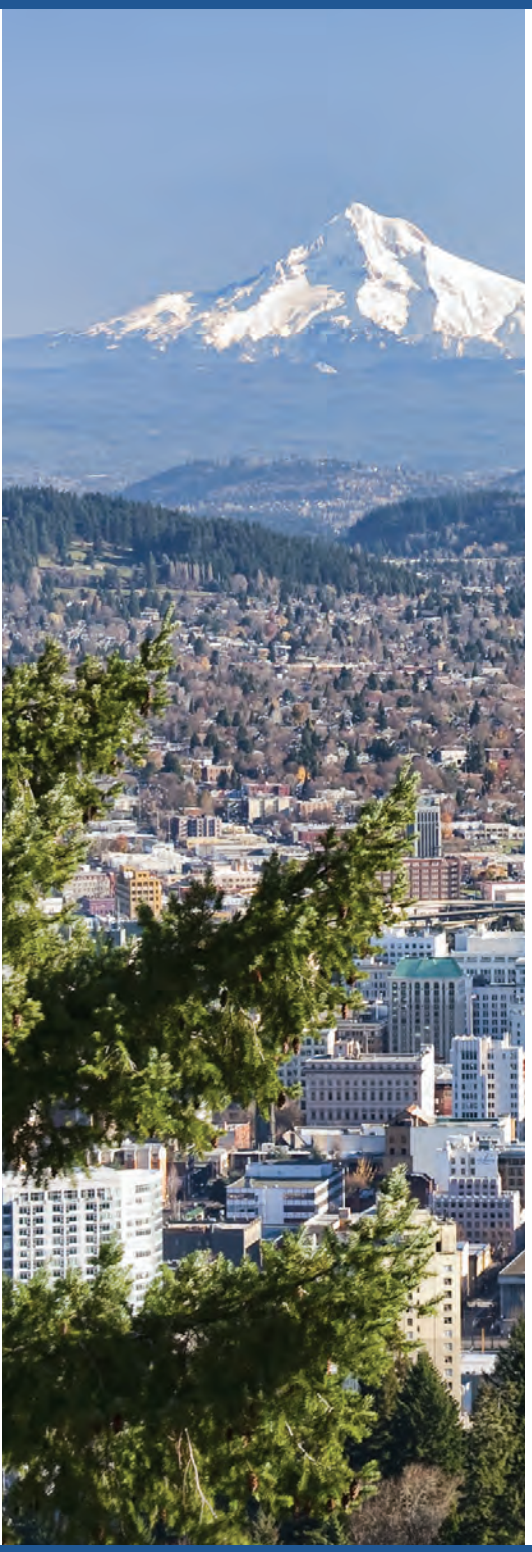
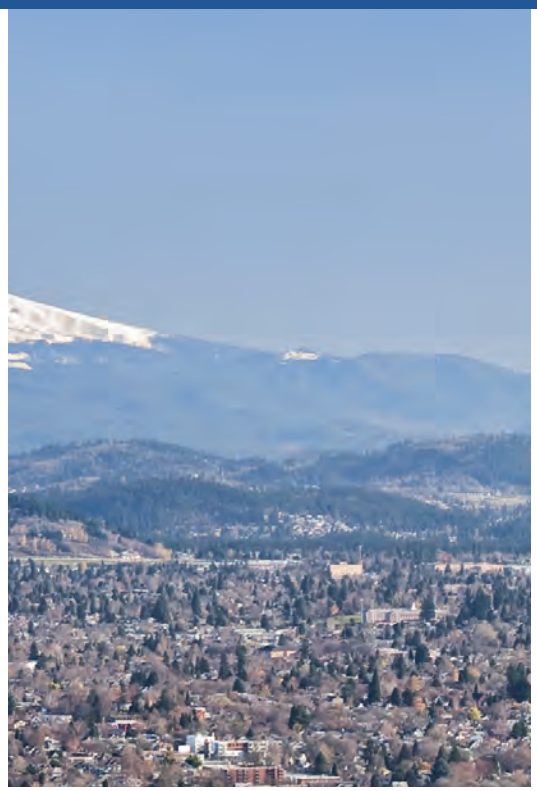
MUSCULOSKELETAL TUMOR SOCIETY





ANNUAL MEETING

October 2-4, 2019

Abstract Book

Marriott Portland Downtown Waterfront Hotel

PORTLAND, OREGON

2019 MSTS Annual Meeting
Preliminary Program

October 2-4, 2019
Marriott Portland Downtown Waterfront Hotel
Portland, Oregon

James B. Hayden, MD, Program Chair
Yee-Cheen Doung, MD, Co-Chair
R. Lor Randall, MD, FACS, MSTS President

Educational Goals and Objectives

At the conclusion of this CME activity, the attendee should be able to:

Understand current trends in cancer research and treatment.

Review principles of Limb Salvage surgery.

Update understanding of the pathophysiology of metastatic bone disease.

Review overall management and operative approach to pelvic bone metastases.

Increase understanding of musculoskeletal treatment needs for adolescents and young adult cancer patients.

Update on basic science research in musculoskeletal oncology.

Identify current and future applications of Quality of Life assessments and patient reported outcomes.

Wednesday, October 2, 2019		
1:00 PM - 6:30 PM	Registration	
1:00 PM - 5:00 PM	Poster Set Up	
1:00 PM - 5:00 PM	Technical Exhibit Booth Set Up	
3:00 PM - 6:00 PM	MORI/MSTS Young Member Session	
6:30 PM - 8:30 PM	Welcome Reception - Mt Hood Room - Marriott Portland Downtown Waterfront Hotel	
Thursday, October 3, 2019		
6:30 AM - 5:30 PM	Registration	
7:00 AM - 8:30 AM	Breakfast	
7:00 AM - 5:30 PM	Poster/Technical Exhibits	
7:30 AM	Introduction and Welcome	James Hayden, MD, Yee-Cheen Doung, MD and R. Lor Randall, MD, FACS

7:45 AM - 8:00 AM	Evaluation of New Bone Lesions - by EBM Committee		Eric R. Henderson, MD
Session I: Registry			
Moderators: Kurt Weiss, MD and Rosanna Wustrack, MD			
8:00 AM - 8:05 AM	Paper 1	Surveillance After Extremity Tumor Surgery (Safety) Patient Survey: A Patient Centered Approach To The Development Of An International Rct	Michelle Ghert, MD, FRCSC
8:05 AM - 8:10 AM	Paper 2	Update On The American Academy Of Orthopaedic Surgeons Musculoskeletal Tumor Registry	Benjamin J. Miller, MD, MS
8:10 AM - 8:15 AM	Paper 3	Affordable Care Act And Insurance Coverage In Orthopaedic Oncology: An Analysis Of The Seer Database	Azeem Tariq Malik, MBBS
8:15 AM - 8:25 AM		Moderated Discussion	
Session II: Soft Tissue Sarcoma			
Moderators: Kurt Weiss, MD and Rosanna Wustrack, MD			
8:25 AM -8:30 AM	Paper 4	Outcome After Surgical Treatment Of Dermatofibrosarcoma Protuberans (Dfsp): Does It Requires All This Follow Up? How Much Resection Margin Is Enough?	Ibrahim S Alshaygy, MD, MSC
8:30 AM - 8:35 AM	Paper 5	Interval Between Preoperative Radiation And Surgery Is Not Associated With Overall Survival For Soft Tissue Sarcomas: An Analysis Of The National Cancer Database	Christopher Collier, MD
8:35 AM - 8:40 AM	Paper 6	Metastatic Bone Disease At Diagnosis In Extremity Soft-Tissue Sarcomas: Risk Factors And Survival Analysis Using The Seer Registry	Manaf H.S. Younis, MD, MPH
8:40 AM - 8:50 AM		Moderated Discussion	
Moderators: Brian E. Brigman, MD and Steven W. Thorpe, MD			

8:50 AM - 8:55 AM	Paper 7	Early Outcomes Of Preoperative 5-Fraction Radiation Therapy For Soft Tissue Sarcoma With Immediate Resection	Joshua M. Lawrenz, MD
8:55 AM - 9:00 AM	Paper 8	Improved Survivorship Following Surgical Resection Of The Primary Tumor In Patients With Metastatic Soft Tissue Sarcoma	Sophia A. Traven, MD
9:00 AM - 9:05 AM	Paper 9	Neoadjuvant Combination Immunotherapy / Radiation For High-Risk Soft Tissue Sarcoma (Nexis): Preliminary Results From An Integrated Phase I/Ii, Single-Arm, Prospective Clinical Trial	Vincent Y. Ng, MD
9:05 AM - 9:15 AM		Moderated Discussion	
9:15 AM - 9:20 AM	Paper 10	Extremity Malignant Peripheral Nerve Sheath Tumor (Mpnst): A Retrospective Analysis Of 185 Cases From Reference Sarcoma Center	Bartek Szostakowski, MD
9:20 AM - 9:25 AM	Paper 11	Vascular Reconstruction In Sarcoma Surgery: Complication, Functional And Vascular Outcomes	Ibrahim S Alshaygy, MD, MSC
9:25 AM - 9:30 AM	Paper 12	Leiomyosarcomas: Recurrence Rates Based On Tumor Depth	Elizabeth Wellings, MD
9:30 AM - 9:40 AM		Moderated Discussion	
9:40 AM - 10:10 AM	Break		
9:40 AM - 10:00 AM		Product Theater- Onkos Surgical	
9:40 AM - 10:10 AM		Poster Viewing	
Session III: Bone Tumors			
Moderators: Amalia M. DeComas, MD and Jared L. Harwood, MD			
10:10 AM - 10:15 AM	Paper 13	Does Surgical Resection Of The Primary Tumor In Patients With Metastatic Osteosarcoma Affect Survivorship	Sophia A. Traven, MD

10:15 AM - 10:20 AM	Paper 14	Age Versus Survival In Primary Bone Cancers (Ewing's Sarcoma, Osteosarcoma, And Chondrosarcoma)	William G Ward, MD, FACS
10:20 AM - 10:25AM	Paper 15	Targeted Muscle Reinnervation Decreases Phantom And Residual Limb Pain In Oncologic Amputees	John Alexander, MD
10:25 AM -10:35 AM		Moderated Discussion	
Session IV: Surgical Treatment			
Moderators: TBD			
10:35 AM - 10:40 AM	Paper 16	Revision Rates For Megaprostheses: A Review Of The Literature And Meta-Analysis	Georges Basile, MD
10:40 AM - 10:45 AM	Paper 17	Custom Stem-Sideplate Preserves At-Risk Hip Joint During Endoprosthetic Reconstruction Of The Femur	Alexander Bryant Christ, MD
10:45 AM - 10:50 AM	Paper 18	Bushing Design And Crosslinked Polyethylene Can Favorably Improve Mechanical Survival Of Rotating Hinge Endoprostheses Around The Knee	Robert M Henshaw, MD
10:50 AM -11:00 AM		Moderated Discussion	
Moderators: Michelle Ghert, MD, FRCSC and Thomas J. Scharschmidt, MD			
11:00 AM - 11:05 AM	Paper 19	Intercalary Endoprosthetic Reconstruction: An Analysis Of Complications	Joseph Benevenia, MD
11:05 AM - 11:10 AM	Paper 20	Comparison Of Reconstructive Techniques Following Oncologic Intraarticular Resection Of Proximal Humerus	Matthew Thomas Houdek, MD
11:10 AM -11:15 AM	Paper 21	Bone Preservation Following Revision Allograft Prosthetic Composite Reconstruction Of The Proximal Humerus	Taylor James Reif, BS, MD
11:15 AM -11:25 AM		Moderated Discussion	

11:25 AM -11:30 AM	Paper 22	Comparison Of Free Vascularized Fibula Grafting To Allograft Strut Grafting To Supplement Spinal Pelvic Reconstruction For Sacral Malignancies	Matthew Thomas Houdek, MD
11:30 AM -11:35 AM	Paper 23	Outcomes Of Sacral Tumor Resection Based On The Mayo Clinic Classification System	Peter S. Rose, MD
11:35 AM -11:40 AM	Paper 24	Navigation-Assisted In Pelvic And Sacrum Resection Provides Benefit In Minimizing Bony Recurrence	David M. Joyce, MD
11:40 AM -11:50 AM		Moderated Discussion	
11:50 PM - 1:00 PM	Lunch		
11:50 AM - 12:10 PM		Product Theater- Artoss, Inc.	
12:15 PM - 12:35 PM		Product Theater- Zimmer Biomet	
11:50 AM - 1:00 PM		Poster Viewing	
Session V: Panel Discussion: Adolescents and Young Adults			
Moderators: Lara E. Davis, MD			
1:00 PM - 1:40 PM		Adolescents and Young Adults (AYA) Panel Discussion	Panelists: Lara E. Davis, MD, Antoinette Lindberg, MD, Susan Hedlund, M.S.W., L.C.S.W., O.S.W.-C, Susan Lindemulder, MD and Elizabeth Barbieri, MD
Session VI: Young Adults			
Moderators: Megan E. Anderson, MD and Nicola Fabbri, MD			
1:40 PM -1:45 PM	Paper 25	Pediatric Sarcoma Patients Have Worse Physical Function But Better Peer Relationships And Depressive Symptoms Than The U.S. General Pediatric Population As Measured By Promis	Anna R Cooper, MD, MPH
1:45 PM - 1:50 PM	Paper 26	Bisphosphonate Therapy For Treating Osteonecrosis In Pediatric Leukemia Patients: A Systematic Review	Shanaz Daneshdoost

1:50 PM - 1:55 PM	Paper 27	Allograft Reconstruction Alone Has An Increased Rate Of Amputation And Worse Functional Outcome When Compared With Vascularized Fibular Reconstruction For Tibial Defects In Pediatric Patients	Amirhossein Misaghi, MD
1:55 PM - 2:00 PM	Paper 28	Clinical Characteristics Of Masses In Pediatric Hand/Wrist	Carlos D. Pargas, MD
2:00 PM - 2:10 PM		Moderated Discussion	
2:10 PM - 2:15 PM	Paper 29	Low Socioeconomic Status Predicts Metastatic Disease At Presentation In Young Patients With Ewing Sarcoma	Sophia A. Traven, MD
2:15 PM - 2:20 PM	Paper 30	The Sarcoma-Specific Quality Of Life Study (Sarc-Qol) (Phase 1): Identifying Key Domains Of Health-Related Quality Of Life In Adult Patients With Extremity Soft Tissue Sarcoma	Krista Anne Goulding, MD, FRCSC, MPH
2:20 PM - 2:25 PM	Paper 31	The Sarcoma-Specific Quality Of Life Study (Phase 1): A Qualitative Study Of Psychological Functioning And Coping Styles In Adult Extremity Soft Tissue Sarcoma Patients	Krista Anne Goulding, MD, FRCSC, MPH
2:25 PM - 2:35 PM		Moderated Discussion	
2:35 PM - 3:05 PM		Break	
2:35 PM - 2:55 PM		Product Theater - Stryker	
2:35 PM - 3:05 PM		Poster Viewing	
3:05 PM - 3:50 PM		MSTS Business Meeting - MSTS Members Only	
Session VII: Research			
Moderators: Patrick P. Lin, MD and Nicholas Bernthal, MD			
3:50 PM - 3:55 PM	Paper 32	A Cross-Species Personalized Medicine Pipeline Identifies The Crm1 Export Pathway As A Potentially Novel Treatment For Osteosarcoma	Alexander Leandros Lazarides, MD

3:55 PM - 4:00 PM	Paper 33	Comparison Of Cachectic And Non-Cachectic Sarcoma Patients Reveals Differences In The Notch Pathway But Similarities In Myogenesis Inhibition	Jonathan Mandell, BS
4:00 PM - 4:05 PM	Paper 34	Systems-Wide Immunophenotyping Defines Distinct Malignancy-Induced Immunological Changes That Follow Disease Burden In An Immunocompetent K7m2 Orthotopic Murine Model Of Osteosarcoma	Brock A Lindsey, MD
4:05 PM - 4:15 PM		Moderated Discussion	
4:15 PM -4:20 PM	Paper 35	Developing A Novel Spheroid Model For Chondrosarcoma Research And Drug Screening	Ruichen Ma
4:20 PM - 4:25 PM	Paper 36	Copper Levels And Aldh1a1 Expression Varies Between Low And Highly Metastatic Human Osteosarcoma Cell Lines And Human Samples	Jonathan Mandell
4:25 PM - 4:30 PM	Paper 37	Cell Cycle Checkpoints P16 And P21 – Strong Predictors Of Clinicopathologic Outcome In High-Grade Osteosarcoma	Elham Nasri, MD
4:30 PM - 4:40 PM		Moderated Discussion	
Moderators: Matthew W. Colman, MD and Raffi Avedian, MD			
4:40 PM - 4:45 PM	Paper 38	Safety And Feasibility Of The Civo Phase 0 Platform For Simultaneous Evaluation Of Multiple Drugs And Drug Combinations In The Tumor Microenvironment (Tme) Of Cancer Patients	Kenneth Gundle, MD
4:45 PM - 4:50 PM	Paper 39	Mitigation Of Post-Radiation Muscle Fibrosis Using Tgf-Beta	Carol D Morris, MD, MS
4:50 PM - 4:55 PM	Paper 40	Treatment Of Soft Tissue Sarcoma With A Novel Cold Plasma Jet	Alan T. Blank, MD, MS

4:55 PM - 5:05 PM		Moderated Discussion	
Session VIII: Miscellaneous			
Moderators: **Matthew W. Colman, MD and Raffi Avedian, MD**			
5:05 PM - 5:10 PM	Paper 41	The Downstream Revenue Impact Of A Dedicated Orthopaedic Oncologist	Zeke Walton, MD
5:10 PM - 5:15 PM	Paper 42	Are We Training Too Many Orthopaedic Oncologists?	Frank Chiarappa, MD
5:15 PM - 5:20 PM	Paper 43	Statistical Fragility Of Surgical And Procedural Clinical Trials In Orthopedic Oncology As Quantified By The Fragility Index: A Systematic Review	Eugene Jang, MD, MS
5:20 PM - 5:30 PM		Moderated Discussion	
5:30 PM		Meeting Adjourns	
	Social Event - Portland World Trade Center		
Friday, October 4, 2019			
6:30 AM- 8:30 AM	Registration		
7:00 AM - 8:30 AM	Breakfast		
7:00 AM - 11:45 AM	Posters/Technical Exhibits		
Session IX: Metastatic			
Moderators: **Kevin A. Raskin, MD and Kevin B. Jones, MD**			
7:30 AM - 7:35 AM	Paper 44	Outcomes In Metastatic Bone Disease: A Comparison Of Academic And Community Programs Using The National Cancer Database	Frank Chiarappa, MD
7:35AM - 7:40 AM	Paper 45	Survival In Patients With Carcinomas Presenting With Bone Metastasis At Diagnosis: A Seer Population-Based Cohort Study	Manaf H.S. Younis, MD, MPH
7:40 AM - 7:45 AM	Paper 46	Survival After Surgery For Skeletal Metastases Is Associated With Preoperative Patient-Reported Assessments	Meredith Bartelstein, MD
7:45 AM - 7:55 AM		Moderated Discussion	

7:55 AM - 8:00 AM	Paper 47	Multicenter Retrospective Comparison Of Failure Rates, Outcomes And Complications Between Plate And Nail Fixation For Metastatic Lesions Of The Humerus	James Norris, MD
8:00 AM - 8:05 AM	Paper 48	Finite Element Fracture Predictions For Patients With Metastatic Lesions Of The Proximal Femur	Timothy A Damron, MD
8:05 AM - 8:10 AM	Paper 49	Can We Do Better Than Mirels In Predicting Fracture Risk For Patients With Multiple Myeloma? Evaluation Of A Novel Scoring System	Gregory Toci, BS
8:10 AM - 8:20 AM		Moderated Discussion	
Moderators: Timothy A. Damron, MD and Daniel M. Lerman, MD			
8:20 AM - 8:25 AM	Paper 50	The Use Of Arthroplasty When Treating Proximal Femur Metastatic Lesions Is Associated With Increased Patient Survival When Compared To Intramedullary Nailing In The Va Healthcare System	Kenneth Gundle, MD
8:25 AM - 8:30 AM	Paper 51	Beyond Bisphosphonates And Denosumab To Protect Bone From Cancer-Induced Bone Loss: Mechanism-Based Therapeutic Targets	Francis Young Lee, MD, PhD
8:30 AM - 8:35 AM	Paper 52	Does Nailing Of Pathologic Fractures Increase Systemic Tumor Burden?	Carol D Morris, MD, MS
8:35 AM - 8:45 AM		Moderator Discussion	
8:45 AM - 9:45 AM		Presidential Guest Lecturer - Cancer, Bone, Muscle and Metabolism: What's the Connection?	Theresa A. Guise, MD
9:45 AM - 10:15 AM		Break	
9:45 AM - 10:05 AM		Product Theater - Onkos Surgical	
9:45 AM - 10:15 AM		Poster Viewing	

10:15 AM - 10:20 AM	Paper 53	Comparative Efficacy Of Receptor Tyrosine Kinase Inhibitors (Rtkis) And Immunotherapy (Anti-Pd-1/Pd-L1) For Treatment Of Osseous Versus Soft Tissue Metastases In Metastatic Renal Cell Carcinoma (Mrcc)	Katherine Tai
10:20 AM - 10:25 AM	Paper 54	Mutation Status And Treatment With Tyrosine Kinase Inhibitors Improves Survival Estimates In Patients With Metastatic Non-Small Cell Lung Cancer	Jonathan Agner Forsberg, MD, PHD
10:25 AM - 10:30 AM	Paper 55	Reamed Versus Unreamed Intramedullary Nailing For The Treatment Of Impending And Pathological Humeral Shaft Fractures: A Retrospective Comparative Study	Manaf H.S. Younis, MD, MPH
10:30 AM - 10:40 AM		Moderated Discussion	
Moderators: Nicholas Tedesco, DO and Kenneth Gundle, MD			
10:40 AM - 10:45 AM	Paper 56	Comparison Of Porous Tantalum Acetabular Implants Versus Harrington Reconstruction For Metastatic Disease Of The Acetabulum	Joshua Johnson, MD
10:45 AM - 10:50 AM	Paper 57	A Novel Percutaneous Osseous Pathway Screw Fixation Technique For Management Of Periacetabular Metastatic Disease	Sahitya Denduluri, MD
10:50 AM - 10:55 AM	Paper 58	Ambulatory Minimally Invasive Image-Guided Ablation-Osteoplasty-Reinforcement-Internal Fixation (Aorif) Reconstruction For Osteolytic Metastatic Cancers In Weight Bearing Bones	Francis Young Lee, MD, PhD
10:55 AM - 11:05 AM		Moderated Discussion	
11:05 AM - 11:10 AM	Paper 59	Pexidartinib For Locally Advanced Tenosynovial Giant Cell Tumor (Tgct): Overall Long-Term Pooled Efficacy And Safety With Characterization Of Hepatic Adverse Reactions (Ars) From Enliven And Other Studies	John H Healey, MD, FACS

11:10 PM - 11:15 AM	Paper 60	Pvns Of The Knee: A Consecutive Series Of 54 Patients Treated Either Arthroscopically Or With Open Synovectomy	Jennifer Thomson
11:15 AM - 11:20 AM	Paper 61	Retrospective Review Of Venous Thromboembolism Prophylaxis In Surgical Resection Of Benign And Malignant Tumors Of Bone And Soft Tissue	Peter Kyriakides
11:20 AM - 11:30 AM		Moderated Discussion	
Session X: Panel Discussion: Teach the Teacher			
Moderator: Valerae O. Lewis, MD			
11:30 AM - 11:35 AM		C. Howard Hatcher Legacy to the Founding of the MSTS	Michael A. Simon, MD
11:35 AM - 12:35 PM		Teach the Teacher -Panel Discussion	Panelists: Robert J. Esther, MD, Ginger E. Holt, MD and Pietro Ruggieri, MD
12:35 PM		Meeting Adjourns	

Thank you for attending the 2019 MSTS Annual Meeting.

PAPER 1

Surveillance AFter Extremity Tumor surgerY (SAFETY) Patient Survey: A patient centered approach to the development of an international RCT

Authors: Patricia Schneider, B.Sc.; Victoria Giglio, M.Sc; Roberto Vélez, MD, PhD; Benjamin Miller, MD, MS, FACS; Robert Turcotte, MD, FRCSC; R. Lor Randall, MD, FACS; James Hayden, MD, PhD, FACS; David Wilson, MD, FRCSC; and Michelle Ghert, MD, FRCSC

Background: Following surgical resection of a high-grade extremity soft-tissue sarcoma, between 40 and 50% of all patients will develop a local or distant recurrence. Earlier detection of a less advanced disease recurrence may prolong survival; therefore, intensive post-operative surveillance, especially of the lungs, is routine practice. However, the adverse effects are also noteworthy, including healthcare costs, the financial/emotional burden on patients, and unnecessary radiation exposure. Our recent musculoskeletal oncology research planning initiative identified post-operative sarcoma patient surveillance as the highest-ranking research priority in the sarcoma field and was endorsed by patient representation. A randomized controlled trial (RCT) designed to identify the optimal post-operative surveillance strategy that balances gains in survival, costs, and quality of life is warranted, but will require widespread multidisciplinary sarcoma specialist and patient support.

Purpose: This study aims to determine international sarcoma patient understanding of clinical research and willingness to be randomized to varying surveillance regimens following their sarcoma treatment. The study also aims to provide important background information to inform a patient-centered and relevant study protocol for a large international RCT that addresses the following question: *Does the frequency and mode of surveillance affect patient survival following extremity STS surgery?* (The Surveillance AFter Extremity Tumor surgerY [SAFETY] randomized controlled trial).

Methods: We are conducting a cross-sectional patient survey to examine international patient willingness to participate in a post-operative sarcoma surveillance RCT. We developed a 57-item patient questionnaire that characterizes: opinions and preferences with respect to cancer research and treatment; and willingness to participate in a study that randomizes to a particular follow-up regimen. All patients who present to a participating site are screened for inclusion. To be eligible, patients must: be at least 18 years of age; be able to read and write in English, Dutch, French or Spanish; be attending clinic for treatment of a high-grade extremity soft-tissue sarcoma; and have consented for surgery. Completed questionnaires are then reviewed for inconsistencies before entry into a study-specific database.

Results: At the time of abstract submission, five sites (Hamilton, Canada; Montreal, Canada; Iowa City, USA; Salt Lake City, USA; and Barcelona, Spain) are open to enrolment and 60 patients have completed the questionnaire. Sixty-two percent of participants indicated they have a good understanding of clinical research. Almost 85% of participants are either comfortable with or indifferent to being randomly allocated to differing surveillance regimens. Ultimately, 80% of participants have indicated they would be willing to participate in a RCT evaluating post-operative surveillance strategies.

Conclusion: Sarcoma patient surveillance has been identified by consensus as the top research priority in the field. Thus far, the patient survey data indicates that an international RCT is feasible with respect to patient willingness to participate. Initial funding for the SAFETY pilot trial has been secured and the first draft of the study protocol is available in pre-print on OSF (https://osf.io/2wjyk/). MSTS investigators interested in the trial are encouraged to visit www.SAFETYrct.com to submit an application to participate.

PAPER 2

Update on the American Academy of Orthopaedic Surgeons Musculoskeletal Tumor Register

Authors: Benjamin J. Miller, MD, MS, Adam Levin, MD, George Calvert, MD, Eric Henderson, MD

Background: In the spring of 2018, the American Academy of Orthopaedic Surgeons (AAOS) and Musculoskeletal Tumor Society (MSTS) began a partnership to create the Musculoskeletal Tumor Registry (MsT). This effort was stimulated by two years of preparatory work by a registry work group and made possible with grant funding from the Orthopaedic Education and Research Foundation and MSTS. MsT is the third in the AAOS family of registries, following the American Joint Replacement Registry (AJRR) and Shoulder and Elbow, and is the first to include patients based on a diagnosis (pelvis and extremity sarcoma) rather than a surgical procedure.

Questions/Purposes: The registry is designed to provide functional and quality-of-life outcome measures, in addition to oncologic end points, and works to minimize provider burden while maximizing accuracy and relevance. A six-center pilot trial formally began in January of 2019 with the focus of establishing a workflow for institutional enrollment, data entry and abstraction, and provider interaction.

Patients and Methods: Our pilot trial included six major academic medical centers, all current members of AJRR and utilizing the same Electronic Health Record (EHR), Epic, to expedite logistical and legal challenges in registry expansion. Our inclusion criteria were patients of any age diagnosed with a primary sarcoma of the bone or soft tissue in the pelvis or extremities treated with surgical resection. We recorded baseline patient demographics, tumor characteristics, adjuvant treatment, procedural details, implants, adverse events, and outcome measures. Whenever possible, we used automatic data abstraction techniques from the EHR rather than direct provider entry. Our goal was to capture 80% complete and accurate data in 80% of patients.

Results: At the time of submission of this abstract, 5 of the 6 sites had obtained institutional approval and were actively implementing EHR forms for data capture. By October 2019, we anticipate preliminary data on patient enrollment, data accuracy, major challenges, and impediments to participation. Additional sites will have been identified to join the society-wide effort.

Conclusions: The MsT Registry has the potential to evolve into an important research tool with an emphasis on quality, patient safety, practice variability, and cost effectiveness; future applications may include hosting prospective clinical trials. Feedback from and acceptance by the community of orthopaedic oncologists is critical to its success, utility, and application. We plan to update the membership of the MSTS on the current status of the effort, answer questions regarding participation and logistics, and present our early experience to date.

PAPER 3

Affordable Care Act and Insurance Coverage in Orthopaedic Oncology: An Analysis of the SEER Database

Authors: Azeem Tariq Malik, MBBS, John Alexander, MD, Safdar N Khan, MD, Thomas J Scharschmidt, MD

Institutions: Division of Musculoskeletal Oncology, The James Cancer Hospital and Solove Research Institute, The Ohio State University Wexner Medical Center

Background: The Patient Protection and Affordable Care Act (ACA) mandate of 2010 was aimed at increasing access to care for uninsured individuals by launching a number of initiatives, such as expanding Medicaid eligibility, subsidization of private insurance and development of state-wide mandates requiring individuals to have a prescribed minimum level of health insurance.

Questions/Purpose: Using a national surveillance dataset, the current study aims to assess the impact of the ACA on insurance coverage rates and access to care among patients with primary bone and/or soft-tissue sarcomas. The study also aims to evaluate whether the introduction of ACA lead to an early diagnosis/screening of orthopaedic oncologies, based on the AJCC Clinical stage at diagnosis.

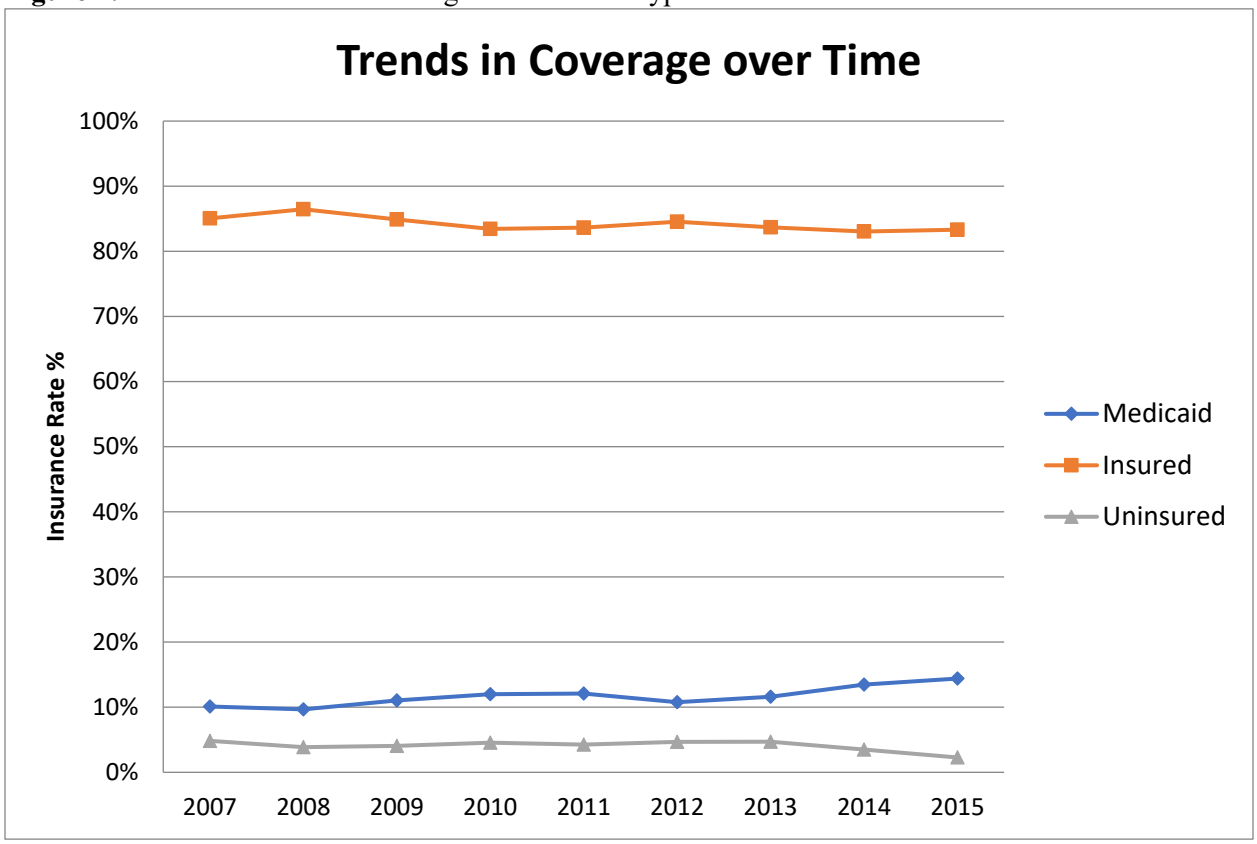
Patients and Methods: The 2007-2015 Surveillance, Epidemiology and End Results (SEER) database was queried, using International Classification of Diseases for Oncology (ICD-O) codes for primary malignant bone tumors of the upper/lower extremity (C40.0-C40.3), unspecified/other overlapping bone/articular cartilage/joint and/or ribs/sternum/clavicle (C40.8-C40.9, C41.3, C41.8-C41.9), vertebral column (C41.2), pelvis (C41.4, C41.8, C41.9) and soft-tissue sarcomas of the upper/lower extremity and/or pelvis (C49.1, C49.2 and C49.5). Patients with unknown insurance status and/or missing survival follow-up were excluded from the study. Trends of insurance coverage rates for Medicaid, Insured (Medicare and/or Private) and uninsured were assessed over time. Trends in insurance coverage were also assessed between states that elected to expand Medicaid eligibility (Georgia, Louisiana, Utah and Alaska; Iowa adopted the expansion mandate completely in 2015) from 2014 onwards versus those who opted out of expansion. We also aimed to assess whether the introduction of ACA led to early diagnoses of cancers, based on AJCC staging.

Results: A total of 15,287 newly diagnosed cancers were included, out of which 3,647 (23.9%) were primary bone tumors and 11,640 (76.1%) were soft-tissue sarcomas. Following the passage of ACA in 2010, the rate of un-insured individuals dropped from 4.3% to 3.9%. The most dramatic reduction was noted following the expansion of Medicaid eligibility (2014 onwards), with uninsured rates decreasing from 4.4%, prior to the 2014 expansion, to 2.9% ($p<0.001$). The decrease in un-insured rates and associated increase in Medicaid coverage was only noted for states that adopted the Medicaid expansion. There was also a decreasing number of Stage IV (pre-ACA: 13.4% vs. post-ACA: 11.4%; $p<0.001$) diagnoses and increasing number of Stage I diagnoses (pre-ACA: 27.7% vs post-ACA: 37.9%; $p<0.001$) following the introduction of the ACA in 2010. The proportion of individuals with unknown stages also went down dramatically from 28.2% to 8.4% after 2010.

Conclusions: Access to cancer care for patients with primary bone and/or soft-tissue sarcomas was improved following the introduction of the ACA, as evidenced by a decrease in rate of uninsured patients and corresponding increase in Medicaid coverage. These outcomes were only demonstrated in states that adopted the Medicaid expansion of 2014. The ACA may have also yielded earlier cancer diagnoses as evidenced by increased rates of Stage I and subsequent decreased rates of Stage IV cancers, and unknown stages.

Level of Evidence: III

Figure 1: Trends in insurance coverage for all cancer types over time.



PAPER 4

Outcome After Surgical Treatment of Dermatofibrosarcoma Protuberans (DFSP): Does it requires all this follow up? How much resection margin is enough?

Authors: Ibrahim Alshaygy MD, Georges Basile MD, Jean-Camille Mattei MD, Anthony Griffin, Brendan Dickson MD, Peter Ferguson MD, Jay Wunder MD

Institutions: University Musculoskeletal Oncology Unit, Mount Sinai Hospital, Toronto, Ontario, Canada

Background: Dermatofibrosarcoma protuberans (DFSP) is a rare, cutaneous tumor of intermediate monoclonal dermal neoplasm. DFSP is known to be locally aggressive and infiltrative. It seems to be associated with high local recurrence rates after surgical intervention and current resection method advocates extra-wide margins or often results in high chance of local recurrence.

Objective: Assess the outcomes of DFSP resection in our facility and shape a new follow-up protocol based on margins and grade if it has fibrosarcomatous changes.

Methods: All DFSP treated in the unit were included through our prospective database: consents were obtained from patients at time of referral to our sarcoma clinic and prospective follow-up data was collected. Patients with and without prior surgery, and patients with fibrosarcoma were included. Each patient was operated with 2.5cm wide-margin resection method, to ensure complete resection of the tumor. Patients were followed up after surgery to monitor complications, recurrence, transformation and/or metastasis. Minimum follow-up was of one year.

Results: N=196 patients (mean age=42.4, standard deviation= 13.7) were included in Mount Sinai Hospital Sarcoma unit, Toronto with minimum follow up of a year. 136 (39.4%) had prior "whoops" surgery before referral. After our surgery, 14 (7.1%) patients were found with positive margins; 8 patients underwent radiation treatment while the other 6 patients were discharged without any further treatment. During follow-up, 1 patient who had local recurrence at time of referral, developed additional local recurrence. 1 other patient developed a lesion at another site. No recurrence was observed in all other patients.

Discussion: The recurrence rate in our DFSP cohort is significantly lower than previous reports. This demonstrates that our minimalist approach to treating DFSP, i.e. wide margins of resection, is viable and effective. Patients treated with our method do not require frequent follow-up. If they have fibrosarcomatous changes within the DFSP, we look into the grade. Grade I we follow them up yearly. Grade two and three we manage them as any high-grade sarcoma. This resection and stratification method can significantly improve patient outcomes and reduce visits to hospitals post-surgery. Future studies should look at if closer margins can also produce similar treatment outcome.

PAPER 5

Interval between Preoperative Radiation and Surgery does not Affect Overall Survival for Extremity Soft Tissue Sarcomas: An Analysis of the National Cancer Database

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Background: Most cancer centers prefer preoperative radiation therapy (preRT) over postoperative therapy for the treatment of soft tissue sarcoma (STS) to limit long-term fibrosis, joint stiffness, and edema. Surgery is often delayed after preRT to allow for tissue recovery and reduce wound complications, reported to range from 27.5-35%. However, the optimal preRT-surgery interval and its association with survival is unknown.

Questions/purposes: This study asked: (1) what factors influence the preRT-surgery interval in STS? and (2) whether a longer preRT-surgery interval is associated with overall survival?

Patients and Methods: The National Cancer Database was reviewed to identify patients that underwent preRT and surgical resection for localized extremity or pelvic STS from 2004-2014. Patients with an unknown radiation sequence or duration, missing vital status, regional or metastatic disease, multimodal radiation treatment, or chemotherapy treatment were excluded. A multiple linear regression model was generated to assess factors associated with a longer preRT-surgery interval. Kaplan-Meier survival analysis was then conducted, stratified by preRT-surgery interval to assess unadjusted 5 and 10-year survival rates. Finally, a multivariate Cox regression analysis model was then constructed to evaluate the effect of the preRT-surgery interval on overall survival, adjusted for demographic, clinicopathologic, and treatment characteristics.

Results: A total of 2,176 patients were included with a mean age of 60 years (standard deviation [SD] 16), 55% were male, and 86% were white. The majority of patients were treated at a high-volume institution (79%) and lived in a metropolitan area (83%). Tumors were located predominately in the lower extremity (73%) with an average tumor size of 11.4 cm (SD 7.2). Preoperative radiation therapy was delivered by conventional external beam for 68% of patients. The mean preRT-surgery interval was 35 days (SD 16), most commonly 3-4 weeks (24%) or 4-5 weeks (23%). The majority of patients had limb-sparing surgery (75%) with positive margins in 9% of cases.
Multiple linear regression analysis (Table 1) demonstrated that increasing age ($\beta = 0.002$, $p = 0.026$), tumor location in the pelvis (compared to lower extremity, $\beta = 0.015$, $p < 0.001$), and MPNST subtype (compared to UPS, $\beta = 0.165$, $p = 0.008$) were associated with a longer preRT-surgery interval. Higher facility volume ($\beta = -0.002$, $p = 0.026$) and higher tumor stage ($\beta = -0.066$, $p = 0.03$ for stage II; $\beta = -0.117$, $p < 0.001$ for stage III) were associated with a shorter preRT-surgery interval.

Kaplan-Meier analysis (Figure 1) demonstrated no significant difference in overall survival when stratified by preRT-surgery interval (Fig 1, $p = 0.74$). Multivariate Cox regression analysis showed that increasing age (Hazard Ratio [HR] = 1.027, $p < 0.001$), tumor size ([HR] = 1.002, $p < 0.001$), stage III cancer (compared to stage I, [HR] = 1.623, $p < 0.001$), and amputation (compared to local resection, [HR] = 1.721, $p = 0.013$) were associated with decreased survival. Female gender ([HR] = 0.739, $p < 0.001$), higher socioeconomic quartile (compared to SES 1, [HR] = 0.685, $p = 0.001$ for SES 3; [HR] = 0.683, $p = 0.003$ for SES 4), fibrosarcoma (compared to UPS, [HR] = 0.708, $p = 0.011$), and liposarcoma (compared to UPS, [HR] = 0.643, $p < 0.001$) were associated with increased survival. The preRT-surgery interval was not associated with survival ([HR] = 1, $p = 0.88$).

Conclusions: This is the first study to demonstrate that the preRT-surgery interval is not associated with overall survival in STS. These findings suggest that a delay in surgery is safe and provides guidance to both clinicians and patients balancing the risks of wound complications with the timeliness of resection.

Table 1. Factors associated with preRT-surgery interval. Based on transformed values.

Variable	Unstandardized β	95% CI	P
Age (years)	0.002	[0.0, 0.004]	**0.026**
Gender			
Male	Ref		
Female	0.028	[-0.012, 0.069]	0.165
Race			
White	Ref		
Black	0.059	[-0.01, 0.128]	0.095
Other	-0.042	[-0.15, 0.066]	0.449
SES Composite			
1	Ref		
2	-0.021	[-0.082, 0.039]	0.489
3	-0.008	[-0.07, 0.055]	0.811
4	-0.017	[-0.086, 0.052]	0.624
Charlson/Deyo comorbidity score			
0	Ref		
1	0.029	[-0.026, 0.084]	0.298
2 or more	-0.051	[-0.155, 0.052]	0.333
Distance from facility (miles)	0	[-0.0, 0.0]	0.909
Urban/rural			
Rural	Ref		
Urban	-0.008	[-0.168, 0.151]	0.918
Metro	-0.006	[-0.162, 0.15]	0.941
Insurance			
Private	Ref		
Medicaid	0.06	[-0.036, 0.155]	0.221
Medicare	0.012	[-0.046, 0.069]	0.695
Other	0.055	[-0.083, 0.193]	0.436
Uninsured	0.052	[-0.061, 0.165]	0.365
Facility volume	-0.002	[-0.003, -0.002]	**<0.001**
Tumor location			
Lower extremity	Ref		
Upper extremity	-0.002	[-0.058, 0.053]	0.939
Pelvis	0.15	[0.082, 0.217]	**<0.001**
Histology			
UPS	Ref		
Fibrosarcoma	0.018	[-0.048, 0.084]	0.596
Liposarcoma	0.052	[-0.004, 0.107]	0.067
Leiomyosarcoma	0.039	[-0.03, 0.108]	0.264
Synovial sarcoma	0.058	[-0.031, 0.147]	0.202

MPNST	0.165	[0.044, 0.286]	**0.008**
Tumor size (mm)	0	[-0.0, 0.0]	0.495
Stage			
I	Ref		
II	-0.066	[-0.126, -0.006]	**0.03**
III	-0.117	[-0.17, -0.065]	**<0.001**
Radiation modality			
Conventional	Ref		
IMRT	0.022	[-0.029, 0.074]	0.393
3-D conformal	0.055	[-0.006, 0.116]	0.077
Surgery type			
Local resection	Ref		
Limb-sparing	-0.04	[-0.087, 0.008]	0.102
Amputation	-0.074	[-0.212, 0.064]	0.29

CI = Confidence Interval; SES = Socioeconomic Status; UPS = Undifferentiated Pleomorphic Sarcoma; MPNST = Malignant Peripheral Nerve Sheath Tumor; IMRT = Intensity Modulated Radiation Therapy.

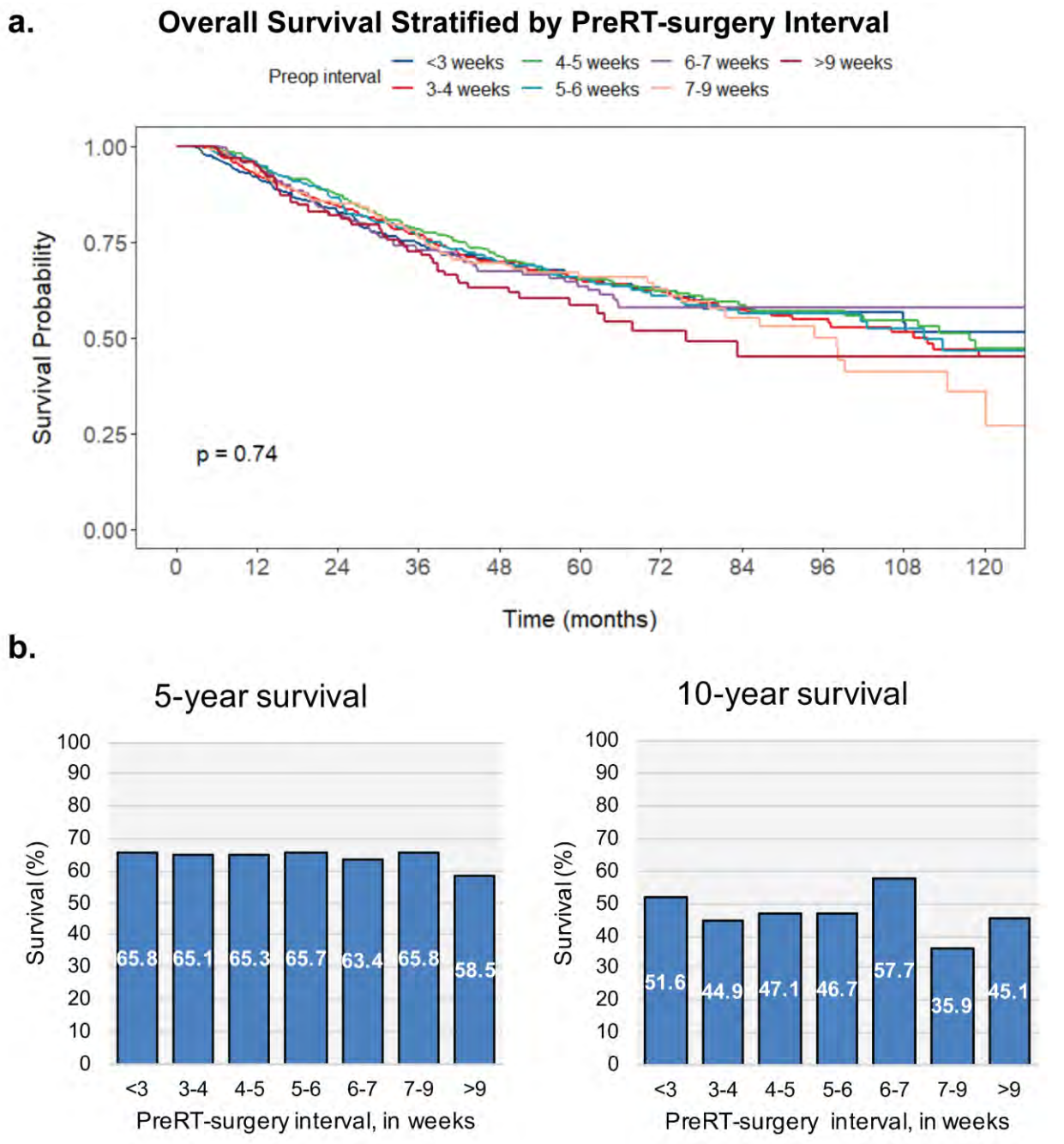

Figure 1 a-b Unadjusted survival analysis vs preRT-surgery interval. Kaplan-Meier survival curve is shown in **(a)** with p = 0.74. Five and ten-year survival, stratified by preRT-surgery interval, is shown in **(b)**.

PAPER 6

Metastatic bone disease at diagnosis in extremity soft-tissue sarcomas: Risk factors and survival analysis using the SEER registry

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Background: While lung is the most common site of metastasis from soft tissue sarcoma (STS), skeletal metastasis is a part of the natural history affecting the quality of life and prognosis of these patients. Although a few studies have reported on the incidence of skeletal metastasis, they are single-institution, retrospective reviews making them susceptible to the inherent limitations of these study types. Understanding the tumor and patient characteristics associated with skeletal metastasis, as well as the effect that metastasis has on patient survival, may influence imaging, surveillance and treatment decisions.

Purposes: (1) What histologic STS subtypes are associated with increased risk of skeletal metastasis? (2) What patient and tumor specific characteristics are associated with increased risk of skeletal metastasis? (3) What is the impact of skeletal metastasis on patient survival when compared to lung metastasis? (4) Does resection of the primary sarcoma improve survival in the setting of skeletal metastasis?

Methods: Patients were identified from the Surveillance, Epidemiology and End Results (SEER) database with extremity soft tissue sarcoma between January 2010 and December 2015. Risk factors for bone metastasis were investigated using univariate and multinomial logistic regression. Survival based on different sites of metastases was evaluated with Kaplan-Meier analysis. Cox proportional hazard models were performed to identify prognostic factors of survival for patients with bone metastasis. Variables were included in the final model if p-value on the univariate analysis was ≤ 0.25

Results: Among 8,234 soft tissue sarcomas, 2.2% (n=180) presented with detectable skeletal metastatic disease, of which 50% had simultaneous pulmonary metastasis. The most common STS subtypes to metastasize to bone were identified (Table 1). Female sex and having health insurance are associated with decreased odds for bone and lung metastases (OR =0.229 and 0.475, respectively; $p<.05$). Higher tumor grade (II or III), deep tumor location, and positive lymph node involvement are associated with increased odds for bone and lung metastasis (OR=5.1, 3.6, 4.5, 12.3, respectively; $p<.05$). The 5-year overall survival rate was 41.2% (26.9%-54.9%) for isolated bone metastasis and 32.9% (21.2% – 45.1%) for patients with bone and lung metastasis (Figure 1). In survival analysis of cases with bone metastasis, radical resection at the site of sarcoma was the only significant predictor of survival (HR=0.44, p=0.021)

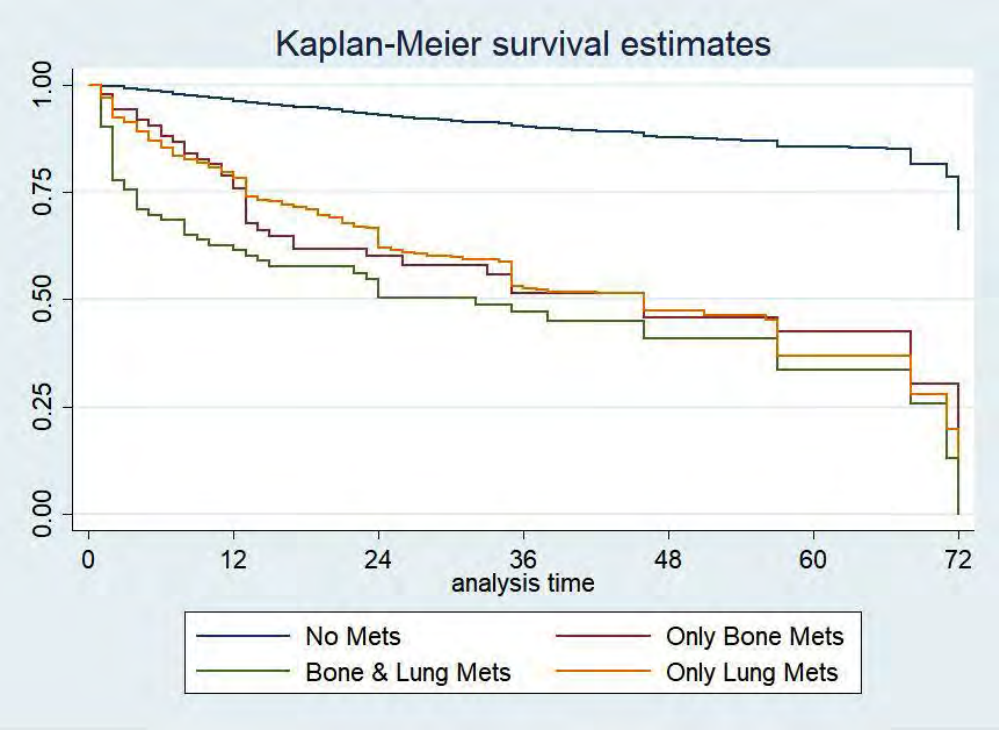
Conclusions: We identified the most common histologic STS subtypes to metastasize to bone. High tumor grade, deep location to fascia and regional lymph node metastasis are significant risk factors for having skeletal metastasis at the time of diagnosis of an extremity STS. While neither systemic

chemotherapy nor radiotherapy of the primary sarcoma has a significant influence on survival in the presence of bone metastasis, radical resection of the primary soft tissue sarcoma is associated with increased survival in these patients.

Table 1: The most common seven soft tissue sarcoma histopathological subtypes according to distant metastasis location in descending order.

	No bone or lung Mets (n=7,578)	Bone Mets only (n=89)	Bone & lung Mets (n=91)	Lung Mets only (n=476)
1	Leiomyosarcoma (10.53%)	Alveolar Rhabdomyosarcoma (11.24%)	Leiomyosarcoma (16.48%)	Pleomorphic Cell Sarcoma (13.03%)
2	Pleomorphic Cell Sarcoma (10.19%)	Spindle Cell Sarcoma (8.99%)	PNET (Ewing Sarcoma) (8.79%)	Leiomyosarcoma (10.08%)
3	Fibromyxosarcoma (9.70%)	PNET (Ewing Sarcoma) (7.78%)	Spindle Cell Sarcoma (6.59%)	Synovial Sarcoma (9.66%)
4	Well-differentiated Liposarcoma (8.58%)	Myxoid Liposarcoma (6.74%)	Alveolar Rhabdomyosarcoma (5.49%)	Undifferentiated Sarcoma (6.30%)
5	Myxoid Liposarcoma (7.14%)	Leiomyosarcoma (6.74%)	Myxoid Chondrosarcoma (5.49%)	Spindle Cell Sarcoma (5.88%)
6	Malignant Fibrous Histiocytoma (6.37%)	Pleomorphic Liposarcoma (4.49%)	Fibromyxosarcoma (4.40%)	Malignant Fibrous Histiocytoma (5.88%)
7	Undifferentiated Sarcoma (3.96%)	Pleomorphic Cell Sarcoma (3.37%)	Synovial Sarcoma (4.40%)	Fibromyxosarcoma (4.20%)

Figure 1: Survival Analysis according to distant metastatic location.



PAPER 7

Early Outcomes of Preoperative 5-fraction Radiation Therapy for Soft Tissue Sarcoma with Immediate Resection

Investigation performed at the Cleveland Clinic, Cleveland, Ohio

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Background: Limited data exists on the use of hypofractionated preoperative radiation therapy (RT) for soft tissue sarcoma.

Questions/Purposes: 1.) To report early clinical, pathologic, and toxicity outcomes of patients receiving hypofractionated RT followed by immediate surgical resection.

Patients and Methods: An IRB-approved database of patients treated with preoperative RT for soft tissue sarcoma was queried. Patients treated with 5-fraction RT followed by immediate (within 7 days) planned, wide surgical resection from 2016-2018 were eligible. Toxicity was graded by CTCAE version 4.

Results: Ten patients met eligibility criteria. Median follow-up was 7.1 months (range 1.6-24.2). Median patient age was 60 years (range 33-83). Histologic findings and pathologic responses are summarized in Table 1. Sarcomas were located in the extremity (7), trunk (2), and retroperitoneum (1). Four patients had metastatic disease at diagnosis. Median radiation dose was 30 Gy in 5 fractions (range 27.5-40 Gy) on consecutive days. Median time to surgical resection following completion of RT was 3 days (range 0-7). Median time from initial biopsy results to surgical resection of the primary tumor was 22 days (range 16-42). Eight patients achieved R0 resection. Of the 9 patients assessed for local control, no patients developed local failure, although one patient had persistently positive margins. Two of ten patients had progression of distant metastatic disease. One patient with a retroperitoneal sarcoma developed acute grade 4 tumor lysis syndrome. No other acute grade ≥3 toxicities were observed. Two patients developed late grade 3 toxicity consisting of fracture and delayed wound healing. The pathologic stress fracture occurred after trauma in a patient who had undergone re-irradiation for persistently positive margins. Nine patients had an uneventful postoperative course without wound healing issues.

Conclusions: This experience of hypofractionated preoperative RT for soft tissue sarcoma with immediate resection resulted in a median of 22 days from biopsy results to resection of the primary tumor. Early outcomes reveal low toxicity. Further prospective data with long-term follow-up is required to determine the oncologic outcomes and toxicity of hypofractionated preoperative RT.

Evidence: Level IV **Table 1.** Histologic findings and pathologic responses.

	Diagnosis	Histologic Findings
Patient 1	Myxoid liposarcoma	0% necrosis
Patient 2	Myxoid liposarcoma	10% necrosis & lymphocytic response
Patient 3	Myxoid liposarcoma	0% necrosis & 10% fibrosis and lymphocytic response
Patient 4	Dedifferentiated liposarcoma	10% necrosis & organizing thrombi
Patient 5	Dedifferentiated liposarcoma	0% necrosis & focal lymphocytic response
Patient 6	Synovial sarcoma	0% necrosis & 10% cystic changes, hemosiderin
Patient 7	Synovial sarcoma	0% necrosis
Patient 8	Undifferentiated pleomorphic sarcoma	75% necrosis
Patient 9	Undifferentiated spindle cell sarcoma	20% necrosis & hemorrhage/ hemosiderin
Patient 10	Pleomorphic rhabdomyosarcoma	80% necrosis

PAPER 8

Improved Survivorship Following Surgical Resection of the Primary Tumor in Patients with Metastatic Soft Tissue Sarcoma

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Background: The decision to remove the primary tumor in the setting of metastatic disease is highly controversial, as it can be argued that it is unnecessary to subject these patients to the inherent risks of surgery in a disease considered incurable. However, recent retrospective studies in metastatic colorectal carcinoma and breast cancer have shown that patients who undergo surgical resection of the primary tumor have significantly prolonged survivorship compared to patients who did not undergo surgery. However, it remains unknown whether or not removal of the primary tumor improves survival in the setting of metastatic soft tissue sarcoma (STS).

Purpose: The purpose of this study is to evaluate survivorship in patients who undergo surgical resection of a primary tumor in the setting of metastatic STS.

Patients and Methods:
The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program was queried for all patients with a diagnosis of musculoskeletal STS with metastatic disease. Patients were excluded if they did not undergo treatment (resection surgery, chemotherapy, and/or radiation) for their disease, were diagnosed at autopsy, or whose diagnosis was not their first tumor. Stepwise, multivariate logistic regression models were then used to isolate and evaluate the impact of surgical resection of the primary tumor on the likelihood of survivorship.

Results: 3,277 patients metastatic STS were identified and 42.5% of the patients underwent primary tumor resection. The mean 5-year survival rate for all patients was 17.6%, whereas it was 23.6% in those who underwent surgery. Patients with a smaller tumor burden, younger age, and certain histologic subtypes including fibrosarcoma, leiomyosarcoma, liposarcoma, rhabdomyosarcoma, and synovial sarcoma had improved survivorship. However, surgery was the strongest predictor of subsequent survivorship.

Conclusions:
Patients with metastatic soft tissue sarcoma have a dismal prognosis. However, those whose primary tumors are amenable to surgical resection have significantly greater survivorship than patients who were treated with chemotherapy or radiation alone.

Level of Evidence: III retrospective case-control

PAPER 9

Neoadjuvant Combination Immunotherapy / Radiation for High-Risk Soft Tissue Sarcoma (NEXIS): Preliminary Results from an Integrated Phase I/II, Single-Arm, Prospective Clinical Trial

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Co-investigators: Edward Sausville, Ken Miller, Ikumi Suzuki, William Regine, James Snider, Michael Kallen, Olga Ioffe, Michael Mulligan, Shamus Carr, Petr Hausner, Eduardo Davila, Nicholas Ciavattone, Xuefang Cao

Background: Patients with localized soft tissue sarcoma (STS) have a significant risk of later manifestation of metastatic disease despite effective treatment of the primary tumor. Cytotoxic chemotherapy in the setting of localized disease has limited efficacy and metastatic STS is not considered curable. Immune checkpoint inhibitors have demonstrated efficacy in other types of malignancy. An abscopal effect has been noted anecdotally with radiation (XRT) and is attributed to an immune-mediated phenomenon.

Purpose: The purpose of this study is to examine the safety and efficacy of NEoadjuvant XRT with Immunotherapy for STS (NEXIS). The hypothesis is that the primary tumor can serve as an in-situ vaccine and that NEXIS will facilitate immune-mediated control or clearance of distant microscopic or minimal residual disease.

Methods: Adult patients with intermediate- or high-grade STS ≥5 cm in size located in the trunk or extremities are prospectively enrolled. Patients presenting with confirmed, unresectable pulmonary metastases or with extra-pulmonary, non-lymph node metastases are excluded. Patients with indeterminate small lung nodules are allowed. Patients receive Durvalumab (anti-PD-L1) and Tremelimumab (anti-CTLA4) on weeks 1/5/9 and external beam XRT 50 Gy (1.8-2 Gy fractions) between weeks 2-8. Tumors >10 cm also receive an initial single 15 Gy fraction of spatially-fractionated GRID. Wide resection is performed on week 13. Postoperatively, patient are given Durvalumab monotherapy q4 weeks for 4 additional doses (if NED) or 9 additional doses (if residual disease). Pre- and post-neoadjuvant MRI and PET scans are compared for RECIST/PERCIST scores. Oncologic outcomes, histologic treatment effects, immune-related adverse effects are recorded. Histologic treatment effect is reported using the EORTC-STBSG response score (A – none; B – single or small clusters; C - ≥1% to <10%; D - ≥10% to <50%; E - ≥50%), and additional histologic response parameters including percent residual viable cells, necrosis, hyalinization/fibrosis, and infarction are recorded. Quantification of PD-L1, CTLA-4, and Ki-67 expression is done by immunohistochemistry in both pre- and post-treatment tumor sections. Additional pending assays include immunohistochemical characterization of tumor-infiltrating lymphocytes and tumor-associated macrophages.

Results: As of submission of this abstract (March 2019), 7 patients have received the full neoadjuvant NEXIS protocol and underwent surgical resection. One additional patient received only 1 dose of immunotherapy before proceeding directly to surgery due to reasons unrelated to the study. Only minor

grade 1 and 2 (CTCAE v4.0) adverse events were noted except for two grade 3 wound healing issues unrelated to the immunotherapy. No local recurrences have been noted.
One patient with myxoid/round cell liposarcoma had rapid postoperative development and progression of liver mets leading to death at 4 months postoperatively. Two patients with indeterminate lung nodules at presentation had initial growth and increased number of lung nodules postoperatively, but have demonstrated stability or decreased size/number at 4 mos and 1 year, respectively. One patient developed significant central granulomatous disease, but multiple biopsies showed no evidence of metastasis and he remains NED at 8 months. Two patients are NED at 1 and 2 months, respectively. One patient who presented with suspicious lung nodules and a small lesion in the adjacent bone had increased size and number of lung nodules and increased size of the bone lesion after neoadjuvant therapy. However, needle and open lung biopsies showed no evidence of viable tumor and wide resection was performed for his primary tumor and adjacent bone. Pathologic examination of the bone showed no signs of tumor.

Histologic treatment effect using the EORTC-STBSG response score was B (1), D (3), and E (3).

Based on RECIST, the primary lesion demonstrated stable disease in 5 patients, partial response in 1 patient and progressive disease in 1 patient. In the single patient with progressive disease, the tumor was a rapidly growing fungating mass prior to initiation of neoadjuvant treatment, peaked in size midway through neoadjuvant treatment, then progressively shrunk in size. Based on PERCIST, the primary lesion demonstrated stable disease in 2 patients, progressive disease in 1, partial response in 2, and complete response in 2.

Conclusions: The NEXIS protocol for high risk STS appears to be well-tolerated by patients. As with other treatment modalities, it is challenging to determine efficacy based on radiologic or histologic response of primary tumor. Radiologically, the responses appear similar to treatment with standard of care. Histologically, there does appear to be some evidence that there may be a salutary treatment effect with NEXIS. Most importantly and concordant with the goal of NEXIS, there appears to be early signs that NEXIS may have an effect on the distant sites of disease in the setting of primary STS.

PAPER 10

Extremity malignant peripheral nerve sheath tumor (MPNST): a retrospective analysis of 185 cases from reference sarcoma center.

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Introduction: Malignant peripheral nerve sheath tumors (MPNSTs) are rare malignant tumors arising from various elements of the nerve sheath like Schwann cell, perineural cell or fibroblast. They account for 5-10% of all soft tissue sarcomas, and about 25% of cases occur in the setting of neurofibromatosis 1(NF1) [1;2] MPNST has limited sensitivity to chemotherapy and radiation and high propensity to metastasize. Surgical resection continues to remain the mainstay of treatment.[3]

Our analysis was aimed at determining factors that influence clinical outcome in a large cohort of patients with extremity MPNSTs treated at a reference sarcoma center.

Methods: A retrospective review of 185 patients with extremity MPNST (93 women and 92 men) who had undergone treatment between 1994 and 2017 was carried out. Patient, tumor size, treatment characteristics, prognosis, and clinical outcome were evaluated.

Results: The median age of our population was 53 years (15-86). 49.7% were male.
The majority of tumors (126) were located in lower and 59 in the upper limb. In 35.14% tumor size exceeded 10 cm.91 patients had low (G1) and intermediate (G2) pathological grade and 92 patients had high-grade (G3) tumors. The NF1 was observed in 13% of cases. 119 were primary tumors, 49 with local recurrence and 17 with a scar after non-radical resection. Median follow up time was 67.9 month, and median overall survival (OS) was 67.5 months.
Perioperative radiotherapy did not influence LRFS in case of R0 resection but improved LRFS when microscopically radical resection was not possible. The primary resection outside the reference center was correlated with shorter LRFS (72.5% vs. 15.8% 5-year LRFS rates, $p < 0.01$), but this did not influence the overall survival. In the multivariable Cox's model for overall survival high grade, size > 10 cm and R1+ resection were independent negative prognostic factors.

Conclusion: Our study shows that surgical excision continues to be the mainstay of treatment for MPNST and high tumor grade and tumor size > 10 cm predict worst DSS. Due to the importance of the proper surgical approach and the complex nature of the disease, it is crucial to refer MPNST patients to specialized sarcoma centers for dedicated treatment.

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PAPER 11

Vascular Reconstruction In Sarcoma Surgery: Complications, Functional And Vascular Outcomes

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Background: Limb salvage surgery with vascular reconstruction is currently considered as the standard treatment for extremity soft tissue and bone sarcoma (STS/BS), with equivalent patient survivals compared with amputation. Few publications assessed this specific type of reconstruction and their vascular outcomes. Depending on specific situations, some surgical teams favour vein reconstruction and other don't.

Purpose: The purpose of this study was to assess surgical and functional outcomes after arterial and/or venous reconstruction in limb salvage surgery for STS.

Methods: We examined our prospective database and all patients who underwent vascular management as part of limb salvage surgery for extremity STS or BS from 1996 to 2016 were included in this study. Incidence of surgical complication, graft patency, and patients' vascular and functional outcome were reviewed.

Results: During the study period, 52 STS patients (29 men, 23 women; mean age: 56 years) were included: 33 had an artery + vein reconstruction, 11 patients had a vein ligation with arterial reconstruction, 5 had their vein alone reconstructed and 3 patients had a vein ligation only. Autologous great saphenous vein (GSV) was the most commonly used vascular conduit in both arterial and venous reconstruction (81% and 77.0%). During a mean follow up of 3 years, 25 patients died (50%), 6 patients (11.5%) needed amputation of the initially salvaged limb because of reconstruction failure (thrombose or leakage). There were 6 post op DVT, 8 superficial infection, and 6 flap failures with deep infection. At the last follow-up, 77 % of assessable arteriovenous reconstructions had a patent graft on US, 100% of venous or arterial only reconstructions were patent. One-year and 5-year post-op mean MSTS scores were of 78 and 88, respectively. Seventy percent had edema and 40% used compression stocking. 50% had significant symptoms (cramps, tightness or heaviness).

Conclusion: Limb salvage surgery of soft tissue tumour combined with vascular reconstruction showed favourable functional outcomes with good local control. Even though amputation was more frequent because of selection bias studying more severe case, limb salvage should be considered (89% limb survival rate) with low impact of vascular symptoms on functional outcomes. Oncological outcomes were comparable to classical survival rates of STS, advocating for limb salvage even when vessels are involved.

PAPER 12

Leiomyosarcomas: Recurrence rates based on tumor depth

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Background: Non-uterine leiomyosarcomas (LMS) are a rare type of soft-tissue sarcoma. Several studies have looked at treatment strategies and outcomes for deep LMS, but few have evaluated the outcomes of superficial LMS. It is known that deep LMS has a higher recurrence rate than superficial LMS, but few have compared recurrence rates stratified by tumor depth (dermal, subcutaneous, deep).

Purpose: The purpose of the study is to characterize treatment outcomes based on depth of LMS with regards to (1) disease specific survival and (2) tumor recurrence.

Methods: 102 (51 males, 51 females) patients, mean age 58±17 years, with LMS of the trunk and extremities were identified between 1990 and 2016. 10 cases were classified as dermal (10%), 51 as subcutaneous (50%), and 41 as deep (40%). The tumors were located in the upper extremity (n=68, 67%), lower extremity (n= 23, 23%) and trunk (n=11, 10%). Mean tumor size was 4.6±4.5 cm. All patients were treated surgical with the goal of achieving a negative margin. Margins were reported as negative in 98 (96%), in 4 patients they were microscopically positive (R1). Mean follow up was 7±5 years. Depth was classified as dermal (confined to the skin not extending into subcutaneous tissue), subcutaneous (below the dermis, above the fascia), and deep (below fascia).

Results: Over the course of the study 20 patients died of disease. The 10-year disease specific survival was 71%. When comparing the disease specific survival based on depth, the 10-year survivals ($P<0.001$) were: dermal 100%; subcutaneous 84%, and deep 46%. Tumor recurrence occurred in 23 patients; classified as metastatic (n=22) and local (n=1). The 10-year metastatic disease free survival was 74%. When comparing the metastatic free survival based on depth, the 10-year survivals ($P<0.001$) were: dermal 100%; subcutaneous 84%, and deep 56%. In addition there was no difference in survival ($P=0.12$) or metastatic disease ($P=0.23$) based on tumor location. Tumor size ≥5 cm was also associated with disease specific mortality (HR 6.49, $P<0.001$) and metastatic disease (HR 3.85, $P<0.001$).

Conclusion: The results of this study indicate that patient survival is related to the depth of the tumor. Patients with dermal LMS can routinely be cured with appropriate surgical treatment; although considered a superficial sarcoma, patients with a subcutaneous LMS should be evaluated and treated by a multidisciplinary sarcoma team due to the risk of metastatic disease.

Table 1: Risk Factors for Disease Specific Survival and Metastatic Disease

Risk Factor	Hazard Ratio Disease Specific Survival (95% CI)	P Value	Hazard Ratio Metastatic Free Survival (95% CI)	P Value
Male Gender	0.69 (0.28-1.71)	0.43	0.70 (0.30-1.65)	0.42
Tumor Size ≥5cm	6.49 (2.24-18.78)	<0.001	3.85 (1.49-9.95)	<0.001
High Grade Tumor	1.55 (0.45-5.33)	0.47	2.13 (0.63-7.22)	0.22

Figure 1:

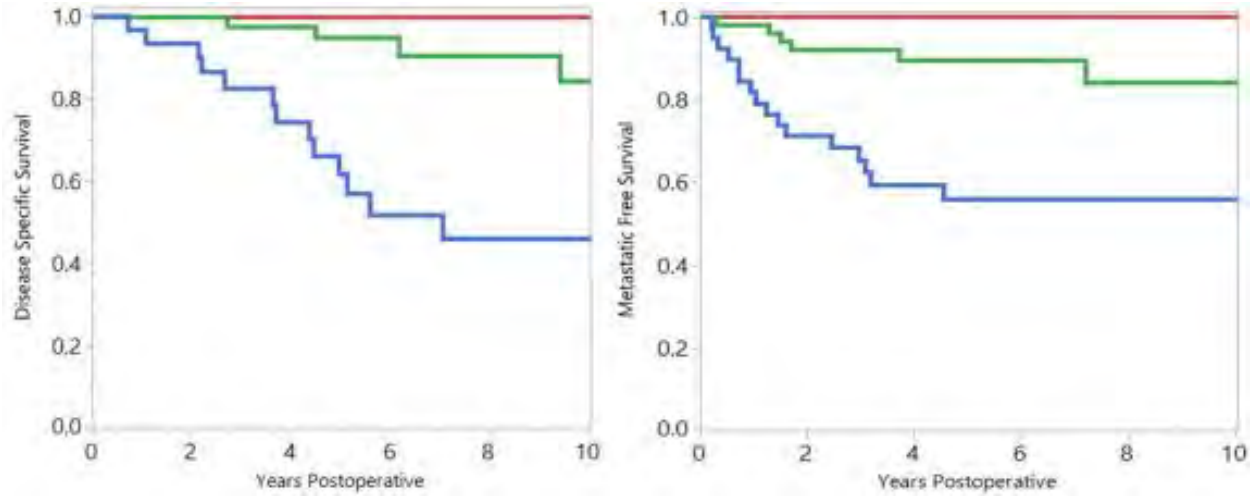

Figure 1: Following surgical resection, patients with dermal (red) leiomyosarcoma had a 100% disease specific and metastatic free survival. The 10- year disease specific and metastatic free survival for subcutaneous (green) and deep (blue) leiomyosarcoma were 84% and 84%, and 46% and 56%, respectively

PAPER 13

Does Surgical Resection of the Primary Tumor in Patients with Metastatic Osteosarcoma Affect Survivorship

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Background: The decision to remove the primary tumor in the setting of metastatic disease is highly controversial, as it can be argued that it is unnecessary to subject these patients to the inherent risks of surgery in a disease considered incurable. However, recent retrospective studies in metastatic colorectal carcinoma and breast cancer have shown that patients who undergo surgical resection of the primary tumor have significantly prolonged survivorship compared to patients who did not undergo surgery. However, it remains unknown whether or not removal of the primary tumor improves survival in the setting of metastatic osteosarcoma.

Purpose: Therefore, the purpose of this study was to evaluate the role of surgery as well as confounding demographic, socioeconomic, and tumor characteristics on the overall and cancer-specific mortality rate in patients with metastatic osteosarcoma.

Patients and Methods: The Surveillance, Epidemiology, and End Results Program was queried for all patients with a diagnosis of metastatic osteosarcoma between the years 2004 - 2014. Patients who did not undergo any treatment (excisional surgery, chemotherapy, and/or radiation) for their disease, were diagnosed at autopsy, or whose histologic subtypes were surface (parosteal and periosteal) or secondary osteosarcomas (Paget's and radiation-induced) were excluded from further analyses. Multivariate models were used to isolate and evaluate the impact of excisional surgery of the primary tumor on likelihood of survivorship.

Results: 3,277 patients were identified, of which 42.5% underwent excisional surgery of the primary tumor. The 5-year survival rate for all patients with metastatic osteosarcoma was 24.4% whereas it was 34.5% in patients who underwent surgery and 5.8% in those who did not undergo surgery. Patients in the lowest quartile for income and education were more likely to present at later disease stages. Older age, axial location, and lower education level portended a much worse overall- and cancer-specific mortality. However, surgical excision was the strongest predictor of subsequent survivorship.

Conclusions: Patients with metastatic osteosarcoma whose primary tumors are amenable to surgical resection have better survivorship than patients who were treated with chemotherapy alone.

Level of Evidence: III, prognostic

PAPER 14

Age versus Survival in Primary Bone Cancers (Ewing's Sarcoma, Osteosarcoma, and Chondrosarcoma)

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Background: Prior studies have investigated the role of age on the prognosis of the "Big Three" primary bone cancers with varying conclusions. Some studies ascribe a significant role for age in prognosis; others disagree. Most studies are institutional-based or study-group based, typically lacking sufficient numbers to calculate survival rates by age except by dividing their study populations into two or three large age groupings.

Question: For patients with one of the Big Three bone cancers, we wanted to determine the
1. likelihood of survival based on age alone for groupings of patients into 10 year of age cohorts at time of diagnosis and
2. approximate ages, if any, of any inflections, trends or significant changes in the survival rates.

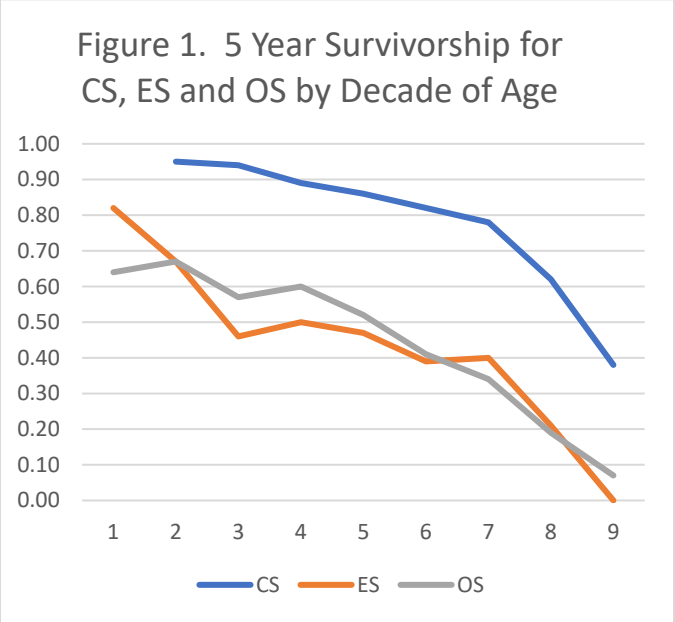
Materials and methods: We queried the National Cancer Database of the American College of Surgeons (data covers approximately 71% of all patients treated for cancer in the USA) for all patients with bone sarcomas treated between 2003 and 2014, inclusive. We determined the survival rates and 95% confidence intervals for these three cancers for patient groupings of every decade of life, including ages 0 through 9, 10 through 19, etc., with the eldest group being 80 years of age and over. We specifically excluded histologic subgroups such as Parosteal, Periosteal and Chondroblastic Osteosarcoma, and Myxoid, Dedifferentiated and Mesenchymal Chondrosarcoma. The resultant study group consisted of 4840 reported cases of Chondrosarcoma, 3997 cases of Osteosarcoma and 3023 cases of Ewing's sarcoma. Excluded Chondroblastic osteosarcomas numbered 982 cases and dedifferentiated chondrosarcomas numbered 504 cases; otherwise no excluded subtype exceeded 400 cases.
Kaplan-Meier 2 and 5 year survivorship was calculated using SAS software for each decade of age and reported as a percent surviving plus and minus the 95% confidence interval. The results are reported in tabular form for the three groups by age and they were analyzed graphically for the appearance of any inflection points or trends. Additional analyses for effect of independent variables such as size, stage and treatment will also be presented.

Results: At a descriptive level, there is clear association between age and survival for each cancer. For Ewings sarcoma, the five year survivorship declines appreciably over the first three decades of life (82%, 67% and 46% respectively) then remains fairly level at 50%, 47%, 39% and 40% for the next four decades, declining further subsequently but with low numbers (Figure 1&2).
Osteosarcoma five-year survival ship is steady at 64% and 67% in the first two decades and then declines to 57% and 60% in the third and fourth decade, thereafter declining steadily, (52%, 41%, 34%, 19% reaching 7% for those 80 and over in their ninth or older decade of life. Thus, both Ewings sarcoma, and Osteosarcoma survivorship declines through the teenage and early adulthood years, plateau somewhat for 20 years, then decline thereafter. See Figure 1.

The Chondrosarcoma survivorship report begins with the second decade of life as there are only 12 cases reported in the first decade. Survivorship declines gradually over the first 60 years of life, from a high of 95% in the second decade, falling to 94%, 89%, 86%, 82% and 78% in the third through seventh decade, dropping rather precipitously thereafter to 62% and 38% in eighth and ninth decades. Thus, the inflection point for chondrosarcoma appears to be at approximately age 70 (figure 1).

Conclusion: These data show a strong association between age and survival prognosis in the big three primary bone cancers. For the high-grade bone sarcomas typically seen in children and young adults, a significant decline in survivorship with age appears much earlier in life than with chondrosarcoma. Additional data will be presented regarding the association of age with other factors widely believed to influence survivorship in primary bone cancers such as stage and treatment. Regardless of the underlying additional factors, at an overall level there is an association between age and prognosis that cannot likely be explained simply by comorbidities and intolerance to chemotherapeutic treatments. Although the cause of the associations with age and the decreasing survivorship with advancing age for all three are not clear, the observation of these associations should trigger additional studies which may provide better understanding of the pathogenetic mechanisms of cancer and of the body's potential healing responses, better understanding of potential therapeutic options, as well as allow for improved public policy understanding and planning for the treatment of these devastating illnesses.

Level of evidence: Level III



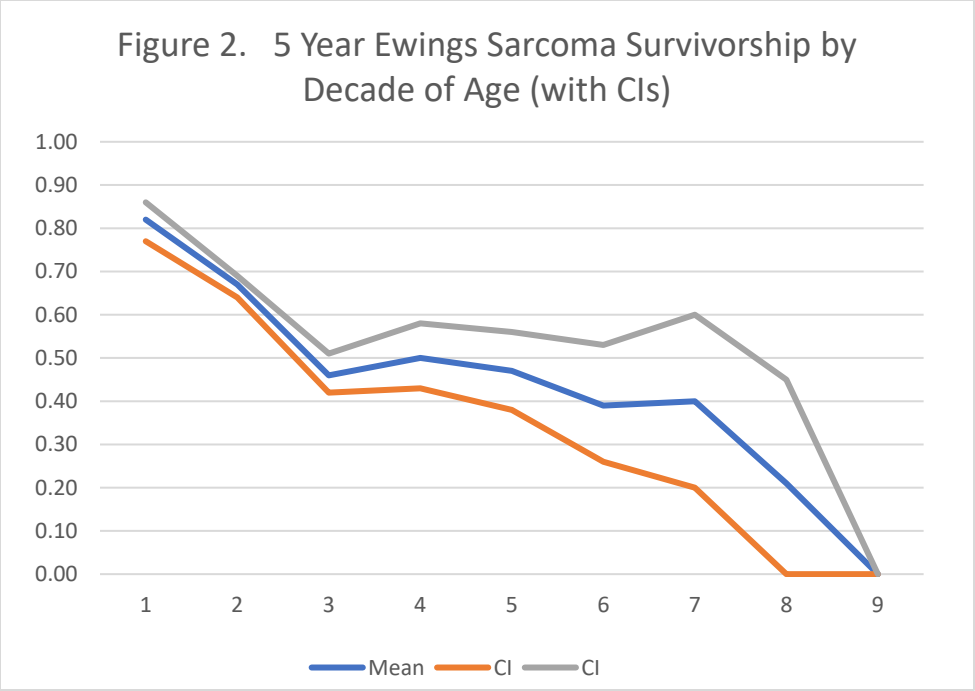


Figure 2. 5 Year Ewings Sarcoma Survivorship by Decade of Age (with CIs)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
1
2
3
4
5
6
7
8
9
Mean
CI
CI

PAPER 15

Targeted Muscle Reinnervation Reduces the Frequency and Severity of Phantom and Residual Limb Pain In Oncologic Amputees

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Background: Approximately 18,000 patients undergo amputation for cancer diagnoses annually, representing a small but significant portion of the amputee population. Oncologic amputees experience high rates of postamputation secondary to symptomatic neuromas and phantom limb pain leading to prosthetic intolerance and poor functional outcomes. Targeted muscle reinnervation (TMR) is a surgical strategy to prevent and minimize residual and phantom limb pain via the transfer of transected peripheral nerves to otherwise redundant target muscle motor nerve units.
Purpose: Compare the effect of targeted muscle reinnervation performed at the time of amputation on patient reported pain outcomes to the current standard of care in non-TMR oncologic amputees. Determine secondary outcomes including local control rates, survival, prosthetic use, post-operative complications and post-operative narcotic dependence.

Methods: Our TMR cohort was compared to a cross-sectional sample of unselected oncologic amputees not treated at our institution (N=58). Patient-Reported Outcomes Measurement Information System (PROMIS) instruments were used to assess residual limb/phantom limb pain. Oncologic outcomes, prosthetic use, complications and post-operative narcotic dependence were noted.

Results: Thirty-one patients underwent amputation with concurrent TMR during the study; 27 patients completed pain surveys; 15 had greater than one year follow-up. Average follow-up was 14.7 months (range, 3-40.2 months). Neuroma symptoms at the amputation site occurred significantly less frequently and with less intensity among TMR cohort. Mean differences for PROMIS pain intensity, behavior, and interference for phantom limb pain were 5.855 (95%CI 1.159, 10.55, p = 0.015), 5.896 (95%CI .492, 11.30, p=0.033), and 7.435 (95%CI 1.797, 13.07, p=0.011) respectively, with lower scores for TMR cohort. For residual limb pain, PROMIS pain intensity, behavior, and interference mean differences were 5.477 (95%CI .528, 10.42, p=0.031), 6.195 (95%CI .705, 11.69, p = 0.028), and 6.816 (95%CI 1.438, 12.2, p = 0.014), respectively. 56% took opioids prior to amputation compared to 22% at one year post-operatively.

Fifteen patients (56%) were taking opioids prior to amputation compared to 22% at one year post-operatively.

Average oncologic follow-up was 16 months with three patients lost to follow-up with no evidence of disease at 0, 5 and 9 months respectively. At clinical last follow-up, 74% were without evidence of disease, one patient (3.2%) had an isolated local recurrence, one patient developed metastatic disease without local recurrence and died of his disease, and three patients (9.7%) developed a local recurrence with concurrent metastatic disease of whom three patients died of their disease. Wound complications requiring a return to the operating room occurred in 16% of patients, including one patient who initially underwent a below-knee amputation with TMR who required conversion to an above knee amputation with TMR due to a non-healing stump wound. Two patients returned to the operating room for neuroma excisions and targeted muscle reinnervation of symptomatic neuromas that developed in pure sensory nerves (medial antebrachial cutaneous nerve and lateral femoral cutaneous nerve) that were not included in the initial nerve transfer. Nineteen (61.3%) patients were fitted with and received their prosthesis on average 3.6 months post-operatively (range 2-7) months.

Conclusions: Multidisciplinary care of oncologic amputees that includes TMR at time of amputation reduces the frequency and severity of residual and phantom limb pain.

Keywords: pain management; neuroma; phantom limb pain; residual limb pain

PAPER 16

Revision Rates For Megaprostheses: A Review Of The Literature And Meta-Analysis

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Institutions: 1. APHM, Marseille, France, 2. Hopital Cochin, Paris, France

Background: Megaprostheses are used to reconstruct joints after resection of a bone tumor. Outcomes such as survival, revision for mechanical, infectious, or recurrence causes vary by anatomical site and design. We conducted a meta-analysis of megaprostheses of major joints over more than 30 years to look for design variables affecting the outcome.

Objectives: The primary objective was to report a summary measure for survival, revision for mechanical, recurrence, and infectious causes, for proximal humerus, proximal femur, distal femur, and proximal tibia megaprostheses. Secondary objectives were to seek for design variables associated with revision for mechanical cause after knee megaprotheses including fixation, modularity, and hinge mechanism.

Patients & Methods: The PRISMA recommendations were followed. Only full-length English-written research articles published in peer-reviewed journals reporting megaprostheses outcomes with no restriction with regards to dates of publication, design or follow-up were included. Two authors (AF and JCM) reviewed titles and abstracts resulting from the search as a first round of exclusion; all studies selected were then retrieved and accurately assessed from full text to evaluate inclusion and exclusion criteria. Any doubtful article was assessed by another author (DB).
Dichotomous outcomes were reported as counts and proportions. Random effects meta-analyses of single proportions were used to estimate pooled rates of events with the DerSimonian–Laird estimate, and a continuity correction was applied for any studies with a zero-cell count. Simple approximation of 95 % confidence intervals is reported. Between studies variability, i.e., heterogeneity, was assessed with the I-squared statistics. Meta-regression models were built to assess the effect of moderators—anatomic site and various variables (modularity, fixation, hinge) on relevant outcomes.

Results: A total of 102 articles were retrieved giving 178 identifiable series (according to anatomical site and design) reporting on 6830 patients. The median follow-up was 45 months [first quartile - third quartile: 27 - 60]. The 5-year revision rate (40 series included) was 20% [17% - 23%] (ie, 5yr survival 80%). Over follow-up, the proportion of revision for mechanical reason was 11% [9% - 13%] with significant differences between anatomical sites (14%, 5.5%, 7.6%, 13% for distal femur, proximal femur, proximal humerus, and proximal tibia; $P<0.001$). The proportion of revision for infection was 6% [5% - 7%] with significant differences between anatomical sites (6.5%, 4%, 4.3%, 11% for distal femur, proximal femur, proximal humerus, and proximal tibia; $P<0.001$). The proportion of local recurrence was 7.5% [6% - 9%] with no difference between anatomical sites ($P=0.48$). Fixation (cemented/uncemented, $P=0.83$), modularity (custom-made/modular, $P=0.31$), and hinge (fixed/rotating, $P=0.19$) had no effect on the risk of revision for mechanical reason.

Conclusions: The 5-year survival rate for megaprosthesis of major joints is 80% [77% - 83%]. The proportion of revision for mechanical reason is significantly different between anatomical sites (6% for proximal femur to 15% for distal femur). The proportion of infection is significantly different between anatomical sites (5% for proximal humerus to 17% for proximal tibia). There is no significant effect of common design variables (fixation, modularity, or hinge) on the risk of mechanical revision in knee reconstruction.

PAPER 17

Custom Stem-Sideplate Preserves At-Risk Hip Joint During Endoprosthetic Reconstruction of the Femur

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Institution: Division of Orthopaedic Surgery, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.

Introduction: Large resections of the distal femur and femoral shaft place the remaining native hip joint at risk. Classic reconstructive options are at higher risk of failure when less than 40% of the native bone is available [1], and full prosthetic replacement of the proximal femur, by way of abductor deficiency, significantly decreases patients' function [2]. Here we report the results of 14 custom stem-sideplate megaprostheses used to preserve the native hip joint in patients with endoprosthetic reconstruction following large tumor resections of the femur.

Questions: Does a custom side-plate stem endoprosthesis reliably preserve the at-risk hip joint in patients with endoprosthetic reconstruction of the majority of the distal femur?

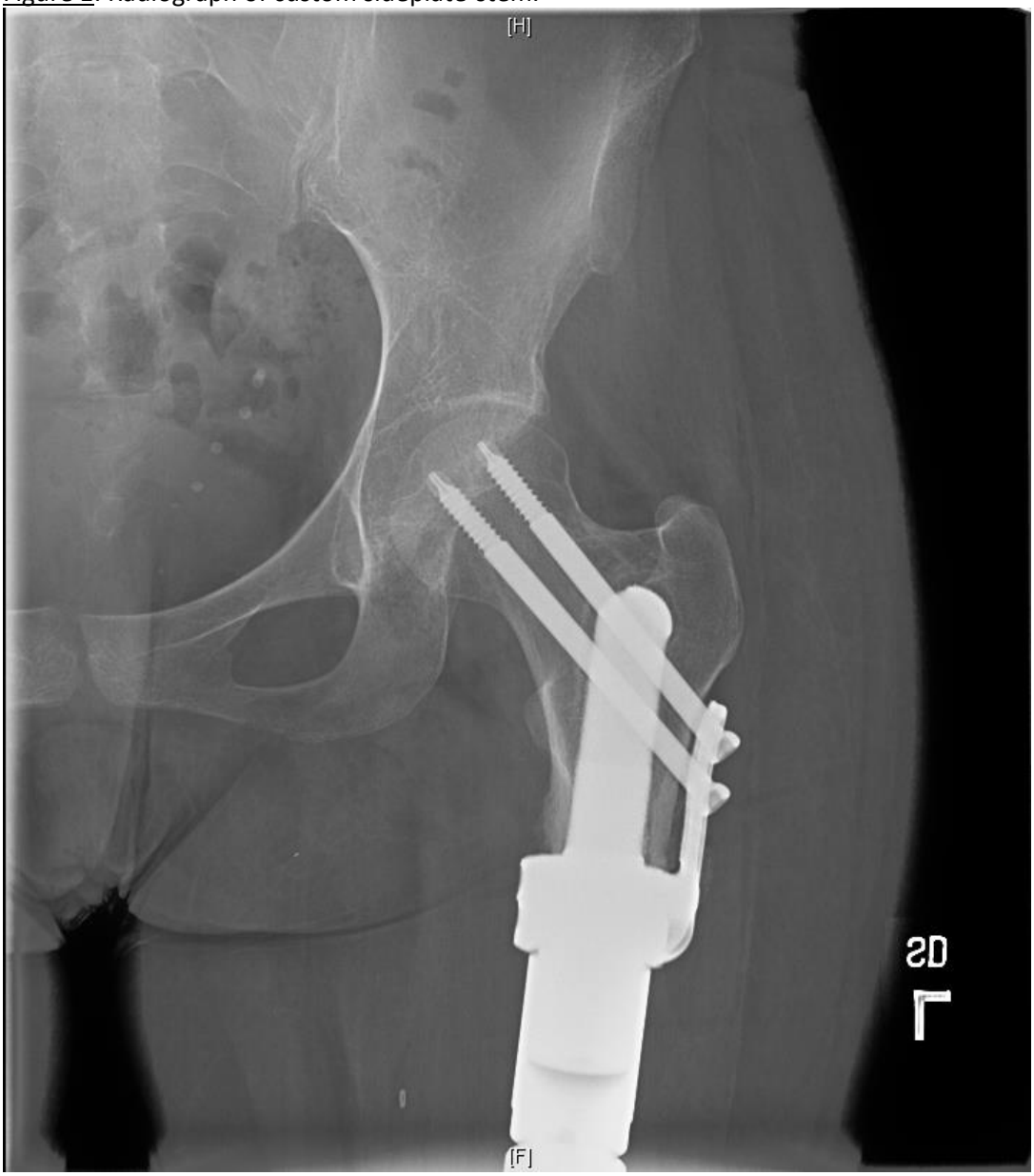
(1) What is the survivorship and complication profile of the custom side-plate stem endoprosthesis?
(2) What functional outcomes are associated with endoprosthetic reconstruction using the custom side-plate stem endoprosthesis?

Methods: Fourteen patients with oncologic diagnoses had either primary or revision reconstruction of a large femoral defect with a short remaining proximal femur using a custom-designed sideplate-stem that attached to a standard endoprosthetic reconstruction system. Patient characteristics, diagnoses, previous operations, reoperations, and final ambulatory status and MSTS score were recorded. Percentage of proximal femur remaining was calculated from follow-up radiographs.

Results: All 14 at-risk native hip joints were preserved at final follow-up of 4.7 years, despite that patients had 25% (range 13-34%) of their native femur remaining. Average age at the time of surgery was 36, and average follow-up was 4.7 years. Initial diagnosis was osteogenic sarcoma in 10, Ewing sarcoma in 2, giant cell tumor of bone in 1, and pleomorphic sarcoma in 1. 8 patients required no reoperation. 3 patients require reoperation due to implant-related issues (1 custom stem revision, 2 modular taper junction fractures), but all maintained their native hip joint and at final-follow-up. One patient required multiple subsequent surgeries for infection, and one required revision of a tibial component for loosening. At final follow-up, the average MSTS score was 24. 9 patients required no ambulation aids, 3 patients required a cane, and 2 required one crutch. Only one patient had a Trendelenburg gait.

Conclusion: This custom stem-sideplate reliably preserves native hip joint function after large femoral resection with a short remaining proximal segment.

Figure 1: Radiograph of custom sideplate-stem.



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PAPER 18

Bushing design and crosslinked polyethylene can favorably improve mechanical survival of rotating hinge endoprostheses around the knee

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Endoprosthetic reconstruction for large segmental defects of the skeleton following tumor resection or other bone loss has become increasingly popular despite complications related to infection, aseptic loosening and mechanical failure. Wear of polyethylene bearing surfaces can lead to mechanical instability and joint failure and the debris may play a role in triggering biologically mediated aseptic loosening. Recent experience in total joint arthroplasty has shown clinical benefit from decreased wear of bearing surfaces manufactured from crosslinked polyethylene. We asked if crosslinked polyethylene could improve clinical outcomes for patients with large endoprostheses featuring a kinematic rotating hinge knee design. The introduction of a redesigned hinge mechanism featuring a larger diameter and thicker bushing made of crosslinked polyethylene as an update to an earlier version of this implant, provided a mechanism to study this question.

We performed a retrospective analysis of all patients identified in our surgical database who had undergone reconstruction around the knee using a kinematic rotating hinge mechanism made by the same manufacturer. This included patients with total femoral replacements, distal femoral replacements, and proximal tibial replacements. Implants included in the study were either custom (prior to 1987) or modular, with the original bushing design (prior to 2004) or the new design (2004 to present). Outcomes for the custom and some modular implants have been previously reported[1]. Collected data included basic demographics, surgical indications, reoperations, polyethylene failures, and dates of death or last follow up.

We identified 233 patients, including 34 custom and 138 original design modular implants (Group 1) and 61 new design modular implants (Group 2) performed between 1980 and 2017 (minimum 2 years from surgery). This included 12 total femurs, 164 distal femurs, and 57 proximal tibias. Polyethylene failure was defined as revision surgery for mechanical instability, pain, and joint effusion related to visible wear, deformation and/or disintegration of the plastic bushings as determined at surgery. There were 19/172 failures in Group 1 (11%), while 0/61 failures were noted in Group 2. This difference was significant on simple analysis [$p < 0.006$, Chi-squared] and Kaplan Meier survival analysis with patients censored at date of failure for any reason or date of last follow up. The median time to polyethylene failure in Group 1 was 8.5 years [1.25 to 22.9 years].

This study is limited due to the retrospective nature of the data collection, the relatively low number of patients in group 2, and the difference in length of follow up as expected for consecutive study groups. In

addition, this study cannot provide determine if the difference in outcome is due to the redesign of the bushing dimensions, use of crosslinked polyethylene or both. Ongoing surveillance of this patient population will be needed to better judge the impact of these changes on survival of the rotating hinge mechanism. To date, our results support the continued use of the redesigned rotating hinge mechanism with crosslinked polyethylene.

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PAPER 19

Intercalary Endoprosthetic Reconstruction: An Analysis of Complications

Authors: Jennifer Thomson B.S., Joseph Ippolito M.D., Kathleen Beebe, M.D., Francis Patterson M.D., Joseph Benevenia M.D.

Introduction: Endoprosthetic options for reconstruction following resection of diaphyseal tumors have historically been limited to megaprostheses involving the joint. Intercalary endoprostheses combine the benefits of early return of function and pain relief with a smaller sized implant.

Questions/Purposes:

1. Report the outcomes and complications of patients treated with intercalary endoprosthetics for diaphyseal segmental defects at a single institution.
2. Report the complications of patients treated with intercalary endoprosthetics for diaphyseal segmental defects at a single institution.

Methods: Thirty-six consecutive patients (40 limbs) treated at a single institution from 2008-2018 with intercalary endoprostheses were retrospectively reviewed. Inclusion criteria were patients who had segmental bone loss from an aggressive or malignant bone tumor with preservation of the joints above and below. Patients underwent cemented reconstruction with a modular intercalary endoprosthesis (OsteoBridge™ IDSF; Merete, Berlin, Germany) of the humerus, tibia, or femur.

Results: Mean age at the time of surgery was 60 ± 17 years with a mean follow-up of 23.8 months (range 1.4-102.6 months). Of the 40 endoprostheses, 17 involved the humerus, 15 the femur, and eight the tibia, with 27 limbs treated for metastatic disease and 13 for primary tumors. Thirty-two patients underwent surgery due to primary resection, while eight had surgery as salvage after failed reconstruction. Mean defect for femur, tibia and humerus reconstruction were 9.7cm, 10.6 cm, and 6.3 cm respectively. Complications were reported in 10 (25%) patients and categorized by according to Henderson et al. (Table 1). The mean MSTS score for patients in the series was 80%.

Conclusions: Intercalary endoprosthetic reconstruction provides an option for limb salvage in patients with diaphyseal tumors, with a complication rate 25% and MSTS scores of 80%. The highest rate of complication is seen with femoral reconstruction. Future prospective large multi-centered studies comparing intercalary endoprotheses and other reconstructive methods are needed prior to broad application of these findings.

Table 1. Implant Complications and Outcomes
*Complications categorized according to Henderson et al.

Failure Mode	Femur	Tibia	Humerus
Type 2	-	3	1
Type 3a	5	-	-
Type 3b	-	-	-
Type 4	1	-	-
Type 5	-	1	1
Total Complications	6	4	2
MSTS score	73%	73%	83%

PAPER 20

Comparison of Reconstructive Techniques Following Oncologic Intraarticular Resection of Proximal Humerus

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Introduction: The proximal humerus is the most common site of primary and metastatic disease in the upper extremity. Historically the goal of an endoprosthesis (EPR) reconstruction was to provide a stable platform for hand and elbow function, with little shoulder function. Allograft prosthetic composites (APC) utilizing a hemiarthroplasty allowed repair of the rotator cuff; however subluxation was common. Newer techniques utilizing a reverse prosthesis which do not rely on the rotator cuff have been developed, however there is a paucity of studies comparing these reconstructions.

Purpose: The purpose of this study is to compare commonly utilized proximal humeral reconstructions and report outcome in terms of (1) patient functional outcome and (2) implant survival and complications.

Method: 78 (40 females, 38 males) consecutive patients undergoing an oncologic intraarticular resection from 2000 and 2016 were reviewed. The reconstruction included hemiarthroplasty EPR (n=35), hemiarthroplasty APC (n=16), reverse EPR (n=18) and reverse APC (n=9). All surviving patients had a minimum of 2-years of clinical follow-up. Mean follow-up was 7±4 years. Mean time to death was 3±3 years.

Results: When comparing the patient groups (Table 1), patients undergoing a hemiarthroplasty APC were younger (39±4 years) at the time of surgery and patients undergoing EPR procedure (hemiarthroplasty (n=29, 83%) or reverse (n=16, 89%)) were more likely to have a non-primary malignancy, presence of a pathological fracture (hemiarthroplasty (n=30, 86%) and reverse (n=14, 78%)), and their surgical procedures were shorter (hemiarthroplasty (219±13 minutes) and reverse (202±20 minutes). When comparing a reverse prosthesis (APC or EPR) to a hemiarthroplasty (APC or EPR), there was no difference in the mean operative time (221±77 minutes vs. 239±86 minutes, P=0.39)

The 2- and 5-year survival following the procedure was 60% and 43%. Patients with metastatic disease had worse 5-year survival compared to those with primary disease (25% vs. 74%, P<0.001).

At most recent follow-up, mean active shoulder range of motion was as follows: forward flexion, 57±37^{o} and external rotation, 21±15^{o}. A reverse prosthesis had improved forward elevation (83±37^{o} vs. 44±29^{o}, P<0.001) and external rotation (28±18^{o} vs. 19±13^{o}, P=0.03) compared to a hemiarthroplasty. When comparing the individual forms of a reconstruction as a whole, patients with a reverse APC (P<0.001) had the greatest arc of motion (forward flexion (101±36^{o}) and external rotation (36±11^{o}).

Following the shoulder reconstruction, the mean Simple Shoulder Test, ASES score and MSTS93 scores were 4±2, 60±14, and 67±14, respectively. A reverse prosthesis had improved Simple Shoulder Tests (7±2 vs. 4±2, P=0.08), ASES scores (67±10 vs. 57±15, P=0.01) and MSTS93 scores (73±11 vs. 63±14, P<0.001) compared to a hemiarthroplasty.

One patient with a hemiarthroplasty APC underwent a revision procedure for instability. Subluxation of the reconstruction was the most common complication (n=23, 29%), and only occurred in patients undergoing a hemiarthroplasty procedure (EPR (n=13, 36%) and APC (n=10, 63%).

Conclusion: The results of our study shows that reconstruction of the proximal humerus should be performed using a reverse prosthesis, either EPR or an APC due to the improvements in function and low incidence of complications. Currently for patients with a primary sarcoma, our preferred technique is a reverse APC and in the setting of metastatic disease a reverse EPR can provide patients with pain relief and functional improvement.

Table 1: Patient Demographics and Function

Demographic	Hemiarthroplasty Endoprosthesis (n=35)	Hemiarthroplasty APC (n=16)	Reverse Endoprosthesis (n=18)	Reverse APC (n=9)	P Value
Mean Patient Age (±SD, Years)	63±17	39±17	61±12	57±17	<0.001
Male Gender	16 (45%)	9 (56%)	8 (44%)	5 (55%)	0.78
Mean Resection Length (±SD, CM)	12±4	13±5	10±2	12±6	0.26
Primary Disease	6 (17%)	14 (87%)	2 (11%)	6 (67%)	<0.001
Non-Primary Disease*	29 (83%)	2 (13%)	16 (89%)	3 (33%)	<0.001
Pathological Fracture	30 (86%)	5 (31%)	14 (78%)	3 (33%)	<0.001
Mean BMI (±SD, kg/m^2)	29.2±6.8	29.7±9.6	29.8±7.9	31.9±8.3	0.83
Mean Operative Time (±SD, minutes)	219±78	281±87	203±75	271±62	0.01
Resection Below Deltoid Insertion	4 (11%)	4 (25%)	7 (39%)	3 (33%)	0.12

*Metastatic or hematological malignancy

Table 2: Postopertative Function and Complications

Postoperative Function	Hemiarthroplasty Endoprosthesis	Hemiarthroplasty APC	Reverse Endoprosthesis	Reverse APC	P Value
Active Forward Elevation (±SD, Degrees)	38±27	54±31	71±34	101±36	<0.001
Active External Rotation (±SD, Degrees)	17±14	21±9	22±21	36±11	0.02
Mean Simple Shoulder Test (±SD)	3±1	5±3	4±1	6±1	<0.001
Mean ASES Score (±SD)	55±16	61±14	62±10	73±8	0.02
Mean MSTS93 Score (±SD, %)	60±13	70±15	67±9	82±9	<0.001
Percent of Patients "Satisfied" with Procedure	24 (68%)	14 (88%)	15 (94%)	9 (100%)	0.059
Complications	**Hemiarthroplasty Endoprosthesis (n=35)**	**Hemiarthroplasty APC (n=16)**	**Reverse Endoprosthesis (n=18)**	**Reverse APC (n=9)**	**P Value**
Subluxation (>25%)	13 (37%)	10 (63%)	0 (0%)	0 (0%)	<0.001
Periprosthetic or Allograft Fracture	2 (6%)	3 (19%)	1 (6%)	1 (11%)	0.45
Infection	1 (3%)	0 (0%)	1 (6%)	0 (0%)	1.0
Reoperation	2 (6%)	3 (19%)	1 (6%)	0 (0%)	0.17
Revision Procedure	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0.32

ASES: American Shoulder Elbow Surgeons
MSTS: Musculoskeletal Tumor Society

PAPER 21

Bone Preservation following Revision Allograft Prosthetic Composite Reconstruction of the Proximal Humerus

Authors: Taylor Reif, MD, Ashley Aratani, MD, Andre Spiguel, MD, Bradley Schoch, MD, Joaquin Sanchez-Sotelo, MD, PhD, Benjamin Wilke, MD

Introduction: Allograft prosthetic composite (APC) reconstruction of the shoulder is a valuable technique following tumor resection or failed shoulder arthroplasty. The purported benefits include a durable joint, repair of the rotator cuff tendons, and restoration of proximal bone stock. A study of proximal femur APC reconstructions suggests the last benefit may be illusory, as nearly three fourths of the constructs had the entire allograft bone removed at the time of revision. Similarly, we hypothesized that proximal humerus allograft bone would not restore usable bone stock at the time of revision surgery.

Methods: Following IRB approval the institutional databases of the Mayo Clinic and University of Florida were queried. One hundred and fifteen APCs were performed over the study period. Fourteen patients underwent documented revision of their APC and were included in the analysis. Revision was defined as any return to the operating room. Medical records including operative reports and radiographs were reviewed. Three categories were used to classify the amount of allograft retention at the time of revision surgery; type (A) = complete allograft retention, type (B) = partial retention, type (C) = no allograft retention.

Results: Fourteen patients (6 males, 8 females) underwent revision of their APC at a mean of 22.8 (± 71.1) months following primary surgery. The average age at the time of initial APC reconstruction was 35 years old. The indication for APC was tumor resection in (11/14) of cases. The indications for revision included nonunion (7/14), glenohumeral instability (5/14), and allograft fracture (2/14). At the time of revision, there were 6 type (A) cases (42.9%), 3 type (B) cases (21.4%), and 5 type (C) cases (35.7%). When comparing patients who had their allograft retained (type A and B) versus removed (type C) at the revision surgery, the average time to revision was significantly longer in those with a type C resection (88 ± 83 months versus 30 ± 47.6 months, respectively) ($p=0.04$).

Conclusion: Unlike the proximal femur, the majority of revisions of proximal humerus APCs maintain a portion of the allograft bone (type A & B, 64.3%). Failures were most commonly related to graft nonunion or instability leading to a bone grafting or conversion arthroplasty (hemi to reverse) procedure allowing salvage of the allograft bone.

PAPER 22

Comparison of free vascularized fibula grafting to allograft strut grafting to supplement spinal pelvic reconstruction for sacral malignancies

Authors: Peter S. Rose, Matthew T. Houdek, Karim Barki, Michael J. Yaszemski, Franklin H. Sim, Steven L. Moran

Institution: Mayo Clinic, Rochester, MN, USA

Introduction: Following resection of sacral malignancies orthopedic and reconstructive surgeons are faced with large composite defects. Previous studies have shown that resections above the level of the S1 neural foramen or one of the sacral iliac joint requires reconstruction based on the load to failure of the residual sacrum and patient quality of life. Different options for reconstruction exist, including spinal pelvic fixation augmented with either allograft and free vascularized fibula grafting (FVFG) in a cathedral style reconstruction; however currently there are no studies comparing these reconstructive techniques.

Purpose: The purpose of this study is to compare the outcomes of spinal pelvic fixation with a strut allograft and FVFG in a cathedral style reconstruction in terms of reconstructive outcomes, complications and patient function.

Method: 37 (18 females, 19 males) patients, mean age 40±17 years, undergoing an en-bloc sacrectomy for a malignant tumor of the sacrum who were reconstructed with a total or hemi-cathedral technique from 1991-2017 were reviewed. Of these patients, reconstruction included total sacrectomy (n=17, 46%), partial sacrectomy requiring reconstruction (n=2, 7%), or hemisacrectomy (n=18, 49%) requiring reconstruction. The mean graft length was 13±4 cm. The reconstructions were supplemented with FVFG struts (n=18, 49%) or allograft struts (n=19, 51%). Based on their histology, 15 (39%) patient received preoperative radiotherapy (mean dose 53±11 Gy). The mean follow-up was 6±5 years.

Results: There was no difference in the mean age, gender, fibula graft length, tumor dimension or volume and proportion of patients with a history of radiotherapy (Table 1) when comparing patients reconstructed with a FVFG and those with an allograft.

Allograft reconstruction was associated with a high risk of non-union (OR 6.87, P=0.01) and a longer mean time to union (12±3 vs. 7±3 months, P=0.03) compared to FVFG. There was a trend towards increased risk of graft fracture (OR 4.66, P=0.12) and revision for pseudoarthrosis (OR 4.66, P=0.12) in patients with an allograft reconstruction compared to a FVFG.

Following the procedure 25 (68%) patients were ambulatory, with 17 (46%) using a single arm or no gait aid. Following the procedure the mean MSTS93 score was 50±24, with a higher mean MSTS 93 score in patients reconstructed with a FVFG (59±24 vs. 41±21, P=0.02).

Conclusion: Bony reconstruction of sacral malignancies is associated with a high rate of complications. Allograft reconstruction was associated non-union, longer mean time to union, and worse functional outcome when compared to FVFG. Spinal pelvic fixation supplemented with a FVFG is our current standard means of reconstruction, in either a cathedral or hemi-cathedral technique following sacral tumor resection.

PAPER 23

Outcomes of sacral tumor resection based on the Mayo Clinic Classification System

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Introduction: Malignant tumors of the sacrum require a multidisciplinary approach to achieve cure and a functional outcome. Previous biomechanical studies have shown resections through or above the level of the S1 neural foramen require reconstruction. In addition if one of the sacroiliac joints is resected, patient function has been shown to be improved if sacropelvic continuity is maintained. Based on these results, we developed a classification system (Figure 1) for sacral resection and indications for reconstruction: total sacrectomy (Type 1A) requiring reconstruction, subtotal sacrectomy (Type 1B) requiring reconstruction(above or through the S1 foramen), subtotal sacrectomy (Type 1C) not requiring reconstruction (below S1 foramen), hemisacrectomy (Type 2), external hemipelvectomy and sacrectomy (Type 3), total sacrectomy external hemipelvectomy (Type 4), and hemicorporectomy (Type 5); however the outcome of these reconstructions has not been reported.

Purpose: The purpose of this study is to report the outcome of sacral tumor resection based on our classification system with regards to (1) oncological outcome, (2) complications and (3) patient functional outcome.

Method: 235 (89 females, 146 males) patients undergoing an en-bloc sacrectomy for a tumor of the sacrum between 1991 and 2017 were reviewed. The mean age and BMI were 49±16 years and 27.1±6.2 kg/m². 165 (70%) were primary malignant tumors, 60 (26%) recurrent colorectal carcinoma, 8 (3%) benign aggressive tumors and 2 (1%) recurrent gynecological malignancies. Resections included Type 1A (n=20, 9%), Type 1B (n=5, 2%), Type 1C (n=137, 58%), Type 2 (n=31, 13%), Type 3 (n=36, 15%), Type 4 (n=5, 2%) and Type 5 (n=1, 1%). Oncologic outcome was assessed for patients with malignant tumors. The mean follow-up was 7±5 years. Of these 54 (23%) were reconstructed with spinal pelvic fixation.

Results: 110 (47%) patients died of disease at a mean of 4±4 years. For a primary malignancy of the sacrum, the 5- and 10- year disease specific survival were 69% and 55%. Based on the Mayo Classification the 5-year disease specific survival for a primary malignancy (Figure 1) were Type 1A (36%), Type 1B (100%), Type 1C (76%), Type 2 (74%), Type 3 (53%), Type 4 (100%) and Type 5 (100%). In patients with a primary sarcoma (n=165), recurrence occurred in 58 (35%) and was defined as local (n=20, 12%), distant (n=27, 16%) and local and distant (n=21, 13%). The mean time to recurrence was 3±3 years. Complications occurred in 172 (73%) patients, of these a wound complication (n=106, 45%) was the most common. In the patients who were reconstructed, 20 had a failure of the hardware (37%), including pseudoarthrosis (n=15, 75%) and infection (n=5, 25%). Following the procedure 176

(75%) patients were ambulatory, with 133 (56%) using a single arm or no gait aid. Following the procedure the mean MSTS93 score was 62±22.

Conclusion: Resection of sacral malignancies associated with a high complication rate, however can be curative in a majority of patients. Following the procedure a majority of patients are ambulatory, with many using no gait aids.

Figure 1: Mayo Clinic Sacral Resection Classification

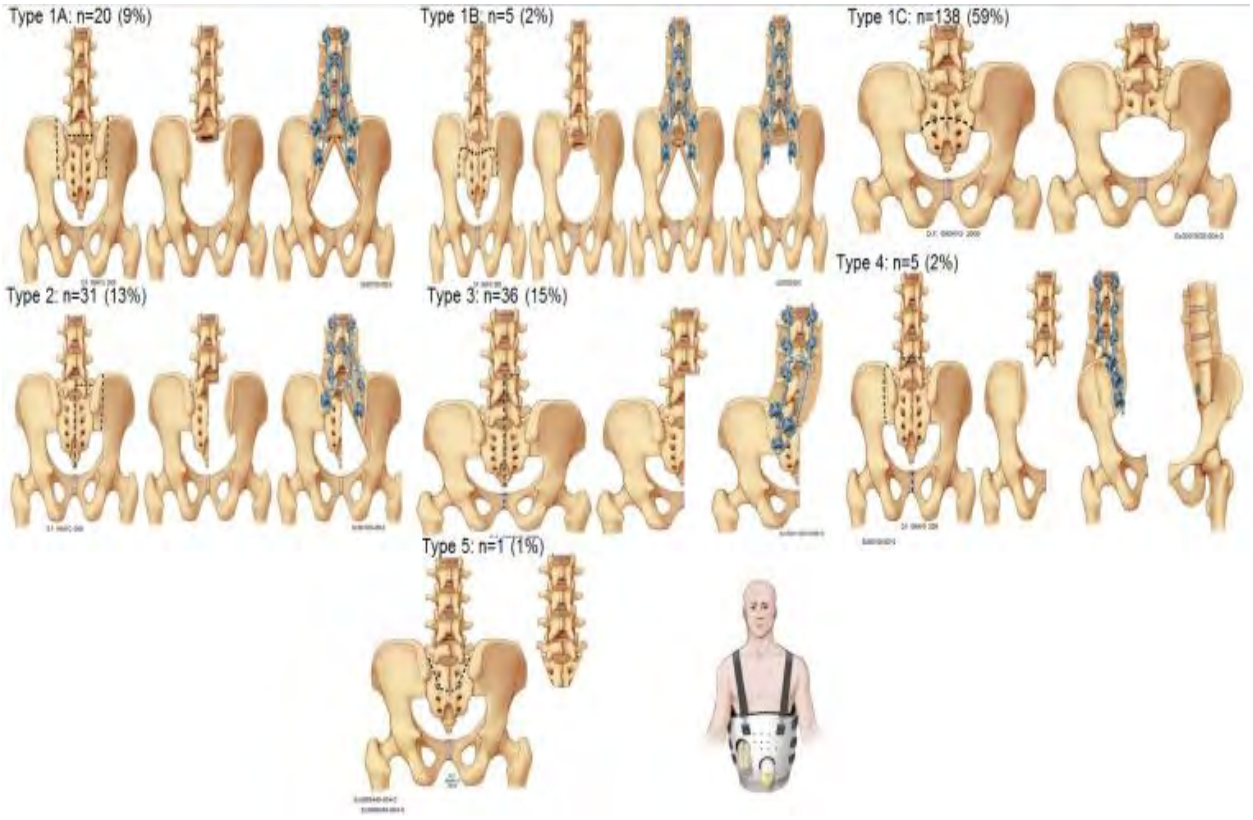

Figure 1: Based on the Mayo Classification sacral resections included Type 1A (n=20, 9%), Type 1B (n=5, 2%), Type 1C (n=137, 58%), Type 2 (n=31, 13%), Type 3 (n=36, 15%), Type 4 (n=5, 2%) and Type 5 (n=1, 1%).

Figure 2: Disease Specific Survival Following Sacral Resection

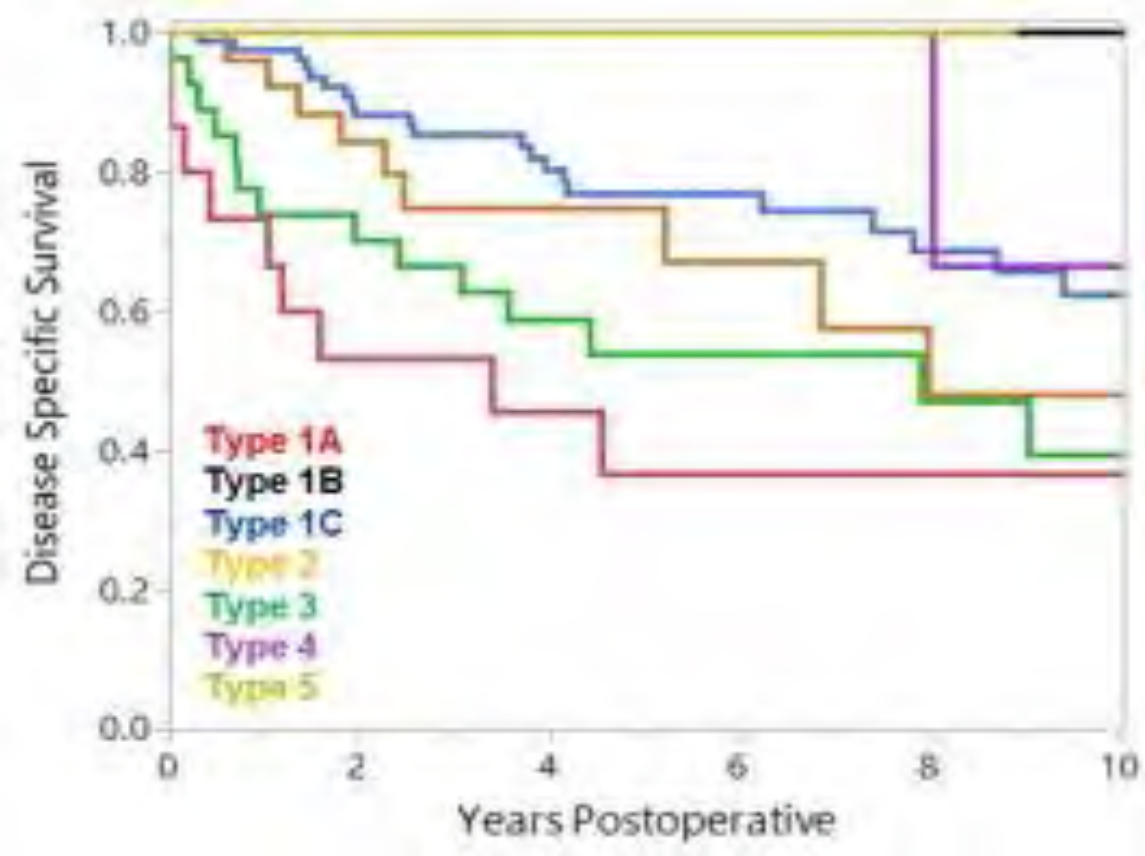

Figure 2: Following sacral resection the 5- and 10-year disease specific survival were 69% and 55%. Based on the Mayo Classification, the 5-year disease specific survival were: Type 1A (36%), Type 1B (100%), Type 1C (76%), Type 2 (74%), Type 3 (53%), Type 4 (100%) and Type 5 (100%).

PAPER 24

Navigation-Assisted in Pelvic and Sacrum Resection Provides Benefit in Minimizing Bony Recurrence

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Background: Computer navigation-assisted resection can be useful as adjunct instrument for resections in the difficult areas such as the pelvis and sacrum. The technique can minimize the amount of bone resection and decrease the probability of positive bone margins, specifically in partial acetabulum resections to preserve the hip joint. This study reports on the local recurrent rate of the bone and soft tissue using computer navigation in the pelvic and sacrum. This study attempts to find an association between zone of resection with local recurrence(bone versus soft tissue), operative time, blood loss and blood transfusion.

Methods: We reviewed all patient's charts who had navigation-assisted resections of the tumors of the pelvis and sacrum between February 2009 and January 2019. Preoperative and postoperative imaging were reviewed along with other demographic data including age, gender, stage, diagnosis, adjuvant therapy, local recurrence, overall survival, margins status, intra op contamination, complication, operative time(resection time only), blood loss and blood transfusion, as well as resection type (Type I, II, III, IV) and reconstruction.

Results: A total of 43 patients were identified with a mean follow-up was 25 months (0-103 months). The mean age was 50.9 years (24–73). 32/43 (74.4%) patients were alive at follow up. Chondrosarcoma was the most common diagnosis 19/43 (44.2%). The mean size of tumor was 10.45 cm. The disease-specific survival at 5 years and 8.5 years was 68.3% and 58.6%, respectively. The local recurrent free survival at 5 and 8.5 year was 57.3% and 57.3% respectively. The local recurrent of the bone free survival at 5 and 8.5 year was 84.3% and 84.3% respectively. The total local recurrent rate was 10/43 (23.3%); bone specific recurrence 3/43 (7%). Partial acetabulum resection under guidance of navigation was successfully 10 from 10 cases without bone local recurrent.

Based on the zone of resection, the most common bone recurrence was found in sacrum area 1/4 (25%) cases. The longest resection time was found in sacrum 561.25 minutes. The highest blood loss: 5,135 cc was found in Type I-II resections. The highest blood transfusion was found in sacrum 15.6 units. The embolization was done in 1/43 (2.3%) of the patients. Post operation complication was found in 15/43 (34.9%), the most common was wound dehiscence 6/43 (13.9%). The significant predictors of local recurrent were a tumor diameter > 10 cm; the hazard ratio was 4.9.

Conclusions: The navigation-assisted resection bony local recurrent rate is less than soft tissue recurrence rate 7% vs 16% respectively. Navigation can allow for acetabular-preserving resection in pelvic surgery. The significant predictors of local recurrent were a tumor diameter > 10 cm.

PAPER 25

Pediatric Sarcoma Patients have worse Physical Function but better Peer Relationships and Depressive symptoms than the U.S. general pediatric population as measured by PROMIS

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Background: Pediatric patients with sarcomas are at risk of poor quality of life outcomes. Patients are faced with complex decisions regarding limb-salvage resection or amputation and those treated with intensive chemotherapy are at risk of life-long effects. The NIH-funded Patient Reported Outcomes Measurement Information System (PROMIS) improves our ability to capture patient-reported outcomes in a standardized fashion. Do physical function, social, and mental health PROMIS outcomes for pediatric patients with non-metastatic malignant sarcomas differ from the U.S. general pediatric population?

Methods: PROMIS questionnaires were collected for all patient visits to orthopaedic oncology at a tertiary referral center. We examined six months of data for patients ages five to 17 years from September 1st to March 31st, 2016. Of the 164 pediatric patients who completed the questionnaires, 30 patients were eligible for this analysis with non-metastatic malignant sarcoma diagnoses. Metastatic disease was detected by chest CT for all sarcomas and whole body bone scan for bone sarcomas. Six Pediatric PROMIS Short Forms were evaluated; parental proxy forms were not included. We assessed whether mean T-scores differed from the reference pediatric population by one-sample t-test. A post-hoc ANOVA analysis compared patients who completed the form preoperatively (n=7), those who did not have surgery (n=3), and those who underwent surgery (n=20).

Results: Of the 30 patients, five had soft-tissue sarcomas and 25 (83%) had bone sarcomas. The mean age of the cohort was 13 years (SD 2.8). For the 20 patients who underwent a surgical intervention, the average time from surgery to survey was 20 months (SD 19.3). Additional cohort characteristics are detailed in Table 1. The primary outcome results are detailed in Table 2. The study cohort had a mean physical function T-score of 39.8 (SD 9.8), which was significantly worse than the reference population. In contrast, the mean peer relationship T-score of 54.3 (SD 8.8) and mean depression T-score of 42.0 (SD 9.1) were significantly better than the reference population. Thirteen (43.3%) of the 30 patients scored the best possible score on depressive symptoms. There were no significant differences in T-scores based on preoperative, nonoperative, or postsurgical status.

Conclusions: Pediatric patients with non-metastatic sarcomas had worse physical function scores but better peer relationship and depression scores than the U.S. reference population as measured by PROMIS short forms. These results did not differ based on surgical status, however the subset numbers are small and may not be appropriately powered to detect a difference in PROMIS measures. Ceiling and flooring effects were found in several measures. The measure of depressive symptoms was notable as 43% of the cohort reported the lowest score. Similarly, anxiety demonstrated a flooring effect with 27% reporting the lowest score. Conversely, peer relationships showed a ceiling effect with 27% reporting the highest score. These results provide normative data and suggest there may be survey validity challenges in the future in the pediatric sarcoma population. Certainly, future studies are necessary with larger cohorts to validate these data and permit further analyses based on specific diagnoses and treatments.

Level of Evidence: III

Table 1: Demographic and clinical characteristics of pediatric patients (5-17 years) with nonmetastatic bone and soft-tissue sarcomas (n=30).

Characteristic	Distribution, n (%)
Age, mean +/- SD, years	12.97 (2.77)
Female Sex	16 (53)
Bone Sarcoma	
Osteosarcoma	17 (57)
Ewing Sarcoma	7 (23)
Chondrosarcoma	1 (3)
Soft-Tissue Sarcoma	5 (17)
Preoperative Survey	7 (23)
Nonsurgical management only	3 (10)
Prior Incomplete resection	3 (10)
Limb-salvage resection	24 (80)
Adjuvant (chemotherapy and/or radiation)	26 (87)
Postoperative Complication	3 (10)
Follow-up in years if surgical candidate (N=20)	1.64 (1.61)

Table 2: Descriptive statistics of PROMIS Short-Form measures in pediatric patients with nonmetastatic sarcomas are shown including floor and ceiling effects. Also shown are test statistics of comparison of patient mean T-Scores with U.S. pediatric reference population by one-sample t-test.

PROMIS Short Form Outcome Measure:	Physical Function Mobility v1.0 (8a)	Peer Relationships v2.0 (8a)	Anxiety v2.0 (8a)	Depressive Symptoms v2.0 (8a)	Fatigue v2.0 (10a)	Pain Interference v2.0 (8a)
Score Range	15.2-58.5	17.7-64.4	32.2-82.8	35.2-81.9	31.1-82.8	34-78
n	30	30	30	30	30	30
Mean	39.53	54.27	46.27	42.03	48.53	52.53
Standard Deviation	9.78	8.82	12.70	9.07	11.67	13.34
25th quartile	33	47	32	35	40	37.75
Median	37.5	54	44	40	49.5	55.5
75th quartile	46	65	57.75	44	57.75	60.5
Floor *n* (%)	0 (0)	0 (0)	8 (27)	13 (43)	5 (17)	7 (23)
Ceiling *n* (%)	3 (10)	8 (27)	0 (0)	0 (0)	0 (0)	1 (3)
Standard Error of the Mean	1.78	1.61	2.32	1.66	2.13	2.44
t	-5.86	2.65	-1.61	-4.81	-0.69	1.04
Mean Difference	-10.47	4.27	-3.73	-7.97	-1.47	2.53
p (2-tailed)	0.000	0.013	0.118	0.000	0.497	0.307

PAPER 26

Bisphosphonate therapy for treating osteonecrosis in pediatric leukemia patients: A systematic review

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Background: Despite improving oncologic outcomes in pediatric leukemia patients, complications such as osteonecrosis remain common. Depending upon the severity of the lesion, treatment options for Osteonecrosis can range from conservative management and bisphosphonate therapy, to surgical interventions like core decompression, autologous bone grafting, and joint arthroplasty. The existing medical literature regarding the utility of bisphosphonate treatment in survivors of pediatric hematologic malignancies is limited to small case series, which similarly limits the reliability in extrapolating these findings.

Questions and purpose: In survivors of pediatric leukemia with osteonecrosis, what is the role of bisphosphonates in 1) reducing pain; 2) improving mobility; and 3) stabilizing osteonecrotic lesions.

Methods: We conducted a systematic literature review of PubMed, Embase, Cochrane, Web of Science, Scopus, CINAHL, and ClinicalTrials.gov electronic databases for relevant articles using the following search terms: ('leukemia'), ('bone necrosis' or 'avascular necrosis' or aseptic necrosis' or 'osteonecrosis' or 'bone infarct'), and ('bisphosphonate' or 'diphosphonate' or 'pamidronate' or 'ibandronate' or 'zoledronic acid' or 'alendronate'). All identified articles were screened for inclusion and PRISMA guidelines were followed. Of the 221 articles retrieved, five studies (retrospective, observational, and interventional) assessed the use of bisphosphonates for treating osteonecrosis in survivors of pediatric leukemia. Case reports, letters to the editor, conference notes, and abstracts without accompanying manuscripts were excluded. All eligible studies were critically appraised using the MINORS criteria. Fisher's Exact Test and one-way ANOVA were used to identify any differences in patient characteristics. Wilcoxon Rank-Sum and Kruskal Wallis Tests were used to examine the association between bisphosphonate or conservative therapy on patient outcomes.

Results: Methodological quality assessed with the MINORS criteria ranged from 9 to 11 points (maximum of 16) for non-comparative studies, and 16 points (maximum of 24) for comparative studies. Patient age and sex did not differ significantly between patient groups and among studies (one-way ANOVA, Fisher's Exact; $p>0.05$). We found that bisphosphonates, especially when combined with

conservative therapies, were associated with improved pain and mobility in 63.0% and 47.4% of patients, respectively. Compared to those treated with conservative therapy alone, patients treated with bisphosphonates demonstrated better pain outcomes, with a higher proportion of patients reporting mild/moderate pain or no pain at all ($p<0.005$). Overall, 63.6% of patients treated with bisphosphonates achieved improved or full mobility, compared to 27.3% of those treated with conservative therapy alone ($p<0.05$). However, 50% of patients demonstrated progressive joint destruction despite bisphosphonate therapy. No adverse events were reported following bisphosphonate therapy, with the exception of acute phase reactions associated with those patients treated with intravenous bisphosphonate infusion.

Conclusions: Our findings suggest that bisphosphonates, when combined with conservative therapy, may be a useful tool for managing pain and improving mobility in pediatric leukemia patients with osteonecrosis, but may not be able to prevent further joint destruction and collapse.

Table 1: Patient outcomes following bisphosphonate treatment compared to baseline

Outcome	Worsened (%)	Stabilized (%)	Improved (%)	Total
Δ Pain from baseline	2 (10.5)	5 (26.3)	12 (63.2)	19
Δ Mobility from baseline	2 (10.5)	8 (42.1)	9 (47.4)	19
Radiological Δ from baseline	23 (50.0)	17 (37.0)	6 (13.0)	46

Table 2: Patient outcomes by treatment

Outcome	Bisphosphonates (%)	Conservative (%)	Total	p-value*
Pain				<0.005
Pain-free	16 (29.1)	0 (0)	16	
Mild/Moderate	27 (49.1)	4 (36.4)	31	
Severe	12 (21.8)	7 (63.6)	19	
Mobility				<0.05
Full/Improved	35 (63.6)	3 (27.3)	38	
Reduced	20 (36.4)	8 (72.7)	28	
Total	55 (100)	11 (100)	66	

*Wilcoxon Rank-Sum

PAPER 27

Allograft reconstruction alone has an increased rate of amputation and worse functional outcome when compared with vascularized fibular reconstruction for tibial defects in pediatric patients

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Introduction: Limb salvage surgery is currently the treatment option of choice for pediatric patients with a sarcoma. In the tibia this can be difficult due to the growth potential of the proximal tibia and functional demands of the pediatric patient population. Multiple reconstruction techniques including allografts, free vascularized fibular grafting (FVFG), bone transport and arthrodesis exist, however the ideal form of reconstruction is yet to be elucidated. The purpose of the current study is to evaluate outcomes in patients with a tibial sarcoma treated with a limb salvage surgery illustrating the evolution of treatments with the goal of identifying a durable reconstruction, allowing pediatric patients to continue normal childhood activities.

Methods: Twenty-nine (16 males, 13 females) pediatric patients, mean age 12±4 years, undergoing en-bloc resection of a tibial bone sarcoma treated between 1981 and 2018 were reviewed. The most common histology were osteosarcoma (n=14, 48%) and Ewing sarcoma (n=5, 17%). Reconstructions included combined intercalary allograft (n= 11, 38%), intercalary allograft and vascularized fibula (n= 10, 34%), intercalary vascularized fibula (n=6, 21%), knee arthrodesis (n=1, 3%), bone transport (n=1, 3%). The mean resection length was 14±3 cm. The mean follow-up was 12±7 years.
Results: Over the course of the study, 3 patients developed a recurrence which was defined as isolated metastatic (n=1) and combined local and metastatic (n=2). Following the procedure complications were common occurring in 21 (72%) patients, most commonly a wound infection (n=5, 17%).

Amputation occurred in 6 patients at a mean 24±19 months. Indications for amputation included infection (n=3), local recurrence (n=2), and fracture (n=1). When comparing patients who had an amputation for a failure of the reconstruction, the incidence of amputation for patients reconstructed with an allograft alone was 36% compared to 0% if the reconstruction was supplemented with a vascularized bone graft (P=0.09).

Following the reconstruction the mean MSTS93 rating was 92±11. Patients reconstructed with a vascularized bone graft had improved MSTS93 rating compared to those reconstructed without a vascularized bone graft (95±8 vs.81±15, P=0.02).

Conclusions: The results of the current series highlight the importance of supplementing the reconstruction with a vascularized bone graft in terms of limb salvage and function. All reconstructions which were performed without a vascularized bone graft were performed prior to 2000. Currently we recommend the addition of a vascularized bone graft whenever possible when reconstructing a tibial defect in pediatric patients.

PAPER 28

Clinical Characteristics of Masses in Pediatric Hand/Wrist

Authors: Carlos Pargas, MD, Mihir Thacker, MD, Jennifer Ty, MD, Kenneth Rogers PhD,ATC

Background: Pediatric hand/wrist masses are usually benign. Some may become symptomatic due to small space of the hand and aggressive growth. 15 % of all soft tissue tumors and 6 % of osseous tumors are located in the hand predominantly in the wrist and phalanges respectively. There are no large epidemiologic studies in children defining hand masses in the pediatric population. Pediatric Hand/wrist masses description could help to narrow down the list of differential diagnosis.

Methods: An *IRB approved* retrospective review of all patients with hand masses seen at our institution from 01/01/2000 to 01/01/2019. We recorded standard demographics, clinical and imaging data, treatment and complications.

Results:
405 patients with hand-wrist masses were identified. 206 (50.86%) were female and 199 (49.14%) male. The average age at presentation was 9.8 years (0.41-19). Most of the children identified as Caucasian (258, 63.70%), with Afro-American (75, 18.02%), and Hispanic (39, 10.50%) being the largest ethnicities. 10 patients had bilateral involvement (10, 18.02%). Soft tissue masses were seen in 317 patients (78.27%) while than 88 patients (21.73%) had bony tumors. Phalanges and distal radius/ulna were the most common affected bone areas. The majority were benign and only 3 (0.74%) were malignant: one Ewing's sarcoma and two soft tissue sarcoma (periosteal 5th metacarpal and tendon sheath of the flexor 4th). The most common diagnosis was ganglion cyst (285, 70.40%). 163 (57.19%) were located in the dorsum of the wrist and 116 (40.70%) on the volar radial side. Osteochondromas (53, 13.1%) were the most common bone tumor. 142 (35.06%) patients had surgery masses usually for symptoms such as pain, functional limitation, and to concerns regarding malignancy.

Conclusions: Pediatric hand-wrist masses mainly affect the soft tissues and the majority are benign. Ganglion cysts and the osteochondromas were the most common diagnoses, which in many cases only required observation. Volar radial wrist ganglions were more common in children compared to adults. Malignant tumors are rare in children. We can narrow down the list of differential diagnosis according to the clinic.

Level of Evidence: IV

PAPER 29

Low Socioeconomic Status Predicts Metastatic Disease at Presentation in Young Patients with Ewing Sarcoma

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Background: Ewing's Sarcoma is the second most common malignant bone tumor in children, and commonly affects adolescents and young adults. There are substantial differences in management and outcomes for patients who have localized disease compared with distant spread at the time of diagnosis.

Purpose: Our objective was to examine risk factors predictive of metastatic disease at presentation.

Patients and Methods: The Surveillance, Epidemiology, and End Results Program database was used to identify patients aged 30 years and younger diagnosed with Ewing's sarcoma from 2004 to 2014. Patient demographic features, socioeconomic factors, and tumor characteristics were analyzed to determine which factors were predictive of an increased rate of distant metastatic disease at presentation. Socioeconomic status included income, employment, education level, and level above or below the poverty line. These factors were analyzed as univariate characteristics as well as in a multivariate logistic regression model.

Results: We identified 1194 cases of Ewing's sarcoma and 363 (30.4%) of the patients presented with metastatic disease. In the unadjusted analysis, patients had increased odds of metastatic disease at presentation if they were older, male, Caucasian, had low socioeconomic status, presented with an axial tumor location, and had larger tumor burden. All these factors remained significant in multivariate models controlling for age, sex, ethnicity, tumor size, anatomic location, and socioeconomic status. In fact, low socioeconomic status was the strongest predictive variable for late stage presentation.

Conclusions: Older, male, Caucasian patients of low socioeconomic status with an axial disease location and larger tumor burden are more likely to have metastatic disease on presentation with Ewing's sarcoma.

Level of Evidence: III, prognostic

PAPER 30

The Sarcoma-Specific Quality of Life Study (SARC-QoL): Identifying key domains of Health-Related Quality of Life in adult patients with extremity soft tissue sarcoma

Authors: Urska Kosir[1]; Kedar Mate, PHD[2]; Argerie Tsimicalis, RN, PhD[3]; Robert E. Turcotte, MD, FRCSC[4]; Carolyn Freeman, MD, FRCPC[5]; Fabio Cury, MD[5]; Thierry Alcindor, MD, MSc[6]; Nancy Mayo, PHD[7]; Krista Goulding, MD, FRCSC, MPH[4,7]

Background: The patient's subjective experience of disease is an increasing focus in health care delivery [1, 2]. Health-related quality of life (HRQoL) is defined as a "functional effect of a medical condition and its consequent treatment" [18]; it is both self-reported and multi-dimensional [3-5]. While functional outcome is well researched among the soft tissue sarcoma (STS) population, few studies have focused on HRQoL [6-13], which gives a broader understanding of the psychological, somatic, social and physical toll of cancer and its treatment from the patient's viewpoint. The biologic and anatomic heterogeneity of sarcomas are considerable: a patient treated with soft tissue resection and free flap will have vastly different needs than an individual treated with an amputation or rotationplasty, for example [14, 6, 7, 15]. A recent systematic review (SR) highlights a small, heterogeneous group of QOL studies in STS, but fails to identify any sarcoma-specific measures [16]. A second SR of 31 articles on HRQoL in sarcoma reported lack of sarcoma-specific outcomes that capture psychosocial impacts and unmet needs to people with sarcoma across healthcare spectrum [17]. Just as the treatments are diverse, we surmise that the indicators of patient HRQoL differ and are not captured in existing generic HRQoL tools for cancer.

Questions/purposes: The study objectives were to explore the domains of HRQoL and functioning in adult patients diagnosed with extremity STS from the patient's perspective from active care through survivorship through qualitative inquiry, so as to form the basis for the development of a patient-derived, sarcoma-specific, preference based HRQoL tool.

Patients and Methods: Study design is a sequential exploratory mixed methods study of patient experience in localized or metastatic adult extremity STS (2007 and 2017). The study was conducted at a high-volume sarcoma centre. Qualitative descriptive design was grounded in an integrated knowledge translation approach and aimed at identifying HRQoL domains through in-person and electronic focus groups, and individual semi-structured interviews in both English and French (N=28). The interview guide topics were selected based on existing knowledge about PROs and HRQoL life [24], including (a) impact of diagnosis on employment or acquisition of academic/vocational skills; (b) physical and psychological functioning; (c) symptom burden; (d) treatment preferences; (e) knowledge of and use of existing resources; (f) impact on family time and resources; and (g) overall experience. Data was analyzed using inductive thematic networks approach using the qualitative software N-Vivo 12. Codes were generated by 2 independent qualitative experts capturing key concepts of HRQoL that is impacted by STS. Basic themes were clustered into organizing themes, and merged into global domains. Attention was paid to deviant cases and within-group dynamics during focus group discussion analysis. Discrepancies or inconsistencies in coding were resolved in consensus meetings. Final sample size was determined when data saturation was reached and no new themes emerged. Qualitative reduction of

identified items to reach a consensus framework was facilitated by a moderator during multi-disciplinary panel meetings comprised of sarcoma experts, patient partners, allied health staff and other stakeholders.

Results: Twenty-nine patients with biopsy-proven localized or metastatic STS of the extremity participated (69% lower extremity STS; mean age 56 years, 25% with local recurrence, 21% metastatic, 18% amputation). Inductive thematic network analysis revealed five domains and subdomains of HRQoL for patients with STS: 1) physical domain (subdomain: physical symptoms, treatment complications), 2) psychological domain (anxiety, distress, mood, body image and identity), 3) medical support (emotional support, practical support, confidence in positive outcome and reluctance to medical personnel), 4) social life (family and social support), and 5) daily living (disruption of routine and finances).

Conclusion: Patient-centered research is crucial to understanding the impact of surgery, adjuvant therapy and the associated complications for patients with extremity STS, and thereby improving the quality of care provision. This study offers a unique perspective on what domains and sub domains are most impactful on HRQoL and provides the basis for our on-going development of a disease-specific, preference-based HRQoL measure.

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PAPER 31

The Sarcoma-Specific Quality of Life (SARC-QoL) Study (Phase 1): A qualitative study of psychological functioning and coping styles in adult extremity soft tissue sarcoma patients

Authors: Urska Kosir[1]; Kedar Mate, PHD[2]; Argerie Tsimicalis, RN, PhD[3]; Robert E. Turcotte, MD, FRCSC[4]; Carolyn Freeman, MD, FRCPC[5]; Fabio Cury, MD[5]; Thierry Alcindor, MD, MSc[6]; Nancy Mayo, PHD[7]; Krista Goulding, MD, FRCSC, MPH[4,7]

Background: While functional outcome is well researched among the soft tissue sarcoma (STS) population, few studies have focused on HRQoL, which is self-reported and multi-dimensional, giving a broader understanding of the psychological, somatic, social and physical toll of cancer and its treatment from the patient's viewpoint [1-13]. The biologic and anatomic heterogeneity of sarcomas are considerable: a patient treated with soft tissue resection and free flap reconstruction will have vastly different needs than an individual treated with an amputation or rotationplasty, for example [14, 6, 7, 15]. Two recent systematic reviews identify several heterogeneous studies based on generic HRQoL measures, but highlight the lack of a disease specific measure for people with STS [16, 17]. These reviews indicate that patients with sarcoma experience higher rates of anxiety, depression and suicide than the general population. Just as the treatments are diverse, we surmise that the indicators of patient HRQoL in those with extremity STS differ and are not captured in existing generic HRQoL tools for cancer.

Questions/purposes: The study objectives were to 1) explore the domain of psychological functioning in adult patients diagnosed with extremity STS through qualitative inquiry and; 2) to investigate the patients' affective responses and coping mechanisms from active care through survivorship, so as to form the basis for the development of a patient-derived, sarcoma-specific, preference based HRQoL tool.

Patients and Methods: Study design is a sequential exploratory mixed methods study of patient experience in individuals diagnosed with a localized or metastatic STS of the extremity, with phase 1 focused on qualitative descriptive design. Purposive sampling based on demographic and disease variables from all patients in our prospective sarcoma database (2007-2018) was utilized to ensure a representative patient population. Three formats of data collection were conducted in French and English; 2 online focus groups (N=12), 2 in-person focus groups (N=12), as well as individual semi-structured interviews (N=4). The interview guide topics were selected based on existing knowledge about PROs and HRQoL life [24], including (a) impact of diagnosis on employment or acquisition of academic/vocational skills; (b) physical and psychological functioning; (c) symptom burden; (d) treatment preferences; (e) knowledge of and use of existing resources; (f) impact on family time and resources; and (g) overall experience. Data was analyzed using inductive thematic networks approach using the qualitative software N-Vivo 12. Codes were generated by 2 independent qualitative experts capturing key concepts of psychological functioning and coping mechanisms. Basic themes were clustered into organizing themes, which were merged into a global domain. Attention was paid to deviant cases and within-group dynamics during focus group discussion analysis. Discrepancies or inconsistencies in coding were resolved in consensus meetings. Final sample size was determined when data saturation was reached and no new themes emerged.

Results: Our analyses of psychological well-being and functioning revealed 3 main themes; mood, anxiety, and body image concerns. Feelings of depression and low mood were prominent, coinciding with physical symptoms and limitations especially during the phase of treatment and early recovery. Women were more likely to report emotional volatility, while men reported more preoccupation. Loss of control and independence, anxiety related to illness recurrence, uncertainty about the future and facing one's mortality significantly impacted HRQoL. Furthermore, while patients were more concerned with limb function, disfigurement and self-consciousness featured prominently in the discussion. Four adaptive coping styles were observed; positive reframing and optimism, finding a purpose, being proactive, and using humor. Among the maladaptive strategies were passive acceptance, avoidance and denial.

Conclusion: A patient-centered approach is crucial to understanding the impact of surgery, adjuvant therapy and the associated complications and toxicities for patients with extremity STS. Psychological well-being is an important domain in the HRQoL of patients with extremity STS. Clinicians should consider encouraging adaptive coping mechanisms such as positive reframing and optimism. Patients endorsing higher levels of psychological distress and maladaptive coping styles should be monitored and multidisciplinary strategies employed to optimize psychological function. Future directions include on-going international validation of this domain to inform the development of a sarcoma specific preference-based outcome measure.

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PAPER 32

A cross-species personalized medicine pipeline identifies the CRM1 export pathway as a potentially novel treatment for osteosarcoma

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Background: Osteosarcoma (OSA) is a rare, but disproportionately lethal cancer that predominantly affects children. Sadly, discovery of new therapies for OSA has largely been unsuccessful in the past 30 years; there is an urgent need to identify new treatments for OSA. Pet dogs with naturally-occurring OSA represent a unique comparative "model" to discover new treatments for OSA. Unlike humans, in which fewer than 1,000 cases of OSA occur each year, there are nearly 50,000 new cases each year of OSA in dogs. In addition, dogs have an intact immune system, a shared environment with humans, and more rapid progression of disease. Together these factors make dogs an important comparative model for new therapies for OSA.

Methods: We developed patient-derived cell lines and xenografts of OSA from both dogs and humans and applied these models to identify new therapies for OSA using high-throughput drug screens *in vitro* followed by *in vivo* validation. Whole exome sequencing was performed on the patient-derived models and original tumors to identify potential driver mutations.

Results: A high-throughput screen in both dog and human OSA identified CRM1 inhibitors as effective at killing dog and human OSA patient-derived cell lines *in vitro*. *In vivo*, CRM1 inhibition led to significant tumor growth inhibition in patient-derived xenografts from dogs and humans. Western blotting demonstrated increased levels of CRM1 protein expression across nine different dog and human OSA cell lines compared to non-transformed human osteoblasts. CRM1 upregulation in OSA cells was further verified by immunofluorescence staining. Increased CRM1 expression was prognostic for poorer metastasis-free survival and poorer overall survival.

Conclusions: Our cross-species personalized medicine pipeline identified CRM1 as a potential therapeutic target to treat OSA in both dogs and humans. Future studies are focused on testing CRM1 inhibitors in canine clinical trials.

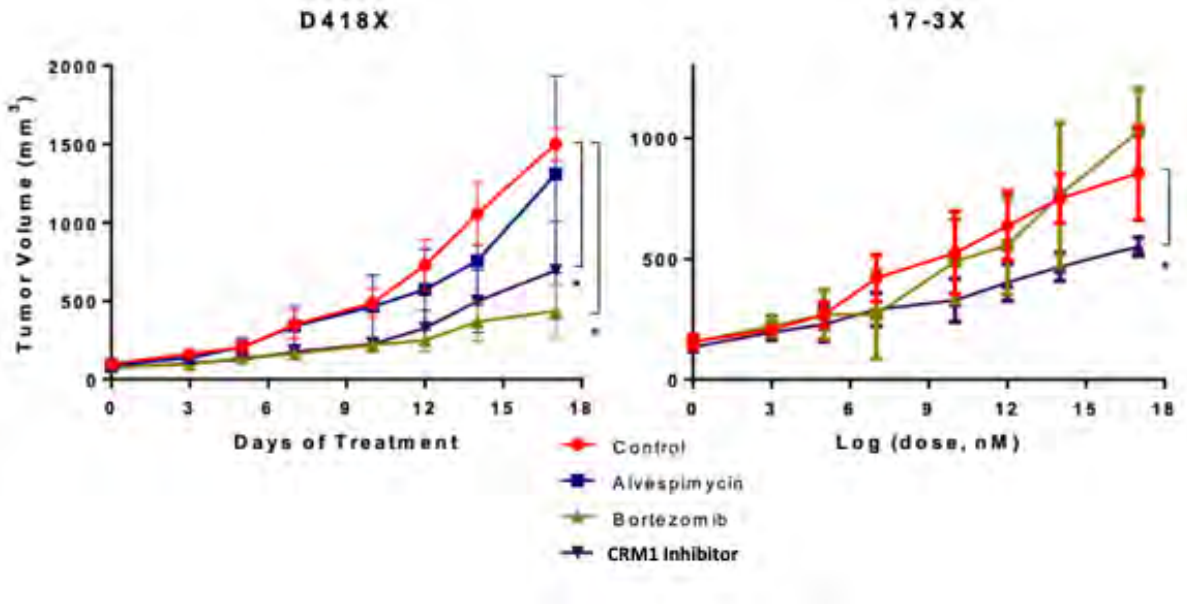

Figure 1. *In vivo*, CRM1 inhibition led to significant tumor growth inhibition in patient-derived xenografts from dogs (D418X) and humans (17-3X)

PAPER 33

Comparison of Cachectic and Non-cachectic Sarcoma Patients Reveals Differences in the Notch Pathway but Similarities in Myogenesis Inhibition

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Background: Cancer cachexia is a wasting syndrome that affects up to 50% of cancer patients. It is defined as weight loss ≥5% over 6 months and characterized by muscle atrophy, fatigue, and anorexia that are refractory to nutritional supplementation. Sarcoma describes a diverse group of malignancies arising from the connective tissues and is often related to musculoskeletal impairment. Sarcoma patients are uniquely susceptible to cachexia given its origins in the musculoskeletal system, but little is known regarding the underlying mechanisms of sarcoma-associated cachexia (SAC). Our previous research suggests that sarcoma cells contribute to SAC via dysregulation of muscle stem cell homeostasis by abnormal Notch signaling.

Questions/Purposes: 1-We hypothesized that cachectic patient sarcoma samples would display upregulation of genes in the Notch signaling pathway compared with non-cachectic patient sarcoma samples. 2-We also hypothesized that cachectic sarcoma patient samples would inhibit the differentiation of muscle-derived stem cells (MDSC), which is a potential mechanism for muscle atrophy.

Patients And Methods: After University of Pittsburgh IRB approval, sarcoma patient weights were collected for 6 months. Linear regression was performed to evaluate weight loss. According to the definition of cachexia (weight loss over 6mo ≥ 5%), sarcoma samples were classified into either the cachexia group or the non-cachexia group. Twelve cachectic and ten non-cachectic patients were selected. The sarcoma samples were minced and enzymatically digested using a human tumor dissociation kit. Primary cell populations were cultured until cells reached 80-90% confluence. Cells were then harvested and cryopreserved. RT-qPCR was performed to evaluate the expressions of Notch pathway factors (DLL1, JAG1, Notch1, Notch3, Hes1) from primary tumors, tumor cell cultures, and MDSCs. Data were normalized to the geometric mean of multiple internal control genes. Relative expression of mRNA was normalized to the non-cachectic group. The co-culture system was composed of MDSCs cultured in the lower chamber of a transwell plate and primary sarcoma cells in the upper chamber. After proliferation for 2 days and differentiation for 4 days, MDSCs were stained for f-MHC and DAPI (nuclear stain) to quantify fusion index and undergo RNA extraction. Data were analyzed using Mann-Whitney U test and presented as Mean ± SD. Statistical difference was defined by $p < 0.05$.

Results: There were significantly greater gene expression levels of *Notch1* and *Notch3* in fresh tumors from the cachexia group. Gene expression levels of *Jagged1*, *Notch1* and *Notch3* were significantly increased in primary cultured cells from the cachexia group. MDSCs co-cultured with primary sarcoma cells from both the cachexia and non-cachexia groups showed decreased fusion indices, increased Notch pathway gene expressions, and increased Pax7 expressions. Interestingly, we also observed a statistically significant (p=0.0083) association of metastatic disease among the cachectic patients compared with the non-cachectic patients.

Conclusions: Upregulation of the Notch signaling pathway is associated with SAC. Sarcoma cells from both cachectic and non-cachectic patients may elaborate factors and affect pathways that inhibit muscle differentiation independent of the Notch pathway. Further investigation is required to determine what these as yet undetermined factors might be, and if Notch inhibition is an effective strategy against SAC. Finally, the possible relationship between SAC and sarcoma metastasis must be explored.

Figure 1. Notch signaling pathway was upregulated in the cachexia group. A) Gene expression levels of Notch1 and Notch3 were increased in the tumors from cachexia group. B) Increased JAG1, Notch1 and Notch3 were maintained in primary cell culture of cachectic tumors. Mann-Whitney test, $p<0.05$.

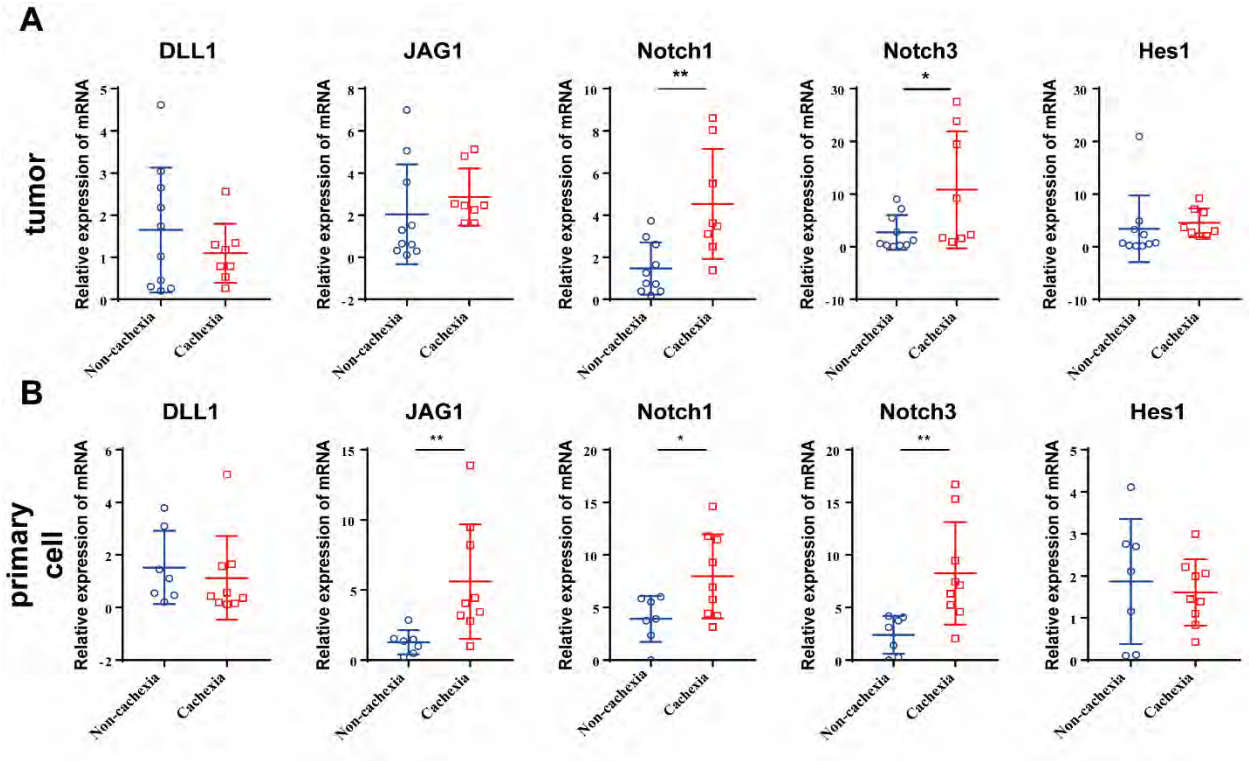
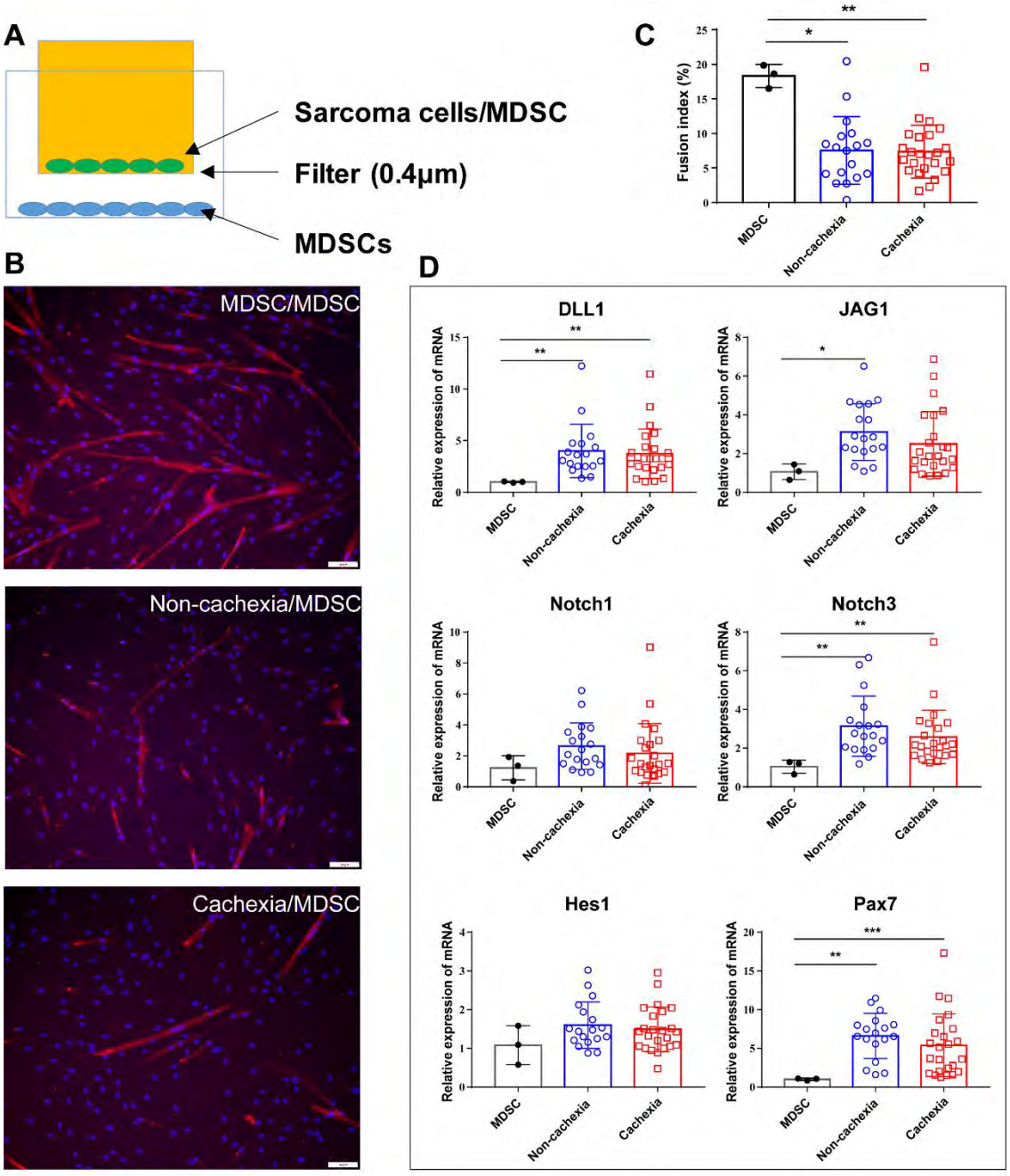


Figure 2. Cachectic and non-cachectic sarcoma primary cells inhibited muscle differentiation and upregulated Notch pathway and Pax7 in MDSCs. A) Schematic figure showing co-culture experimental design. MDSCs were co-cultured with cachectic, non-cachectic primary tumor cells or MDSCs (control group). B) Immunofluorescence images of MDSCs after co-culture (100x). C) MDSCs co-cultured with both cachectic and non-cachectic sarcoma primary cells showed decreased fusion index. D) Notch pathway and Pax7 were upregulated in MDSCs co-cultured with either cachexia (n=8) or non-cachexia (n=6) primary cells. All treatment groups were performed in triplicate.



PAPER 34

Systems-Wide Immunophenotyping Defines Distinct Malignancy-Induced Immunological Changes that Follow Disease Burden in an Immunocompetent K7M2 Orthotopic Murine Model of Osteosarcoma

Authors: Justin E. Markel, Amanda B. Stewart, Ryan A. Lacinski, Justin Vaida, Hillary Pratt, Ryan M. Reinbeau, Brock A. Lindsey

Background: Immunotherapies are revolutionizing the field of cancer therapy, but the majority of treated patients still do not show complete responses. Osteosarcoma is a tumor that, despite being immunologically "hot," has yet to respond favorably to immunotherapies including macrophage-activating agents and checkpoint blockades. These shortcomings are reflected in the body of published literature on the osteosarcoma immunophenotype, which is inconsistent and focused mainly within the primary lesion. This study is the beginning of describing and manipulating the systemic immune reactions that we know to be occurring; it is imperative to harness these immune reactions in a quest to develop successful immunotherapies in osteosarcoma.

Questions/Purposes: With data to support the importance of the systemic immune response to prevent and combat metastasis, we report a 24-color flow cytometry antibody panel that clearly defines key systems-wide immunological events occurring alongside disease progression, from the onset of disease to fulminant metastasis. To our knowledge, this study is the first to pinpoint key immunological disturbances and place them in the context of osteosarcoma disease progression using In Vivo Imaging Systems (IVIS) to quantify and visualize both location and magnitude of tumor burden.

Materials and Methods: In this longitudinal, systems-wide tissue analysis study, male and female tumor-bearing mice were followed from orthotopic luciferase-transfected K7M2 cell implantation in the tibia to primary tumor formation, followed by recurrence and/or lung metastasis while sampling blood, spleen, bone marrow, and lung tissue. Each tissue was subjected to a 24-color flow cytometry antibody panel to define distinct myeloid and lymphoid lineage immunological disturbances that occur in response to osteosarcoma disease progression.

Results: We have clearly defined a subset of immune cells whose overall percent and activation status accurately reflect disease burden. These cells include systemic percent populations of Natural Killer (NK) cells, CD4+ T helper (Th) cells, and CD8+ cytotoxic (Tc) T cells, all of which drastically decrease in both male and female tumor-bearing populations along the course of disease progression and are statistically decreased or trending across all tissues sampled in tumor-bearing mice at both primary tumor amputation (~4 weeks post-inoculation) and euthanasia (~8 weeks post-inoculation). A new metric of osteosarcoma disease burden was displayed during this analysis by using the level of PD-L1^{hi}MHC-II^{lo} monocytic-like myeloid-derived suppressor cells (M-MDSCs) to produce the PD-L1^{hi}/MHC-II^{lo} (P[1]/M[II] ratio); in blood, this ratio correlates positively with IVIS-positive disease burden ($R = 0.93$; $p = 0.003$) and effectively amplifies the immunological impact of disease burden so that it can be more easily monitored for future clinical utility. Tissue-wise, this ratio was significantly higher in tumor-bearing mice versus sham in lung ($p = 0.04$) and blood ($p = 0.04$), trending in marrow ($p = 0.054$), and not significant in

spleen ($p = 0.49$), potentially due to myeloid recruitment because of the trauma of the splenic biopsy. Importantly, the percent of NK cells in the blood was shown to trend negatively with the extent of disease burden as visualized by IVIS, $R = 0.7$; $p = 0.081$. Of the two tissues sampled over time (blood and spleen), the blood showed clearer trends that more directly reflected disease burden. Importantly, all immunological disturbances were shown to normalize upon disease clearance.

Conclusions: We report the first ever placement of osteosarcoma-induced immune disturbances in the context of disease progression which may have major implications on the success of immunotherapy in the future.

PAPER 35

Developing a Novel Spheroid Model for Chondrosarcoma Research and Drug Screening

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Background: Chondrosarcoma (CS) is a primary sarcoma of the bone whose histology resembles cartilage. CS has demonstrated resistance to both chemotherapy and radiation, and complete surgical removal is the only reliable treatment. In the setting of metastatic CS, survival is unlikely. Therefore, it is of importance that preclinical models mimic the disease with the greatest possible fidelity in order to reliably develop new treatments.

Cancer research has been performed for decades with two-dimensional (2D) cell culture. Despite its ubiquity, evidence suggests that 2D cell culture may not provide the most accurate representation of tumor biology. It has been demonstrated that three-dimensional (3D) cancer cell spheroids may recapitulate tumor biology with greater fidelity than traditional 2D techniques. This technology has not been widely reported in chondrosarcoma.

Questions/Purposes: We hypothesize that: 1- The further development of 3D CS spheroid models will provide a better recapitulation of human disease. 2- 3D CS cultures will enable more accurate predictions of novel treatments that are likely to be successful against CS.

Methods: Experiments were performed with the commercially-available HT-1080 CS cell line as well as KSCS, a patient-derived population from a high-grade CS. After University of Pittsburgh IRB approval and informed consent to participate in our tumor registry and tissue bank, CS patient samples were collected fresh from the operative theatre and were digested into single cell suspensions using a human tumor dissociation kit. Primary cells were cultured in flasks, trypsinized, and seeded into 96-well non-treated conical bottom plates with DMED medium containing 0.5% methylcellulose. After spheroid formation, they were monitored daily by brightfield microscopy. With the exception of tissue harvesting, spheroids from HT-1080 CS cells were created in an identical fashion. Spheroids were fixed using paraformaldehyde and embedded with 3% agarose. After isopropanol dehydration, paraffin-embedded spheroids were sectioned and slides were stained with hematoxylin and eosin. RNA was extracted from

2D cell cultures and day 14 spheroids. qPCR was performed to detect CS markers of interest including VEGFα, COL2A1 and COL10A1. Data were normalized by geometric mean of internal control genes (GAPDH, β-actin, 18S). 10,000 cells were seeded into 96-well plates for 2D culture and 3,000 cells in each well for 3D culture. After disulfiram and copper treatment for 48 hours, presto-blue was added to detect cell viability.

Results: Under bright field microscopy, spheroids are round and produce an extracellular matrix. H&E staining reveals that cell-cell attachments are more pronounced at the periphery of the spheroid structure while the core is less dense. Cartilage-like matrix can be observed in the KSCS patient-derived spheroids. In the HT-1080 cell line, VEGFα, COL2A1, and COL10A1 gene expressions are upregulated significantly in spheroids compared with monolayer cells. Disulfiram/copper has high cytotoxicity on HT-1080 cells grown in 2D monolayer, but 3D spheroids are highly resistant to this treatment.

Conclusions: We have demonstrated that the generation of 3D spheroid cultures with both CS cell lines and primary cells is feasible. Furthermore, we observed differences in gene expression and treatment susceptibility with the same CS cells grown under different conditions. CS spheroids demonstrate superior recapitulation of the primary tumor compared with CS cells grown in monolayer and might enable a more reliable path forward in the development of novel CS treatments.

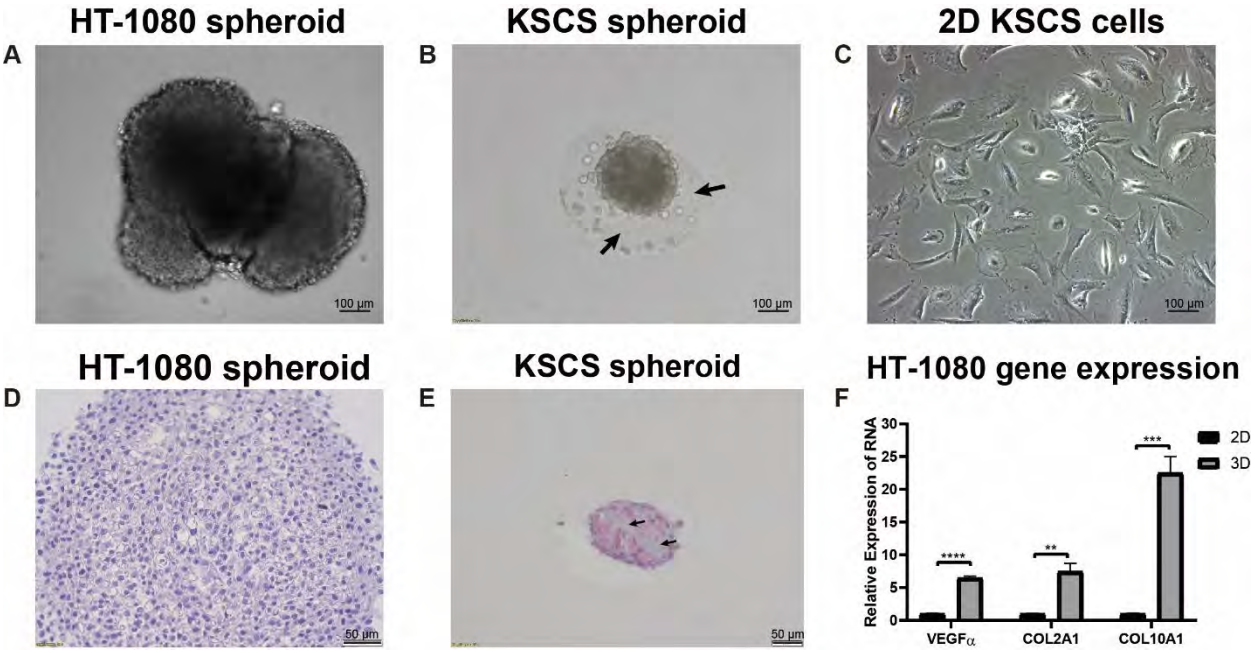

Figure 1. Characterizing 3D CS spheroid cultures in morphological and molecular aspects. A) Day 28 HT-1080 spheroid, 10X. B) Day 11 KSCS spheroid. The spheroid produces a matrix-like substance (arrow) at its periphery, 10X. C) Monolayer KSCS cells, 10X. D-E) H&E staining of HT-1080 and KSCS spheroids. In the KSCS spheroid, extracellular matrix (Arrow) is formed inside, 20X. F) VEGFα expression and CS markers COL2A1, COL10A1 expression are upregulated in the HT-1080 spheroid when compared to HT-1080 2D cultures. **p<0.01, ***p<0.001, ****p<0.0001.

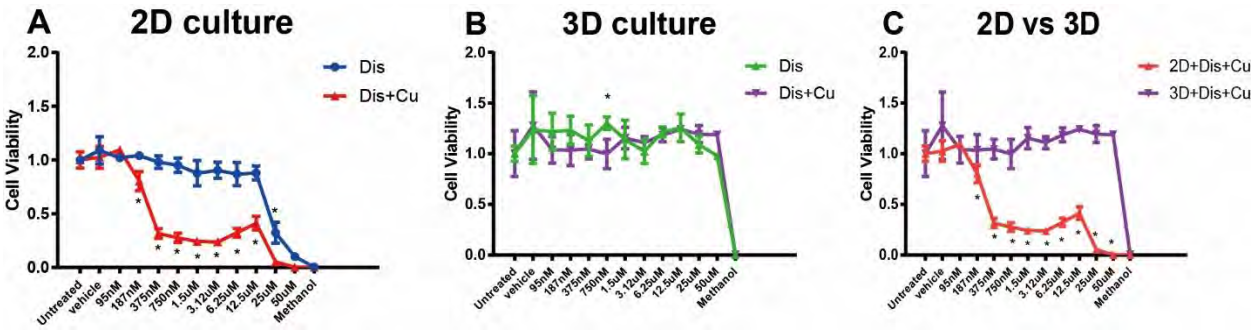

Figure 2. HT-1080 cells grown in spheroid demonstrate greater resistance to chemotherapy than cells grown in monolayer. A) In 2D culture, disulfiram has low cytotoxicity, whereas disulfiram plus 500nM copper decreases the IC50 dramatically. B) Both Disulfiram and Disulfiram/copper have little effect on spheroids. C) Compared to 2D culture, spheroids are highly resistant to Disulfiram/copper. *p<0.05.

PAPER 36

Copper Levels and ALDH1A1 Expression Varies Between Low and Highly Metastatic Human Osteosarcoma Cell Lines and Human Samples

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Background: Osteosarcoma (OS) is the most common primary malignancy of bone. OS undergoes metastasis preferentially to the lungs and is often chemo-resistant. We observed significant differences in both intracellular copper (Cu) levels and aldehyde dehydrogenase 1A1 (ALDH) gene expression between low and highly metastatic murine OS cell lines. Our results demonstrated that highly metastatic OS cells displayed significantly lower amounts of intracellular Cu and higher ALDH expression compared with less metastatic OS cells that display the opposite (high intracellular Cu and low ALDH). Disulfiram, an FDA-approved ALDH inhibitor and Cu chelator, showed effectiveness against murine OS cells in vitro and in our in vivo mouse model of metastatic OS. This study was designed to explore these phenomena and relationships in human OS cell lines and patient samples.

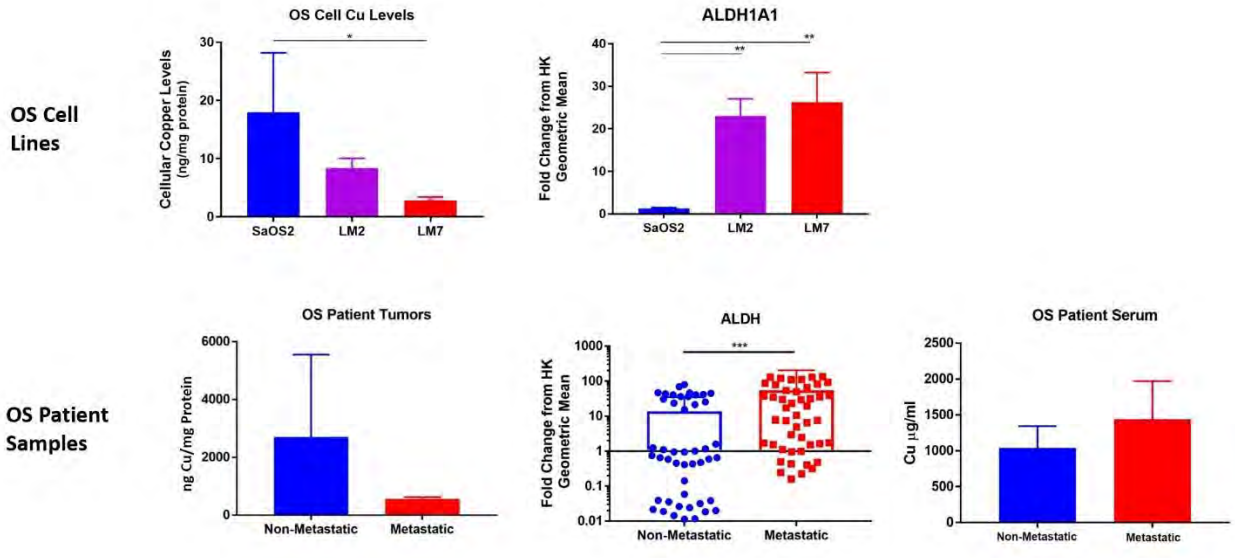
Questions/Purposes: 1-Determine endogenous intracellular Cu levels and ALDH expression levels in SaOS-2, LM2, and LM7 human OS cell lines. 2-Determine patient tumor and blood serum levels of Cu between metastatic and non-metastatic sarcoma patients.

Patients and Methods: SaOS-2, LM2, and LM7 human OS cell lines were generously provided by Dr. Eugenie S. Kleinerman (University of Texas MD Anderson Cancer Center) and cultured with 10% FBS in DMEM. SaOS-2 is the parental cell line from which LM2 and LM7 were derived. LM2 demonstrates low metastatic potential, and LM7 demonstrates high metastatic potential. OS patient tumors and serum were obtained from our clinical sarcoma registry and tissue bank. Protein was quantified using a protein assay (Bio-Rad) following the manufacturer's instructions. Cu concentrations were determined using a Perkin Elmer AAnalyst 600 atomic absorption spectrophotometer adjusted to detect Cu (324.8 nm). mRNA was collected from human OS cell lines as well as primary OS tumors using the RNeasy Kit (Qiagen), and cDNA was obtained using a Reverse Transcriptase Kit (Applied Biosystems). qPCR for ALDH was performed using SYBR Green Supermix (Bio-Rad).

Results: As was the case in murine OS cells, we observed that intracellular Cu is inversely proportional to metastatic phenotype in human OS cell lines (SaOS-2>LM2>LM7). Cu levels were significantly higher in less metastatic SaOS-2 compared with its highly metastatic variant LM7. qPCR showed that LM2 and LM7 have increased ALDH expressions compared with SaOS-2. Tumor samples from OS patients without detectable metastatic disease at the time of primary tumor resection demonstrated increased intratumoral Cu levels compared with patients with known metastatic disease. Conversely, serum Cu levels from OS patients with metastases demonstrated increased blood Cu levels compared with non-metastatic patients. ALDH expression levels were significantly increased in the tumors of metastatic sarcoma patients compared with non- metastatic patients.

Conclusions: We have demonstrated that human OS cells and tumors of varying metastatic potentials display significant differences in Cu metabolism and ALDH activity. Consistent with our observations in murine OS cells, highly metastatic human OS cell lines display decreased intracellular Cu levels and increased ALDH expression compared with less metastatic OS cells. Our analyses suggest that metastatic patients display decreased intratumoral Cu levels, increased blood levels of Cu, and higher ALDH expression.

We hypothesize that less metastatic OS cells have high intracellular Cu to facilitate processes such as proliferation, whereas metastatic OS cells actively pump Cu into their microenvironments to facilitate metastatic spread. High ALDH expression enables metastatic OS cells to withstand the oxidative stress of conventional chemotherapy. Disulfiram is an FDA-approved ALDH inhibitor and Cu chelator that could be utilized as a novel therapeutic adjuvant against metastatic OS. We will continue to test the efficacy of disulfiram, Cu compounds, and traditional chemotherapy drugs in combination to improve treatment success against highly metastatic OS.



PAPER 37

Cell Cycle Checkpoints p16 and p21 – Strong Predictors of Clinicopathologic Outcome in High-Grade Osteosarcoma

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Background: Osteosarcoma (OS) is the most common primary malignant bone tumor in children and adolescents. The mainstay of the treatment is a combination of neoadjuvant chemotherapy, surgical resection, and postoperative chemotherapy. Despite recent improvements in treatment modalities, the long-term survival of patients has remained the same for decades and 40% of patients die of their disease.

Histologic tumor necrosis in response to neoadjuvant chemotherapy has been used as a common prognostic factor for survival of osteosarcoma. Recently however, studies have suggested that evaluation of histologic response as currently interpreted failed to represent a strong prognostic factor relative to disease outcome.

To date, several biomarkers have been evaluated for prediction of survival of osteosarcoma patients; however published results are often contradictory. Our previous in-vitro work on cell lines established from human OS biopsies demonstrated the emerging role of the cell cycle, and spindle assembly checkpoint overrides in tumorigenesis in osteosarcoma. Our gene expression profile highlighted the significance of G1-S checkpoints p16 and p21, in OS cell proliferation, senescence, and response to chemotherapy when applied to monolayer cultured cells in vitro.

In this study, we sought to investigate the role of p16 and p21 as predictive markers of disease outcome in osteosarcoma.

Objectives: To determine the prognostic and predictive value of p16 and p21 in high-grade osteosarcoma.

Method: A total of 104 patients with primary high-grade osteosarcoma of extremities were included in this retrospective cohort study. All patients received contemporary standard neoadjuvant chemotherapy after initial diagnosis, followed by surgical resection. Initial biopsy materials were reviewed to confirm the diagnosis. Immunohistochemistry (IHC) for p16 and p21 performed on paraffin-embedded chemotherapy naïve biopsy specimens. IHC stains were evaluated and the percentage of positive cells estimated, the final results were categorized, and recorded independently by three pathologists. Clinicopathologic data including age at the time of diagnosis, gender, tumor size, clinical stage, margin status, percentage of tumor

necrosis after neoadjuvant chemotherapy, metastasis, recurrence, follow up time (months), and survival were recorded. Relationship of each marker to clinicopathologic outcomes was calculated using Chi-square, Fisher exact test, and ROC curve analysis.

Result: Greater than 90% expression of p16 in the initial biopsy is strongly correlated with good histologic response (i.e., more than 90% necrosis) to neoadjuvant chemotherapy ($p < 0.0001$), a lower rate of metastasis (p 0.0118), and a higher rate of patient survival (p 0.0294). High p16 expression (>90%) also has a stronger relationship to overall survival than does tumor necrosis. P21, on the other hand, shows a classic U-shape effect; p21 expression less than 1% or more than 50% is related to poor chemotherapy induced tumor necrosis (p 0.025), a higher rate of metastatic disease (p 0.002), and overall poor survival (p 0.0305). However, it does not appear to have a stronger relationship to survival versus tumor necrosis. ROC curve analysis shows the cumulative effect of p16 and p21 for predicting necrotic response to chemotherapy, metastasis, and survival compared to each marker individually. Multivariate logistic regression analysis shows p16, and combined p16 and p21 are independent predictors of response to chemotherapy and overall survival. P16, p21, and combined p16 and p21 are also independent predictors of metastatic disease.

Conclusion: Utilization of prognostic markers at the time of diagnosis, prior to any therapeutic intervention, has the potential to guide and perhaps modify the intensity of treatment and introduce new treatment modalities to maximize the response to treatment and ultimately improve the survival of the patients. Ours is the first study in which the predictive and prognostic value of a series of quantitative IHC stains for p16 and p21 in osteosarcoma examined relative to oncologic outcome. Our results demonstrate the strong independent predictive value of p16 and combined p16 and p21 for response to chemotherapy, overall survival, and metastatic disease.

PAPER 38

Safety and feasibility of the CIVO phase 0 platform for simultaneous evaluation of multiple drugs and drug combinations in the tumor microenvironment of cancer patients.

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Background: The high failure rate of investigational anti-cancer agents in the clinic suggests that current translational models of cancer frequently do not predict drug efficacy. The complexities of human solid tumors (genetics, microenvironment, heterogeneity) are not accurately modeled in mice. Genomic approaches to precision medicine have not completely addressed this issue. Better, more functional, and personalized approaches for understanding drug activities in the context of authentic tumors are needed. To address this need, the (Comparative In Vivo Oncology) CIVO® microinjection platform was designed specifically for intratumoral microdosing studies wherein multiple therapeutic agents, injected singly or in combination, are simultaneously evaluated and compared, directly within a patient's own tumor in situ. Biomarker and molecular analyses on the excised tissue enable assessment of localized tumor and tumor microenvironment (TME) responses to the injected drugs without exposing patients to systemic toxicities. This approach was evaluated in a multi-site feasibility study in patients with soft tissue sarcoma.

Questions/Purpose: The primary outcome measure was the quantification of fraction of cells positive for apoptosis and drug target engagement biomarkers around injected drugs. The secondary outcome measures included the number of patients with adverse events related to pain.

Patients and Methods: This was a single arm, pilot study designed to test the feasibility of using the CIVO system in patients with soft tissue sarcoma accessible for percutaneous injection. Subjects who were scheduled for surgical biopsy or tumor resection surgery were injected one to three days prior to surgery using the CIVO device. Minute volumes (up to 8.3 microliters) of saline (negative control) or microdoses of anti-cancer agents were percutaneously injected in a columnar fashion through each of 8 needles into a single enlarged solid tumor. Following the patient's biopsy surgery or tumor resection surgery, the injected portion and a small uninjected portion were used to determine each in situ drug response in the tumor. None of the data from this evaluation was used to make clinical decisions. Participants were followed for adverse events up to 28 days after microinjection. Thirteen patients with soft tissue sarcoma were prospectively enrolled. Inclusion criteria included accessibility for injection with

no impact on surgical resection, and exclusion criteria included tumors under 3 cm in any dimension. This trial is registered at ClinicalTrials.gov (NCT03056599).

Results: The study's primary objective was met, establishing the feasibility and safety of the CIVO platform. Device-related AEs were limited to transient Grade 1 non-serious events. Consistent with historical data, doxorubicin induced localized increases in markers for DNA damage, apoptosis, and immune cell infiltration in most patients, whereas gemcitabine did not induce any observable responses. Importantly, CIVO identified doxorubicin resistance in a patient that had previously failed anthracycline-based therapy. CIVO analysis also revealed potential mechanisms of resistance to systemic therapy, including PDGF and MAPK pathway upregulation.

Conclusions: CIVO enables safe and thorough characterization of drug mechanisms of action and the impact within a naturally occurring tumor. This study positions CIVO as a powerful research tool for translational oncology, via Phase 0 investigation of drug candidates, bridging the knowledge gap between cancer biology and clinical response.

PAPER 39

Mitigation of post-radiation muscle fibrosis using TGF-beta

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Background: Radiation induced fibrosis is a well described long term side-effect of external beam radiation therapy for cancer treatment. It can lead to a multitude of side-effects including pain, loss of function, and decreased quality of life. The mechanism of radiation fibrosis begins with inflammation, followed by fibroblast recruitment and activation with extracellular collagen matrix deposition. Transforming growth factor beta (TGF-β) is believed to play a central role in the development of radiation induced fibrosis, and is implicated in the recruitment of fibroblasts, and the activation of myofibroblasts to secrete excess collagen, fibronectin and proteoglycans – all of which result in increased thickness and stiffening of the affected tissue. In various experimental models, TGF- β inhibition has been shown to decrease the development of fibrosis. The role of TGF- β in scar formation and a fibrotic response has been shown in other models of organ injury, though has never been demonstrated in an animal model of radiation myofibrosis.

Questions and purpose: Does TGF- β inhibition decrease the development of muscle fibrosis induced by external beam radiation in a mouse model?

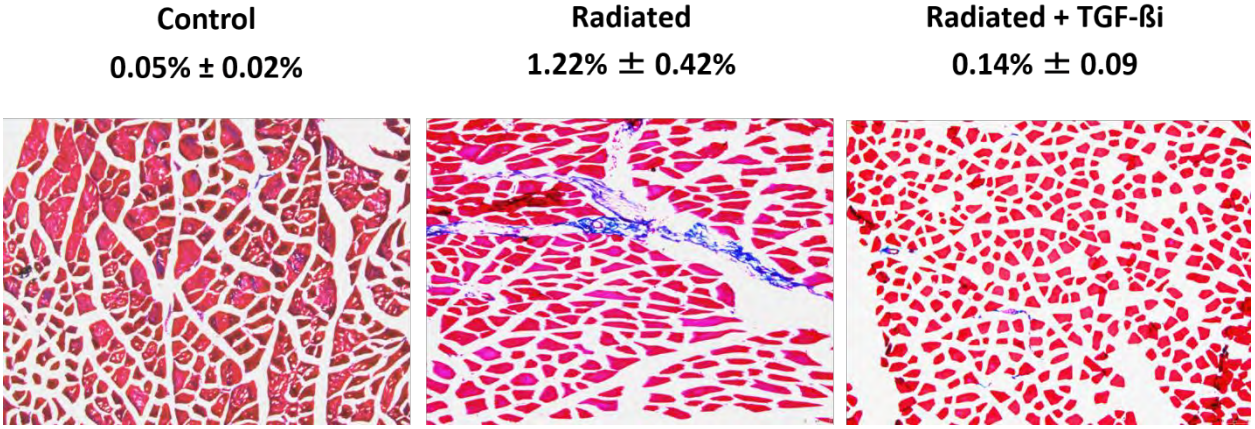
Methods: Twenty 12 week-old male C57/BI6 mice received 50Gray (Gy) of radiation to their right hindlimb. They were divided randomly into 2 equal groups: Group 1 (treated group)received daily intraperitoneal injections of TGF- β inhibitor (1mg/Kg) in a DMSO vehicle (TGF- βi group) for 6 weeks, and Group 2(radiation-only group) received the DMSO vehicle only for 6 weeks. Mice were sacrificed at 9 months following radiation, and the quadriceps of each muscle was sampled. Mason's Trichome stain was used to stain for muscle fibrosis. The staining demonstrates muscle in red, and collagen in blue. Slides were viewed at 10x magnification using bright field microscopy on a LEICA Microscope, and 5 representative images were captured per mouse using Leica Application Suite X (LAS X- Leica, Wetzlar, Germany). Quantification of fibrosis was performed using adobe photoshop CC 2019 (Adobe, San Jose, CA), using the Magic Wand tool to quantify pixel density in the red spectrum (muscle) and blue spectrum (fibrosis). The mean standard deviation of fibrosis pixel density between treated and radiation-only group were compared using Mann-Whitney-U non-parametric test. The ratio of fibrosis to muscle was also calculated using the average fibrosis per slide in the TGF- β inhibitor group to standardize measurements.

Results: In the 10 radiation-only group mice hind limbs, the mean percentage of fibrosis per slide was 1.22 ± 0.42%, compared to 0.13 ± 0.09% in the 7 evaluable TGF-βi group mice hind limbs ($p < 0.001$). (Figure 1) Mice that did not receive TGF-βinhibitor had a 9.1 fold higher density of fibrosis than mice that received TGF-βi.

Conclusion: In a radiated mouse muscle, TGF-βinhibition was associated with a significantly lower percentage of myofibrosis on histopathology. The hind limb muscles of mice that did not receive TGF-β inhibitors had 9.1 times more radiation-induced fibrosis than those that did not receive treatment. Further investigation into the potential role of TGF-β inhibition in animal models may aid in the development of novel therapeutic options to mitigate this complication of radiation treatment.

Figure 1

Histopathology photomicrographs demonstrating muscle fibrosis . The mean fibrosis per slide was significantly lower in the irradiated mice treated with TGF-ßi when compared to mice that were irradiated and did not receive treatment ($p<0.001$). Despite this improvement with TGF-ßi treatment, mice treated with TGF-ßi still did have a significant increased rate of fibrosis compared to the control mice ($p=0.009$)



PAPER 40

Treatment of Soft Tissue Sarcoma with a Novel Cold Plasma Jet

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Background: Soft tissue sarcoma is a malignancy that most often develops in adults, but can occur in children as well. Treatment with radiation, en bloc surgical resection and chemotherapy have achieved long-term survival rates up to 65% to 80% in non-metastatic disease. Local microscopic tumor cells can still exist despite complete R-0 surgical excision of the tumor leading to local recurrence. Cold Atmospheric plasma (CAP) is an emerging technology, which can potentially be utilized at the time of surgery, has shown promising anticancer effects in many other types of malignancy. CAP treatment may have the potential to improve the outcome of sarcoma patients by decreasing local recurrence rates if utilized at the time of surgery. There is still no evidence as to whether the use of CAP has any effect on sarcoma cells.

Questions/Purpose:
1. Does CAP have an anticancer effect on soft tissue sarcoma cell lines compared to a control group?
2. If there is an effect on the sarcoma cells, is it time or power dependent?

Patients and Methods: CAP was generated using a US Medical Innovations LLC (USMI) SS-601 MCa high-frequency electrosurgical generator (USMI, Takoma Park, MD, USA) integrated with Canady Cold Plasma Conversion Unit and connected to a Canady Helios Cold Plasma Scalpel. Three types of human sarcoma cells, synovial sarcoma (SW982), connective tissue fibro sarcoma (HT-1080), and rhabdomyosarcoma (RD) were used in this study to test the effect of the CAP generated by the Canady Cold Plasma Conversion System. Cells were treated with various CAP settings including different helium flow rates (1 and 3 LPM) and power settings (20-120p) in order to establish an optimal treatment condition for each cell line. Viability was performed on the cells using MTT assay 48 hours after CAP treatment. Student t test was performed on the data (*$p<0.05$).

Results: The reduction of the viability of all three sarcomas were dose-dependent and significantly reduced at various time and power combinations tested (Figure 1-3). Helium flow alone did not significantly impact cell viability.The decreasein viability of the sarcoma cells when using 1 LPM required a higher dose. About 20 to 40% of viability reduction was seen on the three cell lines. With 3LPM, viability was reduced to 20% using 80p 2 min for SW982 and HT-1080, and 100p 2min for RD.

Conclusion: Our data demonstrates that CAP reduced sarcoma cell viability in a time- and power-dependent manner. With optimal dosage for each cancer type, this study provides a promising treatment for future therapeutic interventions for soft tissue sarcomas. Future studies may include animal sarcoma models investigated the efficacy of CAP.

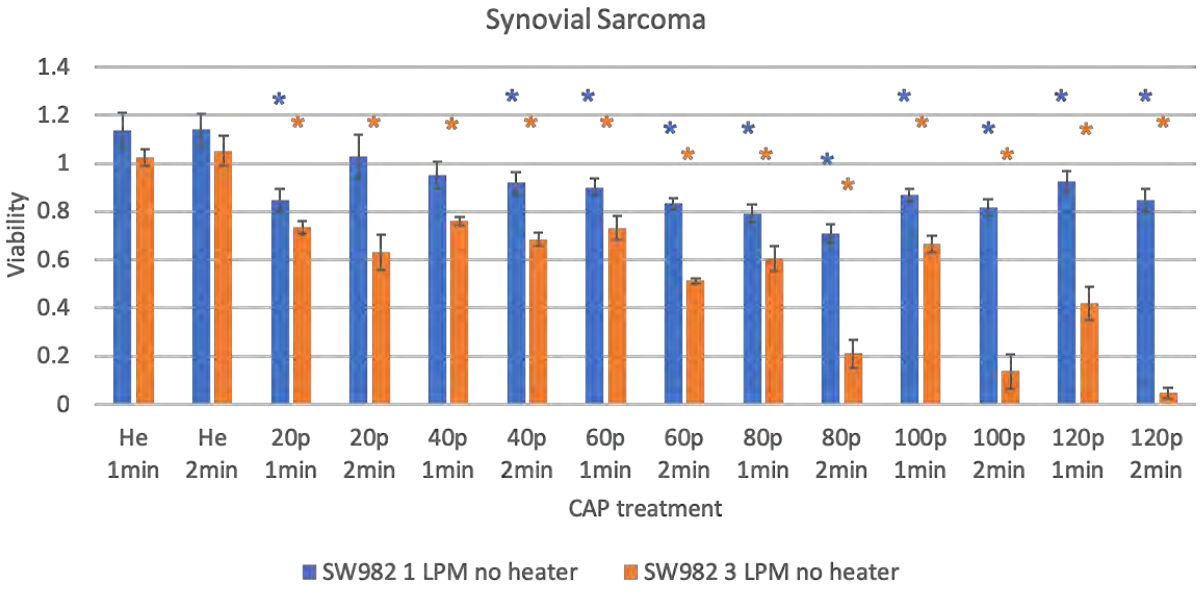

Figure 1 Viability of synovial sarcoma 48 hr post CAP treatment

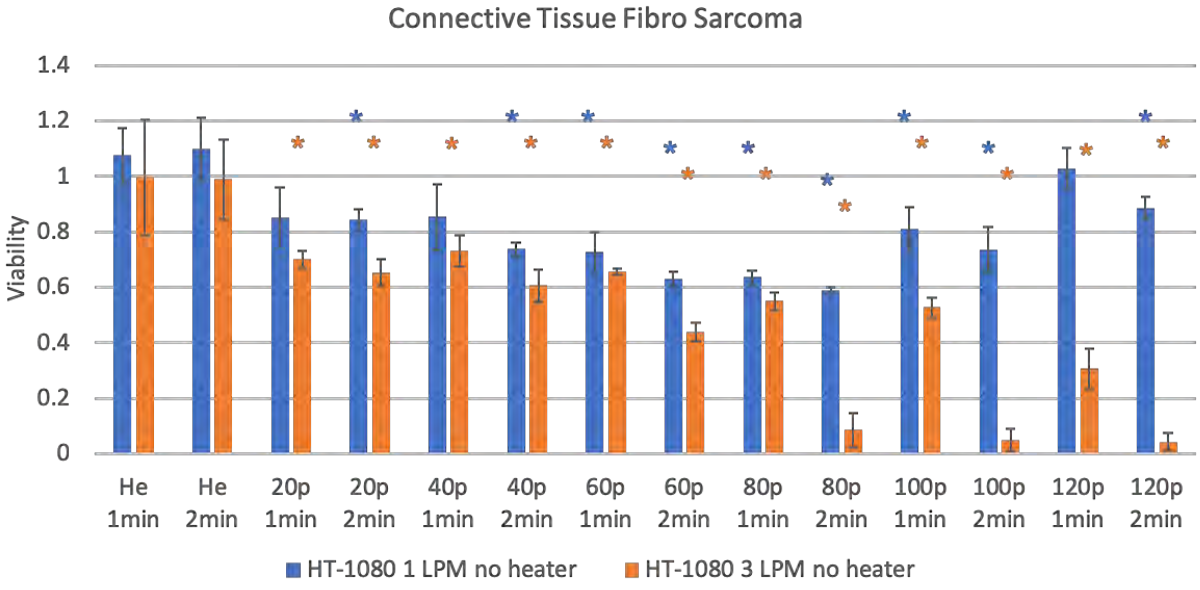

Figure 2Viability of connective tissue fibro sarcoma 48 hr post CAP treatment

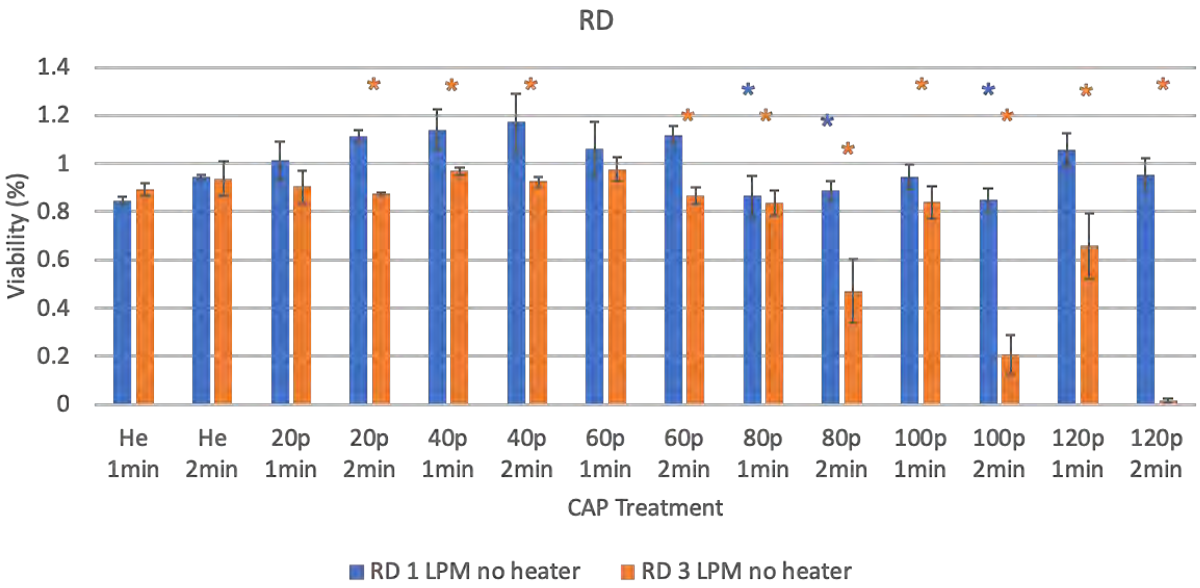

Figure 3Viability of rhabdomyosarcoma 48 hr post CAP treatment

PAPER 41

The Downstream Revenue Impact of a Dedicated Orthopaedic Oncologist

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Background: With so few orthopaedic oncologists in the country, each one serves as a gateway for patient care within their health system that expands beyond the revenue attributed to the initial outpatient office visit or surgical encounter. With increasing competition between physician-practices, hospitals and health systems, all of the revenue associated with each new patient that an orthopaedic oncologist brings into a system of care should be counted as the return on investment for this subspecialty provider's practice.

Purpose: Therefore, the purpose of this study was to quantify the downstream revenue generated by patients that are brought into the health system through a dedicated orthopaedic oncology practice.

Patients and Methods: This was a retrospective single-center review of an orthopaedic oncologist's new patients for an entire year. Any patient previously seen within the health system was excluded. All charges generated and payments collected from those patients were aggregated for the following two years. Once aggregated, a ratio-driven analytical model was developed to highlight the potential systemic return for an institution investing in an orthopaedic oncologist.

Results: For every professional fee dollar collected by the orthopaedic oncologist, the health system collected $38.11 in downstream net income. When adjusted for 1.0 clinical FTE, the ratio of professional fees (PF) to health system fees (HF) collected was $1 PF = $42.35 HF. The aforementioned results are unique to the payor mix of this academic medical center. When the data was normalized to the expected Medicare payment rates for the physician and the hospital, the downstream revenue impact of an orthopaedic oncologist provided an additional twenty six-fold return ($1 PF = $26.35 HF).

Conclusions: The gateway model suggests that, at a minimum, an academic, tertiary and quaternary medical institution could receive a twenty six-fold return on each professional dollar collected for an orthopaedic oncologist. Based on these results, a sound institutional strategy would be to increase the referral streams to orthopaedic oncology versus diluting the physicians' efforts into other sub-specialty work that does not open the gateway to new downstream net payments.

Level of Evidence: III

PAPER 42

Are We Training Too Many Orthopaedic Oncologists?

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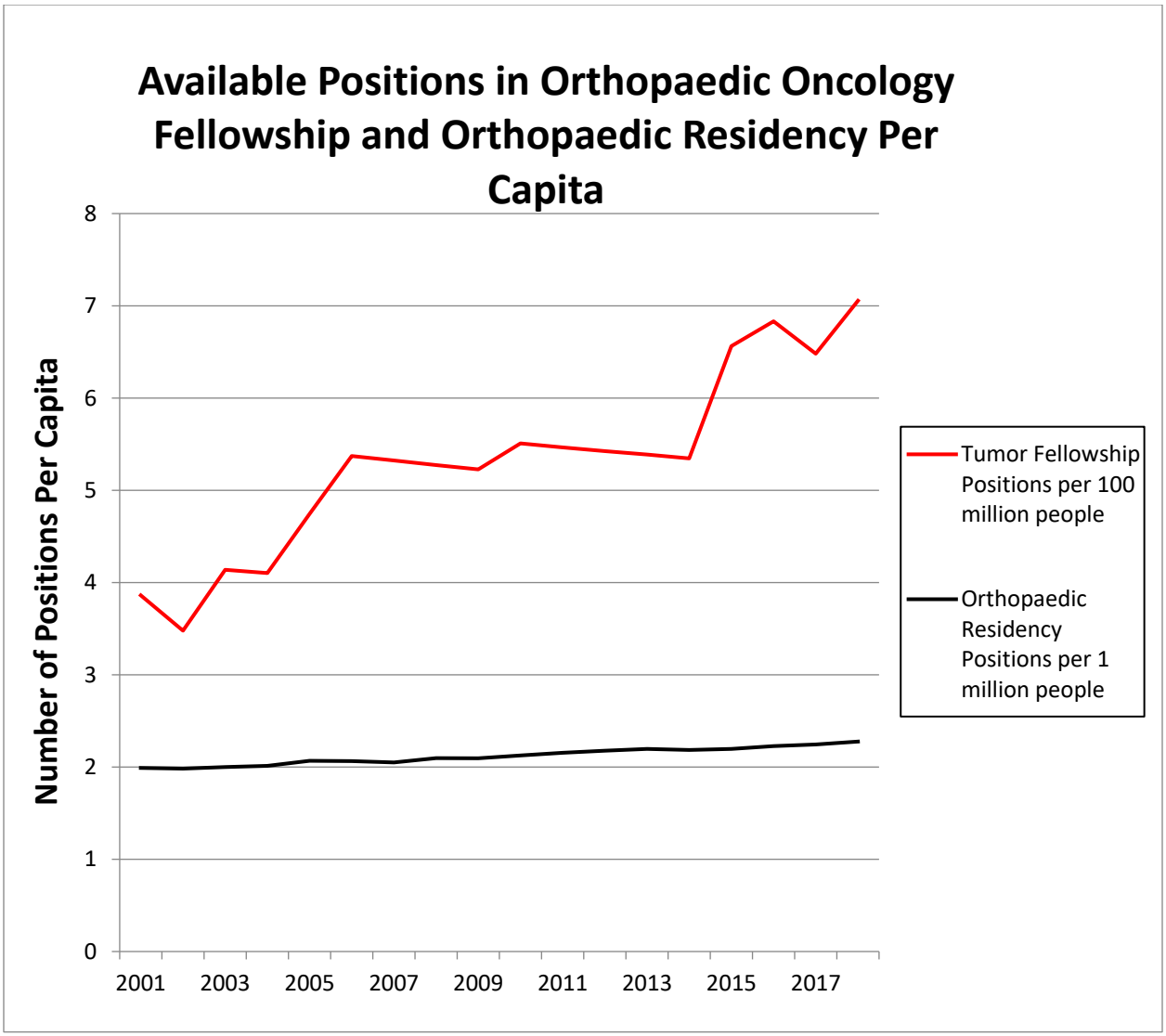
Background: There is a pervasive sentiment within the field of orthopaedic oncology that the job market is becoming increasingly competitive. Over a decade ago, DiCaprio suggested there may be challenges facing those considering orthopaedic oncology as a career, chief among them low number of sarcomas seen in the United States[1]. There is recent evidence that early career orthopaedic oncologists are performing less tumor surgery[2]. In fact, there has been a decline in percentage of oncologic procedures reported by fellowship trained tumor surgeons taking ABOS part II. Additionally, about one quarter of recent trainees also obtained second fellowships[3]. It is unclear if this is due to perceived career challenges or a desire to have a mixed practice. We set out to quantify the number of trainees in relation to the US population, incidence of sarcoma, and the number of orthopaedic residency positions.

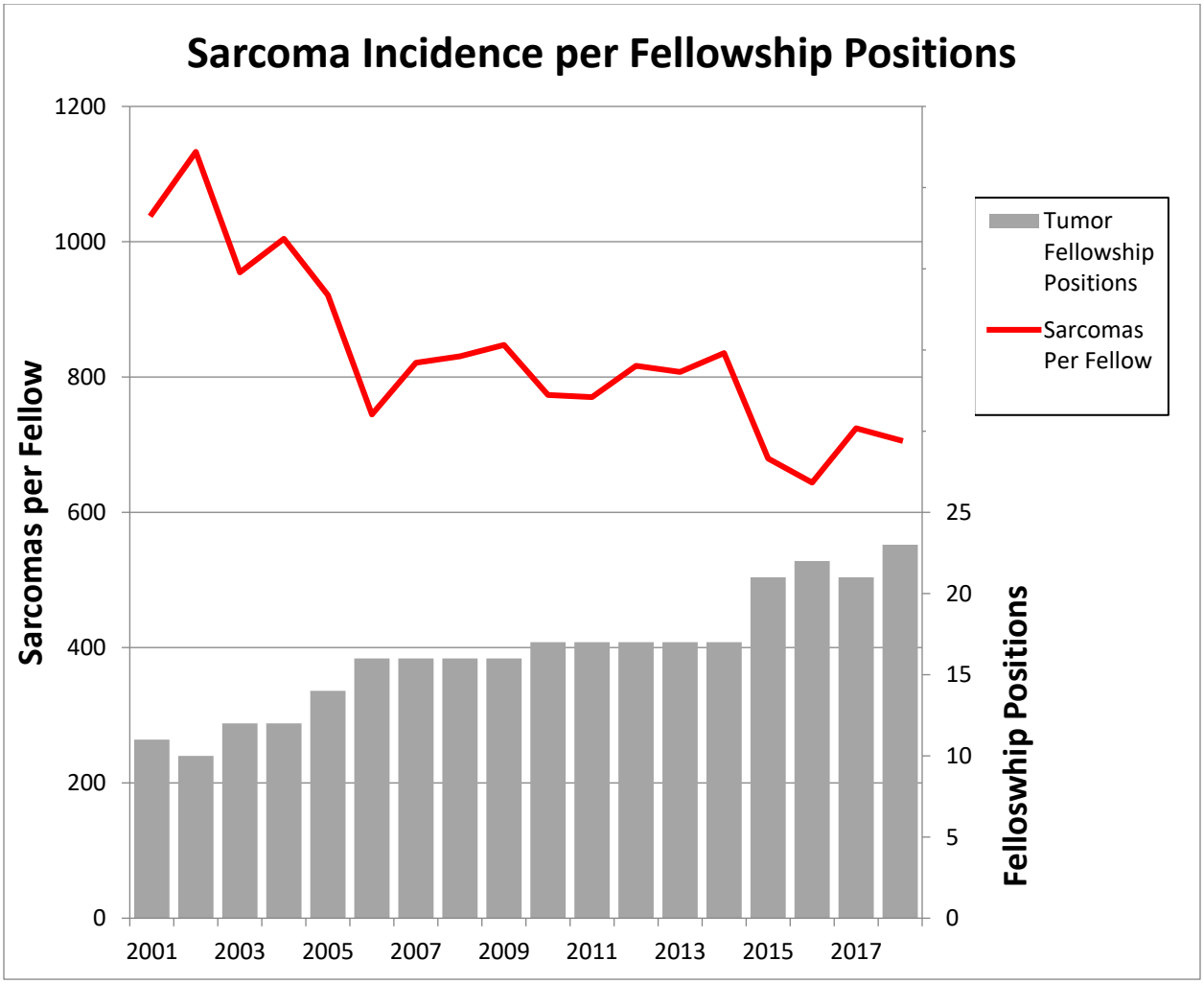
Questions/Purpose:
1. How many orthopaedic oncology fellowship positions are available?
2. How many orthopaedic residency positions are available?
3. Is the number of oncology fellowship positions increasing per capita?
4. What is the relationship of fellowship positions and sarcoma incidence (How many sarcomas per fellow)?
5. Is the proportion of fellowship positions increasing relative to the number of orthopaedic surgery trainees?

Patients and Methods: The absolute number of fellowship trainees is less important than the proportion relative to the population served and incidence of sarcoma. Therefore, the SEER database was used to identify the incidence of bone soft tissue sarcomas from 1998-2018 (mean 12,901, range 10,471-16,250). Population statistics from 1998-2018 were acquired from the United States census. The number of orthopaedic fellowship positions available was obtained from the San Francisco Match for 2012-2018. However, since this data is incomplete prior to 2012, ACGME records were used from 2001-2012. The National Residency Match Program (NRMP) furnished data on the number of available orthopaedic residency positions over the same time interval. Orthopaedic oncology fellowship positions were compared to orthopaedic residency positions, per capita. The number of fellowship positions was also compared to the incidence of sarcomas in the United States. It is important to note that SEER data for 2017-18 and US census data for 2018 were estimates.

Results: The incidence of bone and soft tissue sarcoma per capita has increased over the last 20 years but was not statistically significant. The number of orthopaedic oncology fellowship positions was 11 in 2001 and 23 in 2018. Per capita, that is an increase from 3.86 to 7.06 per 100 million people. By comparison, orthopaedic residency positions have increased from 567 to 693 (1.99 to 2.28 per 1 million people) over the same time interval. The proportion of tumor fellowship positions compared to residency positions has also increased from 1.94% to 3.10%. Comparing the number of fellowship positions to US bone and soft tissue sarcoma incidence (i.e. the number of sarcomas per fellow per year) revealed a decrease from 1,041 to 706. Linear regression analysis revealed a significant change over time for US population, sarcoma incidence, residency positions, and fellowship positions ($r = 0.99, 0.94, 0.99, 0.95$. $p < 0.001$), but a significantly higher rate of change per capita for tumor positions ($b = 0.174$, CI=0.14-0.21) vs residency positions ($b = 0.017$, CI=0.016-0.018).

Conclusions: The number of available orthopaedic oncology fellowship positions has more than doubled since 2001. Per capita, this has out-paced the incidence of sarcoma and the number of orthopaedic residency trainees. When compared to the number of residents entering training, the proportion of oncology positions available has increased 50%. Additionally, the number of sarcomas per fellow has decreased substantially over this same time period. There are many limitations to this study including assuming every position gets filled, fellows taken outside the match, foreign medical graduates returning abroad after training, and assuming all fellows pursue oncology practice. Applicants are likely drawn to orthopaedic oncology because it is rewarding and intellectually challenging. However, they should be aware the field is becoming increasingly competitive. Many fellowship trained tumor surgeons are pursuing second fellowships and this may be due to the perceived challenges outlined above or may reflect the desire to have a mixed practice or make themselves more “marketable”. One area of opportunity may be embracing metastatic bone disease. This may shift the supply-demand curve in favor of the physician desiring to practice full-time oncology. Managing expectations of early practice is critical. As a rewarding subspecialty, many talented and engaging people are drawn to orthopaedic oncology and it is important they be equipped with data that helps them achieve success and fulfillment with their career choice.


Available Positions in Orthopaedic Oncology Fellowship and Orthopaedic Residency Per Capita
Number of Positions Per Capita
0
1
2
3
4
5
6
7
8
2001
2003
2005
2007
2009
2011
2013
2015
2017
Tumor Fellowship Positions per 100 million people
Orthopaedic Residency Positions per 1 million people



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PAPER 43

Statistical Fragility of Surgical and Procedural Clinical Trials in Orthopedic Oncology as Quantified by The Fragility Index: A Systematic Review

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Background: The Fragility Index is a powerful statistical tool that can be used to assess the statistical strength of a study outcome, and represents how many patients would be required to convert a trial from being statistically significant to not significant. No studies to date have used the Fragility Index to evaluate surgical and procedural clinical trials in the orthopedic oncology literature.

Questions/Purposes: The primary purpose of this study was to use the Fragility Index to evaluate the statistical strength of widely cited surgical and procedural clinical trials in orthopedic oncology. A secondary goal of this study was to examine what features of orthopedic oncology clinical trials are associated with greater statistical fragility.

Patients and Methods: We performed a PubMed search for orthopedic oncology trials in the highest impact orthopedics-focused, oncology-focused and general medicine journals. For each study included in this analysis, we calculated the Fragility Index for all identified dichotomous, categorical outcomes.

Results: We identified 23 studies with 48 outcomes. Twelve of these outcomes were statistically significant, and 36 outcomes were not statistically significant. The median Fragility Index for statistically significant outcomes was 2, which is comparable to those of other orthopedic subspecialties.[1-5] Nine papers reported number of patients lost to follow-up. In these papers, the number of patients lost to follow-up was greater than the Fragility Index for a majority of outcomes (65%). Fragility Index was strongly positively correlated with patient sample size ($p<0.001$).

Conclusions: The orthopedic oncology literature has substantial statistical fragility, though is comparable to other orthopedic subspecialties. A high number of patients lost to follow-up and small sample sizes likely contribute to this statistical fragility. This study highlights the need for multi-center, cooperative studies to increase the robustness of clinical research in orthopedic oncology.

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Table 1. Surgical and Procedural Clinical Trials in Orthopedic Oncology, By Journal

Journal Name	Number of Publications included in Analysis
Cancer	6
Clinical Orthopaedics and Related Research	5
Journal of Clinical Oncology	3
Orthopaedics	2
Annals of Oncology	1
Clinical Spine Surgery	1
European Spine Journal	1
International Orthopaedics	1
Journal of Bone and Joint Surgery	1
Journal of Hand Surgery	1
Journal of Spinal Disorders and Techniques	1
Spine	1

Table 2. Publication-Level Associations between Fragility Index and Study Variables

Study Variables	Pearson Correlation Coefficient	P-Value
Patient Sample Size	0.846	<0.001
Relative Citation Ratio	0.321	0.179
Publication Year	-0.365	0.087
Number of Article Citations	0.043	0.850
Journal Impact Factor	0.192	0.380
Number of Journal Citations	-0.035	0.878

PAPER 44

Outcomes in Metastatic Bone Disease: A Comparison of Academic and Community Programs Using the National Cancer Database.

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Background: Treatment of patients with metastatic bone disease (MBD) is changing rapidly. With the advent of biologic therapy survival is improving, including among those with advanced disease. Patients with bone metastasis frequently require orthopaedic intervention. Treatment for actual or impending pathologic fracture incorporates factors such as histology, extent of disease, life expectancy, functional capacity, and patient preferences. It has been established that treatment in high-volume centers is associated with improved survival in sarcoma and other malignancies. Treating metastatic cancer can necessitate resource-intensive care and requires the expertise of an integrated multi-disciplinary team for the best outcomes. It is for these reasons we hypothesized treatment of MBD at academic centers would be associated with improved survival.

Questions/Purpose:
1. Is overall survival of patients presenting with MBD and myeloma improved with treatment in academic cancer centers?
2. Are patient characteristics in MBD and myeloma different between those treated in academic versus community cancer centers?

Patients and Methods: All National Cancer Center Database (NCDB) records from 2004-2016 were evaluated which included 64 histologic subtypes (n=14,002,785). Of these, 2,306,824 had stage IV disease at diagnosis, and 239,943 had available data on both bone metastases and type of treatment facility. Added to these were 109,543 myeloma patients, as they have bone involvement by definition. Academic center was defined using the Commission on Cancer facility designation as reported in the NCDB as an Academic/Research Program (including NCI-designated comprehensive cancer centers). Overall survival from time of diagnosis represented the primary endpoint and was estimated by Kaplan-Meier method with log-rank test for significance. For tumor subtype analyses, only those with >1,000 MBD patients were considered. Continuous variables were compared via Wilcoxon test, categorical variables with Chi-squared, and multivariable Cox models adjusted for confounders. Significance was set at $p<0.05$ and the false-discovery-rate correction adjusted for multiple comparisons.

Results: Among all patients, those treated at academic centers survived significantly longer than those treated elsewhere (median 16.3 vs. 9.3 months, $p<0.0001$). When considering individual histologic subtypes with greater than 1,000 patients, 16 out of 19 tumor types had significantly better survival when treated at academic centers.

The proportion of MBD patients treated at academic centers varied significantly across tumor types and ranged from 26.3% of "other" lung cancers to 48.1% of thyroid cancers (median 35.9%). Myeloma patients had better survival than other tumor types (median 49.2 vs. 7.3 months). When analyzed separately, significantly better survival was observed in both groups at academic centers (63.5 vs. 39.2 months for myeloma, 8.8 vs. 6.5 months for other tumors, $p<0.0001$ for both).

Patients at academic centers were significantly younger (median 65.0 vs. 68.0 years) and had lower Charlson comorbidity scores (mean 0.37 vs. 0.48, $P<0.0001$ for both), yet after correcting for histology, age, Charlson score, insurance status, race, and sex, treatment at an academic center remained independently associated with significantly improved survival (multivariable HR 0.84, 95% confidence interval 0.83-0.85).

Conclusions: In patients with metastatic bone disease at diagnosis, treatment at an academic center was associated with significantly better survival. This difference was even more profound when including multiple myeloma. Although a survival advantage was demonstrated in most cancers, the range of overall survival varied significantly among histologic subtypes. The most pronounced difference was seen in myeloma, prostate and kidney; all of which are commonly treated by orthopaedic surgeons. Unexpectedly, patients treated in academic centers were younger and healthier than those treated elsewhere, potentially indicating referral bias. Despite these differences, multivariable correction for these and other confounders identified treatment at academic centers was independently associated with better survival. The etiology of this survival advantage remains unclear but is likely multifactorial. Some factors that may account for this difference include facility volume, a multi-disciplinary team approach to care, and participation in research and clinical trials.

There are limitations to this study including the inability of the NCDB to delineate patients that transfer care between facilities. Additionally, it does not capture individuals that go on to develop bone metastasis after initial diagnosis. It is unknown how many patients will eventually develop MBD but this subset of patients will be a critical part of understating the scope of this disease process. Although the survival advantage seen in academic centers cannot be attributed to orthopaedic care, many of these patients will require orthopaedic intervention. Therefore, it may be necessary to re-evaluate our approach and develop guidelines for the treatment of metastatic bone disease. This area certainly warrants further investigation and may lead to MBD patients being referred to academic centers or development of protocols that aim to narrow the survival gap between institutions.

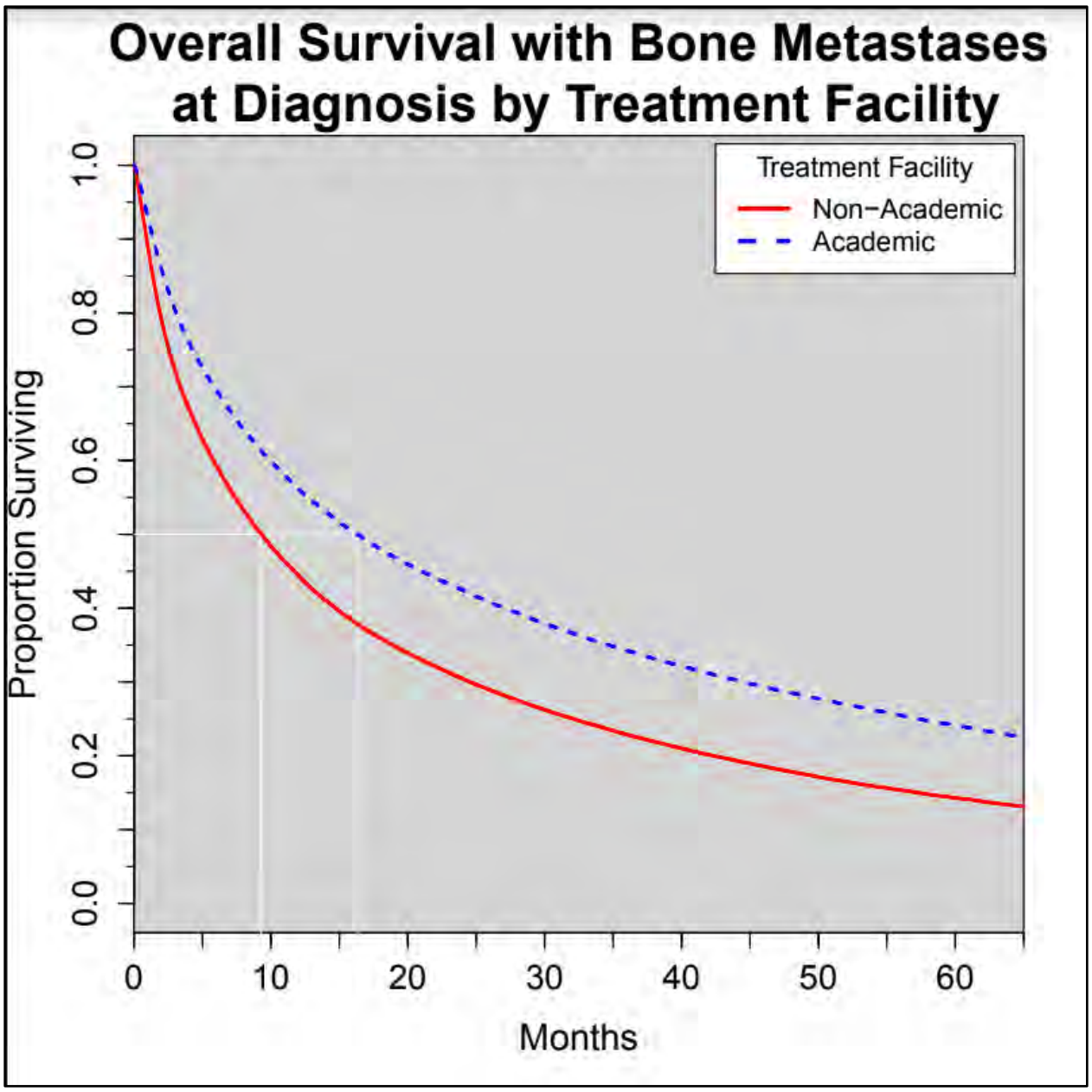

Fig 1: Overall survival in patients with bone metastases and myeloma based on treatment at an academic center (blue dashed line ,n=120,880) or community center (red solid line, n=214,181). Median survival (white line) was significantly longer among patients treated at academic centers (16.3 vs. 9.3 months, p<0.0001)

Treatment Facility and Survival for the 8 Most Common Malignancies with Bone Involvement at Diagnosis

Primary Malignancy	Number of Patients	Median Survival (mo.) (IQR)	Academic Center	Median Age (IQR)	Mean Charlson Score	Survival (mo.) by Facility Type	Academic Center HR for death (95% CI)
Myeloma	109,543	49.2 (48.6-49.9)	No	**70** (61-78)	**0.42**	**39.2** (38.5-39.9)	0.64 (0.62-0.65)
			Yes	**64** (57-72)	**0.33**	**63.5** (62.1-64.6)	
NSCLC	90,015	4.6 (4.6-4.7)	No	**68** (60-76)	**0.55**	**4.3** (4.2-4.3)	0.83 (0.82-0.84)
			Yes	**66** (58-74)	**0.46**	**5.4** (5.3-5.5)	
Breast	35,739	27.1 (26.7-27.6)	No	**64** (55-73)	**0.3**	**24.8** (24.2-25.5)	0.87 (0.84-0.89)
			Yes	**61** (53-70)	**0.23**	**29.2** (28.5-30.3)	
Prostate	30,411	25.3 (24.9-25.8)	No	**73** (64-82)	**0.41**	**22.9** (22.5-23.4)	0.74 (0.72-0.76)
			Yes	**69** (61-78)	**0.31**	**30.3** (29.5-31.2)	
Lung SC	20,598	6.5 (6.3-6.6)	No	**67** (60-74)	**0.68**	**6.3** (6.1-6.4)	0.91 (0.88-0.94)
			Yes	**66** (59-72)	**0.58**	**6.9** (6.7-7.2)	
Kidney	11,326	7.4 (7.1-7.7)	No	**67** (59-76)	**0.46**	**6.3** (6.0-6.6)	0.79 (0.76-0.82)
			Yes	**64** (57-72)	**0.37**	**9.0** (8.5-9.7)	
Lung (other)	8,575	1.5 (1.4-1.5)	No	**74** (66-83)	**0.69**	**1.3** (1.3-1.4)	0.81 (0.77-0.85)
			Yes	**72** (63-80)	**0.59**	**1.8** (1.7-2.0)	
Pancreas	6,017	2.9 (2.8-3.1)	No	**68** (60-76)	**0.52**	**2.6** (2.5-2.7)	0.81 (0.77-0.86)
			Yes	**65** (58-73)	**0.45**	**3.5** (3.3-3.8)	
TOTAL	340,979	11.5 (11.4-11.6)	No	**68** (60-77)	**0.48**	**9.3** (9.2-9.4)	0.72 (0.71-0.72)
			Yes	**65** (57-73)	**0.37**	**16.3** (16.1-16.6)	

*Bold indicates significance at p<0.001

PAPER 45

Survival in patients with carcinomas presenting with bone metastasis at diagnosis: A SEER population-based cohort study

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Introduction: Bone is the third most common site of metastatic disease in patients with carcinomas, and it's a common reason of consult for musculoskeletal oncologists. The presence of bone metastases (BM) is usually associated with terminal-stage illness. Having other synchronous metastases in addition to bone metastases has been associated with impaired prognosis compared with isolated bone metastasis in patients with primary gynecological or prostate cancer. For other carcinoma types, this information is not available in a population-based setting. We hypothesize that survival for other carcinomas will follow the same pattern, being better when no synchronous metastases are observed.

Purpose: The purpose of this study was to (1) Identify the most common carcinomas presenting with bone metastasis at diagnosis, and to analyze (2) The survival of patients with carcinomas and BM at diagnosis, and (3) The effect on survival of synchronous metastasis to BM within that population based on a large population analysis.

Methods: Patients diagnosed with carcinoma between January 2010 and December 2015 were identified from the Surveillance, Epidemiology and End Results (SEER) database. Patients with other type of malignancies were excluded. The most common carcinomas presenting with BM at diagnosed were identified. Survival based on the presence of BM and synchronous metastases (lung, brain, liver, lymph nodes) was evaluated with Kaplan-Meier analysis. Five-year survival (%) and their corresponding 95% Confidence Intervals (CI) stratified by carcinoma type were calculated. Crude and adjusted Hazard Ratio (HR) and their corresponding 95% CI for mortality comparing isolated BM to other synchronous metastases were performed to identify the effect of synchronous metastases on final survival. Analysis was performed with Stata Statistical Software: Release 15, College Station, TX: StataCorp LLC, 2017, and $p \leq 0.05$ was used for statistical significance purposes.

Results: A total of 2,035,204 patients with carcinoma were identified of which 98,606 (4.85%) presented with BM at diagnosis. The most common carcinoma types with bone metastasis were lung (49.4%), prostate (15%), breast (13.6%), renal (4.7%) and pancreas (2.3%). Five-year survival with isolated BM was lowest in patients with pancreatic carcinoma (5.8%, 95% CI 3.0 to 9.9%), and highest in patients with breast carcinoma (41.1%, 95% CI 38.6 to 43.5%) (Table 1). Synchronous metastases increased significantly the risk of mortality within the majority of carcinomas, except pancreatic carcinoma (with any metastases HR: 0.99, p=0.823; with lung HR:1.2, p=0.167; with brain HR:1.3, p=0.746; with liver HR: 1.14, p=0.208; with lymph nodes HR: 1.18, p=0.232) most likely due to its very poor prognosis, and breast carcinoma with synchronous lymph node metastasis (HR: 0.96, p=0.345) (Table 2).

Conclusion: Patients with carcinomas presenting with BM at diagnosis have a poor prognosis which is worsen if synchronous metastasis such as lung, brain, liver and lymph nodes are present. Knowing the survival of these patients is an important information when planning orthopedic interventions.

Table 1: Five-year survival of carcinomas presenting with metastasis to bone, with and without synchronous metastases

Carcinoma	With any Mets			Without Mets			Only bone Mets			Bone + Lung Mets			Bone + Brain Mets			Bone + Liver Mets			Bone + Lymph nodes Mets		
	5y-survival (%)	95% CI (%)		5y-survival (%)	95% CI (%)		5y-survival (%)	95% CI (%)		5y-survival (%)	95% CI (%)		5y-survival (%)	95% CI (%)		5y-survival (%)	95% CI (%)		5y-survival (%)	95% CI (%)	
Lung	8.55	6.26	7.02	31.64	31.19	32.09	8.08	6.18	10.29	7.70	6.17	9.44	10.11	8.15	12.30	6.94	5.45	8.66	8.32	7.77	8.90
Prostate	35.21	26.70	30.13	88.73	88.58	86.06	32.11	29.54	34.69	27.27	16.43	39.27	20.99	10.13	34.48	15.67	10.12	22.33	38.69	36.64	40.74
Breast	32.58	31.86	33.30	86.11	85.96	86.26	41.05	38.57	43.51	31.39	26.30	36.61	23.94	14.80	34.31	24.44	19.68	29.49	42.77	40.99	44.53
Kidney	14.86	14.19	15.55	74.85	74.45	75.24	23.41	20.82	26.09	13.22	10.61	16.12	16.50	7.94	27.78	11.61	6.52	18.29	12.85	9.71	16.44
Pancreas	6.81	6.52	7.10	20.73	20.24	21.22	5.82	3.03	9.89	7.29	3.21	13.61	0.00	.	.	7.05	4.68	10.06	5.58	2.38	10.78

Table 2: Hazard Ratio (HR) and corresponding 95% CIs for mortality after bone metastasis, comparing patients with bone metastasis only with patients with additional synchronous metastases

Carcinoma	Only bone Mets	With any Mets				Without Mets				Bone + Lung Mets				Bone + Brain Mets				Bone + Liver Mets				Bone + Lymph Nodes Mets			
	HR	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI		P-value
Lung	1.0	0.971	0.954	0.989	0.002	0.281	0.275	0.286	<0.001	1.113	1.029	1.204	0.008	1.107	1.017	1.206	0.019	1.404	1.291	1.527	<0.001	1.152	1.106	1.201	<0.001
Prostate	1.0	1.189	1.132	1.249	<0.001	0.083	0.080	0.085	<0.001	1.354	1.159	1.582	<0.001	2.093	1.443	3.037	<0.001	2.256	1.847	2.757	<0.001	1.098	1.029	1.172	0.005
Breast	1.0	1.531	1.466	1.598	<0.001	0.143	0.137	0.148	<0.001	1.379	1.174	1.620	<0.001	1.945	1.458	2.596	<0.001	1.829	1.553	2.155	<0.001	0.960	0.883	1.044	0.345
Kidney	1.0	1.292	1.213	1.375	<0.001	0.121	0.114	0.129	<0.001	1.644	1.460	1.852	<0.001	1.665	1.214	2.284	0.002	1.912	1.517	2.410	<0.001	1.801	1.569	2.068	<0.001
Pancreas	1.0	0.987	0.877	1.110	0.823	0.414	0.368	0.466	<0.001	1.218	0.921	1.611	0.167	1.260	0.311	5.109	0.746	1.143	0.929	1.406	0.208	1.176	0.902	1.532	0.232

PAPER 46

Survival after surgery for skeletal metastases is associated with preoperative patient-reported assessments

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Background: Survival after surgery for metastatic bone disease is an important part of surgical decision making. It helps to avoid both undertreatment and overtreatment of disease. Estimating patient survival is therefore of critical importance. Patient reported assessments have been shown to be of prognostic value in estimating mortality in several oncologic diseases, but this has not previously been applied to patients with metastatic disease to bone.

Questions/Purposes
1. Are patient reported assessments associated with post-operative survival after surgery for skeletal metastases?
2. Do patient reported assessment scores improve after surgery for skeletal metastases?

Patients and Methods: All patients indicated for operative fixation of skeletal metastases between 6/2012 and 9/2017 were entered in a prospective trial after providing informed consent. Patients completed Short Form-36 (SF-36) questionnaires prior to surgical intervention as well as at 3- and 6-months post-operatively. A SF-36 composite score was calculated as the arithmetic average of each of the domains. The association between baseline SF-36 scores and overall survival were assessed using a Cox proportional hazards model adjusted for primary cancer diagnosis, ECOG score, number of bone metastases, presence of visceral metastases, and hemoglobin. Hazard ratios and 95% confidence intervals (CI) are reported.

Results: 195 patients were eligible for analysis. There were 131 deaths with a median survival of 11.2 months (95% CI 7.8, 14.3) post-operatively. In an adjusted model, the mental and physical health component summary (MCS and PCS) scores were significantly associated with overall survival, as was an overall SF-36 composite score (Table 1). General health, vitality, and mental health domains were also significantly associated with overall survival. Post-operatively, the composite SF-36 score improved from baseline to six months.

Conclusions: This study demonstrates that patients' assessment of their health status is associated with their post-operative survival after surgery for skeletal metastases. In this light, patient reported assessments may prove a useful tool to include in models that estimate survival for these patients with the goal of providing optimal, individualized care.

Table 1. General health, vitality, mental health, PCS, MCS, and SF-36 composite score is significantly associated with survival after surgery for skeletal metastases.

SF-36 Scale	Adjusted Hazard Ratio (95% CI)*	Adjusted p-value
Physical function	0.88 (0.75, 1.03)	0.102
Role physical	0.84 (0.69, 1.02)	0.073
Body pain	0.90 (0.74, 1.08)	0.249
General health	0.64 (0.53, 0.78)	**<.001**
Vitality	0.69 (0.56, 0.85)	**<.001**
Social functioning	0.88 (0.76, 1.02)	0.098
Role emotional	0.90 (0.80, 1.01)	0.065
Mental health	0.77 (0.65, 0.90)	**0.001**
Physical component score	0.80 (0.66, 0.96)	**0.015**
Mental component score	0.81 (0.69, 0.93)	**0.004**
Composite score	0.63 (0.49, 0.82)	**<.001**

Note: Hazard ratio is for a 10-unit increase in the SF-36.

PAPER 47

Multicenter Retrospective Comparison Of Outcomes, Failure Rates, And Complications Between Plate And Nail Fixation For Metastatic Lesions Of The Humerus

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Background: The humerus is the second most common site for bony metastases. Osteosynthesis is a common approach to treatment with two predominant construct options – plates and intramedullary nails. Open plating allows for intralesional resection of the mass and cement stabilization but requires larger incisions and potentially longer surgical times. Percutaneous nailing allows for shorter operative times, but does not reduce disease burden and has a potentially higher implant cost. Prior investigations have suggested a higher failure rate, higher reoperation rate and higher estimated blood loss for plate compared to nail fixation. Larger series exist comparing the two constructs, but this represents the largest multicenter comparison of which we are aware.

Questions/Purposes:

1) To compare implant and patient survival between the two constructs
2) To compare complication rates between the two constructs

Patients and Methods: Prospectively collected patient databases of the orthopaedic oncology departments at Vanderbilt University Medical Center (January 1998 to October 2018) and at the Hospital of the University of Pennsylvania (January 2013 to October 2018) were queried retrospectively to identify patients with metastatic lesions of the humerus. Patients were included if they had a pathologically confirmed metastatic lesion between the surgical neck and 3cm proximal to the olecranon fossa, the fracture was amenable to both implant options and had at least 6 months of clinical and/or radiographic follow up. Patients who were deceased or discharged to hospice prior to completing 6 months of follow up were also included. Patients were excluded if metastases were suspected but not confirmed, the fracture was not amenable to one or both implants, or if insufficient data was available. Demographic and clinical data was recorded including age, sex, diagnosis, pathologic diagnosis, surgical time, time to final follow up, mortality, complications, implant failure and need for re-operation.

Results: We identified a total of 101 humeri in 96 eligible patients, 72 treated with plate fixation and 29 with intramedullary nail fixation. Patients were predominantly male (60.3 v 39.7%) with an average age of 63.8 years at the time of surgery and 15.5 months of follow up post operatively. The three most common primary malignancies were renal cell (25.7%), myeloma (23.8%) and lung (14.9%). 52.5% of patients presented with a displaced fracture. The two groups did not differ in regards to age, sex distribution, side nor displacement at presentation. Lesions were significantly larger in the plate group than the nail group, 7.2 (+/-3.7) v 5.2 (+/- 3) cm, $p=0.0027$. Surgical times were significantly longer in the plate group, 146 (+/- 46) v 75 (+/-20) min, $p<0.001$. Estimated blood loss was significantly higher in the plate group, 510 (+/-583) v 221 (+/-225) mL, $p<0.001$. A trend toward a higher rate of failure requiring revision was seen in the plate group, 12.5% v 0%, but this did not reach statistical significance. Four revisions were for loss of fixation, three for disease progression, one for new traumatic fracture and one for instability/persistent bleeding. 3 patients in the plate group experienced loss of fixation that did not require revision and one patient in the nail group experienced disease progression that was treated with further adjuvant therapies. These events occurred at an average of 15.1 months post operatively. 3 patients in the nail group experienced a refracture around the nail that did not require revision. The most common complications experienced in the plate group were pain (15.3%), stiffness (15.3%) and edema/swelling (5.6%) compared to pain (20.7%), refracture (10.3%) and PE (6.9%) in the nail group. At final follow up, 38.6% of patients had either died or were discharged to hospice, a rate that did not differ between the two groups.

Conclusions: In the setting of metastatic humeral lesions, intramedullary nails offer shorter OR times, less blood loss and a lower risk for reoperation. While open plate fixation should be considered for larger lesions or those at the extreme ends of the humerus, the risk of failure remains higher than that seen with intramedullary nails.

PAPER 48

Finite Element Fracture Predictions for Patients with Metastatic Lesions of the Proximal Femur

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Background: Accurate prediction of fracture risk in patients with metastatic lesions remains elusive. One potential technique in this realm is finite element analysis (FEA). Our group has evolving experience with FEA in this clinical setting. Prior work (n=44 subjects) suggested that FEA used to assess fracture risk in level walking (LW) conditions could improve fracture prediction over Mirels scoring in a clinical population.[1]

Questions/Purposes: (1) Determine sensitivity and specificity of FEA based analysis of a larger data set of metastatic lesions of the proximal femur using 3 different loading conditions. (2) Predict fracture status for cases that were prophylactically stabilized to provide an estimate of cases that would likely fracture without surgical intervention and cases that might not fracture.

Patients and Methods: Patient population accrued prospectively from a single institution utilizing cases enrolled in the MSTS Computerized Tomographic Rigidity Analysis[2] (CTRA) study consisting of 82 cases: 6 fracture, 41 no fracture, 35 prophylactic stabilization. Inclusion criteria: Proximal femur or diaphysis lesion, no fracture for 4 months following initial CT with phantom. The senior author assigned Mirels' scores, and FEA was performed based on the CT with phantom.

Three FEA conditions were analyzed: Axial head load (AL), level walking (LW), stair ascent (SA) with 2.5 times body weight (BW) considered to be applied to the femoral head during these activities. Load/strength ratio used to calculate fracture risk, with risk of fracture (ROF) calculated as the applied load (2.5BW) / femur strength. ROF $\geq$ 1 predicts failure by FEA. A second threshold (ROF > 0.65) was also considered to capture ROF with more active motion, corresponding to a femoral head load of 3.85BW.

Results: Overall sensitivity, specificity, positive and negative predictive value results for FEA in each of the conditions analyzed, alone and combined with Mirels' scores, are shown (Table 1). Stair ascent risk of fracture (ROF) ratio versus Mirels' score is also shown for the three clinical outcomes (Fig1). These criteria tend to correctly capture the majority of fracture cases, with few of the no fracture cases. Two of six cases would not be predicted to fracture via FEA SA. For the Stabilized Group with patients having Mirels' pain scores of 1 or 2, 3 of 35 (**9%**) and 8 of 35 (**23%**) would not have been predicted to fracture. Choosing criteria with lower sensitivity, but higher specificity results in a lower fraction of stabilized cases predicted not to fracture.

Conclusions: For the study population analyzed here, predictive modeling with FEA, when combined with Mirels' scoring can improve specificity, beyond Mirels' scoring alone. However, FEA does not appear to improve predictions beyond what was previously found with rigidity analysis (CTRA, see Table). Depending on choice of FEA ROF criteria, between 77 and 91% of the stabilized cases would be predicted to fracture. This suggests that most of the stabilized cases would have fractured if not treated.

Comparing to previous results (Goodheart), sample size is approximately twice that of the original project. However, with the addition of one fracture case (not predicted to fracture), there was a reduction in sensitivity for this small (n=6) group. Overall, predictive modeling via FEA was less promising for the larger population studied here compared to Goodheart.

Limitations were numerous. (1) Prediction was based on CT at one time point, allowing for potential progression of lesion over four months. (2) There are likely confounding effects of increased fracture risk for patients with osteoporosis, as illustrated by the fact that all fractures occurred in females. (3) There is no randomization, no doubt contributing to the very small number of fractures. Selection for treatment (surgery vs not) was likely influenced by CTRA data and surgeon's clinical interpretation. (4) Low number of fracture cases reduced statistical power of sensitivity and positive predictive value.

This study illustrates the many difficulties inherent to working with this patient population, including the difficulty in modeling varying types of defects, the potential for change in defect characteristics over relatively short periods of time, variability in activity by patients that is difficult to capture in easily defined groups, confounding variables including osteoporosis and BMI, and the difficulty in accruing fracture cases due to the clinical tendency treat based on clinical experience and/or Mirels and CTRA criteria. However, ongoing study is warranted.

References:

1. J Orthop Res. (2015) 33(8):1226-34. 2. Clin Orthop Relat Res (2016) 474:643–651.

Table 1: Comparison of Fracture Prediction using Mirels' scoring, FEA for axial, level walking, and stair ascent, and combined Mirels'/FEA. Sensitivity (Sens), Specificity (Spec), Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were calculated for each prediction method.

		Clinical Fx (Y)		Clinical Fx (N)					
	Prediction Criteria	**Predict Fx (Y)**	**Predict Fx (N)**	**Predict Fx (Y)**	**Predict Fx (N)**	**Sens (%)**	**Spec (%)**	**PPV (%)**	**NPV (%)**
MIRELS	Mirels' ≥ 8	6	0	34	7	100	17	15	100
	Mirels' ≥ 9	6	0	23	18	100	44	21	100
FEA AXIAL HEAD LOAD (AL)	ROF ≥ 1.0	2	4	3	38	33	93	40	90
	ROF ≥ 0.65	4	2	14	27	67	66	22	93
	ROF ≥ 1.0 & Mirels' ≥ 9	2	4	2	39	33	95	50	91
	ROF ≥ 0.65 & Mirels' ≥ 9	4	2	9	32	67	78	31	94
FEA LEVEL WALKING (LW)	ROF ≥ 1.0	2	4	3	38	33	93	40	90
	ROF ≥ 0.65	4	2	27	14	67	34	13	88
	ROF ≥ 1.0 & Mirels' ≥ 9	3	3	1	40	50	97	75	93
	ROF ≥ 0.65 & Mirels' ≥ 9	4	2	17	34	67	59	19	92
FEA STAIR ASCENT (SA)	ROF ≥ 1.0	4	2	9	32	67	78	31	94
	ROF ≥ 0.65	6	0	34	17	100	17	15	100
	ROF ≥ 1.0 & Mirels' ≥ 9	4	2	3	38	67	93	57	95
	ROF ≥ 0.65 & Mirels' ≥ 9	6	0	18	23	100	56	25	100
CTRA (2016)	35% Reduction in Rigidity	6	0	35	53	100	61	18	100

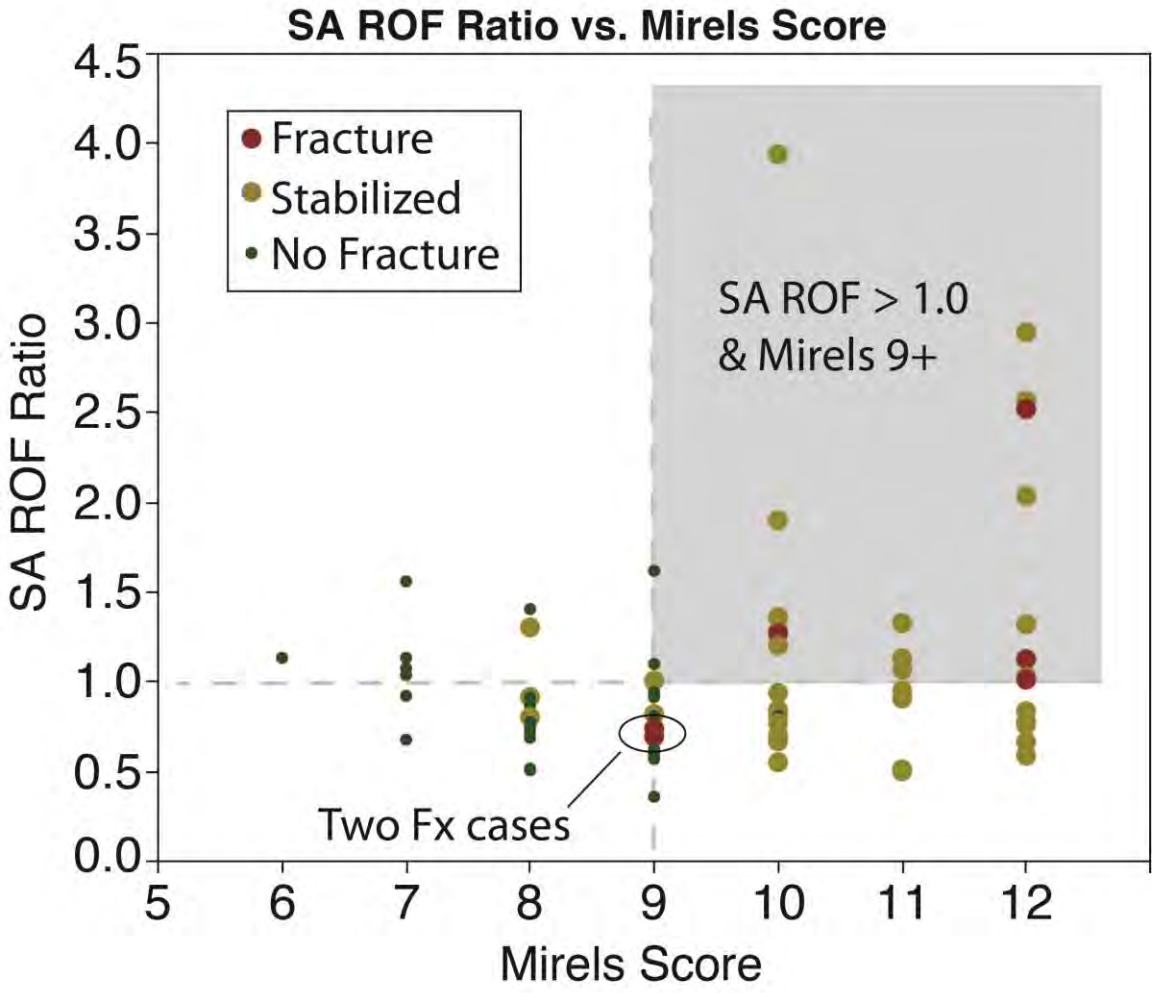

Figure 1: Stair ascent risk of fracture (ROF) ratio versus Mirels' score for the three clinical outcomes. The shaded area shows the combined SA ROF & Mirels criteria. This criteria tends to capture the majority of fracture cases, and few of the no fracture cases. Note there are two cases that would not be predicted to fracture via FEA SA.

PAPER 49

Can We Do Better Than Mirels In Predicting Fracture Risk For Patients With Multiple Myeloma? Evaluation Of A Novel Scoring System

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Background: Multiple myeloma is a neoplastic proliferation of plasma cells frequently characterized by lytic osseous lesions, and it is forecasted to be diagnosed in approximately 32,000 people in the US in 2019. Myeloma bone disease has been found to be associated with up to an 80% risk of pathologic fracture, and patients who experience a pathologic fracture have a 20% higher risk of mortality within 2 years when compared to those who do not. Overall, these make fracture risk stratification a critical part of patient care.

Numerous risk factors for pathologic fracture have been identified, and the Mirels system is a commonly utilized tool to calculate a predicted fracture risk in patients with osseous metastasesy. However, Mirels's initial study included only 11 lesions in patients with multiple myeloma, limiting the generalizability to this patient population. Furthermore, while other methods of pathologic fracture risk assessment, including computed tomography (CT)-based structural rigidity analysis, have improved fracture prediction compared with the Mirels system, they require advanced imaging and analytical tools that may not be widely available.

Questions/Purposes: Our goal was to evaluate the performance of Mirels score in patients with multiple myeloma, and to develop a tool for identifying impending pathologic fractures in this specific patient population. To do this, we aimed to identify factors associated with fracture risk in multiple myeloma patients using clinical factors, physical examination, and standard radiographic findings.

Patients and Methods: Patients with a diagnosis of multiple myeloma between 2003 and 2017 were identified from the cancer registry at Johns Hopkins University and the Sidney Kimmel Comprehensive Cancer Center. Inclusion criteria were the availability of medical records with radiographic and clinical data permitting evaluation of long-bone lesions, clinical records with detailed symptom and disease course information, and follow-up of at least 1 year or until a pathologic fracture occurred or surgical stabilization was performed.

Extremity radiographs in identified patients were evaluated for long-bone lesions. Up to 3 lesions in each patient were characterized, and all were characterized before determining fracture outcome, to prevent bias regarding lesion selection and characterization. Clinical factors, patient demographics, and physical examination findings were extracted from medical records.

We identified 763 patients with multiple myeloma diagnosed during the study period. Of these, 163 patients had available imaging of 351 lytic lesions of long bones and adequate followup. We used receiver operating characteristic curves to develop a novel predictive score. For comparison to Mirels

criteria, both predictive scoring systems were applied to a separate set of 100 new lesions for validation. Net reclassification improvement analysis was performed to evaluate the novel score's performance compared to Mirels score's performance.

Results: Factors associated with fracture were lesion size, lesion latency (time from myeloma diagnosis to lesion identification), Mirels score, pain severity, radiotherapy, and width fraction (Table I). Compared with the Mirels system, the novel system (Table II) had sensitivity of 69% (versus 38%), specificity of 88% (versus 92%), and superior positive and negative predictive values for the 443 total lesions. The novel system was also an improvement in area under the receiver operating characteristic curve when compared to Mirels (0.83 versus 0.74). Of the 9 stabilized lesions from the initial cohort, stabilization was suggested for 6 by the novel system and 5 by the Mirels system. Net reclassification improvement was 0.27, indicating significant superiority of the novel system ($p = 0.02$).

Conclusions: Results of this study indicate that the Mirels scoring system is limited in determining lytic lesions at risk of fracture in multiple myeloma patients, as evidenced by its low sensitivity. The novel scoring system we developed, which uses data on lesion latency, lesion size, and radiation history, shows superior sensitivity, improved positive predictive value, and increased negative predictive value compared with the Mirels system. We also found a significant improvement in net reclassification when using the novel scoring system to predict risk of pathologic fracture.

Tables/Figures

TABLE I. Patient, lytic lesion characteristics, laboratory values, and treatment factors for multiple myeloma patients who experienced a pathologic fracture versus those who did not.

Variable	Non-Fracture Group (n = 317)		Fracture Group (n = 25)		p-value
	Mean ± SD	N (%)	Mean ± SD	N (%)	
Patient characteristics					
Age, yr	61 ± 10		61 ± 9.6		0.990
Body mass index	28 ± 5.3		30 ± 7.7		0.057
Current smoker		17 (5.4)		1 (4.0)	0.770
Diabetes		88 (28)		9 (36)	0.380
Disease duration, yr[a]	6.0 ± 3.5		5.7 ± 4.7		0.579
Female sex		161 (51)		13 (52)	0.930
Pain score[b]	1.2 ± 0.5		1.5 ± 0.5		0.002
Lytic lesion characteristics					
Mirels score	7.1 ± 1.0		7.9 ± 1.2		<0.001
Number of lesions	4.2 ± 3.0		4.0 ± 3.1		0.757
Lesion duration, yr[c]	4.9 ± 3.0		2.6 ± 2.4		<0.001
Lesion latency, yr[d]	1.0 ± 1.6		3.7 ± 4.6		<0.001
Lesion size, cm^2	1.5 ± 2.2		5.4 ± 9.3		<0.001
Scalloping[e]		89 (28)		8 (32)	0.709
Sclerotic rim on initial radiograph		15 (4.6)		2 (8.0)	0.455
Site score[f]	1.5 ± 0.5		1.6 ± 0.5		0.576
Width fraction, %[g]	26 ± 15		38 ± 26		<0.001
Laboratory values					

Albumin, g/dL	6.1 ± 22		3.9 ± 0.5		0.621
Alkaline phosphatase, U/L	80 ± 47		80 ± 33		0.998
Beta globulins, g/dL	0.7 ± 0.4		0.7 ± 0.3		0.940
Calcium, mg/dL	9.7 ± 1.2		9.5 ± 0.8		0.489
Creatinine, mg/dL	1.2 ± 1.0		1.0 ± 0.5		0.307
Gamma globulins, g/dL	1.7 ± 1.9		1.8 ± 2.1		0.715
Hemoglobin, g/dL	11 ± 1.9		11 ± 2.1		0.633
Treatment factors					
Therapy					
Antiproteasomal[h]		255 (80)		21 (84)	0.665
Antiresorptive[i]		284 (90)		22 (88)	0.804
Bone marrow transplant		168 (53)		11 (44)	0.407
Corticosteroid		306 (97)		25 (100)	0.345
Lenalidomide		254 (80)		20 (80)	0.988
Radiation[j]		13 (4.1)		5 (29)	0.003
Follow-up, yr[k]	4.8 ± 3.0		3.1 ± 2.4		0.007

SD, standard deviation.
[a]From multiple myeloma diagnosis to last visit at our health network.
[b]As in Mirels scoring system: mild, 1 point; moderate, 2 points; or functional (i.e., worsened by activity/loading the bone), 3 points.
[c]From lesion identification to latest follow-up or fracture.
[d]From multiple myeloma diagnosis to identification of lesion of interest.
[e]Invasion of the lesion into bone cortex.
[f]As in Mirels scoring system: upper limb, lower limb, or peritrochanteric.
[g]Width of the lesion divided by the width of the bone.
[h]Consisting of bortezomib and carfilzomib.
[i]Consisting of bisphosphonates and denosumab.
[j]History of radiation to the anatomic compartment containing the lesion of interest.
[k]From lesion identification to last visit at our health network.

TABLE II. Novel scoring system to predict risk of pathologic fracture in patients with multiple myeloma–related bone lesions

Category	**Point Value**
Lesion latency, yr[a]	
<1	0
1–2	1
>2	2
Lesion size, cm^2	
<5	0
≥5	2
Pain[b]	
Mild	0
Moderate	1
Functional	2

Radiation[c]	
Yes	2
No	0
Width fraction, %[d]	
<25	0
25–50	1
>50	2

[a]From multiple myeloma diagnosis to identification of lesion of interest.
[b]As in Mirels scoring system; “functional” means worsened by activity/loading the bone.
[c]History of radiation to the anatomic compartment containing the lesion of interest.
[d]Width of the lesion divided by the width of the bone.

PAPER 50

The use of arthroplasty when treating proximal femur metastatic lesions is associated with increased patient survival when compared to intramedullary nailing in the VA healthcare system

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Background: The proximal femur represents the most common site of metastatic disease in the appendicular skeleton and pathologic fractures in this area account for a substantial burden of cancer related morbidity and mortality. Questions remain regarding whether intramedullary nailing or hip hemiarthroplasty represent better treatment options for patients affected by this problem.

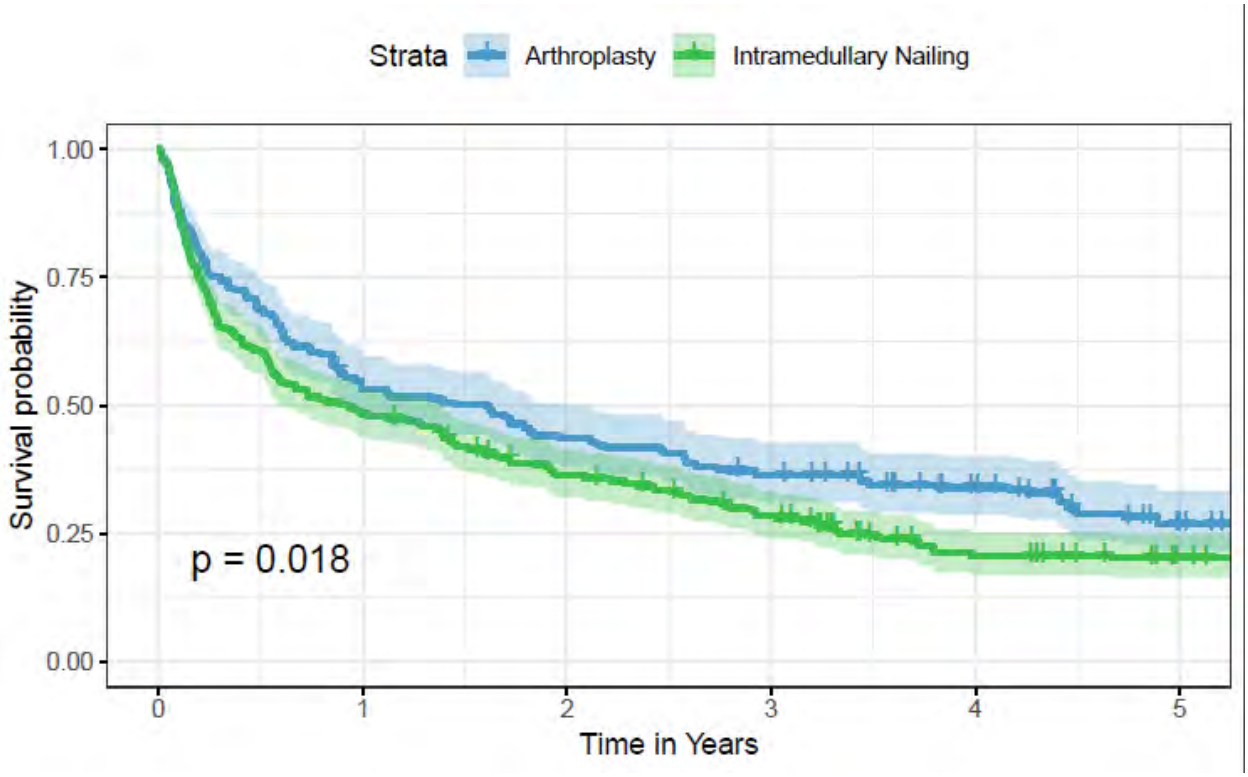
Question: Is the method of treatment of proximal femur metastatic lesions (intramedullary nailing or arthroplasty) associated with differences in mortality in the VA patient population?

Patients/Methods: This retrospective cohort study was performed utilizing a large nationwide clinically integrated relational database within the VA Informatics and Computing Infrastructure Corporate Data Warehouse (VINCI CDW). Records between September 30 2010 and October 1 2015 were queried. The presence of the CPT code 27236 (hip hemiarthroplasty) and an ICD-9 code of 733.14 (pathologic fracture of neck of femur), 733.15 (pathologic fracture of other specified part of femur) or 733.10 (pathologic fracture, unspecified site) were used to define the hemiarthroplasty cohort. CPT code 27245 (treatment of intertrochanteric, pertrochanteric or subtrochanteric femoral fracture) and any of the above listed ICD-9 codes was used to define the intramedullary nailing (IMN) group. A cox proportional hazards model was constructed with adjustments for age and comorbidities using the Gagne comorbidity score to compare survival between the groups.

Results: 679 patients were included (265 arthroplasty and 414 nails) with mean follow up of 2 years (2.3 for arthroplasty, 1.9 for IMN, $p=0.01$). The arthroplasty group was older than the IMN group (73 vs 69, $p<0.0001$) and had fewer comorbidities (Gagne 7.2 vs 6.3, $p=0.003$). Lower Gange comorbidity score and age were both associated with survival ($p<0.0001$). Arthroplasty was associated with survival by log rank test ($p=0.018$) and this difference persisted when adjusting for age and comorbidities with a hazard ratio of 1.3 ($p=0.008$).

Discussion: In this nationwide retrospective cohort, treatment of proximal femur metastatic disease with hemiarthroplasty was associated with increased survival when compared to intramedullary nailing even when adjusting for age and comorbidity. While an open and arguably more invasive operation,

arthroplasty techniques were not associated with increased mortality when treating patients with proximal femur metastatic disease. These results may aid surgeons as they consider treatment options in this population. Weaknesses of this study include the retrospective nature of the study, lack of external validity given the largely male VA population, and the potential for coding errors inherent to any database study.



PAPER 51

Beyond Bisphosphonates and Denosumab to Protect Bone from Cancer-Induced Bone Loss: Upcoming Mechanism-Based Therapeutic Targets

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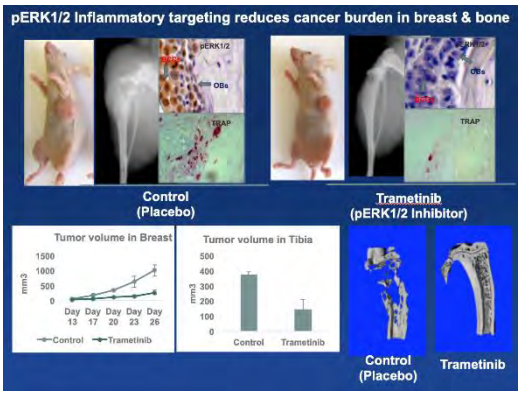
Background: Breast cancer metastases to bone are commonly osteolytic. We were very enthusiastic about bisphosphonates 10 years ago but now we hear only about Denosumab. Zometa patent expired in 2013 and price dropped from $700 to $45 USD. Industry does not promote Zometa while denosumab is heavily marketed for metastatic bone cancers and giant cell tumors of bone because the price is over $2,200 and its patent will be good until 2023. Zometa, Denosumab, and radiation do not consistently prevent fractures. We do not have the next line of bone-protective agents available. We need to understand molecular mechanisms by which metastatic cancer cells destroy bone for better treatments of cancer-induced bone loss.

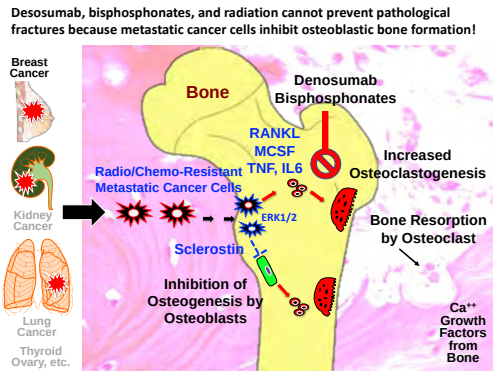
Questions and Purposes: In order to define a key pathway leading to aggressive bone destruction, we intended to identify key biological factors that are distinct in osteolytic metastatic cancer cell-bone resident cell interactions compared to non-osteolytic metastatic cancer cells.

Patient-Derived Cells, Human Bones, Mice, and Methods: we implanted different types of well-established human breast cancer cells into the nude mouse tibiae and breast regions. At 4 weeks, we measured the tumor size and bone destruction using radiographs and microCT. We then compared expression of inflammatory genes between the least and most osteolytic breast and lung cancer cells. We next defined downstream pro-osteoclastogenic, anti-osteogenic proteins, kinases, and therapeutic effects using RT-PCR array, immunoblotting, and microCT. We also examined human pathology specimens (N=12) from the pathological fracture sites. We then conducted in vivo and in vitro experiments. We also conducted transplantation of human bone + human cancer cells in mice for avatar cancer-induced bone loss experiments.

Results: Examination of pathologic specimens revealed that breast cancer cells which were metastasized into bone express sclerostin. Co-culture experiments showed that breast cancer cells inhibit mineralization of osteoblasts. In line with this, breast cancer cells activate calcium channels to adapt to calcium-rich environments. Furthermore breast cancer cells stimulated osteoblasts to produce pro-osteoclastogenic chemokines. These pro-osteoclastogenic and anti-osteogenic proteins are under the regulation of pERK1/2-CREB. Inhibition of osteoblastic bone formation in vitro and in vivo by breast cancer cells were suppressed by pERK1/2 inhibition. Likewise, human bone xenografts were protected by MEK1/2-ERK1/2 inhibitors in vivo.

Conclusions: Aggressive breast cancer cells directly inhibit osteoblastic bone formation in addition to by increasing osteoclastogenesis. Targeting osteoclast activity alone with bisphosphonates or denosumab is not sufficient to prevent pathological fractures secondary to osteolytic metastases. Although sclerostin could be a target to protect host bone repair process but sclerostin antibody (Romosozumab) is approved by FDA in 2019 but its efficacy in the setting of metastatic bone cancers is unknown. There is a need for supplemental pharmacologic treatment using targeted pathway inhibitors other than zometa and denosumab. Targeting cancer- and osteolysis-specific pathways is logical in reducing cancer burden and protecting host bone from cancer-induced bone loss.





PAPER 52

Does Nailing of Pathologic Fractures Increase Systemic Tumor Burden?

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Introduction: The majority of pathologic fractures of long bones require surgical treatment usually in the form of intramedullary nail or long-stemmed arthroplasty. We hypothesize these surgical interventions intended to improve quality of life and in some cases survival, inadvertently cause rapid dissemination of tumor and theoretically may hasten the clinically relevant metastatic burden to lung and other viscera. We propose to demonstrate that tumor cells in the medullary canal of long bones are forced into the circulation during intramedullary pressurization when treating pathologic fractures.

Methods: We performed a proof of concept study to determine if circulating tumor cells (CTCs) could be quantified in the perioperative period during pathologic fracture fixation. Two patients with metastatic bladder cancer involving 3 long bones (2 humeri, 1 femur) underwent IM nailing for completed or impending pathologic fracture. Blood samples were collected from peripheral vein, peripheral artery and central vein at four time points (TP). TP1 was at the time of incision; TP2 was during the passage of the first reamer; TP3 was during wound closure; and TP4 was 24 hours post-operatively. CTCs were quantified using the AccuCyte-CyteFinder system (RareCyte, Inc., Seattle, WA). This selection-free method enumerates and characterizes CTCs from peripheral blood samples (PB) via immunofluorescent staining and scanning. The criteria for defining a CTC is DAPI positive, CK/EpCAM positive, and CD45 negative.

Results: A dramatic increase in circulating tumor cells was observed in all 3 cases during the passage of the first reamer (Table 1). Many CTC clusters were seen for TP2 venous samples, but rarely seen for the other samples. CTCs returned to base line within 24 hours in 1 case and remained elevated in 2 cases though markedly decreased compared to peak concentration during reaming.

Conclusions: A surge in CTC number during the nailing procedure was observed in all cases. Our data suggest that the palliative nailing procedure may contribute to further CTC dissemination. Whether the surge of CTCs results in clinical relevant disease warrants further investigation.

	Fracture 1	Fracture 2	Fracture 3
Site	Humerus	Humerus	Femur
# CTCs			
TP1 (incision)	8	259	27
TP2 (during reaming)	**3314**	**3616**	**2507**
TP3 (wound closure)	8	322	917
TP4 (24 hours post-op)	2	548	433

Table 1. CTC concentration fluctuation during different collection times before, during, and after reaming of pathologic long bone fractures secondary to metastatic bladder cancer. A surge of CTCs is observed after passage of the first reamer.
Abbreviations: TP= time point, CTC=circulating tumor cell.

PAPER 53

Comparative efficacy of receptor tyrosine kinase inhibitors (RTKIs) and immunotherapy (anti-PD-1/PD-L1) for treatment of osseous versus soft tissue metastases in metastatic renal cell carcinoma (mRCC)

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Background: Renal cell carcinoma (RCC) represents ~3.8% of all newly diagnosed malignancies in the U.S., and around 20-30% of metastatic RCC (mRCC) patients ultimately develop osseous metastases. Biologic agents such as receptor tyrosine kinase inhibitors (RTKI) and immunotherapy agents (anti-PD-1) have improved survival outcomes for mRCC patients. The presence of osseous metastases often herald a poorer prognosis among mRCC patients, and there is some evidence that it may also be a predictor of poor response to targeted therapy.[i] Anecdotally, there are suggestions that the response to biologic agents may be greater in visceral sites of metastatic disease than in osseous sites. A dichotomous response between visceral and osseous metastases to these biologic agents may ultimately lead to an increased risk of patients' survival being longer than implant survival in the management of skeletal metastatic disease in these patients.

Question / Purposes: Our study aimed to evaluate whether osseous and visceral RCC metastases responded concordantly or discordantly with treatment using systemic biologic agents (RTKI and anti-PD-1).

Patients and methods: Our institutional Cancer Registry database was queried for RCC patients treated at Johns Hopkins Hospital/Sidney Kimmel Cancer Center from 1997-2017 (n = 2212). Inclusion criteria included at least 18 years of age, measurable osseous and visceral metastatic sites of disease, no radiation or surgical treatment at the measurable site during or prior to systemic biologic agent use, and first line use of the biologic agent. *(Table 1)* Overall, 68 patients were identified who had measurable bone as well as soft tissue metastatic disease who were treated with RTKIs and/or PD-1 inhibitors over the study period (14 patients had courses of RTKI and PD-1 and both disease courses were followed, resulting in a total of 82 disease courses).

Measurements were performed using CT imaging at the time of biologic therapy initiation, and at 3 months, 6 months, and 1 year into treatment. Changes in disease status from baseline were categorized as complete response (CR), partial response (PR), stable (S), mixed (M) or progressive disease (PD), based

upon RECISTv1.1 and MDA criteria for soft tissue and bone metastases, respectively. We applied the MDA criteria for osseous evaluation, as RECISTv1.1 criteria classifies bone metastases as unmeasurable. These five disease categories were further organized into *Controlled Disease* (PR, CR, S) or *Evidence of Progression* (M, PD) in order to generate a generalized linear effects model with the patient as the random effect, bone tissue response as the dependent variable, and soft tissue response, time point, and their interaction, as the independent variables. By allowing each patient to serve as their own control, we determined whether response in soft tissue is correlated with similar response in bone metastases.

Results: Descriptive statistics demonstrate that bone metastases were more likely to remain stable following treatment than soft tissue metastases *(Figure 1).* The difference between the proportion of osseous disease and the proportion of soft tissue metastasis demonstrating stable disease status was 26% at 3 months, 17% at 6 months, and 50% at 12 months. Conversely, a greater proportion of soft tissue metastases demonstrated both PD and PR than bone metastases. The difference between the proportion of soft tissue disease demonstrating PD disease status vs. the proportion of PD in osseous disease was 16% at 3 months, 8% at 6 months, and 32% at 12 months. The difference when compared to the proportion of osseous demonstrating PR is 13% at 3 months, 8% at 6 months, and 2% at 12 months.

Regarding the model results, visceral response correlates closely with bone response at 3 months ($p=0.005$, $n=76$) and 6 months ($p=0.017$, $n=48$). Of patients with controlled soft tissue disease, only 19% had progression in bone at 3 months (32% at 6 months). Of patients with progression in soft tissue, 42% had controlled bone disease at 3 months (41% at 6 mos.). With the small number of patients on treatment at one year, the data at that time period did not demonstrate significance.

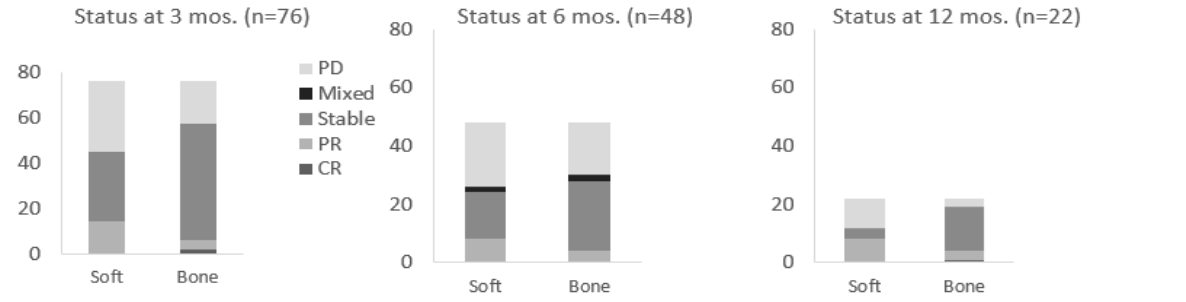
Conclusions: This analysis suggests that, contrary to anecdotal reports of a discordant response to biologic therapy, osseous metastases do not appear to respond worse than soft tissue metastases following treatment with these agents. Further investigation may be necessary to determine why osseous metastases are a predictor for poor prognosis and poor response to targeted therapy.

[i] Beuselinck B, Oudard S, Rixe O, et al. Negative impact of bone metastasis on outcome in clear-cell renal cell carcinoma treated with sunitinib. Ann Oncol. 2011;22(4):794-800.

Table 1: Characteristics of 82 disease courses (68 patients) with metastatic spread to both bone and soft tissue and treated with RTKI and / or PD-1 (1997-2017)

Characteristics		Total N (%)
Sex		
	Female	18 (22%)
	Male	64 (78%)
Drug class		
	PD-1	30 (37%)
	RTKI	52 (63%)
Smoking		
	Never	29 (35%)
	Unknown	27 (33%)
	Former	21 (26%)
	Current	5 (6%)
Disease type		
	Clear cell	50 (74%)
	N/A	6 (9%)
	Sarcomatoid	4 (6%)
	Papillary	3 (4%)
	chromophobe	2 (3%)
	Clear cell and papillary features	2 (3%)
	Clear cell with sarcomatoid features	1 (1%)
Unique lesions (soft tissue)	Sum	389
	Average	4.7
	STD	2.6
Unique lesions (bone)	Sum	229
	Average	2.79
	STD	2.71

Figure 1: RCC soft tissue and bone metastasis response to RTKI or PD-1 therapy at 3 mos., 6 mos., and 12 mos. classified by RECIST v1.1 and MDA criteria respectively and compared to baseline measurements



	CR	PR	Stable	Mixed	PD
Soft	0%	18%	41%	0%	41%
Bone	3%	5%	67%	0%	25%
Diff.	**-3%**	**13%**	**-26%**	**0%**	**16%**

	CR	PR	Stable	Mixed	PD
Soft	0%	17%	33%	4%	46%
Bone	0%	8%	50%	4%	38%
Diff.	**0%**	**8%**	**-17%**	**0%**	**8%**

	CR	PR	Stable	Mixed	PD
Soft	0%	36%	18%	0%	45%
Bone	5%	14%	68%	0%	14%
Diff.	**-5%**	**22%**	**-50%**	**0%**	**32%**

PAPER 54

Mutation Status and Treatment with Tyrosine Kinase Inhibitors Improves Survival Estimates in Patients with Metastatic Non-Small Cell Lung Cancer

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Background: The PATHFx tool currently groups oncologic diagnoses according to historical rates of survival. As such, all forms of lung cancer, gastric cancer and melanoma are grouped together. In recent years, however, significant survival improvements have been reported in sub-groups of patients with non-small cell lung cancer (NSCLC) characterized by targetable mutations of the Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK) genes. In this setting, the use of specific tyrosine kinase inhibitors (TKIs) targeting EGFR and ALK genes has been associated with prolonged response and survival. These clinical results prompt the need to develop disease-specific models rather than rely on diagnosis grouping.

Questions/Purpose: The purpose of this study was to determine whether knowledge of (1) mutation status of the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and (2) whether a tyrosine kinase inhibitor (TKI) targeting either of these mutations could improve survival estimates in patients with NSCLC.

Patients and Methods: We collected the records of 148 patients who underwent surgical stabilization for metastatic bone disease due to NSCLC. From these records, we created ten unique training and test sets and created two groups of Bayesian Belief Network models designed to estimate the likelihood of 1, 3, 6, 12, 18, and 24-month postoperative survival—one set that contained the EGFR, ALK and TKI information in addition to the original PATHFx variables (combined model), and one that contained the PATHFx variables alone (original model). Each was cross validated on its corresponding test set and evaluated using Brier scores, area under the receiver operator characteristic (AUC), and decision curve analysis (DCA).

Results: The mean Brier scores for the combined models containing EGFR, ALK and TKI information were similar to the original models. In addition, the AUCs for the 12-month models were also similar (0.81). However, the AUCs for the 1, 3, 6, 18, and 24-month models were higher for the combined models (0.79, 0.72, 0.76, 0.87, 0.87 vs. 0.76, 0.69, 0.76, 0.84, 0.83). Decision analysis also demonstrates

physicians may achieve better outcomes by using the combined models rather than relying on the original models, and this difference was most pronounced with the longer, 18 and 24-month timepoints.

Conclusions: Inclusion of EGFR and ALK mutation status, as well as TKI treatment improves survival estimates made by the PATHFx models. Although the Brier scores were similar and the improvements in AUCs were small, DCA indicates the differences were clinically significant. These results justify further external validation studies, which will be necessary before these models can be recommended for clinical use. As such, we plan to include EGFR and ALK mutation status, as well as TKI treatment in the International Bone Metastasis Registry.

PAPER 55

Reamed Versus Unreamed Intramedullary Nailing for the treatment of Impending and Pathological Humeral Shaft Fractures: A Retrospective Comparative Study

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Background: There remains a compelling biological rationale for both reamed and unreamed intramedullary nailing for the treatment of long bone fractures. This particular question has never been addressed for impending and pathological fractures of the humeral shaft.

Purpose: (1) To compare uncemented reamed (R) versus unreamed (UR) intramedullary (IM) nailing for the treatment of Impending and Pathological fractures of the humeral shaft in terms of: (A) 24-h Post-operative pain; (B) Blood transfusion requirements; (C) Surgical time; (D) Surgical Complications; (E) Medical complications and length of stay; and (F) Consolidation rates (pathological fractures).

Methods: A retrospective comparative study of adult patients with an impending or pathological humerus shaft fracture treated with either reamed (R) or unreamed (UR) intramedullary nailing without cementation between January 2013 and December 2018 was conducted. Humerus fractures treated non-operatively or with plating with or without cementation were excluded. Perioperative care was standardized, and the surgical indication was surgeon's preference. Demographic characteristics between both groups were similar (Table 1). The primary outcome was pain during the first 24 hours postoperatively measured by visual analogue score (VAS) and total daily dose of opioid (in morphine milligram equivalents (MME) per day. Secondary outcomes were: Blood requirements (Estimated blood loss; Need for blood transfusion and 24-h change in HB), surgical time, surgical complications (Intra-operative fracture, radial nerve palsy, early and late infection, and need for revision surgery), medical complications (cardiovascular events), length of stay, and fracture consolidation. Student t-test, Mann-Whitney-U and Chi-square tests were used to detect significant differences between the variables within the two study groups. Multiple linear regression was done to adjust for possible confounders of the primary outcome.

Results: A total of 53 patients (33 R vs 20 UR) underwent humeral nailing. Fifteen (28%) were impending fractures (7 R vs 8 UR). The average age was 65.17+/- 11.9. Females were 52.83% (28/53). Multiple myeloma (49%) followed by metastatic carcinoma (39.6%) were the most common etiologies. Other associated fractures were observed in 26.42% (14/53) of patients (6 R vs 8 UR; p=0.081). Impending fractures constituted 28% of whole sample (15 fractures). Radiotherapy was performed in 73.58% (39/53) of patients. Average follow up was 6.75 months (range: 1-48 months) (Table 1).

Pain score (5.13+/-0.68 R vs 6.78+/-0.62 UR; p=0.082) and total dose of opioids (33.125+/-27.6 R vs 33.3+/-22.28 UR; p=0.462) during the first 24 hours after surgery didn't show statistical significant difference. Blood transfusion was more common within the reamed nails group (12 R vs 4 UR; p=0.021) with a tendency of higher blood loss (238.39+/- 215.18 R vs 129.25+/-119.63 UR; p=0.061). There was not statistical significant difference in terms of surgical time, surgical and medical complications, and length of stay. There was a consolidation rate of 71.05% (27/38) with no statistical difference between both groups (73.08% (19/26) R vs 66.67% (8/12) UR; p=0.685) (Table 2).

Conclusion: Unreamed IM nailing of impending or pathological humeral shaft fractures is a safe, rapid and effective procedure. The present study demonstrates a possible benefit in terms of less need for blood transfusions, and a tendency of less blood loss with no difference in consolidation rates within the pathological fracture group.

Table 1: Baseline characteristics of patients with pathological humerus shaft fractures treated with reamed or unreamed intramedullary nails

Characteristic	Total (N=53)	Reamed Intramedullary Nailing (N=33)	Unreamed Intramedullary Nailing (N=20)	P value
Age (years)	65.17±11.9 (range:19-86)	65.76±1.79	64.2±3.26	0.648
Gender				
Male	25 (47.17%)	16 (48.48%)	9 (45%)	
Female	28 (52.83%)	17 (51.52%)	11 (55%)	0.805
Diabetes	13 (24.53%)	5 (15.15%)	8 (40%)	0.042
Hypertension	28 (52.83%)	17 (51.52%)	11 (55%)	0.805
Dyslipidemia	23 (43.40%)	15 (45.45%)	8 (40%)	0.698
Coronary Heart Disease	7 (13.21%)	5 (15.15%)	2 (10%)	0.591
Medications				
NSAIDs	12 (22.54%)	7 (21.21%)	5 (25%)	0.749
Steroids	24 (45.28%)	12 (36.36%)	12 (60%)	0.094
Bisphosphonates	17 (32.08%)	11 (33.33%)	6 (30%)	0.801
Pathology				
Metastatic Carcinoma	21 (39.62%)	14 (42.42%)	7 (35%)	
Metastatic soft tissue sarcoma	1 (1.89%)	1 (3.03%)	0	
Malignant Melanoma	1 (1.89%)	0	1 (5%)	
Lymphoma	2 (3.77%)	1 (3.03%)	1 (5%)	
Multiple Myeloma	26 (49.06%)	16 (30.19%)	10 (50%)	
Benign lesions	2 (3.77%)	1 (3.03%)	1 (5%)	
Impending fracture	15 (28.30%)	7 (21.21%)	8 (40%)	0.141
Time from fracture to surgery (days)	15.05±1.91 (range:1-45)	16.81±2.46	11.25±2.70	0.180
Nail diameter (mm)				
7	3 (5.66%)	1 (3.03%)	2 (10%)	
8	42 (79.25%)	27 (81.82%)	15 (75%)	
9	8 (15.1)	5 (15.15%)	3 (15%)	0.565
No. of proximal locking screws				
1	2 (3.77%)	1 (3.03%)	1 (5%)	
2	37 (69.81%)	22 (66.67%)	15 (75%)	
3	14 (26.42%)	10 (30.3%)	4 (20%)	0.686
No. of distal locking screws				
1	37 (69.81%)	24 (72.73%)	13 (65%)	
2	16 (30.19%)	9 (27.27%)	7 (35%)	0.553
Other associated fractures	14 (26.42%)	6 (18.18%)	8 (40%)	0.081
Radiotherapy	39 (73.58%)	27 (81.82%)	12 (60%)	0.081
Chemotherapy	25 (47.17%)	14 (42.42%)	11 (55%)	0.374
Follow-up (months)	6.75±1.10 (range:1-48)	7.63±1.65	5.21±0.85	0.753

Table 2: Outcome measures of reamed and unreamed intramedullary nailing of humeral pathological fractures

Outcome/ complication	Total (N=53)	Reamed Intramedullary Nailing (N=33)	Unreamed Intramedullary Nailing (N=20)	Odds Ratio	P value
Surgical time (min) (mean)	244.9±93.7 (range:80-450)	274.44±22.12	230.95±23.49	-	0.259
Estimated blood loss (ml) (mean)	194.9±187.99	238.39±215.18	129.25±119.63	-	0.061
Blood transfusion	17 (32.08%)	12 (36.36%)	4 (20%)	2.29	0.021
24-h change in Hb (mean)	1.07±0.28	1.33±0.28	0.54±0.44	-	0.126
Iatrogenic fractures	2 (3.77%)	1 (3.03%)	1 (5%)	0.59	0.718
Nerve palsy	1 (1.89%)	1 (3.03%)	0	-	0.436
VAS score (mean)	6.03±0.47	5.13±0.68	6.78±0.62	-	0.082
24-h Total opioid dose (mean)	33.24±25.36	33.125±27.6	33.3±22.28	-	0.462
Length of hospital stay (days) (mean)	5.29±1.05 (range:1-33)	4.19±1.09	7.75±2.17	-	0.118
Early infection	1 (1.89%)	0	1 (5%)	-	0.199
Late infection	0	0	0	-	-
Post-op Cardio-vascular events	14 (26.42%)	10 (30.3%)	4 (20%)	1.74	0.414
Fracture consolidation	27/38 (71.05%)	19/26 (73.08%)	8/12 (66.67%)	1.36	0.685
Revision of surgery	0	0	0	-	-

PAPER 56

Comparison of Porous Tantalum Acetabular Implants versus Harrington Reconstruction for Metastatic Disease of the Acetabulum

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Introduction: The pelvis and acetabulum are common locations for the development of metastatic disease. Due to the mechanical forces transmitted through the hip, patients can have substantial pain and disability with ambulation. Surgical treatment, when required, often involves a large reconstruction that restores the mechanical stability of the hip while providing pain control and allowing for immediate weight-bearing. Historically the Harrington technique was the primary treatment option for patients with periacetabular neoplastic disease. This technique transmitted the load of the weak acetabulum to the stronger, intact iliac bone. Recently the use of porous tantalum shells to reconstruct metastatic lesions of the acetabulum has shown excellent short-term results. Currently there are no series directly comparing the outcome of both reconstructive techniques.

Purpose: The purpose of this study is to investigate the mid-term follow-up results comparing the use of the Harrington technique and tantalum acetabular components for (1) overall implant survival, (2) rates of complications and reoperation, and (3) patient function.

Method: One-hundred and six patients (64 females, 42 males) with a diagnosis of metastatic disease to the acetabulum were treated with complex hip reconstruction between 2002 and 2014 at two tertiary sarcoma centers. Of these, 29 were tantalum reconstructions and 77 were reconstructed with the Harrington technique.
We found no difference when comparing the tantalum to the Harrington group in terms of mean age (64 vs. 60 years, *P*=0.17), proportion of males (28% vs. 44%, *P*=0.18), Class III defects (48% vs. 55%, *P*=0.66), or presence of a pelvic discontinuity (24% vs. 22%, *P*=1.0) (**Table 1**). Patients in the tantalum group were more likely to have received preoperative radiotherapy (76% vs. 47%, *P*=0.008) while patients with a Harrington reconstruction were more likely to have received postoperative radiotherapy (7% vs. 39%, *P*=0.001). Likewise the surgical procedure was significantly longer in the Harrington group compared to the tantalum group (383 minutes vs. 305 mins, *P*=0.001).

Results: Over the course of the study 85 (80%) patients died due to disease at a mean of 16-months postoperatively (range postoperative day 1-112 months). The 2- and 5-year overall survival was 34% and 12%, respectively. We found no difference in the 2-year (34% vs.35%) and 5-year (17% vs. 8%) overall survival between the tantalum and Harrington cohorts (*P*=0.37).

Over the course of the study 23 patients underwent a reoperation for any cause. Patients in the Harrington cohort were more likely to undergo a reoperation (HR 3.76, 95% CI 1.27-16.09, *P*=0.01) compared to the

tantalum group. The acetabular reconstruction failed in 13 (12%) patients at a mean 27 months postoperatively (range 3 weeks-82 months) with no difference in the incidence of failure between the tantalum and Harrington groups (10% vs. 13%, *P*=1.0). Failures included acetabular loosening (n=5), dislocation (n=4), infection (n=2), and hardware fracture (n=2). All cases of acetabular loosening were in the Harrington cohort, with no cases of acetabular component loosening in the tantalum group (*P*=0.02). Prior to the reconstruction the mean Harris Hip Score was 30 (range, 4-77), which significantly improved to 68 (range, 19-93) at last follow-up (p<0.001). Patients in the tantalum cohort had a significantly increased mean preoperative Harris Hip Score compared to the Harrington group (35 vs 28, *P*=0.01); however postoperatively we found no difference in the mean scores between cohorts (67 vs. 69, *P*=0.41).

Conclusion

Compared to tantalum components the Harrington technique is more likely to require longer operative time and is associated with an increased risk of reoperation. However, in patients with periacetabular metastatic disease that requires reconstruction, utilizing either technique will provide a construct that is likely to last the duration of a patient's life and provide an improvement in functional outcomes. We recommend either technique based on the experience and comfort of the treating surgeon.

Table 1: Patient Demographics and Function

Demographic	Tantalum (n=29)	Harrington (n=77)	P Value
Mean Patient Age (±SD, Years)	64±12	60±13	0.17
Male Gender	8 (28%)	34 (44%)	0.18
Harrington Class III Defects	14 (48%)	42 (55%)	0.66
ECOG ≥3	9 (31%)	38 (49%)	0.12
Pelvic Discontinuity	7 (24%)	17 (22%)	1.0
Preoperative Radiotherapy	22 (76%)	36 (47%)	0.008
Postoperative Radiotherapy	2 (7%)	30 (39%)	0.001
Operative Factors			
Use of Reconstructive Cage	17 (57%)	21 (27%)	0.003
Mean Number of Screws (±SD)	8±3	5±2	0.001
Mean Acetabular Shell Diameter (±SD)	58±4 mm	52±4 mm	0.001
Mean Operative Time (minutes, ±SD)	305±78 minutes	383±83 minutes	0.001
Functional Assessment			
Preoperative Mean Harris Hip Score (±SD)	35±14	28±12	0.01
Postoperative Mean Harris Hip Score (±SD)	67±14	69±14	0.41

PAPER 57

A novel percutaneous osseous pathway screw fixation technique for management of periacetabular metastatic disease

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Background: The goals of surgical fixation for periacetabular metastatic disease are to reduce pain, decrease risk of fracture, facilitate early mobilization, and avoid reoperation, all while minimizing operative risks. The traditional Harrington fixation method for periacetabular metastatic disease has been described with Steinman pins placed from the ipsilateral ilium into the defect, or vice versa, often with cement augmentation. However, this only provides limited trajectories for pin placement that are not in the true bony columns. To address this, we have developed a new osseous pathway fixation technique that places percutaneous screws into the anterior column, posterior column, supraacetabular region, and/or ilium. We believe this modified technique to be more accurate anatomic reconstruction than the harrington technique that can more effectively cross-link the pelvis, and provide a reliable buttress for total hip arthroplasty (THA).

Questions/Purposes: This study sought to understand the feasibility and safety of a new osseous pathway fixation technique to be used in conjunction with cemented-cup THA in patients with periacetabular disease. Specifically, we asked how many screw bone breeches, screw cutouts, and inadvertent nerve, vessel, and visceral organ injuries occurred using this percutaneous technique.

Patients and Methods: IRB approval was obtained for this retrospective study. We reviewed all patients who underwent osseous pathway screw fixation along with THA at our institution by a single surgeon between October 2016 and January 2019. For each patient, we reviewed the diagnosis, pattern of screw fixation, additional procedures, intra-operative screw placement time and complications, and post-operative medical and hardware complications related to surgery. Intra-operative fluoroscopy images were used to calculate screw placement time.

Results: 11 patients, aged 48 to 71, were included in this study: 10 with metastatic periacetabular disease, 1 with a solitary plasmacytoma. All patients had supra-acetabular bone loss in the weight-bearing dome with pathologic fracture into the joint. 8 patients were noted to have pelvic discontinuity. All underwent total hip arthroplasty with a cemented cup. 3 patients were treated with an anti-protrusio cage. 9 patients had at least 3 osseous pathway screws placed. All but 2 (6.5mm) were 7.3mm cannulated screws. All screws were successfully placed percutaneously. Average placement time was 17 minutes per screw, ranging from an average of 12 minutes for anterior column screws to an average of 20 minutes for supra-acetabular screws. There were no instances of screw bone breeches, screw cutout, or inadvertent nerve, vessel, or visceral organ injury. Post-operative complications included 1 thigh hematoma unrelated to screw placement. There were no complications associated with THA, including dislocation, cup loosening, broken screws, or failed buttress, and none required revision.

Conclusions: We demonstrate that a novel percutaneous osseous pathway screw fixation technique is a safe and promising alternative in the treatment of periacetabular disease with improved rebar and durability when combined with THA. Future studies will evaluate long-term functional outcomes and complications.

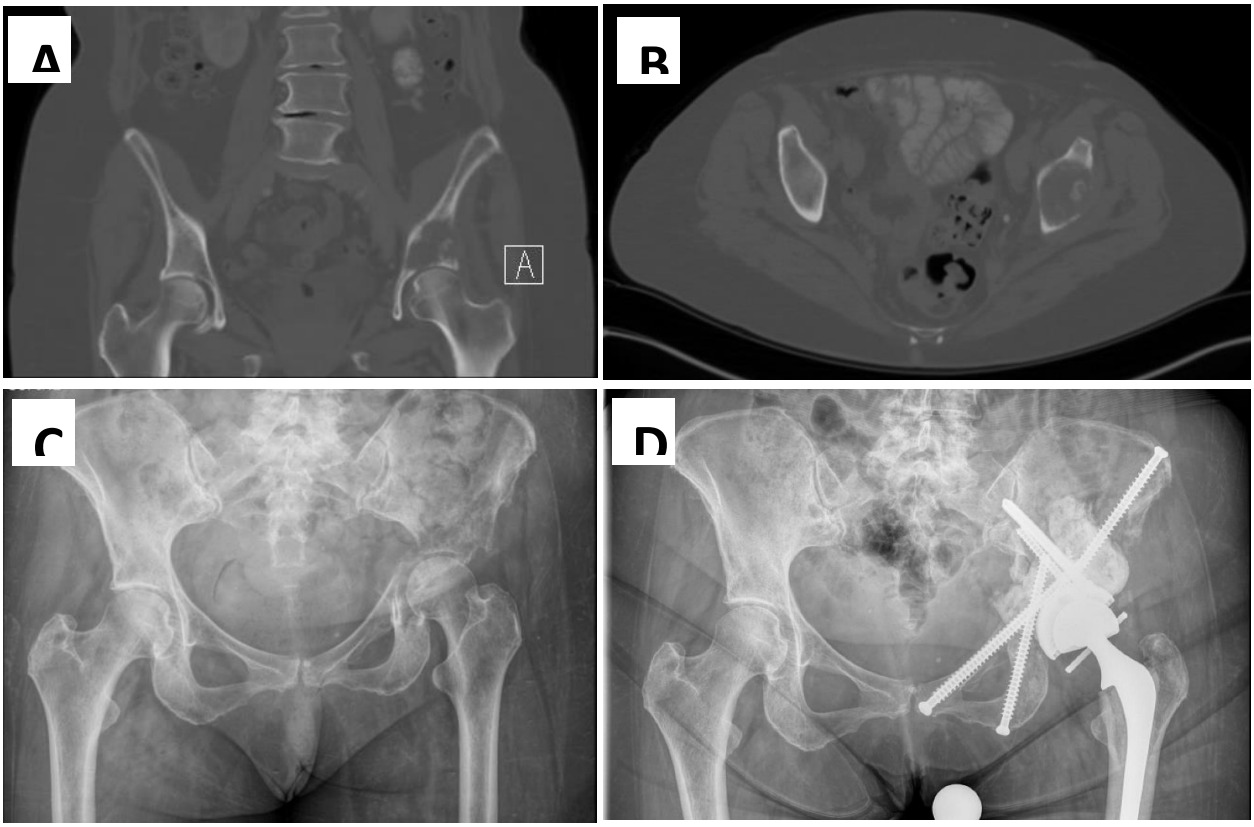

Figure 1. Pre-operative (A-C) and post-operative (D) imaging of a 70-year-old female with squamous cell carcinoma of the renal pelvis treated with tumor curettage, osseous fixation pathway screws (anterior and posterior columns, supraacetabular, and ilium), and total hip arthroplasty with cup cementation.

PAPER 58

Ambulatory Minimally Invasive Image-Guided Ablation-Osteoplasty-Reinforcement-Internal Fixation (AORIF) Reconstruction For Osteolytic Metastatic Cancers In Weight Bearing Bones

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Background: Presence of metastatic cancer cells in bone initiate bone destruction by promoting osteoclastic bone resorption and inhibiting osteoblastic bone repair. Anti-resorptive drugs such as bisphosphonates and denosumab are often insufficient to overcome metastatic cancer-induced bone loss unless metastatic cancer cells are dead. Metastatic cancers cells frequently exhibit chemoresistance and radiation-resistance. Therefore, local control of cancer cells is very important to prevent progressive bone loss after surgical stabilization of osteolytic metastasis. While osteolytic metastases in long bone diaphyses are commonly managed with intramedullary nailing, surgical reconstruction of pelvic bone defects and periarticular lesions around the knee or ankle require large skin incisions and deep surgical dissections, which are associated with high incidences of muscle weakness, infection, prolonged morbidity, transfusion, and delayed pharmacologic cancer therapies. It is most ideal if big open surgeries can be avoided for patients with advanced cancers without knowing remaining life span.

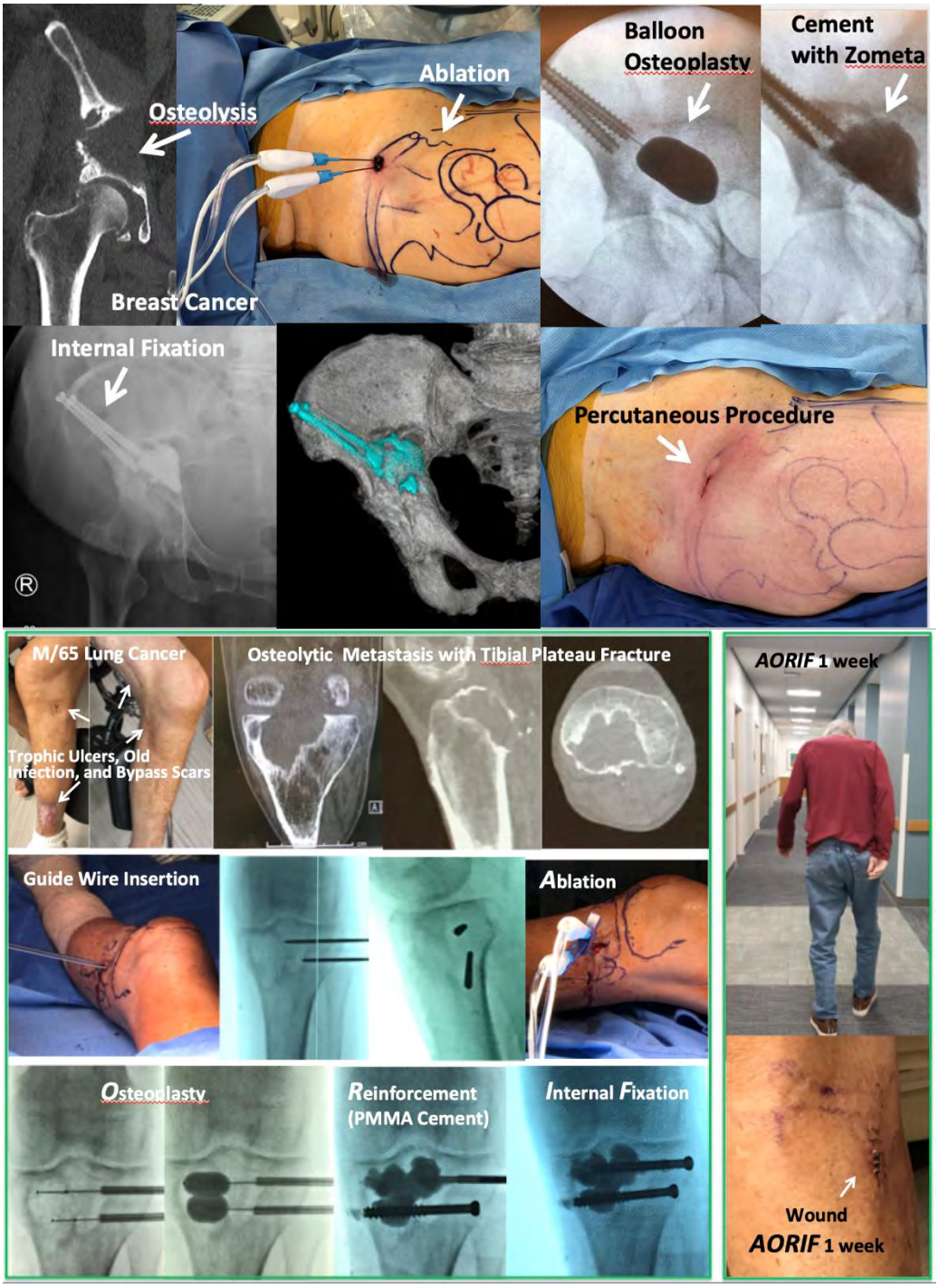
Questions and Purposes: The purpose of our study is to describe minimally invasive percutaneous **A**blation-**O**steoplasty-**R**einforcement-**I**nternal **F**ixation (**AORIF**) with respect to indications, surgical techniques, and surgery-related outcomes.

Patients & Methods: We have developed a minimally invasive AORIF as a novel surgical strategy for management of radiation-resistant osteolytic metastatic cancers in the pelvis and periarticular lesions around the knee and ankle. 21 patients with 23 osteolytic metastatic lesions to pelvis (N=17), proximal tibial plateau (N=2), femur (N=3) and calcaneus (N=1) underwent AORIF. Primary cancers were from lung (lung cancers), breast (breast cancers), kidney (clear cell carcinoma), skin (melanoma), oral cavity, and bladder (endocrine cancer). AORIF begins with insertion of a guide wire for a 8 mm cannulated screw that has a 3.2 mm-diameter hollow channel in the center under CT image guidance through a 1-2 cm skin incision instead of a long surgical incision and soft tissue dissection. This cannulated screw is used as a port for cancer ablation, osteoplasty, and delivery of bone cement. The screw is inserted through the most intact bone in the anterior or posterior iliac crest toward metastatic cancers in the destroyed bone so that mechanical integrity of the pelvis is best preserved (Figure). If guide wires or screws are inserted from the destroyed bone toward the intact bone, cancers may be extruded out with bleeding and loss of control of screw track. Through a cannulated screw, ablation of metastatic cancers is conducted with radiofrequency or microwave ablation probe in order to decrease cancer burden and halt the process of cancer-induced bone loss (Figure). In order to displace ablated tumors, necrotic coagulum, or blood clots,

a balloon is inflated in the ablated region so that polymethylmethacrylate (PMMA) bone cement can be injected through the screw (Figure). Baloon osteoplasty was also used for reduction of depressed articular surface. The cannulated screw is then completely advanced through the PMMA bone cement that provides immediate reinforcement of the destroyed bone and anti-cancer effects through exothermic curing.

Results: AORIF is illustrated in **Figures**. None of out-patients required transfusion or hospital admissions. Infection, delay in chemotherapy, and prolonged morbidity from surgical dissections were avoided while functional improvement and decreased pain were observed in all patients. Morbidity from our percutaneous procedure was minimal, allowing the same-day discharge. One patient had an osteolytic metastasis around the acetabular component of the prior total hip arthroplasty (impending pathological implant loosening) that were salvaged by our percutaneous AORIF revision acetabuloplasty. Zoledronate was added to the bone cement if osteolysis is progressive. Combined pain-function score improved as early as 1 day without suffering pain from conventional long open incision and deep surgical dissections.

Conclusions: AORIF, although very satisfactory, is another non-curative but minimally invasive cancer-burden reducing procedure for osteolytic skeletal metastases. Skeletal defects secondary to metastatic cancers in deep anatomic locations can be effectively stabilized while avoiding extensive open surgeries. AORIF is indicated for large osteolytic defects around or near the acetabulum, sacroiliac joints, pelvic ring, proximal tibia, and calcaneus in patients with advanced cancers that did not respond to radiation, chemotherapy, bisphosphonates, and denosumab before open surgeries are considered. Periprosthetic metastases require a confirmatory biopsy in order to differentiate wear particle-induced osteolysis vs. metastasis. Developing new pharmacologic or minimally invasive interventional orthoopaedic oncologic treatments for metastatic cancers and cancer-induced bone loss need to be continuously pursued for advanced oncologic care.


Osteolysis
Ablation
Balloon Osteoplasty
Cement with Zometa
Breast Cancer
Internal Fixation
Percutaneous Procedure
M/65 Lung Cancer
Trophic Ulcers, Old Infection, and Bypass Scars
Osteolytic Metastasis with Tibial Plateau Fracture
AORIF 1 week
Guide Wire Insertion
Ablation
Osteoplasty
Reinforcement (PMMA Cement)
Internal Fixation
Wound
AORIF 1 week

PAPER 59

Pexidartinib for Locally Advanced Tenosynovial Giant Cell Tumor (TGCT): Overall Long-Term Pooled Efficacy and Safety With Characterization of Hepatic Adverse Reactions (ARs) From ENLIVEN and Other Studies

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Background: TGCT is a rare, locally aggressive neoplasm of the joint/tendon sheath related to colony-stimulating factor 1 (CSF1) overexpression, with no currently approved systemic therapy. Pexidartinib, a selective inhibitor of the CSF1 receptor, KIT, and FLT3-ITD, had compelling activity in TGCT cohorts of 2 phase 1 trials: PLX108-01 (NCT01004861) and NCT02734433. In ENLIVEN (NCT02371369), a randomized, placebo-controlled phase 3 study in TGCT, pexidartinib showed a robust and clinically relevant tumor response vs placebo at week 25 by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (39% vs 0%, respectively; $P<0.0001$) and by tumor volume score (TVS) (56% vs 0%; $P<0.0001$). Pexidartinib, like other tyrosine kinase inhibitors (eg, nilotinib, imatinib), is associated with hepatic ARs. Here we report long-term overall efficacy and safety from pooled ENLIVEN and PLX108-01, and treatment-emergent hepatic ARs across TGCT studies: ENLIVEN, PLX108-01, NCT02734433, and NCT03291288 (pharmacokinetics study).

Purpose: This analysis assessed long-term pexidartinib efficacy and safety data in pooled populations. For ENLIVEN and PLX108-01, the primary endpoint was centrally reviewed objective response rate at week 25 by RECIST v1.1. Secondary endpoints included response rate by range of motion, TVS, patient-reported outcomes, and duration of response (DOR). For ENLIVEN, PLX108-01, NCT02734433, and NCT03291288, hepatic ARs were reported and assessed for any long-term safety signals.

Patients and Methods: ENLIVEN and the multicenter, single-cohort extension of PLX108-01 enrolled patients ≥18 years of age with histologically confirmed locally advanced symptomatic TGCT that was inoperable or for which surgery was associated with worsening functional limitation or severe morbidity. In ENLIVEN double-blind phase, patients were centrally randomized 1:1 to receive either pexidartinib (1000 mg/d × 2 wk, then 800 mg/d × 22 wk) or matching placebo for 24 weeks. In the open-label phase, patients receiving placebo could cross over to receive pexidartinib. In PLX108-01, patients received pexidartinib 1000 mg/d. Both ENLIVEN and PLX108-01 assessed best overall response (BOR; complete response [CR] or partial response [PR]) and DOR, by both RECIST v1.1 and TVS based on independent central review. ENLIVEN assessed efficacy at baseline, week 13, and week 25, and PLX108-01 assessed it at baseline and every 2 months. The pooled overall efficacy and safety analysis included ENLIVEN and

PLX108-01, whereas pooled hepatic AR analyses (aminotransferase elevations, and mixed and cholestatic hepatotoxicity) also included the NCT02734433 (600 mg/d pexidartinib) and NCT03291288 (800 mg/d pexidartinib) studies. Hepatic ARs were assessed by type and magnitude of liver test abnormalities in TGCT patients across studies.

Results: For long-term pooled overall efficacy and safety, 130 patients across 2 studies (ENLIVEN and PLX108-01) received pexidartinib; 61 (47%) were still on treatment at data cutoff. Median follow-up from first dose to data cutoff was 23 months (range, 16, 67), and median treatment duration was 17 months (range, 1, 60+). Only 5 patients (4%) discontinued pexidartinib due to progressive disease. The pooled RECIST-based BOR rate was 54%, with a trend toward increased BOR with treatment prolongation. DOR results are provided in **Table 1**. The most frequently reported adverse events (AEs) in the overall safety analysis were hair color change (74%), fatigue (57%), and nausea (42%) **(Table 1)**.

In 130 patients assessed for hepatic ARs from ENLIVEN and PLX108-01, the mean pexidartinib duration was 75 weeks (range, 2.14, 259.14); 10 additional pexidartinib-treated patients from 2 other phase 1 studies are included in **Table 2** (N=140). Hepatic ARs were of 2 types: (1) aminotransferase elevations, which were most common, dose-dependent, and responded to dose interruption and reduction, and (2) mixed and cholestatic hepatotoxicity, which were uncommon and sometimes prolonged. All serious hepatic ARs developed within the first 2 months of treatment. Four serious but nonfatal mixed and cholestatic cases with increased bilirubin (1 ductopenia) resolved after 1-7 months. In the non-TGCT patients, 2 severe cases of liver toxicity (1 leading to liver transplant, 1 death with ongoing cholestasis and tumor progression) were observed with pexidartinib.

Conclusions: Pexidartinib is the first systemic therapy evaluated within a randomized study to demonstrate significantly improved tumor response in locally advanced TGCT. Long-term follow-up showed a trend toward increased tumor response with prolonged pexidartinib treatment. The safety profile was consistent with earlier reports, with no new safety signals. With liver test monitoring, pexidartinib may offer a relevant treatment option for select patients with symptomatic TGCT associated with severe morbidity or functional limitations, and not amenable to improvement with surgery.

Table 1. Long-term pooled overall efficacy and safety (ENLIVEN and PLX108-01)

Endpoint	Phase 3 ENLIVEN Randomized (1000 mg/d)* n=61	Phase 3 ENLIVEN Crossover (800 mg/d)* n=30	Phase 1 PLX108-01 (TGCT Cohort) (1000 mg/d)* n=39	Pooled TGCT Population N=130
First dose to data cutoff (follow-up)				
Median (range), mo	22 (16, 31)	18 (116, 27)	49 (32, 67)	23 (16, 67)
Mean (SD), mo	22 (4)	19 (3)	49 (10)	29 (14)
Treatment duration				
Median (range), mo	16 (1, 30)	17 (2, 27)	17 (1, 60+)	17 (1, 60+)
RECIST (v1.1)-based BOR				
CR/PR, n (%) [95% CI]	32 (53) [40, 65]	16 (53) [36, 70]	22 (56) [41, 71]	70 (54) [45, 62]
RECIST (v1.1)-based DOR				
Median (range), mo	NR (3+, 25+)	NR (3+, 23+)	34 (2, 53+)	NR (2, 53+)
TVS-based BOR				
CR/PR, n (%) [95% CI]	39 (64) [51, 75]	20 (67) [49, 81]	24 (62) [46, 75]	83 (64) [55, 72]
TVS-based DOR				
Median (range), mo	NR (0+, 28+)	NR (6+, 23+)	37 (2, 53+)	NR (0+, 53+)
Most common AEs				
Hair color change	43 (71)	25 (84)	28 (72)	96 (74)
Fatigue	34 (56)	5 (17)	35 (90)	74 (57)
Nausea	24 (39)	6 (20)	25 (64)	55 (42)
Arthralgia	17 (28)	6 (20)	21 (54)	44 (34)

*Pexidartinib starting dose.
NR=not reached.

Table 2. Liver Test Abnormalities

Clinical Parameter	Phase 3 ENLIVEN Randomized (1000 mg/d)* n=61	Phase 3 ENLIVEN Crossover (800 mg/d)* n=30	Phase 1 NCT01004861 TGCT Cohort (1000 mg/d)* n=39	Other Phase 1† (600 or 800 mg/d)* n=10	Total§ N=140
Aminotransferase elevations, n (%)					
ALT or AST					
≥1 < 3 × ULN	48 (79)	21 (70)	27 (69)	6 (60)	102 (73)
3 < 5 × ULN	8 (13)	3 (10)	4 (10)	2 (20)	17 (12)
5 < 10 × ULN	7 (11)	2 (7)	2 (5)	0	11 (8)
10 < 20 × ULN	3 (5)	1 (3)	2 (5)	0	6 (4)
>20 × ULN	2 (3)	0	0	0	2 (1)
Mixed and cholestatic hepatotoxicity, n (%)					
ALT or AST ≥3 ×, TBIL ≥2 ×, and ALP ≤2 × ULN (Hy's law)	0	0	0	0	0
ALT or AST ≥3 ×, TBIL ≥2 ×, and ALP ≥2 × ULN	3 (5)	0	1 (3)‡	1 (10)	5 (4)‡
TBIL ≥2 × ULN (in absence of ALT ≥3 × or ALP >2 × ULN)	0	0	1 (3)	0	1 (1)

*Pexidartinib starting dose.
†Includes 1 TGCT patient receiving 600 mg/d in NCT02734433 and 9 TGCT patients receiving 800 mg/d in NCT03291288.
‡Includes 1 TGCT patient with an isolated elevation of TBIL considered unrelated to treatment.
§Mean pexidartinib duration of all studies was 71 weeks (range, 2.14, 259.14).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ULN, upper limit of normal.

PAPER 60

PVNS of the knee: A consecutive series of 54 patients treated either arthroscopically or with open synovectomy

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Introduction: Pigmented Villo-nodular Synovitis (PVNS) is an uncommon proliferative condition which commonly affects the knee. Currently, treatment may include arthroscopic synovectomy or open synovectomy. The current study aims to report outcomes of patients with PVNS treated at a single institution.

Questions/Purposes:
Do the rates of complications differ between open and arthroscopic synovectomy?
Is there a difference in tumor size between open and arthroscopic synovectomy?
Is there a correlation between anatomic location of the PVNS and the decision to do open and arthroscopic synovectomy?

Methods: From 2002-2019, 54 patients were treated for PVNS at the knee by either arthroscopic debridement or open synovectomy. Patient charts were evaluated for tumor volume, local recurrence rates, rates of infection, and demographic data. Patients were followed for a mean of 33 (median 12, range 0-189) months. Patients with localized disease in the anterior portion of the knee were indicated for arthroscopy. Patients with diffuse disease in the anterior compartment were also indicated for scope, unless tumor burden was deemed large enough to warrant open synovectomy. If the posterior compartment of the knee was involved, open synovectomy was utilized.

Results: A total of 40 patients were diagnosed with diffuse PVNS (DPVNS) of the knee, and 14 patients were diagnosed with localized PVNS (LPVNS). Of the patients with diffuse PVNS, 26 involved only the anterior compartment, 6 involved only the posterior compartment, and 8 involved both the anterior and posterior compartments. Of the patients with localized PVNS, 11 involved only the anterior compartment, and 3 involved only the posterior compartment. Open synovectomy was utilized for 25 patients (63%) with DPVNS, including 15 anterior synovectomies, 4 posterior synovectomies, and 6 anterior and posterior synovectomies. Arthroscopy was utilized in 15 patients with DPVNS, with 7 requiring conversion to open synovectomy. Of the cases converted to open synovectomy, 4 involved the anterior compartment, 2 the posterior, and 1 the anterior and posterior compartments. Five patients with LPVNS underwent open synovectomy, including 3 anterior synovectomies and 2 posterior synovectomies. Nine patients with LPVNS underwent arthroscopic synovectomy. Three patients, all with anterior LPVNS required conversion from arthroscopic synovectomy to open synovectomy. Patients treated with open synovectomy had significantly larger tumor volume (196.1+/-311.0 vs. 42.7+/- 64.6; p=0.0350. There was an overall complication rate of 20%. Most (80%) complications were related to local disease recurrence. Complication rates were comparable between open and arthroscopic treatment (p=0.129). The overall rate of recurrence was, with comparable recurrence rates after arthroscopic and open synovectomy (15% vs. 27%; p=0.500).

Conclusions: PVNS at the knee poses a challenging problem for orthopaedic surgeons. Decision making for treatment of PVNS arthroscopically versus open is multifactorial, and is dependent on factors including tumor volume, anatomic location of disease, and surgeon preference or comfort with arthroscopy. Both treatment options were associated with less than 30% risk of recurrence and comparable complication rates.

		Localized PVNS	**Diffuse PVNS**
Compartment	Anterior	11	26
	Posterior	3	6
	Both		8
Treatment	Arthroscopy	6	8
	Arthroscopy + Synovectomy	3	7
	Anterior Synovectomy	3	15
	Posterior Synovectomy	2	4
	Anterior and Posterior Synovectomy	0	6

PAPER 61

Retrospective Review Of Venous Thromboembolism Prophylaxis In Surgical Resection Of Benign And Malignant Tumors Of Bone and Soft Tissue.

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Institution:
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Background: Venous thromboembolic (VTE) prophylaxis is an important part of orthopedic care as it is a major source of surgical complication [1,2] . Though heparin and novel oral anticoagulants have been described as being more potent against thrombosis, there has been pushback against over-anticoagulation due to increased risks of bleeding, wound dehiscence (WD), and immobilization.

Purpose: Orthopedic oncology represents a diverse procedural field involving soft tissue and, bone resection, arthroplasty and amputation. Previous studies have questioned the hypercoagulable state of sarcoma patients[3]. Therefore, it is important to evaluate the risks and benefits surrounding VTE prophylaxis in patients undergoing surgical resection of primary sarcomas and benign neoplasms of the bone and soft tissue.

Patients and Methods: In this retrospective chart review, we describe the rates of VTE in patients treated at one tertiary referral center. A retrospective search from 1/1/2012-10/1/2018 (n=225) was conducted for patients who underwent surgical resection for primary sarcomas of the bone and soft tissue. Surgical resection of benign neoplasm of bone or soft tissue were also reviewed (n=682). Only patients whose diagnoses were confirmed postoperatively by pathology were included in this study. Patients were grouped based on VTE prophylaxis given perioperatively and up to three days postoperatively. All patients were treated with sequential compression devices. The patients were stratified into aspirin, heparin or no prophylaxis groups. VTE and WD rates were then assessed by clinical diagnosis for complications up to 6 months postoperatively.

Results: In sarcoma patients, the results showed no statistically significant VTE rates in any of the groups (Aspirin vs None RR= 0.820, 95% CI 0.4294 to 1.5963, p=0.573), (Aspirin vs Heparin RR= 1.6104, 95% CI 0.8297 to 3.1255, p=0.159) (Heparin vs None RR=1.333, 95% CI 0.7737 to 2.2977, p=0.3002). There was statistically significant increased risk in WD rates in the Aspirin and Heparin groups compared to no prophylaxis (Aspirin vs None RR= 2.8978 95% CI 1.1291 to 7.4372, p=0.0269), (Aspirin vs Heparin RR= 0.8598 95% CI 0.4175 to 1.7706, p=0.6819) (Heparin vs None RR=3.3704 95% CI 1.3511 to 8.4076, p=0.00902). Surgical resection of benign neoplasms (n=682) showed a statistically significant increase in VTE risk in the Aspirin and Heparin groups compared to no prophylaxis (Aspirin vs None RR= 4.3472, 95% CI 2.0980 to 9.0079, p=0.0001), (Aspirin vs Heparin RR= 0.3873 95% CI 0.2196 to 0.6830, p=0.0011) (Heparin vs none RR=11.2255, 95% CI 5.6462 to 22.3177, p<.0001)There was also a statistically significant increase in WD rates (Aspirin vs None RR= 2.2139, 95% CI 0.9750 to 1.7290, p=0.0575), (Aspirin vs Heparin RR= 0.4107, 95% CI 0.1824 to 0.925, p=.0317) (Heparin vs none RR= 5.39, 95% CI 2.4692 to 11.766, p<.0001).

Conclusions: In comparison to recent literature, this study shows increased rates of VTE but similar WD rates with chemical prophylaxis 1. This could be explained by the lower specificity of a clinical diagnosis of VTE and lack of definitive confirmation by ultrasound. Overall, this study suggests that aspirin or heparin do not decrease the risk of VTE in sarcoma patients while increasing the risk of WD. Similarly, in the benign group, there is increased risk of VTE and WD in the prophylaxis cohort compared to the nil group. Overall, this study is limited by its retrospective nature and we do not exclude the possibility of selection bias. We suggest that no prophylaxis for patients treated with surgical resection of a bone or soft tissue sarcoma is a reasonable alternative given comparable VTE rates and a statistically significant decrease in WD rates. This warrants a more comprehensive look at VTE prophylaxis in orthopedic oncology as a whole, including a prospective randomized control clinical trial.

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