MEDICAL COLLEGE OF WISCONSIN
DEPARTMENT OF SURGERY

SURGERY UPDATE
LEADING THE WAY

WINTER 2016 • VOLUME 8, NUMBER 1

From the Chair
DOUGLAS B. EVANS, MD

Pictured above are representatives of our Advanced Practice Provider team of nurse practitioners and physician assistants in the Department of Surgery. *Front row:* Carolyn Firth, NP; Samantha Vicker, PA; Kerry Short, NP; Anna Hausler, PA; Barbara Provo, NP; Debra Lanza, NP; Brittany Price, PA; Trisha Wilcox, NP; Gina Muscato, PA. *Back row:* Kaitlin Grady, PA; Anna Purdy, NP; Suzette Erickson, NP; Colleen Trevino, NP, PhD; Michael Barnes, PA; Timothy Sie, NP; Beth Krzywda, NP; Marie Bruce, NP; Pamela Kexel, PA; Susan Arnsdorf, NP; Claire Heighway, PA.

The scientific content of this edition of *Leading the Way* is exceptional, as are these individuals highlighted on the cover. This cover is dedicated to the Advanced Practice Providers (nurse practitioners and physician assistants) in the Department of Surgery who *lead the way* in caring for patients with the entire spectrum of medical problems. The Department of Surgery is very fortunate to have 64 Advanced Practice Providers employed across eight clinical divisions. •

IN THIS ISSUE:

INNOVATION wecare DISCOVERY

We Care Fund Grant Recipients

by Meg M. Bilicki, Director of Development for the Department of Surgery

Johnny C. Hong, MD

Muthusamy Kunnimalaiyaan, PhD

Kirkwood A. Pritchard, Jr., PhD

The Department of Surgery is pleased to announce the recipients of the **2015 We Care Fund for Medical Innovation and Research** faculty seed grants. The We Care Scientific Review Committee carefully reviewed a total of 10 exceptional submissions and selected three grant proposals for funding by the Department of Surgery.

Three researchers were awarded a combined total of $75,000. The recipients and their proposals are:

- Johnny C. Hong, MD; Associate Professor of Surgery; Mark B. Adams Chair in Surgery, Chief of the Division of Transplant Surgery, Director of Solid Organ Transplantation
  Quantitative Assessment of Hepatic Ischemia-Reperfusion Injury Measured by Bile Transporter Expression in a Rat in Situ Hepatic Warm and Cold Ischemia Model
- Muthusamy Kunnimalaiyaan, PhD; Assistant Professor of Surgery, Division of Surgical Oncology
  Preclinical Studies on Pancreatic Cancer
- Kirkwood A. Pritchard, Jr., PhD; Professor of Surgery, Division of Pediatric Surgery
  The Role of Myeloperoxidase in Peripheral Vascular Disease

This internal award encourages and supports funding for innovative basic, clinical, and translational research by investigators within the Medical College of Wisconsin's Department of Surgery.

Established in 2010, the "We Care Fund" has raised over $400,000 from more than 700 grateful patients, families, friends, faculty, and alumni. Contributions to the We Care Fund support physicians and researchers in the Department of Surgery for innovative medical research and clinical projects in the fields of cancer, cardiovascular disease, gastrointestinal diseases, diseases of the newborn/child, organ transplantation, and trauma.

The We Care Committee plays a critical role in both raising private funds for research and increasing community awareness. Committee Chair Arlene Wilson said, "One hundred percent of the money raised by the We Care Fund provides seed grants to promising young investigators in the Department of Surgery. All grant proposals submitted are peer-reviewed and I am proud we have been able to award seven grants in the past three years. These research discoveries can lead to much larger grants from the National Institutes of Health." The committee includes a number of professional business and community leaders who are committed to advancing sophisticated medical research at MCW and have generously donated their time and many extra efforts.

Because the We Care Fund is sustained by private gifts, grant cycles are not predetermined and each cycle is announced to eligible faculty members in the Department of Surgery. Philanthropic support plays a vital role in providing seed grants.

If you would like to learn more about the We Care Fund, or are interested in making a gift, please visit the website at **www.mcw.edu/wecare** or contact Meg Bilicki, Director of Development in the Department of Surgery at mbilicki@mcw.edu or 414.805.5731. •

We Care Fund for Medical Innovation and Research Committee, 2015–2016

Arlene A. Wilson, *Chair*
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Maggy Schultz
Aaron Valentine
Mark S. Young

Bile Transporter Expression as Early Marker of Hepatic Ischemia-Reperfusion Injury

JOHNNY C. HONG, MD
Division of Transplant Surgery

While liver transplantation is a definitive life-saving treatment for patients with irreversible liver failure, a significant number of patients die due to lack of suitable organs for transplantation. The focus of our Solid Organ Transplantation Research Laboratory is to develop innovative therapies to optimize and increase the number of available organs for transplantation, converting otherwise discarded organs to transplantable ones in the hopes of saving more lives. Ischemia and reperfusion injury (IRI) is an inherent adverse factor in organ transplantation. The degree of IRI has a critical influence on the suitability of an organ for transplantation, as well as on the initial graft function after transplantation. Regulated hepatic reperfusion (RHR),[1] a novel organ resuscitative therapy, has been developed to circumvent the adverse effects of ischemia and reperfusion injury, facilitate recovery of the pre-damaged hepatocytes, and improve liver function after ischemic insults. In the swine model of prolonged hepatic warm ischemia, RHR mitigated IRI and improved survival as compared to the conventional method of liver reperfusion. While the novel RHR strategy has potential applicability to clinical liver transplantation when using organs procured after circulatory death (donation after circulatory death, DCD), a mechanistic study on the impact of warm and cold ischemic injuries on the hepatocyte bile transporter of the liver after DCD is warranted prior to its clinical application.

Severe cholestasis, a key feature of severe hepatic IRI, is an impairment of bile secretion which results either from a functional defect at the level of the hepatocytes (hepatocellular cholestasis) or from an impairment in bile secretion and flow at the level of bile ductules or ducts (ductular/ductal cholestasis). At present, there are fifteen known subtypes of bile transporters that are responsible for bilirubin metabolism. We previously demonstrated in our N-nitrosodimethylamine-induced (via intraperitoneal administration) cirrhosis rat model that hepatocyte injury resulted in a significant reduction in expressions of bile transporters: the organic anion-transporting polypeptide 1 (OATP1) on the basolateral membrane, and the multidrug resistance protein 2 (MRP2) on the canalicular membrane. Our present research proposal, "Quantitative Assessment of Hepatic Ischemia-Reperfusion Injury Measured by Bile Transporter Expression in a Rat *in situ* Hepatic Warm and Cold Ischemia Model," aims to identify hepatocyte membrane bile transporters that could serve as early markers of severe IRI. Using an *in situ* warm and cold hepatic ischemia rat model (Figure 1), we will investigate the expression of bile transporters in hepatic tissue samples from groups with different warm and cold ischemic times, and analyze any correlation between warm and cold ischemic times and bile transporter expression as well as its impact on 7-day animal survival. Information gained from this research project will be applied towards our RHR swine DCD liver transplantation model and subsequently to human liver transplantation.

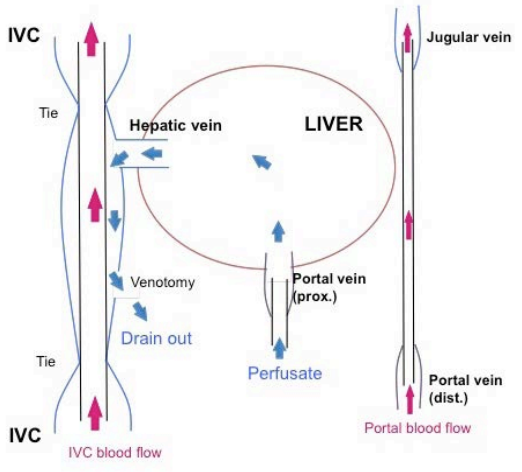

FIGURE 1: *In situ* liver perfusion model. Three separate catheters are used. A catheter in the inferior vena cava (IVC) diverts blood flow (red arrows) to a level superior to that of the hepatic veins. Two ties around the IVC catheter isolate hepatic venous flow from the blood flow in the IVC. The second catheter delivers perfusate (blue arrows) into the liver, which drains through a venotomy on the IVC. The third catheter diverts portal venous blood flow into the jugular vein.

Research grants such as the We Care Fund for Medical Innovation and Research allow for the transformation of novel ideas into discoveries that will improve the lives of our patients. We are greatly appreciative and highly honored to be recipients of the We Care Fund Grant. •

FOR ADDITIONAL INFORMATION on this topic see reference below, visit mcw.edu/surgery or contact Dr. Hong, 414-955-6928, jhong@mcw.edu.

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Xanthohumol: A Novel Agent for the Treatment

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Pancreatic adenocarcinoma will soon become the second leading cause of adult cancer death; better treatments are needed. This is mainly due to the development of resistance to current treatment modalities. One of the causes of resistance to drug treatment in pancreatic cancer is an increase in nuclear transcription factor kB (NF-kB) promoter activity through the Notch1 signaling pathway.

Notch1 signaling, a highly conserved pathway throughout the animal kingdom, plays an important role in cellular differentiation, proliferation, and survival. Both the Notch1 receptor and its ligands (Delta1 and Jagged1, for example) are transmembrane proteins with large extracellular domains. Binding of the Notch ligand promotes two proteolytic cleavage events in the Notch receptor, resulting in the release of the Notch1 intracellular domain (NICD).[1,2] The released NICD translocates to the nucleus and binds with the DNA-binding protein complex CSL (CBF1, Su (H), and LAG-1) and activates various target genes such as Hairy and Enhancer of Split (HES)-1, cyclin D1, survivin, etc.[1,2] Activated Notch (NICD) in its free, unbound state is unstable and quickly degraded, which facilitates the regulation of Notch signaling (Figure 1).

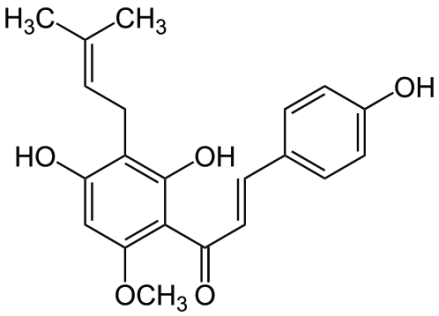

Figure 2: Chemical structure of the compound Xanthohumol.

Increased expression of Notch receptors and their ligands has been detected in human pancreatic cancer tissues and cell lines.[3–5] Inhibition of Notch1 or the Notch signaling pathway by Notch1 siRNA in pancreatic cancer cells enhanced chemosensitivity to the traditional chemotherapeutic agent gemcitabine (Gem) in a preclinical model.[6] Unfortunately, clinical trials utilizing Notch pathway inhibitors in patients with solid tumors resulted in significant side effects. Alternatively, several clinical trials are underway based on the inhibition of the Notch pathway via antibody therapy or by gamma secretase inhibitors.[7,8]

We have recently reported that xanthohumol (XN), a prenylated chalcone compound (isolated from the cones of the hop plant, Humulus lupulus L., Figure 2), inhibits pancreatic cancer and hepatocellular carcinoma cellular proliferation *in vitro* via inhibition of the Notch signaling pathway.[9, 10] Furthermore, inhibition of the Notch signaling pathway is most likely the predominant

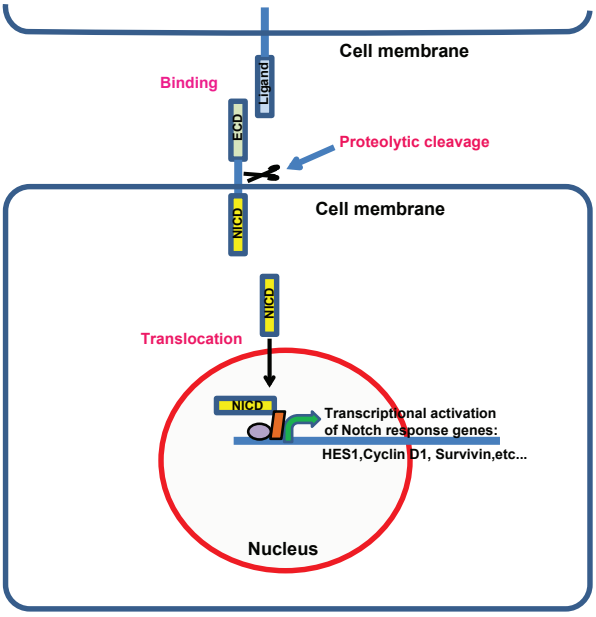

Figure 1: Schematic diagram of Notch signaling pathway. Upon binding of the ligand to the Notch receptor, it promotes the cleavage of the Notch receptor and the release of the Notch intracellular domain (NICD) which then binds to the CSL complex and activates various target genes.

# of Pancreatic Cancer

mechanism of action of XN. Importantly, treatment of gemcitabine-resistant cells (L3.6plGemRes) with XN in combination with Gem showed higher reduction in growth than either alone. Based on our preliminary results, we hypothesize that XN-mediated growth suppression in pancreatic cancer is predominantly through inhibition of Notch signaling, and XN potentiates the attenuation of the growth effect. The similarity of XN metabolism between animals and humans, high oral bioavailability and long half-life *in vivo*,[11] the ability to measure XN and its metabolites in plasma and liver tissue,[11–13] safety studies on mice,[14–16] and our preliminary results on the antiproliferative effects on pancreatic cancer cells *in vitro* led us to hypothesize that XN could safely and effectively inhibit pancreatic cancer progression *in vivo*. Also, we propose a pathway by which XN induces apoptosis in pancreatic cancer cells, suggesting a possible cross-talk between Notch, PI3K-Akt pathway, and the NF-κB pathway (Figure 3).

With the support of the We Care Fund for Medical Innovation and Research, we are studying the effect of XN in an *in vivo* animal model. The proposed studies are significant because XN has significant potential for the treatment of pancreatic cancer either alone or in combination as a neo-adjuvant or adjuvant therapy. The knowledge gained by the proposed studies may not only reveal a much-needed, targeted therapeutic approach for pancreatic cancer, but also have implications beyond pancreatic cancer, as the mechanistic insights are also likely to be applicable to other cancers that express Notch. •

FOR ADDITIONAL INFORMATION on this topic see references below, visit mcw.edu/surgery or contact Dr. Kunnimalaiyaan, 414-955-2840, mkunnima@mcw.edu.

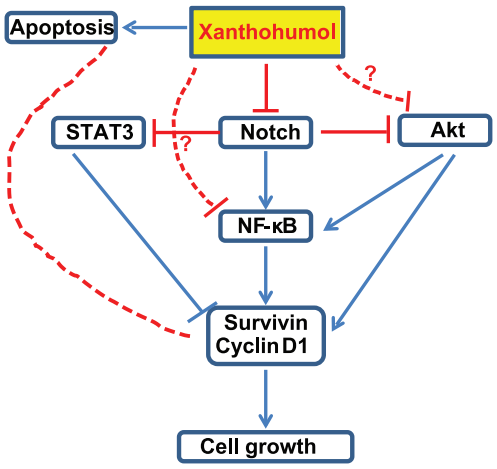

Figure 3: Proposed working model of XN in pancreatic cancer. Schematic representation of XN-induced apoptosis through the Notch1 signaling pathway via inhibition of Akt and NF-kB.

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The Role of MPO in Peripheral Vascular Disease

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Diabetes is growing at alarming rates world-wide. Unfortunately, having diabetes increases the risk of developing peripheral vascular disease (PVD), a form of atherosclerosis that occurs most often in the legs and feet rather than the heart. One of the complications of PVD is poor circulation, which appears as leg pain when walking. Left untreated, this poor circulation in PVD, especially in patients with diabetes, increases the risk of blood clots in the lower legs. When a blood clot does occur, not only do the feet and legs receive less nutrients, but they are also unable to rid themselves of waste products that build up during ischemia. Failure to restore blood flow by removing blood clots increases tissue death and the risk of developing gangrene. When this occurs, surgical removal of the toes, the foot or even the lower leg may be necessary to save the patient's life. Researchers at the Medical College of Wisconsin have shown that oxidative stress plays an important role in how blood flow is impaired in the lower limbs of diabetic mice, an established animal model for studying how diabetes impairs vascular function. Findings from studies using diabetic mice have relevance for humans with diabetes and PVD.

Our research team has discovered that the major enzyme responsible for increasing oxidative stress in the legs of diabetic mice is myeloperoxidase (MPO). When MPO is activated, it generates a wide variety of toxic oxidants that damage tissues, kills cells in the blood vessel, impairs blood flow and increases atherosclerosis. Others have shown that MPO is released by activated polymorphonuclear cells (PMN) as they pass through blood vessels with atherosclerosis. We reasoned that if MPO plays an important role in PVD in diabetes, then inhibiting MPO activity should decrease damage to the blood vessels and improve blood flow in hindlimbs of diabetic mice.

To inhibit MPO, we developed a novel tripeptide inhibitor, KYC (N-acetyl lysyltyrosylcysteine amide), that actually "steals" oxidants from MPO before they have a chance to leave and damage cells in the blood vessel. Our studies show that treating diabetic mice with KYC dramatically restored blood flow in those subjected to experimentally-induced hindlimb ischemia. In other studies, we have confirmed that KYC reduces oxidative stress and inflammation in the hindlimbs in diabetic mice.

In new studies supported by the We Care Fund, we will determine if KYC inhibits MPO- and PMN-dependent injury to blood vessels and muscle tissues in mice with experimentally-induced blood clots in their hindlimbs. We will dissolve the blood clots in the hindlimbs of diabetic mice using tPA, the same thrombolytic agent used by vascular surgeons to remove blood clots in diabetic patients with PVD. In addition, we will add KYC to blood samples from patients with diabetes and PVD to determine if KYC can inhibit human PMN activation and MPO release, and if our novel drug inhibits PMN activation and MPO release in diabetic mice with hindlimb ischemia. Successful completion of our studies will provide some of the first *in vitro* data in humans that KYC holds great promise as an effective therapeutic agent for treating PVD in humans with diabetes. •

FOR ADDITIONAL INFORMATION on this topic visit mcw.edu/surgery or contact Dr. Pritchard, 414-955-5615, kpritch@mcw.edu.

Unique Surgical Approach to Esophageal Cancer at the Medical College of Wisconsin

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Cancer of the esophagus remains a major unsolved health problem. In the U.S. this year, there will be approximately 90% as many deaths from the disease as there are new cases. The primary reason for this is that most cases are diagnosed at a relatively advanced stage. The most common histology in the U.S. is distal adenocarcinoma, though worldwide squamous cell carcinoma remains the most common.

For patients with non-metastatic esophageal cancer, the most common treatment approach is chemotherapy and radiation, followed at a 6–12 week interval by an esophagectomy. The surgical approaches for esophagectomy vary by center, and to some extent, by location of the tumor. No particular approach has proven superior to any other in the surgical literature. The transhiatal approach is less morbid because it avoids a thoracotomy, though it comes at a cost of possible recurrent nerve injury and less fastidious intrathoracic lymph node dissection. Despite these drawbacks, long-term cancer outcomes are comparable to other approaches.

At MCW, Drs. William Tisol and Mario Gasparri developed a novel approach to the traditional "blind" transhiatal esophagectomy. This utilizes the endoscopic vein harvesting device to completely dissect the intrathoracic esophagus via a small neck incision, including retrieval of subcarinal and paraesophageal nodes. As a two-team operation, with one surgeon working from the neck and the other working via a laparotomy, blood loss and operating time have been reduced with results comparing favorably to those from other large-volume esophagectomy centers. We call this the TEEM (Transcervical Endoscopic Esophageal Mobilization) approach.

Since June 2012, we have performed 94 TEEM esophagectomies at Froedtert Hospital and the Zablocki VA. The patients were predominantly male (84%) with an average age of 62. Preoperative chemotherapy and radiation was delivered in 89% of patients. The median length of stay was 10 days. The average operating time was under three hours, blood loss was 240 c.c., and a mean of 14 lymph nodes were retrieved (the national standard is at least 13 nodes). Complications included 8.6% anastomotic leaks, 22% temporary vocal cord paresis with < 3% permanent palsy. We have had no mortalities, compared with 3-8% at most large centers nationally.

In response to an initially high rate of postoperative atrial fibrillation, we adopted routine use of perioperative IV amiodarone. In an abstract presented this fall at the MCW Research Day, and in preparation for submission, we demonstrated a significant reduction in atrial fibrillation rates with this approach.

In addition, we have modified our transcervical mobilization technique, changing from a Ligasure cautery device to a Harmonic scalpel, in hopes that this will reduce what we assume is vagal trauma in the upper chest resulting in vocal cord palsies. It is too early to know whether this change will improve that outcome.

We receive referrals from a broad geographic swath of Wisconsin, and many patients from outside the primary Froedtert Hospital area receive their diagnostic tests and preoperative therapy outside of Milwaukee. We have developed good relationships with oncology providers in the wider Wisconsin market, based on our work at Froedtert and the Medical College of Wisconsin. Presently we have one of the busiest esophageal surgical programs in Wisconsin.

Future surgical innovations may include adoption of a laparoscopic or robotic abdominal approach, as used in minimally invasive esophagectomies elsewhere. While this may reduce immediate postoperative pain, we have rarely had wound problems with the laparotomy, and a minimally invasive approach is likely to add time to the procedure and may make jejunostomy feeding tube placement more difficult.

Another consideration stems from the knowledge that about one-third of our esophagectomy patients have no demonstrable malignancy in the resected specimen, yet we have no definitive way to identify the "complete responders" preoperatively. One option is to adopt a "salvage" approach to esophagectomy, in which patients are re-evaluated with imaging and endoscopy after their chemotherapy and radiation, and offered surgery when there is high suspicion of residual or locally recurrent disease. Early reports in the literature suggest that the overall outcomes with this approach are similar to routine esophagectomy in this population. To this end, we are close to launching a pilot trial of MRI for T staging of the esophagus, which may augment or replace current modalities of endoscopic ultrasound or PET CT.

Overall, the esophageal cancer program at Froedtert and the Medical College of Wisconsin is a distinct success, and credit must go not only to the medical oncologists, radiation oncologists, gastroenterologists, radiologists, and surgeons involved on campus and regionally, but also to the excellent perioperative care provided by our anesthesiologists, nurse practitioners, nurses and physician assistants, and not least by our cardiothoracic residents. This is truly a TEEM sport. •

FOR ADDITIONAL INFORMATION on this topic see references, visit mcw.edu/surgery or contact Dr. Johnstone, 414-955-6902, djohnstone@mcw.edu.

Multidisciplinary Treatment of Congenital

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Esophageal atresia, with or without tracheoesophageal fistula (EA/TEF), is a rare congenital anomaly in which the esophagus is in discontinuity, most commonly resulting in a proximally dilated esophageal pouch and an abnormal connection between the distal esophagus and the trachea. The incidence of EA/TEF is estimated to be 1 in 2,500 live births. In the state of Wisconsin, where the birth rate has remained relatively flat at approximately 67,000 live births per year, there are an average of 27 infants diagnosed with esophageal atresia every year.

Prior to the advancement of surgical and neonatal care, EA/TEF was uniformly fatal. With the advent of mechanical ventilators, total parenteral nutrition and surgical techniques, the mortality has fallen to 7%. All patients with EA/TEF will require surgical correction of their anomaly and this typically occurs within the first few days of life.

More than two-thirds of infants born with EA/TEF will have additional congenital anomalies. VACTERL is an acronym used to remember the most common associated anomalies and stands for vertebral, anorectal, cardiac, tracheoesophageal, radial, renal and limb anomalies. Infants born with EA/TEF are screened with x-ray to look for vertebral and limb defects, echocardiogram for cardiac defects, rectal exam to exclude anorectal malformation, and a renal ultrasound. Congenital heart disease is reported in 35% of EA/TEF cases, making it the most frequently associated anomaly. Complex congenital heart disease is the cause of the majority of deaths in EA/TEF children.

Infants born with EA/TEF require comprehensive care from pediatric specialty providers including pediatric surgeons, anesthesiologists, neonatologists, gastroenterologists, speech pathologists and dieticians. This multi-disciplinary approach is essential to providing safe and effective care, and has been implemented at Children's Hospital of Wisconsin (CHW) in the peri-operative setting as well as in the long-term management of EA/TEF patients. In 2014, CHW and Medical College of Wisconsin (MCW) pediatric surgeons and gastroenterologists created the Midwest's only multidisciplinary clinic dedicated to patients with EA/TEF. The clinic has three missions: 1) to provide comprehensive and cutting edge surgical and medical expertise, 2) to provide long-term longitudinal care to a complex patient population with multiple medical needs and resource requirements, and 3) to enroll patients in research studies seeking to improve outcomes and develop best practice guidelines.

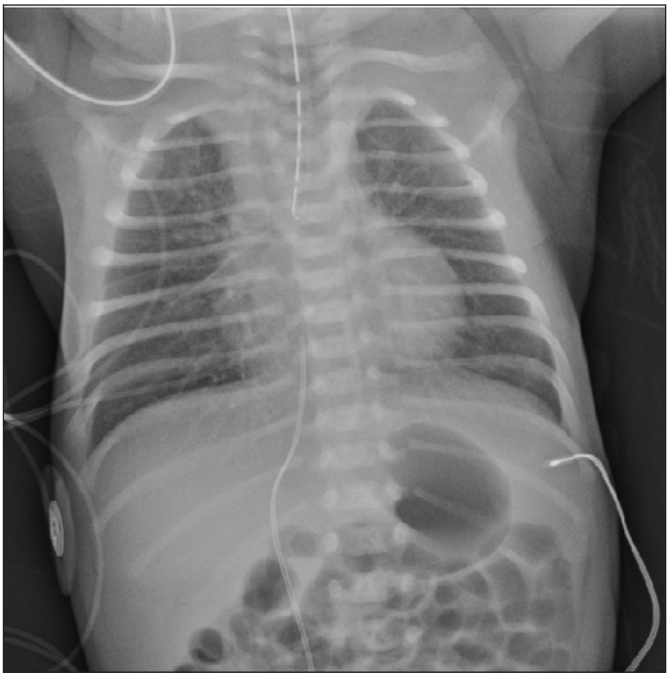

FIGURE 1: X-ray of a newborn with esophageal atresia. Note the nasogastric tube position in the blind-ending upper esophageal pouch.

After surgical repair of EA/TEF defects, patients continue to require follow-up due to high rates of anastomotic stricture, feeding difficulties, asthma, tracheomalacia and associated anomalies. Many of these patients have multiple providers and require frequent office visits resulting in a substantial burden to the families. The advantage of our multidisciplinary clinic is that it assembles the critical, necessary providers to create one comprehensive clinic visit that can address all of the patients' needs. Patients who are scheduled to be seen in our multidisciplinary clinic are discussed in depth during a conference held immediately prior to the clinic. Present at the conference are pediatric surgeons, gastroenterologists, otolaryngologists, pulmonologists, speech pathologists and dieticians. The goal of the conference is to review each patient's detailed history, associated anomalies and previous procedures to create a comprehensive management plan. The multidisciplinary team then sees the patient in a single clinic visit.

In order to advance the care of patients with EA/TEF, research is an integral component of the multidisciplinary clinic. All patients are asked to participate in an IRB-approved registry that records clinical outcomes and measures quality of life metrics. Additionally, researchers at MCW/CHW are principal investigators in a retrospective, multi-institutional trial conducted through the Midwest Pediatric Surgery Consortium (MWPSC) to examine demographics, outcomes and the variability in peri-operative

Esophageal Atresia

management in EA/TEF patients. The MWPSC (www.MWPSC.org) is composed of pediatric surgeons at 11 major Children's Hospitals that have come together to study rare surgical diseases. This collaboration has led to the largest contemporary cohort (396 patients) of patients with EA/TEF ever compiled. The study's findings were presented in October at the 2015 Congress of the American Academy of Pediatrics Meeting. Prospective trials are being developed in collaboration between CHW/MCW and the MWPSC to create evidence-based treatment protocols with a goal to unify care, improve outcomes and reduce costs.

Our institution has become a regional and national leader in the care of patients with EA/TEF. We are proud of the success of our multidisciplinary clinic and its ability to provide comprehensive care to patients in a single visit. Our commitment to families and patients with EA/TEF begins in the prenatal setting and extends into adulthood. We are providing patients and their families with exceptional and innovative care while advancing the field through research. Please feel free to contact us if we can provide further information regarding our clinic or research, or if you would like to refer a patient. •

FOR ADDITIONAL INFORMATION on this topic see references, visit mcw.edu/surgery or contact Dr. Lal, 414-266-6550, dlal@mcw.edu.

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2015 C. MORRISON SCHROEDER VISITING PROFESSOR: PIERRE-ALAIN CLAVIEN, MD, PHD

By: Johnny C. Hong, MD

Photo by Jay Westhauser

The annual C. Morrison Schroeder Visiting Professor Lectureship began in 1985 and honors C. Morrison Schroeder, MD, for his 30 years of service at the Medical College of Wisconsin. Dr. Schroeder, who joined the faculty in 1948, earned the reputation of being a tireless, dedicated, and highly esteemed surgeon, patient advocate, and educator. Our Schroeder Visiting Professor on October 2, 2015, was Pierre-Alain Clavien, MD, PhD, Professor and Chairman of the Department of Visceral and Transplant Surgery at the University Hospital of Zurich, Switzerland. Dr. Clavien has made significant contributions to the understanding of basic pathophysiology in liver disease, especially in the areas of organ preservation, ischemia reperfusion, liver regeneration, and cancer. In addition, he developed predictive scores for outcomes of liver operations, including the Clavien-Dindo classification system used for grading the severity of surgical complications. His Schroeder Memorial Lecture was entitled "Surgical Leadership: Do we need it and can we measure it?".

This year's lectureship was held in conjunction with the 3rd Annual Solid Organ Transplantation Research Symposium, on October 1-2. The Symposium is an interactive program that showcases state-of-the-art basic science and clinical/translational research in organ transplantation and immunobiology. Dr. Clavien presented the Solid Organ Transplantation Grand Rounds during the Research Symposium, "Liver Regeneration from Basic Science to the Clinic." He also led the group of representatives from the University of Zurich in formalizing an academic affiliation agreement between their University and the Medical College of Wisconsin. •

Identifying Exceptional Responders to Neoadjuvant

SUSAN TSAI, MD, MHS
Division of Surgical Oncology

In contrast to the remarkable strides being made with many other solid tumors, survival among patients with pancreatic cancer has not improved over the last thirty years. Even among patients with localized disease who undergo margin-negative resections, early disease recurrence occurs in the majority of patients. In the CONKO-001 study, a randomized trial which compared adjuvant gemcitabine to observation in patients with resected pancreatic cancer, 60% of patients developed recurrent disease within 6 months of successful surgery.[1] Preclinical experiments using genetically engineered murine models have also demonstrated that pancreatic cancers metastasize early in the pathogenesis of the disease, even before a primary tumor is large enough to be radiographically detected.[2] As a result, a growing number of clinicians and scientists now support the hypothesis that the majority of patients with pancreatic cancer will have systemic disease at the time of diagnosis, even in the absence of radiographic evidence of distant metastases.[3] Therefore, surgery is likely overutilized in patients who are treated with a surgery-first approach. The appropriate sequencing of surgery has important implications for oncologic therapy, as perioperative morbidity may temporarily or irrevocably delay systemic therapy. Given the limitations of diagnostic imaging to accurate identify micrometastatic disease, appropriate patient selection for surgery remains challenging and the development of prognostic biomarkers is needed.

One of the advantages of neoadjuvant treatment sequencing is that clinicians can, in part, overcome the limitations of diagnostic sensitivity to detect metastases by assessing a patient's biologic response to therapy over a limited time period. Approximately 10% of patients receiving neoadjuvant therapy will develop radiographic evidence of disease progression prior to surgery and an additional 10% of patients will have radiographically occult metastatic disease at the time of diagnostic laparoscopy. Identification of these patients, who have unfavorable tumor biology, is essential to avoid perioperative morbidity or mortality from an operation which will yield no oncologic benefit. Importantly, among patients who do not have disease progression during neoadjuvant therapy and are able to complete all neoadjuvant therapy and surgery, the median overall survival is 34 months – a number unmatched by any series of patients treated with a surgery-first approach[4, 5]

Despite the nearly 12 month improvement in overall survival among patients who are able to complete all intended neoadjuvant therapy and surgery, as compared to those treated with surgery-first, it is important to note that disease recurrence remains common. Additional prognostic markers are needed to further discriminate which patients are likely to develop early disease recurrence following completion of all intended therapy and surgery, and those who are more likely to have a prolonged survival benefit. We have recently identified two prognostic biomarkers which may further stratify patient survival following neoadjuvant therapy and surgery. In patients with pancreatic cancer, carbohydrate antigen (CA) 19-9 is a valuable tumor biomarker which has been inversely associated with survival. In particular, very elevated pre-treatment CA19-9 levels have been associated with median overall survival rates of only 12 months among patients treated with surgery-first.[6] We examined the prognostic value of post-treatment (pre-operative) CA 19-9 among patients with localized pancreatic cancer. We observed that pre-treatment CA 19-9 was inversely associated with survival, however among patients who were able to complete all intended neoadjuvant therapy and surgery, the prognostic value of the pre-treatment CA19-9 was attenuated.[7] In contrast, overall survival was correlated with post-treatment (preoperative) CA19-9 levels, independent of pre-treatment CA19-9 values. The median overall survival for patients who achieved normal (<35 mg/dL) post-treatment (pre-operative) CA19-9 levels was 46.2 months as compared to 26.4 months among patients with elevated post-treatment CA19-9 levels (log rank p = 0.03; Figure 1). Interestingly, among patients who completed all intended neoadjuvant therapy and surgery, failure to normalize post-treatment CA19-9 values after

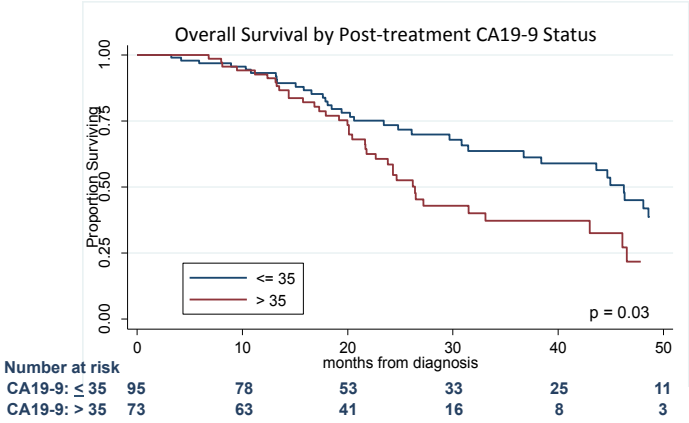

Figure 1: Overall survival of patients with resected pancreatic cancer after neoadjuvant therapy by post-treatment CA19-9 status. Overall survival of the cohort was 38.4 months. The median overall survivals for normal (blue) vs. elevated (red) post-treatment CA19-9 groups were 46.2 and 26.4 months (p=0.03).

t Therapy: Insights into Pancreatic Cancer Biology

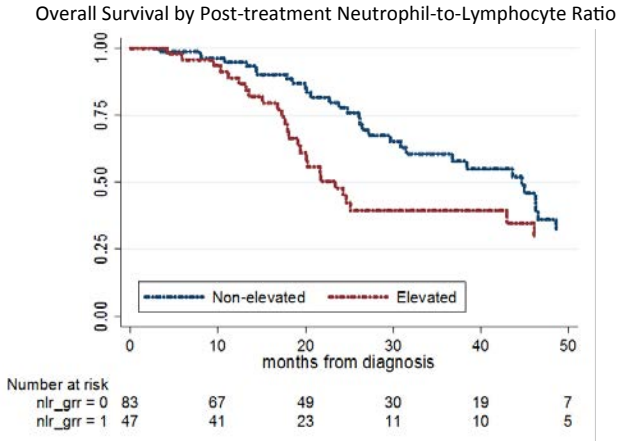

Figure 2: Overall survival of patients with resected pancreatic cancer by post-treatment (preoperative) Neutrophil-to-Lymphocyte Ratio (NLR). The overall survival of the cohort was 38.4 months. Patients with elevated NLR (red) had a median survival of 23.4 months as compared to 44.7 months among patients with a non-elevated NLR (blue). Log rank p-value = 0.02.

neoadjuvant therapy was the most powerful predictor of survival (HR: 1.74; 95%CI: 1.08-2.81, p =002), even after adjusting for borderline resectable disease (HR 1.55; 95%CI: 0.97-2.48, p =0.07) and node positive disease (HR 1.37; 95%CI : 0.84-2.24, p =0.21). These findings suggest that elevated pre-treatment CA19-9 should not be a contraindication to embarking on a potentially curative treatment program, and the magnitude of treatment response may be as important as the clinical and pathologic disease stage.

Another prognostic biomarker that has been examined in pancreatic cancer is the neutrophil to lymphocyte ratio (NLR), which is a marker of systemic inflammatory response. In the IMPACT trial, which randomized patients with metastatic pancreatic cancer to gemcitabine versus gemcitabine and nab-paclitaxel, elevated NLR was associated with decreased overall survival, independent of treatment assignment.[8] We hypothesized that post-treatment (preoperative) NLR would be a prognostic marker in patients with localized pancreatic cancer. We identified 174 patients who received neoadjuvant therapy for pancreatic cancer and observed that NLR was not associated with other prognostic factors including disease stage or post-treatment CA19-9 levels. Elevated NLR was inversely associated with survival; the median overall survival of patients who completed all neoadjuvant therapy and surgery was 23.4 months versus 44.7 months for patients with elevated versus non-elevated NLR (log rank p = 0.02; Figure 2). Interestingly, as with CA19-9, we observed that post-treatment (preoperative) NLR, but not pre-treatment NLR, was associated with overall survival. This is an unexpected observation, which suggests that the neoadjuvant therapy may be effective not only through direct tumor cytoreduction but may also modify the host immune response. The monitoring of prognostic biomarkers during neoadjuvant therapy may provide clinicians with a more accurate estimation of a patient's tumor biology than can be obtained through clinical and pathologic staging alone. In the future, significant prognostic factors can be combined and used for risk prediction to better predict individual oncologic outcomes. Moving forward, we plan to develop a nomogram for patients with pancreatic cancer who have completed neoadjuvant therapy, to assist patients and physicians conceptualize disease burden and to improve decision-making regarding the utility of surgery at an individual level. •

FOR ADDITIONAL INFORMATION on this topic see references, visit mcw.edu/surgery or contact Dr. Tsai, 414-805-5084, stsai@mcw.edu.

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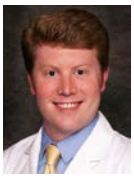
Improving Metastatic Colorectal Cancer Survival: Colorectal Liver Metastases



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Colorectal cancer is the third most common cancer diagnosis in the United States, and the second leading cause of cancer death. Although screening and treatment have improved with surgical technique, chemotherapy, and radiation advances, about half of patients will present or develop colorectal liver metastases (CRLM). Data in the literature from the past decade has shown that with resection, 5-year survival rates can reach 75%. The presence of metastases in both lobes may exclude patients from surgical resection if an adequate remnant of liver is not available.[1] Recent data shows that in well-selected patients, a two-stage liver resection can achieve similar survival rates to those with a single-stage approach used for more limited disease.[2]

Two-stage hepatectomy is performed for patients with bilobar metastatic disease. In most cases, the right lobe carries the majority of the disease burden, with the left lobe relatively spared (Figure 1). In these cases, patients typically receive systemic chemotherapy, and tumor response is assessed. Patients then undergo an operative approach to "clear" the left lobe with ablation or wedge resection.[3] Shortly following surgery, portal vein embolization (PVE) of the right lobe is typically performed, which provides hypertrophy of the future liver remnant on the left side (Figure 2).[4] Patients may receive additional chemotherapy during the six weeks that the left lobe increases, and are then taken back to the operating room for a right hepatectomy. The remaining left lobe has then grown to provide sufficient hepatic reserve (Figure 3).

Patients with bilobar CRLM clearly benefit from coordinated multidisciplinary care, including appropriate imaging techniques with delayed and diffusion-weighted MRI or dual-phase computed tomography, skilled interventional radiologists able to perform PVE, and a surgeon proficient at liver resection in addition to thoughtfully administered chemoradiotherapy.[5] Patients are frequently reassessed for tumor response to locally directed and systemic therapies prior to planning a two-stage approach, functional liver remnant volume and liver hypertrophy following PVE are assessed to avoid postoperative hepatic insufficiency.

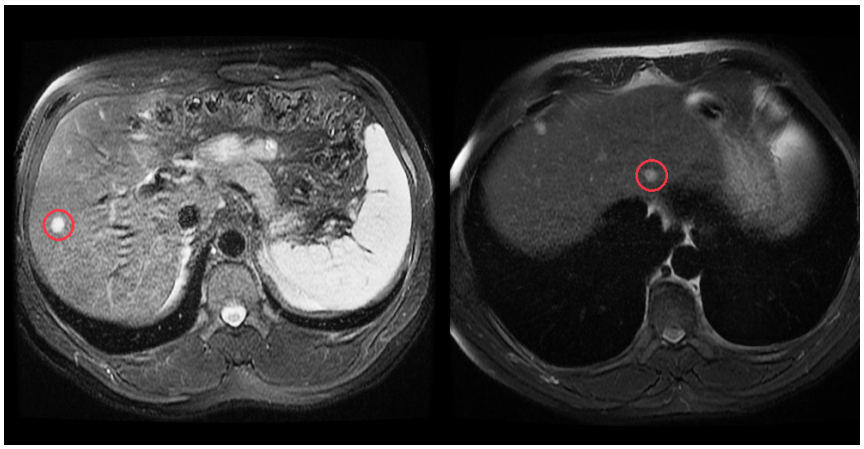

Figure 1: Liver MRI showing bilobar colorectal metastases.

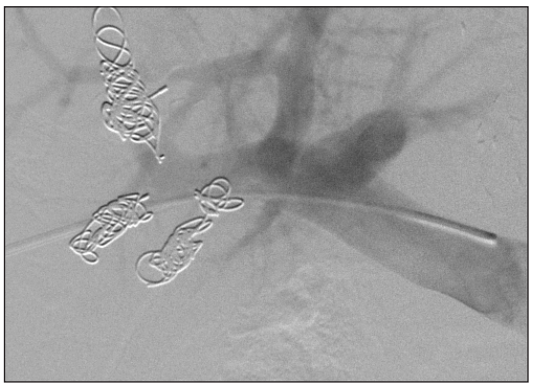

Figure 2: Right portal vein embolization for extensive right lobe disease.

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is another new technique for managing bilobar CRLM. In this technique, the liver is divided partially or fully along the segmental line (Cantlie's line), and the portal vein supplying the lobe with the highest disease burden is ligated. The remaining lobe hypertrophies, and the patient is then taken back to surgery for completion hepatectomy during the same hospitalization. This typically occurs 7-10 days following the first operation. While successful at removing disease, preliminary data demonstrates a concerning 13% short-term mortality.[6] Dr. Pierre-Alain Clavien recently visited the Medical College of Wisconsin and reported impressive ALPPS results from his unit in Switzerland. Compared to ALPPS, the two-stage approach reports short-term mortality less than 5%, but most studies are small in size, and a large multi-institutional report has not occurred.[2,7]

The Role of Two-Stage Hepatectomy for Bilobar

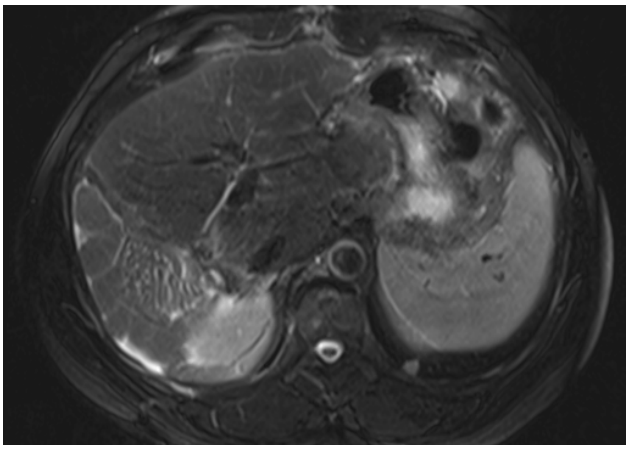

Figure 3: Follow-up liver MRI after left wedge resections/ablations, right PVE and right hepatectomy.

Research being performed in the Department of Surgery's Division of Surgical Oncology is focusing on multi-institutional experiences with two-stage hepatectomy for colorectal liver metastases. Through collaboration, this information could prove powerful in directing therapy for patients with bilobar liver metastases, and reinforce data supporting surgical resection as a key prognostic factor in metastatic cancer. This research could also provide valuable insight into systemic and locoregional therapy options as adjuncts to colorectal cancer treatment and the effectiveness of portal vein embolization.

In conclusion, bilobar liver colorectal metastases are challenging and require multidisciplinary care. Liver resection is effective in the management of metastatic disease. Portal vein embolization combined with surgical resection of cancer in a single lobe allows healthy tissue to hypertrophy to an acceptable volume and thus provide a curative second-stage approach. More outcomes research are needed regarding locoregional and systemic therapy for bilobar colorectal liver metastases. Safer treatment options are now available for patients with advanced disease, allowing for improved survival. •

FOR ADDITIONAL INFORMATION on this topic, see references, visit mcw.edu/surgery or contact Dr. Gamblin, 414-805-5020, tcgamblin@mcw.edu.

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Transarterial Chemoembolization: An Effective Transjugular Intrahepatic Portosystemic Shunts

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Transarterial chemoembolization (TACE) has emerged as an effective treatment strategy for patients with hepatocellular carcinoma (HCC).[1] Unlike surgery or transplantation, which are dependent on patients having resectable disease or the availability of suitable organs, studies have demonstrated TACE to be effective for patients with advanced disease.[2] However, TACE is not without its limitations, as current treatment guidelines recommend patients have compensated liver disease along with overall good performance status when considering this approach.[3] The presence of cirrhosis and its associated complications from portal hypertension, which include variceal bleeding and ascites, often complicates decision-making and traditionally may preclude a patient from receiving TACE.

Placement of transjugular intrahepatic portosystemic shunts (TIPS) has become a widely used technique in managing the sequelae of portal hypertension. However, since TIPS reduces hepatic perfusion by diverting portal venous flow and may potentiate arterioportal shunting, TACE has not been commonly performed in this subgroup due to concern for potential worsening of hepatic dysfunction, transient increase in portal hypertension, and risk of hepatic infarct. Unfortunately, with the rising incidence of HCC among western countries, there has been a corresponding increase in the number of HCC cases with TIPS in need of loco-regional therapy. In recent years, several studies have investigated the feasibility of TACE in patients with a functional TIPS[4-6]. While all the studies were limited by a small sample size, the rates of TACE-related complications are variable (5-70%). Due to the paucity of data surrounding this subject, we recently evaluated our institution's experience surrounding the safety and efficacy of TACE for HCC patients after TIPS placement.

From 1999–2014, 16 patients with HCC and TIPS underwent a total of 27 TACE procedures at the Medical College of Wisconsin. Eight of the 16 patients required at least two treatments (50%), while an additional three patients (18.8%) underwent a third TACE session. Selective chemoembolization was performed using a standard protocol consisting of 100 mg cisplatin (Baxter, Glendale, CA), 50 mg doxorubicin (Pharmacia & Upjohn, Peapack NJ), and 10 mg mitomycin-C (Super Gen, Dublin, CA), combined with Ethiodol (Guerbet LLC, Bloomington, IN) in a 1:1 ratio without PVA particles. Due to a drug shortage, six patients did not receive cisplatin as part of their TACE regimen. Prior to initial TACE, the median MELD score was 12.5 (7.5-13), with the vast majority being either Child's Class A or B (n=14, 87.5%). While current treatment guidelines often advise against routine TACE in Child's Class C patients, two individuals in the present series underwent therapy. In both patients, a super selective TACE approach involving only the third order or greater hepatic artery branches was utilized in order to minimize exposure of the normal hepatic parenchyma to the cytotoxic agents.

Within six weeks of each TACE session, Clavien grade 3 or higher complications occurred three times (11.1%, Table 1). Of the 16 patients that underwent TACE, four patients accounted for all reported complications (25%). The most common hepatobiliary severe adverse event (SAE) was the development of ascites post-TACE (n=3, 11.1%). Hepatic failure, which was defined as the evolution of encephalophathy or asterixis, occurred in two patients (7.4%). A greater frequency of peri-procedure complications was observed during subsequent TACE sessions (n=5, 45.4%) as compared to the initial treatment (n=2, 12.5%). There were no peri-procedural (within 30 days) deaths following TACE.

Treatment Strategy for Patients with

	First TACE (n=16)	Subsequent TACE (n=11)	All TACE (n=27)
Clavien Grade ≥III Complication, n (%)	0	3 (27.3)	3 (11.1)
Hepatobiliary Severe Adverse Events			
Total Bilirubin, n (%) Grade 3/4: Total bilirubin > 3 x ULN	0	2 (18.2)	2 (7.4)
AST, n (%) Grade 3/4: AST > 5 x ULN	0	0	0
ALT, n (%) Grade 3/4: ALT > 5 x ULN	0	0	0
Ascites, n (%) Grade 3: severe symptoms requiring invasive intervention	0	3 (27.3)	3 (11.1)
Hepatic Failure, n (%) Grade 3: asterixis, mild encephalopathy	2 (12.5)	0	2 (7.4)
Mortality, n (%) Within 30 days of procedure	0	0	0

Table 1. TACE-related morbidity among HCC patients with a TIPS TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; TIPS, transjugular intrahepatic portosystemic shunt.

After TACE, by mRECIST criteria, two patients (12.5%) demonstrated a complete response, 7 patients (43.8%) experienced a partial response, 6 (37.5%) had stable disease, and one had disease progression (6.2%). The objective response (complete + partial response) and disease control (complete + partial response + stable disease) rate were 56.3% and 93.8%, respectively. The median progression-free survival and overall survival, after censoring for liver transplantation, were 9 and 22 months, respectively. Additionally, at one year, the OS survival rate was 73.9%.

Our institutional experience provides further evidence supporting locoregional therapies as a safe and effective therapy for HCC patients with a TIPS. While several other series have reported their outcomes surrounding this patient subgroup, treatment-related morbidity has been variable, which can be partially attributed to the lack of standardized protocols. Although the omission of embolic particles, as routinely performed at MCW, may limit the extent of ischemic necrosis that occurs with TACE, it did not appear to affect treatment efficacy. For non-TIPS HCC patients, prior studies that utilized a TACE regimen consisting of cisplatin, doxorubicin, and mitomycin-C have demonstrated median OS survival rates ranging from 15-18 months following TACE,[7] a survival benefit similar to what we have demonstrated here at MCW for HCC patients with a TIPS. Moreover, TACE without embolic material has the potential to be a safer approach for patients with TIPS, as it spares normal hepatic parenchyma from further damage. Therefore, the presence of a TIPS should not preclude HCC patients from receiving a therapy that can achieve a durable survival benefit. These results provide further evidence to support an expanded role for TACE that now includes patients with a TIPS. •

FOR ADDITIONAL INFORMATION on this topic, see references, visit mcw.edu/surgery or contact Dr. Gamblin, 414-805-5020, tcgamblin@mcw.edu.

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Leading the Way

John A. Weigelt, MD, DVM, FACS

John A. Weigelt Receives American College of Surgeons' Distinguished Award

The American College of Surgeons' annual Clinical Congress was held in Chicago on October 4–8, 2015. The Annual Clinical Congress gives surgeons the opportunity to interact with colleagues, present their most recent work and learn the current advances in surgical research and technology.

Each year the American College of Surgeons chooses one person to receive the Distinguished Service Award. This award is considered their highest honor. This year, John A. Weigelt, MD, DVM, FACS, Division of Trauma/CC/ACS, was selected for this award. The American College of Surgeons' chose Dr. Weigelt to receive this award according to the citation "in appreciation of his continuous and devoted service as a Fellow of the American College of Surgeons" and "in recognition of his superb skills in synthesizing and applying surgical knowledge and conveying effectively critical concepts to learners that have positively impacted the practices of numerous surgeons." Dr. Weigelt has directed the SESAP program and is largely responsible for continuing medical education for surgeons throughout the world. The Department of Surgery congratulates Dr. Weigelt on this great honor; it is well-deserved and reflects his many years of leadership and accomplishments at the Medical College of Wisconsin and in the American College of Surgeons.

Kathleen O'Connell, MD

General Surgery Resident Awarded MCWAH 2015 Research Award

Kathleen O'Connell, MD, was among the recipients for the MCWAH 2015 Research Awards, which recognizes housestaff employed by MCWAH for excellence in research. Dr. O'Connell was nominated by her program director, and selected by the MCWAH Research Committee, comprised this year of Drs. Jonathan Bock, Thomas Ebert, Tina Yen and Kenneth Simons.

The award-winning research, titled *Availability of Post-Discharge Nursing Facilities and the Impact on Discharge Disposition and Location of Death in Elderly Trauma Patients* was presented in December, 2014 at the Region 5 Committee on Trauma Annual Meeting.

Dr. O'Connell is currently completing her fellowship in Critical Care and masters degree in Public Health at the University of Washington in Seattle.

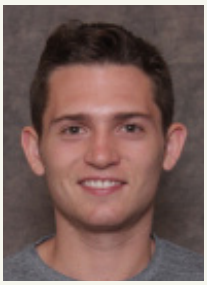
Jason Glenn, MD

General Surgery Residents Win Research Awards

Nathan Kugler, MD

Congratulations to our General Surgery residents who won awards at the annual Wisconsin Surgical Society meeting on November 13-14, 2015. Jason Glenn, MD, won the *Wisconsin Surgical Society Clinical Science Research Award – Cancer Competition* with his abstract titled "Management of Suspected Adrenal Metastases: A Bi-institutional Review." Jason completed this project under the mentorship of Dr. Tracy Wang.

Nathan Kugler, MD, won *Best Trauma Paper November 2015* with his abstract titled "Thoracostomy Tube Function, Not Intra-Thoracic Placement Dictates Need for Secondary Intervention."
Nathan completed this project under the mentorship of Thomas Carver, MD; Paul Knechtges, MD; David Milia, MD; Lawrence Goodman, MD; and Jasmeet Paul, MD.



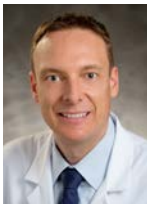
Joseph Katz, BS

2015 Fall Research Symposium Winner

Congratulations to Joseph Katz, second-year Medical Student, winner of the *2015 Fall Research Symposium – Medical Student Division*, with his abstract titled "Absence of IAP Leads to Increased Bacterial Translocation." He worked on this project with David Gourlay, MD, Division Chief of Pediatric Surgery. MCW Medical Students were given the opportunity to submit and present their research to faculty and staff on Friday, October 23, 2015.

DEPARTMENT OF SURGERY
Education Award Recognitions

At the 2015 MCW Convocation Ceremony, the Department of Surgery was well represented for the educational excellence of its faculty. **Brian Lewis, MD**, was recognized as one of the new members elected to the MCW Society of Teaching Scholars (STS). The mission of the STS is to, "by example and action, stimulate innovation in medical education and represent excellence in education in faculty forums." Dr. Lewis joins other surgical faculty as current STS members including Philip Redlich, MD, PhD, Travis Webb, MD, MHPE, John Weigelt, DVM, MD, and Stuart Wilson, MD. Dr. Lewis serves as the Surgery Clerkship Director and recently attained Fellow Certification from the Association of Surgical Education Academy of Clerkship Directors.



Andrew Kastenmeier, MD, was recognized as a recipient of the *Edward J. Lennon Endowed Clinical Teaching Award.* The STS presents this award to faculty members early in their career who have clearly "made a difference" in MCW's teaching programs. Dr. Kastenmeier also serves as Associate Clerkship Director for the Department of Surgery.

Kellie Pettit, MD, was recognized as a recipient of the *Marvin Wagner, MD, Clinical Preceptor Award*. The STS presents this award to volunteer clinical faculty who exhibit enthusiasm, selfless dedication, effective teaching and outstanding commitment to medical education. Dr. Pettit serves as the site director at Waukesha Memorial Hospital for the Surgery Clerkship and actively participates in teaching on our campus as well.

Additional recognition went to **Theresa Krausert, BA**, Education Program Coordinator in the Division of Education, who received a *Learning Resources Fund Innovative Educational Project Award* as a co-author on the project entitled "Standardized Patients as Teachers of the Physical Exam."

Munyaradzi Chimukangara, MD, PGY4 General Surgery Resident, was recognized with the *Resident Research Day Poster Award* for his research presentation entitled "The Impact of Frailty on Outcomes Following Paraesophageal Hernia Repair Using NSQIP Data," co-authored with Matthew J. Frelich, MS, Matthew Bosler, BA, Lisa E. Rein, MS, Anika Szabo, PhD, and Jon C. Gould, MD.

Outstanding Medical Student Teachers Recognized

The Curriculum and Evaluation Committee (CEC) annually awards the MCW Outstanding Medical Student Teacher recognition pins. The CEC wishes to "recognize and affirm those individuals who, through their teaching excellence, advance student learning and provide added value to students' required medical training." Pins are awarded to faculty and residents for contributions in courses, clerkships, pathways, subinternships, or electives. The 2014-2015 Outstanding Medical Student Teacher Pin recipients from the Department of Surgery include the following individuals:

Full-Time Faculty

G. Hossein Almassi, MD; Marshall Beckman, MD, MA; Kellie Brown, MD; Thomas Carver, MD; Mario Gasparri, MD; Matthew Goldblatt, MD; David Gourlay, MD; George Haasler, MD; Christopher P. Johnson, MD; Fabian Johnston, MD; David Johnstone, MD; Jeremy Juern, MD; Andrew Kastenmeier, MD; Dean Klinger, MD; Amanda Kong, MD, MS; Dave Lal, MD, MPH; Brian Lewis, MD; Todd Neideen, MD; Mary Otterson, MD; Jasmeet Paul, MD; Philip Redlich, MD, PhD; Allan Roza, MD; Kiran Turaga, MD, MPH; and Amy Wagner, MD.

Volunteer Faculty

Joseph Battista, MD; Alysandra Lal, MD; Anthony Nelson, MD; Zane Prewitt, MD; Craig Siverhus, MD; and Mark Timm, MD.

Residents

Fadwa Ali, MD; Betsy Appel, MD; Ryan Berg, MD; Nicholas Berger, MD; Jacqueline Blank, MD; Justin Dux, MD; Charles Fehring, MD; Stephen Masnyj, MD; Thejus Jayakrishnan, MD; Robert McMillan, MD; and Lindsey Zimmerman, MD.

MEDICAL COLLEGE OF WISCONSIN

HISTORY CORNER

Multiple Coronary Artery Vein Bypass: A Milwaukee Innovation (1968)

By Stuart D. Wilson, MD, Division of Surgical Oncology

The Edwin Ellison era of the 1960s brought together a unique group of physician–scientists to the Milwaukee County Medical Complex at a time when Marquette University School of Medicine Department of Surgery's new Allen-Bradley Medical Science Laboratory (ABMSL) had just opened for business. Dr. Derward Lepley Jr. was one of Dr. Ellison's first faculty recruits and was appointed Chief of Cardiovascular Surgery at the Milwaukee County Hospital in 1962. Dr. Lepley completed his General Surgery and Thoracic Residency at the Wood VA Hospital, and then did a Cardiovascular Fellowship with Dr. Walton Lellehei in Minneapolis. Dr. Dudley Johnson completed his General Surgery and then a Thoracic-Cardiovascular Residency at the Milwaukee County and Marquette-Affiliated Hospitals (1959–65) before joining Dr. Lepley on the faculty.

Derward Lepley Jr., MD

Dudley Johnson, MD

In 1965, the favored method for revascularizing ischemic heart muscle for angina pectoris was the Vineberg procedure – achieved with a pedicle system of the left mammary artery. A typical vascular pedicle had 5–9 side branches that were implanted into heart muscle. Direct coronary artery surgery procedures were first initiated by Dr. Dudley Johnson in 1967 at the Milwaukee County Hospital. While a "single" coronary artery bypass graft technique had been done at the Cleveland Clinic in 1967, the Milwaukee group was the first worldwide to perfect, report, and study outcomes of the multiple coronary graft technique which was based on the important concept of "total revascularization." A single coronary vessel bypass could revascularize only a small portion of the heart wall muscle, so multiple coronary vein grafts proved to be a great advantage.

The Department of Surgery Allen-Bradley Medical Science Lab was the site for early cardiac surgery research. This research was supported by Ken Kayser (engineering), "Ace" Adams (cardiac perfusionist), and the surgical residents and cardiothoracic fellows doing research rotations. Devices and methods for identifying and measuring cardiac conduction systems, cardiac oxygenation and perfusion, and blood flow in vein grafts were developed.

Multiple coronary artery bypass graft (CABG) procedures rapidly evolved in Milwaukee; more than 4,000 procedures were performed over the next decade. An average of 4.3 grafts per patient was accomplished during 1979. Coronary endarterectomy was also done on 27% of these patients.

The first multiple CABG cases were done at the Milwaukee County Hospital and the Wood VA. Froedtert Hospital would not be completed on the Milwaukee County campus until 1980. In those days (late 1960s), referred/private patients could not be operated on in the county institutions, so Dr. Ellison's full-time faculty operated in other Milwaukee hospitals. The medical school had no medical service plan, no clinical revenues, and few resources, so these outside operations were necessary to retain and grow the faculty and keep the medical school solvent at a time of great financial stress. Between 1968–1969, Drs. Johnson and Lepley operated on many patients at St. Luke's Hospital, training cardiothoracic fellows from the Marquette Medical School (now MCW) surgery program.

One of the world's first heart transplants was carried out by the Lepley/Johnson team in 1968. That patient was the world's longest-surviving heart transplant (8 years) at that time—before modern immunossuppressant drugs.

The volume of cardiac operations, particularly CABG's, grew very rapidly. Several other cardiac surgeons were recruited to join the Lepley/Johnson team. These surgeons were Drs. Robert Flemma, Alfred Tector, and James Auer. The cardiologists who initially had leadership roles and/or trained in the Milwaukee County Hospital were most important for the successes in the early cardiac surgery program. Among the first were Drs. John Walker, John Houston, and Jack Manley. They spearheaded the cardiac group's efforts in developing the Milwaukee Cardiovascular Data Registry which led to important discoveries about key risk factors, natural history, and outcomes of coronary bypass operations. More than 12,000 patients with follow-up were registered. Dr. Dudley Johnson hosted the world's first conference on coronary artery vein bypass surgery. Dr. Lepley stepped down as the full-time Chairman of Cardiothoracic Surgery at the Medical College of Wisconsin in 1974.

It has been said that "everything happened in the 1960s." The MCW Department of Surgery leaders had an early vision for a cardiac program to train medical students, surgical residents and cardiovascular fellows as well as to care for patients and advance medical knowledge through research. These surgical pioneers left their legacy. The coronary bypass procedure would soon become the world's most frequently performed cardiac operation.

Open heart operations and CABG procedures are now performed in six Milwaukee area hospitals. Most of the cardiac surgeons working in these hospitals can trace their surgical lineage and skills back to the original Lepley/Johnson team and the Department of Surgery's Allen-Bradley Medical Science Laboratory. •

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MARK YOUR CALENDARS

Upcoming Events

March 8-9: Robert Higgins, MD – 43rd Annual Edwin H. Ellison Visiting Professor

April 22: Acute Care Surgery Symposium – Miller Park

May 6: MCW & University of Texas M. D. Anderson Cancer Center Endocrine Surgery Symposium – Lambeau Field

May 10-11: Bruce Gewertz, MD – 9th Annual Jonathan B. Towne Visiting Professor

May 17-18: Rosemary Kozar, MD – 36th Annual Milton Lunda Visiting Professor

June 17: David Hoyt, MD – 56th Annual Carl W. Eberbach Visiting Professor

June 22: Ron Hirschl, MD – 15th Annual Glicklich Visiting Professor

September 27-28: Steven Libutti, MD – 30th Annual C. Morrison Schroeder Visiting Professor

October 13: Vascular Access Symposium – Medical College of Wisconsin

November 11: NANETS Symposium – Milwaukee Marriott Downtown

NEW FEATURE: *We now offer ABMS MOC Part 2 Self-Assessment credit for our Grand Rounds Lectures. Scan the QR code to proceed.*

Please contact Heidi Brittnacher (hbrittna@mcw.edu) for more information on any of these events.

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- Surgical Oncology
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