)	0.85	***<0.001***
PROMIS Pain Interference	143 (71)	65 (56 - 70)	50	***<0.001***
PROMIS Anxiety	138 (68)	53 (39 - 61)	50	***0.011***
PROMIS Depression	136 (67)	48 (38 - 57)	50	*0.171*

*Significant p-values in **bold**.*

IQR = interquartile range; EQ-5D = EuroQol 5 Dimension Questionnaire; PROMIS = Patient Reported Outcomes Measurement Information System.

PAPER 47

The Burden of Metastatic Disease of the Femur on the Medicare System

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Background: In the United States, over 1,650,000 new cases of cancer are being diagnosed yearly with almost 50% of them being the top 5 bone-seeking cancers. Since cancer risk increases with age, this suggests that orthopedic oncology services may be a strain on the Medicare system. The femur is the most common site of long bone metastases. Prophylactic fixation techniques prevent pathologic fractures, reduce morbidities, and enhance the quality of life of patients with femoral metastases. This study aims to assess the rate of metastatic disease to the skeleton and evaluate the use and financial burden of femoral prophylactic fixation techniques on the Medicare system.

Questions/Purposes
(1) In the Medicare population, has the number of skeletal metastases increased?
(2) In the Medicare population, has the use of prophylactic fixation techniques increased?
(3) How has the financial burden of prophylactic fixation changed over the study period?

Methods: The Medicare database was searched between 2005-2014 with the assistance of PearlDiver Technologies Inc. and the RBRVS DataManager Online from the American Medical Association. Searches were completed by using International Classification of Disease-9 (ICD-9) and Current Procedural Terminology (CPT) codes for secondary malignant neoplasms and prophylactic fixation techniques. Facility charges, Medicare reimbursement and length of hospital stay were extracted from the Medicare database.

Results: (1) In the Medicare population, has the number of skeletal metastases increased?
While the number of Medicare patients with skeletal metastases has increased from 132,452 in 2005 to 155,819 in 2012 ($p = 0.01$, $r^2 = 0.72$), the prevalence of skeletal metastases in this population remained constant at 30.66 cases per 10,000 Medicare patients in 2012 ($p = 0.56$, $r^2 = 0.06$).
(2) In the Medicare population, has the use of prophylactic fixation techniques increased?
The number of prophylactic fixation techniques has not increased from 2005-2014 ($p = 0.68$, $r^2 = 0.02$); however, the rate of prophylactic fixation among those diagnosed with skeletal metastases has significantly decreased from 94.6 per 10,000 in 2005 to 82.72 per 10,000 in 2012 ($p = 0.006$, $r^2 = 0.74$).
(3) How has the financial burden of prophylactic fixation changed over the study period?

Both total and average hospital charges increased after adjusting for inflation in the total Medicare population; however, only the average Medicare reimbursement changed to reflect this. The total amount Medicare spent on prophylactic fixation techniques in 2012 was $20,245,957 after adjusting to 2014. Despite the increase in hospital charges and average Medicare reimbursement, the average length of hospital stay in the total Medicare population showed a significant decreased trend – down from 7.51 days in 2005 to 5.86 days in 2012 ($p = 0.02$, $r^2 = 0.81$).

Conclusions: Although the prevalence of metastatic disease to the skeleton remained stable between 2005 and 2012 in the Medicare population, prophylactic femoral fixation techniques declined in elderly adults between 2005 and 2014. This most likely signifies an increase in other treatment modalities that can prevent pathologic fractures such as prophylactic hemiarthroplasy, bisphosphonates, and/or radiation therapy.

Level of Evidence
Level IV, Cross-sectional Study

PAPER 48

Variation in Management of Metastatic Humeral Fractures

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Background: Metastatic humeral fractures are treated by trauma surgeons, general orthopaedic surgeons, and orthopaedic oncology surgeons. Many factors (e.g. tumor type) are considered when deciding upon treatment. It is unclear how surgeon characteristics (e.g. subspecialty training, years in practice) and patient characteristics (e.g. tumor type, life expectancy) relate to the decision for specific treatment options.

Questions/Purposes: We aimed to evaluate: (1) if there was a difference between orthopaedic oncology surgeons and trauma surgeons in addressing metastatic humeral fractures, and (2) what patient characteristics guide the decision for treatment.

Patients and methods: One hundred sixty surgeons participated in this cross-sectional survey study; 77 (48%) were orthopaedic oncology surgeons (Group A). The remainder (Group B) were predominantly trauma surgeons (46% [73/160]). All participants evaluated 24 fictional case scenarios of metastatic humeral fractures including radiographs. Scenarios varied with respect to: tumor type (breast carcinoma, renal cell carcinoma, and lung carcinoma), life expectancy (less than 3 months, more than 3 months), fracture type (pathological fracture, impending fracture), and anatomical location of the metastatic lesion (proximal humerus, diaphyseal humerus). Participants were subsequently asked for their treatment recommendation: intramedullary nailing, endoprosthetic reconstruction, plate-screw fixation, or nonoperative management.

Results: Among the 160 participants, 148 (93%) were men, and the mean years in practice was 15 (±9.2); most participants were from North America (49%) and Europe (38%). Intramedullary nailing was the most commonly recommended treatment (58%), followed by nonoperative management (22%), plate-screw fixation (14%), and endoprosthetic reconstruction (6.0%). We found a difference between orthopaedic oncology surgeons (Group A) and other subspecialties (Group B) in recommendation for

specific treatments: intramedullary nailing was less often recommended by orthopaedic oncology surgeons (53%) compared to other subspecialties (62%) ($p = 0.024$); while endoprosthetic reconstruction (orthopaedic oncology surgeons: 8.7%, other subspecialties: 3.6%, $p < 0.001$) and plate-screw fixation (orthopaedic oncology surgeons: 20%, other subspecialties: 9.6%, $p = 0.002$) were more often recommended by orthopaedic oncology surgeons compared to other subspecialties; there was no difference in recommendation for nonoperative management between both groups (orthopaedic oncology surgeons: 19%, other subspecialties: 25%, $p = 0.052$). Recommendation for specific treatments varied based on tumor type, life expectancy, and location of the metastatic lesion. However, recommendation for treatment did not differ based on the type of fracture (impending versus pathological fracture).

Conclusions: There is substantial variation in management of metastatic humeral lesions among surgeons. Our findings support the need for studies comparing different treatment options.