2018

Rush Orthopedics Journal

⊕ RUSH

LEADING, THEIR WAY. What makes pediatric orthopedic surgeon Monica Kogan, MD (center and on the cover), adult reconstructive surgeon Aaron G. Rosenberg, MD, and primary care sports medicine physician Kathy Weber, MD, MS (left), such inspiring leaders, what inspires them to lead, and why do they have such loyal followings? Find out on pages 26, 36 and 49.

Faculty Editors

Articles

Chairman's Letter

"Follow your bliss."

This quote by anthropologist Joseph Campbell immediately springs to mind when I think about leadership—which, in addition to being the theme of this year's *Rush Orthopedics Journal*, is one of the greatest strengths of our orthopedics program here at Rush.

What constitutes a great leader? Ask 100 people and you'll likely get 100 different answers. I've always believed that your success as a leader should be judged not by your own accomplishments, but by the accomplishments of those you lead. A leader, therefore, should first and foremost inspire greatness. The servant-leadership model (also known as "flipping the pyramid") is something my predecessors, Jorge O. Galante, MD, DMSc, and Gunnar B. J. Andersson, MD, PhD—among the finest leaders that orthopedics has ever known—impressed upon me and my peers; and it's something I try to impress upon our faculty today. Any clinical program will flourish if the faculty and staff are encouraged and supported to pursue their passions. Or, as Professor Campbell so eloquently stated, to follow their bliss. If, as a department chairperson, you provide your faculty with the tools they need to succeed, then get out of their way, you will ultimately have a highly engaged, productive, and accomplished department.

Individuals have different interests, and it's the complementary nature of our faculty's interests that makes the Department of Orthopedic Surgery at Rush consistently strong. While all of our faculty contribute to our department's success, they do so in different ways. Some are renowned for their surgical or therapeutic innovations. Others are engaged in impactful basic or translational research, or are passionate about resident and fellow education. Still others have a keen interest in and aptitude for the business of academic medicine, striving to deliver the highest quality of care while minimizing costs in the rapidly changing health care marketplace. We have faculty who are team physicians, caring for world-class athletes, and faculty who treat the poorest of the poor in disaster-ravaged conditions.

And, of course, many of our faculty serve in leadership positions within our department, within Rush University, regionally, nationally, and globally. This includes the boards and leadership lines of some of our most important professional organizations. I'm extremely proud to share that 5 of our clinical faculty are currently in the presidential lines of prominent specialty societies, and one of our adjunct research faculty recently joined the presidential line of one of the nation's premier orthopedic research societies:

- **Craig J. Della Valle, MD,** is president of the American Association for Hip and Knee Surgeons (AAHKS), the premier professional organization for adult reconstructive orthopedic surgery; he is the first physician from Rush to be serve as president of AAHKS in its 30-year history. This honor is an acknowledgement not only of his many contributions to AAHKS, but of his leadership abilities and the confidence that his colleagues, nationwide, have in him.

- **Anthony A. Romeo, MD,** is the president of the American Shoulder and Elbow Surgeons, the leading organization of its kind in the US. Romeo is a recognized authority in complex reconstructive procedures of the shoulder and a pioneer in arthroscopic treatment of common shoulder disorders. He is the first Rush physician to lead this organization.

- **Charles A. Bush-Joseph, MD,** is the immediate past-president of the American Orthopaedic Society for Sports Medicine (AOSSM), an honor that recognizes his leadership role over several decades within both the society and the field of sports medicine. In addition to serving on the AOSSM board of directors for many years, he was president of the MLB Team Physician Association in 2012. **Bernard Bach, Jr, MD,** has been the only other Rush physician to serve in this role (2007–2008).

Distinguished Spine Surgeon and *Rush Orthopedics Journal* Editor in Chief David Fardon, MD, Retires

BY ADAM YANKE, MD, PHD

As you may have noticed, the *Rush Orthopedics Journal* (ROJ) has a new editor in chief. I am privileged to be taking over leadership of the journal from David Fardon, MD, who retired in February after a career spanning more than 5 decades—including 8 years at Rush and 6 years as the ROJ's editor in chief.

Dr Fardon brought to the ROJ the same passion, creativity, intelligence, and standards of excellence that he brought to his clinical practice. With each issue of the journal, he strived to raise the bar, always focused on how best to spotlight our faculty's accomplishments in the most engaging way possible—and the body of work he helped to create speaks for itself. I truly enjoyed working with Dr Fardon on the journal and look forward to building upon the foundation of excellence that he and his predecessor, Steve Gitelis, MD, have established.

On a personal note, I also had the privilege of being trained under the guidance of Dr Fardon, so I can speak firsthand about his thorough and thoughtful approach to everything he did. Dr Fardon is a shining example of the true difference between knowledge and wisdom.

An exemplary career

A medical graduate of the Kansas University Medical School, David Fardon completed his orthopedic residency at the University of Missouri Medical Center.

He came to Rush in 2008 from Southeastern Orthopaedics, where he had a distinguished career in clinical orthopedic medicine, spinal surgery, academic pursuit, and national leadership. He authored numerous scientific articles, textbook chapters, and books addressing disorders related to the spine, including coeditorship of the prestigious *Orthopaedic Knowledge Update for Spine II*. This academic volume, published by the American Academy of Orthopaedic Surgery and the North American Spine Society (NASS), is used as a core curriculum text for graduate training in spine.

In 1996 and 1997, Dr Fardon served as president of NASS, and in 2000, the society awarded him with its Selby Award for Outstanding Contributions to Spine Care. He also participated in NASS's Clinical Guidelines and was a faculty presenter at the American Academy of Disability Examining Physicians course on AMA Guidelines.

A true patient advocate

Above all else, Dr Fardon was fully committed to providing the best possible care to every patient—as a surgeon, and as a non-operative spine specialist after he stepped back from the operating room—as his colleagues attest.

"David was an excellent clinician: honest, ethical, and a true patient advocate," says spine surgeon Edward J. Goldberg, MD. "With his vast experience, he was also an excellent teacher, not only to the residents and fellows, but to his partners as well."

As a testament to his standing among fellow physicians, Dr Fardon was named by his peers to "Best Doctors in America" each of the past 14 years. He is a member of the prestigious American Orthopaedic Association, and has served on the editorial boards of 5 major orthopedic, spine-related journals.

Frank M. Phillips, MD, director, Division of Spine Surgery at Rush, reflected on Dr Fardon's legacy: "He has left an indelible mark at Rush. He has been a leader and teacher in the spine world as well as a passionate physician who always put his patients first."

Kern Singh, MD, co-director of the Minimally Invasive Spine Institute at Rush, shared that Dr Fardon was, "the consummate gentlemen, educator, and patient advocate."

"It has been a great honor and privilege to have David at Rush for the past 10 years," adds spine surgeon Howard S. An, MD. "His teaching of residents and fellows is truly exemplary, and he is a role model as a physician and a person. It is a great honor to have him as my colleague and friend." ❖

Orthopedic Faculty and Fellows

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Director, Section of Research
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Associate director, Orthopedic Surgery
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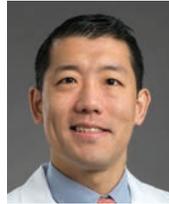
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The Claude N. Lambert, MD/Helen S. Thomson
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Professor, Department of Orthopedic Surgery
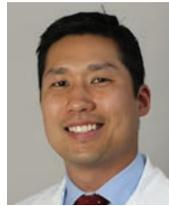
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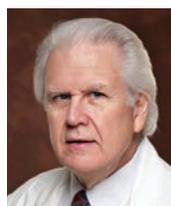
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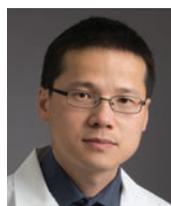
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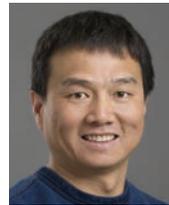
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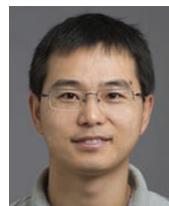
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Director, the Joan and Paul Rubschlager
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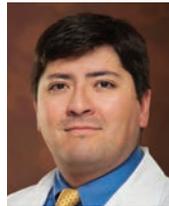
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Alfons Fischer, PhD

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Bryan M. Saltzman, MD
Medical school – Rush Medical College

Robert A. Sershon, MD
Medical school – Rush Medical College

Matthew W. Tetreault, MD
Medical school – University of Pittsburgh School of Medicine

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Kevin Campbell, MD
Medical school – University of Wisconsin School of Medicine and Public Health

Philip Louie, MD
Medical school – University of Washington School of Medicine

Timothy Luchetti, MD
Medical school – Columbia University College of Physicians and Surgeons

Allison Rao, MD
Medical school – Stanford University School of Medicine

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Medical school – Yale University School of Medicine

Islam Elboghdady, MD
Medical school – Rush Medical College

Charles Hannon, MD
Medical school – Georgetown University School of Medicine

Mick Kelly, MD
Medical school – University of Wisconsin School of Medicine and Public Health

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Ian MacLean, MD
Medical school – University of Virginia School of Medicine

Arash Sayari, MD
Medical school – University of Miami Leonard M. Miller School of Medicine

David Zhu, MD
Medical school – Yale School of Medicine

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William M. Cregar, MD
Medical school – Virginia Commonwealth University School of Medicine

Joshua A. Greenspoon, MD
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Timothy C. Keating, MD
Medical school – Virginia Commonwealth University School of Medicine

Michael T. Nolte, MD
Medical school – University of Michigan Medical School

CLASS OF 2023

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Medical school – Medical University of South Carolina

Robert Burnett, MD
Medical school – University of Iowa Roy J. and Lucille A. Carver College of Medicine

Edward Hur, MD
Medical school – University of Michigan Medical School

Nabil Mehta, MD
Medical school – The Warren Alpert Medical School of Brown University

Elizabeth Terhune, MD
Medical school – Georgetown University School of Medicine
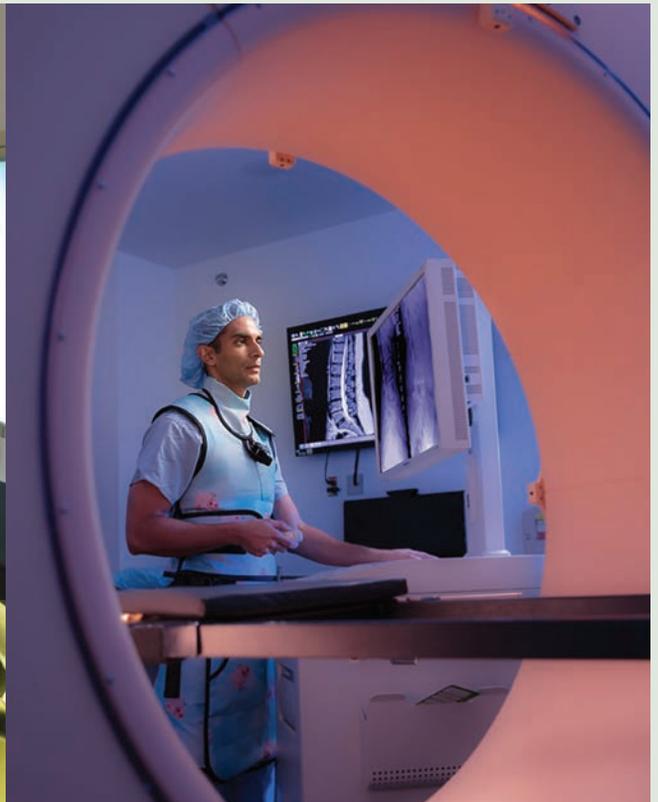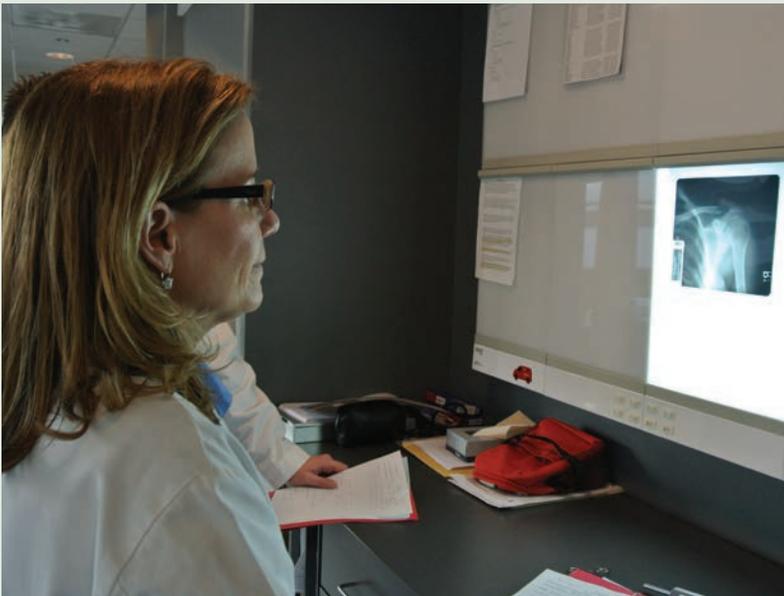
A Culture of Leadership

In the Department of Orthopedic Surgery at Rush, leadership isn't just a buzzword: It's part of our DNA. The manuscripts and interviews that follow illustrate some of the many ways our faculty are blazing trails and advancing musculoskeletal and spinal care—in the operating room, in the clinic, in the classroom, in the community, and around the globe.

"…the clinical failure rate after hip arthroscopy may be lower than previously reported, and younger, more active patients without a mental health disorder are less likely to require additional surgery in the short term."

High Survivorship After Hip Arthroscopy to Treat Femoroacetabular Impingement Syndrome With Capsular Plication
Factors Associated With Inferior Outcomes and Failure

SHANE J. NHO, MD, MS / GREGORY L. CVETANOVICH, MD / WILLIAM H. NEAL, BS / BENJAMIN D. KUHNS, MD
JOSHUA D. HARRIS, MD / ALEXANDER E. WEBER, MD / RICHARD C. MATHER, MD, MBA

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INTRODUCTION

Technical advances in hip arthroscopy have led to exponential growth in the treatment of femoroacetabular impingement syndrome (FAIS).[1] Originally an open procedure, hip arthroscopy has evolved into the primary surgical approach to correct osseous and chondrolabral FAIS pathomorphology.[2] Study investigators have reported that hip arthroscopy yields reliable pain relief and improvement in hip function for most patients in the short to medium term.[3-9]

Although results from multiple series have demonstrated that hip arthroscopy for FAIS is safe and effective, the understanding of which patients will benefit the most as opposed to only marginally still is evolving. This information is critical for effective shared decision making because the risk of requiring future surgery is important when making treatment decisions.[10] Results from prior studies have demonstrated that older patients,[8,11,12] especially female patients,[8] with decreased preoperative joint space[13,14] and higher Tönnis grade[15,16] are at higher risk for inferior clinical outcomes or failure requiring reoperation. These studies are limited by methodological issues, including nonconsecutive series with all patients treated with arthroscopy for FAIS[8,11,12,16]; a lack of prospective data[11-14]; and reporting only statistical, but not clinically important, differences in outcomes.[11,12,15,16]

In addition to patient selection, surgical technique also may affect patient outcomes and minimize risk of failure. Investigators in previous studies have illustrated the importance of appropriate surgical technique in regard to the osseous and soft-tissue pathomorphology of FAIS. Inadequate femoral osteochondroplasty or failure to address osseous deformity are the leading causes of clinical failure and need for revision surgery.[17,18] Likewise, results from multiple studies have demonstrated that superior clinical outcomes are achieved with labral refixation rather than debridement.[19-21] In addition, the rapid evolution of the understanding of FAIS has created a situation in which results from previously published outcomes studies inherently do not reflect contemporary surgical techniques, which is true of capsular management in the arthroscopic treatment of FAIS.[5,22-24] Frank et al[5] demonstrated improved clinical outcomes with lower revision rates when surgeons performed complete capsular closure after hip arthroscopy for FAIS.[5] Wylie et al[23] reported on improvements in all patient-reported outcomes (PROs) after revision
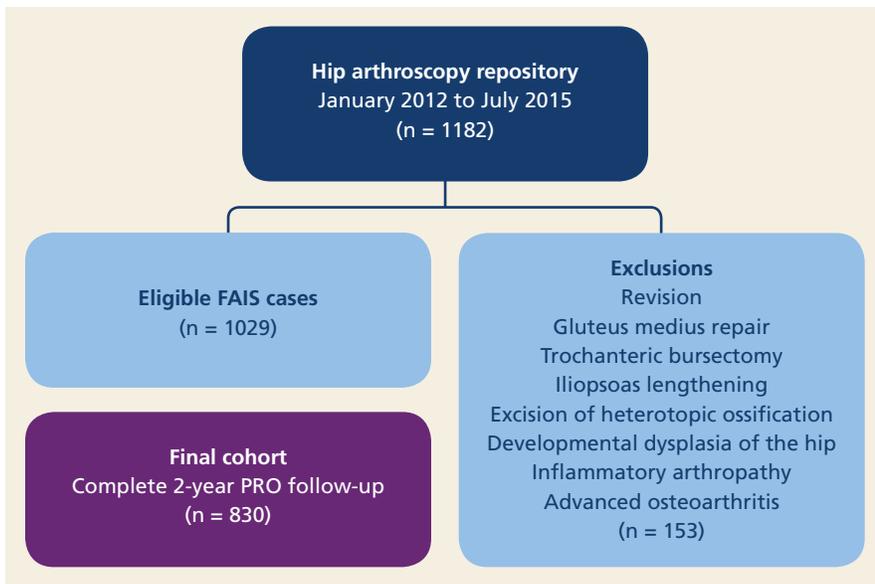
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagram[29] of Final Cohort Selection. FAIS indicates femoroacetabular impingement syndrome; PRO, patient-reported outcome.

hip arthroscopy and capsular closure in 33 patients who previously had had symptoms after an index hip arthroscopy procedure during which the surgeons did not perform capsular closure.

These studies have led to increased awareness that patient selection and surgical technique alter the clinical outcome after arthroscopic treatment of FAIS. However, questions remain regarding predictors of clinically meaningful success and failure. Investigators in prior studies at our institution reported that most patients undergoing primary arthroscopy for FAIS experienced clinically significant improvements; factors associated with successful outcomes included younger age, Tönnis grade 0, lower body mass index (BMI), not receiving workers' compensation, and running as an activity.[8,25,26] The purpose of this study was to highlight patient- and imaging-related factors associated with clinical failure defined by short-term reoperation (revision arthroscopy or conversion to total hip arthroplasty [THA]) and inferior clinical outcomes defined by the inferior quartile of Hip Outcome Score-Activities of Daily Living (HOS-ADL) scores. The hypotheses

are as follows: (1) using evidence-based surgical indications and modern surgical technique, the clinical failure rate should be lower than the previously reported 5% to 15%[4,9,27,28]; (2) there are specific patient- and imaging-related factors that predict inferior clinical outcomes.

MATERIALS AND METHODS

Patient Selection

This study received institutional review board approval, and no funding was involved. We identified in a database patients treated with primary hip arthroscopy for FAIS by a single, fellowship-trained surgeon, and we retrospectively reviewed data prospectively collected from January 2012 to July 2015. In addition to data on patient-related factors (eg, demographic characteristics, regular athletic activity, medical comorbidities, prior surgeries, range of motion, and physical examination results), all patients had a minimum of 2 years of follow-up data with patient-reported outcomes (PROs), including the modified Harris Hip Score (mHHS) and HOS-ADL score. Inclusion criteria were that patients were skeletally mature at the time of

arthroscopy and that radiographic and clinical signs and symptoms were consistent with a diagnosis of FAIS that was refractory to nonsurgical management (including physical therapy, activity modification, and oral or intramuscular injection of anti-inflammatory agents). Exclusion criteria were a history of prior ipsilateral open or arthroscopic hip surgery, developmental dysplasia of the hip, inflammatory arthropathy, advanced osteoarthritis, and undergoing hip arthroscopy for an indication other than FAIS (eg, gluteus medius repair, trochanteric bursectomy, iliotibial band [ITB] release, excision heterotopic ossification) (Figure 1).

SURGICAL TECHNIQUE

The surgeon performed all arthroscopic procedures with the patient under general anesthesia in the supine position on a standard traction table. After well padding all pressure points, the surgeon applied traction to the leg on which the operation was to be performed. The surgeon accessed the central compartment via the anterolateral and modified anterior portals. The surgeon performed an interportal capsulotomy (approximately 2-4 cm) to expose the acetabular rim. Once in the central compartment, the surgeon performed a diagnostic arthroscopy and treated the labrum, chondral surfaces, and acetabular rim. The surgeon repaired all labral tears, when possible leaving debridement and reconstruction as secondary and tertiary options, respectively. After work in the central compartment was complete, the surgeon released traction and accessed the peripheral compartment.

All patients underwent T-capsulotomy through the distal anterolateral accessory portal to assist with arthroscopic visualization of the femoral neck. The surgeon performed femoral osteochondroplasty in the peripheral compartment to correct the cam morphology. The surgeon used dynamic fluoroscopic and arthroscopic examination to confirm complete bony resection and absence of residual deformity. At the conclusion of the case, the surgeon repaired the entire capsulotomy with high-strength nonabsorbable sutures.

The surgeon closed the longitudinal portion of the T-capsulotomy by using 3 simple, interrupted, #2 high-tensile-strength sutures passed with a suture-shuttling device (SlingShot; Stryker Sports Medicine, Greenwood Village, CO). The surgeon subsequently closed the interportal capsulotomy with 2 or 3 simple, interrupted, #2 high-tensile-strength sutures in simple interrupted fashion by using a capsular closure device (InJector; Stryker Sports Medicine). Table 1 outlines patient characteristics and the procedures performed.

POSTOPERATIVE REHABILITATION

After surgery, all patients underwent rehabilitation through the same 4-phase protocol lasting between 24 and 32 weeks. Patients remained on crutches for 3 weeks, with a 20-pound, flatfoot weight-bearing restriction. They used a hip orthosis and night abduction pillow for the first 3 weeks, aiming to prevent active abduction, hip flexion beyond 90°, and extension with external rotation. All of the aforementioned motions could compromise the labral and capsular repair. Physical therapists encouraged passive and gentle active motions, including circumduction, to prevent stiffness. At 3 weeks, patients progressed to weight bearing as tolerated without crutches or a brace. Also at 3 weeks, therapists progressed hip range of motion, including gentle stretching in all planes, and progressed core and hip muscle strengthening. At 6 weeks, closed chain exercises began, and stretching was advanced. At 12 weeks, patients participated in running using an antigravity treadmill and performed plyometrics. We typically cleared patients to return to sports 4 to 6 months postoperatively on the basis of individual therapy milestones.

RADIOGRAPHIC ANALYSIS

All patients underwent radiography preoperatively and at final follow-up.[30] Each series consisted of a standing anteroposterior pelvis, an anteroposterior hip, a false-profile hip, and a Dunn lateral hip radiograph.[31] We measured joint-space width in 3 locations (lateral, medial, apical) on the anteroposterior radiograph, as well as the lateral center edge angle (LCEA) of Wiberg, on the anteroposterior hip radiograph.[21,31] We measured the α angle on the Dunn lateral hip radiograph.[32] We determined the Tönnis grade.[21,33]

FUNCTIONAL OUTCOME EVALUATION

We collected preoperative data, including demographic characteristics such as sex, age, operative extremity, BMI, sports participation, acute versus insidious onset, duration of symptoms, and comorbidities, from all patients. All patients had complete preoperative and minimum 2-year postoperative hip-specific PROs, including the HOS-ADL subscale[34,35] and the mHHS.[36,37] In addition, patients graded their pain and satisfaction levels postoperatively with a paper 0-to-10 visual analog scale. By means of visual estimation, a physician assistant nonauthor, independent examiner examined patients preoperatively and at final follow-up for measures of hip flexion, hip internal rotation at 90° of flexion, and hip external rotation at 90° of flexion.

DETERMINATION OF CLINICAL FAILURE AND INFERIOR OUTCOMES

We tracked all complications throughout the study. Based on standards from the literature, we defined clinical failure as the need for ipsilateral revision hip arthroscopy or conversion to THA.[9,12,13,16,38-40] During the study, we tabulated all revision surgeries, performed by the surgeon from the database or performed elsewhere, to calculate a revision surgery rate.

Table 1. Patient Characteristics and Procedures Performed

Characteristic	Patient Data (n = 830)
Demographic characteristic or comorbidity	
Age, y, mean (SD)	33.6 (12.8)
Body mass index, mean (SD)	25.4 (11.3)
Female, %	549 (66.1)
Smoking (current or past), %	78 (9.4)
Regular exercise, %	635 (76.5)
Hypertension, %	61 (7.3)
Diabetes (type 1 or 2), %	17 (2.0)
Anxiety or depression, %	127 (15.3)
Radiographic parameter	
α angle, mean (SD)	61.2 (10.1)
Tönnis grade ≥ 1, %	8.7
LCEA, mean (SD)	33.1 (7.0)
Joint space, mean (SD)	12.7 (2.1)
Operative procedure, %	
Femoral osteochondroplasty	822 (99.0)
Labral debridement	810 (97.6)
Synovectomy	798 (96.1)
Labral repair	797 (96.0)
Capsular plication	830 (100)

Abbreviation: LCEA, lateral center edge angle.

Table 2. Clinical Failures and Other Complications (January 1, 2012, Through July 8, 2015)

Failure or Complication	Frequency, No. (%)
Clinical Failure	**14 (1.7)**
Revision hip arthroscopy	6 (0.7)
THA conversion	8 (1.0
Other Complication	**20 (2.4)**
Superficial infection	5 (0.6)
Neuropathy	14 (1.7)
DVT	1 (0.1)
OVERALL FAILURE/COMPLICATION RATE	**34 (4.1)**

Abbreviations: DVT, deep vein thrombosis; THA, total hip arthroplasty.

We defined inferior clinical outcome as the bottom quartile HOS-ADL absolute value score, the most common clinical outcome measure in previous studies of hip arthroscopy.[5,8,23,41,42]

STATISTICAL ANALYSIS

We calculated descriptive statistics with mean (SD) or frequencies with percentages for continuous and categorical data, respectively. We compared pre- and postoperative patient- and imaging-related factors with paired t tests. Patient-related factors included age, sex, BMI, smoking status, sports participation, workers' compensation status, psychosocial comorbidities (self-reported depression, anxiety, and bipolar disorder), duration of symptoms before surgery, and preoperative hip range of motion. Imaging-related factors included preoperative α angle, preoperative LCEA, preoperative Tönnis grade, and preoperative joint-space width.

To determine factors associated with inferior clinical outcome and clinical failure, we conducted separate analyses. We conducted stepwise linear analysis for all preoperative and postoperative patient- and imaging-related factors as predictors of inferior outcomes and clinical failure.

The independent variables we considered were age, sex, workers' compensation status, medical comorbidities, whether patients participated in running or sports, smoking status, BMI, bilateral procedures, radiographic parameters (α angle and LCEA preoperatively and postoperatively; preoperative joint-space width laterally, apically, and medially; crossover sign; and preoperative Tönnis grade), preoperative range of motion, acute versus insidious onset of pain, relief from preoperative injection, and intraoperative variables (labral repair versus debridement, cartilage delamination, femoral chondral defect, and combined femoroacetabular impingement versus isolated cam or pincer lesion). We included factors that were significant at $P < .05$ on the stepwise analysis in the final regression model.

RESULTS

The surgeon performed 1182 hip arthroscopy procedures within the study period, with 1029 patients available for follow-up and 830 (80.7%) completing patient-reported outcomes at a minimum of 2 years postoperatively. Mean (SD) patient age was 33.6 (12.8) years, with a mean (SD) BMI of 25.4 (11.3) (Table 1). The overall clinical failure rate was 1.7% (Table 2), including 6 cases of revision hip arthroscopy (0.7%) and 8 cases of conversion to THA (1.0%).

FACTORS ASSOCIATED WITH CLINICAL FAILURE

By final follow-up, 8 patients (1.0%) went on to THA because of recurrent symptoms and joint-space loss (Figure 2). An additional 6 patients (0.7%) underwent revision arthroscopy: 2 for lysis of adhesions, 1 for excision of heterotopic ossification, and 3 for residual femoroacetabular impingement morphology (1 in combination with capsular insufficiency). According to results of stepwise analysis of all patient- and imaging-specific factors, patients with clinically failed treatment requiring reoperation or conversion to THA were more likely to have a preoperative Tönnis grade of 1 ($P = .008$), lack daily exercise
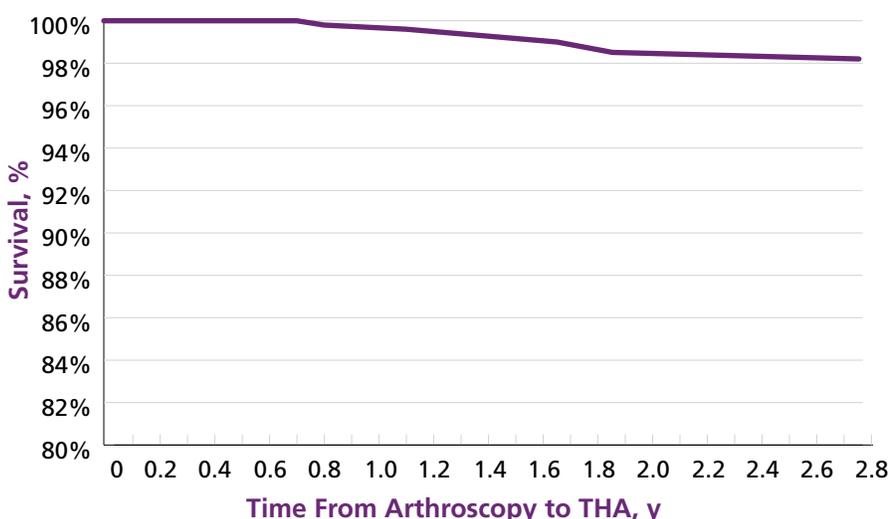
Figure 2. Kaplan-Meier Survival Curve Indicating Time From Hip Arthroscopy to Conversion to Total Hip Arthroplasty (THA).

Table 3. Clinical Failure Stepwise Regression Results

Characteristic	Odds Ratio (95% CI)	P Value
Body mass index	1.02 (0.99-1.05)	.192
No regular athletic activity	4.65 (1.47-14.72)	.009[a]
Tönnis grade 1	2.66 (0.80-8.85)	.111
Diabetes (type 1 or 2)	2.60 (0.25-26.62)	0.42
Snapping iliotibial band	0.55 (0.28-1.08)	.081
Pain at palpation of hip flexors	0.57 (0.28-1.17)	.127

[a] Indicates statistically significant predictor of clinical failure.

Table 4. Pre- and Postoperative Patient-Reported Outcome Measures After Hip Arthroscopy for Femoroacetabular Impingement Syndrome

Patient-Reported Outcome Measure	Preoperative Score (95% CI)	Postoperative Score (95% CI)	P Value
HOS-ADL	65.87 (64.49-67.43)	86.83 (85.49-88.11)	< .001
mHHS	57.60 (56.40-58.86)	79.90 (78.46-81.22)	< .001

Abbreviations: HOS-ADL, Hip Outcome Score-Activities of Daily Living; mHHS, modified Harris Hip Score.
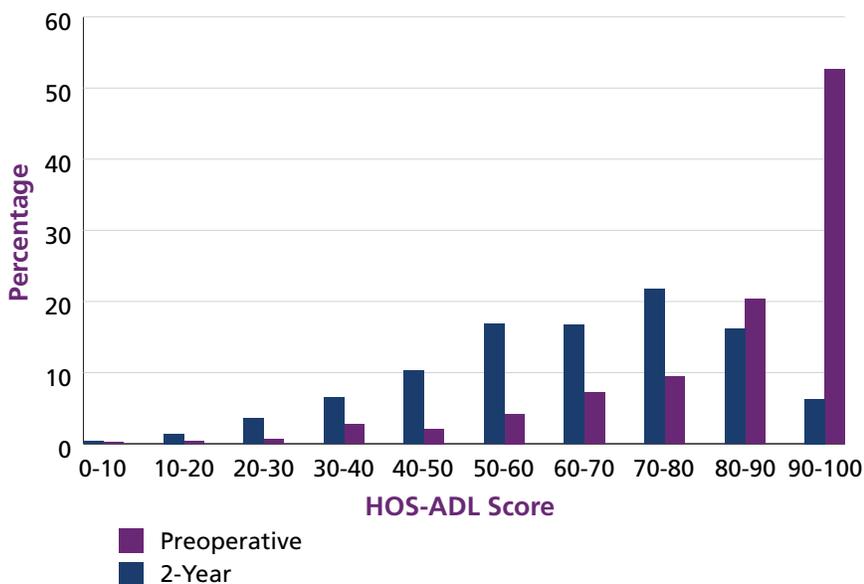
Figure 3. Distribution of preoperative and 2-years postoperative Hip Outcome Score-Activities of Daily Living (HOS-ADL) scores.

(P = .024), have type 1 or 2 diabetes (P = .007), have a higher BMI (P = .013), and at physical examination have a snapping ITB (P = .006) or pain at palpation of the hip flexors (P = .016).

In the stepwise regression model, patients with failed treatment were significantly more likely not to participate in regular preoperative athletic activity (odds ratio, 4.65; P = .009) (Table 3).

DISTRIBUTION OF OUTCOME SCORES

After hip arthroscopy, most patients experienced excellent postoperative outcomes with statistically significant improvements seen in both HOS-ADL and mHHS from baseline (Table 4). However, a small subset experienced inferior clinical outcomes, defined as having scores from the bottom quartile of the HOS-ADL (≤78.67) or mHHS. The distribution of all pre- and postoperative HOS-ADL and mHHS score are displaced in histogram format in Figures 3 and 4, respectively.

FACTORS ASSOCIATED WITH INFERIOR CLINICAL OUTCOMES

We defined inferior clinical outcome as scores in the bottom quartile of the HOS-ADL at a minimum of 2 years postoperatively. For comparison, we defined a superior outcome as the top quartile of HOS-ADL scores. The superior group contained 169 patients with a mean HOS-ADL score of 100, and the inferior group contained 191 patients with a mean HOS-ADL score of 78.67 or lower. In the stepwise analysis, patients in the inferior outcome group were older (P = .001), were current or former smokers (P = .002), had a higher BMI (P = .042), had self-reported a psychiatric comorbidity (P = .008), and had a snapping ITB at physical examination (P = .018). Regression analysis results revealed that older age (P < .001), a psychiatric comorbidity (P < .001), and a snapping ITB at physical examination (P = .026) were predictive of inferior outcomes (Table 5).

DISCUSSION

In this retrospective review of prospectively collected data in a 2-year follow-up study in consecutive patients undergoing primary hip arthroscopy with routine capsular closure for the treatment of FAIS, we found that the combined rate of revision or conversion to THA (1.7%) was much lower than previously reported. In addition, lack of regular preoperative athletic activity may be predictive of short-term clinical failure. Lastly, patients can have
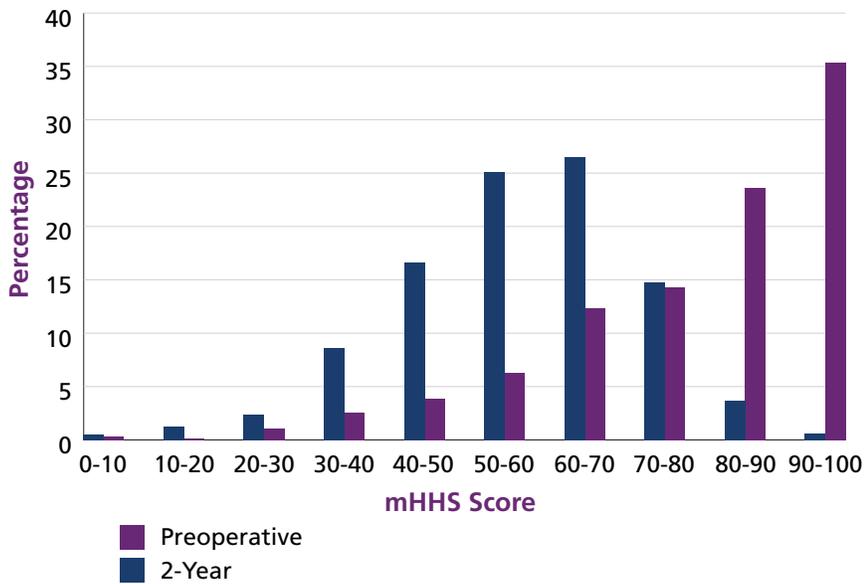
Figure 4. Distribution of preoperative and 2-years postoperative modified Harris Hip Score (mHHS) scores.

statistically significant improvements in PROs, but older patients, those with a psychiatric comorbidity, or those with a snapping ITB at physical examination may experience inferior outcomes when compared with their counterparts.

Understanding the reason for inferior outcomes and clinical failure aids in refining the indications for arthroscopic treatment of FAIS and assisting in shared decision making and setting appropriate expectations. Investigators previously have defined clinical failure of primary hip arthroscopy as revision hip arthroscopy[28,38,39] or conversion to THA,[9,12-14,28,43] and

investigators in previous studies have documented failure rates between 1% and 50%.[9,12,16,28,38,39,43] In the most complete systematic review, to our knowledge, including more than 6000 patients across 90 studies, Harris et al[9] found that the reoperation rate was 6.3% at an average of 16 months and that conversion to THA was the most common (2.9%) operation after hip arthroscopy. A strength of the current study is the consecutive nature of the prospective series, and, at an average follow-up of 2.32 years, we observed a 0.7% reoperation rate and a 1.0% conversion rate.

The previously reported patient- and imaging-related factors associated with inferior outcomes and clinical failure have been older age[9,12,28] and osteoarthritis (joint-space loss or Tönnis grade).[3,9,13,14,16,38,39] From England's national hip arthroscopy database, Malviya et al[28] found that age was a significant predictor of conversion to THA; however, as with many national database studies, these authors were unable to account for confounding variables such as preoperative joint space or Tönnis grade in their logistic regression model. McCarthy et al[12] retrospectively reviewed data in 106 patients after arthroscopic FAIS correction. Despite using methodology similar to that used in the current study and controlling for patient- and FAIS-related variables, they found age to be an independent predictor of future THA. One possible explanation for the discrepancy between studies is the older population in the former study (39 [13] years) when compared with the age of the population in the current study (33.6 [12.8] years). Investigators in a previous study in patients older than 50 years found that joint space, more than age, predicted the need for reoperation.[44] Frank et al[8] conducted a study of 2-year outcomes after hip arthroscopy for FAIS on the basis of sex and age. They found that all patients had significant improvements in all PROs; however, patients older than 45 years had inferior outcomes compared with those in younger patients.[8] Findings in the current study corroborate these findings in suggesting that greater age may predict

Table 5. Factors Associated With Inferior Clinical Outcomes[a]

Factor	Odds Ratio[b] (95% CI)	Inferior Outcome, Mean (SD) or %	Superior Outcome, Mean (SD) or %	P Value
Age	1.03 (1.02-1.05)	37.3 (11.9) y	31.4 (12.5) y	< .001
Smoking (current or former)	1.41 (0.97-2.06)	21.5%	7.1%	.074
Psychiatric comorbidity	2.58 (1.68-3.96)	26.7%	10.1%	.< .001
Body mass index	1.00 (0.99-1.02)	26.6 (5.5) kg/m^2	24.1 (4.1) kg/m^2	.867
Snapping iliotibial band	0.82 (0.68-0.98)	17.3%	5.3%	.026

[a] Scores in the bottom quartile of the Hip Outcome Score-Activities of Daily Living (≤ 78.67).
[b] Odds ratios for age are per unit change in variable.

inferior clinical outcome but not the need for reoperation.

In a 2014 study of the effects of mental disorders on clinical outcomes after primary hip arthroscopy for FAIS, Frank et al[5] found that patients with psychiatric comorbidities had significantly lower HOS-ADL, HOS-Sport Specific, and mHHS scores at baseline, as well as 2 years postoperatively, when compared with patients without. There is a clear link between mental health and physical outcomes before and after surgical treatment that authors have described in articles about hip arthroscopy and various orthopedic procedures.[45,46,47] By displaying the predictive value of psychiatric comorbidities toward an inferior clinical outcome, this study's results support findings in the current literature.

One explanation for the low reoperation rate in the current study is routine, complete capsular closure at the conclusion of the procedure. Mounting biomechanical evidence suggests that capsulotomy leads to joint microinstability but that capsular repair restores the stability profile similar to that of the native hip.[22,24] Results from clinical studies[5,23] have corroborated biomechanical evidence; Frank et al[5] demonstrated that complete capsular repair led to improved outcomes and decreased revision rates compared with results with partial repair. Wylie et al[23] demonstrated improvement in PROs 2 years after revision arthroscopy with capsular repair in a population of patients who previously had had symptoms due to microinstability after an index hip arthroscopy without capsular repair. As in these reports, the current series of consecutive, primary hip arthroscopies had a 100% rate of complete capsular closure, with revision and conversion rates

of 0.7% and 1.0%, respectively. In contrast, when investigating a comparable population with similar surgical technique aside from capsular management, Chandrasekaran et al[16] noted revision and conversion rates of 6.8% and 10.8%, respectively; the capsular repair rate was 17.6%. This markedly lower capsular repair rate may have contributed to the differences in revision rates and survivorship.

To our knowledge, a previously unreported predictor of clinical failure after primary hip arthroscopy for FAIS is the lack of preoperative athletic activity. In this study, we found that preoperative athletic activity (eg, recreational or higher-level athletics) was possibly protective against revision surgery or conversion to THA. Another explanation for this association is the type of patient undergoing hip arthroscopy. The impetus to undergo surgical intervention is varied: pain relief, improvement in ADLs, or athletic performance. The present study may highlight patients who prioritize athletic activity and are more likely to show improvement in postoperative PROs. Kamath et al[48] found that higher preoperative activity levels were predictive of improved postoperative outcomes after hip arthroscopy for the treatment of symptomatic labral tears. Although it is intuitively the case that active patients will want to return to activity, it is less so that preoperative athletic activity will reduce the risk of future reoperation. In combination with results from the stepwise model, these findings can guide patient expectations and the delivery of surgical care.

Despite the consecutive nature and high follow-up rates, this study has several limitations, including a relatively short-term follow-up, results from a single surgeon, and no criterion standard

definition of inferior outcome or clinical failure. Hip arthroscopy, still in its infancy, is a demanding procedure regarding the preoperative planning and technical skill required to address all relevant diseases. Because of the steep learning curve,[49,50] results from a single surgeon may lead to underestimation of failure rates of all hip arthroscopists and should be extrapolated cautiously. It would be appropriate for investigators in future studies to assess hip arthroscopy failure rates in a nationwide database. Finally, it would be ideal if patients could define *inferior outcome* or *clinical failure* by applying individual preferences within a formal, transparent, shared decision-making framework. Future investigators must develop technology and approaches to communicate predicted individual patient outcomes efficiently to allow for personalized, shared decision making.

CONCLUSION

This study's results demonstrated that primary hip arthroscopy with routine capsular closure for FAIS yielded predictable and significant improvement in outcomes at a minimum of 2 years of follow-up. The lack of preoperative athletic activity predicted reoperation, and older patients and those with psychiatric comorbidities were more likely to experience inferior outcomes. Finally, the clinical failure rate after hip arthroscopy may be lower than previously reported, and younger, more active patients without a mental health disorder are less likely to require additional surgery in the short term. ❖

"The implementation of MMA protocols has demonstrated superior outcomes when compared with traditional pain management techniques."

Multimodal Analgesia
Reducing Opioid Consumption for Patients Undergoing Spinal Surgery

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INTRODUCTION

Pain management continues to be an evolving paradigm in patient care. Although physicians often prescribe opioid medications, especially in the perioperative period, unfortunate and unanticipated consequences have been documented over the past 2 decades. Opioids currently are the most abused commercial medication.[1] Between 1997 and 2012, the number of opioid drug prescriptions in the United States increased from 145 million to 260 million annual prescriptions.[2] In addition, when comparing opioid prescriptions on a global scale, the United States accounted for nearly 100% of hydrocodone/acetaminophen (Vicodin; Abbott, North Chicago, IL) prescriptions and 81% of oxycodone/acetaminophen (Percocet; Endo Pharmaceuticals, Malvern, PA) prescriptions.[3] This increased distribution has affected medication abuse substantially in the United States. In a study conducted by the Centers for Disease Control and Prevention examining the effect of opioids on overdose deaths, the authors reported that the age-adjusted rate of drug overdose deaths increased by 14% from 2013 (7.9 per 100 000 people) to 2014 (9.0 per 100 000 people), which reflects the increase in documented published opioid prescriptions compared with those in the preceding years.[3,4] In addition, the death rate related to opioid drug overdoses has increased 200% from 2000 to 2014.[4] Patients with low back pain have a particularly high risk of opioid abuse and, thus, present a complex picture when determining perioperative pain management after spine-related surgery. In this review, we will describe the current opioid crisis affecting the United States and provide commentary on the various methods being used in spinal surgery to reduce the risk of opioid abuse, with a particular focus on multimodal analgesia (MMA).

THE RISE OF THE OPIOID CRISIS

To understand the opioid crisis in the United States, we must identify the sentinel events that fueled the momentum behind prescription opioid use. In 2001, the Joint Commission introduced pain as the fifth vital sign in an effort to address patient pain better and improve satisfaction.[5] Physicians who were seeing patients for reasons unrelated to pain now were asking them to comment on their pain level, which may have led to unnecessary treatment. In 2006, the Centers for Medicare & Medicaid Services introduced the Hospital Consumer Assessment of Healthcare Providers and Systems survey to assess patients' satisfaction during their hospital stay.[6] If they reported inadequate pain control on these surveys, the treating physician would face a financial penalty. As a result, providers began using opioid pain medications more frequently to help ensure patients' satisfaction with their pain control. The pharmaceutical industry also played a major role in the evolution of the opioid epidemic. The prescription opioid oxycodone (OxyContin; Purdue Pharma, Stamford, CT) originally was marketed as a long-acting agent that could relieve pain for up to 12 hours, with lower potential

for abuse and addiction than competing short-acting narcotics such as oxycodone/acetaminophen and hydrocodone/acetaminophen.[7] These claims were largely false because patients developed increasing levels of tolerance and subsequently would receive larger doses of the medication.[8] In only 8 years on the market, oxycodone became the most abused commercial drug in the United States, and the manufacturer eventually was fined more than $600 million for inaccurate advertising.[8]

OPIOID USE WITH SPINAL SURGERY

Orthopedic patients are among the most at-risk groups for opioid abuse because patients often present with pain as the chief symptom. In 2009, orthopedic surgeons were the third highest prescribers of opioids (6.1 million) among physicians in the United States, behind primary care physicians (22.9 million) and internists (11.6 million).[9] This trend in opioid use has continued despite research demonstrating opioid consumption can lead to worse clinical outcomes after orthopedic surgery, including spinal surgery.[10] Low back pain accounts for a considerable portion of health care use in the United States, with an estimated 80% of the population seeking treatment for low back pain at some point in their lives.[11,12] Approximately 15% of adult and 27% of elderly patients will experience back pain for longer than 6 months, increasing their risk for opioid use.[13] This use is of particular concern among patients undergoing spinal surgery, with reports of preoperative opioid use ranging from 20% to 55%.[14,15] Given the robust percentage of patients with spine disease who take opioid medications before undergoing spinal surgery, the need to minimize opioid use during the perioperative period is critical.

PREVENTING OPIOID ABUSE WITH SPINAL SURGERY

Physicians have made efforts to prevent opioid abuse and dependence in patients undergoing spinal surgery. Screening patients for the risk of opioid abuse presents a difficult situation because of

Figure 1. A team of surgeons and anesthesiologists at Rush, including senior author Kern Singh, MD, developed a standardized MMA protocol for all patients undergoing spinal fusion procedures.

the subjective nature of pain. The use of objective measures, including opioid risk assessment tools, urine drug tests, and prescription monitoring programs, can help prevent opioid abuse.[1] The recent focus on setting expectations regarding postoperative pain and the risks of opioid overuse has led to greater patient satisfaction after spinal surgery.[16] The provider is responsible for appropriately

addressing preoperative pain and counseling patients about expected pain after treatment. Clear communication with patients about the various methods available for pain control without reliance on opioids can build trust and improve patient satisfaction, all while achieving acceptable pain control.

Advances in minimally invasive spinal surgery techniques have reduced

Table 1. Multimodal Analgesia Agents[a]

Category	Agent	Mechanism of Action
NSAID	Toradol Ketorolac Indomethacin	Reversibly inhibits COX-1 and COX-2 to block prostaglandin synthesis; acts centrally and peripherally
Analgesic or antipyretic	Acetaminophen	Mechanism of action is unclear; weakly inhibits COX-1 and COX-2 in peripheral tissues; may inhibit a third enzyme, COX-3, centrally
Neuropathic agent	Pregabalin Gabapentin	Inhibits voltage-gated calcium ion channels through action as a GABA analog
Skeletal muscle relaxant	Cyclobenzaprine	Centrally acting skeletal muscle relaxant whose mechanism of action has not been determined fully
Opioid analgesic	Hydrocodone Oxycodone Tramadol	Act at opioid receptors to inhibit the release of pain-associated neuromodulators

Abbreviations: COX, cyclooxygenase; GABA, γ-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drug.
[a] Adapted from Katzung et al.[41]

postoperative opioid use. This approach involves using smaller incisions and specialized surgical instruments to provide muscle-sparing maneuvers that are not possible in a traditional open procedure. The limited tissue trauma and intraoperative blood loss attributed to these techniques have led to several advantages over open procedures, including decreased postoperative pain, fewer total complications, shorter hospital stay, and lower levels of postoperative opioid use.[17,18]

Advances in perioperative pain management regimens also have contributed to decreased opioid use. Physicians have implemented MMA protocols with the intention of providing adequate pain relief while minimizing opioid use by incorporating nonopioid treatment modalities. Investigators in a number of studies in populations undergoing total joint replacement or spinal surgery have demonstrated an association between MMA and decreased postoperative opioid requirements, theoretically decreasing the risk of opioid dependence after surgery.[19-26] Limiting opioid consumption decreases the risk for opioid-related adverse events and increases the likelihood of an expedited discharge.[27] Partly because of the introduction of MMA protocols, outpatient procedures have become increasingly viable options for patients undergoing spine procedures.[28-33]

MMA PROTOCOLS FOR SPINAL SURGERY

Physicians have constructed MMA protocols with the intention of achieving adequate pain management through modulation of nociceptive, neuropathic, and inflammatory pain signals at different sites in the nervous system. With use of agents that decrease pain through variable mechanisms, MMA can offer synergistic analgesia, leading to a greater analgesic effect than any 1 agent can provide independently.[27] As a result, physicians can minimize the use of opioids without sacrificing adequate pain control.

The inflammatory pain response is a primary target for pharmacologic pain control. Principal mediators of inflammatory pain, including prostaglandin E_2 and interleukin 6, act on nociceptors to cause local sensitization and lower pain thresholds in the tissues surrounding the surgical site.[27,34-36] Therefore, agents that block the production of inflammatory pain mediators can be an effective component of MMA protocols. Nonsteroidal anti-inflammatory drugs limit the synthesis of prostaglandins peripherally through the inhibition of cyclooxygenase-2. Acetaminophen acts in a similar manner, through blockade of centrally located cyclooxygenase-2. Physicians also have used neuropathic as part of MMA

protocols; these agents bind to voltage-gated calcium ion channels in the brain and spinal cord to modulate levels of neurotransmitters, including prostaglandin E_2, thereby decreasing pain intensity.[37] Patients can use muscle relaxants both preoperatively and postoperatively to limit the incidence of muscle spasm, which is a common complaint among patients with chronic back pain and which is a contributor to pain. In addition, physicians have used cryotherapy techniques, such as cooling gel packs and cold therapy systems, in MMA protocols to reduce postoperative inflammation.[38-40] Lastly, opioid medications remain an important component in MMA protocols because of their effectiveness in reducing pain through modulation of γ-aminobutyric acid receptors. Table 1 details MMA mechanisms of action.[41]

AN INSTITUTIONAL MMA PROTOCOL

At Rush University Medical Center, a team of surgeons and anesthesiologists, including author A.B. and senior author K.S. (Figure 1), developed a standardized MMA protocol for all patients undergoing any spinal fusion procedure. This protocol begins with preoperative counseling regarding anesthesia and analgesia. On the day of surgery, we initiate preemptive pain

Table 2. Multimodal Analgesia Protocol

Protocol Time Point	Agent Amount
Before admission **Preoperative counseling regarding anesthesia and analgesia**	
Preoperative[a]	
Cyclobenzaprine	10 mg PO
Pregabalin	150 mg PO
Oxycodone	10 mg PO
Intraoperative	
Bupivacaine 0.5% with epinephrine	20-30 cc local infiltration/side
Propofol[b] (induction)	
Ketamine (induction)	50 mg IV
Sevoflurane[b] (maintenance)	
Acetaminophen	1000 mg IV
Ondansetron	4 mg IV
Famotidine	20 mg IV
Dexamethasone	10 mg IV
Fentanyl	1-2 mcg/kg IV (titrated)
Postoperative day 0	
Cryotherapy[c]	PRN
Pregabalin	75 mg PO, every 12 h
Cyclobenzaprine	10 mg PO, every 8 h
Hydrocodone/acetaminophen	10 mg PO, every 4 h
Tramadol	50-100 mg PO, every 6 h
Oxycodone IR	5-10 mg PO, every 4 h PRN
Postoperative day 1 (discharge)	
Cyclobenzaprine	10 mg PO, PRN (90[d])
Hydrocodone/acetaminophen	10/3 mg PO, 1-2 tablets PRN (60[d])

Abbreviations: IR, immediate release; IV, intravenous; PO, by mouth; PRN, as needed.
[a]In the preoperative holding area or operating room.
[b]The ranges of propofol and sevoflurane used vary depending on the anesthesiologist.
[c]Ice packs applied over surgical site.
[d]Number of tablets prescribed at discharge.

management either in the preoperative holding area or in the operating room before the start of the procedure. We continue pain control intraoperatively and use a variety of modalities, including cryotherapy, muscle relaxants, neuropathic pain relievers, acetaminophen, and opioids, for postoperative pain control. We discharge patients with muscle relaxants, acetaminophen, and opioids. Table 2 shows the details of this protocol.

OUTCOMES WITH THE USE OF MMA

The implementation of MMA protocols has demonstrated superior outcomes when compared with traditional pain management techniques. Authors of reports in the arthroplasty and upper extremity literature have associated MMA with improved pain control, decreased narcotics use, lower rates of complications, and increased patient satisfaction postoperatively.[42-45] Rajpal et al[46] compared postoperative pain management among patients undergoing a variety of spine procedures. They compared a prospective cohort of 100 patients who received MMA with a historical cohort of 100 patients who had received patient-controlled analgesia (PCA). In the first 24 hours postoperatively, patients who received an MMA protocol consumed significantly fewer opioids than did those who received PCA. Although both cohorts reported similar scores for their "worst" pain, patients who received MMA reported significantly lower scores for their "least" pain. Patients receiving MMA also experienced significantly lower rates of nausea; drowsiness; and interference with walking, coughing, and deep breathing.

Similarly, Garcia et al[47] performed a randomized controlled trial evaluating the effectiveness of MMA in patients undergoing lumbar decompression procedures. Twelve patients received intravenous morphine, and 10 received MMA consisting of celecoxib, pregabalin, and oxycodone. All patients were allowed additional intravenous morphine as needed postoperatively. Patients who received MMA required less morphine in the first 36 hours postoperatively than did patients who received only intravenous morphine. In addition, patients who received MMA reported greater pain control up to 36 hours postoperatively. These results suggest that the use of MMA after lumbar decompression procedures reduces postoperative opioid consumption and may improve pain control.

Physicians also have evaluated the effectiveness of MMA after spinal fusion procedures. Mathiesen et al[19] compared patients undergoing multilevel posterior spinal fusions before and after the implementation of an MMA protocol. Patients receiving MMA consumed significantly fewer opioids on postoperative day 1 and postoperative day 2 than did patients receiving unimodal therapy with opioids. Patients receiving MMA also demonstrated faster mobilization from bed and earlier walking with or without a

Figure 2. Author Asokumar Buvanendran, MD (left), and US Sen Dick Durbin (Illinois) at a press conference in June 2018. Sen Durbin chose Rush as the location to unveil the Addiction Prevention and Responsible Opioid Practices Act (A-PROP), new legislation that requires physicians, pharmacists, legislators, pharmaceutical companies, and organizations like the Food and Drug Administration and Centers for Disease Control and Prevention to work together to find a solution to the opioid crisis.

walking frame. However, the investigators did not compare postoperative pain, nausea and vomiting, and sedation between cohorts.

Investigators have compared the MMA protocol used at our institution with the PCA used in historical cohorts among patients undergoing cervical fusion and among patients undergoing lumbar fusion. Bohl et al[48] performed a retrospective cohort study in 239 patients who underwent anterior cervical discectomy and fusion and received either MMA (n = 55 [23%]) or PCA (n = 184 [77%]) for perioperative pain management. Patients who received MMA consumed

significantly fewer narcotics than did those receiving PCA. However, pain control was comparable between cohorts, with no difference observed in mean visual analog scale pain scores on postoperative day 0. Patients receiving MMA also demonstrated lower rates of postoperative nausea and vomiting and shorter lengths of hospital stay than did patients receiving PCA. The investigators observed no differences in rates of narcotic dependence at the first 2 postoperative visits between groups.

Similarly, Singh et al[49] compared 39 patients (28.1%) receiving MMA and 100 patients (71.9%) receiving PCA for pain management

after minimally invasive transforaminal lumbar interbody fusion. Patients receiving MMA had a lower rate of inpatient narcotics consumption, a lower rate of postoperative nausea and vomiting, and a shorter length of hospital stay than did patients receiving PCA, with no difference in postoperative pain scores. The results of these studies suggest that MMA is an effective option for immediate postoperative pain control; however, long-term benefits of MMA have not yet been borne out in the literature.

CONCLUSION

The current opioid crisis in the United States has gained major attention in recent years (Figure 2). Despite the increasing national attention on abuse potential, the number opioid prescriptions continue to increase. Excessive and long-term opioid use remains a substantial concern for spine surgeons because of the high prevalence of low back pain. Efforts to prevent opioid abuse among patients undergoing spinal surgery are important considerations in improving patient outcomes and satisfaction. In particular, MMA protocols for perioperative pain management can help minimize postoperative opioid use and may reduce the risk for continued abuse. However, the literature regarding the effect of MMA on long-term postoperative opioid abuse is limited, and further studies are needed to characterize this association fully. ❖

References and financial disclosures are available online at www.rush.edu/orthopedicsjournal.

Creating Change Through Leadership and Fellowship

As director of the orthopedic surgery residency program at Rush, Monica Kogan, MD, re-imagines how and what surgeons learn to prepare them for practice.

"I think a leader's primary purpose is to inspire a group to excel," says Monica Kogan, MD, a pediatric orthopedic surgeon at Rush. "A rising tide raises all ships," she says.

As director of the Orthopedic Surgery Residency Program at Rush and a Carol Emmott Fellow, she is doing just that: transforming the delivery of health care by creating a challenging yet supportive and responsive training ground for the orthopedic leaders of tomorrow.

THE POWER OF ASKING … AND LISTENING

After serving as associate director of the Orthopedic Surgery Residency Program for 3 years, Kogan took over the reigns as director about 3 years ago. "I'm continuing with an initiative that had begun previously and taking it to the next level: implementing improvements based on feedback from the residents themselves," she says. "We want to create an environment that's a safe place where

residents can feel free to speak up about ways to make improvements."

By listening to the concerns and suggestions of residents, Kogan believes they are improving the program, whether that means changing resident interview days to a more convenient format, making improvements to certain rotations, or adding a trauma rotation. One suggestion has been especially popular: team-building activities outside of the hospital. Several times a year, residents step out together to

enjoy time away from the pressures of the operating room. Recently, they took on bubble soccer, in which residents left their white coats at home and donned inflatable balls while dribbling toward the goal line.

MAKING A LASTING IMPACT

As one of 18 recipients of the 2018 Carol Emmott Fellowship—which aims to decrease the disparities in upper-level leadership by women throughout the health care field—Kogan joins an impressive group of female health leaders from across the country. The fellowship gives Kogan an opportunity to focus on an impact project that she believes will further help residents. Her project: "A Transition to Practice" curriculum for orthopedic surgery residents that will help them navigate the realities of medical practice today, such as billing and coding, reimbursement, and the nuances of health care reform.

Kogan finds inspiration from Emmott, who died in 2015. Emmott earned a doctorate in public policy in the 1970s, helped found the California Association of Public Hospitals—which focused on underserved populations—and went on to work in executive health care recruitment.

"Carol came into the field when most women were in secretarial, office support positions, or getting college degrees and then getting married. She wanted something else, and that's why she never learned to type," Kogan says with a laugh. "And toward the end of her life, when her friends suggested a scholarship for women in her name, Carol said 'nope.' She wanted a *fellowship for women leaders* in her name."

A UNIQUE LEARNING AND TEACHING ENVIRONMENT

Perhaps one of the most impactful experiences Kogan helps bring to orthopedic residents is caring for patients in the Dominican Republic. In 2005, a Rush organization, Community Empowerment, formed a partnership with the community of Peralta, Azua Province, Dominican Republic, sending various specialists to the community. In 2014 the orthopedics team at Rush joined this effort, and for the past 3 years, Kogan has been leading a group of 5 to 6 residents (ranging from first-year to fifth-year residents) on a yearly surgical mission trip in January to perform desperately needed surgical procedures in this remote and resource-poor community. The patients would otherwise not have access to medical care due to a lack of

insurance or financial means. The first year there were limited implants. Now, thanks to implant grants and supplies generously donated by implant companies, the team performs more complex procedures. But even with the extra resources, the trip is not easy—by any means.

The 1-week trip requires a full year of planning, Kogan says. Since they must bring everything, Kogan must apply for grant funding as well as coordinate the donations and acquisition of resources. Compared to the advanced technologies and state-of-the-art facilities offered at Rush, the operating conditions in Azua are primitive. The team must bring the gowns, gloves, hand wash, prepping and draping supplies, and power drills, along with sutures, dressings, and implants. If they don't bring it, there is no back-up at the hospital. Only 1 room has surgical lights, the electrocautery works only half the time, and there is no fluoroscopy. The orthopedic residents must cover every aspect of the surgery—from picking the instruments and implants they will need, to sterilizing the equipment, to preparing the OR for the next patient.

"It definitely takes the residents out of their comfort zone," Kogan says. "And that's not just because of the physical environment and lack of resources. Surgical decisions—such as incision placement or how to perform the case without fluoroscopy—may be more challenging, as it may not be the way they have done the procedure in the states. They are accustomed to having more instruments at their disposal. If they drop it on the floor, then they need to make do with what they have."

Creative problem solving, thinking on your feet, and an appreciation for the work typically done by other members of the operating room team are just a few takeaways for residents. For Kogan, the work is draining but rewarding. And she knows that the lessons learned on these trips will help her and her residents be better and more compassionate surgeons. Each year, the team returns, thankful for the environment they live in, the resources available to all patients, and the environment in which they train.

To improve the residency program, Kogan routinely solicits feedback from the residents. One of the most popular ideas: off-site team-building and stress-relieving activities, like a recent bubble soccer game.

> "I think a leader's primary purpose is to inspire a group to excel. A rising tide raises all ships."

THE ROAD TO A REWARDING CAREER

Kogan came to orthopedic surgery after considering a career in general surgery. But after a fellow medical student at the University of Illinois College of Medicine at Chicago encouraged her to take an orthopedics elective, she soon realized that orthopedics offered her the professional satisfaction she sought. "I liked the idea of fixing things that were broken or structurally not working correctly in a diverse population, in which the patients were otherwise pretty healthy."

It wasn't until a rotation during her own residency at Northwestern University in Chicago that she decided to zero in on the pediatric population. "Kids are just so resilient. They want to get better and they *do* get better," she says. A fellowship at Primary Children's Hospital and Shriner's Hospital in Utah followed, and Kogan was convinced a stand-alone children's hospital was her destiny. But an interview at Rush—where Rush University Children's Hospital is embedded into the Medical Center—changed her mind. She was sold on Rush, and she joined the team.

Here, Kogan works with innovative physicians, researchers, and industry leaders, bringing the latest advances to her patients. In fact, she was the first in Chicago to use PRECICE, an internal magnetic limb-lengthening device. The device, a titanium rod implanted by surgeons, allows patients to lengthen their legs—by about one millimeter per day—using a type of remote control for a couple of minutes, several times daily. Although not all patients are candidates for PRECICE, the device has helped patients who have limb length inequalities walk with equal limb lengths using a more patient-friendly method of lengthening than what was available in the past.

FEELING EMPOWERED AND EMPOWERING OTHERS

Kogan, currently the only female orthopedic surgeon at Rush (although there are several female primary care sports medicine physicians), has seen a shift when it comes to gender—and diversity in general—in orthopedics. "The entire perspective of women in orthopedics has changed. You're not necessarily viewed as 'the girl in the program' anymore, as programs today want all kinds of diversity. They're looking for women and under-represented minorities. As the world's view has changed, the mindset of orthopedics has definitely become more open as well, and has seen the need to have diversity."

That said, finding a mentor can still be a challenge for women in orthopedics. "If mentors aren't easily found in your office or department, look to other areas of the hospital," Kogan recommends.

And what makes a good mentor? "They push you a little bit more than you think you want to be pushed," Kogan explains. "They bring you opportunities to help you be a better version of yourself, as a physician and a person. They don't have an agenda when helping you and want what is best for you."

As residency director, Kogan herself is now a mentor to many—a role that has heightened her appreciation for the professional and personal support she's received throughout her career at Rush, both within and outside of her department. "There's no doubt that there are some really big names in the Department of Orthopedic Surgery at Rush. The thing that may be surprising: They're not only smart and innovative, they are also incredibly supportive and giving to those around them. I could not feel more supported and am very thankful." ✣

Kogan recognizes the importance of staying on the leading edge of treatment, as evidenced by her pioneering use of PRECICE to treat patients with limb length inequalities.

> *"…a team provides the highest value when the surgeon concentrates on complex decision making and critical elements of operating, while shifting remaining care to colleagues."*

Decisions and Incisions

Lessons Learned in Building a Value-Driven Practice

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PREAMBLE

Ben and I trudged through the darkness as the cold Boston wind whipped our faces till we were numb. As an African immigrant and the son of Indian immigrants, neither of us was ever truly prepared for the frigid New England air. Still, even the biting cold couldn't dampen our excitement as we discussed our grand plans for the years to come. It was the winter of 2009, and as the US populace debated the merits of the Affordable Care Act, Ben and I had stumbled upon a new hero—Michael Porter. Dr Porter was already well known as an economist, but his foray into health care was only recently being discovered by physicians. As part of the Harvard system, Ben and I were able to listen to the wizard himself speak—his prose was hauntingly poetic in its simplicity. Here stood a

financial genius before us, but his unsung brilliance was that he made us feel brilliant. We learned 1 word from him—*value*—and this was how we were going to make a name for ourselves. He taught us that value is defined as *health outcomes per dollar spent*,[1] and, as luck would have it, I was earning a master of public health degree with a concentration in clinical outcomes research, and Ben was earning a master of business administration focusing on health care cost accounting. Ben Nwachukwu and I were experts in the numerator and denominator of this equation, and we wanted to make haste before everyone else figured it out. The Charles River moved slowly by us, but we gained speed as we moved through the blackness of night, giddy to begin our academic careers.

As the years rolled by, Ben and I began writing treatises and conducting value-based research. Under the tutelage of our mentor, Dr Kevin Bozic, we penned the inaugural article of *JBJS Reviews* titled, "Measuring Value in Orthopaedic Surgery."[2] Subsequently, we wrote more articles with increasingly pun-based titles: "Lights, Camera, Action: How to Make Arthroscopy a Star in Value-Based Healthcare"[3] as a guest editorial in

Arthroscopy and "Competing in Value-Based Healthcare: Keys to Winning the Foot Race"[4] for *Foot & Ankle International*. Finally, we arrived at our magnum opus in the *Journal of Bone and Joint Surgery, American Volume:* "Decisions and Incisions: A Value-Driven Practice Framework for Academic Surgeons."[5] This was our crown jewel, a year's labor of love published as a thought-provoking guide on how to succeed in providing valuable clinical care, education, and research. The central premise was that a team provides the highest value when the surgeon concentrates on complex decision making and critical elements of operating, while shifting remaining care to colleagues.

With my academic accolades in hand, I left the nest of training and steadied myself to flourish in practice.

REALITY

Mike Tyson reportedly said that "everyone has a plan until they get punched in the face." He must have been referring to my first year in practice. As a deluge of patients poured through the door, I wasn't thinking about value or decisions or incisions, I was thinking of how not to drown. For all the rhetoric about value that I had learned

through my studies, the pragmatic aspect of injecting it into my practice was missing. I am now 2 years into my practice and am finally emerging from the darkness. For the young and uninitiated, I've laid out the hard-earned practical lessons of starting a practice on the basis of my own dealings and the advice of my respected colleagues.

1. Get help. Quick.

My partner, Dr Richard Berger, runs an orthopedic practice that is a bastion of efficiency. His advice is to get help before you need it. My first several months seeing patients were full of long nights filling out disability paperwork, entering orders from my computer during the weekend, and performing surgeries by myself. My bank account grew, but so did the bags under my eyes. I hired physician assistant (PA) Tara Behnke 5 months into practice before we got too busy so I had time to train her. By the time the practice was in full-steam-ahead mode, she was excelling (Figure 1). The type of assistant you need depends on your practice model and patient population. If you have plenty of hands in the operating room, then a nurse is ideal to handle phone calls and paperwork while you are in surgery. If you have a high-volume outpatient surgical practice or are often left without assistance in the operating room, a PA may be a suitable alternative. PAs have the added benefit of obtaining collections for assisting in surgery or running independent clinics that can offset their cost.

2. Learn how to manage personalities.

For all our education in diagnoses and treatment, few orthopedic programs train residents and fellows in how to manage employees and engage in team building, negotiation, and conflict resolution. Read books on the subjects, ask for advice from your senior partners, get tips from human resources, and don't get frustrated. Set rules early on. People are governed by expectations, and, as the team leader, you now set the expectations. For a practice with few employees, you may consider the following: limit only 1 employee

Figure 1. Hire Clinical Colleagues Early to Help Build Your Practice. Pictured here are Dr Hamid (left) and physician assistant Tara Behnke (right), marking an exceptional day.

(not counting yourself) out from the office at a time, require employees to request days off a minimum of 6 weeks in advance, and be clear about job requirements.

3. Incentivize employees. Overpay the good ones.

Physician assistants are an interesting bunch—they have nearly limitless job opportunities. If they can find a boss who is nicer than you and facilities that are better than yours, how do you get them to

stay? Profit sharing. Incentivize them to be a co-owner of the practice more than an employee. When you're profitable, they get a piece of the pie. Paying more than alternative jobs is the strongest motivator to have them stay. When you take into account the productivity losses of switching PAs, as well as the cost of training and assimilating a new team member, paying above-market price is more cost effective than replacing an excellent employee.

4. Don't forget what it's like to be a resident.

For those of us fortunate enough to work with residents, we may find it's easy to take them for granted. How quickly we forget all the menial work they do in the background of the hospital. In addition, we are not incentivized to involve residents in the operating room because they negate possible collections for physician extenders and potentially slow down the case. But when worked with appropriately, residents can add value to clinical care and your own learning by stimulating discussion and asking insightful questions. They are generally young and more creative than their more experienced colleagues, thus making them ideal candidates for developing novel health delivery improvements. Also, if you provide them with meaningful, hands-on surgical experiences, they will go out of their way to help you when you have no help (Figure 2).

5. Research takes time.

I was hired to enhance the foot and ankle research in my division. A year into my practice, research was unchanged from the year before. Our patient-reported outcome measures were being collected but with an abysmal compliance rate of less than 30%, and we had plenty of ideas but no means to follow through. Two years in, we have nearly 40 active projects. The difference was an extra year in practice, a PA to increase my free time, and patience. Take the first year or 2 to establish your clinical competence and write an occasional review paper. Once you're settled in, you can begin the process of building a research program.

6. Buy people lunch.

Small gifts show your team members that you care. It's not the size or value of the gift but truly the thought that counts. Sometimes the gift is simply buying lunch or saying thank you at the end of the day. If you create a positive work environment, everyone will be more productive.

It's been nearly a decade since Ben and I took a stroll by the Charles. Today, we learn more of our lessons from our patients and colleagues than we do from books and lectures. However, the central tenet to success remains the same: Treat people well. ✣

References and financial disclosures are available online at www.rush.edu/orthopedicsjournal.
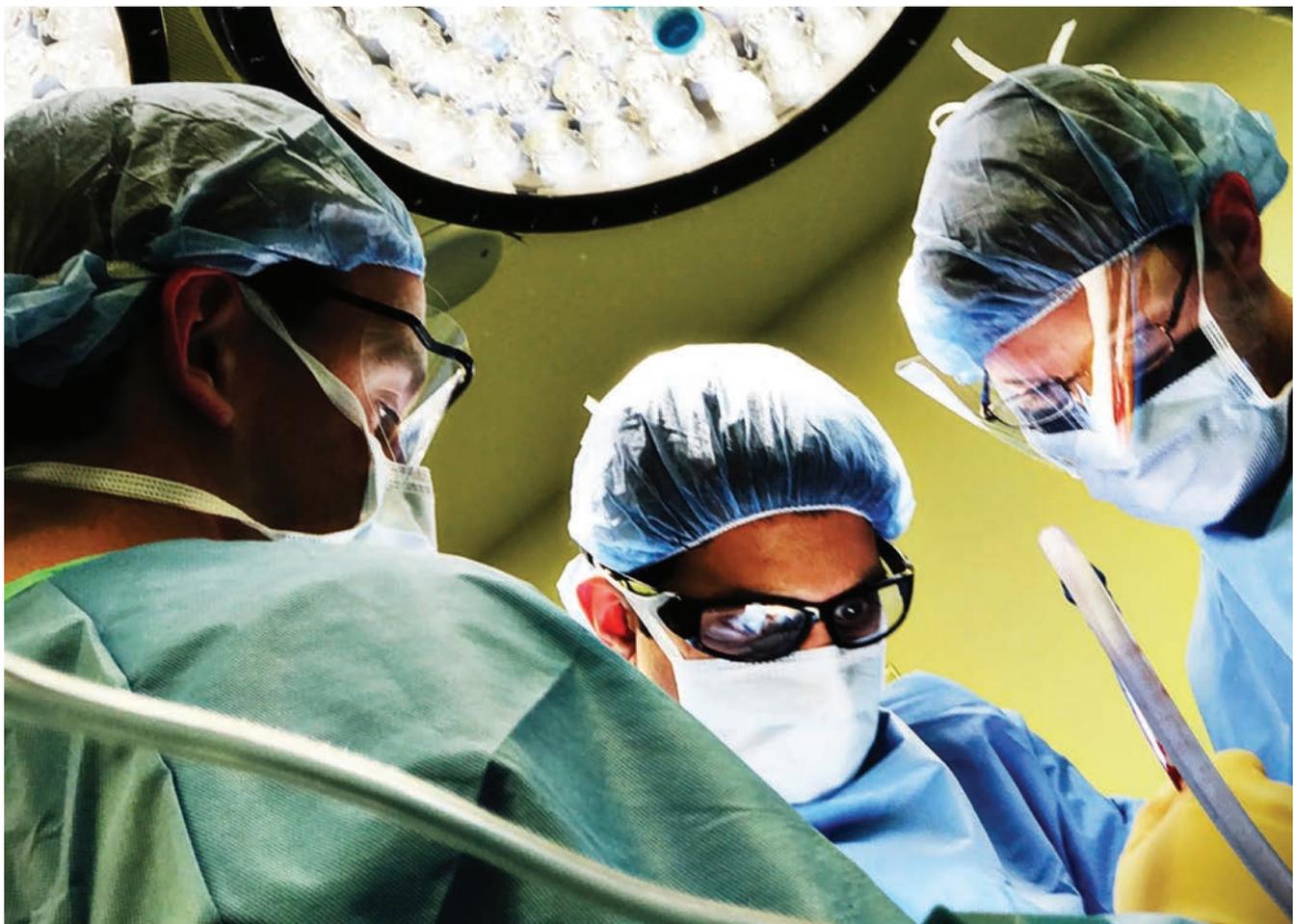
Figure 2. Educating Residents Can Provide Value to Patients and Health Systems. Residents Charles Hannon (center) and Bryan Saltzman (right) assist Dr Kamran Hamid (left) in the operating room.

"Diagnosis of SAPHO syndrome is difficult because…
clinical manifestations may be subtle, can manifest
in isolation, and can occur at different times."

Vertebral Osteitis as the Sole Manifestation of SAPHO Syndrome

A Case Report and Review of the Literature

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INTRODUCTION

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is characterized by a constellation of bone, joint, and skin lesions, first recognized, to our knowledge, by Chamot in 1987.[1] The spine commonly is affected (32%-52% of patients) in SAPHO syndrome.[2,3] The aseptic skeletal inflammatory manifestations of these lesions often mimic those of lymphoma, osteomyelitis, metastasis, Ewing sarcoma, and seronegative spondyloarthropathies.[4-6] Often, patients undergo multiple rounds of serologic testing, antibiotic administration, and biopsies before clinicians make the diagnosis. Skin manifestations associated with SAPHO syndrome, including palmoplantar pustulosis, acne fulminans, and pustular psoriasis, usually occur simultaneously with the bone lesions but may appear before or after the bone lesions.[7]

CASE REPORT

A 37-year-old previously healthy man experienced 3 months of persistent, moderate, mildly progressive, midthoracic back pain exacerbated by exercise. He had no history of fever, weight loss, joint pain or swelling, ocular issues, trauma, or urinary symptoms. In his early 20s, he had 2 separate episodes of sloughing of skin from his hands. He was undergoing a lot of change in his life and dismissed it as being stress related. Both times, there were no sores or pustules, and healing occurred without residual effects. He had no chronic medical conditions, previous surgery, regular medications, or allergies. His mother had a lumbar disc herniation; however, no other family members had a history of any clinically significant spinal disease or rheumatologic disorders. He had no history of smoking, excess alcohol intake, or substance abuse. He worked as a consultant and has traveled to Europe several times and once to Saudi Arabia 10 years previously. He knew of no exposures to toxins.

At physical examination, he appeared healthy, with normal cardiopulmonary examination results, normal chest expansion, and neutral spinal alignment. He had no skin lesions, no lymphadenopathy, and no joint pain or swelling. Posterior thoracic pain occurred with palpation, as well as with forward flexion and extension of the thoracolumbar spine. He had normal neurologic examination results.

Laboratory study results revealed a normal white blood cell count and hemoglobin level, normal C-reactive protein level, and normal erythrocyte sedimentation rate (< 20 mm/h). Computed tomography (CT) (Figure 1) and magnetic resonance (MR) images (Figure 2) of the thoracic spine showed sclerosis, edema, and enhancement centered along multiple end plates. There were Schmorl nodes in the upper thoracic spine adjacent to the costovertebral joints.

Clinicians originally interpreted these data as probably indicating lymphoma and consulted an oncologist. Iliac bone marrow biopsy results were normal, and results of fine-needle aspiration of the T8 lesion demonstrated nonspecific acute and chronic inflammation. Results of a core biopsy of the T8 lesion showed chronic inflammation and sclerosis. A bacterial culture from this sample initially grew *Dermabacter hominis*, which we believed to

Figure 1. Sagittal Computed Tomographic Scan Through the Thoracic Spine Shows Mild Sclerosis in the T8 Vertebral Body and Mild Irregularities Involving Its End Plates.

be a skin contaminant; culture results were otherwise negative for bacteria, fungus, or tuberculosis. Positron emission tomography (PET) results were unremarkable. Serologic test results were negative for human leukocyte antigen B27 and tuberculosis.

After consultation with a rheumatologist, the patient underwent repeat serologic testing, the results of which were negative. After a second T8 lesion core biopsy, we concluded that neoplasm and infection were unlikely and that the appearance was most consistent with the spondyloarthritic findings of SAPHO syndrome. We repeated MR imaging, and the results showed a new L5 end-plate lesion and slight improvement at several thoracic levels. Many lesions had a stable appearance, not consistent with infection. We initiated use of celecoxib, physical therapy, and activity modification. The patient experienced marked improvement of pain, but after a few weeks, mild pain returned. At MR imaging 1 year after the onset of symptoms, the bone marrow edema in the body of T8 had resolved (Figure 3).

DISCUSSION

Diagnosis of SAPHO syndrome is difficult because, as seen in this case, clinical manifestations may be subtle, can manifest in isolation, and can occur at different times. Benhamou et al[6] defined the most common diagnostic criteria for SAPHO syndrome as the presence of at least 1 of the following: osteoarticular manifestations with severe acne, osteoarticular manifestations with palmoplantar pustulosis, hyperostosis with or without dermatosis, or chronic recurrent multifocal osteomyelitis involving the axial or peripheral skeleton with or without dermatosis. Although this case involves an incomplete expression of the syndrome, there were some confirmatory findings and many negative observations that excluded other possible explanations. Most notably, MR imaging findings of a semicircular pattern of bone marrow signal intensity in contiguous vertebral body segments are characteristic of SAPHO (Figure 2).[8,9]

The remote history of dermatologic symptoms supports the diagnosis of SAPHO, and previous reports document occurrence of skin lesions at long intervals from the osseous manifestations.[4,10] This patient's improvement with oral nonsteroidal anti-inflammatory drugs (NSAIDs) is also consistent with SAPHO; however, such improvement also may occur with other spondyloarthropathies. The differential diagnosis for SAPHO includes infection, neoplasia, and other spondyloarthropathies. The lack of disease progression with observation for more than 1 year, as well as negative culture results (save for 1 likely skin contaminant), 2 negative biopsy results, and an unremarkable PET scan make infection or neoplasm unlikely.

Some features of SAPHO syndrome occur in other spondyloarthropathies, such as psoriatic arthritis, idiopathic ankylosing spondylitis, reactive arthritis, and spondyloarthropathy associated with inflammatory bowel disease.[8] Psoriatic arthritis with axial skeletal involvement and pustular psoriasis can be similar to SAPHO, but radiographic signs of osteitis

Figure 2. Sagittal Magnetic Resonance Images. **A,** T2-weighted image. **B,** Short inversion time inversion-recovery (STIR) image. **C,** T1-weighted image obtained before the administration of contrast material. **D,** Fat-suppressed T1-weighted image obtained after the administration of contrast material. The images demonstrate T2-weighted and STIR hyperintense and T1-weighted hypointense bone marrow edema (arrows in **A** and **B**) in a semicircular or curvilinear pattern (dashed line in **C**) in contiguous vertebral body segments (T7-T9) with associated avid enhancement (straight arrow in **D**). Note the absence of abnormal signal intensity and enhancement in the intervening disc spaces. There is mild associated prevertebral enhancement (curved arrow in **D**) and an additional enhancing lesion in the T3 vertebral body (dashed arrow in **D**) with similar signal intensity characteristics.

with hyperostosis are not seen in psoriatic arthritis.[10] Axial psoriatic arthritis typically involves nonmarginal, bulky, coarse asymmetric syndesmophytes and commonly is associated with sacroiliitis and sparing of
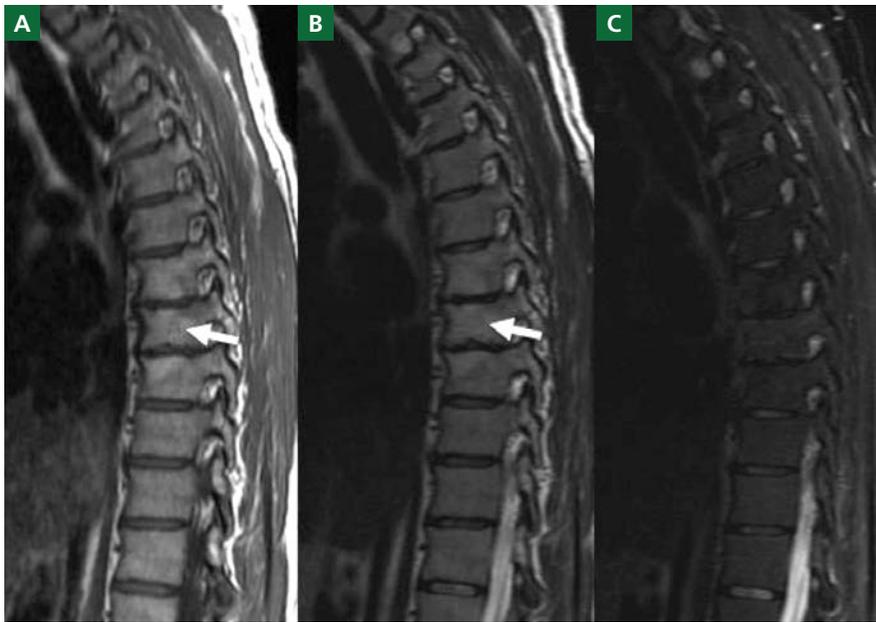
Figure 3. Sagittal Magnetic Resonance Images. **A,** T1-weighted image. **B,** T2-weighted image. **C,** Short inversion time inversion-recovery image. Images obtained after treatment show resolution of the bone marrow edema and development of fatty marrow changes in contiguous T7 through T9 vertebral body segments (arrows).

the facet joints.[11] Typically, ankylosing spondylitis is characterized by the onset of sacroiliitis that progresses to ankylosis. In the spine, fine symmetric syndesmophytes develop, and spinal involvement can be earlier than, contemporary with, or subsequent to the onset of sacroiliitis.[11] Unlike with axial psoriatic arthritis, facet joints are not spared in ankylosing spondylitis.

Reactive spondyloarthritis is believed to be a component of a systemic autoimmune response that may occur 1 to 4 weeks after an infection of the conjunctival, intestinal, or urethral-genital mucosa. Although reactive spondyloarthritis often manifests as asymmetrical oligoarthritis of large synovial joints of the lower limbs, involvement of the sacroiliac joints is also common and has the same radiological features as psoriatic sacroiliitis. Spinal involvement is rare and is characterized early by coarse syndesmophytes, similar to findings in psoriasis.[11] The lack of an associated inciting illness or mucosal findings in the patient in this case report makes this diagnosis unlikely. Enteropathic spondyloarthritis is associated with 2 major chronic inflammatory bowel diseases,

ulcerative colitis and Crohn disease, which have radiologic features of spondylitis and sacroiliitis similar to those of ankylosing spondylitis.[11,12] The lack of intestinal findings in the patient in this case report excludes this diagnosis.

Several aspects of the clinical presentation of the case presented here are unusual for descriptions of SAPHO, indicating that this case may be a variant or incomplete expression. First, the patient described the dermatologic manifestations as palmar sloughing without pustules, whereas classic descriptions of SAPHO report pustulosis. In addition, although skin lesions can occur remotely from osseous manifestations, the gap of more than 1 decade between these findings is unusual. He also did not have peripheral joint synovitis and did not demonstrate disease of the sternocostoclavicular region, which occurs in 70% to 90% of SAPHO cases.[11,13,14] However, there was a suggestion of costovertebral joint synovitis at imaging.

The most common site of skeletal involvement in SAPHO syndrome is the anterior chest wall followed by the spine.[13,14] Spinal involvement visible on

conventional radiographs may include vertebral body osteosclerosis, hyperostosis, and discovertebral junction lesions.[8]

With technetium-99m bone scanning, active and subclinical chronic lesions demonstrate increased tracer uptake.[8,9,14] PET is used to differentiate active from chronic healed inflammatory lesions because increased metabolic activity occurs only in lesions with active inflammation.[8] However, in undiagnosed SAPHO syndrome with PET-positive lesions, biopsy may be necessary to exclude metastatic disease, especially in patients with a history of cancer.

With MR imaging, active lesions demonstrate bone marrow edema, which appears as low (hypointense) signal intensity on T1-weighted images and high (hyperintense) signal intensity on T2-weighted images. Chronic lesions demonstrate sclerosis, which appears hypointense on T1-weighted and T2-weighted images.[14] In a 2016 study, the most suggestive MR imaging finding of spinal involvement was a curvilinear or semicircular pattern of bone marrow signal intensity in contiguous vertebral body segments.[8] This pattern of vertebral marrow involvement may be helpful in differentiating SAPHO syndrome from metastatic disease, which tends to have a random distribution in the spine, and the patient in this case report displayed these characteristic lesions (Figure 2).[8]

Combined with the low prevalence of hyperintense signal intensity on T2-weighted images and enhancement in the intervening disc spaces, MR imaging may help exclude discitis-osteomyelitis.[8] Correlation with CT results may be helpful because of associated sclerosis with the abnormal MR imaging signal intensity.[8]

Another finding at MR imaging is anterior vertebral corner erosions suggestive of enthesitis with associated adjacent vertebral body marrow signal intensity changes.[13] Hyperintense signal intensity and enhancement on T2-weighted images within the disc space in up to 30% of patients with SAPHO syndrome makes differentiation from discitis-osteomyelitis

difficult, especially when pre- and paravertebral soft-tissue changes are present.[14]

The diagnosis of SAPHO syndrome cannot be confirmed histopathologically. The benefit of biopsy is to exclude infection.[14] The detection of multifocal osseous involvement in the absence of inflammatory arthropathy or history of cancer suggests the diagnosis of SAPHO syndrome.

Clinicians can use whole-body MR imaging including sagittal T1-weighted and fat-suppressed T2-weighted sequences in SAPHO syndrome to demonstrate the multifocal involvement, to show active lesions with bone marrow edema, and to monitor therapeutic response.[14] Bone scanning also may aid the diagnostic process by demonstrating the multifocal osseous lesions and the bull's head pattern of sternocostoclavicular lesions, which is considered specific when present.[14]

The causes of SAPHO syndrome are not understood fully yet,[10] and the pathogenesis may involve genetic, infectious, and immunologic components. Human leukocyte antigen B27 is associated with SAPHO in some studies and not in others.[10] Investigators also have hypothesized an infectious cause because bacteria have been isolated from bone and skin lesions, with *Propionibacterium acnes* being identified most often.[10,11,15]

Investigators also have reported abnormalities in the immune system in SAPHO.[10,15] Perhaps SAPHO is caused by a combination of these factors, and it may be an autoimmune reaction, triggered by an infectious agent, in people who are genetically predisposed.[11]

Investigators have not clearly defined optimal treatment for SAPHO syndrome.[2,10,15-20] NSAIDS generally are considered first-line agents for treatment. Given the possible infectious causes, investigators have tried antimicrobial therapy and reported some success in patients with positive biopsy culture results. Investigators have used corticosteroids to treat both bone and skin features. Dermatologists have used topical corticosteroids, psoralen plus ultraviolet A therapy, and retinoids. Disease-modifying agents, particularly infliximab, are effective in treating both osseous and cutaneous lesions. Clinicians have used physical therapy as an adjunct treatment for skeletal manifestations, but there is sparse evidence for effectiveness. Surgical treatment may be beneficial when there is deformity or loss of function due to pain or rapidly destructive lesions.[2]

The majority of patients have a relapsing-remitting course or a chronic indolent pattern, and a minority of patients have a self-limited course.[10] Although the cutaneous and bone manifestations are generally benign in nature, investigators have reported rapidly progressive destructive spondylitis requiring surgical stabilization.[2]

The long-term prognosis appears to be rather good. Colina et al[21] reported that at a mean follow-up of 10 years, only 2 of 71 patients had severe disabling complications due to osteoarticular symptoms, and neither of these patients had issues related to the spine.

CONCLUSION

Isolated vertebral osteitis is an unusual manifestation of SAPHO syndrome. As seen in this case, it is important for SAPHO syndrome to be part of the differential diagnosis, even when skin manifestations are not present.[2-6] Although treatment still is poorly defined, NSAIDS generally have been effective in controlling symptoms. Further work is needed to identify SAPHO syndrome more accurately, understand the disease better, and improve treatments. ❖

A Leader With a Following

While long-time adult reconstructive surgeon Aaron Rosenberg, MD, recently hung up his scalpel, his positive influence on former residents and fellows can be seen in operating rooms across the country.

While long-time adult reconstructive surgeon Aaron Rosenberg, MD, recently hung up his scalpel, his positive influence on former residents and fellows can be seen in operating rooms across the country.

Some people just have it: that knack for inspiring others to perform at the highest levels; the brainpower to understand something thoroughly and explain it well; a contagious passion for lifelong learning.

For surgeons trained at Rush during the past 35 years, one such gifted teacher and mentor can be found in Rush's Department of Orthopedic Surgery: Aaron Rosenberg,

MD, retired chief of adult reconstructive surgery, former adult reconstructive fellowship director, and currently a professor of orthopedic surgery. Through example and through human connection, Rosenberg has helped lead surgeons to fulfilling careers in orthopedic surgery by sharing with them the art of joint replacement.

FAN FOLLOWING LEADS TO ENDOWED CHAIR

For more than 3 decades, Rosenberg has not only taught surgeons at Rush, he has drawn them to Rush and to

orthopedic surgery itself. Just ask Craig J. Della Valle, MD, the current chief of adult reconstructive surgery at Rush and president of the American Association for Hip and Knee Surgeons. He met Rosenberg 20 years ago when he was in his third year of training as a resident.

"Shortly after meeting Aaron, I knew I wanted to pursue my advanced fellowship training at Rush. There's no other way to say it: When I met Aaron, I fell in love. He's the one I wanted to train with, and he's the reason I wanted to come to Rush," Della Valle says.

> "One of the hardest things about being a mentor is realizing that every individual needs to find their own path to achieve their greatest success."

Not surprisingly, Della Valle isn't a fan club of one. Rosenberg has a legion of former residents and fellows who attribute their successes to his mentorship. And in recognition of their admiration, in 2014, they pooled their resources to establish the Aaron G. Rosenberg, MD, Chair of Orthopedic Surgery.

Former fellow Craig Silverton, DO, hatched the plan for the endowed chair, which is currently held by Della Valle, along with Rosenberg's long-time nurse Reggie Barden, RN. Before coming to Rush, Silverton—a veteran with the Joint Special Operations Command—had led the Air Force orthopedic department in preparation for the Gulf War. After 2 years in that position, he applied for a fellowship in adult reconstructive surgery at Rush and trained under Rosenberg. "When I showed up, I had a very basic understanding of total joints, but Aaron still took me under his wing. He changed the path of my life."

Silverton would later go on to serve 2 tours in Iraq and 1 in Afghanistan as a combat orthopedic surgeon, then pursue a successful career as an orthopedic surgeon in the Henry Ford Health System in Detroit.

Persuading Rosenberg's former fellows, residents, and peers to donate wasn't difficult. Ray Wasielewski, MD, director of the Bone and Joint Center at Grant Medical Center, Ohio Health in Columbus, was particularly grateful to Rosenberg for teaching him to approach difficult situations calmly when they arise. "I thought there couldn't be a more worthy individual," Wasielewski says.

But what exactly makes Rosenberg so admired and respected?

"He is one of the most intelligent and charismatic people I've ever met," Della Valle says. "You just want to be around him. And if you hang around people like him, who are really smart, you can't help but learn from them; you learn by osmosis."

Rosenberg also brings out the best in his residents and fellows, according to Wasielewski. "I don't think anyone else could identify my exact weaknesses and strengths, and then make my strengths better while also gently helping me correct my weaknesses," he says.

WHEN MENTEE BECOME MENTOR

Rosenberg himself had mentors when he first came to Rush as a resident in orthopedics in 1978, including joint replacement pioneer Jorge O. Galante, MD, DMSc, who was the department's first chairperson. After Rosenberg completed his fellowship in adult reconstruction and oncology at Massachusetts General Hospital in Boston, he then considered a move to California. But Galante and Rosenberg's wife—who had no desire to live in California—conspired and convinced him otherwise.

Rosenberg returned to Rush to specialize in hip and knee replacement surgery, and to focus on the education of surgeons both in the United States and around the world. During his long career, he has written hundreds of scientific papers and made hundreds of scientific presentations at meetings around the globe. He co-edited the definitive textbooks for hip and knee surgeries (The Adult Hip and The Adult Knee), and served on several editorial boards. Along the way, he's been instrumental in the design of several joint replacement devices, including the VerSys Hip System, The Nex Gen Knee System, and The ZMR Revision Hip System.

And, of course, there's the role he really relished: director of the Adult Reconstructive Surgery Fellowship Program at Rush.

Rosenberg has been interested in teaching since his days as a resident. "I so much enjoyed the experience of learning, and learning something well enough to explain it to others," he says. "For me, real satisfaction comes from how you teach

Rosenberg's myriad contributions to the field of hip replacement and knee replacement surgery are rivaled by the lasting impact he's had on his patients, colleagues, and trainees.

things—how you create the mechanism by which you can transfer information from one individual to another. That human connection is so important, in medicine as in teaching. And, as a teacher, you learn so much from your students. It's truly an interactive process."

LEADERSHIP NAVIGATES CHANGE

When he came to Rush as a new attending, the Department of Orthopedic Surgery was transitioning from a model where surgeons worked independently to one in which there was a greater level of collaboration and specialization. "A lot of other things have changed over the years, but we've been fortunate to have very strong leadership and a good model for maintaining academic productivity and scientific excellence," he says. "And over the years, we've built a stronger and stronger teaching program that has produced outstanding surgeons, we have maintained a reputation for and a willingness to tackle the most complex clinical problems, and we've developed a reputation for being an honest broker in terms of studying and publishing the results of our clinical endeavors."

REFLECTIONS ON SURGICAL EDUCATION

While Rosenberg no longer operates, he still sees patients, remains a teacher and mentor to those around him, and continues to contemplate how orthopedic surgeons can improve the care they deliver.

"One thing we don't pay enough attention to in educating surgeons is balancing the need to be cautious and careful with having a certain amount of courage to do what's required for the patient," he says. "That balance is essential."

While he no longer operates, Rosenberg remains a dedicated teacher and mentor to the adult reconstructive surgery fellows and residents at Rush.

And while he still fine tunes his fine motor skills through calligraphy and guitar playing, Rosenberg believes the most important tool a surgeon uses—more important than hands and retractors—is the brain.

"It's your brain that's constantly refining, through your senses, what you're actually accomplishing. It's the brain making those adjustments that allow you to play the right note on the violin or shave off the right amount of bone to get bone surfaces to fit each other perfectly," he says. "Continuing research in the areas of how physicians can better use their cognitive skill set around preoperative and intraoperative decision making—such as determining who gets surgery and who doesn't, and at what point you can safely move on to the next step of surgical procedure—that's a strong interest of mine."

Meanwhile, he never forgets the lessons learned from his own mentor, Jorge Galante, who passed away in 2017 but whose presence is still strongly felt within the department. "One of the hardest things about being a mentor is realizing that every individual needs to find their own path to achieve their greatest success," Rosenberg says. "One of the greatest gifts to me was when Jorge gave up on trying to make me into his mold and said 'Aaron's going to have to be what Aaron has to be.' "

And what Rosenberg became will impact joint replacement surgeons, at Rush and beyond, for generations to come. ✜

*"We established that the optimal knee flexion angle
to tension the ALL graft is from 20° to 40° of flexion because
there was minimal length change at these angles of flexion."*

Dynamic 3-Dimensional Mapping of Isometric Attachment Sites on the Lateral Aspect of the Knee for Anterolateral Ligament Reconstruction

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INTRODUCTION

Concomitant anterolateral ligament (ALL)
injury has been observed in 33% to 79% of
patients with an anterior cruciate ligament
(ACL) injury.[1,2] The ALL functions as
an internal rotation stabilizer, especially
at knee flexion angles greater than 35°,
where the contribution of the ALL exceeds
that of the ACL.[3-5] Intra-articular ACL
reconstruction restores anterior-posterior
kinematics; however, internal laxity may
remain, most likely due to the deficiency of
the ALL.[6,7] Concomitant anatomical ALL
reconstruction during ACL reconstruction
reduces internal laxity and recently
has been shown to provide satisfactory
patient outcomes.[8] The association
between ALL injury with a positive
pivot-shift examination result after ACL
reconstruction has led some to recommend
concurrent ALL reconstruction.[6,9]

Several investigators have described
the anatomical insertion points of
the ALL with great heterogeneity,
specifically the femoral insertion site.
Investigators consistently have described
the tibial insertion site as posterior
to the Gerdy tubercle approximately
10 mm below the joint line.[5,10,11] The
femoral insertion site has been described
as posterior-proximal,[10-12] anterior,[13]
anterior-distal,[14] or directly on the lateral
femoral epicondyle.[5,15] With ligament
reconstruction, it is imperative to restore
desirable ligament length changes;
however, the optimal locations for
fixation may not correspond to the
native ALL anatomy. Investigators have
argued that the ALL is isometric only
during a portion of range of motion or
is completely anisometric,[10,16-18] thus
making identification of locations that
optimize length change properties
increasingly important.

To define a superior method of ALL
reconstruction, the clinician must
evaluate the length change properties of
the ALL. The purpose of this investigation
was to identify the anatomical locations
on the lateral aspects of the femur and
tibia that provide the most isometric
behavior of the ALL throughout range of
motion from 3-dimensional (3D) computed
tomography (CT) reconstructed models.
The aims of this investigation were to
(1) identify the optimal combination of
tibial and femoral insertion sites that
allow for isometric ALL reconstruction
and (2) determine whether altering the
position of femoral and tibial fixation
affects ALL isometry.

MATERIALS AND METHODS

3D CT Knee Models at Various Flexion Angles

We used 6 fresh-frozen, unpaired, cadaveric human knees meeting our inclusion criteria in the investigation. We included specimens with no history of trauma, arthritis, cancer, surgery, congenital defects, or any ligamentous knee injury in this study. Before CT scanning, we examined each specimen with a Lachman test to ensure that an intact ACL was present. Mean donor age for the collected knees was 47 years (range, 26-59 years). We preserved each knee at −20°C and thawed it for 24 hours before performing CT scanning (BrightSpeed; GE Healthcare, Chicago, IL) in the coronal, axial, and sagittal planes with use of 0.625-mm contiguous sections (20-cm field of view, 512 × 512 matrixes) at 0°, 10°, 20°, 30°, 40°, 90°, 110°, and 125° of knee flexion. We used an external fixation device to ensure consistent and neutral knee flexion. We scanned the knees at 10° increments from 0° to 40° of flexion because most techniques of ALL reconstruction are conducted at less than 40° of flexion. Using smaller increments of knee flexion allows for identification of the optimal angle of knee flexion that allows for isometric fixation of the ALL. We converted CT scans to a Digital Imaging and Communications in Medicine format and segmented them by using 3D reconstruction software (Mimics; Materialise, Leuven, Belgium) to generate the 3D knee models.

Determination of Tibial ALL Insertion Sites

We determined 24 virtual tibial insertion sites on the proximal lateral tibia at 0° of flexion (Figure 1). We identified anatomical markers such as the Gerdy tubercle, the fibular head, and the lateral tibial plateau as boundaries for placement of a grid. We appropriately sized and placed the planar grid to provide analytic points on the lateral tibial condyle and the Gerdy tubercle while providing adequate spacing for several fixation sites posterior to the Gerdy tubercle and anterior to the fibular head.[5,10,11] We sized and oriented the grid
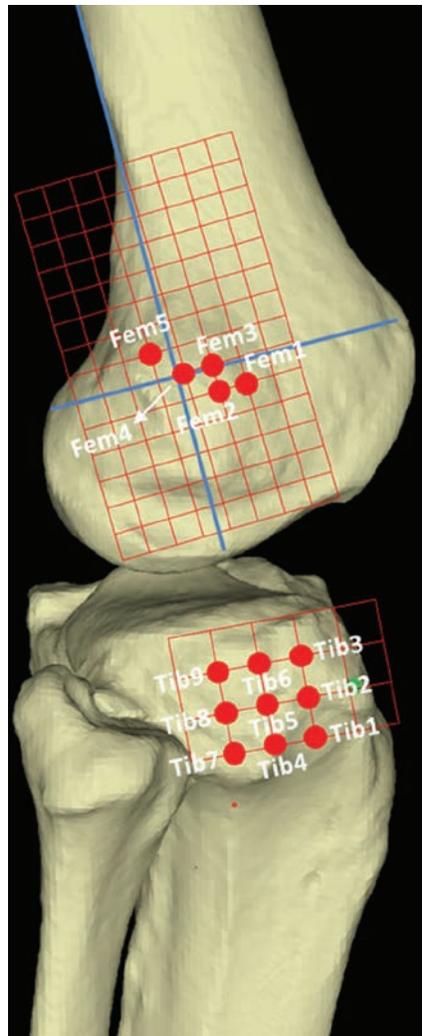

Figure 1. Three-Dimensional (3D) Computed Tomographic Model Illustrating Grid Placement and Matrix Transformation. Sites of ALL fixation on the femoral epicondyle and tibial plateau are identified and labeled. 3D-3D registration allows for the position of these points to be maintained throughout range of motion. Fem1, 5 mm below the midpoint of the Blumensaat line; Fem2, anterior-inferior to the lateral femoral epicondyle; Fem3, anterior to lateral femoral epicondyle; Fem4, lateral femoral epicondyle; Fem5, proximal-posterior to lateral femoral epicondyle; Tib1, anteroinferior; Tib2, anteromedial; Tib3, anterosuperior; Tib4, inferior; Tib5, central; Tib6, superior; Tib7, posteroinferior; Tib8, posteromedial; Tib9, posterosuperior. The green marker represents the Gerdy tubercle.

such that osseous landmarks corresponded to the same relative coordinates across samples. We then projected the planar grid

onto the 3D model of the proximal lateral tibial plateau and obtained coordinates of each insertion point. We used a 3D-3D registration technique to transform the matrixes from the tibial model at 0° to the tibial models in each angle of flexion. 3D-3D registration is a mechanism of transforming data or a function onto itself in a different spatial orientation that allows for alignment of data sets in a consistent model. This procedure allowed for identically creating femoral and tibial insertion points at 0° of flexion for each 3D model at different angles of knee flexion.

Determination of Femoral ALL Insertion Sites

Similar to the way we determined the ALL insertion sites on the tibia, we virtually placed a 59-point grid on the lateral wall of the lateral femoral condyle at 0° of flexion by using the lateral femoral epicondyle and the Blumensaat line as anatomical boundaries (Figure 1). We appropriately sized and placed the planar grid to provide analytic points on the lateral femoral condyle while providing adequate spacing for several fixation sites of the ALL on and around the lateral femoral epicondyle.[15,19] We aligned the 59-point grid parallel to the inferior aspect of the lateral femoral condyle, with a point fixated on the midpoint of the epicondyle. We placed the grid to ensure complete coverage of the ALL's anatomical and surgical fixation points. We sized and oriented the grid such that anatomical landmarks corresponded to the same relative coordinates across samples. We projected the grid on the 3D lateral femoral condyle model and obtained 3D coordinates of each insertion point. We determined a total of 42 to 51 insertion points to lie on the lateral wall of the lateral femoral condyle for each specimen, and we obtained 3D coordinates of each insertion point on the femur. We observed a range of points on the lateral femoral condyle due to the anatomical differences in the size of the condyle across cadaveric samples. We calculated the insertion points in the flexed conditions by using the same procedure described earlier for the proximal lateral tibia.
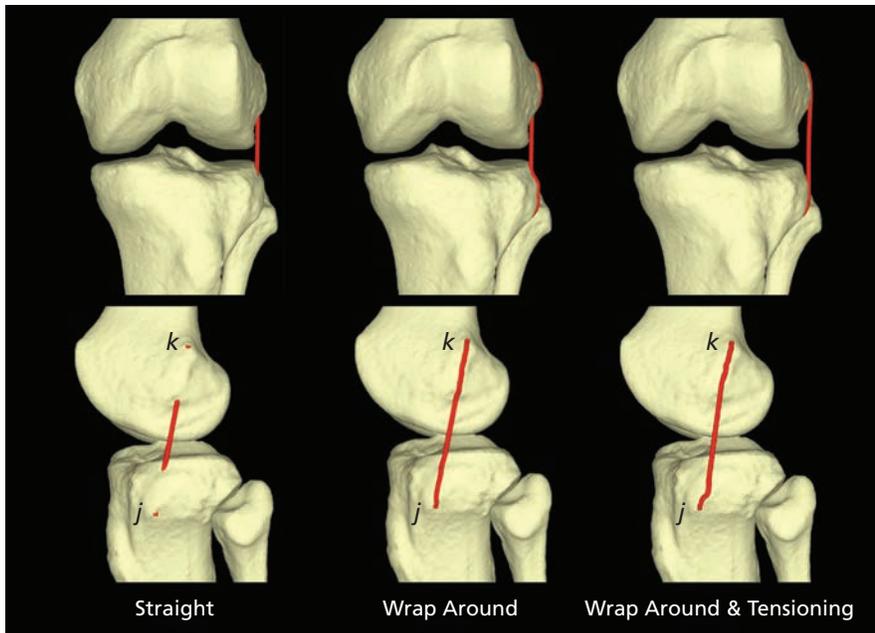
Figure 2. Anterior and Lateral View of the Three-Dimensional (3D) Computed Tomographic Model Illustrating the Wrap-Around Algorithm for Improved Depiction of *in vivo* Length of a Reconstructed Ligament. This technique accounts for the osseous landmarks that the ligament travels around, allowing for a better depiction of physiologic motion of the ALL.

ALL Length Calculation

Because a reconstructed ALL must wrap around the femur and tibia, we have introduced a 3D wrap-around algorithm to calculate the length of the ligament. This wrap-around technique, unlike the straight-line method, is able to conform to the osseous landmarks, allowing for a better depiction of physiologic motion (Figure 2). We used the following steps for the wrap-around algorithm:

1) We created a line between the tibial origin at point j and the femoral insertion at point k at the knee flexion angle i and set 100 equidistant control points on the line.

2) If a control point was located in the bone (Figure 2, left), we moved this point laterally until it was located on the bone surface or outside of the bone (Figure 2, middle).

3) We realigned the control points outside of the bone to straighten the ligament outside of the bone (Figure 2, right).

4) We calculated the ligament length by summating the lengths between all control points.

We calculated isometry between the tibial and femoral insertion sites at a given knee flexion angle, using the length change, Δ, in reference to the length at 0° of knee flexion. A value of 0 indicated isometry, a positive value indicated elongation of the anterolateral ligament, and a negative value indicated shortening of the anterolateral ligament during knee flexion. We calculated lengths from every tibial point to each of the femoral points for all angles of knee flexion.

Femoral Insertion Site Analysis

We used 5 femoral fixation points for isometry analysis. We systematically chose these points on the basis of previously described anatomical descriptions and reconstruction techniques of the ALL.[13,19-24] Isolating an individual numbered point as a fixation marker across samples would cause variation in the femoral origin because of differences in specimen condylar size. Thus, we chose points serving as femoral insertion sites of the ALL relative to the morphologic osseous landmarks on each specimen. The femoral points we chose for isometric analysis included the lateral

femoral epicondyle (Fem4),[13,20] proximal-posterior to lateral femoral epicondyle (Fem5)[21], anterior to lateral femoral epicondyle (Fem3),[22] anterior-distal to lateral femoral epicondyle (Fem2),[23] and 5 mm below the midpoint of the Blumensaat line (Fem1)[19,24] (Figure 1).

We identified 9 sites along the tibial plateau located posterior to the Gerdy tubercle, anterior to the fibular head, and below the tibial plateau (Figure 1): the anteroinferior aspect of the tibial plateau (Tib1), anteromedial (Tib2), anterosuperior (Tib3), inferior (Tib4), central (Tib5), superior (Tib6), posteroinferior (Tib7), posteromedial (Tib8), and posterosuperior (Tib9). We calculated distances for each potential combination from points on the tibia to the aforementioned points on the femur (45 total points) for all flexion angles (7 angles of flexion, 315 total distances). We defined the combination of femoral and tibial fixation sites by combining Fem1 with each tibial point, then Fem2 with all tibial points, through Fem5 (eg, combination 1, Fem1-Tib1; combination 45, Fem5-Tib9) (Table 1, p. 43).

We defined the maximum and minimum ligament lengths throughout range of motion for each point combination. We then normalized ligament lengths at each flexion angle to the maximum length to allow for more direct comparisons across specimens. We calculated the mean normalized lengths among all specimens for each combination of points at all angles of flexion. We calculated the rate of change in ligament length over the entire range of motion for each combination of points.

Statistical Analysis

We performed statistical analyses with Stata 14 (StataCorp, College Station, TX) and Excel (Microsoft, Redmond, WA). We performed a 3-way analysis of variance (ANOVA) with Bonferroni correction, with femoral fixation position, tibial fixation position, and knee flexion angle as independent variables and the normalized ligament length serving as the dependent variable. We performed a 1-way ANOVA with Bonferroni correction, with knee flexion angle as the independent variable
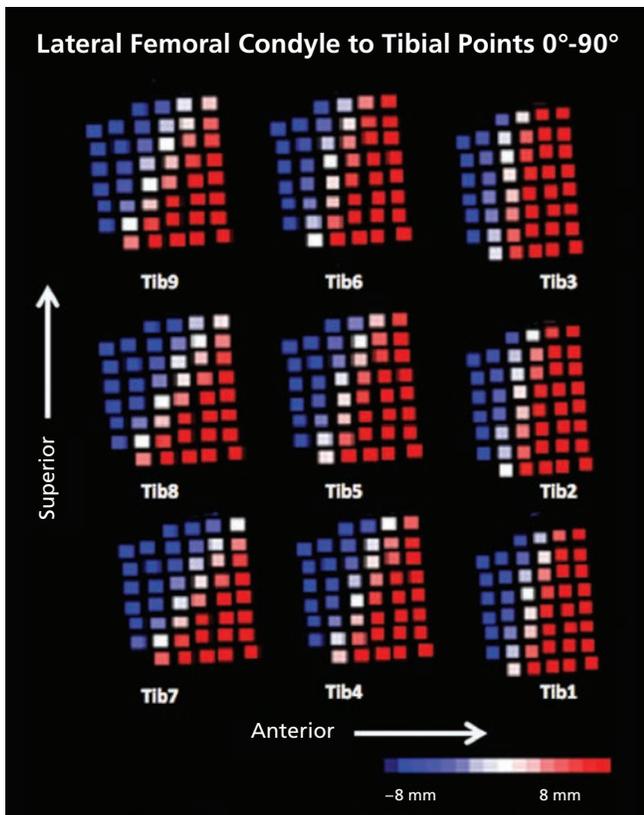
Figure 3. Anterolateral Ligament Length Change to All Points on the Lateral Femoral Epicondyle for All Examined Tibial Points From 0° to 90° of Knee Flexion. Blue represents ligament shortening, white represents isometry, and red represents ligament lengthening. Tib1 indicates anteroinferior; Tib2, anteromedial; Tib3, anterosuperior; Tib4, inferior; Tib5, central; Tib6, superior; Tib7, posteroinferior; Tib8, posteromedial; Tib9, posterosuperior.
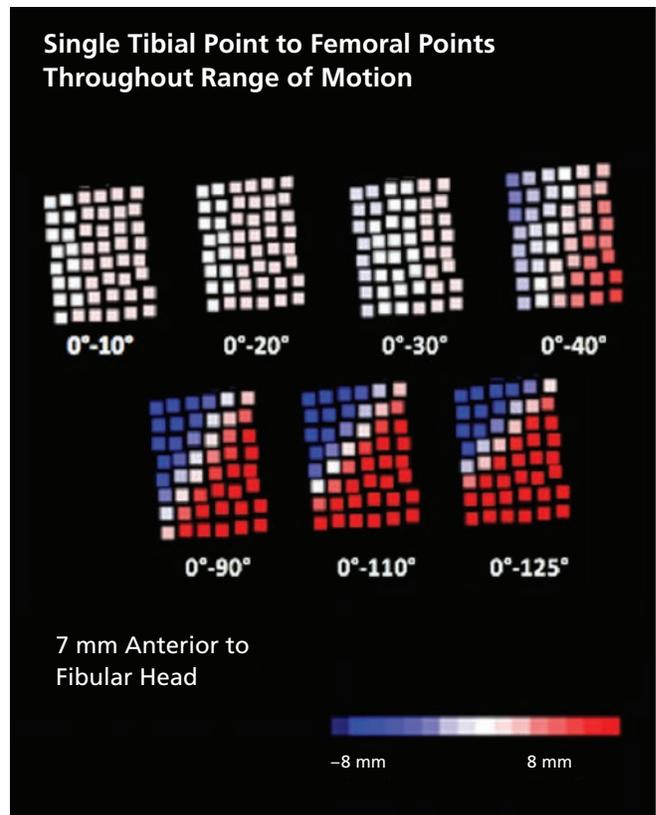

Figure 4. Length Change of the Anterolateral Ligament From a Single Tibial Point (Posterosuperior, or Tib9) to All Points on the Lateral Femoral Epicondyle Throughout Range of Motion. Blue represents ligament shortening, white represents isometry, and red represents ligament lengthening.

and the normalized ligament length as the dependent variable. Finally, we performed an ANOVA with Tukey post hoc adjustment to evaluate for any differences between normalized ligament length at the most isometric fixation combinations for all flexion angles during range of motion. We defined significance for these tests as $P < .05$.

RESULTS

Mapping of Ligament Length Changes

Using the 9 points identified on the tibia, we measured the length of the ALL to each point on the lateral wall of the lateral femoral condyle. The length of the ALL at 0° of knee flexion served as the reference length, which we illustrated in length change maps. Figure 3 illustrates the length change from analyzed points on the lateral femoral epicondyle of a single specimen from 0° to 90° of flexion for each tibial point. Figure 4 illustrates a length change map of the same specimen used in Figure 3 for points on the lateral femoral epicondyle from a single point on the tibia (Tib9) throughout range of motion. The ALL exhibits relative isometry to all femoral points on the lateral wall of the lateral femoral condyle from 0° to 30° of flexion.

ALL Length Change

Fixation at Fem3 and Fem4 demonstrated the smallest average normalized range for all positions on the tibia (13.9% and 11.2%, respectively), whereas fixation at Tib7 and Tib8 demonstrated the smallest

average normalized range for all positions on the femur (12.8% and 13.8%, respectively). Fem1 exhibited the greatest change in mean normalized length, with an average length change of 22.5% across all tibial points, whereas Tib3 exhibited the greatest average change in normalized length, with an average change of 23.4% across all femoral points. Table 2 illustrates the range of normalized length change for each combination of points throughout the entire range of motion. Point combinations that demonstrated the least amount of length change (combinations 25, 26, 31, 34, 35) corresponded to fixation on the lateral femoral epicondyle and fixation 5 mm anterior to the lateral femoral epicondyle with tibial fixation inferoposterior on the tibial condyle (14-21 mm posterior to the

Table 1. Definitions of Analyzed Femoral and Tibial Point Combinations

Combinations of Femoral and Tibial Points					
Tibial Point	**Fem1**	**Fem2**	**Fem3**	**Fem4**	**Fem5**
Tib1	1	10	19	28	37
Tib2	2	11	20	29	38
Tib3	3	12	21	30	39
Tib4	4	13	22	31	40
Tib5	5	14	23	32	41
Tib6	6	15	24	33	42
Tib7	7	16	25	34	43
Tib8	8	17	26	35	44
Tib9	9	18	27	36	45

Abbreviations: Fem1, 5 mm below the midpoint of the Blumensaat line; Fem2, anterior-distal to lateral femoral epicondyle; Fem3, anterior to lateral femoral epicondyle; Fem4, lateral femoral epicondyle; Fem5, proximal-posterior to lateral femoral epicondyle; Tib1, anteroinferior; Tib2, anteromedial; Tib3, anterosuperior; Tib4, inferior; Tib5, central; Tib6, superior; Tib7, posteroinferior; Tib8, posteromedial; Tib9, posterosuperior.

Table 2. Mean Range of Normalized Lengths Throughout Range of Motion

Mean Range of Normalized Lengths (%)					
Tibial Point	**Fem1**	**Fem2**	**Fem3**	**Fem4**	**Fem5**
Tib1	23.7	20.5	14.8	10.3	13.7
Tib2	27.8	24.6	18.5	12.7	13.9
Tib3	32.5	29.3	23.0	16.7	15.4
Tib4	19.1	16.2	10.5	**8.4**	17.3
Tib5	22.6	19.9	13.4	10.3	16.7
Tib6	27.3	24.9	17.8	13.2	16.0
Tib7	13.4	11.1	**7.4**	**9.8**	22.1
Tib8	16.1	13.5	**8.7**	**9.2**	21.7
Tib9	19.9	17.5	11.0	10.4	21.2

Abbreviations: Fem1, 5 mm below the midpoint of the Blumensaat line; Fem2, anterior-distal to lateral femoral epicondyle; Fem3, anterior to lateral femoral epicondyle; Fem4, lateral femoral epicondyle; Fem5, proximal-posterior to lateral femoral epicondyle; Tib1, anteroinferior; Tib2, anteromedial; Tib3, anterosuperior; Tib4, inferior; Tib5, central; Tib6, superior; Tib7, posteroinferior; Tib8, posteromedial; Tib9, posterosuperior.
Note: Mean changes less than 10% are bolded.

Figure 5. Fixation of the Anterolateral Ligament at a Combination of the Femoral and Tibial Points that Provides the Most Isometric Behavior of the Ligament Throughout Range of Motion. Fem3 indicates anterior to lateral femoral epicondyle; Fem4, lateral femoral epicondyle; Tib4, inferior; Tib7, posteroinferior; Tib8, posteromedial. The green marker represents the Gerdy tubercle.

Gerdy tubercle and 13-20 mm below the joint line) (Figure 5).

Results from 1-way ANOVA between the average range in normalized length throughout range of motion for every femoral and tibial fixation combination revealed statistically significant differences between several combinations (eg, combination 42 and combination 3; $P < .005$), whereas there were no statistically significant differences in ligament length for other combinations of fixation points (eg, combination 42 and combination 22; $P > .05$).

Results from 1-way ANOVA demonstrated a statistically significant difference in the ALL length at 40° of flexion in comparison with the ALL length at 0° of flexion ($P = .006$) and at 125° of flexion ($P = .001$). Results of 1-way ANOVA for all point combinations that illustrated length change less than 10% demonstrated no statistical difference in average normalized length throughout range of motion ($P > .05$). However, the length of the ALL at 125° for combination 34 (Fem4-Tib7) was statistically significantly shorter than the length of the ligament at 20° of flexion ($P = .046$), 30° of flexion ($P = .017$), and 40° of flexion ($P = .007$).
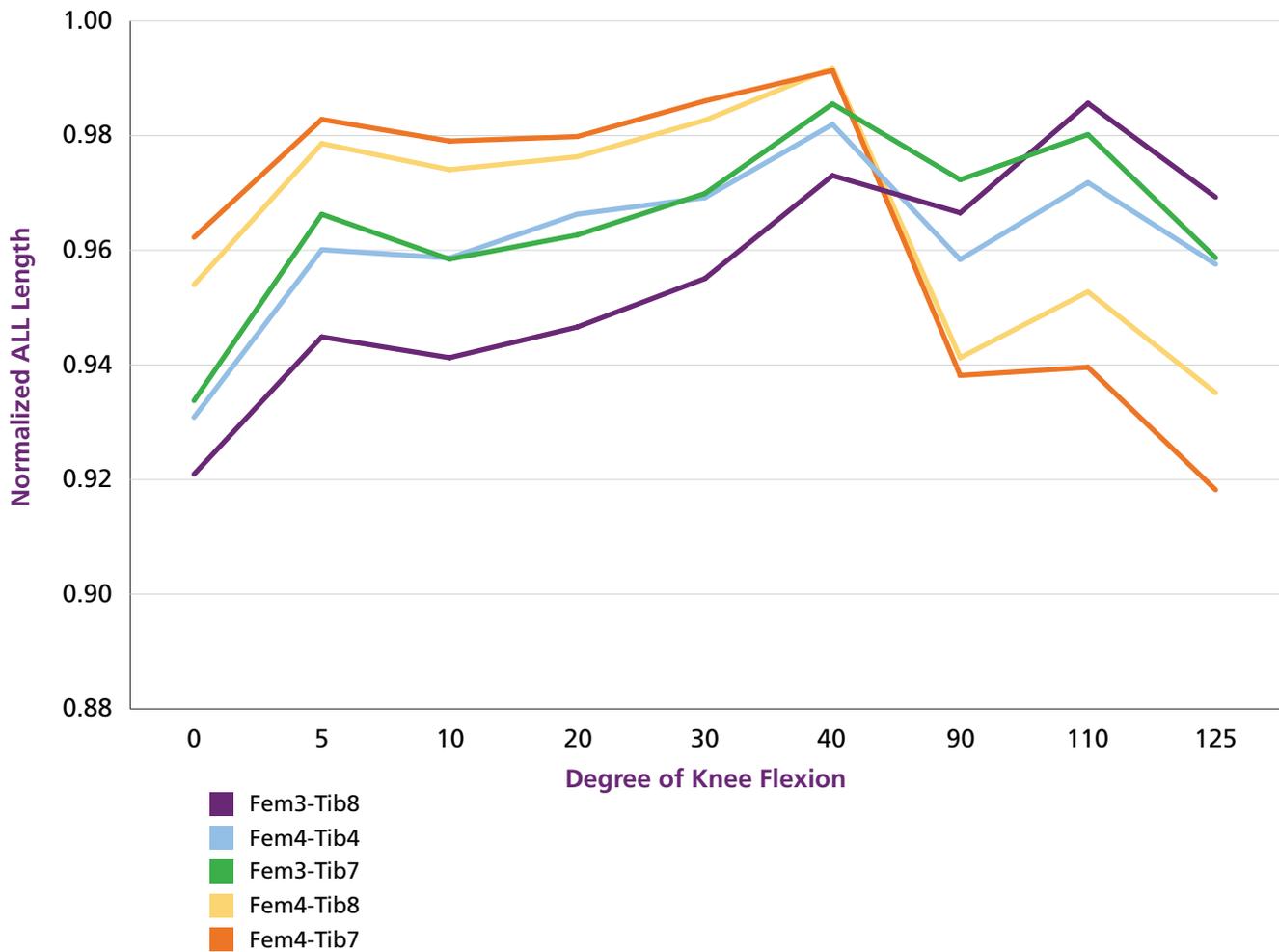
Figure 6. Normalized Anterolateral Ligament (ALL) Length Change Throughout Range of Motion for All Fixation Combinations That Illustrate Minimal Length Change. Fem3 indicates anterior to lateral femoral epicondyle; Fem4, lateral femoral epicondyle; Tib4, inferior; Tib7, posteroinferior; Tib8, posteromedial.

For each combination of femoral and tibial points that exhibited a length change less than 10% (Fem3-Tib7, Fem3-Tib8, Fem4-Tib4, Fem4-Tib7, Fem4-Tib8) throughout range of motion exhibited minimal length change between 20°and 40° of knee flexion (Figure 6). In addition, the ALL exhibited shortening as the knee approached full extension and full flexion.

DISCUSSION

In this investigation, we identified the femoral and tibial fixation points of the ALL that displayed the most isometric behavior throughout full range of motion. Fixation of the ALL to the lateral femoral epicondyle or 5 mm anterior to the lateral femoral epicondyle with tibial fixation on the posteroinferior aspect of the tibial condyle (14-21 mm posterior to the Gerdy tubercle and 13-20 mm below the joint line) provided the lowest average length change. Of the 45 examined fixation combinations, only 5 fixation combinations demonstrated a change in length less than 10%. Although there was not a statistically significant difference between the most isometric fixation points and all other examined combinations, all nonstatistically significant point combinations demonstrated a length change greater than 10%. A ligament that stretches by more than 10%

is subjected to increased forces throughout range of motion, which increases graft strain and risk of failure.[25,26] For the isometric combinations of femoral and tibial fixation, the minimal length change we observed was from 20° to 40° of flexion, which identifies the angle of flexion where graft tensioning should occur. Lastly, the length of the ALL was longest at 40° of flexion and exhibited shortening as the knee approached maximal extension and flexion.

Investigators previously have studied the isometric properties of the ALL; however, previously described fixation points do not replicate ideal knee kinematic properties.

To our knowledge, Claes et al[5] were the first to describe length changes of the ALL, and they noted that the length of the ALL at its native anatomical origin and insertion sites increased from full flexion to full extension. More recently, investigators have identified femoral fixation of the ALL posterior and proximal to the lateral femoral epicondyle and directly superior to the epicondyle to be the most isometric.[12,27] The corresponding isometric tibial fixation point was located at 37% of the anterior-posterior length of the tibial plateau and 10 mm below the joint line.[27] Although fixation at these sites maximizes isometry, ideal biomechanical behavior of the knee may not be restored. Results from biomechanical studies have demonstrated that ALL fixation posterior and proximal to the lateral femoral epicondyle restored normal knee kinematic properties but caused overconstraint of internal rotation beyond 30° of flexion.[28] In addition, ALL fixation superior to the lateral femoral epicondyle may be the most isometric fixation point, but biomechanical evidence supporting that fixation in this location restores normal knee kinematic properties without overconstraining the knee is lacking.

In this investigation, we measured the change in ALL length in 10° increments from 0° to 40° of knee flexion. We established that the optimal knee flexion angle to tension the ALL graft is from 20° to 40° of flexion because there was minimal length change at these angles of flexion. Neri et al[12] concluded that graft tensioning should occur between 0° and 30° of knee flexion during reconstruction. However, that investigation's limitation was measuring the length of the ALL only at 0°, 30°, 60°, and 90° of knee flexion. Our findings are an important modification to the findings of Neri et al[12] because they had insufficient length change data at lower flexion angles to draw a definitive conclusion regarding optimal tensioning angles.

The primary purpose of ALL reconstruction is not to reestablish isometry but to reproduce the biomechanics of the native ALL. Prioritizing isometric repair of the ALL may result in knee stiffness at larger angles of knee flexion. Some investigators have demonstrated that anatomical restoration of the ALL provides promising clinical results because the rate of graft rupture is low.[29,30] However, results from several studies demonstrate that fixation of the ALL into its native site is nonisometric and causes overconstraint of the knee.[6,18,31] In this investigation, we did not demonstrate that anatomical reconstruction is the most isometric. Rather, we illustrated that the most isometric fixation of the ALL is located on the lateral femoral epicondyle or anterior to the lateral femoral epicondyle with tibial fixation on the inferoposterior aspect of the tibial condyle. Fixation at these locations reconstitutes isometry, and fixation on the lateral femoral epicondyle or anterior to the lateral femoral epicondyle does not cause overconstraint of the knee.[32]

The positions on the femur and tibia that we identified as most isometric are in line with results from prior reports on the ALL. Claes et al[5,17] and Helito et al[5,17] indicated that the ALL was most isometric at a more anterior and distal location. However, our results differ from those of Wieser et al,[27] who determined the most isometric sites of ALL fixation to be superior to the lateral femoral epicondyle and a tibial fixation site more proximal to the joint line than we have described. Wieser et al[27] used a singular tibial point to assess isometry on the lateral aspect of the femur and then used that femoral point to identify isometry to 3 previously described anatomical tibial insertion sites.

Unlike previous investigations, which used a straight-line method to calculate the length of the anterolateral ligament, the present study utilized a wrap-around technique that takes into account the path that ligament traverses around the native bony anatomy of the femur and tibia. Additionally, we assessed femoral fixation sites of previously described ALL reconstruction techniques through 24 tibial fixation sites and 7 different angles of flexion to identify the most isometric ALL fixation combination. Thus, the results of the present investigation are more applicable towards ALL reconstruction versus previous investigations, which examined the isometric behavior of native ALL anatomy.

This investigation has some limitations. The first limitation was the sample size, given that only 6 knees fit the inclusion criteria, with a mean age of 47 years, which is higher than the average age of a patient undergoing ACL reconstruction.[33] Although we used osseous landmarks to place the grids systematically, there could be some variability in grid placement. In this study, we used advanced modeling methodology to test multiple different points and combinations of points that would not be possible with standard cadaveric or clinical studies. Investigators should evaluate the results both biomechanically and in the clinical setting to determine the true performance of ALL reconstruction with the findings of this study. Lastly, because we cycled the knees through the range of motion, we applied no additional rotational torque to the knees to maintain neutrality. Therefore, we could not evaluate a rotational component for ALL isometry in this investigation. However, there was some degree of inherent internal or external rotation throughout range of motion for all specimens.

CONCLUSION

With the use of 3D reconstructed models of knee CT scans, we observed that there was no ALL fixation point that was truly isometric throughout range of motion. Fixation of the ALL on the lateral femoral epicondyle or anterior to the lateral femoral epicondyle and on the inferoposterior aspect of the tibial condyle reconstituted the isometry of the ligament. In addition, we observed minimal length change between 20° and 40° of flexion, which is the most appropriate range of knee flexion to tension the graft. ❖

"Overall, a text-messaging bot has the potential benefits of creating an inherently simple and smooth patient experience, without overburdening the office staff…"

Engaging Patients in Technology-Driven Times

Introducing a Patient Engagement Text-Messaging Bot Into an Orthopedic Surgery Practice

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INTRODUCTION

The field of total joint arthroplasty has evolved drastically over the last couple of decades. Not too long ago, patients undergoing total joint arthroplasty had no other option than to prepare for an in-hospital stay. Today, outpatient surgery has become increasingly appealing as results from numerous studies have shown lower complication rates, better outcomes, lower costs, and equivalent outcomes with outpatient surgery compared with inpatient surgery.[1,2] Despite advances in operating room efficiency and in-hospital care, innovations in the perioperative surgical process for outpatient arthroplasty have not occurred at the same speed, despite health care providers attempting to provide care outside of the traditional hospital setting. Office visits are less frequent, and patients also have reported a lack of perioperative education, poor access to their physician, and frustration as their care is commoditized.[3-5]

To improve the doctor-patient relationship, streamline the coordination of patient care, and optimize delivery of health care, digital patient engagement platforms (PEPs) have undergone a recent surge in development. In this review, we will discuss the growing trend of patient engagement, present the benefits of an automated text-messaging bot, and describe our experience incorporating this type of platform into the clinical setting.

PATIENT ENGAGEMENT DEFINED

In its simplest sense, patient engagement refers to the degree to which a patient is participating actively in his or her care. An engaged patient is educated regarding his or her care, understands the specific treatment goals, and makes behavioral changes to reach specific care milestones. It is generally accepted that patients who are engaged in their recovery do better than patients who are confused regarding their recovery course.[3,4] Study results have shown that patient engagement modalities may play a substantial role in improving population health, lowering health care costs, and improving patient satisfaction and outcomes.[6-8] Improvements in patient engagement also have the potential to increase office efficiency, create more time and space for value-added services, and lower the cost of the care encounter. If done correctly, a focus on patient engagement could increase or restore the goodwill of a practice by creating a care environment that is convenient, supportive, and thoughtful.

HOW PHYSICIANS ENGAGE PATIENTS

Most physicians constantly are looking to engage their patients. It usually begins during office visits, as patients are counseled on their medical conditions and available treatment options. Given low rates of patient health literacy, clinicians have tried to improve their ability to communicate key treatment details with the implementation of procedure-specific instructions and frequently asked question sheets. In joint arthroplasty, preoperative teaching classes are designed to provide patients with an opportunity to learn more outside of the traditional clinic setting.

Some providers call their patients in the early postoperative period to triage any acute issues that may arise and provide some encouragement during the notoriously challenging early postoperative phase.

As patients have become comfortable using their computers and phones to manage important aspects of their life, health care entrepreneurs have designed electronic PEPs to supplement the efforts of the clinical team. Examples of PEPs include online portals where patients can check test results or schedule an appointment, secure messaging platforms that allow patients to ask their providers questions, and smartphone applications that remind patients about medication use or rehabilitation exercises to complete.

Despite many physicians offering some type of PEP, existing platforms have had low patient and provider adoption rates.[5,7] Most are Web-based platforms or mobile applications that require downloads or log-ins and are not straightforward for patients to use. These first-generation PEPs also do not allow for surgeon customization and typically require a team of clinicians to manage, often creating another clinician in-box that has to be monitored for messages from patients, thus defeating their scalability and effectiveness. In 2016, the Centers for Medicare & Medicaid Services launched the provider-facing Patient Engagement Playbook in an attempt to help cure the low clinical adoption of PEPs.[9]

WHAT A TEXT-MESSAGING BOT IS

A short message service (SMS) text-messaging bot is a software program that automates communication. In a clinical setting, this translates to the automated and timed delivery of relevant information directly to patients' cell phones. In contrast to a mobile application or a Web-based patient portal, SMS does not require downloads, log-ins, or a learning curve and is a natural way for patients to receive information. Messages are delivered to the same in-box where patients receive texts from friends and family members, making the consumption of this information inherently easy. SMS contrasts with

Figure 1. Example of the Senior Author's Instructional Therapy Videos.

mobile apps, Web portals, and physician websites that require patients to navigate the platforms to find which instructions are relevant to their recovery stage.

The value in SMS has been reported widely, including its effectiveness in a health care setting. Investigators in previous reports have linked SMS content with increased patient compliance and outcomes by means of medication adherence and decreased surgical infections with antiseptic showers.[4,6-7] Study investigators also have found that 99% of patients review a text message within 3 minutes.[10] By carefully selecting the most relevant recovery information, bots can deliver patients easily digestible texts that contain surgery-specific information at the right time. Moreover, the messages can be customized to the physician, which enhances the treatment preferences and care culture that the surgeon already has in place. This creates a completely new level of patient

support and encouragement, which translates into higher engagement and meaningful improvements in patient care.

In addition to text messages, bots can deliver other media, including recovery videos and personalized physician videos that help coach and encourage patients. Overall, a text-messaging bot has the potential benefits of creating an inherently simple and smooth patient experience, without overburdening the office staff, and can be broadly successful among a group of patients, despite their socioeconomic status or payer mix.

THE CLINICAL PERFORMANCE OF A TEXT-MESSAGING BOT

Intrigued by the capabilities of a bot, we introduced a text-messaging bot into a busy arthroplasty practice (Figure 1). Each participating physician had a bot that was preprogrammed to deliver text messages
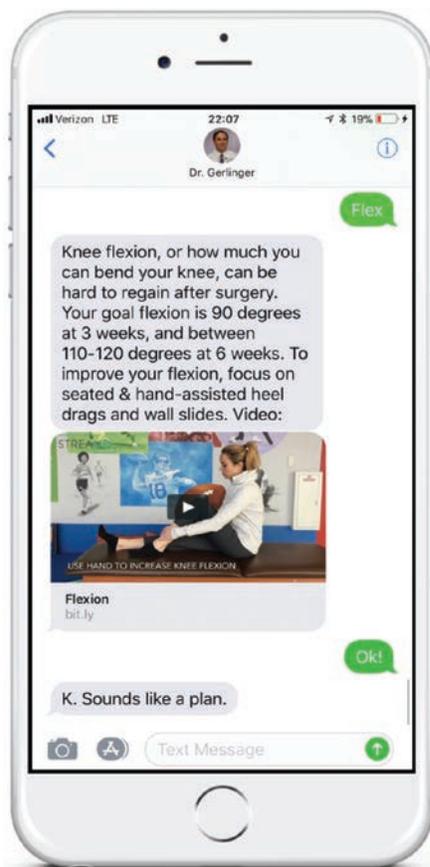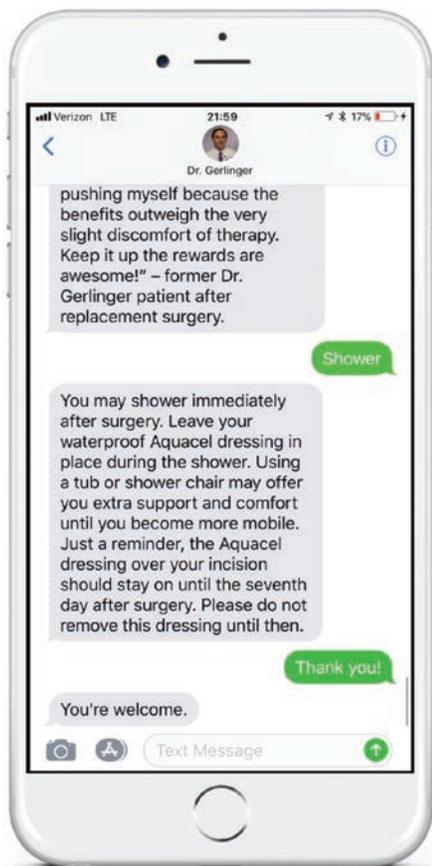
Figure 2. Example of the Senior Author's Short Message Service (SMS) Recovery Messages.

and videos to patients before and after surgery (Figure 2). Over an 18-month period, 1,400 patients enrolled into their physician-specific text-messaging bot. At the completion of the messages, patients were asked to complete a survey about their experience. Of those 1,400 patients, 99% said the messages had had a positive effect on their recovery, 98% said they would recommend the service to a friend undergoing a similar procedure, 96% said they did not have to call the office because their questions were answered through the text messages, and 89% said they felt a more personal connection to their physician because of the messages. Because of the automated and outbound nature of the bot, no inbound messages from patients were monitored by the surgeon or his team. The attending surgeons and ancillary staff members have described fewer office phone calls, increased number of positive reviews on their Internet physician review sites, and patients thanking them for continually updating them through the perioperative period. We currently are conducting a randomized clinical trial to quantify better the effect a bot can have on patients undergoing hip and knee replacements.

CONCLUSION

In an era of high-volume surgery and value-based reimbursement, clinicians are paying more attention to new products and services that improve patient engagement and the effectiveness of the perioperative surgical home. The orthopedic landscape is ripe for a simple and effective PEP. The currently available mobile applications and Web-based portal solutions have had low adoption rates among patients and providers and have left room for continued development and innovation.[4,6-7] A bot may be a good alternative because it is inherently easy to use by a broad spectrum of patients and providers and may lend itself to increased patient satisfaction and decreased office workload. ✣

References and financial disclosures are available online at www.rush.edu/orthopedicsjournal.

At the Top of Her Game

When it comes to firsts in the world of sports medicine,
Kathy Weber, MD, MS, team physician for both the Chicago Bulls
and Chicago White Sox, knocks it out of the ballpark.

You don't need to be a superfan to know that men have historically dominated professional sports both on the field and off. But just as more women begin to share sports commentary on ESPN and sign autographs for adoring fans, an increasing number of women provide vital health care to professional athletes—both male and female—as trainers and physicians.

While she'd rather talk about medicine than gender, Kathy Weber, MD, MS, director of primary care/sports medicine and women's sports medicine at Rush, helped lead the way in bringing about this change.

LEAGUE LEADER

Back in 2004, Weber became the first female team physician for Major League Baseball (MLB) when she and her colleagues in the Department of Orthopedic Surgery at Rush signed on to be team doctors for the Chicago White Sox. She was also one of the first 2 female team physicians for the National Basketball Association (NBA), caring for Chicago Bulls players along with other physicians from Rush. Weber continues in those roles today, plus she is head team physician for the DePaul Blue Demons and Malcolm X

College, and a physician consultant for the Hubbard Street dance company—all in Chicago. She also serves as a member of the Ladies Professional Golf Association (LPGA) Medical Advisory Board and the NBA research committee.

"I never really looked at the gender component of what I do. Rather, I looked at myself as part of the team," Weber says. "And my job was—and still is—to do the best I can do every day."

The Major League Baseball Team Physicians Association (MLBTPA)

recognized that dedication and her medical expertise in 2014 when they elected Weber president, a 3-year stint in which she served as President-elect, President, and then past-President. This leadership role marked yet another first for women in professional sports.

As head of the MLBTPA, Weber worked with fellow team physicians to bring players high quality medical care to ensure their safety, health, and well-being. A key component of that mission: to share important medical research and develop injury prevention recommendations and policies.

SHARING THE SPOTLIGHT

Given her background in academic sports medicine at Rush, Weber relished the opportunity to organize the MLBPTA's annual meeting, where she could help disseminate the latest evidence-based research to her peers in sports medicine, such as recent findings on the use of biologics and injury care. She

> "That desire to stay at the top of my game in terms of the latest treatment options and learning from others—whether they're in the lab or from another discipline—is part of my DNA."

also welcomed the chance to invite both orthopedic colleagues and other specialists—including plastic surgeons—to the meeting to get their perspectives on caring for sports-related injuries.

"As a physician at Rush, that desire to stay at the top of my game in terms of the latest treatment options and learning from others—whether they're in the lab or from another discipline—is part of my DNA," Weber says. "To have shared all of that knowledge and expertise at this meeting, so physicians can deliver the highest quality of care to their athletes, was extremely rewarding."

ADVANCING CARE ON AND OFF THE FIELD

Helping athletes achieve optimal health so they can play at the highest levels of sports and lead healthy lives once their careers end inspires much of Weber's practice and research.

In fact, she played a role in drawing attention to the threat of concussions in professional baseball. "I was fortunate to be a part of a pioneering study on the rate of concussions in Major League Baseball, and we were able to identify which positions were higher risk," she says. These findings led to rule changes designed to protect catchers from collisions at home plate.

And it was due to her and her colleagues' work on concussion injuries that the MLB changed their disabled list protocols in 2011: They created a new 7-day disabled list, allowing team doctors and injured players more flexibility in addressing injuries to the head.

Weber brings that same energy and drive to all of her patients, whatever their age or skill level. "I just want to help people have the best possible quality of life," she says.

LEARNING THE ROPES

Weber attributes her successes to the strong work ethic instilled in her by her family, and a team-oriented approach borne from her experiences as an athlete in high school and college. Her interests in helping others and in medicine, however, weren't initially directed toward athletes. Early on, she wanted to be a veterinarian, and later—based on the advice of her mother— she pursued a nursing degree. That experience and its emphasis on bedside manner and patient care gave Weber the

Among her other achievements, Weber has led the way when it comes to treating female athletes, including looking at anatomical factors that increase the risk of certain injuries in girls and women.

tools to become a good doctor. But a career in nursing wasn't what she ultimately wanted, so she opted for a master's degree in exercise physiology.

Eventually, Weber found her way to Rush Medical College and earned her medical degree, then stayed at Rush for her residency in internal medicine. To combine her talents in medicine with her love of sports, she moved to California for a fellowship in sports medicine at the University of California - San Diego Medical Center.

PROVIDING A SOLID TRAINING GROUND

She returned to Rush to join the orthopedics program in 2001. Since then, in addition to becoming part of the Bulls and White Sox's medical teams, she and a colleague launched Rush's primary care sports medicine fellowship program.

"Our fellows have a great clinical experience because Rush is a tertiary care center. We see all the common issues—like tendonitis—but also highly complicated problems," Weber says. "Our fellows are also exposed to a wide range of sports—and the health concerns that often accompany them. They leave our program feeling confident that they can cover any sport they desire."

The program is unique, according to Weber. "We have sports medicine-trained physicians from multiple specialties, allowing us to welcome physicians from all the primary care fields," she says.

HELPING GIRLS IN THE GAME OF LIFE

While busier than ever clinically, Weber still finds time for the nonprofit organization Girls in the Game, which is dedicated to empowering girls through sports, health education, and leadership development programs.

Having volunteered for the program in a variety of ways for more than a decade, Weber currently is an emeritus board member and takes the time to meet

Weber is the founder and director of the Primary Care Sports Medicine fellowship at Rush. She and her colleagues provide sports medicine trainees with a diverse clinical experience, treating a wide range of sports and athletes at all levels.

with girls to help mentor them through various activities, including mock job interviews. "The program's approach is really holistic; it's about the entire girl. That said, sports—its health benefits and the life lessons that can be learned from it—is always the centerpiece."

INSIDE THE LOCKER ROOM: NO SWEAT

While women's roles in sports and sports medicine continue to evolve, Weber sees only the positives with respect to her gender and her ability to care for male athletes.

"I receive lots of favorable feedback from the male players I care for. In fact, I sometimes think they're even more up front with me about pain because I am a woman. Maybe they feel a little less pressure to be tough or macho," she says. "Or maybe," she laughs, "I just remind them of their mom."

HOME TEAM ADVANTAGE

As she looks at her career, Weber feels extremely fortunate.

"I landed the dream job: I have the greatest people around me, including some of the best minds in orthopedics

and sports medicine," she says. "They drive and inspire me, because they are highly motivated and doing amazing things in the lab, in the clinic, in partnership with innovative medical companies, and across all disciplines. The professionals at Rush are like a train that just keeps moving forward, and if you work here, you have to get running and jump on because they never stop in their efforts to improve patient care—whether it's for a professional athlete, a weekend warrior, or the woman who lives down the street. And I just love that." ✣

"…we found that the maximum perceivable subjective improvement occurs at 1 year, with most of the improvement occurring by 3 months."

Establishing Maximum Medical Improvement After Anatomic Total Shoulder Arthroplasty

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INTRODUCTION

Anatomic total shoulder arthroplasty (TSA) continues to surge in the United States, with nearly 35 000 procedures performed in 2013[1] and an annual increase as high as 12.1%.[2] Recent projections have indicated that the demand for this procedure will increase 755.4% by 2030.[2] As health care's share of the total US economic budget continues to grow,[3] a heightened emphasis is being placed on resource optimization and value-based health care. This trend involves a departure from previous volume-based models toward a focus in health outcomes achieved as a result of the provided care per dollar spent.[4]

The issue that arises with outcome-based medicine is how properly to define and measure quality outcomes after procedures and when to follow up with patients to capture maximum medical improvement (MMI) while avoiding unnecessary visits.

The outcome metrics patients most value in orthopedic surgery are improvements in quality of life, as measured by decreased pain and increased function.[5,6] Clinicians assess these metrics by means of validated patient-reported outcome measures (PROMs), which produce summative scores of patients' limitations, symptoms, and satisfaction.[6] In the assessment of recovery from orthopedic surgery, especially across large patient cohorts, statistically significant changes in these PROMs may not result in a detectable change in pain or function for the patient.[5] The minimal clinically important difference (MCID) of PROMs, or "the smallest difference in score … which patients perceive as beneficial,"[7] is a more valid assessment of meaningful clinical outcome than is statistical significance. Using the MCIDs for PROMs ensures that measurements of quality outcomes remain patient centered.[8]

TSA provides excellent pain relief and restoration of function in the short to medium term[9,10] and has excellent long-term implant survivorship.[11] Current follow-up schedules after arthroplasty typically include patient visits empirically scheduled at several time points over a 2-year period.[12,13] These short-term clinic visits are typically to assess patient recovery, whereas visits after 2 years are typically less frequent and exist to monitor for signs of late complications.[14] Once MMI is reached, clinic visits potentially could be deferred until later time points when relevant changes, such as glenoid loosening, are more likely to occur.[11] Reducing the amount of inconsequential follow-up visits would improve health care efficiency and value while minimizing patient and provider burden. In addition, a time frame for outcome report should be established as value-based reimbursement schemes are evolving.

The purpose of this systematic review was to establish when maximal improvement occurs after TSA. We hypothesized that patients continue to perceive improvements until 1 year after their operation but would detect no additional improvements between 1 and 2 years.
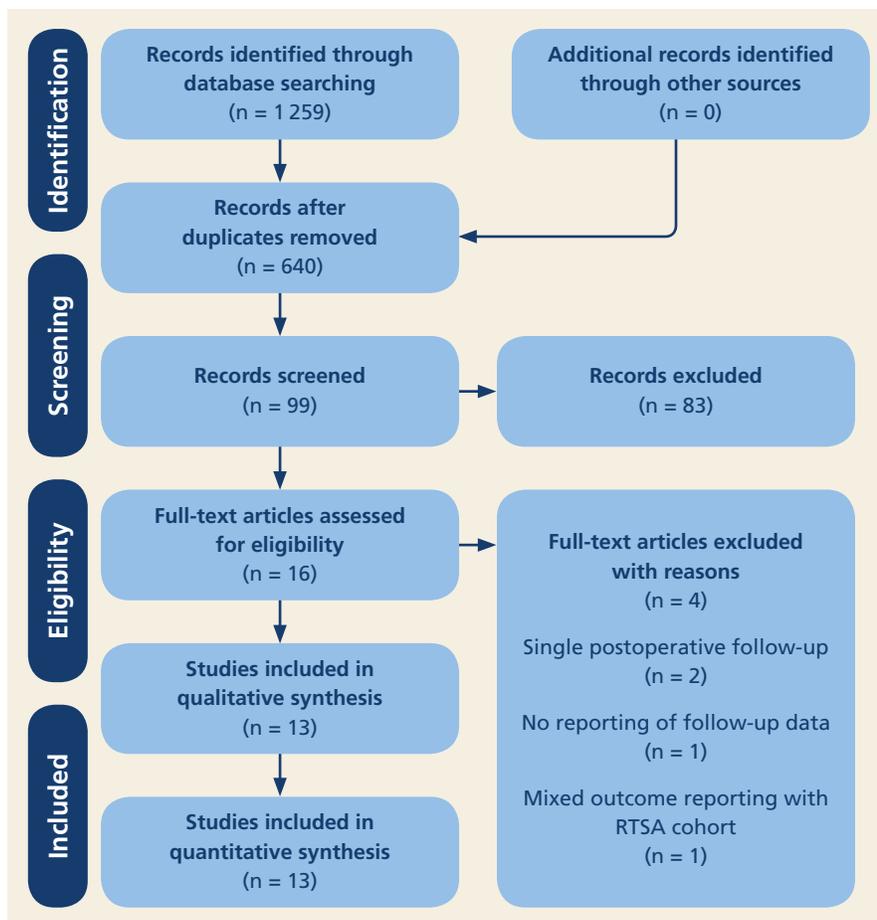
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram of the Inclusion Process for the Systematic Review. RTSA indicates reverse total shoulder arthroplasty.

MATERIALS AND METHODS

Systematic Review and Data Extraction

Two reviewers (A.A., R.P.) independently searched the MEDLINE database on October 17, 2017. We used the following search terms: *TSA* or *total shoulder replacement* in combination with *recovery*, *outcome*, or *clinical results*. We included studies if the investigators reported clinical outcomes of anatomic TSA, using either a stemmed or stemless humeral implant, for the indication of glenohumeral osteoarthritis (OA), with outcomes reported for at least 2 separate postoperative time points and a minimum of 2 years of follow-up. We excluded articles if the study investigators did not perform a TSA, if they did not list outcomes in numerical form, if they did not

report the outcomes at 2 years, or if they reported outcomes at only 1 postoperative time (Figure 1). We evaluated full-text articles if we were considering inclusion of the study or if there was uncertainty about a study. If a study's methods seemed to meet inclusion criteria, but insufficient data were reported, we contacted the corresponding authors for the data. We allowed 4 weeks for the corresponding author to respond; otherwise, we excluded the study. We also independently reviewed the citations of each included study for articles that we may have missed in the initial search. If disagreement existed regarding inclusion of a study, the reviewers discussed for final determination.

We extracted the following PROMs from the articles fitting inclusion criteria: Western Ontario Osteoarthritis of the

Shoulder (WOOS), American Shoulder and Elbow Surgeons (ASES), 12-Item Short-Form Health Survey (SF-12) physical and mental health summary scales, Simple Shoulder Test (SST), Single Assessment Numeric Evaluation (SANE), Penn Shoulder Score (PSS), visual analog scale (VAS) for pain and function, Absolute Constant-Murley Score (ACMS), Relative Constant-Murley Score (RCMS), Quick Disabilities of the Arm, Shoulder and Hand (QDASH), and Shoulder Pain and Disability Index (SPADI). We also extracted clinical examination data for active range of motion (ROM) and strength when reported.

We also searched the MEDLINE database for articles elucidating the MCID after TSA for OA for each PROM. We used the following search terms: MCID or minimally clinically important difference, in combination with total shoulder replacement or total shoulder arthroplasty.

Data Analysis

We pooled and analyzed data separately for each outcome score by using the techniques described by Zuke et al.[15] We pooled the weighted means for each study in which the investigators reported outcomes at a given time point, and then we calculated the pooled SD. If a single study's investigators reported a particular PROM at a given time point but did not report a mean score with an SD, then we did not analyze that PROM at that time point. We compared the pooled weighted means at the following intervals: preoperative to 3 months (or 6 months if data at 3 months were not available), 3 to 6 months, 3 months to 1 year, 6 months to 1 year, 6 months to 2 years, and 1 to 2 years. We analyzed nonconsecutive time points to help elucidate further the point of MMI. We established a clinically significant improvement between time points if an improvement in an outcome score significantly exceeded the previously established MCID for the specific outcome measure (*P* < .05).

Jaeschke et al first described MCID "as the smallest difference in a score in a domain of interest that patients perceive

Table 1. Pooled Characteristics and Demographic Characteristics

Characteristic	No. (%) of Patients[a]
Sex	
Male	384 (44.0)
Female	492 (56.0)
Stemless humeral implant	
Total Evolutive Shoulder System[b]	58 (6.4)
Simpliciti[c]	157 (17.5)
Eclipse[d]	20 (2.2)
PROMOS RES[e]	37 (4.1)
Stemmed humeral implant	
Global Advantage[f]	79 (8.8)
Encore[g]	166 (18.5)
Neer II[h]	36 (4.0)
Aequalis[c]	45 (5.0)
Univers II[d]	20 (2.2)
PROMOS[e]	37 (4.1)
Bigliani/Flatow[b]	240 (26.8)
Bio-Modular[b]	15 (1.7)

[a] Mean (SD) patient age was 67.7 (9.1) years. Mean follow-up was 3.89 years (range, 2-15 years).
[b] Zimmer Biomet, Warsaw, IN
[c] Tornier, Bloomington, MN
[d] Arthrex, Naples, FL
[e] Smith & Nephew, London, UK
[f] DePuy Synthes, Warsaw, IN
[g] DJO Global, Vista, CA
[h] Stryker, Kalamazoo, MI

as beneficial."[16] To remain consistent with this definition of MCID, if multiple MCIDs were previously reported for an individual PROM, we used the smallest MCID for analysis. We used this method rather than finding an average among the scores because patients noted a discernable change in pain or function at the lowest MCID, which justifies a minimally clinical important improvement in outcome score. In addition, use of this method errs on the side of more frequent visits because of increased sensitivity of detecting change. We used the following MCIDs for analysis: ASES, 6.3[17]; SST, 2.4[18]; ACMS, 5.7[18]; PSS, 11.4[19]; VAS for pain, 1.4[20]; SPADI, 20.6[18]; SF-12 mental, 5.7[21]; and SF-12 physical, 5.4.[21] We could not calculate clinical significance for PROMs that did not have previously reported MCIDs.

The ASES, SST, and VAS pain scores were the only PROMs with multiple MCIDs reported in the literature. The additional MCIDs of these PROMs reported but not used are VAS for pain, 2.7[18]; ASES, 24.5,[18, 20] 17[18]; and SST, 2.1.[18, 20] Werner et al[17] established MCIDs for ASES by using the anchor-based approach, but they used several satisfaction-based anchor questions to establish multiple MCIDs in different domains of function. Regarding patient satisfaction in the ability to do yard work or housework, the MCID was 6.3; regarding satisfaction of improving ability to do recreational activities, the MCID was 9.1; regarding overall satisfaction, the MCID was 13.5. Wong et al[21] established MCIDs for ASES pain and ASES function subscales separately by using a distribution-based method; they were 5.4 and 8,

respectively. We did not use these MCIDs because the investigators in the studies included in this systematic review did not report ASES subscores separately. The investigators in the remaining studies used a single anchor-based question pertaining to general satisfaction to determine one MCID per PROM.[18, 20]

We used the *t* test to calculate levels of significance. We determined the point of MMI to be the latest time point at which a clinically significant increase occurred from a previous time point and from which further clinically significant improvement did not occur. This method has been described previously to establish MMI after rotator cuff repair.[15]

For objective clinical outcomes, inconsistent techniques used to measure ROM and strength between studies prevented pooled analysis. However, because methods of measurement were consistent within a study, the interval differences in ROM and strength between time points could be pooled and used for statistical calculation of a weighted average and SD. We used the following MCIDs for analysis of ROM: active abduction, 7°[18]; active forward flexion, 12°[18]; and active external rotation, 3°.[18] We determined MMI for ROM to have occurred at the last time point at which the interval change from the previous time point exceeded the MCID and from which further clinically significant interval change did not occur. MCIDs for strength have not been published, so we could not calculate clinical significance.

RESULTS

Study Characteristics

In this review, we identified 13 studies for final inclusion (Table 1).[11, 22-33] Investigators in the combined studies reported a total of 984 TSAs. The average time to final follow-up was 3.89 years (range, 2-15 years). The average number of follow-up time points was 3.8. Seven of the included studies had physical examination outcomes reported at each follow-up time point. Eight of the included studies were prospective, and the remaining 2 were retrospective (Table 2).

Table 2. Studies Meeting Inclusion Criteria for Analysis

First Author	Year	Journal	Study Design	Level of Evidence
Cheah[22]	2017	JSES	Randomized controlled trial	II
Churchill[23]	2016	JBJS	Case series	IV
Clinton[24]	2007	JSES	Prospective cohort study	II
Gascoyne[25]	2017	Canadian Journal of Surgery	Randomized controlled trial	I
Glanzmann[26]	2017	International Orthopaedics	Retrospective cohort study	III
Levy[27]	2014	JSES	Retrospective cohort study	III
Litchfield[28]	2011	JSES	Randomized controlled trial	I
Raiss[11]	2014	JBJS	Case series	IV
Razmjou[29]	2013	JSES	Prospective cohort study	II
Razmjou[30]	2014	BMC Musculoskeletal Disorders	Prospective cohort study	II
Sandow[31]	2013	JSES	Randomized controlled trial	II
Scalise[32]	2010	JBJS	Retrospective cohort study	III
Uschok[33]	2017	JSES	Randomized controlled trial	II

Abbreviations: JBJS, Journal of Bone and Joint Surgery; JSES, Journal of Shoulder and Elbow Surgery.

Table 3. Absolute Values for Patient-Reported Outcomes

Instrument	Mean Absolute Value (SD)				
	Preoperative	3 Months	6 Months	1 Year	2 Years
ASES	33.5 (15.9)	71.8 (17.1)	76.2 (14.7)	79.8 (13.9)	79.7 (13.6)
SST	3.7 (2.7)	7.7 (2.6)	10.0 (2.2)	10.2 (1.9)	10.2 (1.7)
ACMS	33.8 (12.0)	66 (12.3)	70.3 (9.2)	77.2 (10.9)	78.2 (13.3)
PPS	29.0 (15.6)	NA	NA	83.0 (10.0)	80.0 (6.0)
VAS for pain	6.5 (2.5)	1.9 (1.8)	1.1 (1.6)	0.9 (1.3)	1.0 (1.2)
SPADI	37.1 (17.8)	NA	78.1 (18.8)	81.5 (18.1)	81.2 (19)
QDASH	54.7 (16.6)	NA	27.1 (17.3)	23.3 (17.9)	21.8 (18.7)
WOOS	27.2 (16.2)	73.2 (21.6)	79.6 (18.4)	84.1 (18.4)	84.1 (19.8)
RCMS	42.3 (15.7)	84.1 (17.1)	82.5 (14.0)	91.3 (12.8)	94.2 (14.1)
SF-12 mental	49.6 (11.4)	NA	54.3 (10.6)	54.0 (9.8)	54.0 (9.5)
SF-12 physical	31.8 (6.4)	40.4 (10.1)	42.1 (11)	41.4 (11.5)	41.2 (11.7)
External rotation	18.6 (6.8)	40.9 (3.7)	43.9 (3.4)	46.9 (3.2)	48.1 (0.7)
Forward flexion	86.4 (12.3)	111.7 (4.6)	123.2 (1.0)	132.3 (4.4)	134.4 (4.6)
Abduction	60.8 (10.4)	NA	102.4 (18.4)	111.4 (7.0)	113.2 (4.6)

Abbreviations: ACMS, Absolute Constant-Murley Score; ASES, American Shoulder and Elbow Surgeons; NA, not available; PSS, Penn Shoulder Score; QDASH, Quick Disabilities of the Arm, Shoulder and Hand; RCMS, Relative Constant-Murley Score; SF-12, 12-Item Short-Form Health Survey; SPADI, Shoulder Pain and Disability Index; SST, Simple Shoulder Test; VAS, visual analog scale; WOOS, Western Ontario Osteoarthritis of the Shoulder.

Patient-Reported Outcomes

The absolute pooled means and SD for each PROM and objective clinical measurement at each time point are in Table 3. Table 4 contains the changes in mean scores between postoperative time points for PROMs that were reported previously, and MCIDs, as well as the P values used for determination of clinical significance. We saw a clinically significant improvement from the preoperative time point to 3 months postoperatively for each of these outcome scores. There were further clinically significant improvements from 3 to 6 months for only the SST and from 3 months to 1 year for the ASES, SST, and ACMS scores. We saw no clinically significant improvements for any PROM from 1 to 2 years of follow-up. For these reasons, we deemed MMI to have occurred 1 year after surgery. There was a clinically significant improvement between nonconsecutive time points of 6 months and 2 years for the ACMS; however, the clinically significant improvement occurred between 6 months and 1 year, and not 1 to 2 years.

Of the PROMs that had multiple published MCIDs, only the ASES score reached a plateau in clinically significant improvement at a different time point if we used an MCID other than the lowest. No clinically significant improvement occurred beyond 3 months for the ASES score if we used the higher reported MCIDs as the threshold for significant clinical improvement. However, this finding does not affect the establishment of MMI at 1 year.

We could not test for clinically significant improvements between time points for the PROMs for which MCIDs were not reported. The absolute pooled means and SDs for these PROMs are in Table 3. Figure 2 displays the trends in improvements of the PROMs for which there were sufficient data for measurements at each time point. The values plotted in this figure are normalized to the maximum score possible for each PROM.

Three of the included studies had additional follow-up time points extending beyond 2 years.[11,31,33] Sandow et al[31] followed up with patients 10 years postoperatively but

Table 4. Changes in Pooled Score Means for Patient-Reported Outcomes

Instrument[a]	Preoperative to 3 Months	3 to 6 Months	3 Months to 1 Year	6 Months to 1 Year	6 Months to 2 Years	1 to 2 Years
ASES (MCID = 6.3[b]; n = 741)						
Significant clinical improvement?	Y	N	Y	N	N	N
Difference between means	37.5	4.5	8.9	4.4	4.3	−0.2
P value	<.001	>.999	<.001	>.999	>.999	>.999
SST (MCID = 1.8[b]; n = 373)						
Significant clinical improvement?	Y	Y	Y	N	N	N
Difference between means	3.9	2.3	2.4	0.1	0.1	−0.0
P value	<.001	<.001	<0.001	>.999	>.999	>.999
ACMS (MCID = 5.7; n = 441)						
Significant clinical improvement?	Y	N	Y	Y	Y	N
Difference between means	32.2	4.3	11.2	6.9	7.8	1.0
P value	<.001	>.999	<.001	.022	<.001	>.999
PSS (MCID = 11.4; n = 35)						
Significant clinical improvement?	Y[c]	NA	NA	NA	NA	N
Difference between means	54.0	NA	NA	NA	NA	−3.0
P value	<.001	NA	NA	NA	NA	>.999
VAS for pain (MCID = 1.4[b]; n = 340)						
Significant clinical improvement?	Y	N	N	N	N	N
Difference between means	4.6	0.8	1.0	0.3	0.2	0.1
P value	<.001	>.999	>.999	>.999	>.999	>.999
SPADI (MCID = 20.6; n = 74)						
Significant clinical improvement?	Y[d]	NA	NA	N	N	N
Difference between means	41.0	NA	NA	3.5	3.1	−0.4
P value	<.001	NA	NA	.999	.999	.999
SF-12 mental (MCID = 5.7; n = 316)						
Significant clinical improvement?	N	NA	NA	N	N	N
Difference between means	4.8[c]	NA	NA	−3.0	−0.3	0.1
P value	.827	NA	NA	>.999	>.999	>.999
SF-12 physical (MCID = 5.4; n = 150)						
Significant clinical improvement?	Y	N	N	N	N	N
Difference between means	8.6	1.7	1.1	−0.6	−0.9	−0.3
P value	.004	>.999	>.999	>.999	>.999	>.999

Abbreviations: ACMS, Absolute Constant-Murley Score; ASES, American Shoulder and Elbow Surgeons; MCID, minimal clinically important difference; NA, not available; PSS, Penn Shoulder Score; SF-12, 12-Item Short-Form Health Survey; SPADI, Shoulder Pain and Disability Index; SST, Simple Shoulder Test; VAS, visual analog scale.

[a] We calculated the sample sizes at the preoperative time point for each study because the investigators in the included studies did not report follow-up at every time point being analyzed.

[b] The lowest previously reported MCID for each outcome score was used for the highest sensitivity of detecting a change.

[c] Investigators in only 1 study recorded these scores, and they reported outcomes at 1 and 2 years postoperatively. Accordingly, this is the difference in scores from the preoperative score to the score 1 year postoperatively.

[d] Investigators in only 1 study recorded SPADI scores, and they reported outcomes at 6 months and 1 and 2 years postoperatively. Accordingly, this is the difference in scores from the preoperative score to the score 6 months postoperatively.
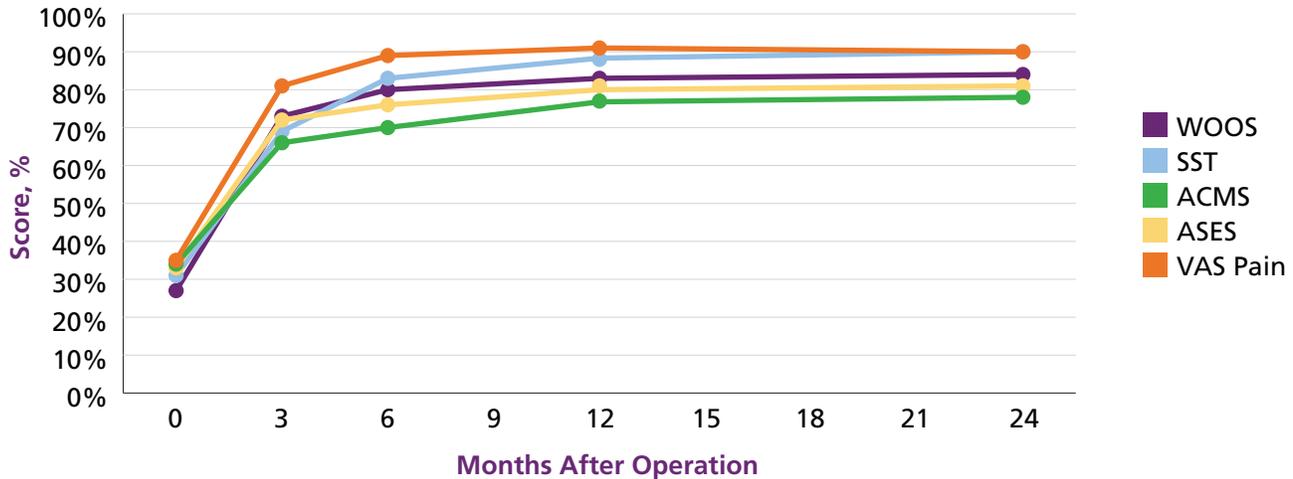
Figure 2. Graph Showing Normalized Patient-Reported Outcome Measure Scores Up to 2 Years of Follow-Up. ACMS indicates Absolute Constant-Murley Score; ASES, American Shoulder and Elbow Surgeons; SST, Simple Shoulder Test; VAS Pain, visual analog scale for pain; WOOS, Western Ontario Osteoarthritis of the Shoulder.

lacked statistical power to compare results appropriately; therefore, they did not report outcome values at this time point. Investigators in 2 studies reported ACMSs at 5 years of follow-up in 68 patients, which resulted in a pooled mean (SD) score of 70.5 (13.2),[11,33] a decrease from the mean score at 2 years. Raiss et al[11] reported several follow-up time points up to 15 years, but they found the clinical measurements of ROM and ACMS to reach a plateau at 1 year without any further statistical improvement beyond this point.

ROM and Strength

The weighted average interval improvements, MCIDs, and statement of clinical significance for each ROM are in Table 5. We saw a clinically significant improvement from the preoperative time point to 3 months postoperatively for each of these outcome scores. There were further clinically significant improvements through 1 year only for abduction. We saw no clinically significant improvements for any ROM from 1 to 2 years. In addition, Churchill et al[23] found statistically significant improvements in internal rotation at 90° of abduction from the preoperative time point to 3 months of follow-up (P = .04) but not during any subsequent interval. Figure 3

displays the trends in improvements for the ROM measures for which we could calculate pooled interval changes. To show proper relative increases between ROM measures, we normalized the values in this figure to maximum values of 180° for forward flexion and abduction and 90° for external rotation.

Failures and Complications

Investigators in 7 studies reported postoperative complications and revisions,[11,22,23,28,29,31,33] amounting to a total of 32 revisions (6.1%), but investigators in only 3 of the studies reported the time from surgery to revision procedures[11,23,26] (Table 6). Investigators in 1 study reported the mean time to revision surgery (n = 13) to be 8.8 years, with an implant survival rate of 98% 5 years postoperatively.[11]

DISCUSSION

This systematic review of the available literature provides a time frame for which MMI occurs for patients receiving a TSA for OA. Using previously established MCIDs for the reported outcome scores, we found that the maximum perceivable subjective improvement occurs at 1 year, with most of the improvement occurring by 3 months. We noted no further clinically

significant improvement from 1 to 2 years postoperatively. Objective measures of ROM followed a similar trend, with clinically significant interval improvements occurring within the first 3 months, and through 1 year for abduction only.

The inconsistency of clinically significant improvement at 1 year of follow-up among the outcome scores with reported MCIDs may be attributed to the differences in the construct and specificity of each score. The short forms are generalized health-related quality-of-life measures, which have been shown to have more modest improvements than do shoulder-specific PROMs for patients undergoing TSA.[9] Wong et al[21] demonstrated that only 25% of patients undergoing TSA had improvement greater than the SF-12 mental component score MCID, so they theorized that the effect of TSA on mental and emotional health improvements is questionable. Our results corroborate these findings because the SF-12 mental component score lacked the sensitivity to detect meaningful change at any time point when applied to the TSA population.

In addition, we did not observe a clinically appreciable change in VAS pain scores after 3 months of follow-up. Recurrent pain is expected to be present only in the

Table 5. Pooled Changes in Range of Motion and Strength Measurements

Measurement	Preoperative to 3 Months	3 to 6 Months	6 Months to 1 Year	1 to 2 Years
External rotation (MCID = 3°)				
Significant clinical improvement	Yes	No	No	No
Pooled mean (SD) difference	22.3 (3.7)	2.97 (3.4)	2.98 (3.2)	1.2 (0.7)
Sample size	n = 472	n = 473	n = 519	n = 519
95% CI	22.0-22.7	2.7-3.3	2.7-3.3	1.2-1.3
Forward flexion (MCID = 12°)				
Significant clinical improvement	Yes	No	No	No
Pooled mean (SD) difference	25.3 (4.6)	11.5 (1.0)	9.1 (4.4)	2.1 (4.6)
Sample size	(n = 318)	(n = 318)	(n = 531)	(n = 531)
95% CI	24.8-25.8	11.4-11.6	8.7-9.5	1.7-2.4
Abduction (MCID = 7°)				
Significant clinical improvement	Yes	NA	Yes	No
Pooled mean (SD) difference	41.6 (18.4)[a]	NA	9.0 (7.0)	1.8 (4.6)
Sample size	n = 348		n = 348	n = 348
95% CI	39.7-43.5	NA	8.3-9.7	1.35-2.3

Abbreviations: MCID, minimal clinically important difference; NA, not available.
[a]No study reported 3-month abduction ROM results. Change in abduction from preoperative to 6 months is reported here.

perioperative period, with rapid pain relief shortly thereafter, because TSA quickly ameliorates the effects of OA and surgical pain dissipates quickly in the postoperative time frame. Although we could not calculate clinical significance for some PROMs, the ASES score and ACMS have the largest effect sizes and are the most responsive to changes in function after TSA.[34] Thus, the results of our study suggest that MMI occurs at 1 year because the 2 most sensitive PROMs for TSA demonstrated clinically significant improvements up to, but not beyond, this time point. Although a clinically significant improvement occurred from 6 months to 2 years for the ACMS, nearly 90% of this improvement occurred from 6 months to 1 year, and there was not a clinically significant improvement from 1 to 2 years.

In today's health care and economic climates, there is an increasing demand to demonstrate the effect or value of

therapeutic interventions. For these systems to remain patient centered, there must be congruence between professional standards and patient preferences.[35] Quality improvement in the current health care structure starts with valid public reporting of performance and outcome measures that are of clinical relevance.[36] By systematically reviewing the literature and evaluating for changes in patients' subjective outcomes that are perceivable by the patient, we have created a patient-centered model for the value of TSA. To assess the quality and value of a patient care properly, we need to gather these outcomes over a period that encompasses the ultimate result of the care provided.[37] By assessing the time to reach MMI for a large heterogeneous population not adjusted for comorbidity risks, we have established a reference time frame for a proper and maximized assessment of value for this procedure.

Cost-effectiveness is a priority for health care stakeholders to optimize value and

justly distribute limited physician time and resources. Implementing change in follow-up schedules may be the most direct method of lowering the costs of care and maximizing resources. However, efficient practices should not be at the expense of appropriate postoperative care, monitoring for complications, and rehabilitation guidance. Schoch et al[12] have suggested optimizing follow-up after TSA by using planned and periodic mail contact in lieu of in-person surveillance after 2 years of follow-up. This model is based on the reoperation and revision data for 208 shoulders, 30% of which occurred within the first 2 years, and the conditional probability of failure staying below 1% between 1 and 5 years postoperatively.[12] Werner et al[14] similarly found that 49% of revision arthroplasties occur within 1 year after surgery.

The modes of failure are also substantially different for early (<1 year) versus late (>1 year) revision. The most common causative factors are dislocation for early revision and implant loosening for late revisions.[11,14,38] Simple pooling among the studies included in this review in which the investigators reported revisions indicated the revision rate to be 6.1%, and investigators in 1 study reported an average time to revision surgery of 8.8 years.[11] Schoch et al[12] reported TSA to fail at an average rate of 1.1%, supporting their conclusion that routine in-person follow-up visits after this time are unnecessary health care costs. With such infrequent incidence of reoperation after the first year, and the evidence we have reported of MMI occurring at 1 year, regular in-person follow-up after this time may not be necessary unless there is a dramatic change in symptoms that the patient readily perceives. However, reoperation rates alone may not reflect adequately how patients are doing in the long term. Thus, intermittent follow-up still may be necessary to monitor for glenoid loosening, although the relationship between radiolucent lines and glenoid loosening is not well understood.[39] For this reason, radiographic evaluation in the long term is of undetermined clinical significance.
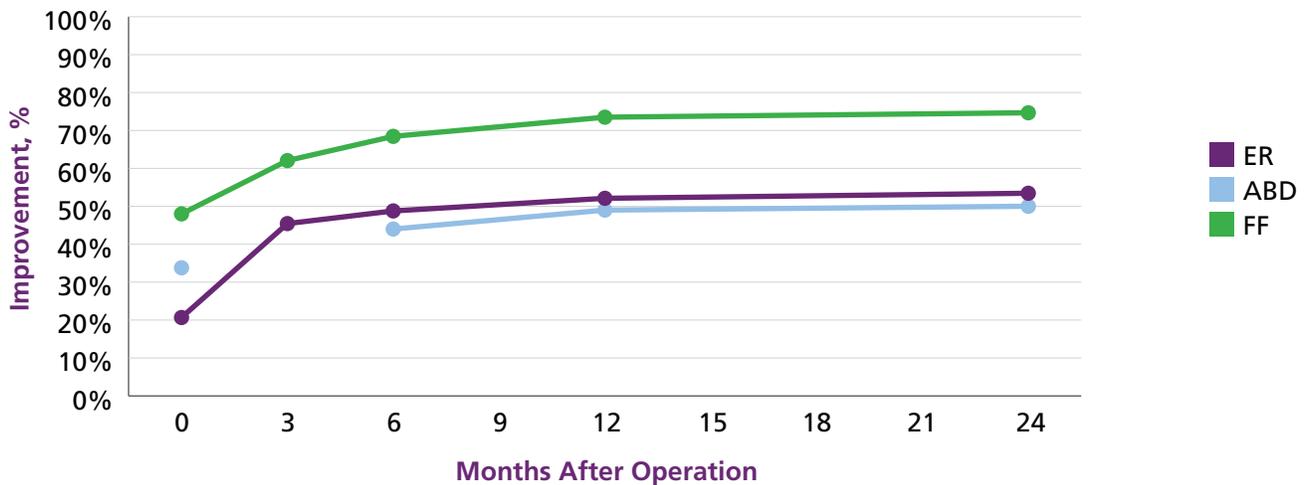
Figure 3. Graph Showing Additive Normalized Interval Improvements in Range of Motion Up to 2 Years of Follow-Up. There was insufficient data to calculate the interval improvement at 3 months for abduction. ABD indicates abduction; ER, external rotation; FF, forward flexion.

Table 6. Failures and Complications

Parameter	Patients, No. (%)
Indication for revision procedure	
Atraumatic glenoid loosening	20 (62.5)
Traumatic loosening of the humeral implant	2 (6.3)
Rotator cuff arthropathy	5 (15.6)
Implant malpositioning	1 (3.1)
Spontaneous implant malrotation	1 (3.1)
Infection	3 (9.4)
Revision procedures within 1 y of surgery[a]	5 (46.0)

[a]Mean (SD) time to revision procedure was 12.3 (10.3) months (range, 0.25-30.0 months).

We can attribute the limitations of this study to the relative heterogeneity of the included studies, including differences in operative techniques and rehabilitation protocols, which the investigators inconsistently reported. There was a lack of reporting of data at earlier time points, which prevented analysis at these intervals for some of the outcome scores. In addition, the lack of outcome reporting at 3 or 6 months in some studies, and between 6 and 12 months for all studies, does not capture improvements that may have occurred earlier. Furthermore, the use of the lowest published MCID for a PROM or ROM weighs the analysis to a conservative side for later postoperative visits that may be considered unnecessary on the basis of our definition of MMI.

Another potential limitation to this study is that 10 of the 13 included studies were of level II evidence or lower (Table 2). However, we contend that the level of evidence does not necessarily affect the outcomes of this study. The design of the included studies, whether constructed retrospectively or without use of a control group used, does not affect the quality of our investigation because PROMs are always collected prospectively. One final limitation of this study is that MCIDs are specific to patient populations within the study from which they were derived; using a particular MCID and applying it to other studies makes the assumption that those populations are similar.[40] Although all patients within this systematic review had primary TSAs performed for the indication of OA, their comorbidities and baseline demographic characteristics were not compared. Despite the limitations of this study, the sample sizes were large enough to power measurements sufficiently at each interval, which justifies a high level of confidence in the results of this study.

CONCLUSION

After anatomic TSA, we saw a clinically significant improvement in PROMs up to 1 year after the procedure. Statistically significant improvements in ROM may be seen up to 2 years, but most of improvement is seen within 3 months after surgery. These conclusions are useful for counseling patients and their expectations before surgery, as well as establishing a time frame for evaluating MMI the better to define the value of this procedure. ❖

References and financial disclosures are available online at www.rush.edu/orthopedicsjournal.

"…an important goal is to identify factors that control apoptosis in cells treated with MDM2 antagonist (Nutlin) because these factors could be potential targets to enhance the therapeutic response."

The Insulin-Like Growth Factor-1 Receptor/Protein Kinase B Pathway Has Opposing Effects on Nutlin-Induced Apoptosis

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INTRODUCTION

p53 is a stress-responsive transcription factor and potent tumor suppressor. p53 levels are low in most cells because of mouse double minute 2 homolog (MDM2), an E3 ubiquitin ligase that binds p53 and promotes its degradation.[1,2] However, DNA damage and other stresses induce posttranslational modifications in p53 and MDM2 that disrupt their binding and cause p53 protein levels to increase.[3] Increased levels of p53 then activate expression of downstream target genes whose protein products can cause apoptosis or cell cycle arrest.[4] In recent years, investigators have developed small-molecule MDM2 antagonists as potential therapeutic agents.[5] These compounds occupy the p53 binding site in MDM2, thus blocking p53-MDM2 binding and unleashing p53 to induce cell cycle arrest or apoptosis. Nutlin-3a (Nutlin) is the prototype MDM2 antagonist first described, to our knowledge, in 2004.[5] Nutlin inhibits proliferation and induces apoptosis in p53 wild-type cancer cell lines and blocks the growth of p53 wild-type human tumors grown in mice.[6,7] Second-generation Nutlin derivatives have entered clinical trials against various solid and hematologic cancers.

Not all p53 wild-type cancer cells respond to MDM2 antagonist treatment in the same way. For example, most hematologic cancer cell lines undergo apoptosis as their primary response to Nutlin, whereas most but not all nonhematologic cancer cell lines undergo cell cycle arrest.[7,8] Tovar et al[7] reported that SJSA-1 and MHM, 2 osteosarcoma (OS) cell lines with amplification of the *MDM2* gene, were highly sensitive to Nutlin-induced apoptosis, whereas HCT116 (colon), A549 (lung), and H460 (lung), which do not contain *MDM2* gene amplification, were least sensitive. This finding suggested *MDM2* gene amplification may predispose cells to Nutlin-induced apoptosis. In contrast, Kitagawa et al[9] found Nutlin treatment did not induce abundant apoptosis in the choriocarcinoma cell line JAr, which is known to have *MDM2* gene amplification. This finding would suggest that MDM2 amplification is not a perfect predictor of Nutlin sensitivity. We and others have found that the cell cycle arrest induced by Nutlin is reversible and, in some cases, can give rise to tetraploid cells that are resistant to radiation- and chemotherapy-induced apoptosis.[10-12] Thus, being able to target Nutlin-treated cells down the more desirable apoptotic pathway conceivably could increase its therapeutic
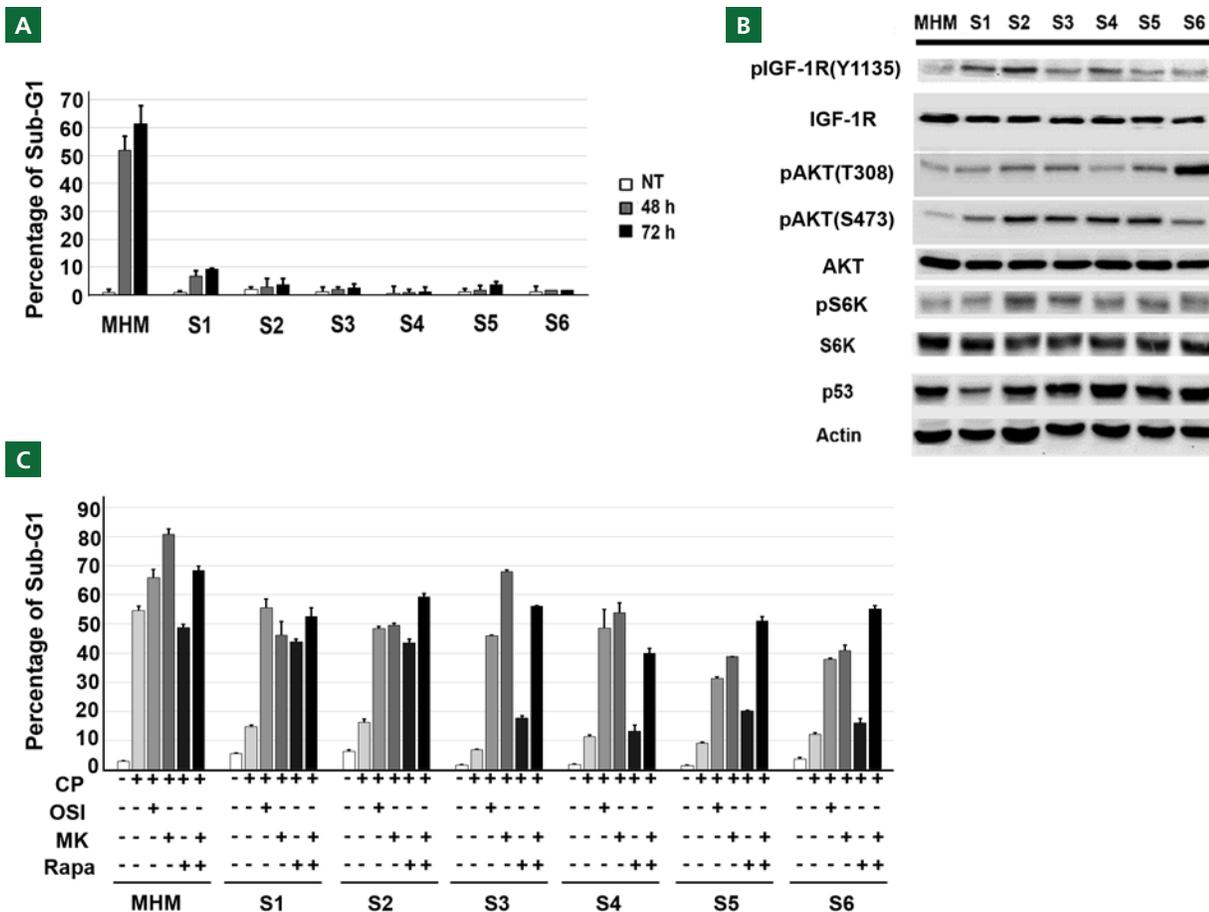
Figure 1. Cisplatin (CP)-Resistant Cells Had Heightened Activation of the Insulin-Like Growth Factor (IGF)-1 Receptor (IGF-1R)/Protein Kinase B (AKT)/Mammalian Target of Rapamycin Complex (mTORC)1 Pathway. **A,** MHM cells and clones S1 through S6 were either untreated (NT) or treated with 10 μM CP for 48 and 72 hours. We determined the percentage of cells with sub-G1 DNA. Shown are the mean results of 3 separate experiments. **B,** We immunoblotted parental and CP-resistant clones for the indicated proteins under untreated conditions. **C,** Parental MHM and CP-resistant clones were untreated (−) or treated (+) with CP (10 μM) alone or in combination with OSI-906 (OSI; 10 μM), MK2206 (MK; 10 μM), rapamycin (Rapa; 0.5 μM), or rapamycin plus MK2206 for 72 hours. We determined apoptosis by means of the percentage of cells with sub-G1 DNA content. NT indicates untreated. The bars indicate the extent of apoptosis under each treatment condition. The error bars indicate the standard error of the mean from three separate experiments.

potential. Therefore, it is important to identify factors that regulate whether cells undergo apoptosis or arrest in response to Nutlin treatment.

The insulin-like growth factor (IGF)-1 receptor (IGF-1R)/protein kinase B (AKT)/mammalian target of rapamycin complex (mTORC)1 pathway is activated in multiple cancers and is associated with chemotherapy resistance and poor patient outcome.[13] In this pathway, ligands IGF-1 and -2 bind the receptor IGF-1R, stimulating its autophosphorylation on tyrosines, which leads to recruitment and

activation of phosphoinositide 3-kinase (PI3-K). Phosphorylation subsequently activates the kinase AKT at 2 sites: serine-473 (S473) is phosphorylated by mTORC2, and threonine-308 (T308) is phosphorylated by phosphoinositide-dependent kinase-1. Activated AKT can promote survival by phosphorylating and inhibiting or activating various pro- or anti-apoptotic factors.[14-16] mTORC1 is activated downstream of AKT and promotes protein synthesis and cell growth by phosphorylating its substrates (eg, ribosomal protein S6 kinase [S6K]).[17,18]

Activated mTORC1 also inhibits autophagy,[19] the self-eating process in which cells degrade damaged organelles and proteins to maintain nutrient and energy levels for survival.[31,32]

There is abundant crosstalk between p53 and the IGF-1R/AKT/mTORC1 pathway that potentially could influence cancer cell sensitivity to Nutlin or other MDM2 antagonists. For example, Zhu et al[20] reported that leukemia cells with basal or elevated phosphatase and tensin homolog (PTEN) expression, and thus low PI3K/AKT signaling, were more susceptible
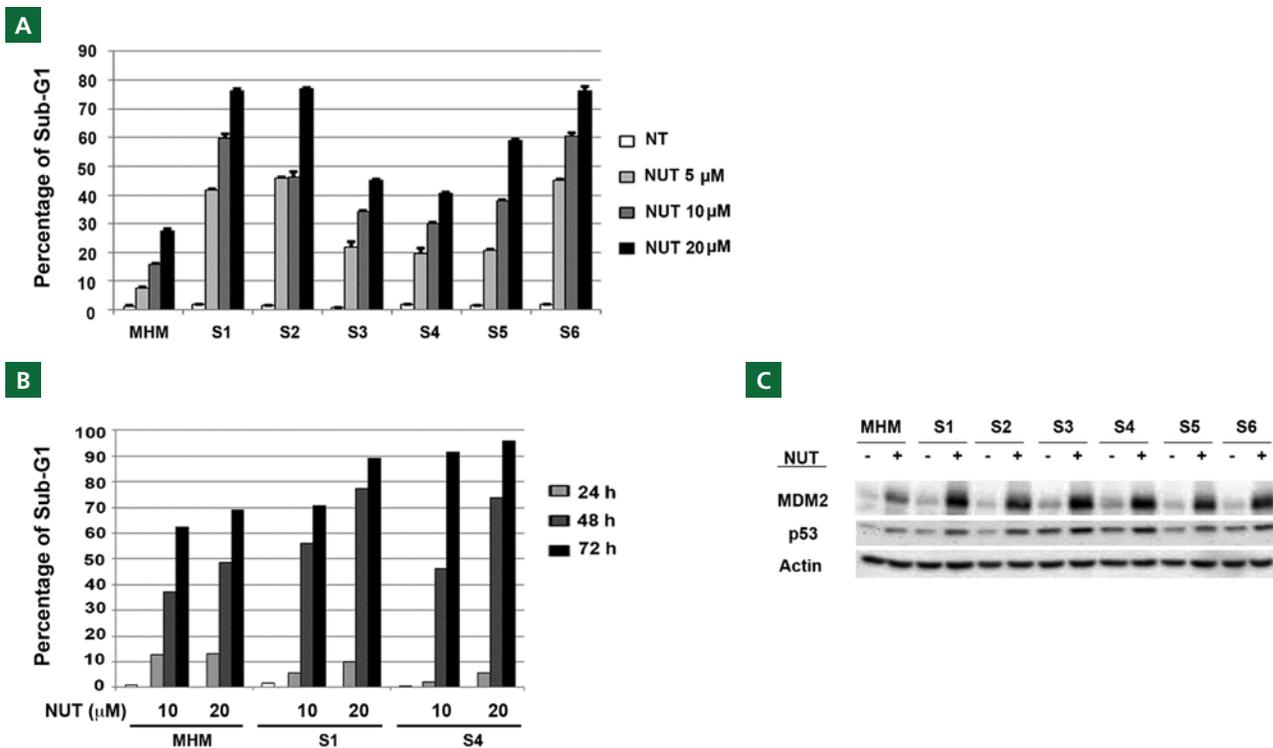
Figure 2. Cisplatin (CP)-Resistant Cells Were Hypersensitive to Nutlin-Induced Apoptosis. **A,** Parental MHM and CP-resistant S1 through S6 cells were untreated (NT) or treated with Nutlin (NUT; 5, 10, and 20 μM) for 48 hours, and we determined the percentage of cells with sub-G1 DNA content. **B,** Parental MHM and CP-resistant S1 and S4 cells were treated with NUT (10 or 20 μM) for 24, 48, and 72 hours, and we determined the percentage of cells with sub-G1 DNA content. **C,** MHM and CP-resistant S1 through S6 cells were untreated (−) or treated (+) with NUT (10 μM) for 24 hours, and we determined p53, mouse double minute 2 homolog (MDM2), and β-actin levels by means of immunoblotting. NT indicates untreated.

to Nutlin-induced apoptosis than were cells without PTEN expression. More recently, Saiki et al[21] reported that AKT and mTORC1 inhibitors could synergize with the MDM2 antagonist C-25 to reduce viability in a subset of p53 wild-type cancer cell lines. Together, these findings support the idea that AKT/mTORC1 signaling can reduce apoptosis sensitivity in response to MDM2 antagonists such as Nutlin. In contrast, we and others have found that IGF-1R/AKT/mTORC1 signaling promotes p53 protein synthesis and maintains p53 expression levels in stressed cells.[22-25] These findings raise the possibility that heightened IGF-1R/AKT/mTORC1 activation potentially could increase cancer cell sensitivity to Nutlin by maintaining high p53 protein levels. In 2015, we found the autophagy inhibitors bafilomycin A1 and chloroquine could increase

apoptosis sensitivity in Nutlin-treated cells, indicating that autophagy promotes apoptosis resistance.[26] Given that AKT/ mTORC1 signaling inhibits autophagy, the results suggest heightened AKT/mTORC1 activation could increase apoptosis in Nutlin-treated cells by blocking or reducing prosurvival autophagy.

OS is an aggressive bone cancer that primarily affects children and adolescents.[27] Standard OS treatment includes pre- and postoperative chemotherapy and surgical resection.[28] Nonetheless, treatment fails in approximately 30% of patients, and they die due to tumor relapse at metastatic sites.[29] The primary reason for treatment failure is tumor therapy resistance. Cisplatin (CP) is a standard chemotherapy agent for OS. MHM is an OS cell line that has *MDM2* gene amplification and

expresses wild-type p53. We treated MHM with increasing doses of CP and expanded surviving clones (the clones are termed S1 through S6). In a previous study, we reported that clone S4 is resistant to CP-induced apoptosis compared with MHM.[23]

In the current report, we isolated CP-resistant clones from the MHM OS cell line. The clones showed heightened basal IGF-1R/AKT activation that contributed to their CP resistance. The clones also displayed hypersensitivity to apoptosis by Nutlin. IGF-1R and AKT inhibitors increased apoptosis in response to Nutlin, demonstrating that IGF-1R/AKT activation can promote Nutlin resistance in these cells. However, p53 was induced to a higher level, and AKT was more activated in response to Nutlin in the CP-resistant clones than in the parental MHM cells.
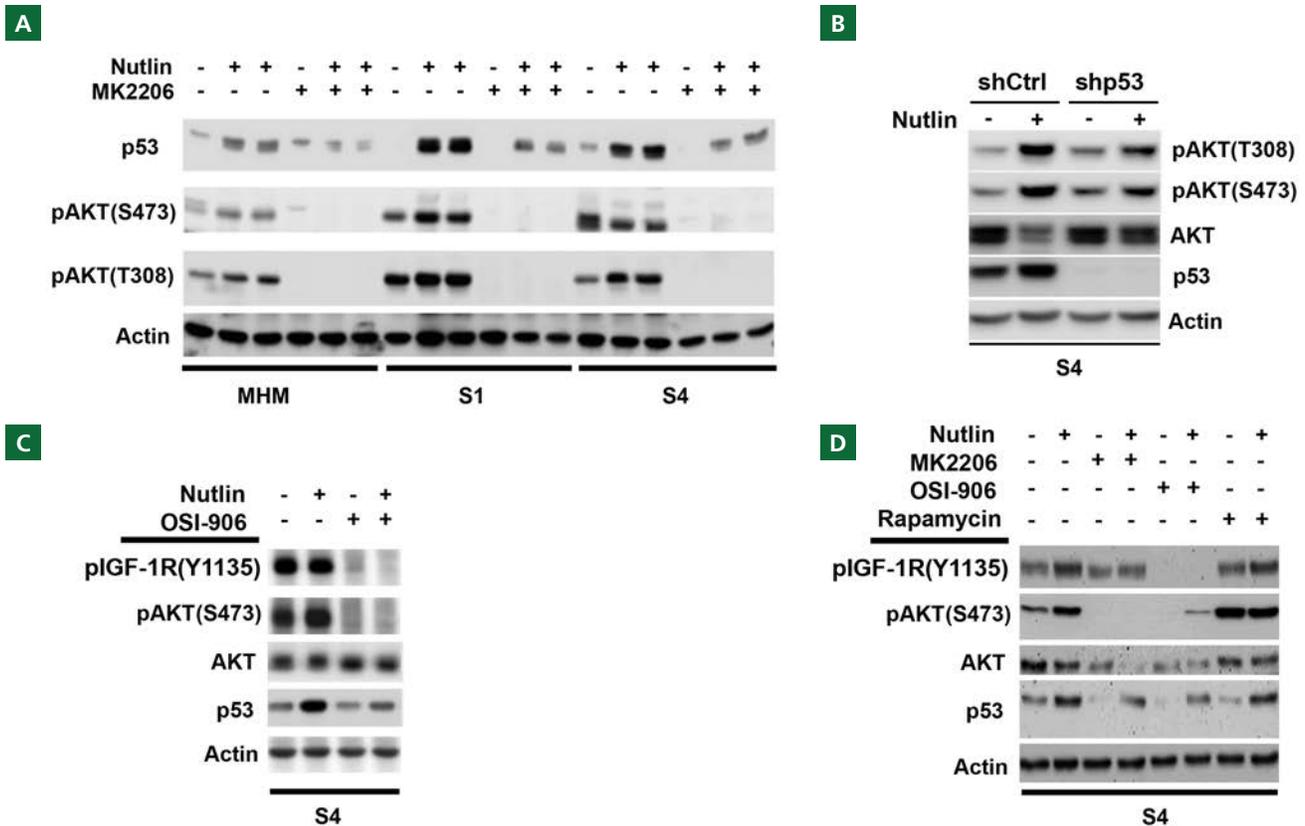
Figure 3. The Insulin-Like Growth Factor (IGF)-1 Receptor (IGF-1R)/Protein Kinase B (AKT)/Mammalian Target of Rapamycin Complex (mTORC)1 Pathway Was More Highly Activated in Nutlin-Treated S1 and S4 Cells and Contributed to Apoptosis Resistance. **A,** We either treated (+) or did not treat (–) MHM, S1, and S4 cells with Nutlin (10 μM) for 24 hours. We determined levels of p53, AKT phosphorylated (pAKT) at S473, pAKT at T308, and β-actin by means of immunoblotting. **B,** We treated S4 cells stably infected with virus encoding control short hairpin RNA (shCtrl) or p53 short hairpin RNA (shp53) with Nutlin (10 μM) for 24 hours and immunoblotted for the indicated proteins. **C,** We treated S4 cells with Nutlin (10 μM) and OSI-906 (10 μM) for 24 hours and immunoblotted for the indicated proteins. **D,** We treated S4 cells for 24 hours with Nutlin (10 μM), OSI-906 (10 μM), MK2206 (10 μM), and rapamycin (0.5 μM) as indicated and immunoblotted for the indicated proteins.

IGF-1R and AKT inhibitors reduced p53 levels in response to Nutlin, demonstrating IGF-1R/AKT activation also contributes to the accumulation of p53. Finally, the CP-resistant and Nutlin-hypersensitive clones showed reduced autophagic flux that was AKT dependent, and autophagy inhibitors increased Nutlin sensitivity in parental MHM cells. Our findings suggest that in addition to reducing apoptosis in response to Nutlin, IGF-1R/AKT pathway activation also can increase apoptosis sensitivity through a combination of maintaining p53 protein levels and inhibiting prosurvival autophagy.

MATERIALS AND METHODS

Cell Lines

Dr Ola Myklebost, Norwegian Radium Hospital, provided MHM and *MDM2*-amplified OS cells. To isolate CP-resistant MHM clones, we treated MHM cells with increasing doses of CP (1, 2.5, 5, and 10 μM) for 48 hours, and surviving cells expanded after each treatment. We plated cells expanded after 10 μM of CP treatment at single cell density in drug-free medium (minus CP), and we isolated and expanded colonies that formed after 2 weeks. We obtained 6 colonies (S1 through S6). We grew MHM and clones S1 through S6 in Roswell Park Memorial Institute medium (Gibco, Waltham, MA) supplemented with 10% fetal bovine serum (Atlanta Biologicals, Flowery Branch, GA) and a solution of penicillin (100 U/mL) and streptomycin (100 μg/mL; Corning, Manassas, VA).

Drug Treatments

We plated cells 24 hours before being treated. The CP was from Bedford Laboratory (Bedford City, OH). We obtained linsitinib (OSI-906), MK2206, and rapamycin from Selleck Chemicals (Houston, TX) and bafilomycin A1 from Sigma-Aldrich (St. Louis, MO).

We obtained Nutlin from Cayman Chemical (Ann Arbor, MI). We treated cells with these drugs at the following final concentrations: CP (10 μM), OSI-906 (10 μM), MK2206 (10 μM), rapamycin (0.5 μM), Nutlin (5, 10, and 20 μM), and bafilomycin A1 (10 nM).

Immunoblotting

We prepared whole cell extracts by resuspending cell pellets in lysis buffer (150 mM sodium chloride, 5 mM ethylenediaminetetraacetic acid, 0.5% octylphenoxypolyethoxyethanol, 50 mM tris[hydroxymethyl]aminomethane, pH 7.5; Sigma-Aldrich), resolved by means of sodium dodecyl sulfate polyacrylamide gel electrophoresis, and we transferred them to polyvinylidene difluoride membranes (NEN Life Science Products, Boston, MA). We used the following antibodies (Cell Signaling Technologies, Danvers, MA) at a 1:1000 dilution: phosphorylated (p)IGF-1R (Y1135), IGF-1R, pAKT (S473), pAKT (T308), AKT (C67E7), p-p70S6K (T389), p70S6K (49D7), and p62 (5114). Antibodies to β-actin (C4) and p53 (Ab-6) were from Santa Cruz Biotechnology (Santa Cruz, CA), and we also used them at a 1:1000 dilution. We detected primary antibodies with goat anti-mouse (Pierce; Thermo Scientific, Waltham, MA) or goat anti-rabbit (Life Technologies, Carlsbad, CA) secondary antibodies conjugated to horseradish peroxidase by using chemiluminescence (Clarity; Bio-Rad Laboratories, Hercules, CA). We used both secondary antibodies at a 1:10 000 dilution.

Flow Cytometry Analysis

For apoptosis (percentage of sub-G1-ohase cells) and cell cycle analysis, we harvested cells and fixed them in 25% ethanol overnight. We then stained the cells with propidium iodide (25 μg/mL; Calbiochem, San Diego, CA). We performed flow cytometry analysis with a flow cytometer (Gallios; Beckman Coulter, Brea, CA), and we analyzed the results with software (FlowJo 8.7; Tree Star, Ashland, OR). For each sample, we collected 10000 events.

RESULTS

In the current study, we compared parental MHM cells and clones S1 through S6 in a side-by-side experiment to determine apoptosis sensitivity in response to CP. For this purpose, we monitored the percentage of cells with sub-G1 DNA content as an indicator of apoptosis. As shown in Figure 1A, compared with MHM, the S1 through S6 clones were resistant to CP-induced apoptosis. We previously reported that the IGF-1R/AKT/mTORC1 pathway can contribute to CP resistance in primary OS cells and OS cell lines.[23] Therefore, we assessed activation of this pathway by monitoring phosphorylated (activated) levels of IGF-1R, AKT, and S6K in MHM cells and the CP-resistant clones. As shown in Figure 1B, the S1 through S6 clones expressed basally higher levels of pIGF-1R, pAKT, and pS6K (indicative of mTORC1 activity) when compared with levels in parental MHM cells. Finally, we monitored

apoptosis by determining the percentage of cells with sub-G1 DNA content after treatment with CP alone or in combination with an IGF-1R inhibitor (OSI-906), AKT inhibitor (MK2206), mTORC1 inhibitor (rapamycin), or combination rapamycin plus MK2206. As shown in Figure 1C, cotreatment with OSI-906 and MK2206 increased apoptosis in CP-treated MHM cells and each of the CP-resistant clones, supporting the idea that IGF-1R and AKT contribute to apoptosis resistance. Rapamycin also increased CP-induced apoptosis, and this effect of rapamycin was especially evident in clones S1 and S2. This finding suggests S1 and S2 are more dependent on mTORC1 for apoptosis resistance than are either MHM or clones S3 through S6.

Rapamycin can cause feedback activation of AKT,[30] so we tested the combined effect of rapamycin plus the AKT inhibitor MK2206. We found that rapamycin plus MK2206 increased apoptosis in the S3
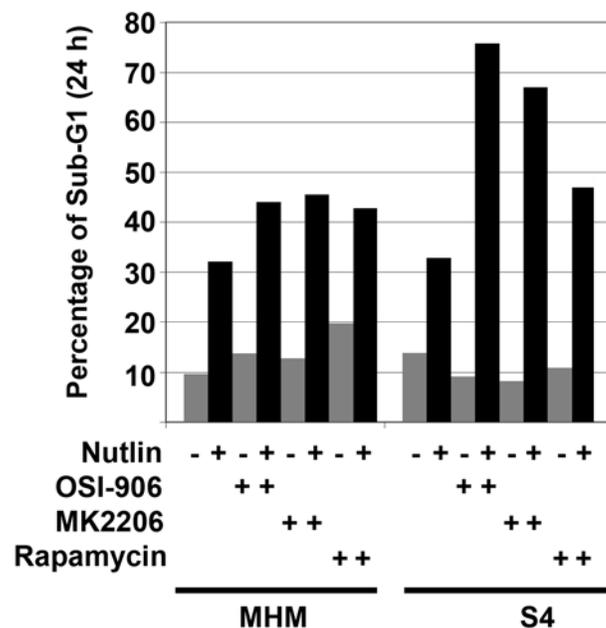

Figure 4. The Effect of Insulin-Like Growth Factor-1 Receptor/Protein Kinase B Inhibitors on Nutlin-Induced Apoptosis. We treated (+) or did not treat (−) MHM, S1, and S4 cells with Nutlin alone (10 μM) or in combination with inhibitors of IGF-1R (OSI-906 10 μM), AKT (MK2206 10 μM), rapamycin (0.5 μM), or rapamycin plus MK2206 for 24 or 48 hours. We determined the percentage of cells with sub-G1 DNA content. The bars indicate the percentage of sub-G1 cells.
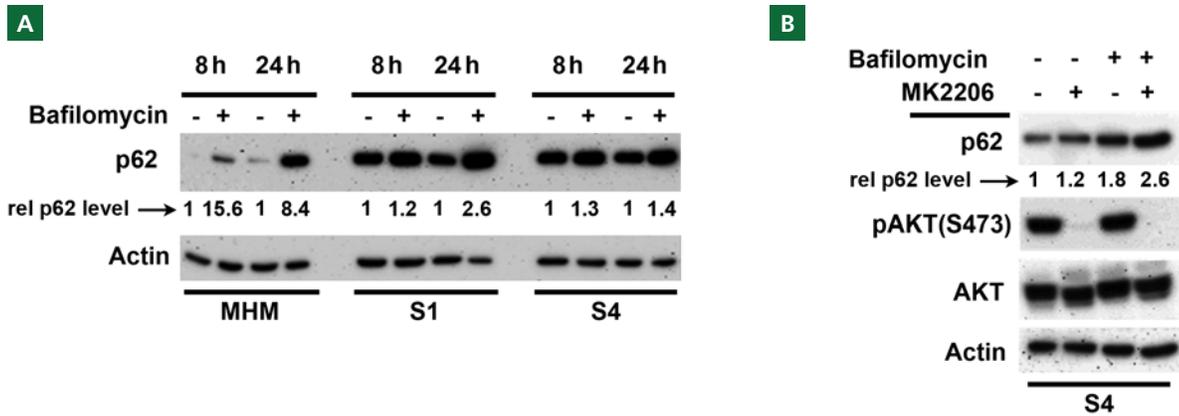
Figure 5. Autophagic Flux Was Different in MHM, S1, and S4 Cells. **A,** We treated (+) or did not treat (−) MHM, S1, and S4 cells with bafilomycin A1 (10 nM) for 8 and 24 hours. We determined p62 levels by means of immunoblotting. We quantified p62 and β-actin levels by using ImageJ software. The relative (rel) p62 level is indicated after normalization to β-actin levels. **B,** We determined p62 levels in S4 cells treated with bafilomycin A1 (10 nM) alone or in combination with MK2206 (10 μM) for 16 hours. The rel p62 level is indicated after normalization to β-actin levels. p62 increased to a greater extent in cells cotreated with bafilomycin A1 plus MK2206 than in those treated with bafilomycin A1 alone, indicating that MK2206 increased autophagic flux.

through S6 clones above the level seen with MK2206 or rapamycin alone (Figure 1C). The results suggest that the relative lack of apoptosis sensitivity in the rapamycin-treated S3 through S6 clones could result from feedback activation of AKT.

Because MHM cells express wild-type p53, we considered that the CP-resistant MHM clones (S1-S6) might be sensitive to MDM2 antagonists that stabilize and activate p53. To test this possibility, we first treated MHM and clones S1 through S6 with increasing doses of the MDM2 antagonist Nutlin for 48 hours. We then monitored apoptosis by determining the percentage of cells with sub-G1 DNA content (Figure 2A). In these studies, MHM cells showed approximately 30% apoptosis in response to the highest (20 μM) Nutlin dose tested. In contrast, clones S1 through S6 were hypersensitive to Nutlin-induced apoptosis, in some cases showing 75% to 80% apoptotic cells in response to 20 μM Nutlin (Figure 2A).

Next, we carried out a time-course experiment by treating MHM and 2 of the CP-resistant clones (S1 and S4) with Nutlin (10 or 20 μM) and monitoring apoptosis between 24 and 72 hours after

treatment. As shown in Figure 2B, MHM, S1, and S4 cells had comparable and relatively low levels of apoptosis when treated with Nutlin for 24 hours. However, S1 and S4 cells displayed much higher levels of apoptosis than did MHM cells when treated with Nutlin for 48 and 72 hours, again indicating that at these later times the CP-resistant S cells were hypersensitive to apoptosis by Nutlin.

Finally, we performed immunoblotting to determine whether increased apoptosis sensitivity coincided with higher levels of induced p53 (Figure 2C). The data revealed that p53 was induced to a higher level with Nutlin treatment in the S1 through S6 clones than were parental MHM cells, and MDM2 also was induced to a higher level, supporting the idea that higher levels of p53 led to increased p53 activity (Figure 2B). In summary, the S1 through S6 clones were resistant to CP-induced apoptosis but were hypersensitive to apoptosis by Nutlin, and the Nutlin hypersensitivity was associated with a greater induction of p53.

Next, we examined the relationship between IGF-1R/AKT signaling and p53 induction by Nutlin in MHM cells

and the CP-resistant clones. To this end, we treated MHM cells and 2 of the CP-resistant clones (S1 and S4) for 24 hours with Nutlin alone or Nutlin plus the allosteric AKT inhibitor MK2206. As shown in Figure 3A, p53 was again induced to a higher level by Nutlin in S1 and S4 cells than in MHM cells. Levels of activated AKT (phosphorylated at S473 and T308) were increased in the Nutlin-treated cells and to a higher level in S1 and S4 than in MHM (Figure 3A). pAKT was less induced in S4 cells in which p53 was depleted by short hairpin RNA, confirming that the increase in pAKT was largely p53 dependent (Figure 3B). As expected, we did not detect pAKT in cells cotreated with Nutlin and the allosteric AKT inhibitor MK2206. p53 was less induced in cells cotreated with Nutlin plus MK2206 than in cells treated with Nutlin alone, indicating that AKT activation contributed to the accumulation of p53 in Nutlin-treated cells.

To test whether IGF-1R contributes to the accumulation of p53, we monitored p53 levels in S4 cells treated with Nutlin alone or Nutlin plus the IGF-1R inhibitor OSI-906. As shown in Figure 3C, cotreatment with OSI-906 reduced p53 accumulation in

Nutlin-treated S4 cells, indicating IGF-1R contributed to the accumulation of p53. Levels of activated (S473 phosphorylated) AKT were completely absent in cells treated with OSI-906, indicating AKT activation in these cells was IGF-1R dependent (Figure 3C).

Finally, to determine whether mTORC1 activity is required for p53 accumulation, we cotreated S4 cells with Nutlin and the mTORC1 inhibitor rapamycin. As shown in Figure 3D, OSI-906 and MK2206 again reduced p53 levels in Nutlin-treated S4 cells, indicating IGF-1R and AKT contributed to p53 accumulation in Nutlin-treated cells. However, rapamycin did not reduce p53 accumulation in Nutlin-treated S4 cells (Figure 3D), suggesting mTORC1 activity is not required for the accumulation of p53. mTORC1 inhibition can cause feedback activation of AKT.[30] Consistent with this finding, pAKT (S473) levels were increased in S4 cells treated with either rapamycin alone or Nutlin plus rapamycin (Figure 3D). In total, the results shown in Figure 3 indicate that p53 can activate AKT in Nutlin-treated cells in a manner that is IGF-1R dependent, that S1 and S4 cells express higher levels of activated AKT in response to Nutlin than do MHM cells, and that IGF-1R and AKT contribute to the Nutlin-induced accumulation of p53.

Higher levels of p53 usually lead to increased apoptosis. The fact that IGF-1R/AKT activity contributed to p53 accumulation in Nutlin-treated cells suggests that IGF-1R and AKT could increase p53-dependent apoptosis. However, IGF-1R/AKT signaling can inhibit apoptosis and increase survival by altering the activity of various apoptosis regulators.[13] To examine the effect of IGF-1R, AKT, and mTORC1 on apoptosis in Nutlin-treated cells, we treated MHM and S4 cells with Nutlin alone or in combination with OSI-906, MK2206, or rapamycin. We determined apoptosis by means of the percentage of cells with sub-G1 DNA content. As shown in Figure 4, approximately 30% of MHM cells treated for 24 hours with 10 μM Nutlin had sub-G1 DNA content (apoptosis). Cotreatment with OSI-906, MK2206, or rapamycin increased the percentage of apoptotic, sub-G1 MHM cells to 40% to 50% (Figure 4). Approximately 30% of S4 cells also had sub-G1 DNA content (apoptosis) when treated for 24 hours with 10 μM Nutlin. Cotreatment of S4 cells with Nutlin and either OSI-906 or MK2206 increased the percentage of apoptotic, sub-G1 cells to approximately 65% to 75%, and cotreatment with rapamycin increased the percentage of apoptotic, sub-G1 cells to approximately 45% (Figure 4). The results indicate that IGF-1R/AKT/mTORC1 signaling promotes apoptosis resistance in Nutlin-treated MHM and S4 cells. IGF-1R/AKT activation appears to contribute more to apoptosis resistance in S4 cells than in MHM cells.

Autophagy is a process of self-eating in which damaged organelles, misfolded proteins, and other components are broken down and degraded in autophagolysosomes. This degradation allows cells to maintain nutrient and energy levels critical for survival.[31,32] mTORC1 is activated downstream of AKT and normally inhibits autophagy by phosphorylating and inhibiting uncoordinated 51-like kinase (ULK)1 and ULK2, which are components of the autophagy-initiating complex.[31,32] We previously reported that autophagy inhibits apoptosis and promotes survival in Nutlin-treated cells.[26] Therefore, we asked whether AKT regulates autophagy in MHM, S1, and S4 cells and whether this function affects apoptosis sensitivity in response to Nutlin. Sequestosome 1 (p62) is an autophagy protein that is degraded in autophagolysosomes and that facilitates
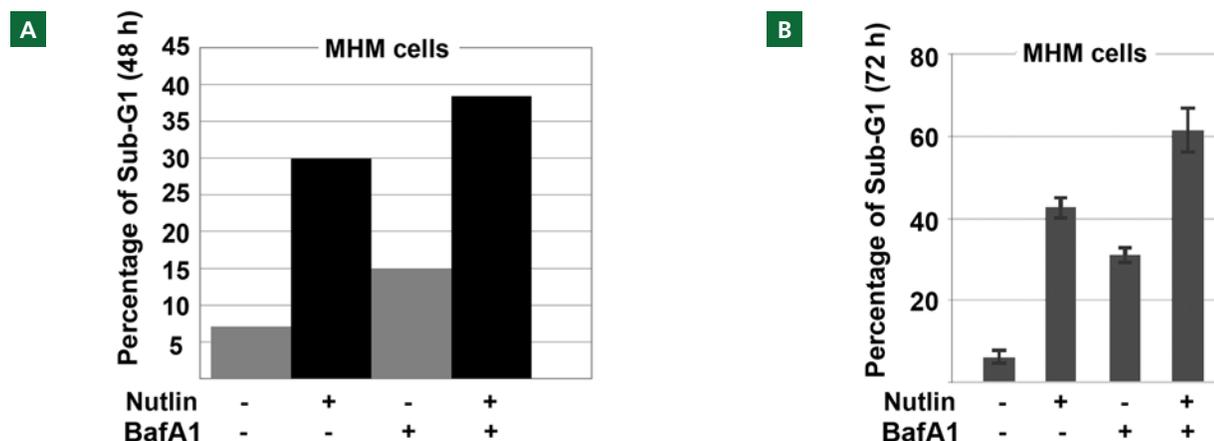
Figure 6. Autophagy Inhibition Increased Nutlin-Induced Apoptosis. We treated (+) or did not treat (−) MHM cells with Nutlin alone (10 μM) or in combination with bafilomycin A1 (BafA1; 10 nM) as indicated. We determined the percentage of cells with sub-G1 DNA content 48 hours (**A**) and 72 hours (**B**) after treatment. The bars indicate the extent of apoptosis under each treatment condition. The error bars indicate the standard error of the mean from three separate experiments.

recruitment of misfolded, ubiquitinated proteins and damaged organelles to autophagolysosomes for degradation. Bafilomycin A1 disrupts autophagosomes and inhibits autophagic protein degradation, including degradation of p62. Thus, the extent to which p62 increases in response to bafilomycin A1 reflects the rate with which autophagic degradation is occurring, or autophagic flux.

We compared autophagic flux in MHM, S1, and S4 cells by treating the cells with bafilomycin A1 for 8 or 24 hours and monitoring p62 levels by means of immunoblotting (Figure 5A). p62 levels increased in MHM cells treated with bafilomycin A1 alone, indicating autophagic degradation was occurring. By using ImageJ software (National Institutes of Health, Bethesda, MD), we quantified the extent to which p62 levels increased in cells treated with bafilomycin A1 as an indication of autophagic flux, and we used β-actin as a normalization control. The results showed that p62 levels increased approximately 8- to 15-fold in MHM cells in response to 8 or 24 hours of bafilomycin A1 treatment. Basal p62 levels were strikingly higher in S1 and S4 cells than in MHM cells; moreover, p62 increased to a lesser extent (only 1.5- to 2-fold) in S1 and S4 cells treated with bafilomycin A1 for 8 or 24 hours. These results indicate that S1 and S4 cells have reduced autophagic flux compared with that of MHM cells.

Next, we asked whether AKT regulates autophagic flux in these cells and what its effect is on Nutlin sensitivity. For this question, we treated S4 cells with bafilomycin A1 and the AKT inhibitor MK2206, either alone or in combination, and determined p62 levels. As shown in Figure 5B, p62 increased by 1.8-fold in S4 cells treated with bafilomycin A1 alone but increased by 2.6-fold in cells cotreated with bafilomycin A1 and MK2206. Thus, AKT inhibition by MK2206 increased autophagic flux in these cells, indicating that AKT activation normally inhibits autophagy. We speculated that reduced autophagy in S1 and S4 cells may contribute or lead to their increased

sensitivity to apoptosis by Nutlin. If this hypothesis is true, then autophagy inhibition should increase apoptosis in Nutlin-treated MHM cells. To test this hypothesis, we treated MHM cells with Nutlin alone or in combination with bafilomycin A1 for 48 or 72 hours and then monitored apoptosis by means of the percentage of cells with sub-G1 DNA content. As shown in Figure 6, the combination of Nutlin plus bafilomycin A1 caused a greater amount of apoptosis in MHM cells than did either agent alone, indicating autophagy inhibition can increase Nutlin-induced apoptosis. We conclude that reduced autophagic flux that is dependent on AKT activity contributes to greater apoptosis sensitivity in Nutlin-treated S1 and S4 cells.

DISCUSSION

In recent years, investigators have developed MDM2 antagonists (eg, Nutlin) as potential therapies in cancers with wild-type p53. Nutlin occupies the p53-binding pocket in MDM2, thus blocking p53-MDM2 binding and unleashing p53 to inhibit cancer cell proliferation or induce apoptosis. Some p53 wild-type cancer cells are resistant to apoptosis in response to Nutlin and can survive and resume proliferation on Nutlin removal. Thus, an important goal is to identify factors that control apoptosis in cells treated with MDM2 antagonist (Nutlin) because these factors could be potential targets to enhance the therapeutic response.

MHM is an MDM2-amplified OS cell line that is relatively sensitive to Nutlin-induced apoptosis. We isolated CP-resistant MHM cell clones after repeated exposure to increasing CP doses. These clones (S1 through S6) had heightened IGF-1R/AKT signaling that contributed to CP resistance. These CP-resistant clones expressed elevated p53 levels in response to Nutlin compared with those for the parental MHM cells and were hypersensitive to Nutlin-induced apoptosis. IGF-1R and AKT inhibitors increased apoptosis in response to Nutlin, helping to confirm that IGF-1R/AKT activation can
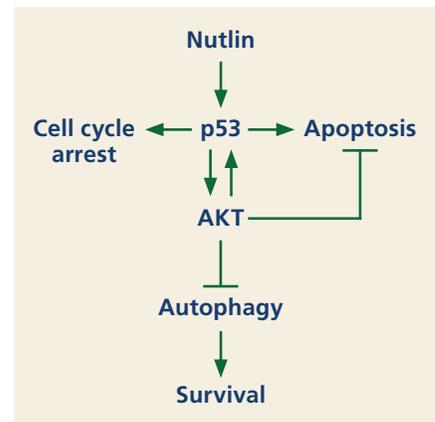

Figure 7. Model of How Insulin-Like Growth Factor (IGF)-1 Receptor (IGF-1R)/Protein Kinase B (AKT) Pathway Activation Affects Apoptosis Sensitivity in Response to Nutlin. p53 induced by Nutlin promotes AKT activation dependent on IGF-1R. IGF-1R/AKT activation also promotes the accumulation of p53. Activated AKT can reduce apoptosis and promote survival by regulating the activity of pro- and anti-apoptotic factors, such as B-cell lymphoma-2 (bcl-2), bcl-2-like protein 4, and bcl-2-like protein 11, that localize to the mitochondria. AKT also inhibits autophagy, which can promote survival.

promote apoptosis resistance. However, IGF-1R/AKT signaling also contributed to p53 accumulation in Nutlin-treated cells and reduced autophagy, which we showed can protect cells against apoptosis. On the basis of these findings, we propose that IGF-1R/AKT pathway signaling has dual and opposing effects on Nutlin sensitivity (Figure 7). First, this signaling can inhibit apoptosis, consistent with its well-established role as a survival-signaling pathway. Second, it can enhance Nutlin sensitivity through a combination of maintaining p53 levels and inhibiting prosurvival autophagy.

The survival kinase AKT is activated downstream of IGF-1R. AKT can promote survival by phosphorylating and inhibiting the activity of pro-apoptotic B-cell lymphoma-2 (bcl-2) family members such as bcl-2-associated death promoter and bcl-2-like protein 4, while also phosphorylating

and inhibiting the activity of forkhead box 03, a transcription factor that promotes apoptosis by activating expression of bcl-2 homology domain 3 domain-containing proteins like p53 upregulated modulator of apoptosis and bcl-2-like protein 11.[14-16] In the current study, IGF-1R and AKT inhibitors increased apoptosis by Nutlin, and it is likely that IGF-1R/AKT signaling promotes survival, at least in part, through AKT-dependent phosphorylation of 1 or more bcl-2 family members or forkhead box 03. Our results suggest that, in addition to promoting survival, IGF-1R/AKT signaling can increase apoptosis through a combination of maintaining p53 protein levels and inhibiting autophagy. Evidence that IGF-1R and AKT maintain p53 protein levels comes from the finding that IGF-1R/AKT inhibitors reduced p53 accumulation in Nutlin-treated cells. Increasing Nutlin doses causes a progressive increase in p53 levels and a corresponding increase in apoptosis. The finding that IGF-1R/AKT inhibitors reduced p53 suggests that IGF-1R and AKT could contribute to apoptosis in Nutlin-treated cells by maintaining or promoting high p53 protein levels. mTORC1 can be activated downstream of AKT, and results from previous studies have suggested that mTORC1 can promote p53 protein synthesis.[23,25] However, in this study, the mTORC1 inhibitor rapamycin did not reduce p53 accumulation in Nutlin-treated cells (Figure 3). This finding suggests that the mechanism by which AKT maintains p53 protein levels is not through mTORC1-mediated p53 synthesis.

In continuing studies in other cells, we have found that AKT inhibition reduces p53 protein levels in Nutlin-treated cells without reducing levels of p53 mRNA. This finding suggests that IGF-1R and AKT affect p53 levels at a posttranscriptional level. Boehme et al[24] reported that AKT is required for efficient stabilization of p53 in response to ionizing radiation. The model proposed in the study by Boehme et al[24] was that AKT promotes p53 stabilization by phosphorylating and inhibiting glycogen synthase kinase 3 β, which normally functions with MDM2

to promote p53 degradation. It is possible that, in the current study, AKT maintained p53 protein levels in Nutlin-treated cells through a similar mechanism.

Results from most studies suggest the IGF-1R/AKT pathway and p53 have opposing effects on cancer cell survival. IGF-1R/AKT signaling promotes cancer cell survival, whereas p53 inhibits cancer cell proliferation and promotes apoptosis, but in the current study, Nutlin-induced p53 caused activation of AKT. This finding raises the question of why p53 would activate AKT. Although p53 can promote cancer cell killing in response to stress, it also can promote survival. The choice between p53-mediated cell killing and survival depends on multiple factors, including the level of stress.[3] Thus, low levels of DNA-damaging stress trigger p53-dependent cell cycle arrests, which allow DNA repair and survival, whereas high levels of DNA damage can trigger p53-dependent apoptosis.[3] The ability of p53 to activate AKT may constitute part of the mechanism by which p53 promotes survival.

There are several possible ways p53 induced by Nutlin in the current study could activate AKT. The finding that OSI-906 blocked AKT activation by Nutlin indicates it is IGF-1R dependent. Thus, 1 possibility is that p53 in some way increases IGF-1R activity, leading to AKT activation. Against this idea are reports that p53 can repress expression of both IGF-1R and its activating ligand IGF-1.[33,34] However, in some, but not all, experiments, we observed increased activation of IGF-1R (phosphorylation at Y1135) in Nutlin-treated cells (eg, compare Figure 3C and Figure 3D), suggesting that increased p53 may lead to IGF-1R activation. A second possibility is that p53 activates AKT via the 5′ adenosine monophosphate-activated protein kinase (AMPK)/tuberous sclerosis complex (TSC)2/mTORC2 pathway. p53 can activate AMPK, which then can activate TSC2.[35] TSC2, in turn, can activate mTORC2, which can phosphorylate AKT directly at S473.[36] Thus, Nutlin-induced p53 potentially

could increase AKT by activating AMPK, TSC2, and mTORC2. p53 can inhibit mTORC1,[37] and inhibition of mTORC1 can cause feedback activation of AKT by relieving the feedback inhibition of PI3K/AKT signaling mediated by S6K.[30] Thus, a third possibility is that p53 could activate AKT by inhibiting mTORC1. Finally, Manfe et al[38] reported that p53 can increase expression of microRNA-122, which then can trigger AKT activation. Thus, a fourth possibility is that p53 activates AKT by increasing miR-122. These possibilities are not mutually exclusive. Notably, AKT was activated to a greater extent by Nutlin in S1 and S4 cells than in MHM cells. Therefore, whatever the mechanisms are for AKT activation by Nutlin, they appear to be more active in S1 and S4 cells than in MHM cells.

CONCLUSION

In summary, our findings indicate that AKT, activated downstream of IGF-1R, can inhibit apoptosis in Nutlin-treated cells but also can increase apoptosis through maintaining p53 protein levels and inhibiting autophagy. These findings have potential clinical implications. For example, investigators have developed a number of IGF-1R and AKT inhibitors for cancer clinical trials. Our results suggest that although these inhibitors may increase cancer cell killing, their effectiveness may be limited by a reduction in p53 protein levels and an increase in prosurvival autophagy. Overcoming these limitations could be an important goal for future drug development. �

"Because of the test's validity, as well as ease of use, PROMIS is an ideal tool to evaluate patient-reported outcomes in pain and function after surgical treatment for MBD."

Early Results of Patient-Reported Outcomes Measurement Information System Scores in Patients Undergoing Surgery for Metastatic Bone Disease

A Multicenter, Prospective Study

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INTRODUCTION

Nearly $12 billion are spent managing skeletal-related events annually in the United States.[1,2] These numbers are so staggering because currently in the United States more than 250000 patients are living with metastatic bone disease (MBD).[3,4] The prevalence of MBD increases each year as patients continue to live longer with their disease. Skeletal-related events, including acute pathologic fractures, can have a substantial effect on patient quality of life when they occur. Surgeons are able to determine which lesions are at high risk for fracture with the help of risk stratification tools such as the Mirels criteria.[5] Prophylactic surgery in patients with MBD usually consists of either internal fixation or arthroplasty.[6] Results from a number of studies have demonstrated the usefulness of treating metastatic skeletal lesions in this setting with prophylactic surgery. Some of these published benefits include improved function, decrease in hospital morbidity, and substantial cost savings when compared with a group that sustained a fracture before surgery.[7-11]

Historically, clinicians have evaluated patient outcomes by using a number of different means, including the Harris Hip Score; Oxford Knee Score; Disabilities of the Arm, Shoulder and Hand Score; 36-Item Short Form Health Survey; and visual analog scale pain scores. However, these scoring systems were developed for a different patient population, and using them in patients with MBD does not necessarily provide an accurate view of postoperative status. More recently in the orthopedic oncology literature, some authors have developed and used oncology-specific scoring systems, including the Musculoskeletal Tumor Society score and Toronto Extremity Salvage Score.[12-16] Critiques of these systems exist as well, and some argue that physician bias and length of survey are inherent flaws in these systems developed for the patient with cancer.

The Patient-Reported Outcomes Measurement Information System (PROMIS) offers simple, validated, computerized adaptive questionnaires that collect information about patient physical, mental, and social health.[17] Physicians can use calculated *t* scores to compare raw scores to those of the general US

population (*t* score of 50 with SD of 10). These tests often take no longer than a few minutes to complete and can consist of as few as 5 questions. Investigators have used PROMIS measures extensively in the medical literature and shown them to be validated and easily used.[18-20] Because of the test's validity, as well as ease of use, PROMIS is an ideal tool to evaluate patient-reported outcomes in pain and function after surgical treatment for MBD.

Investigators have used PROMIS scores extensively in the oncology literature, but, to date, to our knowledge, no study investigators have evaluated postoperative outcomes in patients treated for MBD. Although results in the existing literature show strong evidence that this patient population benefits from prophylactic surgery, the validity and ease of assessment involved in PROMIS may make it an ideal tool for evaluating these patients. Our group sought to perform a multicenter, prospective study recording PROMIS measures for pain and functional assessment in patients treated surgically for MBD. In our study, we aimed to determine whether collecting PROMIS measures was feasible in this group and to determine whether patients' pain or functional outcomes improved with surgery.

PATIENTS AND METHODS

We performed an institutional review board–approved, multicenter prospective study in patients treated surgically for MBD. We enrolled patients if they were planning to be treated surgically for a metastatic bone lesion. We did not include patients if they did not consent to the study or had insufficient data collected. Patients were enrolled preoperatively and contacted by a research coordinator or surgeon (D.M.L., S.S., K.B.J., or R.L.R.) from each of the 2 clinical sites (Huntsman Cancer Institute, Salt Lake City, Utah; University of Maryland Medical Center, Baltimore, Maryland) who was able to record their preoperative, or baseline, PROMIS data as well as basic demographic characteristics. They then contacted the patients postoperatively at routine

intervals to obtain postsurgical outcomes data. They recorded basic demographic and disease-related data, as well as the PROMIS instruments for Pain Interference and Physical Function, at each time point. We performed descriptive analysis of all data. We (D.M.L., S.S., K.B.J., or R.L.R.) collected PROMIS scores longitudinally and summarized them at each time point to evaluate average change in score across each period. We used statistical software (SAS 9.4; SAS Institute, Cary, NC).

RESULTS

We collected basic demographic, disease, and surgical data in 43 records in 13 patients at 9 possible time points: baseline (preoperative); 1, 2, 4, 6, and 10 weeks; and 3, 5, and 6 months. A total of 61.5% of patients were female; 92.3% of patients were not Hispanic or Latino. Regarding site of surgery, 1 patient (7.7%) had impending acetabular fracture; 9 patients (69.2%) had impending femur fracture; 1 patient (7.7%) had impending femur and acetabular fracture; and 2 patients (15.4%) had realized acetabular fracture, impending femur fracture. Regarding preoperative pain, 1 patient (7.7%) had mild pain, 6 patients (46.2%) had functional pain, and 6 patients (46.2%) had severe pain even at rest. Regarding type of malignancy, 5 patients (38.5%) had breast cancer, 1 patient (7.7%) had melanoma, 3 patients (23.1%) had multiple myeloma, 3 patients (23.1%) had prostate cancer, and 1 patient (7.7%) had urachal carcinoma. Five patients (38.5%) had received prior radiation therapy to the area of planned surgery. Regarding type of surgery, 8 patients (61.6%) received treatment with an intramedullary nail, 1 patient (7.7%) received a plate-and-screw construct, and 4 patients (30.8%) underwent total hip arthroplasty. Regarding additional sites of metastases, 7 patients (53.8%) had a bone site, 2 patients (15.3%) had a visceral site, 1 patient (7.7%) had both sites, and 3 patients (23.1%) had none.

The average physical function score was 29.3 (SD, 9.4; median, 27.2) at baseline,

28.8 (SD, 11.6; median, 25.3) at week 1, 32.6 (SD, 13.9; median, 32.5) after 2 weeks, 40.8 (SD, 20.2; median, 33.5) after 4 weeks, 42.8 (SD, 10.4; median, 38.2) after 6 weeks, 45.8 (SD, 1.5; median, 45.8) after 10 weeks, 45.7 (SD, 8.5; median, 47.6) after 3 months, 36 (only 1 patient) after 5 months, and 35.4 (only 1 patient) after 6 months. The average change in physical function score from baseline was −2.5 (SD, 5.4; median, −1.5) at week 1, 1.7 (SD, 7.6; median, 0.7) after 2 weeks, 6.9 (SD, 10; median, 6.9) after 4 weeks, 6.4 (SD, 10.9; median, 4.1) after 6 weeks, 15.3 (SD, 3.1; median, 15.3) after 10 weeks, 8.6 (SD, 7.6; median, 8.6) after 3 months, 6.7 (1 patient) after 5 months, and 6.1 (1 patient) after 6 months (Figure 1). Although we observed a trend comparing patients' pre- and postoperative PROMIS scores, none of these data reached statistical significance at a level of $P < .05$.

The average pain inference score was 65 (SD, 7.6; median, 69.1) at baseline, 61 (SD, 11.8; median, 62.7) at week 1, 62.5 (SD, 11.4; median, 59.7) after 2 weeks, 54.7 (SD, 15; median, 59.7) after 4 weeks, 53.5 (SD, 10.3; median, 57.9) after 6 weeks, 51.5 (SD, 2.8; median, 51.5) after 10 weeks, 48.6 (SD, 3; median, 48.1) after 3 months, 56.1 (1 patient) after 5 months, and 37.9 (1 patient) after 6 months. The average change in pain inference score from baseline was −1.2 (SD, 7.3; median, −1.4) at week 1, −2.1 (SD, 9.5; median, −4.2) after 2 weeks, −12.6 (SD, 4.5; median, −12.6) after 4 weeks, −8.3 (SD, 10.2; median, −11.2) after 6 weeks, −16.6 (SD, 4.3; median, −16.6) after 10 weeks, and −11.4 (SD, 8.2; median, −11.4) after 3 months (Figure 2). Although we observed a trend comparing patients' pre- and postoperative PROMIS scores, none of these data reached statistical significance at a level of $P < .05$.

DISCUSSION

In our study, we demonstrated the early enrollment results of PROMIS physical function and pain interference scores in patients with MBD. We observed trends in decreasing pain scores and improving
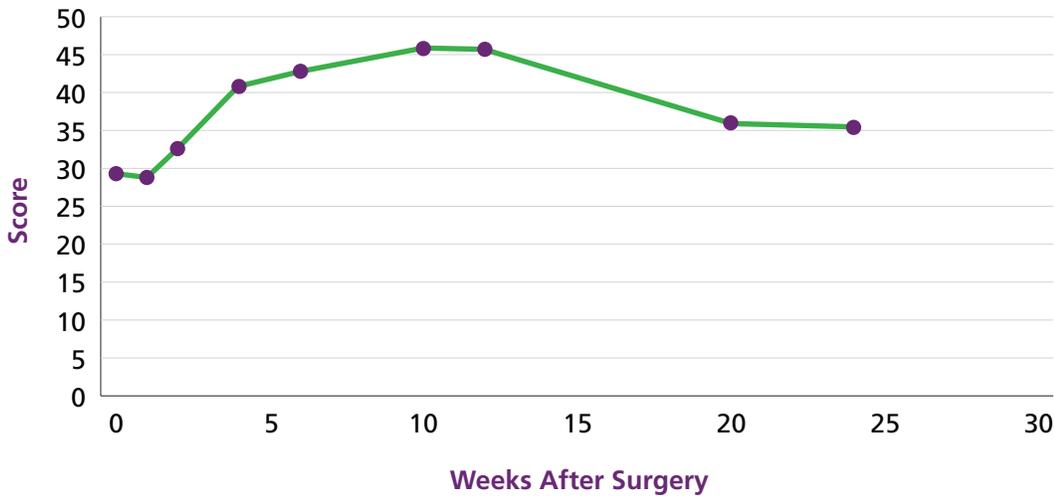
Figure 1. Change in Patient-Reported Outcomes Measurement Information System Physical Function Score by Postoperative Week. Positive changes indicate improving patient function.
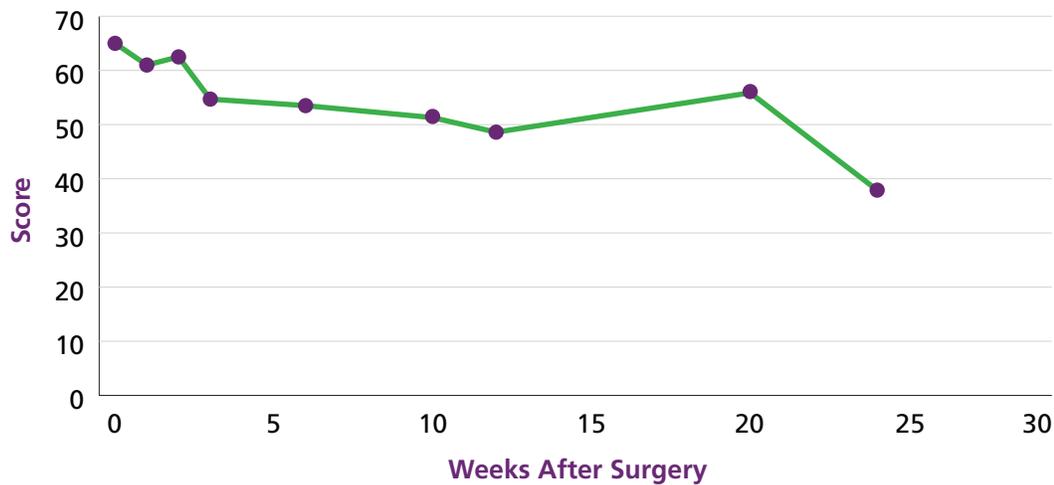

Figure 2. Change in Patient-Reported Outcomes Measurement Information System Pain Score by Postoperative Week. Negative changes indicate decreasing pain levels.

functional scores. The early results indicate proof of concept that performing a prospective, multicenter study in this setting is feasible. Results in the literature have demonstrated the usefulness of treating metastatic skeletal lesions surgically.[7-11] However, perhaps the most difficult outcomes to assess in this patient population are postoperative pain and functional outcomes. Study investigators have focused on oncology-related outcomes and physical assessment tools such as the Musculoskeletal Tumor Society score and Toronto

Extremity Salvage Score.[12-16] Although these tools are an improvement, physician bias and length of survey are inherent flaws in these systems. Few would argue that collecting validated, reliable accurate data for patients with cancer is crucial to assessing patient outcomes accurately.[21]

The basic patient demographic data showed a slight majority of female patients at 61.5%, and most of the enrolled patients were not Hispanic or Latino. These findings are likely because more than 90%

of the enrolled patients were from a single center in which the geographic location had a larger percentage of patients who were not Hispanic or Latino. In regard to the disease-related data, the most common diagnosis was metastatic breast cancer (38.5%), which helps to explain that 61.5% of patients were female. A majority of cases involved an impending metastatic femur fracture (61.5%), which agrees with the data showing our most commonly performed surgery was placement of an intramedullary nail (53.8%).

The data demonstrated a trend in improvement in physical function after surgery for MBD. The average change in score from baseline (presurgical) to 10 weeks postoperatively was 15.3. The patients' baseline average physical function score of 29.3 was more than 2 SDs below global averages for the general US population, emphasizing the severity of disease in this patient population.[22] In this data set, positive changes indicate improving function. However, because of the small sample size and relatively large SD, statistical significance was not reached.

The data also demonstrated a trend in improvement in pain scores after surgery for MBD. The patients' baseline average pain score of 65 was more than 1 SD above the global average for the US population, emphasizing the severity of disease in this patient population.[22] The average change in score from baseline (presurgical) to 10 weeks postoperatively was −16.6. For this data set, negative changes indicate decreasing pain levels. However, because

of the small sample size and relatively large SD, statistical significance was not reached in this category as well.

Limitations to this study include the small sample size because of relatively early patient enrollment in this multicenter, prospective study. We are continuing to enroll institutions to contribute to this data set and hope to have 5 medical centers involved by the end of 2018. Other limitations include the data collection means. Our primary enrollment site has an actively involved research coordinator to contact patients for data collection; however, patient availability, willingness to complete scores, and loss to follow-up or death may interfere with obtaining full data sets.

CONCLUSION

Patients with MBD are a unique population, and physicians should use appropriate measurement tools to assess their postoperative outcomes. Physicians have used a number of different systems

in the past to record postoperative pain and function in this group, yet the ideal system has not yet been elucidated. We believe that PROMIS offers an effective option for determining postoperative pain and functional outcomes in these patients. Our pilot data show proof of concept that collecting these data in this cohort is feasible. We observed trends of improving physical function and decreasing pain levels after surgery. As we continue to enroll more centers and patients into this prospective study, we expect to reach a level of statistical significance. Physicians have validated and used PROMIS measures with success in many surgical and oncologic fields. We believe that PROMIS will be equally effective in patients with MBD, as well as in those with other orthopedic cancers. ✣

Continued from page 2

- **Brian J. Cole, MD, MBA,** is the second vice president of the Arthroscopy Association of North America, a position he earned after many years of productive service to this organization and as a result of his contributions in the area of cartilage restoration, biologics, and soft tissue healing. He is the first Rush physician to serve as president of this association.

- **Susan Chubinskaya, PhD,** the Klaus Kuettner Professor of Arthritis Research and vice-chair, research and faculty development; and professor in the departments of pediatrics, orthopedic surgery, and medicine, is in the presidential line for the ORS. She follows in the recent footsteps of adjunct faculty member **D. Rick Sumner, PhD,** the Mary Lou Bell McGrew Presidential Professor for Medical Research and chairperson, Department of Cell & Molecular Medicine, who is the immediate past-president.

- **Finally, I am proud** to serve as first vice president of the Hip Society, an organization that consists of the leading hip surgeons in North America, following **Wayne Paprosky, MD,** and the late **Jorge Galante** as Rush physicians who have led this esteemed society.

These honors reflect the national and international prominence of our faculty, who are considered authoritative sources of knowledge and skill within their specialties. In turn, when our faculty serve in leadership roles in these organizations, it keeps Rush on the cutting edge of orthopedic care: We are able to leverage the latest advances in technology and patient management advances to improve our patients' lives, which is of course our most important charge as physicians.

It is my privilege to lead a group so rich in both talent and passion, though I take credit only for supporting—or, rather, not

getting in the way of—their pursuit of excellence. In the pages that follow, you will see some of the ways our faculty are leading by example: in the clinic, in the lab, in developing countries, on the playing field, in lecture halls, in the halls of Rush, and, most important, in the hearts and minds of those they inspire.
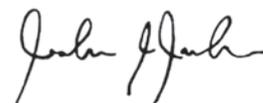
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Chairman, Department of Orthopedic Surgery

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