Surgery Research Conference

2017-2018 Surgery Research Residents Update

June 13, 2018

Research Highlights

2018 MCWAH Research and Quality Award Winners

Nicholas G. Berger, MD

Overall survival after resection of retroperitoneal sarcoma at academic cancer centers versus community cancer centers: An analysis of the National Cancer Data Base

12th Annual Academic Surgical Congress & Surgery

Joseph Helm, MD

Perioperative Blood Transfusions Increase Risk of Surgical Site Infection Development in Ventral Hernia Repairs

International Hernia Congress - America's Hernia Society

American Association for the Surgery of Trauma

77th Annual Meeting 2018
9/26/18-9/29/18

Abstract Acceptance Notice

Congratulations to:

Savo Bou Zein Eddine, MD
Kelly Boyle, MD
Pam Walsh
Amber Brandolino

MEDICAL COLLEGE OF WISCONSIN

DIVISION OF RESEARCH SURGERY

Manpreet Bedi, MD
awarded the
Sharon K. Wadina Chair
in
Sarcoma Research

Christopher S. Davis, MD, MPH

Christopher S. Davis, MD, MPH
Assistant Professor
Division of Trauma and Acute Care Surgery

Recipient of the 2018

Milwaukee Academy of Medicine Award
for
Excellence in Teaching

This award is given by the Academy and graduating MCW seniors to a physician who distinguishes themselves through exemplary teaching and serves as a role model.

Funding Announcements

Contributions of epithelial-mesenchymal transition (EMT) to promote the metastasis of estrogen receptor-positive breast cancer

Qing Miao, PhD
MCW Cancer Center &
WI Breast Cancer Showhouse

Evaluation of Rectal Cancer Response to Neoadjuvant Chemoradiation by 7T MRI

Timothy Ridolfi, MD
MCW Digestive Disease Center

Publications

Pediatric Surgery

"National Practice Patterns for Prenatal Monitoring in Gastroschisis: Gastroschisis Outcomes of Delivery (GOOD) Provider Survey.."
Fetal Diagnosis & Therapy
(**Amin R, Domack A, Bartoletti J**, Peterson E, Rink B, **Bruggink J, Christensen M**, Johnson A, Polzin W, **Wagner AJ**)

"Delivery of small interfering RNA against Nogo-B receptor via tumor-acidity responsive nanoparticles for tumor vessel normalization and metastasis suppression."
*Biomaterials (*Wang B, Ding Y, Zhao X, Han X, Yang N, Zhang Y, Zhao Y, Zhao X, Taleb M, **Miao QR**, Nie G)

Factors Known to Influence the Development of Necrotizing Enterocolitis to Modify Expression and Activity of Intestinal Alkaline Phosphatase in a Newborn Neonatal Rat Model.
European Journal of Pediatric Surgery
(Rentea RM, Rentea MJ, Biesterveld B, Liedel JL, **Gourlay DM**)

General Surgery

"Perioperative bleeding and blood transfusion are major risk factors for venous thromboembolism following bariatric surgery." Surgical Endoscopy
(Nielsen AW, Helm MC, Kindel T, Higgins R, Lak K, Helmen ZM, Gould JC)

Research

"Co-occurrence of a maternally inherited DNMT3A duplication and a paternally inherited pathogenic variant in EZH2 in a child with growth retardation and severe short stature: atypical Weaver syndrome or evidence of a DNMT3A dosage effect?"
Cold Spring Harbor Molecular Case Studies (Polonis K, Blackburn PR, **Urrutia R, Lomberk GA**, Kruisselbrink T, Cousin MA, Boczek NJ, Hoppman NL, Babovic-Vuksanovic D, Klee EW, Pichurin PN)

"Distinct epigenetic landscapes underlie the pathobiology of pancreatic cancer subtypes." *Nature Communications* (**Lomberk G,** Blum Y, Nicolle R, Nair A, Gaonkar KS, Marisa L, Mathison A, Sun Z, Yan H, Elarouci N, Armenoult L, Ayadi M, Ordog T, Lee JH, Oliver G, Klee E, Moutardier V, Gayet O,Bian B, Duconseil P, Gilabert M, Bigonnet M, Garcia S, Turrini O, Delpero JR, Giovannini M , Grandval P, Gasmi M, Veronique S ,De Reyniès A,Dusetti N, Iovanna J, **Urrutia R.)**

Transplant & Cardiothoracic Surgery

"Central ECMO for circulatory failure following pediatric liver transplantation." *Perfusion*
(Scott JP, **Hong JC**, Thompson NE, **Woods RK**, Hoffman GM)

Transplant Surgery

Donating Another Person's Kidney: Avoiding the Discard of Organs by Retransplantation.
Transplantation
(Veale J, Lum EL, Cowan NG, **Wong M**, Skovira K, Armijo M, Danovitch G, Mone T)

Publications

May

Cardiothoracic Surgery
"Long-term Results of Stereotactic Body Radiation Therapy in Medically Inoperable Stage I Non-Small Cell Lung Cancer." *JAMA Oncology*
(Timmerman RD, Hu CM, Michalski JM, Bradley JC, Galvin J**, Johnstone DW**, Choy H)

"Dissolution is not the solution."
Journal of Thoracic & Cardiovascular Surgery
(Hossein, AG)

Pediatric Congenital Cardiac Surgery
"Validation of a definition of excessive postoperative bleeding in infants undergoing cardiac surgery with cardiopulmonary bypass."
Journal of Thoracic & Cardiovascular Surgery
(Bercovitz RS, Shewmake AC, Newman DK, Niebler RA, Scott JP, Stuth E, Simpson PM, Yan K**, Woods RK**)

"Multiple mechanical support modalities and cardiac transplantation in a young child with corrected transposition." *Journal of Thoracic & Cardiovascular Surgery*
(Woods RK, Neibler RA, Kindel SJ, Mitchell ME, Hraska V, Tweddell JS)

Vascular Surgery
"Explanting the Nellix Endovascular Aortic Sealing Endoprosthesis for Proximal Aortic Neck Failure."
Annals of Vascular Surgery
(**Lee, CJ** and Cuff, R)

Surgical Oncology
"Gallbladder carcinoma: An analysis of the national cancer data base to examine Hispanic influence."
Journal of Surgical Oncology (**Liu C, Berger NG**, Rein L, Tarima S, **Clarke C, Mogal H, Christians KK, Tsai S, Gamblin TC**)

"Locally advanced pancreas cancer: Staging and goals of therapy." *Surgery*
(Chatzizacharias NA, Tsai S, Griffin M, Tolat P, Ritch P, George B**, Barnes CA, Idakkak M,** Khan AH, Hall W, Erickson B, Evans DB, Christians KK)

"The effect of prior upper abdominal surgery on outcomes after liver transplantation for hepatocellular carcinoma: An analysis of the database of the organ procurement transplant network." *Surgery*
(Silva JP, Berger NG, Yin Z, Liu Y, **Tsai S, Christians KK, Clarke CN, Mogal H, Gamblin TC)**

"Antiproliferative and apoptotic effect of LY2090314, a GSK-3 inhibitor, in neuroblastoma in vitro."
BMC Cancer (**Kunnimalaiyaan S, Schwartz VK, Jackson IA, Clark Gamblin T, & Kunnimalaiyaan M**)

"The Word on Medicine: where Knowledge is changing life"

Lyme Disease   June 23rd, 2018 at 5:00pm

Infectious disease experts and patients discuss the diagnosis and treatment of Lyme Disease. The show will also feature the stories of two grateful patients who were willing to share their stories.

Dr. John Fangman
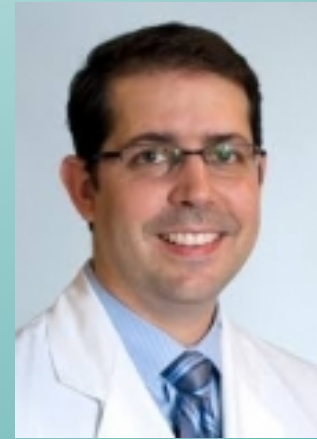Dr. Joyce Sanchez
Dr. Michael Kron
Jenifer Coburn, PhD

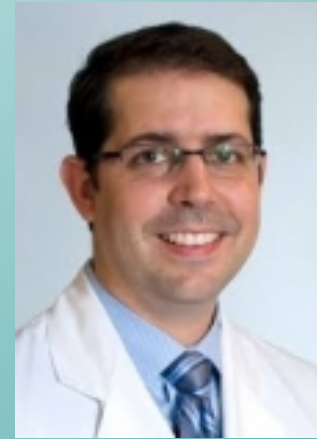*Next Month:*

Trauma Surgery Research Update

Terri A. deRoon Cassini, PhD

Marc Anthony De Moya, MD

Wednesday, July 11
5:00-6:00 pm
Location: Cancer Center Conference Room M

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SURGERY**

Trauma Surgery Research Update

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Location: Cancer Center Conference Room M

Surgery Research Conference

Division of Trauma and Acute Care Surgery, Medical College of Wisconsin

Kelly A. Boyle MD

Marc A. De Moya MD

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Vascular and Trauma Surgical Specialists Have Equivalent Outcomes with Management of Traumatic Peripheral Vascular Injuries

Division of Trauma and Acute Care Surgery, Medical College of Wisconsin

Kelly A. Boyle MD, Savo Bou Zein Eddine MD, Thomas W. Carver MD, David J. Milia MD, Jeremy S. Juern MD, Rachel S. Morris MD, Lewis B. Somberg MD, Jacob R. Peschman MD, Terri deRoon-Cassini PhD, Marc A. De Moya MD

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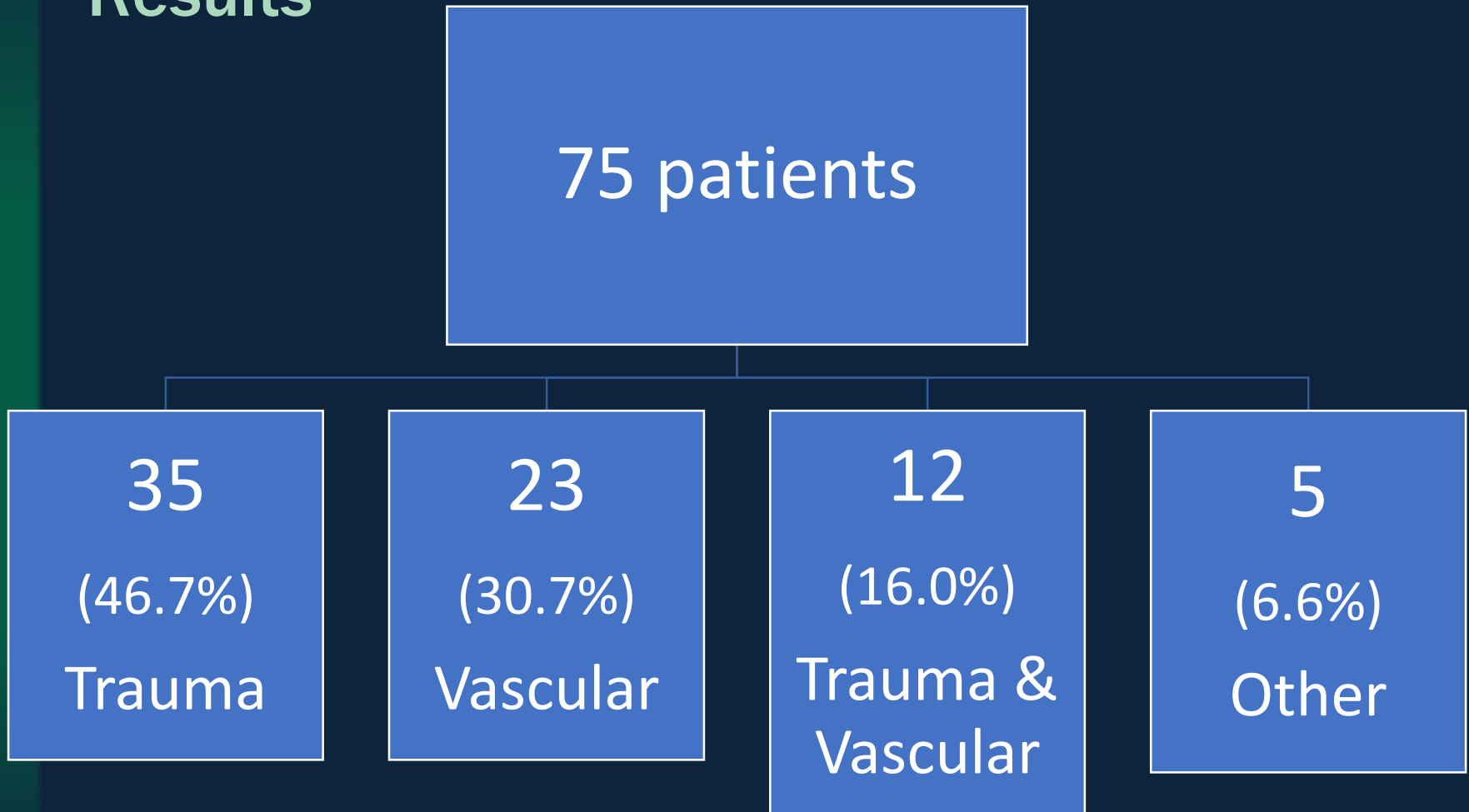knowledge changing life

Introduction

- Incidence of extremity vascular injury ~1-2%
- Significant morbidity and mortality
- Managed by several surgical specialties
- Shackford *et al,* 2013
  - No difference in limb salvage or graft patency
  - 69.9% general surgeons, 30.1% subspecialty
- He *et al*, 2015
  - No difference in outcomes
  - 40% trauma surgeons, 37% vascular surgeons

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Hypothesis

In patients with extremity vascular trauma, there are equivalent surgical outcomes regardless of surgical specialty performing the vascular repair.

Results

```
            ┌─────────────────────────┐
            │       75 patients       │
            └─────────────────────────┘
   ┌────────────┬──────────────┬──────────────┐
┌──────┐   ┌──────┐       ┌──────────┐    ┌──────┐
│  35  │   │  23  │       │   12     │    │  5   │
│(46.7%)│  │(30.7%)│      │ (16.0%)  │    │(6.6%)│
│Trauma│   │Vascular│     │Trauma &  │    │Other │
└──────┘   └──────┘       │Vascular  │    └──────┘
                          └──────────┘
```

Results

	Popliteal Artery Included		
	Trauma Surgeon N = 35	**Vascular Surgeon N = 35**	**p-value**
Injury Type	**4 (11.4%) Blunt** 3 upper extremity 1 lower extremity **31 (88.6%) Penetrating** 5 upper extremity 26 lower extremity	**13 (37.1%) Blunt** 2 upper extremity 11 lower extremity **22 (62.9%) Penetrating** 6 upper extremity 16 lower extremity	0.003
Popliteal artery injury	0 (0%)	19 (54.3%)	<0.001

Results

Popliteal Artery Excluded			
	Trauma Surgeon N = 35	**Vascular Surgeon N = 16**	**p-value**
Injury type	4 (11.4%) Blunt 31 (88.6%) Penetrating	4 (25%) Blunt 12 (75%) Penetrating	NS
ISS <16 **ISS ≥ 16**	27 (77.1%) 8 (22.9%)	11 (68.8%) 5 (31.3%)	NS
Fasciotomy	14 (40.0%)	7 (43.8%)	NS
Time to OR **Median minutes**	21 (IQR 17 – 36)	69 (IQR 26 – 247)	0.026
OR duration **Median minutes**	231 (IQR 159 – 272)	251 (IQR 194 – 343)	NS

Results

Popliteal Artery Excluded			
	Trauma Surgeon N = 35	**Vascular Surgeon N = 16**	**p-value**
Type of repair	19 (51.4%) primary repair 8 (21.6%) PTFE 7 (18.9%) saphenous vein 1 (2.7%) bovine patch	6 (37.5%) primary repair 2 (12.5%) PTFE 8 (50%) saphenous vein	NS
Systemic heparin	20 (57.1%)	14 (87.5%)	0.033
Vascular re-intervention	In-hospital 1 (2.9%) 30 day 0 1 year 1 (2.9%)	In-hospital 1 (6.3%) 30 day 0 1 year 0	NS
Hospital LOS **Median minutes**	4 (IQR 2 – 7)	6.5 (IQR 3.25 – 14.75)	0.024
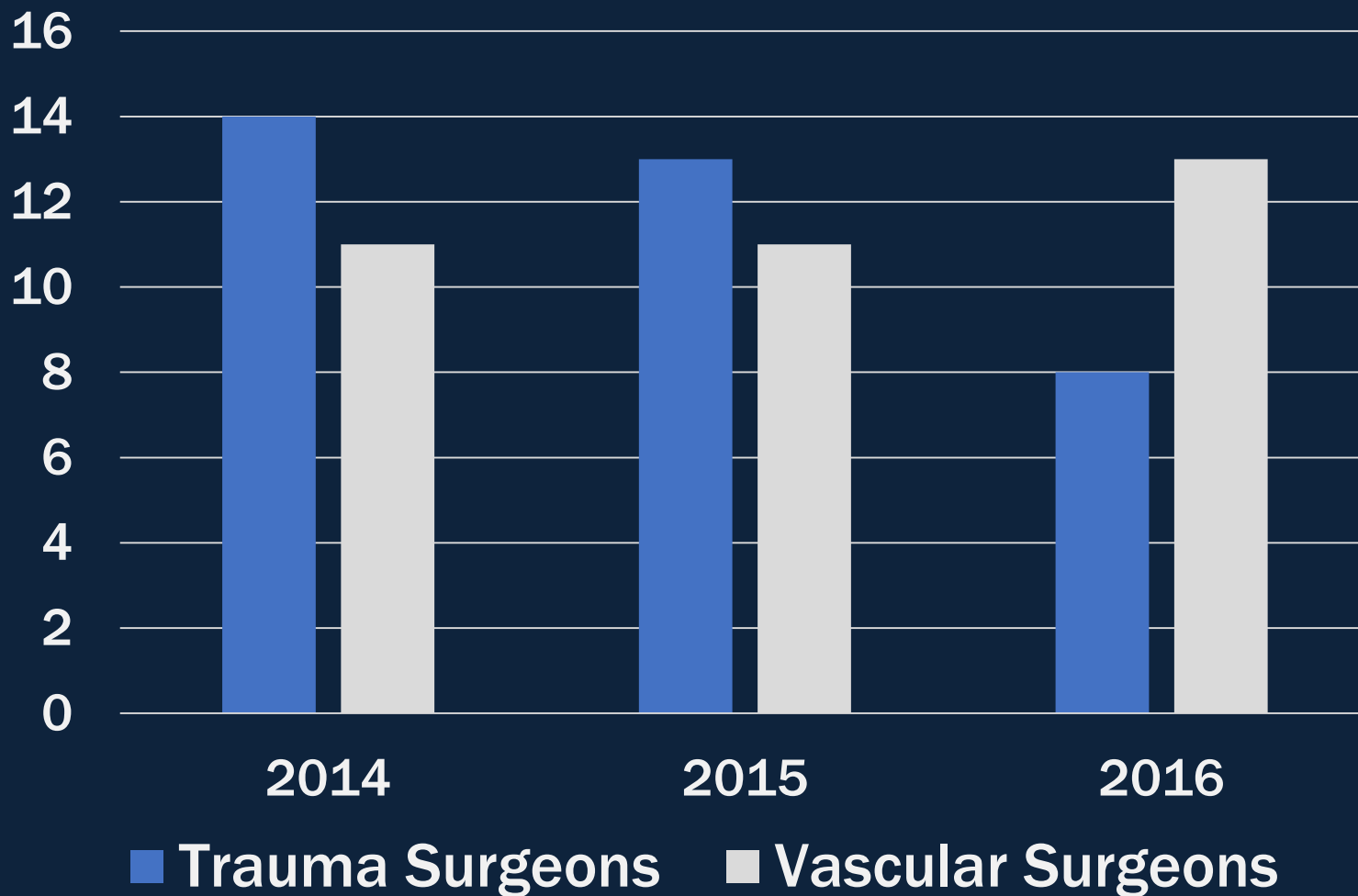
Conclusion

There are no significant clinical outcome differences between Trauma & Vascular surgical specialists for open peripheral vascular repairs.

Surgery Resident Skill Retention after Focused Assessment with Sonography in Trauma (FAST) Training

Division of Trauma and Acute Care Surgery, Medical College of Wisconsin

Kelly A. Boyle MD, Amber Brandolino BA, Philip N. Redlich MD, PhD, Michael J. Malinowski MD, Robert W. Treat PhD, Thomas W. Carver MD

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Methods

- PGY 1 & PGY 2 surgery residents
- Assessed Pre-/Post-training, 1 month, 3 months
- Survey
  - Previous experience, confidence, interim
- Written Assessment (21 questions – 2 versions)
  - US basics or image adjustment (7)
  - Image interpretation (10)
  - FAST specific questions (4)

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Methods

- Quality of Ultrasound Images and Competence (QUICk) score
    - Global Rating Scale (GRS)
    - Task Specific Checklist (TSC)

- Image review
    - Video recorded learner's performance (GRS)
    - Image clips saved of each FAST area (TSC)

- 2 reviewers scored performance retrospectively

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Results

- 19 surgery residents
  - 12 PGY 1
  - 7 PGY 2
- 36.8 % previous FAST training
- 100% completed 3 months
- No differences noted for year of training
- Previous FAST experience & confidence had no correlation with performance

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Total QUICk Score
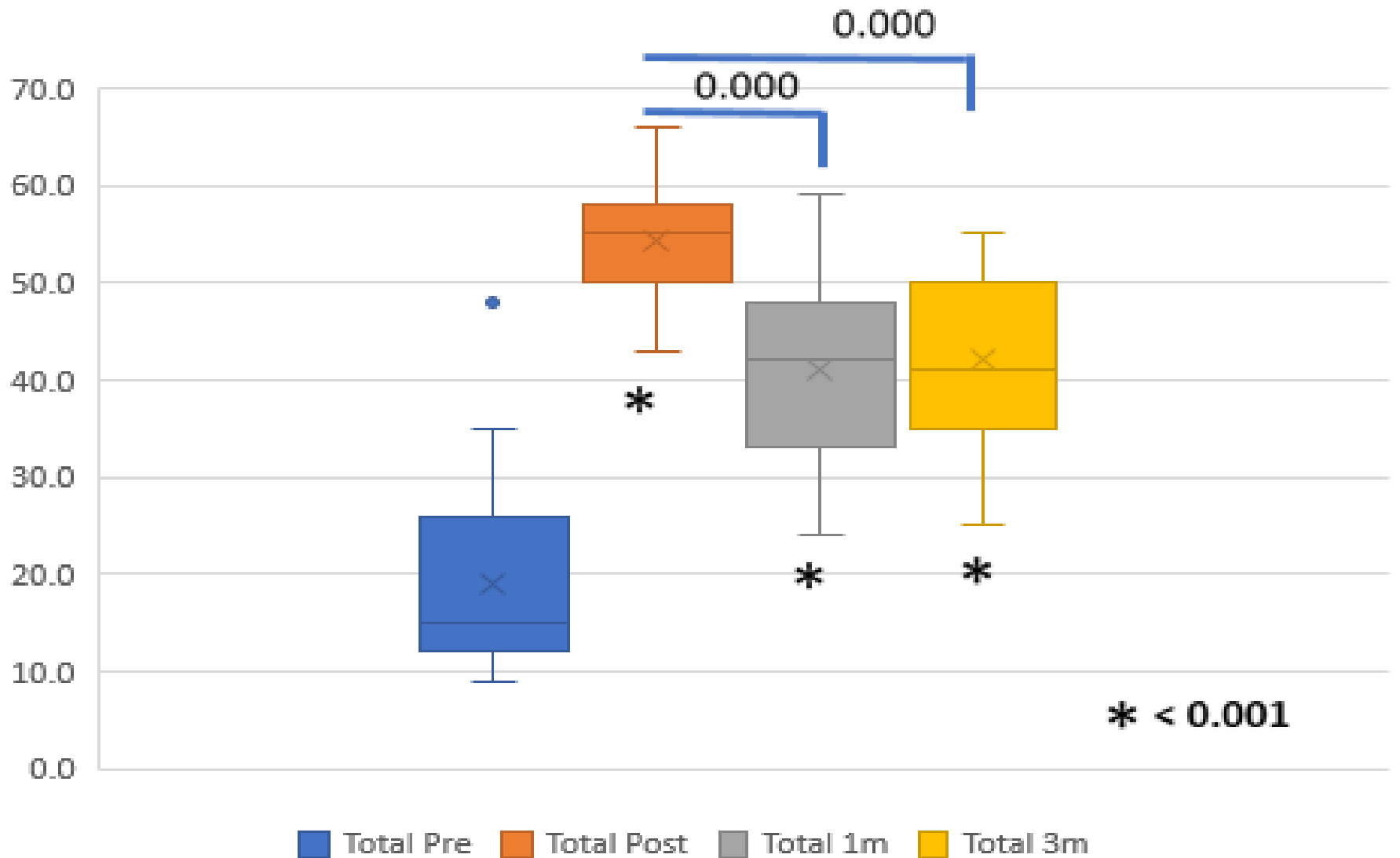
Conclusion

- At 1 month FAST performance declines (but stabilizes)
    - Knowledge decay is slower
- Massed training does not lead to long term retention

What is the best way to provide FAST education?

Stay Tuned...

- Thoracic Irrigation: AAST MIT
- Quality of Life after Rib Fractures: Ketamine RCT patients
- Vital Capacity as a Predictor of Outcomes in Rib Fracture Patients
- Haemonetics TEG Validation
- Penetrating Torso Trauma: Role of CT Scan
- Management of Zone 2 Retroperitoneal Penetrating Trauma
- Defining Clinically Significant Reduction in Oral Morphine Equivalents
- Redefining the Role of "The Box"
- Review of Spinal Cord Injury MAP Goals
- Trauma / ACS job hours: Structured National Interview

- Pigtail TT vs Large Bore TT RCT
- 35 mm Rule for Observing Pneumothoraces
- Percent Change from Pre-injury BP is an Independent Predictor of Mortality in Elderly Trauma Patients
- Predictors of Fasciotomy Post-Revascularization
- Review of the Management of Traumatic Bile Leaks
- Operation vs Observation for Anterior Abdominal Stab Wounds
- Tracheostomy Pressure Ulcers: Pre / Post Change in Management
- Wound Closure after Abdominal Trauma
- EAST MIT Appendicitis

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Thank You!

- ## Division of Trauma & Acute Care Surgery
- **Marc de Moya, MD**
- **Thomas Carver, MD**
- **David Milia, MD**
- **Rachel Morris, MD**
- **Terri deRoon-Cassini, PhD**
- **Colleen Trevino, MSN, FNP, PhD**
- **Pam Walsh**
- **Amber Brandolino**
- **Savo Bou Zein Eddine, MD**

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Resident Research Update

Surgery Research Conference

Lindsey N. Clark, MD

June 13, 2018

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Mentor: Dr. Jon Gould

Research Projects

- ➢ Readmission Timing
- ➢ Paraesophageal Hernia Repair Outcomes
- ➢ Postdischarge VTEs after Bariatric Surgery

Very Early vs. Early Readmissions in General and Vascular Surgery Patients

Very Early vs. Early Readmissions in General and Vascular Surgery Patients

- Readmissions
  - Quality metric
    - 2012 Hospital Readmission Reduction program
  - Hospital Rankings
  - FMLH: 72 hour interest

Hypothesis

Very early readmissions (0-3 days after discharge)
have a different cause than
early readmissions (4-30 days after discharge)

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METHODS

- NSQIP 2014-2015
  - Prior to discharge variables

- Stepwise logistic regression

- Multinomial Logistic Regression
  - Relative Odds-Ratio

$$\frac{\text{VERY EARLY}}{\text{NO READMISSION}} : \frac{\text{EARLY}}{\text{NO READMISSION}}$$

RESULTS
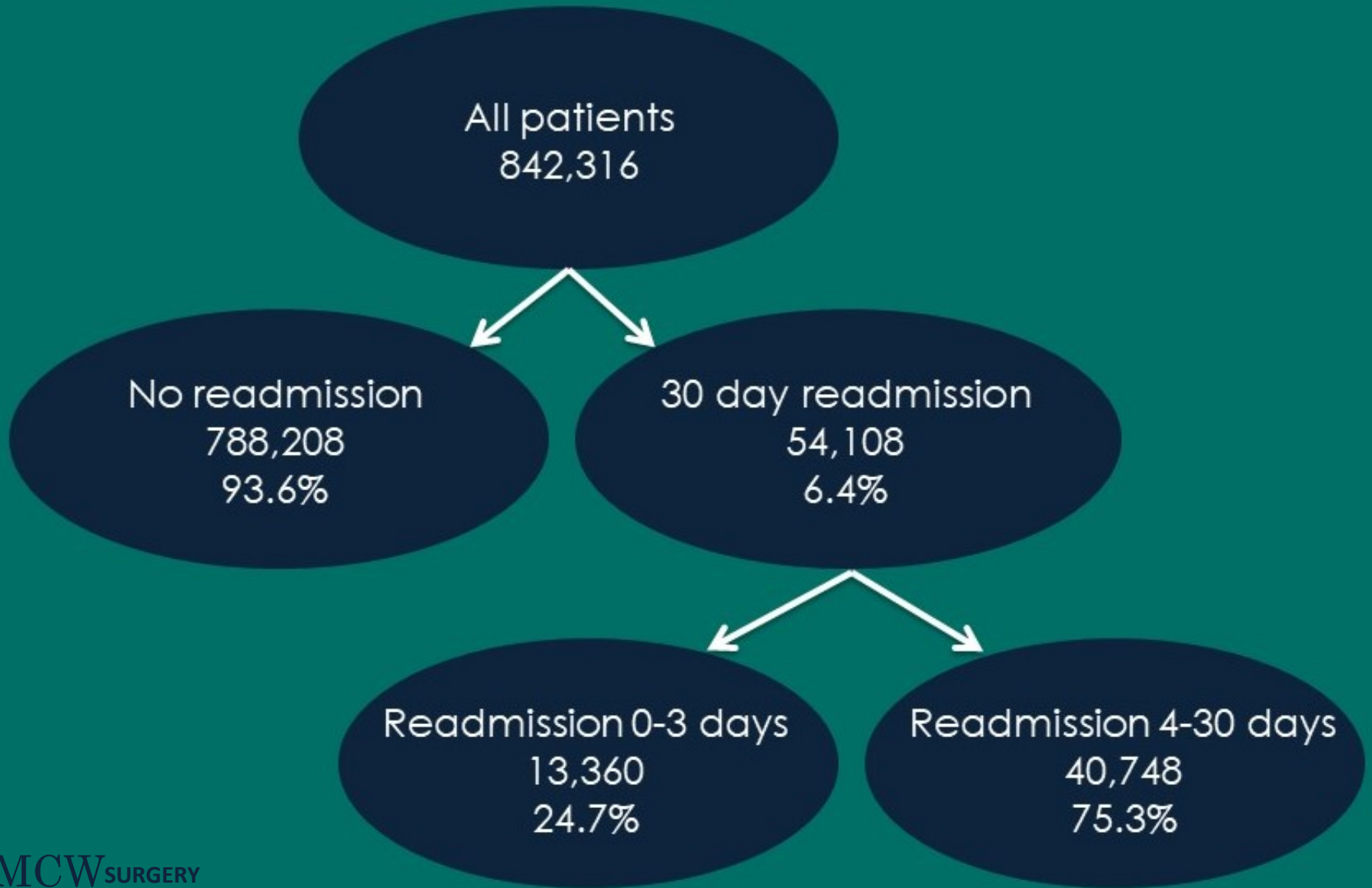
Number of readmissions by day
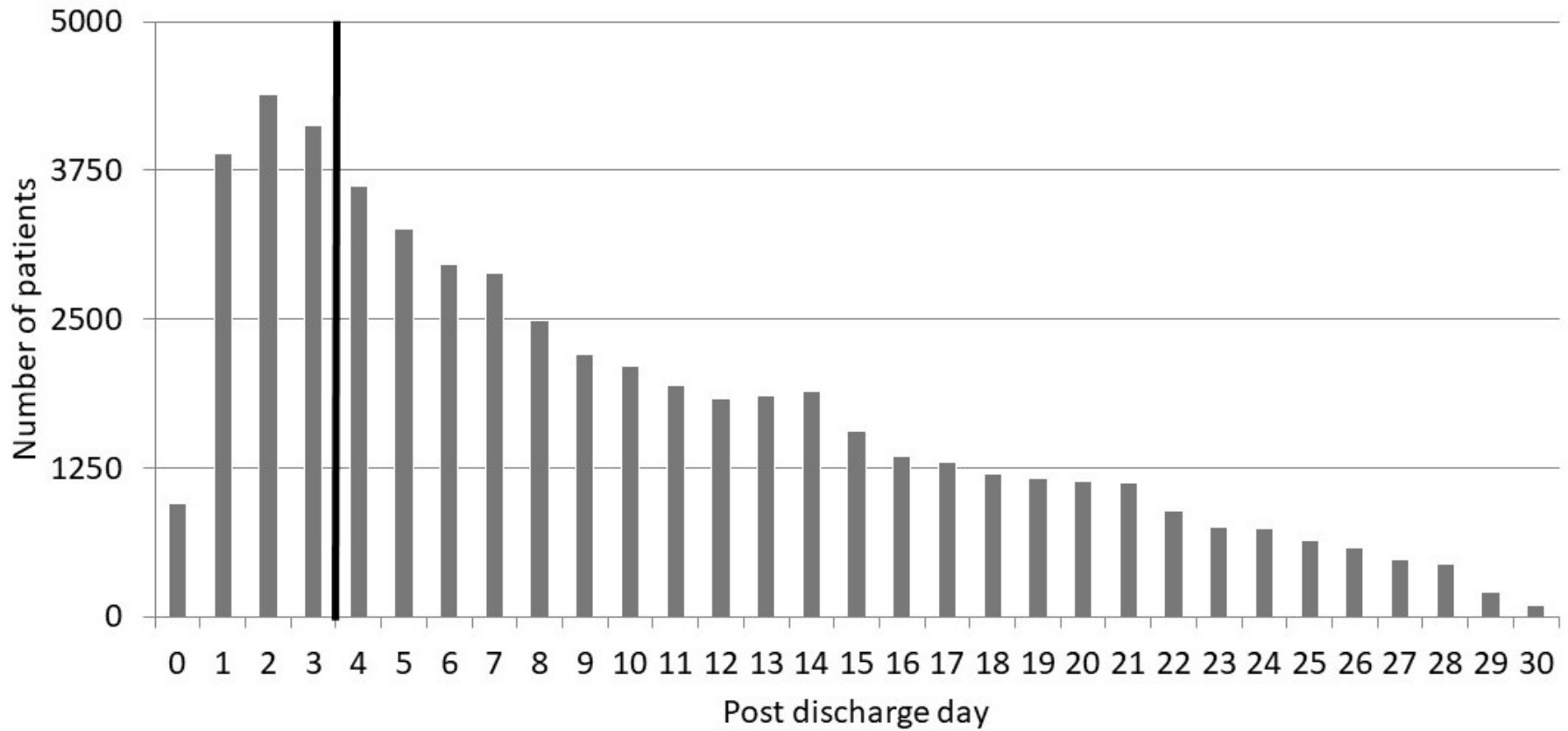
RESULTS – any 30 day readmission

ANY READMISSION	Odds Ratio (95% Confidence Interval)	*p*-value
Surgical Specialty (Vascular)	1.14 (1.10-1.17)	*<0.0001**
Sex (male)	1.02 (1.00-1.04)	0.1155
Comorbidities, 3 or more	1.49 (1.45-1.52)	*<0.0001**
Inpatient surgery	1.53 (1.48-1.58)	*<0.0001**
Operative time > 60 minutes	1.27 (1.24-1.30)	*<0.0001**
Postoperative Length of Stay: 3-7 days	1.81 (1.77-1.86)	*<0.0001**
Postoperative Length of Stay: 8-30 days	1.99 (1.93-2.06)	*<0.0001**
ASA 3-5	1.45 (1.42-1.49)	*<0.0001**
Wound Class 2- Clean Contaminated	1.15 (1.12-1.18)	*<0.0001**
Wound Class 3- Contaminated	1.18 (1.14-1.23)	*<0.0001**
Wound Class 4- Dirty/infected	1.19 (1.15-1.24)	*<0.0001**
Severe complication prior to discharge	0.98 (0.94-1.02)	0.2598

p<0.0001

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RESULTS – very early readmission

	Odds Ratio (95% Confidence Interval)	p-value
Sex (male)	1.128 (1.083-1.175)	<0.0001*
Comorbidities, 3 or more	0.905 (0.858-0.954)	0.0002*
Surgical Specialty - Vascular	0.764 (0.713-0.819)	<0.0001*
Operative time > 60 minutes	1.108 (1.051-1.168)	0.0001*
Postoperative Length of Stay: 3-7 days	0.845 (0.799-0.893)	<0.0001*
ASA 3-5	0.895 (0.851-0.941)	<0.0001*
Wound Class 2- Clean Contaminated	1.241 (1.173-1.313)	<0.0001*
Wound Class 3- Contaminated	1.271 (1.179-1.370)	<0.0001*
Severe Complication prior to Discharge	1.414 (1.299-1.540)	<0.0001*

*p<0.001

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Very Early vs. Early Readmissions in General and Vascular Surgery Patients

- Nearly 1 in 4 readmissions is within 3 days of discharge

- Serious complication during index admission is most significant risk factor for very early readmission
  - 40% increase risk

- Quality Improvement
  - Transition of Care
  - High Risk Patients

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The Impact of Preoperative Anemia and Malnutrition on Outcomes in Paraesophageal Hernia Repair

- ➢ Complications
  - ➢ Hypoalbuminemia
    - ➢ Diet modification → weight loss
  - ➢ Anemia
    - ➢ 9-15% incidence
    - ➢ Cameron lesions

- ➢ Impact in other surgeries
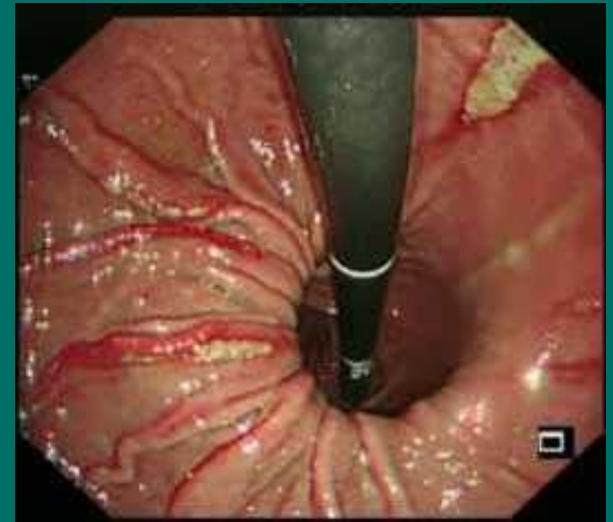
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The Impact of Preoperative Anemia and Malnutrition on Outcomes in Paraesophageal Hernia Repair

- ➢ NSQIP database 2011-2015
  - ➢ Laparoscopic
  - ➢ Open
  - ➢ Thoracic
  - ➢ Thoracoabdominal

- ➢ Anemia
  - ➢ Preoperative hematocrit
    - ➢ <36% females
    - ➢ <39% males
- ➢ Malnutrition
  - ➢ Preoperative albumin
    - ➢ < 3.5 g/dL

RESULTS

Anemia
➤ 13,139 patients
➤ 23.1% anemia

Malnutrition
➤ 7,943 patients
➤ 13.9% hypoalbuminemia

Both Anemia and Malnutrition
➤ 6,102 patients
➤ 4.5% both anemia and hypoalbuminemia

The Impact of Preoperative Anemia and Malnutrition on Outcomes in Paraesophageal Hernia Repair

Figure 1: Morbidity and mortality in setting of anemia
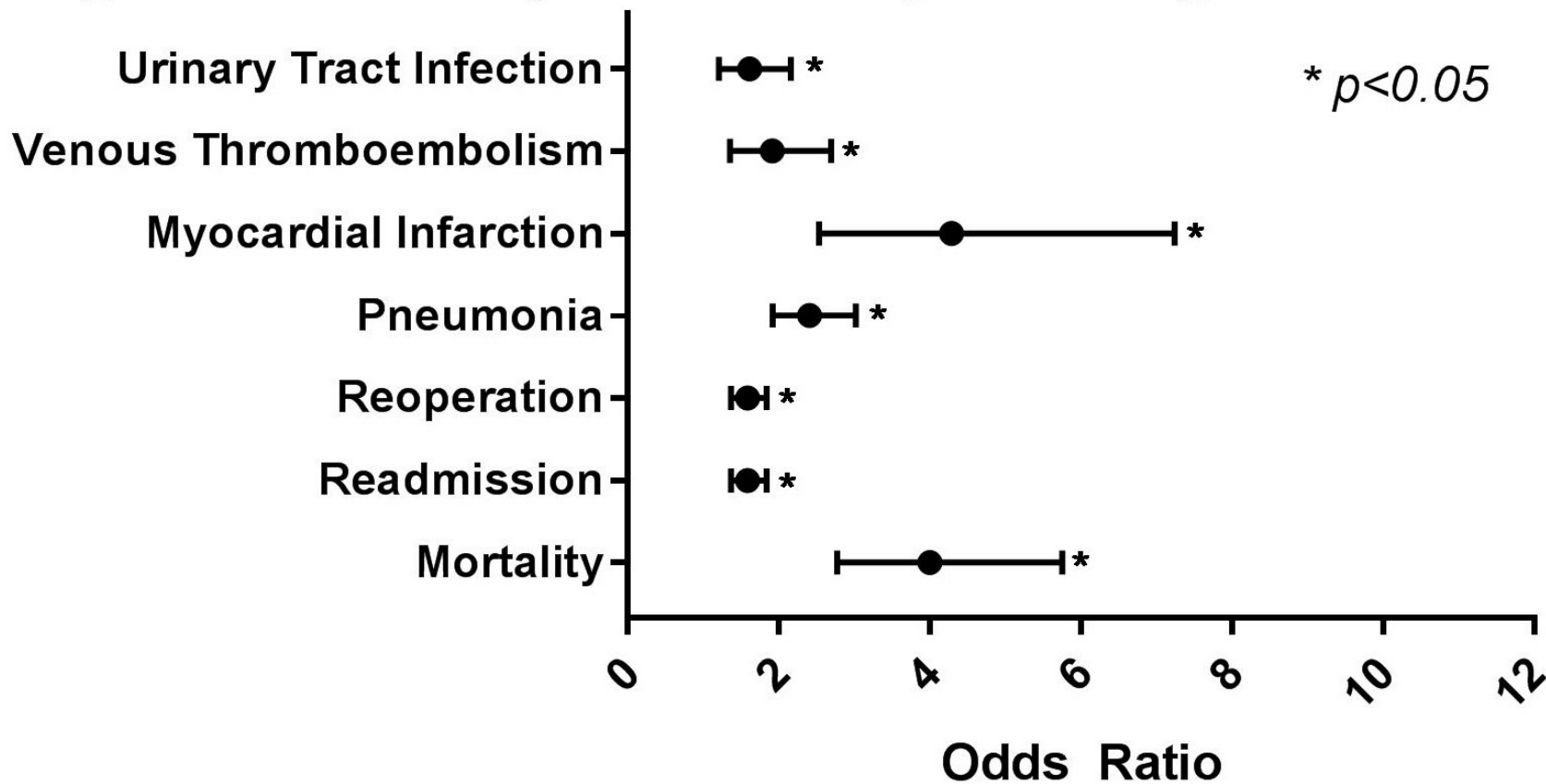
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The Impact of Preoperative Anemia and Malnutrition on Outcomes in Paraesophageal Hernia Repair

Figure 2: Morbidity and mortality in setting of malnutrition
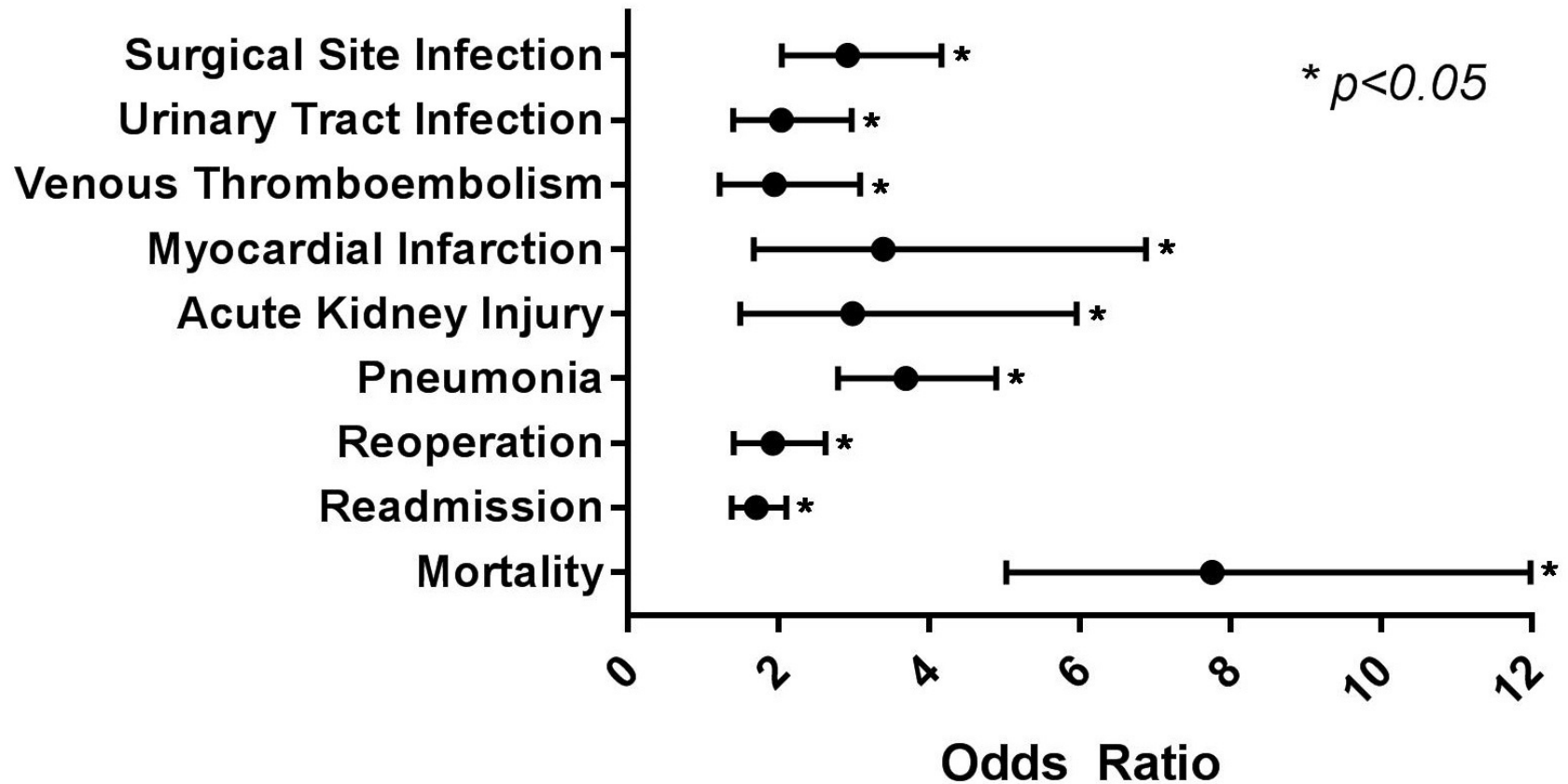
* p<0.05

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The Impact of Preoperative Anemia and Malnutrition on Outcomes in Paraesophageal Hernia Repair

Figure 3: Morbidity and mortality in setting of anemia and malnutrition
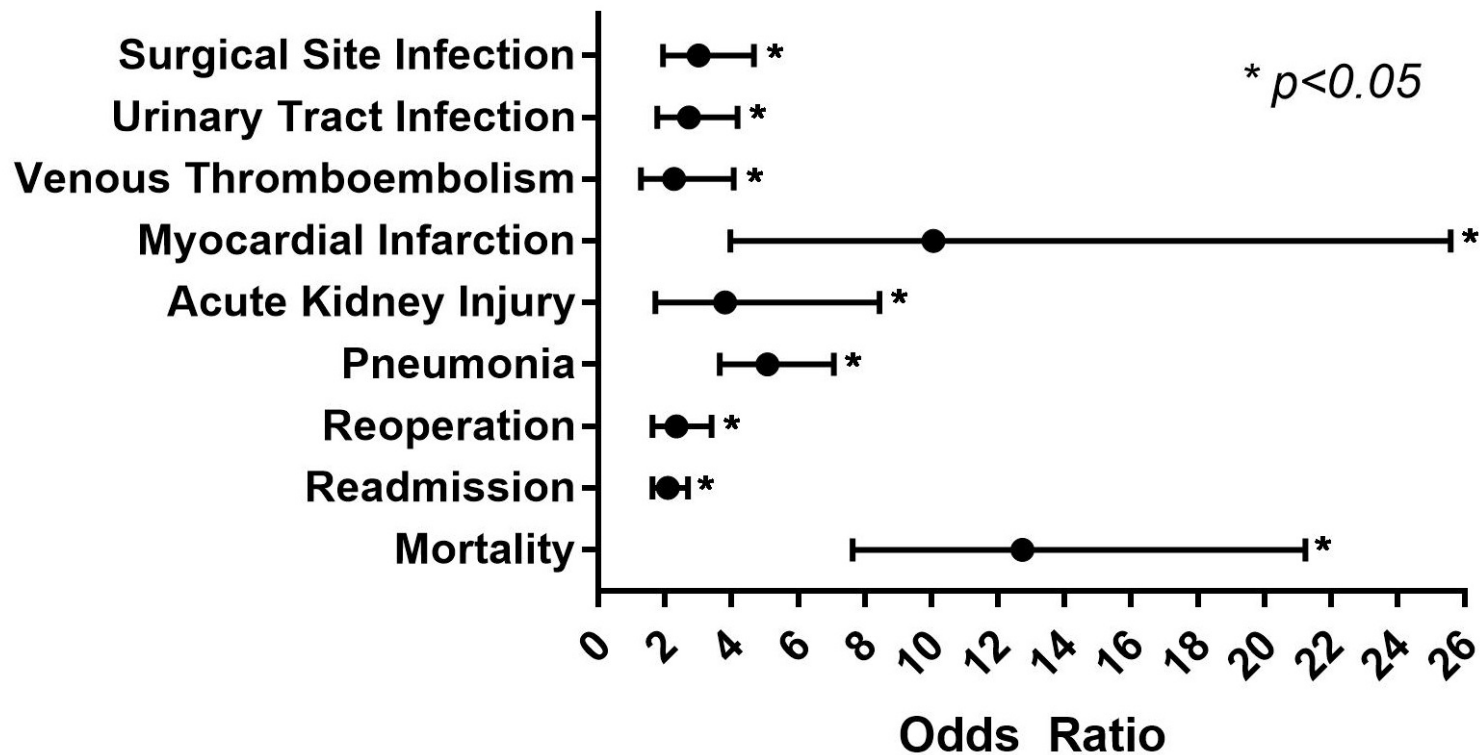
RESULTS

Postoperative Length of Stay

> Anemic: 4.1 days
> Not anemic: 2.8 days
> > *p*<0.0001

> Malnourished: 6.1 days
> Not malnourished: 3.1 days
> > *p*<0.0001

> Anemic and Malnourished: 6.7 days
> Neither: 3.0 days
> > *p*<0.0001

The Impact of Preoperative Anemia and Malnutrition on Outcomes in Paraesophageal Hernia Repair

- ➤ Anemia and hypoalbuminemia associated with increased morbidity, mortality, length of stay

- ➤ Target nutritional deficits to optimize patient outcomes

- ➤ Realistic expectations regarding risk of repair during preoperative education

Practice Patterns Regarding Extended Chemoprophylaxis for Venous Thromboembolism following Bariatric Surgery in the United States

Practice Patterns Regarding Extended Chemoprophylaxis for Venous Thromboembolism following Bariatric Surgery in the United States

- No consensus regarding optimal VTE prevention after bariatric surgery
- High risk patients
  - Extended chemoprophylaxis recommended
  - Little supporting data

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Practice Patterns Regarding Extended Chemoprophylaxis for Venous Thromboembolism following Bariatric Surgery in the United States

- Truven Health MarketScan Research database
  - Insurance database
  - Encounters
- Laparoscopic sleeve gastrectomy or Roux-En-Y gastric bypass
- 90 days postoperative

- Logistic regression
  - Impact of anticoagulation administration on VTE
- State variation

Practice Patterns Regarding Extended Chemoprophylaxis for Venous Thromboembolism following Bariatric Surgery in the United States

- N=104,421
- Outpatient chemoprophylaxis 11.3%
  - Enoxaparin 88%
- VTE after discharge 1.3%
  - Majority within one month
  - 29% within first week of discharge
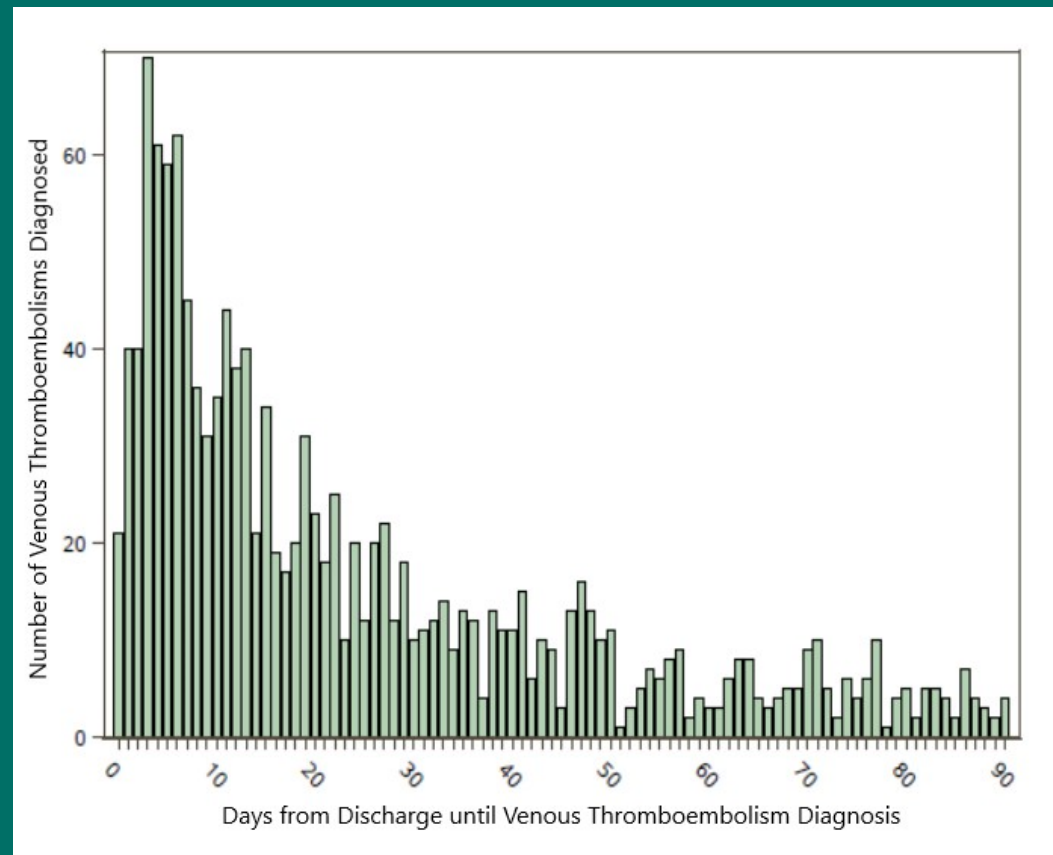
Practice Patterns Regarding Extended Chemoprophylaxis for Venous Thromboembolism following Bariatric Surgery in the United States

	Odds Ratio	95% Confidence Interval	p-value
Outpatient anticoagulation	2.05	1.80-2.34	<0.001*
IVC filter placement	15.61	7.62-32.01	<0.001*
Hypercoagulable disorder	13.64	11.26-16.53	<0.001*
Age ≥ 60	2.25	1.73-2.92	<0.001*
Female sex	0.76	0.68-0.86	<0.001*
Injectable anticoagulation during admission	0.69	0.43-1.08	0.107
Metabolic syndrome	1.05	0.77-1.42	0.770

*$p<0.05$

Practice Patterns Regarding Extended Chemoprophylaxis for Venous Thromboembolism following Bariatric Surgery in the United States

➤ Practice patterns by state
  ➤ Significant variability

➤ Outpatient chemoprophylaxis
  ➤ 0.49%-37.42%
➤ VTE rates
  ➤ 0.39%-2.46%

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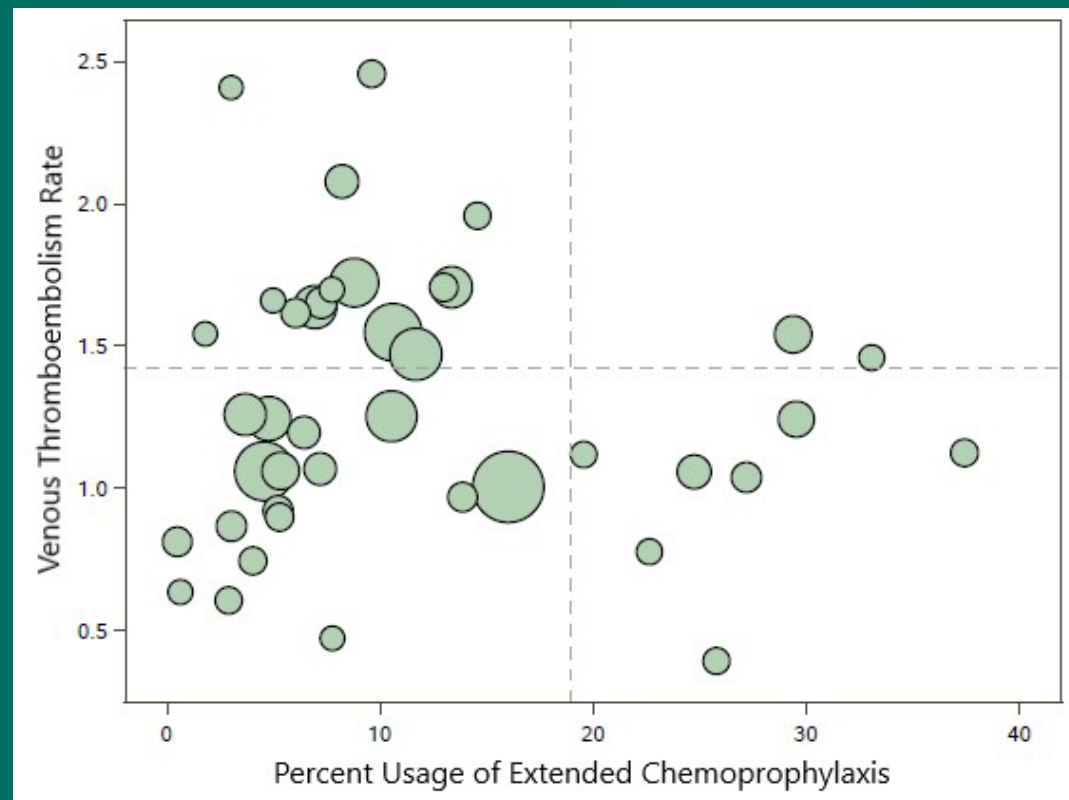
Thank you

- Dr. Gould
- Department of Surgery
- Quality Department
- Committee members
  - Quality Minute
  - Rothman Index
  - Discharge When Medically Ready
  - FMLH Safety & Adverse Events Committee
  - Accountable Care Teams

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Surgery Research Conference

Jacqueline Blank MD

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Research Projects, 2016-2018

- 7T MR imaging of rectal cancer
- Auricular Neurostimulation for Postoperative Pain Control
  - Froedtert Hospital & VAMC
- Young Patients with Rectal Cancer and Correlation with BMI
  - MARCH Consortium
  - SHOW Database
- IV Acetaminophen Meta-Analysis
- Induction Chemotherapy in Rectal Cancer
- 5HT in Low Anterior Resection Syndrome

- LifeBond
- Iatrogenic Aortic Graft Infections
- Spinal Cord Injury Unit research (VA)
- Medical student projects:
  - Rates of Postoperative Urinary Retention after Hyperbaric Spinal Anesthesia
  - Management of Horseshoe Abscesses
  - Predictors of Anal Condyloma Burden in HPV
  - Imaging Characteristics of Patients with Ulcerative Colitis
  - Rates of Hand-assisted Laparoscopic Surgery
  - Retroileal Routing of Colorectal Anastomoses
- Medical student teaching opportunities:
  - Clerkship Orientation
  - Suture Clinic
  - Professor Rounds

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Initial Experience with 7T MR Imaging of Rectal Cancer: A Promising Technology for Superior Staging

Jacqueline Blank MD,[1] Nicholas Berger MD,[1] Paul Knechtges MD,[2] Robert Prost PhD,[2] Carrie Peterson MD MS,[1] Kirk Ludwig MD,[1] Timothy Ridolfi MD[1]

1. Division of Colorectal Surgery, Medical College of Wisconsin
2. Department of Radiology, Medical College of Wisconsin

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Introduction

10-30% Complete Response - Observe

Stage II-III → **ChemoRT** → **7T MRI**

Surgery

$$\text{Signal} = \sqrt{\Delta T}$$

increase in spatial resolution:
152% over 3T
216% over 1.5T

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Methods

- Phase 1: 7T Imaging of excised rectal specimens
  - Feasibility
  - Identify ideal 7T sequences
  - Radiologist interpretation of T, N status compared to pathology

- Phase 2: Identify ideal 3T sequences for comparison to 7T MRI

- Phase 3: 7T MR imaging

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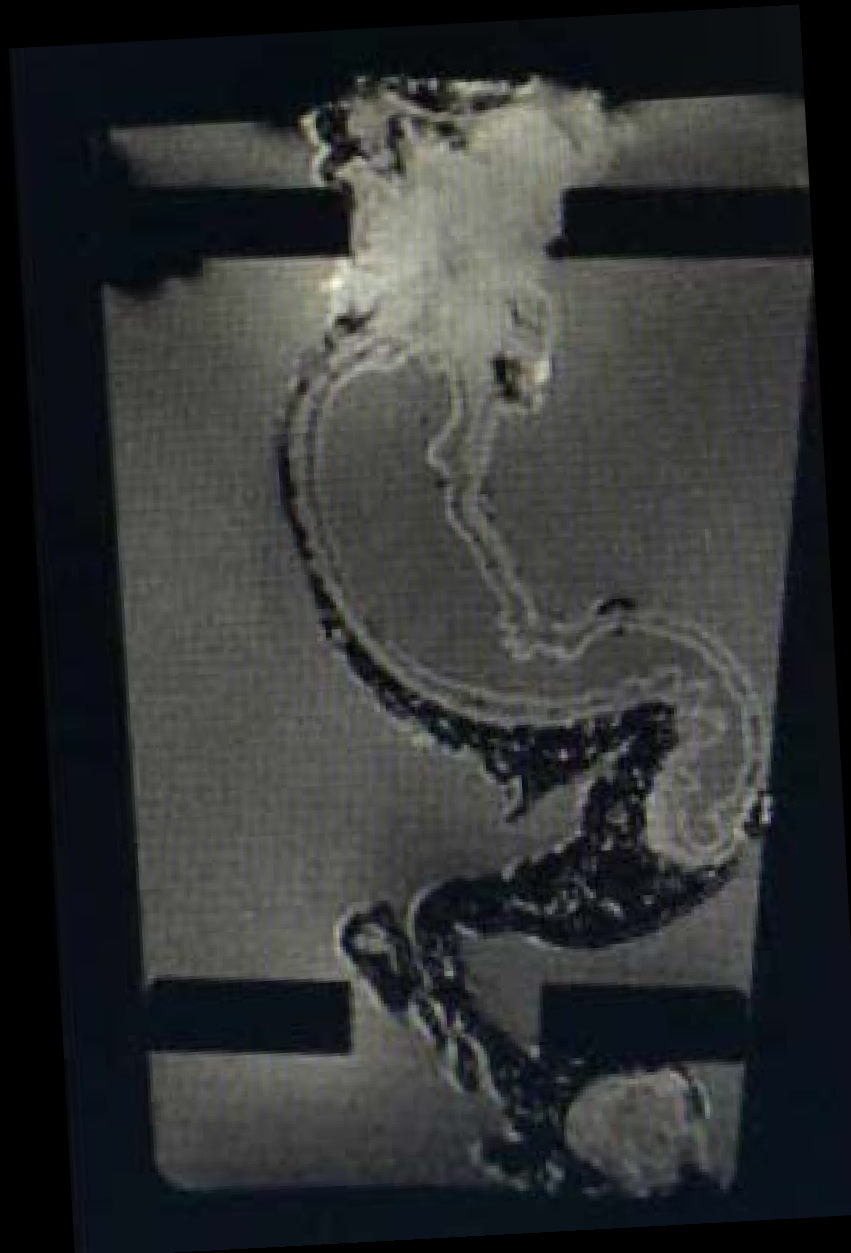
7T MRI

Conclusions

- Minimal discrepancy between 7T MRI radiologic interpretation and post-neoadjuvant chemoradiation pathologic interpretation

- 7T MRI holds promise in accurately staging post treatment rectal cancer and possibly predicting response to neoadjuvant therapy

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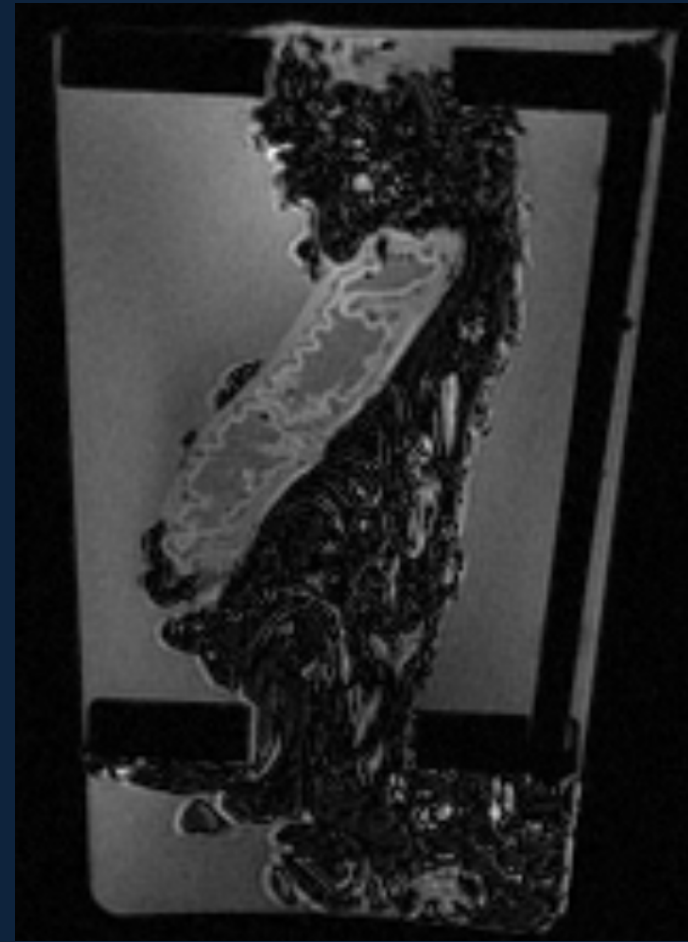
Auricular Neurostimulation for Non-Pharmacologic Post-Operative Pain Control: A Randomized Controlled Trial

Jacqueline J Blank MD,[1] Ying Liu PhD,[2] Ziyan Yin MS,[2] Christina M Spofford MD PhD,[3] Timothy J Ridolfi MD,[1] Kirk A Ludwig MD,[1] Mary F Otterson MD MS,[1] Carrie Y Peterson MD MS[1]

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Introduction

- Opioids are the cornerstone for postoperative pain control
  - Adverse effects:
    - Distension
    - Ileus
    - Constipation
    - Hallucinations
    - Nausea
    - Bladder dysfunction
    - Addictive potential
    - Decreased respiratory drive

- Up to 10% of previously opioid-naïve patients may become dependent on opioids after colorectal surgery

- The United States has seen an alarming increase in the illicit use of opioid medications
  - 2015: over 33,000 deaths due to opioid overdoses

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Introduction

Introduction

Introduction

1. Great auricular nerve
2. Lesser occipital nerve*
3. Auricular branch of vagus nerve
4. Auriculotemporal nerve
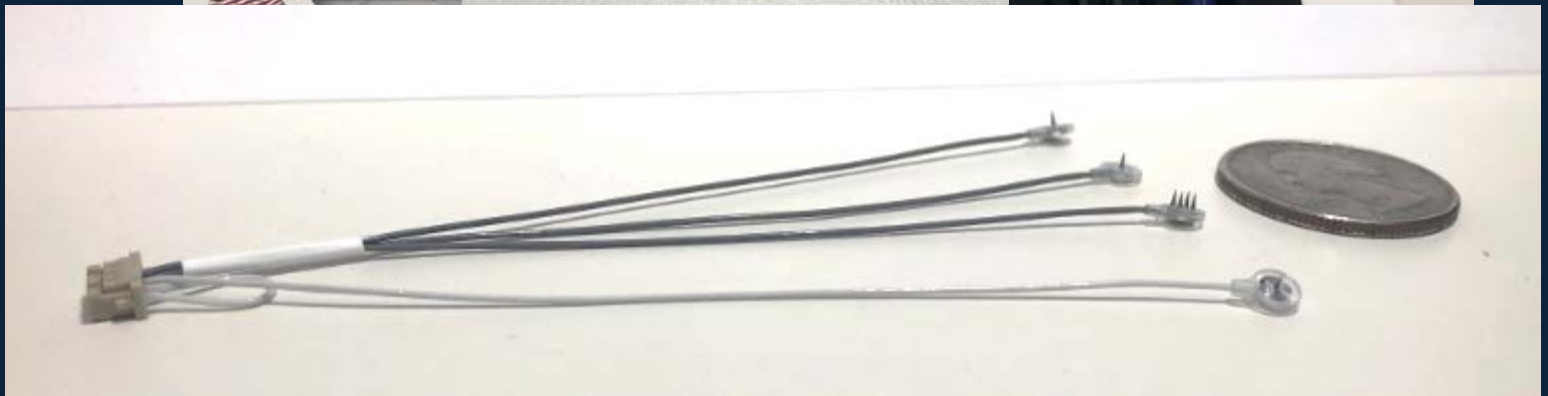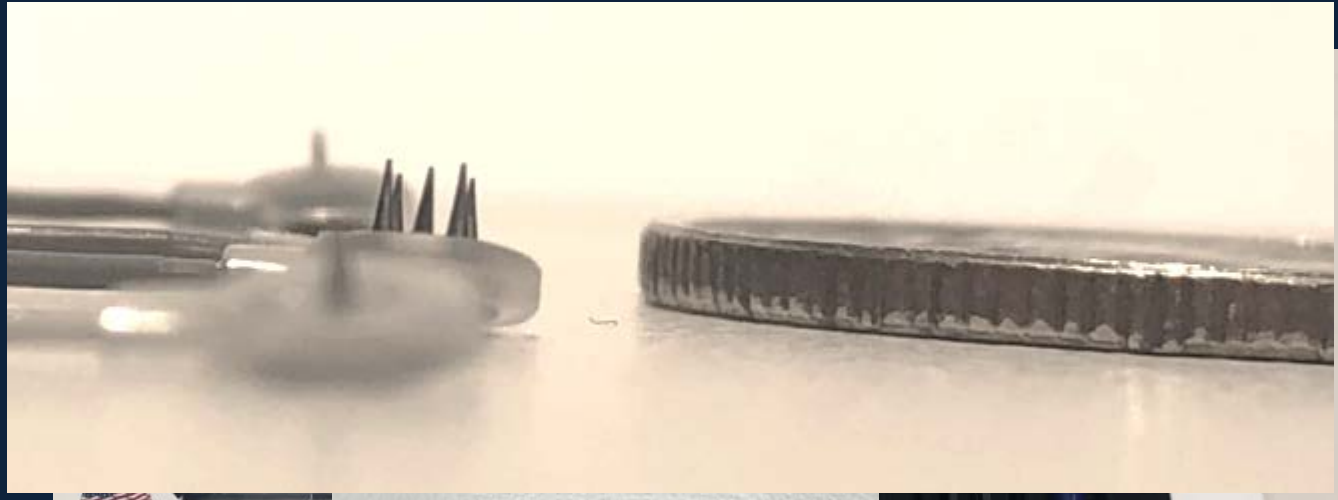
*Communication with VII, IX, GON

CNs V, VII, IX, X → Nucleus Tractus Solitarius →

Periaqueductal gray
- Aversive behavior
- Cardiovascular changes
- Micturition
- **Antinociceptive modulation**

Hypothalamus
- Feeding
- Reproduction
- Stress response

Amygdala
- Sensory input
- Physical and emotional comfort

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Hypothesis

- The use of the BRIDGE device, a percutaneous electrical nerve field stimulator, will cause decreased narcotic consumption

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Methods

- Double-blind, placebo-controlled randomized trial
  - ClinicalTrials.gov: NCT02892513

- Inclusion criteria:
  - Patients ≥ 18 years
  - Froedtert Hospital & Zablocki VAMC
  - Elective bowel resection
    - Laparoscopic, open
    - Small bowel, colon

- Exclusion criteria:
  - History of narcotic abuse
  - Emergent procedures, ICU admission, prolonged intubation
  - History of seizures, CVA, cerebral aneurysms
  - Presence of implanted on-demand device

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Methods

- Active and inactive devices randomized by manufacturer

- Device placed preoperatively, remained for 5 days

- Primary outcome:
  - Total inpatient narcotic consumption

- Secondary outcomes:
  - VAS scores, anxiety scores, nausea, return of bowel function, hospital length of stay, complications, readmissions, narcotic use at 2 weeks and 30 days
  - Blood and saliva samples BID

Results

209 Assessed for eligibility

156 Excluded
- Not meeting inclusion criteria
- Refused to participate
- Other reasons (patient factors)

53 Randomized

28 Assigned to receive active device
  28 Received active device as assigned
  0 Did not receive active device

25 Assigned to receive sham device
  24 Received sham device as assigned
  1 Device removed

0 Lost to follow up
5 Discontinued intervention
  2 Intractable nausea
  3 patient request

0 Lost to follow up
6 Discontinued intervention
  3 Intractable nausea
  3 patient request

28 Included in analysis
0 Excluded from analysis

24 Included in analysis
1 Excluded from analysis

MCW **SURGERY**
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Results – baseline characteristics

Variable	All patients N=52	Active device N=28	Inactive device N=24	P-value
Age	58.6 ± 11.7	56.0 ± 11.5	61.5 ± 11.5	0.095
Sex				0.366
Male	30 (55.8%)	14 (50%)	15 (62.5%)	
Female	23 (44.2%)	14 (50%)	9 (37.5%)	
BMI	28.9 ± 5.8	29.5 ± 6.6	28.1 ± 4.6	0.415
Indication for surgery				0.416
Adenoma	8 (15.4%)	4 (14.3%)	4 (16.7%)	
Cancer	21 (40.4%)	13 (46.4%)	8 (33.3%)	
Diverticulitis	10 (19.2%)	5 (17.9%)	5 (20.8%)	
IBD	7 (13.5%)	5 (17.9%)	2 (8.3%)	
Prolapse	1 (1.9%)	0	1 (16.7%)	
Other	5 (9.6%)	1 (3.6%)	4 (16.7%)	
Comorbidities				
DM2	5 (9.6%)	2 (7.1%)	3 (12.5%)	0.514
HTN	23 (44.2%)	12 (42.9%)	11 (45.8%)	0.829
CAD	1 (1.9%)	0	1 (4.2%)	0.275
Prev cancer	5 (9.62%)	1 (3.6%)	4 (16.7%)	0.110
Obesity	20 (38.46%)	12 (42.9%)	8 (33.3%)	0.482
IBD	8 (15.4%)	5 (17.9%)	3 (12.5%)	0.594

Results – baseline characteristics

Variable	All patients N=52	Active device N=28	Inactive device N=24	P-value
Procedure				0.884
Ileocecectomy	2 (3.8%)	1 (3.6%)	1 (4.2%)	
SBR	4 (7.7%)	3 (10.7%)	1 (4.2%)	
TAC	2 (3.8%)	1 (3.6%)	1 (4.2%)	
R hemi	13 (25.0%)	7 (25.0%)	6 (25.0%)	
L hemi	4 (7.7%)	3 (10.7%)	1 (4.2%)	
Sigmoid	15 (28.8%)	7 (25.0%)	8 (33.3%)	
LAR/APR	8 (15.4%)	3 (10.7%)	5 (20.8%)	
Ext R	3 (5.8%)	2 (7.1%)	1 (4.2%)	
Other	1 (1.9%)	1 (3.6%)	0	
Mode (final)				0.106
HAL	37 (71.2%)	22 (78.6%)	15 (62.5%)	
Open	9 (17.3%)	2 (7.1%)	7 (29.2%)	
Robotic	6 (11.5%)	4 (14.3%)	2 (8.3%)	
Ostomy				0.5246
Yes	13 (25%)	6 (21.43%)	7 (29.17%)	
No	39 (75%)	22 (78.57%)	17 (70.83%)	
Early termination of device	10 (19.2%)	5 (17.9%)	5 (20.8%)	0.786

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Results

Variable	All patients N=52	Active device N=28	Inactive device N=24	P-value
Total inpatient narcotic use (OME/ day)	90.56 ± 49.79	90.79 ± 54.93	90.30 ± 43.03	0.9721
Need for opioid reversal	0	0	0	
Need for RAAPS consult	1 (1.9%)	0	1 (4.2%)	0.275
Return of bowel function (postoperative day) First flatus First bowel movement	3.2 ± 1.1 3.3 ± 1.1	3.3 ± 0.9 3.4 ± 1.0	3.1 ± 1.2 3.2 ± 1.1	0.482 0.436

Results

Variable	All patients N=52	Active device N=28	Inactive device N=24	P-value
Hospital length of stay (days)	5.0 ± 3.7	4.7 ± 1.8	5.5 ± 5.2	0.662
Complications	7 (13.5%)	3 (10.7%)	4 (16.7%)	0.531
Readmissions (30 days)	3 (5.8%)	2 (7.14%)	1 (4.17%)	0.650

Discharge destination
  Home
  LTACH
	51 (98.1%)
	1 (1.9%)
		28 (100%)
		0
			23 (95.8%)
			1 (4.2%)
				0.275

Narcotic use
  2 weeks
  30 days
	5 (11.9%)
	1 (3.3%)
		2 (9.1%)
		1 (5.9%)
			3 (15.0%)
			0
				0.555
				0.374

Results – subgroup analyses

Variable	Active device		Inactive device		P-value
	N	OME/day	N	OME/day	

Gender
  Male
  Female
	
	14
	14
		
		98.97 ± 66.19
		82.60 ± 44.42
			
			15
			9
				
				100.73 ± 51.11
				72.92 ± 20.86
					
					0.7114[1]
					0.7795[1]

BMI
  < 20
  20-25
  25-30
  30-35
  >35
	
	1
	7
	8
	6
	6
		
		30.2
		100.98 ± 73.80
		100.59 ± 60.19
		59.65 ± 31.59
		107.06 ± 42.14
			
			0
			4
			13
			5
			3
				
				76.46 ± 30.94
				95.23 ± 53.37
				57.88 ± 42.44
				111.33 ± 17.85
					
					0.2727[2]

BMI
  Not obese (BMI < 30)
  Obese (BMI>30)
	
	16
	12
		
		96.36 ± 64.66
		83.35 ± 43.29
			
			17
			7
				
				90.81 ± 48.82
				89.05 ± 32.30
					
					0.9283[1]
					0.6455[1]

1. Mann Whitney U test
2. Kruskal-Wallis

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Results – subgroup analyses

Variable	Active device		Inactive device		P-value
	N	OME/day	N	OME/day	
Age					**0.0109**[2]
< 40	4	142.64 ± 70.24	1	124	
40-50	2	135.53 ± 59.21	3	104.71 ± 1.94	
50-60	10	94.82 ± 44.88	5	100.87 ± 53.01	
60-70	10	69.80 ± 47.40	6	103.92 ± 58.80	
>70	2	27.08 ± 19.55	9	66.80 ± 30.56	
Mode of operation					
Open	2	29 ± 1.70	7	84.95 ± 27.22	**0.0278**[3]
HAL/ Robotic	26	95.54 ± 55.23	17	92.5 ± 49.80	0.9920[1]
Smoking status					
Never smoker	13	90.12 ± 60.12	13	110.03 ± 45.27	0.2801[1]
Present/past smoker	11	105.06 ± 50.41	7	69.94 ± 21.80	0.0854[1]
Diagnosis					
Cancer/ polyp	17	73.19 ± 50.37	12	76.69 ± 33.47	0.4413[1]
Benign disease	11	117.98 ± 55.21	12	103.91 ± 50.12	0.5619[1]

1. Mann Whitney
2. Kruskal-Wallis
3. student's T

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Conclusions

- No overall benefit for neurostimulation regarding postoperative narcotic consumption, subgroup analysis suggests

    - patients older than 60 years

    - open incisions

might benefit from neurostimulation.

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Rectal Cancer in Young Patients: Is Obesity Truly a Risk Factor?

Jacqueline J Blank MD,[1] Rasika Deshpande BS,[2] Kirk A Ludwig MD,[1] Carrie Y Peterson MD MS,[1] Timothy J Ridolfi MD[1]

1. Division of Colorectal Surgery, Medical College of Wisconsin
2. Medical College of Wisconsin

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Introduction

- Rates of rectal cancer are increasing in younger patients
  - Delay in diagnosis
  - More aggressive tumor biology
- Reason for increase in younger population?
  - Obesity epidemic
  - Unidentified genetic risk factors

Get screened for colorectal cancer.

Call your doctor today.

American Cancer Society®

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Figure. Trends in adult overweight, obesity, and extreme obesity among men and women aged 20–74: United States, 1960–1962 through 2013–2014
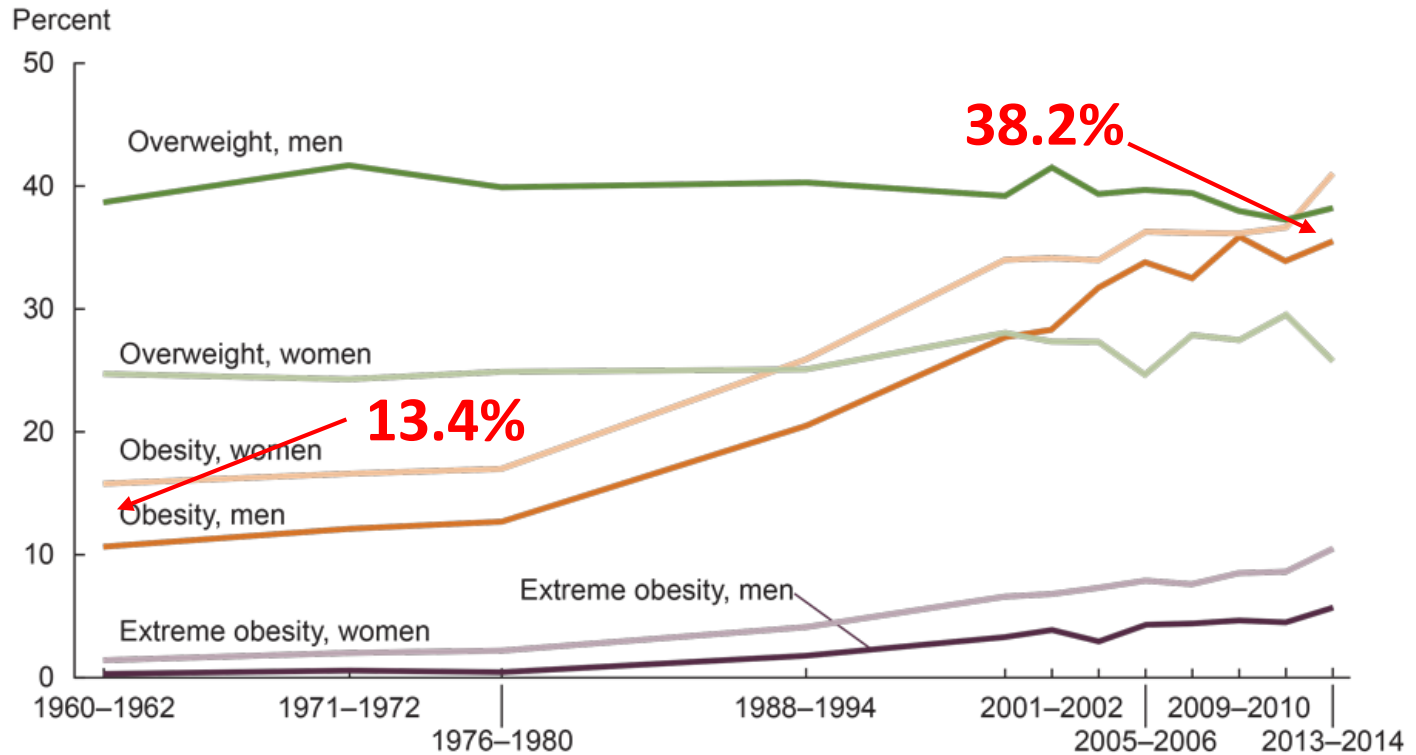
From: https://www.cdc.gov/nchs/data/hestat/obesity_adult_13_14/obesity_adult_13_14.htm

- Patients diagnosed with rectal cancer before age 40, 2008-2017

- Physical measurements, health history, physical activity, sleep, environmental, socioeconomic, mental health
  - 2008-2013: adults 21-74
  - 2014-2016: all ages
  - 2017: resampling of 2008-2013 respondents
- Biorepository
  - Serum, plasma, urine, DNA samples
  - 2018: soil, dust, water, appliance surfaces

	MCW SURGERY N=19 Rectal adenocarcinoma	**MARCH** MIDWEST AREA RESEARCH CONSORTIUM FOR HEALTH N=506 Rectal adenocarcinoma	**shoW** survey of the health of Wisconsin N=1117 No diagnosis of rectal adenocarcinoma
Age at Diagnosis (range)[1]	34.39 (24.80-39.84)	34.72 (18.83-40.50)	30.86 (18-40)
BMI at Diagnosis (range)[1]	26.93 (19.26-39.24)	26.88 (13.64-57.16)	28.72 (14.54-85.92)
Gender Male (%) Female (%)	13 (68.42) 6 (31.58)	274 (54.15) 232 (45.85)	602 (44.85) 616 (55.15)
Smoking status Past or present (%) Never (%) Missing data (%)	7 (36.84) 11 (57.89) 1 (5.26)	112 (22.13) 162 (32.02) 187 (36.96)	439 (39.30) 678 (60.70) 0
DM2[2] Yes (%) No (%) Missing data	2 (10.53) 16 (84.21) 1 (5.26)	8 (1.58) 497 (98.22) 1 (0.19)	39 (3.49) 1078 (96.51) 0

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Conclusion

- Patients with rectal cancer may not necessarily have a higher BMI than non-rectal cancer peers
  - Dose-response relationship vs threshold BMI?
  - Are all rectal cancer patients more obese than previously?
  - Time exposed to obese BMI?

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Thank you!

- Dr. Kirk Ludwig
- Dr. Mary Otterson
- Dr. Carrie Peterson
- Dr. Tim Ridolfi

- Kathryn Hoffman
- Sam Wolff
- Sarah Lundeen
- Kim Spitz
- Deb Andris
- Jean Gilomen

MCW SURGERY
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Treatment Sequencing for Pancreatic Cancer (PC)

- **PC is a systemic disease at diagnosis**
  - Over 60% have nodal metastases[1]
  - Over 70% develop recurrent PC[2]
  - Median of 6.9 months to first recurrence without systemic therapy[3]

- **Adjuvant (postoperative) therapy**
  - Recommended for all PC stages[4]
  - Improves disease-free and overall survival (OS) for patients treated with a surgery-first approach[3]

1. Basturk et al. ASO 2015
2. Groot et al. Ann Surg 2018
3. Oettle et al. JAMA 2013
4. NCCN 2017

Basturk et al.

77%

CONKO-001

6.9 mo

MCW *Surgery*
knowledge changing life
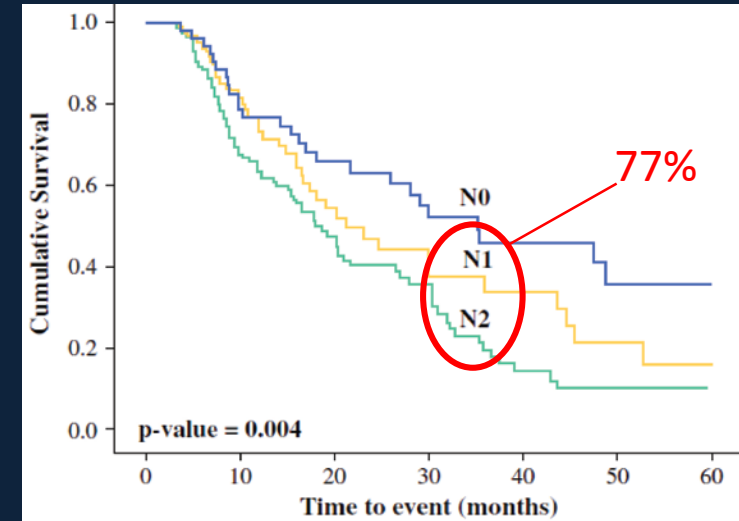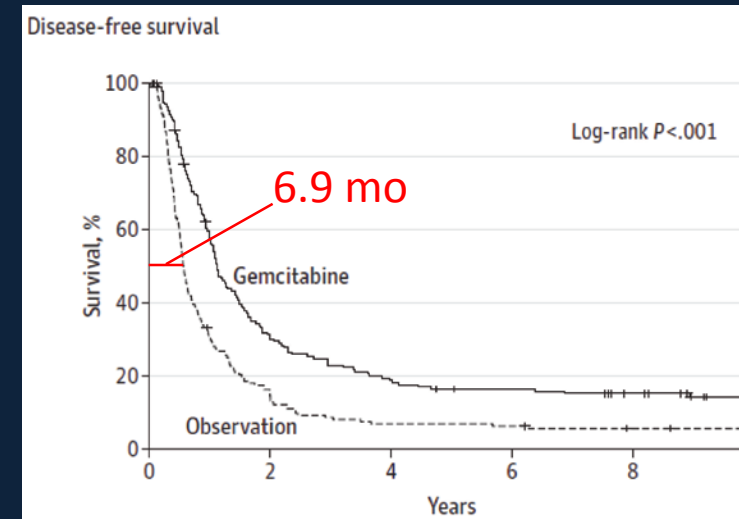
Limitations of a Surgery-First Approach

Approximately 50% of patients do not receive adjuvant therapy due to perioperative complications, failure to recover from surgery or early disease recurrences.[1,2]

SEER Database:

1. Mayo et al. JACS 2012
2. Wu et al. Ann Surg Oncol 2014
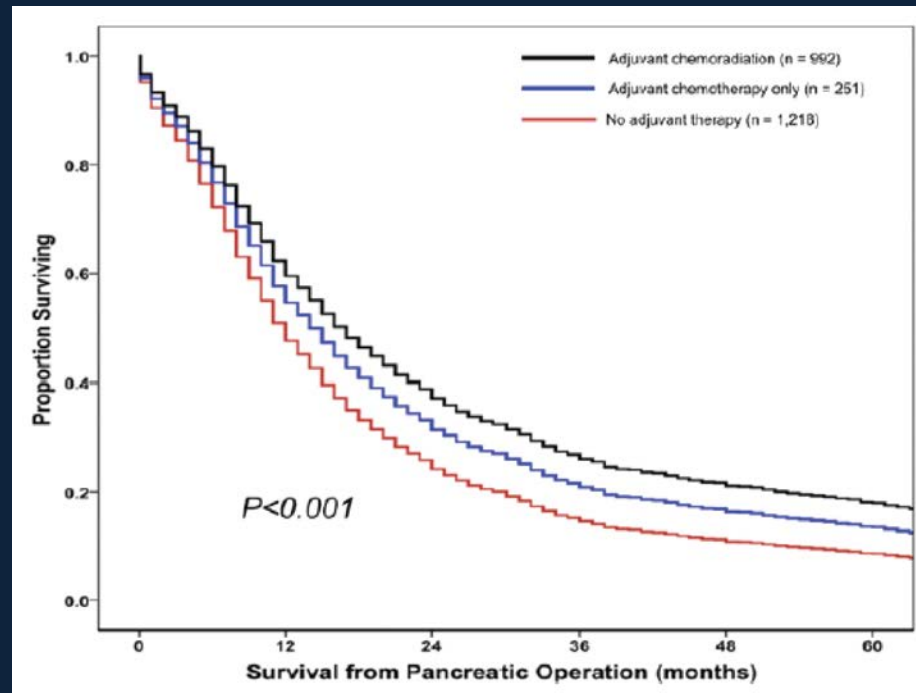
Preoperative (Neoadjuvant) Therapy

VOLUME 26 · NUMBER 21 · JULY 20 2008

JOURNAL OF CLINICAL ONCOLOGY — ORIGINAL REPORT

Preoperative Gemcitabine-Based Chemoradiation for Patients With Resectable Adenocarcinoma of the Pancreatic Head
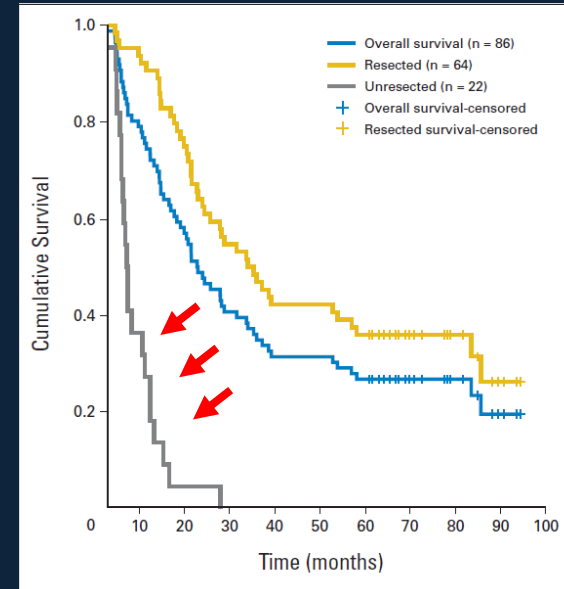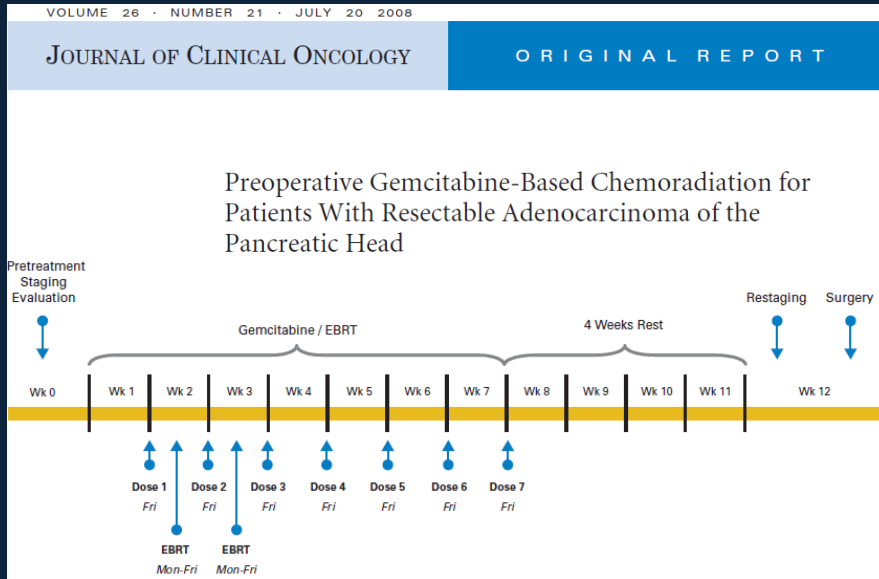
Goals: Identify patients with clinically occult metastatic disease and to avoid a potentially morbid operation

Criteria for Surgery: Absence of metastatic disease progression

Median OS for patients who completed all therapy: **34 mo**

Courtesy of Susan Tsai, MD, MHS

Neoadjuvant Treatment Sequencing

Benefits:

- Early delivery of systemic therapy

- Improved tolerability of multimodality therapy

- Enrichment of the population of patients undergoing surgery

- Improved overall survival for patients who completed all therapy

MCW Data
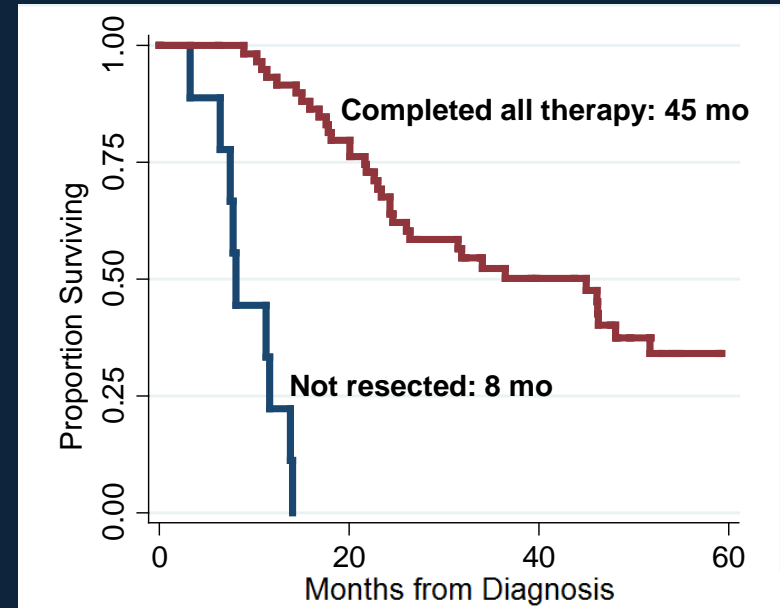
Christians et al. Surgery 2016

Unanswered Questions:

- Pre- and postoperative prognostic factors for patients who complete all therapy

- Survival benefit of additional adjuvant therapy

- Patterns of treatment failure after completion of all therapy

Presentation Outline

- Prognostic value of nodal status

- Survival impact of adjuvant therapy following neoadjuvant therapy and surgery

- Patterns of treatment failure upon completion of multimodality therapy

- How to improve preoperative risk stratification using FDG-PET/CT imaging

Survival by N Stage

6th/7th AJCC Nodal Staging

N0	No regional lymph node metastases
N1	Regional lymph nodes metastases

8th AJCC Nodal Staging

N0	No regional lymph node metastases
N1	1-3 regional lymph node metastases
N2	≥4 regional lymph node metastases
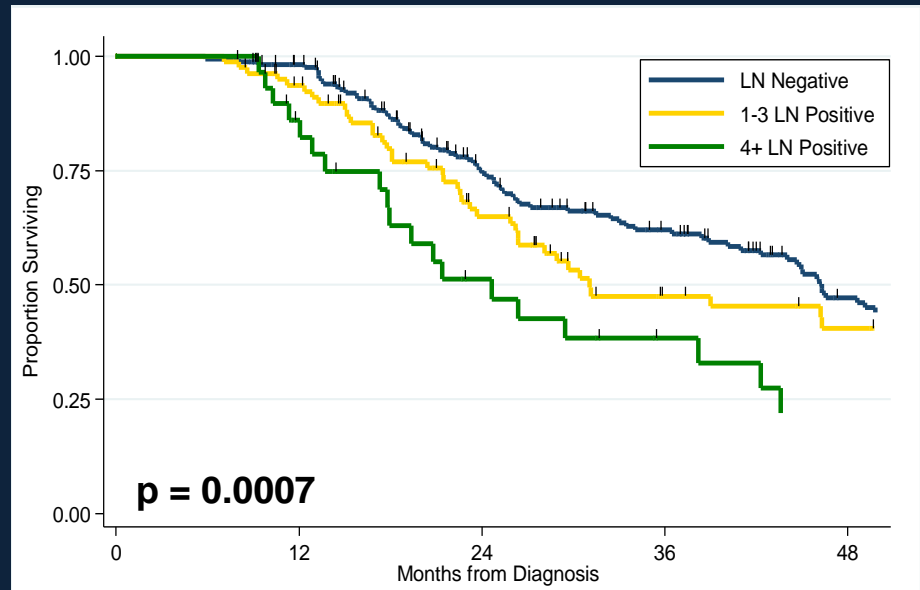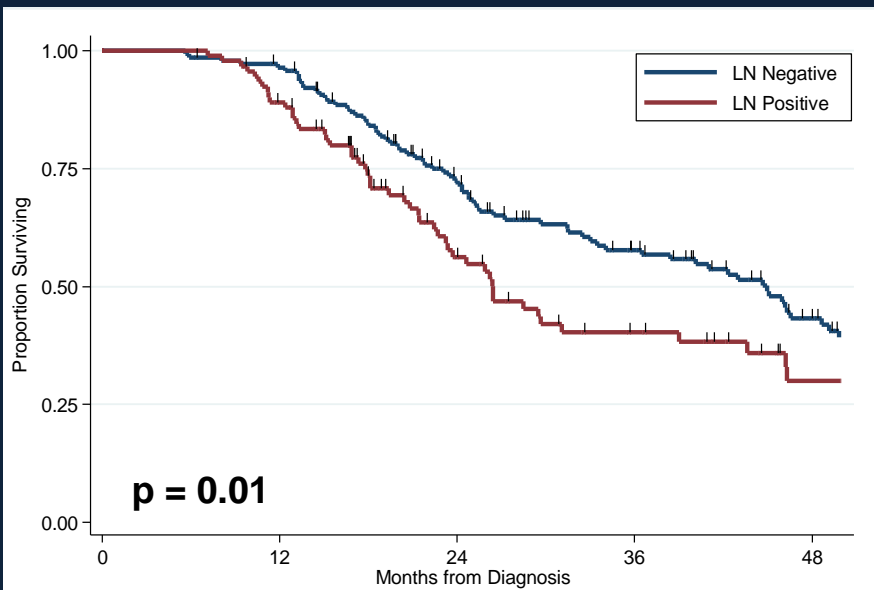
Better prediction of patient outcomes using the new AJCC lymph node staging classification

Impact of Treatment Sequencing N Stage
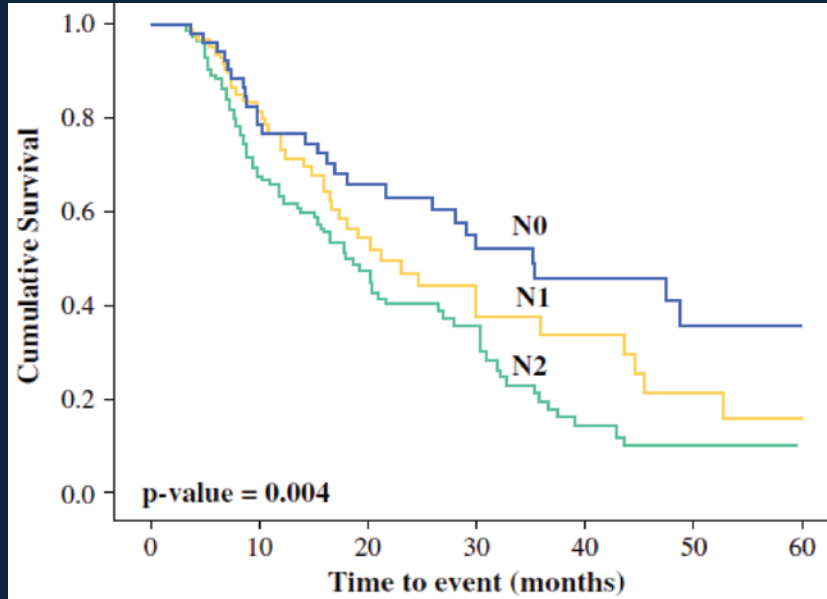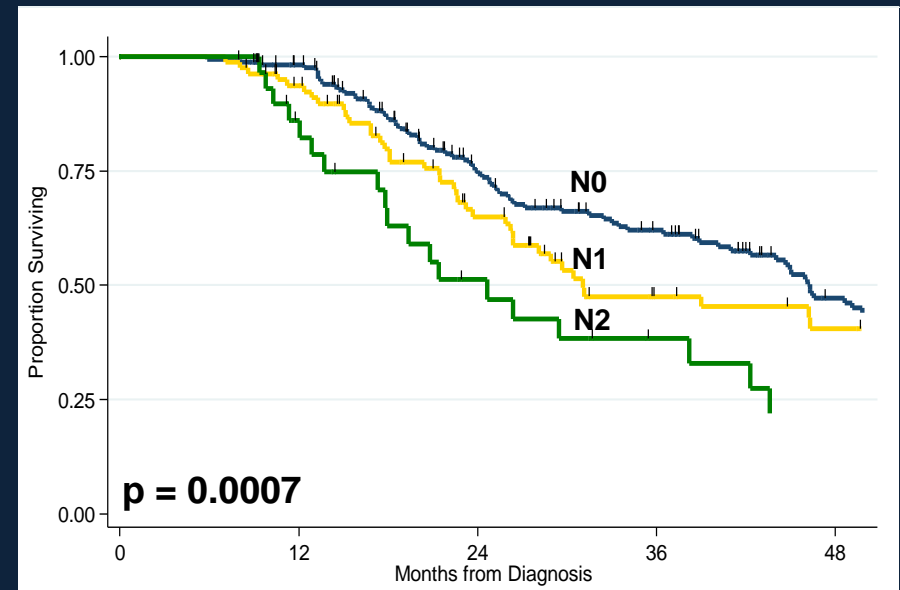
Basturk et al. Ann Surg Oncol 2015

Stage	N (%)	Median Survival
N0	52 (23)	35 mo
N1	90 (40)	21 mo
N2	85 (37)	18 mo

Medical College of Wisconsin

Stage	N (%)	Median Survival
N0	179 (61)	46 mo
N1	85 (29)	30 mo
N2	29 (10)	25 mo

Nodal Status Conclusions

- The new AJCC N staging enhanced patient risk stratification

- Neoadjuvant therapy resulted in superior local-regional disease control

- Neoadjuvant therapy was associated with an improved survival

How to improve the survival of patients with persistent disease after neoadjuvant therapy and surgery?

Includes

- Node
- Positiv
- Persis
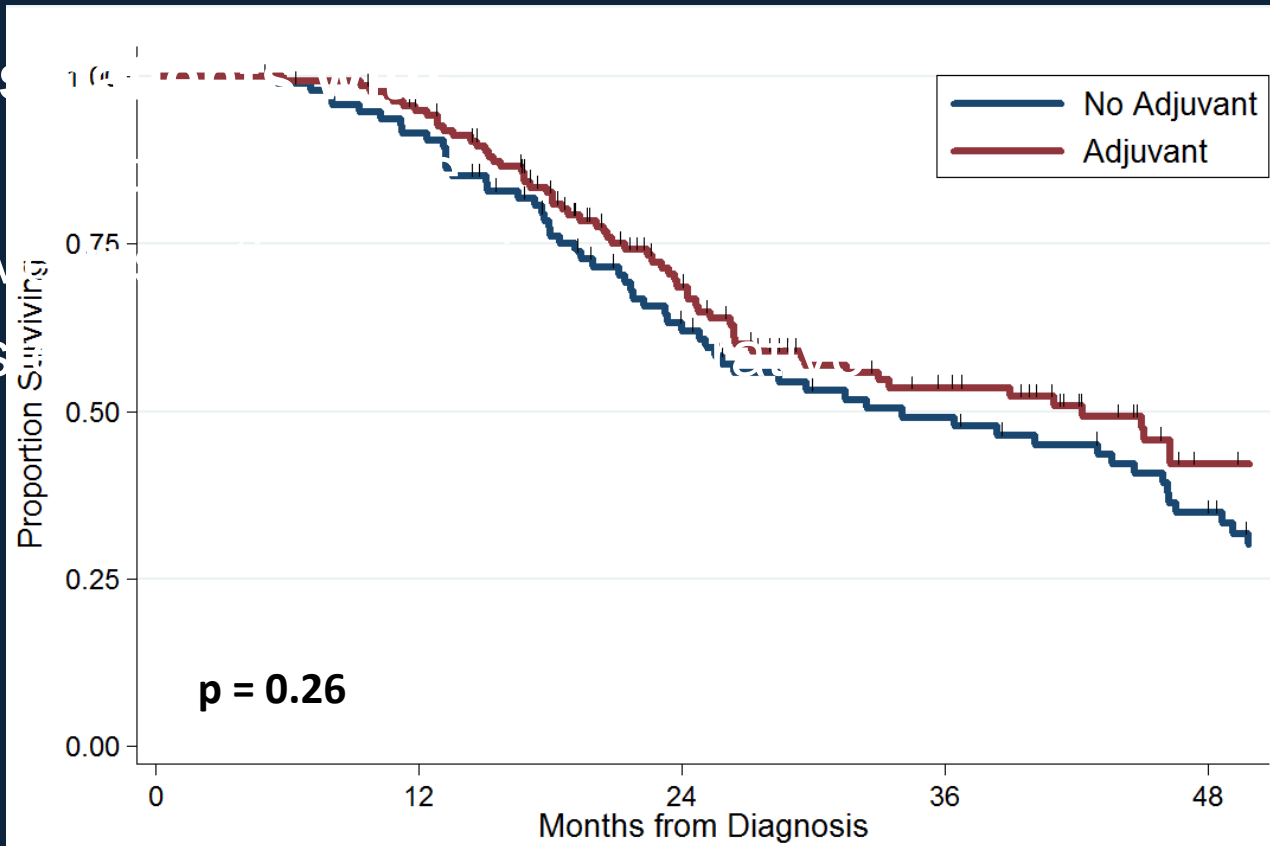
No significant difference in overall survival with or without additional adjuvant therapy

Impact of Adjuvant Therapy on Survival after Neoadjuvant Therapy

LN Negative Patients
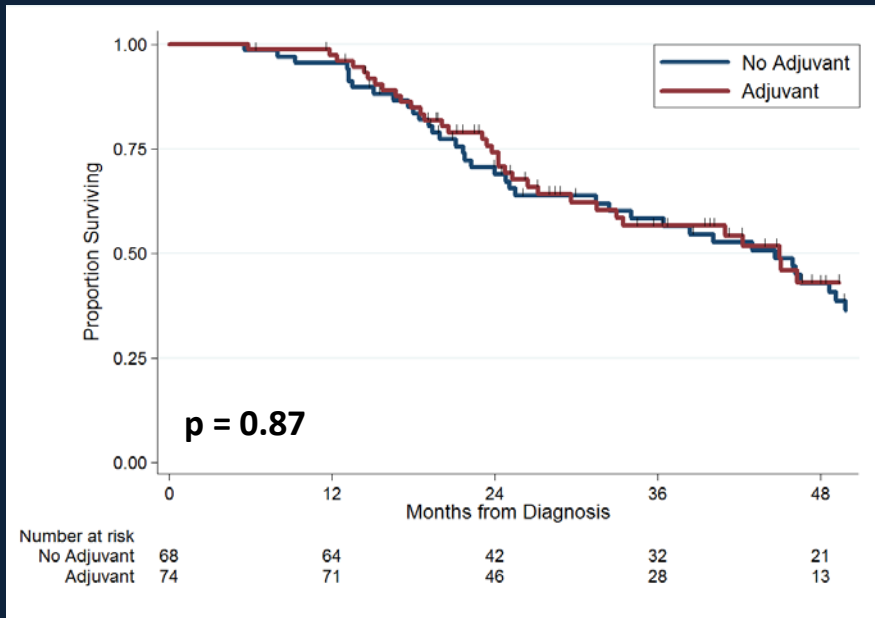
LN Positive Patients
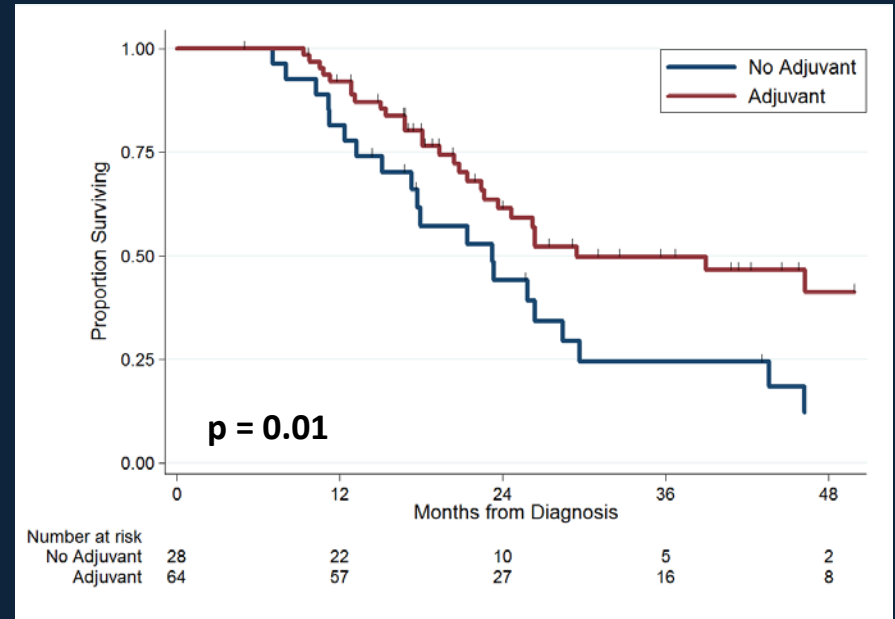
Multivariable Hazards Analysis

	HR	95% CI	p-value
Adjuvant Therapy (Ref: No Adjuvant)	0.65	0.21-2.07	0.47

Multivariable Hazards Analysis

	HR	95% CI	p-value
Adjuvant Therapy (Ref: No Adjuvant)	0.36	0.20-0.66	0.002

Impact of Adjuvant Therapy on Survival after Neoadjuvant Therapy

LN Negative Patients
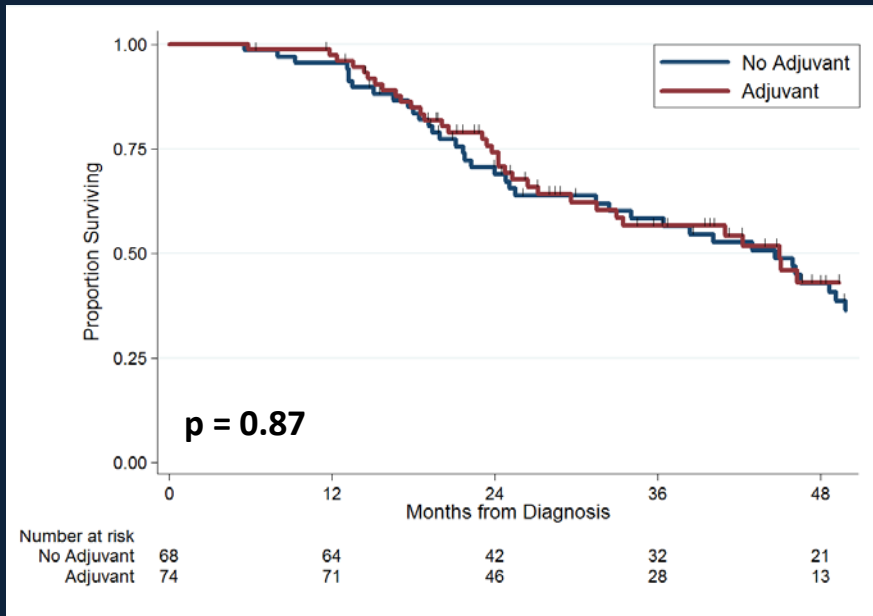
LN Positive Patients
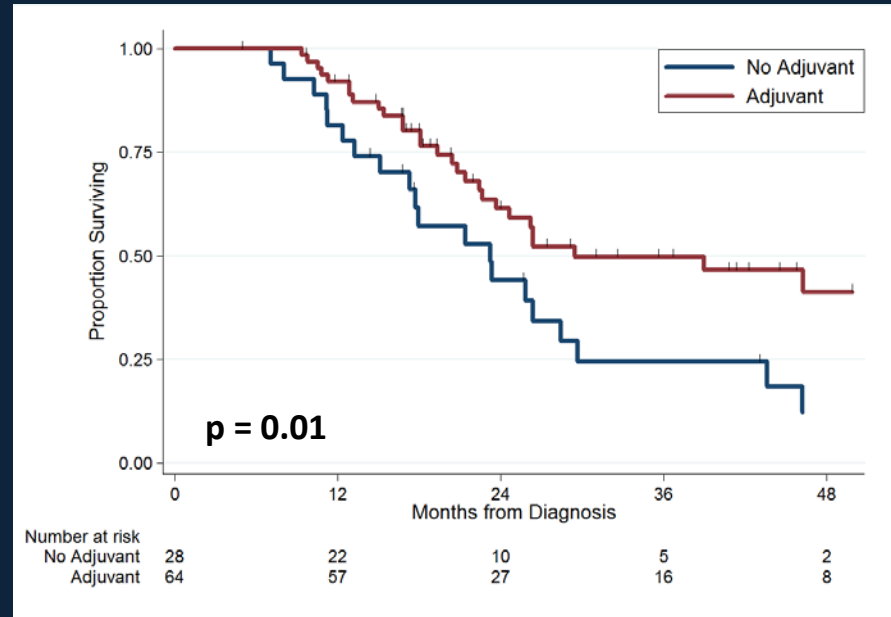
Conclusion: The survival benefit of adjuvant therapy after prior neoadjuvant therapy may be <u>stage</u> dependent.

Characterizing Patterns of PC Recurrence

LOCAL

- Pancreas
- Resection bed
- Perivascular

REGIONAL

- Peritoneum
- Abdominal wall

SINGLE SITE DISTANT

- Liver
- Lung
- Bone
- Ovary
- Lymph Nodes

MULTISITE

More than one organ site with recurrent disease

Patterns of First Disease Recurrence
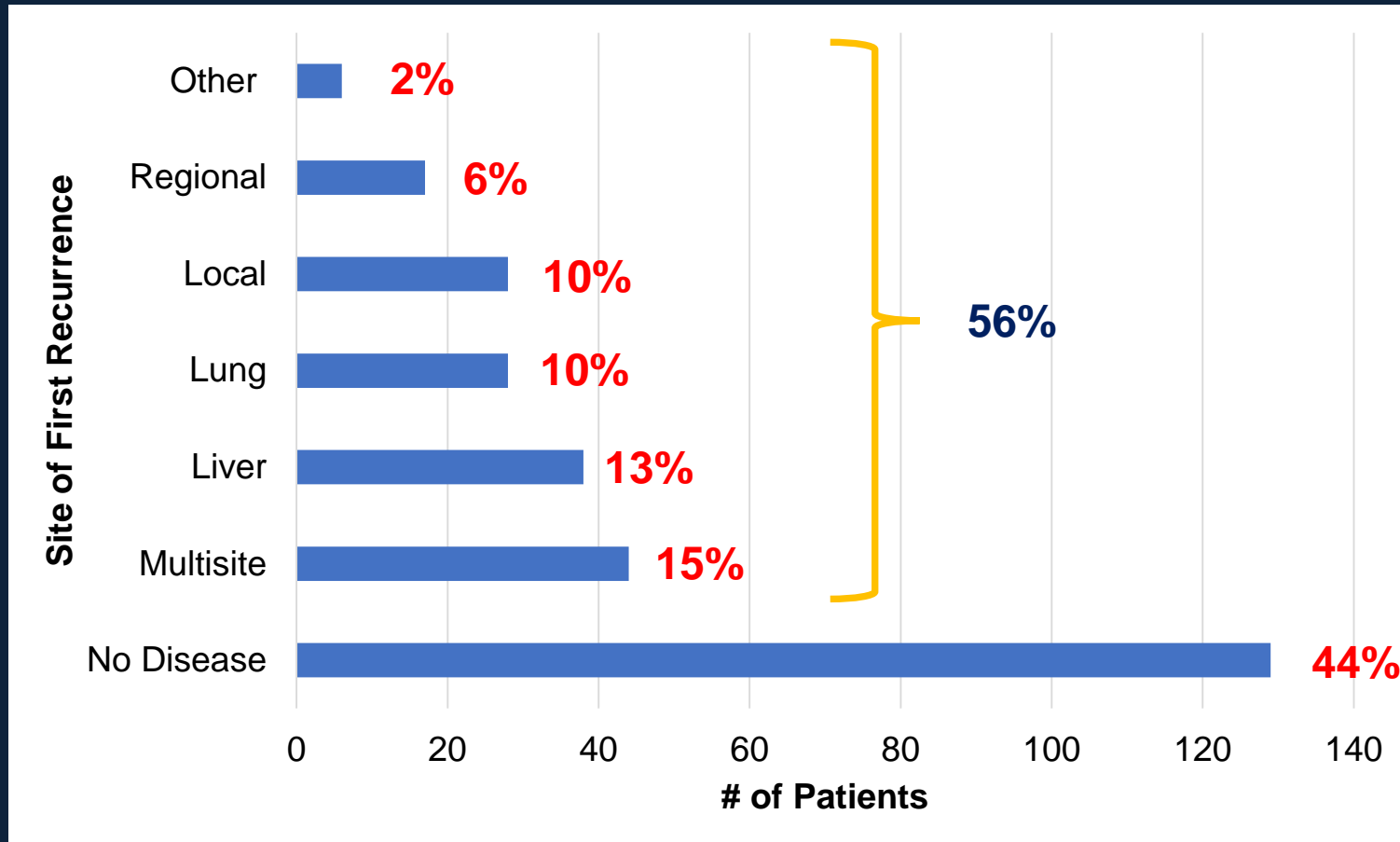
The median disease-free survival was 18 months for all patients and 10 months for patients who recurred.

Time to First Disease Recurrence by Treatment Sequencing

SURGERY-FIRST
Johns Hopkins (Groot, Ann Surg 2017)
Recurrence in 531 (**77%**) of 692 pts
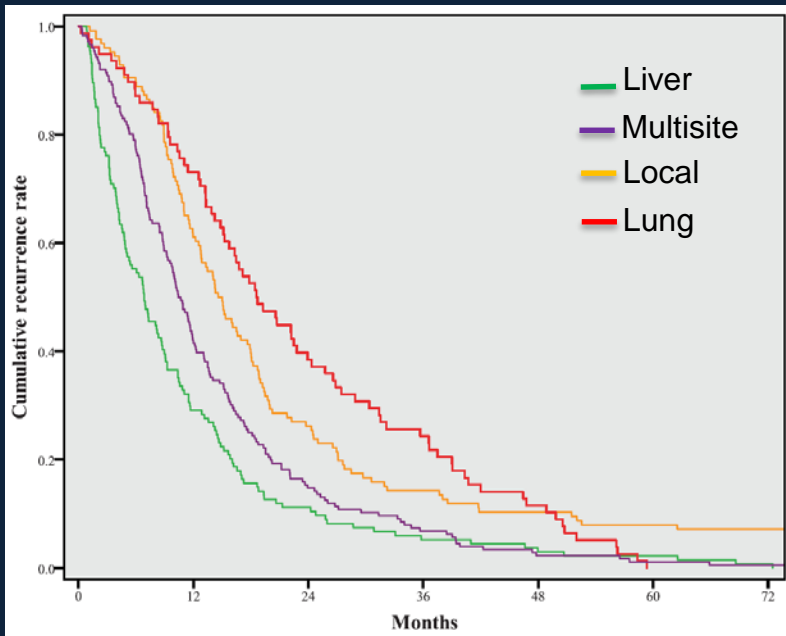
NEOADJUVANT
Medical College of Wisconsin (2017)
Recurrence in 153 (**56%**) of 272 pts
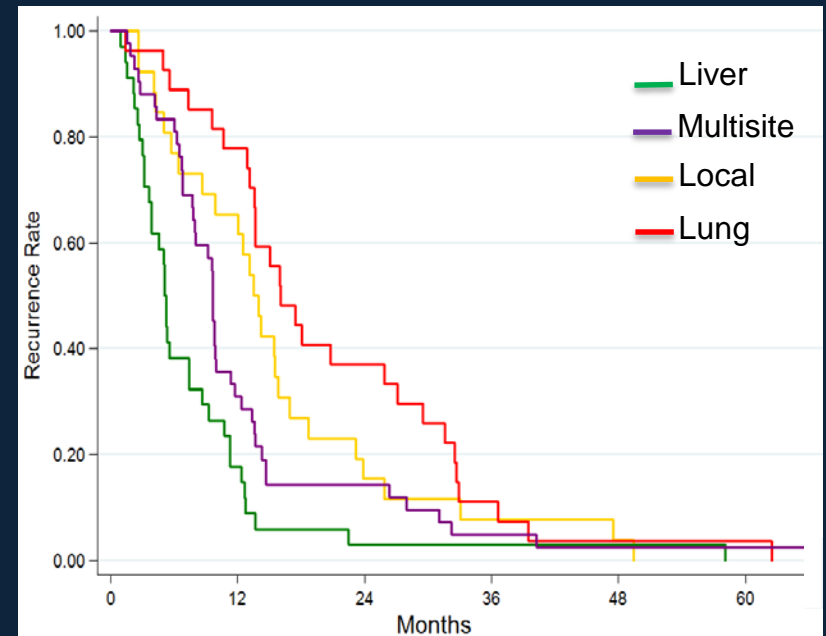
Neoadjuvant therapy was associated with lower rates of recurrence. However, if patients recurred, the timing and patterns of first disease recurrence were similar.

Post Recurrence Survival by Treatment Sequencing

	Recurrence Rate	Time to First Recurrence (Months)	Survival after Recurrence (Months)	Overall Survival (Months)
NEOADJUVANT				
MCW (2017)	56%	10	11	26
SURGERY FIRST				
Wangjam (2015)	83%	10	5	18
Groot (2018)	79%	12	8	21

Fewer PC recurrences after neoadjuvant therapy and patients live longer after recurrence

Patterns of Recurrence Conclusions

- Fewer patients have disease recurrence after neoadjuvant therapy and surgery as compared to upfront surgical resection.

- However, if disease recurs the location and timing of recurrence(s) are similar to those observed with a surgery first approach.

- Median survival of ~1 year following the first disease recurrence.

How do we identify which patients are at risk for poor treatment outcomes <u>prior</u> to surgery?

Preoperative Prognostic Factors:

- Age
- Performance status
- Stage/Resectability
- CA 19-9 level

Postoperative Prognostic Factors:

- Age
- Performance status
- AJCC stage (TNM)
- Grade
- PNI/LVI
- Margin status
- Perioperative complications

Original article

Nuclear Medicine Communications

Role of SUV_{max} obtained by ^{18}F-FDG PET/CT in patients with a solitary pancreatic lesion: predicting malignant potential and proliferation

Hu et al. Nucl Med Comm 2013

Pretreatment PET SUV and Preoperative CA19-9

Neoadjuvant Therapy

Pretreatment PET SUV
(Biologic aggressiveness)

→

Preoperative CA19-9
(Responsiveness to therapy)
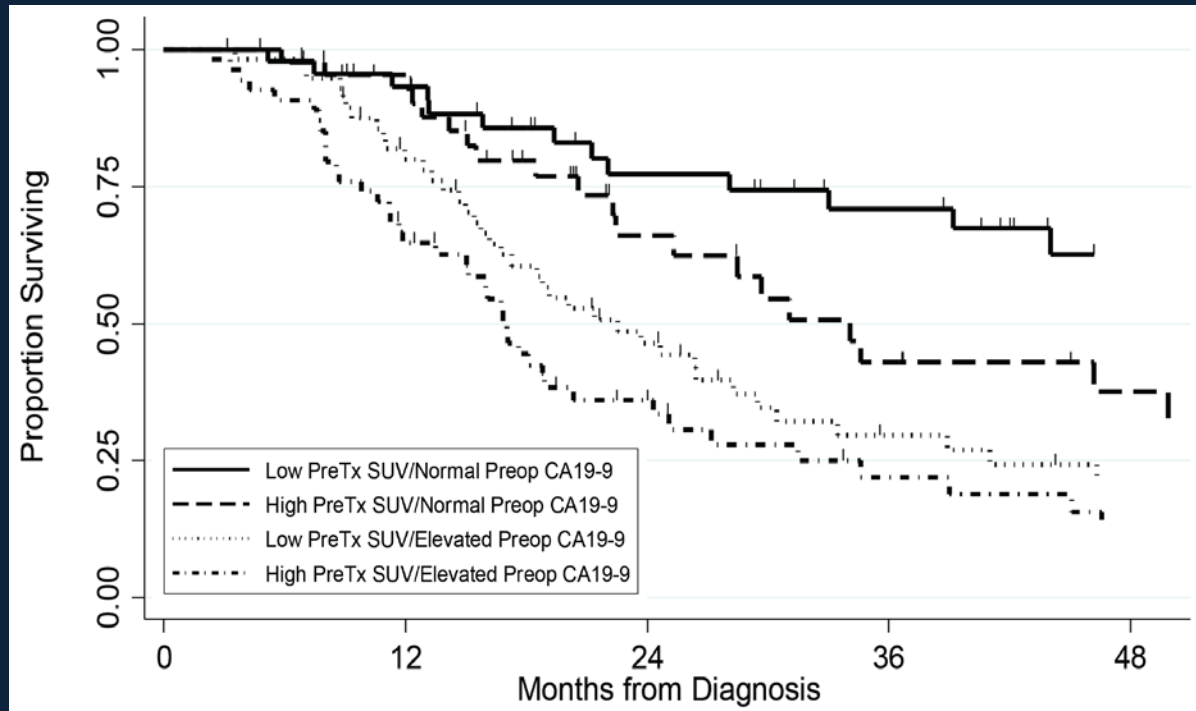
Conclusions: Monitoring of dynamic quantitative endpoints such as FDG avidity and CA19-9 may be important surrogate endpoints for assessment of treatment efficacy and may improve prognostication

MCW Pancreatic Cancer Program

Pancreatic Cancer Group

- Murad Abu Rajab, MD
- Callisia Clarke, MD
- Kulwinder Dua, MD
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