The Department of Cardiothoracic Surgery at UPMC

CARDIOTHORACIC SURGERY UPDATE

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As founding chairman of the UPMC Department of Cardiothoracic Surgery, I am proud to present this issue of *Cardiothoracic Surgery Update*.

Throughout our history, our department has served as a source of pioneering advancements and innovation in the fields of thoracic and foregut surgery, adult cardiothoracic surgery, pediatric cardiothoracic surgery, and cardiothoracic transplant. Today, we continue to strive for excellence in patient care, high-quality training for the next generation of surgical leaders, and continuous innovation, including the use of the latest technologies and engagement in leading scientific and clinical research.

In this issue, we celebrate the accomplishments of our dedicated faculty and provide updates on upcoming events, clinical trials, and research initiatives. From the Division of Lung Transplant/Lung Failure, we share the innovative work of chief Jonathan D'Cunha, MD, PhD, FACS, as he works to decrease instances of organ rejection in transplant patients. We explore the determination of Victor Morell, MD, chief of the Pediatric Cardiothoracic Surgery division and co-director of the UPMC Heart and Vascular Institute, to find better solutions for children requiring RVOT reconstruction. We are also pleased to share our progressive work with near-infrared fluorescence imaging and expertise with the POEM operation for achalasia. Additionally, this issue discusses TAVR for aortic stenosis and expanding the donor pool for heart transplant.

I am extremely proud of our department and our continued plans for clinical and academic growth. I look forward to keeping you up to date on future progress and developments.

Please visit UPMCPhysicianResources.com/ThoracicSurgery for more information about our program.

James D. Luketich, MD, FACS

Henry T. Bahnson Professor and Chairman,
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Chief, Division of Thoracic and Foregut Surgery

Director, UPMC Esophageal and Lung Surgery Institute

Director, Thoracic Surgical Oncology

UPMC LIFE CHANGING MEDICINE

Expanding the Donor Pool in Heart Transplantation: A Clinical Trial Examining the Use of Hepatitis C-positive Donor Hearts in Hepatitis C-negative Recipients

Christopher Sciortino, MD, PhD
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The biggest hurdle to heart transplantation is the availability of donor organs. Approximately 2,500 heart transplants are conducted in the U.S. each year, despite a transplant waiting list of about 4,000 patients. The UPMC Department of Cardiothoracic Surgery, Division of Adult Cardiac Surgery and Heart Transplant, is conducting a clinical trial to test the feasibility of expanding the donor pool by allowing transplantation of hearts from donors with hepatitis C virus (HCV) to recipients who are not infected with hepatitis C. This trial could unearth an evidence-based, safe, and feasible way to expand the pool of acceptable donated organs from young, high-quality donors and improve the standard of care for heart transplant patients.

Although organs from HCV-positive donors have occasionally been offered to HCV-positive recipients, individuals with HCV are traditionally excluded from the donor pool, especially for heart transplantation. Before they are transplanted, all organs are screened for anti-HCV antibodies and undergo HCV nucleic acid testing (NAT), which detects an active virus. A positive test for HCV antibodies coupled with a negative HCV-NAT usually means that the donor had an active HCV infection that spontaneously resolved or was effectively treated. In a small percentage of donors, an HCV-antibody-positive/HCV-NAT-negative status is the result of a false-positive or false-negative result in one of the assays. In 2016, the American Society of Transplantation published a position statement in support of examining the use of HCV-antibody-positive organs in HCV-negative recipients in light of the effective, oral, direct-acting antiviral therapies against HCV that are now available and the pressing need to increase the donor pool for organ transplantation.

Demand for transplantable organs vastly outpaces the supply of donor organs for all types of solid organ transplants. In the U.S., 1.8% of the population has HCV. A study published in the June 2017 issue of *American Journal of Transplantation* estimated that 37 more hearts would be available for transplant per year if HCV-antibody-positive/HCV-NAT-negative donors were considered. These donors represent the same population being analyzed in UPMC's ongoing clinical trial. Others have estimated that organ availability may increase by about 15% if donors who are HCV-positive, but medically suitable otherwise, can be included in the donor pool.

As recently as 2010, this approach was not possible. Medical treatment of hepatitis C was only effective in a subset of patients with HCV and could not be used in immunocompromised patients. However, over the last seven years, treatment for hepatitis C has advanced from interferon-based therapies to direct-acting antiviral agents. These newer medicines, such as sofosbuvir/velpatasvir, have a much higher cure rate in patients with active HCV (>95% as measured by sustained virologic response); produce manageable side effects; and can be used in immunosuppressed patients. Although they are relatively new, direct-acting antiviral agents are changing treatment paradigms for patients with HCV. These treatment advances, combined with the donor organ shortage, mean that patients in need of a heart transplant are generally more likely to die while on the transplant waiting list than from hepatitis C or its treatment.

UPMC's clinical trial (NCT03222531) began enrollment on Aug. 1, 2017. We plan to enroll 100 patients in what is anticipated to be a two-year study. In terms of outcomes, we will primarily assess survival after heart transplant, along with the incidence of HCV viremia and rate of HCV seroconversion. Each time blood is drawn from the transplant recipient during routine follow-up appointments, the blood will be screened for HCV. Because organs from donors with hepatitis C antibodies and not donors with active hepatitis C infection (NAT-negative) are only being accepted, the risk of transmission of HCV from donor to recipient may be low. Additionally, the heart is not a lymphatic organ or a target organ for HCV, which may also lower the risk of HCV transmission.

Patients who contract HCV will be treated with direct-acting antiviral therapy. There is no evidence suggesting that anti-HCV therapy will affect either allograft rejection or cardiac function in the transplanted hearts. Nonetheless, these will be assessed as part of the trial to verify the safety of the approach. Major side effects of the drugs are not expected in heart transplant recipients. The donor hearts accepted for the trial must meet more stringent criteria than a standard heart transplant. The match between donor and recipient must also be better. We included these measures to give the clearest answers regarding the safety and efficacy of the strategy in this first study. To move forward, the concept must be tested in a measured and progressive fashion. We anticipate that the trial will allow for at least two heart transplants per month that would not have been performed using standard criteria and currently accepted extended-donor criteria. The effect of this increased availability of donor hearts, and shortening of waitlist times, will be assessed.

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Aortic Valve Replacement at UPMC: Customizing Treatment Options for Patients with Aortic Stenosis — Open Surgery vs. TAVR

Ibrahim Sultan, MD
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Thomas G. Gleason, MD
Ronald V. Pellegrini Professor and Chief, Cardiac Surgery
Co-Director, UPMC Heart and Vascular Institute

Approximately 180,000 Americans are diagnosed with aortic stenosis every year, with 2% of people over age 65 and 4% of people over age 85 affected by the disease. Aortic stenosis is one of the most common pathologies that cardiac surgeons treat. Aortic stenosis can lead to heart failure and other complications, as the narrowing of the aortic valve forces the heart to work harder to meet the body's needs, eventually leading to sudden death if untreated. Medications are available to treat some symptoms of aortic valve stenosis, but not the stenosis itself. Until recently, open surgical aortic valve replacement was the only option for patients with severe aortic stenosis, and open surgery continues to be the standard of care for treating aortic stenosis. Patients who could not undergo surgery had no other options. Fortunately, this situation is being rectified with the advent of transcatheter aortic valve replacement (TAVR). Prosthetic valves, which are less than a quarter-inch wide initially, are inserted peripherally via the femoral artery or subclavian artery. Once placed, the prosthetic valve expands and resumes the function of the diseased aortic valve.

The surgeons in the Division of Adult Cardiac Surgery within the UPMC Department of Cardiothoracic Surgery are experts in both open surgical aortic valve replacement and TAVR, having performed nearly 1,000 TAVR procedures since 2011. UPMC is the only program in the region to have four different types of catheter valves available for implantation, two of which are FDA-approved (Medtronic CoreValve® and Edwards SAPIEN 3 valve) and two of which are available in the U.S. through clinical trials only.

Our patients benefit from this access to multiple devices. The anatomy of some patients is not amenable to certain types of valves or valve delivery systems, but with more than one choice available, we can precisely match the valve to the patient's needs. For example, some TAVR systems offer better protection against paravalvular leaks and others have smaller delivery systems. Additionally, at UPMC, every TAVR procedure is performed by a surgeon and a cardiologist. We meet multiple times per week and work together every day to take care of our patients. Our goals and the goals of our colleagues in the Division of Cardiology are the same, so the patient gets double the expertise for the entirety of the TAVR procedure. This collaborative environment at UPMC is advantageous to both the patients and the physicians, improves patient safety, and allows for customized care.

The most common TAVR approach is through the femoral artery in the groin. At UPMC, the patient often remains awake while the transfemoral TAVR is performed, avoiding the risks associated with general anesthesia. If transfemoral access is not feasible, alternative access routes must be utilized. UPMC is one of the leading sites in the U.S. using alternative access through the left subclavian artery in patients with poor transfemoral access. We perform subclavian TAVR frequently and with equally good results.

The UPMC Division of Adult Cardiac Surgery is among an exclusive group of centers driving innovation in TAVR and expanding the indications for this minimally invasive procedure. UPMC has been a participating center in all the major groundbreaking studies of TAVR. Currently, we are enrolling patients in a trial sponsored by Medtronic examining TAVR in patients who are considered to be at a low risk for mortality from aortic valve surgery — less than 3% as calculated by the Society of Thoracic Surgeons' predicted risk of mortality (PROM) score. The patients in this trial are randomized to receive either open surgical valve replacement (the current standard of care) or TAVR, so equal numbers of patients will undergo each procedure. The patients will be followed for up to 10 years, allowing us to assess long-term outcomes with confidence. This trial (ClinicalTrials.gov identifier: NCT02701283) tests the standard of care for aortic stenosis against a powerful new technique and, as such, is promoting important advances in cardiac surgery.

In Allegheny County and the surrounding counties, 15-19% of the total population is over the age of 65. In caring for this patient population, we perform a large number of valve surgeries and have developed innovative techniques that we use routinely during aortic valve replacement. Through these surgical innovations and our participation in clinical trials, such as the low-risk trial, we are able to offer our patients either TAVR or open surgery, as needed, to address their aortic disease. Open surgery for aortic valve replacement is still the gold standard for treatment of aortic valve stenosis, and we have achieved extremely good results with the procedure.

In summary, TAVR provides an excellent alternative treatment option for patients with severe aortic valve stenosis who have an extremely high, high, or intermediate risk for mortality as a result of surgery. We are currently testing the role of TAVR in low-surgical-risk patients. The TAVR program at UPMC is one way that we are driving innovation to improve and customize care for our patients with aortic valve disease.

Reconstruction with Valved PTFE Conduits in Patients with Congenital Heart Defects Affecting the Right Ventricular Outflow Tract

Victor Morell, MD
Eugene S. Wiener Professor of Pediatric Cardiothoracic Surgery
Vice Chair and Director, Cardiovascular Services, Department of Cardiothoracic Surgery
Chief, Pediatric Cardiothoracic Surgery
Co-Director, UPMC Heart and Vascular Institute
Co-Director, Heart Institute, Children's Hospital of Pittsburgh of UPMC

Some babies are born with no connection or a very narrow connection between the right ventricle of the heart and the pulmonary circulation, requiring right ventricular outflow tract (RVOT) reconstruction to fix the defect. As a highly established program with outcomes that are among the best in the U.S., the UPMC Department of Cardiothoracic Surgery, which includes the Division of Pediatric Cardiothoracic Surgery, provides cardiothoracic surgical intervention for neonates, infants, children, and adults with congenital heart defects, as well as surgical interventions for a full range of congenital and acquired heart and lung disorders. Two congenital heart defects account for most patients requiring RVOT reconstruction: tetralogy of Fallot with pulmonary atresia, which occurs in seven out of every 100,000 live births, and truncus arteriosus, which occurs in five to 15 out of every 100,000 live births.

Many different conduits have been utilized to correct congenital defects of the RVOT, and most pediatric surgical services in the U.S. currently use cadaveric homograft conduits or bovine jugular vein conduits for RVOT reconstruction. In 2008, UPMC cardiothoracic surgeons began using polymer conduits with valves that we constructed from polytetrafluoroethylene (PTFE). The outcomes and utility of the valved PTFE conduits have been so favorable that they have become our standard approach for RVOT reconstruction. To date, we have performed more than 100 RVOT reconstructions using valved PTFE conduits, with 10 to 20 reconstructions per year.

The PTFE conduits offer many advantages. The primary advantage is that patients do not become sensitized to the conduit. For patients who eventually require a transplant, sensitization can be a problem with homografts. PTFE conduits are well suited to our institution, because UPMC is one of the leading transplant centers in the nation and sees many transplant patients who have undergone RVOT reconstruction.

A secondary advantage is that PTFE conduits are available in a wide range of diameters (from 8 mm to 24 mm), so we are better able to match the size of the conduit to each patient's anatomy. In contrast, it can be difficult to obtain a homograft or bovine conduit with the needed diameter. In this way, PTFE conduits are more customizable to our patients.

PTFE conduits are also more cost-effective than either homograft or bovine jugular vein conduits. Additionally, a homograft may shrink over time as a result of the body's reaction to it. PTFE is inert and does not shrink, so the PTFE conduits have the potential to last longer than other conduits, especially in adult patients or fully grown adolescent patients.

We have also found that the Melody® Transcatheter Pulmonary Valve (Medtronic, Minneapolis, Minn.) can be easily implanted into the PTFE conduit of an adult patient if the PTFE valve eventually fails. This is, in part, due to the absence of shrinking in the PTFE conduits. Finally, due to somatic growth, replacement surgery is almost always necessary for very young children who receive a conduit. In such cases, PTFE conduits may be safer because they are thicker and tougher. At UPMC, we feel more comfortable performing a repeat sternotomy in a child with a PTFE conduit than with a homograft or bovine conduit.

The primary, and possibly sole, disadvantage to using PTFE conduits versus other types for RVOT reconstruction is that conduits with valves to replace a missing or defective pulmonary valve are not commercially available. The valved conduits must be created in-house by our surgical team (Figure 1). As UPMC is a high-volume transplant center, we have been particularly

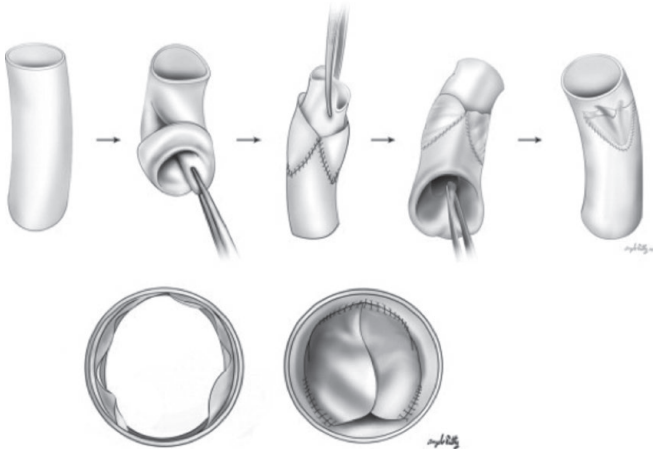

Figure 1. *Drawings of the steps to make a bicuspid valved conduit. (From Yoshida, Ann Thorac Surg 91:1235)*

motivated to optimize the valved PTFE conduits. We face problems due to sensitization from implanted homografts more frequently than surgical services at hospitals that don't perform transplants.

Based on our extensive experience and laboratory studies (Figure 2), we have developed templates for valved conduits ranging from 8 mm to 24 mm in diameter. The conduits feature both greater and lesser curvatures, and we optimize blood flow relative to this geometry by performing fluid dynamic studies in collaboration with engineers at Carnegie Mellon University (Figure 3). We found that a trileaflet valve is best for conduits ≥14 mm in diameter. If the diameter of the conduit is <14 mm in diameter, we construct a bicuspid valve.

In April 2017, we presented our outcomes using valved PTFE conduits in 55 children younger than two years of age at the American Association for Thoracic Surgery (AATS) Centennial meeting. The PTFE conduits — both the valve leaflets and the tubes — performed as well as homograft conduits. There were no differences in time to explant or re-intervention between the two conduits. Age at the time of RVOT reconstructive surgery was the biggest risk factor for conduit explant, and approximately 50% of conduits had been explanted within five years of conduit placement regardless of whether a PTFE conduit or a homograft conduit was used. There were also no significant differences in conduit stenosis or insufficiency. The approach was well received by the pediatric cardiac surgeons in attendance at this major professional society meeting.

PTFE conduits have been used extensively for RVOT reconstruction in Japan, where innovation has been driven by far lower levels of tissue donation for homografts than in the U.S. At the AATS meeting, the outcomes of a series of more than 1,000 Japanese patients who underwent RVOT reconstruction using valved PTFE conduits were presented. The reconstructions were performed over a 14-year period (2001 to 2015) at 65 hospitals. Ten different-sized conduits (ranging from 6 mm to 24 mm) were placed in patients ranging from birth to 57 years of age. In many instances, a centrally located surgeon made the conduits and sent them to other hospitals. Conduit durability and longevity were outstanding. The valved PTFE conduits performed better than any other conduit with respect to longevity and resistance to infections.

Our approaches to RVOT reconstruction are unique to the UPMC Department of Cardiothoracic Surgery, Division of Pediatric Cardiothoracic Surgery at Children's Hospital of Pittsburgh of UPMC. Surgeons from all over the world have come to UPMC to learn how to create and implant valved PTFE conduits. Our pioneering work with PTFE conduits continues our long-standing tradition of exceptional patient care, innovation, and intellectual curiosity to positively impact the lives of children with congenital heart defects.

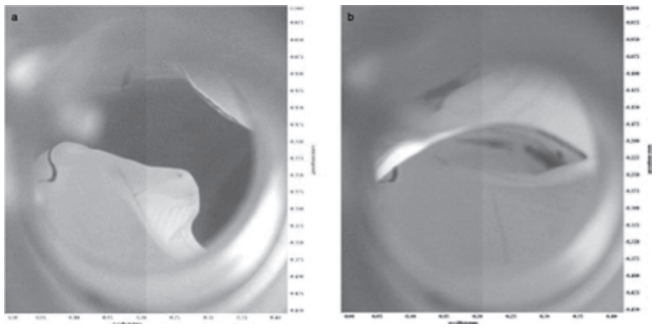

Figure 2. *In vitro testing of a bicuspid PTFE valve. (Reprinted from Dur et al. In vitro evaluation of right ventricular outflow tract reconstruction with bicuspid valved polytetrafluoroethylene conduit. Artif Organs 34:1010, with permission from Wiley and Sons)*

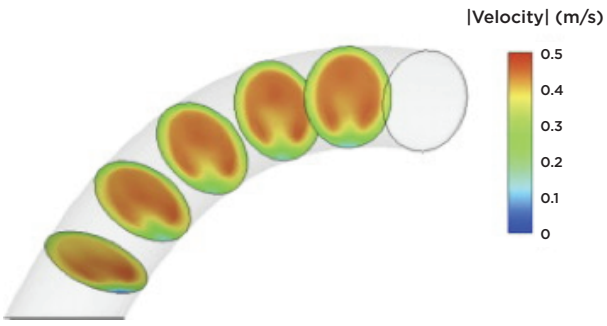

Figure 3. *Flow velocity study of a valved PTFE conduit. Contours shown during systole indicated lower velocity at the lesser curvature of the conduit. (From Dur, Artif Organs 34:1010)*

Expanding the Donor Pool in Heart Transplantation: A Clinical Trial Examining the Use of Hepatitis C-positive Donor Hearts in Hepatitis C-negative Recipients

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One shortcoming of current direct-acting antiviral therapies for HCV is that they cannot be used if the patient is experiencing renal failure. For this reason, we are excluding patients with a moderate-to-high risk of renal failure from the current study to avoid a situation where a patient might develop a full-blown, active hepatitis C infection that cannot be effectively treated.

Based on the results of the current trial, future studies will expand in different directions. The trial has been received with enthusiasm throughout its approval process at UPMC. This promising approach highlights how UPMC is driving innovation in our heart transplant program and challenging the status quo throughout the UPMC health care system.

Sequential Lung and Bone Marrow Transplantation: Leading the Way Through Innovative Science

Jonathan D'Cunha, MD, PhD, FACS
Chief, Division of Lung Transplant/Lung Failure
Vice Chairman, Research Affairs and Education
Associate Professor, Cardiothoracic Surgery

John F. McDyer, MD
Associate Professor, Division of Pulmonary, Allergy and Critical Care Medicine
Director, Lung Transplantation Translational Research Program

Transplant surgeons, pulmonologists, and researchers continuously seek better ways to prevent a transplant recipient's immune system from attacking and rejecting the transplanted organ. While immunosuppressive therapies can allow for successful transplantation, they have undesirable side effects. To establish transplant tolerance, there is a focus on targeting damaging allograft-specific immune responses while maintaining the protective responses of a competent immune system. Ideally, establishing transplant tolerance will eliminate graft rejection and the need for immunosuppression and improve long-term graft function.

Transplant tolerance is of particular interest to lung transplant surgeons because bronchiolitis obliterans syndrome (BOS), a form of chronic lung graft rejection, occurs in at least 50% of lung transplant recipients within five years of transplant. Additionally, chronic lung allograft dysfunction (CLAD) is a persistent problem. As a result, the long-term outcomes after lung transplantation tend to be less favorable than long-term outcomes for other types of solid organ transplants. Published reports suggest that achieving immune tolerance for transplanted lungs will be more challenging than for other organs. Lung allografts are particularly immunogenic, in part because they are constantly exposed to infectious and non-infectious foreign stimuli through the air and through microaspiration due to the airway's proximity to the upper digestive tract.

Bone marrow transplant resulting in persistent engraftment of donor-derived hematopoietic stem cells and a chimeric immune system may be one way to achieve tolerance. The team at the Division of Lung Transplant /Lung Failure, within the UPMC Department of Cardiothoracic Surgery, is testing the efficacy of sequential lung and bone marrow transplants (lung/BMT) from the same donor to achieve tolerance and improve outcomes after lung transplant. Bone marrow will be collected from the lung allograft donor at the time of organ harvest and stored. Later, when the lung transplant recipient is healthy enough to undergo the procedure, bone marrow transplant hematologists will perform a bone marrow transplant. The National Institute of Allergy and Infectious Diseases has funded this study via a grant to our collaborators: Paul Szabolcs, MD, at Children's Hospital of Pittsburgh of UPMC, and John McDyer, MD, in the UPMC Comprehensive Lung Center.

For this exploratory trial, we are transplanting lungs into patients for whom a bone marrow transplant is indicated due to a primary immunodeficiency syndrome. These patients often develop end-stage lung disease complications, such as severe bronchiectasis or pulmonary fibrosis. Prior to this trial, patients with primary immunodeficiency syndromes and end-stage lung disease have been deemed ineligible for either bone marrow transplant or lung transplant, so their clinical needs have thus far been unmet. The combined transplant should correct both immunodeficiency and lung dysfunction, restore pathogen-specific immunity, and establish immune tolerance that may allow withdrawal of immunosuppressive therapies. If successful, the project would be a paradigm shift for therapy in both the lung and bone marrow transplant fields. By examining these patients, the approach can be explored and potentially developed for application in any lung transplant recipient, before possibly extending it to other solid organ transplants.

Protocols for sequential lung and bone marrow transplants in this context are being developed at UPMC in collaboration with Dr. Szabolcs. We anticipate that bone marrow transplants can be performed on patients three to six months after lung transplant. The hope is that immunosuppressive medication can then be decreased or eliminated because patients have achieved tolerance. The patients will be monitored for graft function and rejection and will then be examined for mixed chimerism sufficient to establish long-term tolerance of the lung allograft and the transplanted marrow. Immunosuppression will gradually be decreased according to whether the patient establishes immune tolerance, as engraftment of the lung donor hematopoietic system will recognize the allograft as "self." As of November 2017, we had enrolled adult patients who received a lung transplant, with one recently undergoing bone marrow transplant and another preparing for bone marrow transplant. Additionally, two patients are currently listed and awaiting a lung transplant. Our program is now part of the newly established Immune Transplant and Therapy Center (ITTC) at UPMC, under the direction of Timothy Billiar, MD, George Vance Foster Professor and chair, Department of Surgery, at the University of Pittsburgh School of Medicine; and Steven Shapiro, MD, executive vice president, chief medical and scientific officer, and president of the Health Services Division. We are now extending combined lung/BMT to patients with advanced pulmonary fibrosis and bone marrow failure due to the short telomere syndrome.

In the 1990s, transplant pioneer Thomas E. Starzl, MD, PhD, championed approaches to promote recipient tolerance rather than relying on sustained immunosuppressive therapies. Consistent with Dr. Starzl's vision, current UPMC initiatives in the ITTC encourage a focus on modulation of the immune system to understand and treat chronic diseases, including solid organ transplantation. The lung/BMT clinical research program at UPMC promotes our goals of creating tolerance for organ transplants through innovative solutions and applying our research and clinical expertise to define the future of immunotherapy.

Department News

The Department of Cardiothoracic Surgery Congratulates Our Team

- James D. Luketich, MD, FACS, accepted an invitation to serve as the 4th Annual Manjit S. Bains Visiting Professor at Memorial Sloan-Kettering Cancer Center.
- James D. Luketich, MD, FACS, accepted an invitation to serve as Guest of Honor and Keynote Speaker at the 2017 European Society for Diseases of the Esophagus in Utrecht, Netherlands.
- James D. Luketich, MD, FACS, was appointed Deputy Editor for *The Annals of Thoracic Surgery*.
- Arjun Pennathur, MD, was awarded the 4th Annual James D. Luketich Chairman's Alumni Award.
- Inderpal S. Sarkaria, MD, FACS, was awarded a $100,000 grant from the Pittsburgh Foundation to develop the use of a novel and less invasive robotic approach to the treatment of esophageal cancer.
- Julie Phillippi, PhD, received a five-year, $1.9 million R01 award from the National Heart, Lung, and Blood Institute for her project entitled "Matrix Mediated Vasa Vasorum Dysfunction in Thoracic Aortic Disease."
- Danny Chu, MD, FACS, was awarded a $191,006 grant from the Department of Veterans Affairs for pilot testing a home-based prehabilitation intervention designed to improve outcomes of frail veterans following cardiothoracic surgery.
- Olugbenga Okusanya, MD (PGY 7), was selected by the AATS Graham Foundation as an Intuitive Surgical Robotics Fellowship recipient for 2017.
- Patrick Chan, MD (PGY4), received an NIH F32 Ruth L. Kirschstein National Research Service Award (2017-2019). Research under this award is being performed in the laboratory of Thomas G. Gleason, MD, FACS.
- Leonid Emerel, MD (PGY4), received a Clinician Scientist Training Program Grant from the American Heart Association (2017-2019). Research under this award is being performed in the laboratory of Thomas G. Gleason, MD, FACS.

Meetings and Conferences

- The department was well represented at the 97th Annual Meeting of the American Association for Thoracic Surgery in Boston. UPMC experts contributed six oral presentations, one poster presentation, and invited presentations by Matthew J. Schuchert, MD; Inderpal S. Sarkaria, MD, FACS; and Jose da Silva, MD.
- During the 53rd Annual Meeting of the Society for Thoracic Surgeons in Houston, UPMC experts contributed five oral presentations and three poster abstracts. Contributing members of the Department of Cardiothoracic Surgery include James D. Luketich, MD, FACS; Thomas G. Gleason, MD; Rajeev Dhupar, MD; Ibrahim Sultan, MD; Inderpal S. Sarkaria, MD, FACS; Robert L. Kormos, MD, FAHA, FRCS(C), FACS; and Ernest Chan, MD (PGY2).

The Department of Cardiothoracic Surgery Welcomes Two New Attending Surgeons

Pablo Sanchez, MD, PhD, FACS
Assistant Professor of Cardiothoracic Surgery
Associate Director, Lung Transplantation and ECMO
Director, Lung Transplant Research
Director, EVLP Program

Pablo Sanchez, MD, PhD, FACS, is an assistant professor of cardiothoracic surgery at the University of Pittsburgh School of Medicine and the associate director of lung transplantation and extracorporeal membrane oxygenation (ECMO) at UPMC. He also directs the UPMC Ex Vivo Lung Perfusion (EVLP) Program and lung transplant research. He is board-certified in thoracic surgery.

Dr. Sanchez earned his medical degree at Universidad Nacional de Cordoba in Argentina and completed his residency in thoracic surgery at Santa Casa Hospital Pereira Filho in Brazil. He also completed the following fellowships: pediatric thoracic surgery at Hospital da Crianca Santo Antonio in Brazil; thoracic surgery research at the University of Pennsylvania; and artificial organ research at the University of Baltimore.

His clinical emphases lie in organ donation, lung transplantation and injury, ECMO, EVLP, and bone marrow derived mesenchymal stem cells.

Arman Kilic, MD
Assistant Professor of Cardiothoracic Surgery
Director, Surgical Quality and Analytics, Cardiac Surgery

Arman Kilic, MD, is an assistant professor of cardiothoracic surgery at the University of Pittsburgh School of Medicine and director of surgical quality and analytics for cardiac surgery at UPMC. He is board-certified in surgery.

Dr. Kilic earned his medical degree at the University of Pittsburgh School of Medicine and completed his residencies in general surgery and research at the Johns Hopkins Hospital in Baltimore. He completed his fellowship in cardiac surgery at the Hospital of the University of Pennsylvania in Philadelphia.

His clinical practice encompasses all aspects of adult cardiac surgery, with emphasis on valvular disease, mitral valve repair, ventricular assist devices (VADs), and cardiac transplantation.

Near-Infrared Fluorescence Imaging in Thoracic Surgery: Making Tumors Glow

Inderpal Sarkaria, MD, FACS
Vice Chairman for Clinical Affairs, Department of Cardiothoracic Surgery
Director, Thoracic Robotic Surgery
Co-Director, UPMC Esophageal and Lung Surgery Institute

Near-infrared fluorescence imaging (NIFI) is an established technology that has been used to assess blood flow in the retina, provide images of the heart and liver, and examine blood vessel pathology. It is associated with less autofluorescence and less scattering than imaging at visible wavelengths. With my colleagues at the Division of Thoracic and Foregut Surgery in the UPMC Department of Cardiothoracic Surgery, I am exploring NIFI as an emerging method to visualize tumors and blood vessels intraoperatively in real time and working to identify the best applications of NIFI for our field. NIFI has the potential to improve detection of pulmonary nodules and other cancers and improve visualization of anatomic structures that can be difficult to see during surgery.

During NIFI, fluorophores that target the tissue of interest are excited with a laser, and fluorescence is detected with a camera. This instrumentation exists as a single tool, with the ability to toggle between multiple wavelengths, including white light for traditional visualization. NIFI instruments are also available for robotic surgery platforms, allowing seamless application of NIFI in robot-assisted surgical procedures. For example, the Firefly™ Fluorescence Imaging system can now be integrated with the robotic da Vinci® Surgical System.

Customized NIFI dyes for specific body tissues, various cancers, blood vessels, and nerves are in various stages of research and development in clinical trials. Using different fluorophores, the

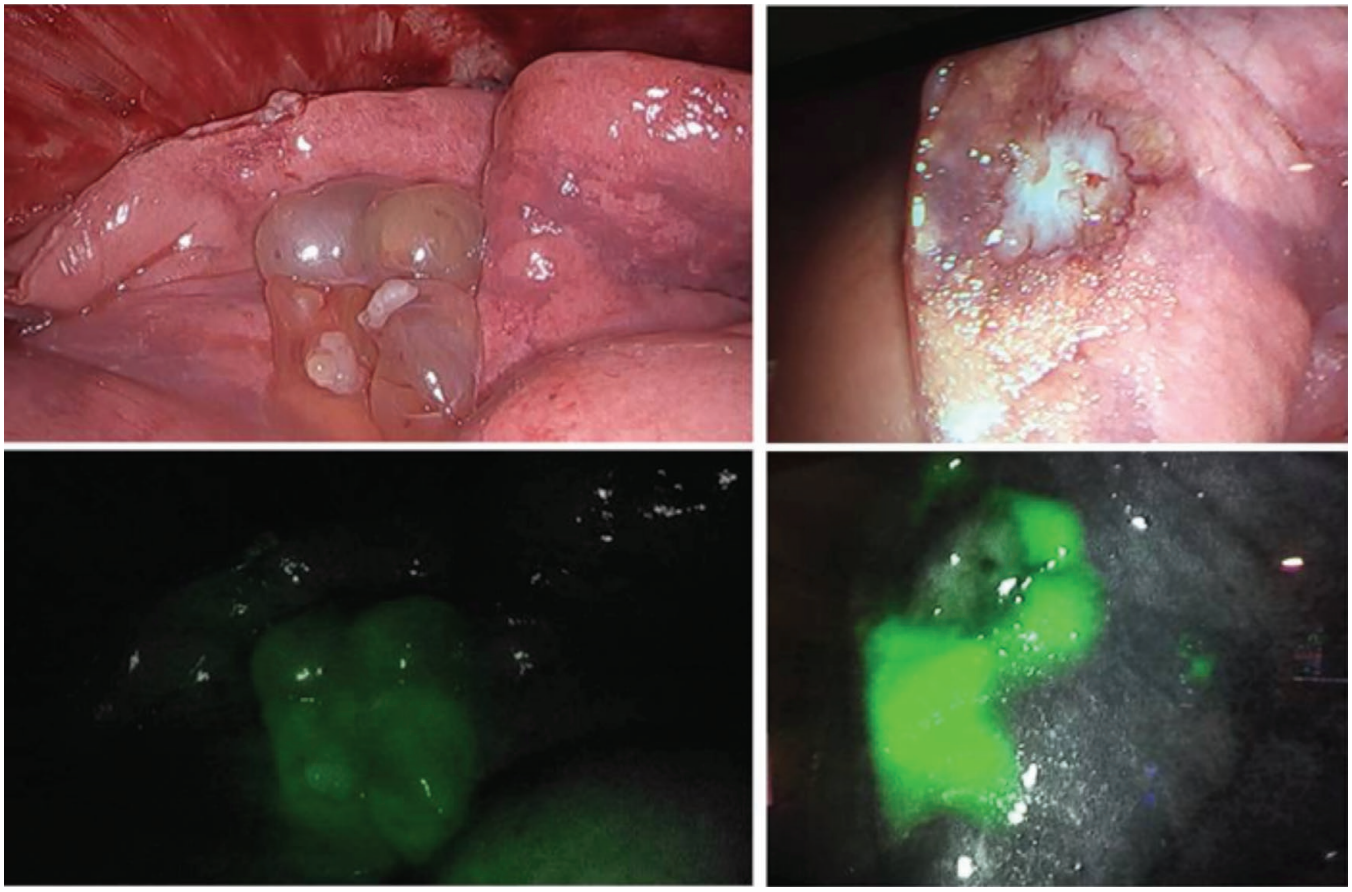

Figure 1. *Lung nodules visualized using white light (top panels) and/or NIFI with ICG (bottom panels).*

view afforded by NIFI has the potential to resemble the colorful human anatomy depicted in medical atlases, revealing critical structures that are not immediately apparent under normal white light. Increased visualization provided by this technology may potentially improve the safety of any surgical procedure and decrease iatrogenic injuries.

Our team at UPMC has begun an investigation using NIFI with indocyanine green (ICG), a commonly used, FDA-approved compound with decades of verified safe use, as the primary fluorophore. ICG is a broadly applicable fluorophore and moves throughout tissues in the body by attaching to proteins. When injected into the bloodstream during surgery, it immediately highlights blood vessels and can be used to assess the blood supply and its perfusion of different tissues or organs. ICG can also be injected the day before surgery. During the operation the following day, fluorescence appears to be concentrated at higher levels in tumor tissue or inflamed areas, making such areas glow under near-infrared wavelengths and allowing them to be easily targeted (Figure 1).

Using these properties of ICG, we recently completed accrual of a clinical trial (ClinicalTrials.gov identifier: NCT02851368) and determined that NIFI may be very helpful in identifying pulmonary nodules and cancers intraoperatively, assessing tumor margins, and finding additional tumors that were missed in previous imaging.

The UPMC Department of Cardiothoracic Surgery is also participating in a clinical trial of a new marker for NIFI (OTL38) that may specifically identify lung adenocarcinoma (ClinicalTrials.gov identifier: NCT02872701). Lung adenocarcinomas bind serum folate 1,000 to 10,000 times more avidly than normal pulmonary epithelial cells. OTL38 targets the folate receptor alpha protein by mimicking a folate ligand. In addition to its specificity for malignant masses, OTL38 is beneficial because it is injected the morning of the operation rather than the day before, which is more convenient for the patient.

Preliminary safety trials with OTL38 have already been performed, and UPMC is one of a small number of sites participating in a phase 2, multi-institution trial to determine the utility of OTL38 in detecting adenocarcinoma and defining tumor margins for resection intraoperatively. The trial will determine clinical efficacy and confirm the safety and tolerability of OTL38 as a NIFI marker in a broader setting. OTL38 as a marker for NIFI could be a very powerful diagnostic tool in the treatment of lung adenocarcinoma.

NIFI may also be beneficial for localizing pulmonary nodules for removal, which is a particular challenge during minimally invasive thoracic surgery. During minimally invasive surgery, surgeons typically cannot feel the nodule by palpation and must rely on visual observation or secondary tactile detection through instrumentation. Primary tactile detection is limited to what we can reach through small incisions. Methods previously used to mark pulmonary nodules for resection are invasive and time-consuming. Newer methods rely on dyes injected into the tumor or areas of interest using techniques such as navigational bronchoscopy. While these methods have advanced the practice of pulmonary nodule marking, they are still time- and labor-intensive. NIFI with ICG, OTL38, or other fluorescent markers may be helpful in marking pulmonary nodules for resection without the need for additional invasive procedures.

NIFI investigations in the UPMC Division of Thoracic and Foregut Surgery are currently focused in the lung, but NIFI methods should improve the detection and resection of any number of solid tumors, so we plan to expand analysis to the esophagus and mediastinum. During esophagectomy, NIFI can be a powerful tool to examine the blood supply when constructing the gastric tube. Gastric vessels are visible with high contrast within 45 seconds of injection of ICG. Surgeons can then determine if the stomach is adequately perfused and identify the best site for the esophagogastric anastomosis by clearly demarcating the blood supply. We have found this improved visualization of the blood vessels to be particularly helpful when working with trainees. NIFI helps to highlight the vital anatomy early in trainees' learning curve for these complex operations.

NIFI markers that are specific to nerves also have the potential to improve the outcomes of thoracic surgery. Especially appealing is the ability to visualize, and therefore preserve, the phrenic nerve during thymectomy; the vagus nerve during Nissen fundoplication and repair of giant hiatal hernias; and the recurrent laryngeal nerve during lung and esophageal cancer resections. Tissue-specific molecular markers detected with NIFI in real time could also greatly enhance the safety of surgery by improving visualization of critical anatomy across many surgical fields and operations.

While the future of NIFI is promising, there is more work to be done. The primary limitation of NIFI is the inability to image deeply into tissues. This hurdle must be overcome, either by improving NIFI or combining NIFI with one or more complementary imaging modalities, to expand the utility of NIFI and broaden its clinical applications. Combinations of NIFI with ultrasound and radioactive markers are also being examined. UPMC is at the forefront of these technologies, and we are excited to engage in active clinical protocols with strong collaborative partners to pioneer advances in near-infrared imaging applications in thoracic surgery.

Peroral Endoscopic Myotomy (POEM) Surgery for Minimally Invasive Treatment of Achalasia

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Achalasia is a primary motor disorder of the esophagus with a prevalence of 10 cases in every 100,000 people. Achalasia leads to difficulty when swallowing (dysphagia) because it prevents lower esophageal sphincter (LES) relaxation and affects the pumping of food down the esophagus (peristalsis). In addition to dysphagia, patients with achalasia may experience regurgitation of undigested food that is stagnant in the esophagus. Such food aspiration can contribute to a chronic cough and sometimes pneumonia. Additionally, reflux-like symptoms are common, due to food stasis and esophageal inflammation. Symptoms typically become progressively worse over time, decreasing the patient's quality of life. There is no effective medical treatment for achalasia. BOTOX® injections provide reasonable temporary relief, but in most patients, symptoms recur within weeks to months. Pneumatic balloon dilation of the LES through an endoscope can also provide relief of symptoms, and is somewhat durable, but the risk of perforation requiring emergent surgical intervention has been as high as 11%. In the early 1990s, the laparoscopic Heller myotomy with Dor partial fundoplication became the standard of care for achalasia to replace open myotomy, which was associated with significant pain and morbidity. While none of these procedures cures achalasia, performing a myotomy to divide the muscles in the LES addresses the inability of the LES to relax, allowing passage of a food bolus (obstruction) and relieving the patient's symptoms.

Surgeons in Japan began developing peroral approaches to esophageal myotomy almost a decade ago. The LES is accessed through the mouth, using a flexible endoscope, without incisions in the skin or abdominal muscles. Peroral endoscopic myotomy (POEM) surgery has gained remarkable momentum over the last several years and is becoming the standard approach to achalasia at a number of advanced endoscopic centers in the U.S. The concept of correcting internal disorders of the human body using natural orifice access (such as the mouth, vagina, or anus) instead of a skin incision, is often referred to as NOTES (natural orifice translumenal endoscopic surgery). UPMC cardiothoracic surgeons have previously used NOTES for correction of Zenker's diverticulum of the upper esophagus, performing transoral endoscopic stapling with good results in more than 200 patients. In 2012, after studying the practices of other advanced centers, we undertook our first POEM surgery at UPMC. We have now performed POEM on more than 70 patients, with high patient satisfaction and excellent results. POEM is a powerful addition to the well-established and constantly expanding arsenal of minimally invasive esophageal procedures available at our high-volume esophageal center of excellence in the UPMC Department of Cardiothoracic Surgery, Division of Thoracic and Foregut Surgery.

Before considering POEM surgery, our typical patient work-up includes contrast imaging with a barium esophagram, direct

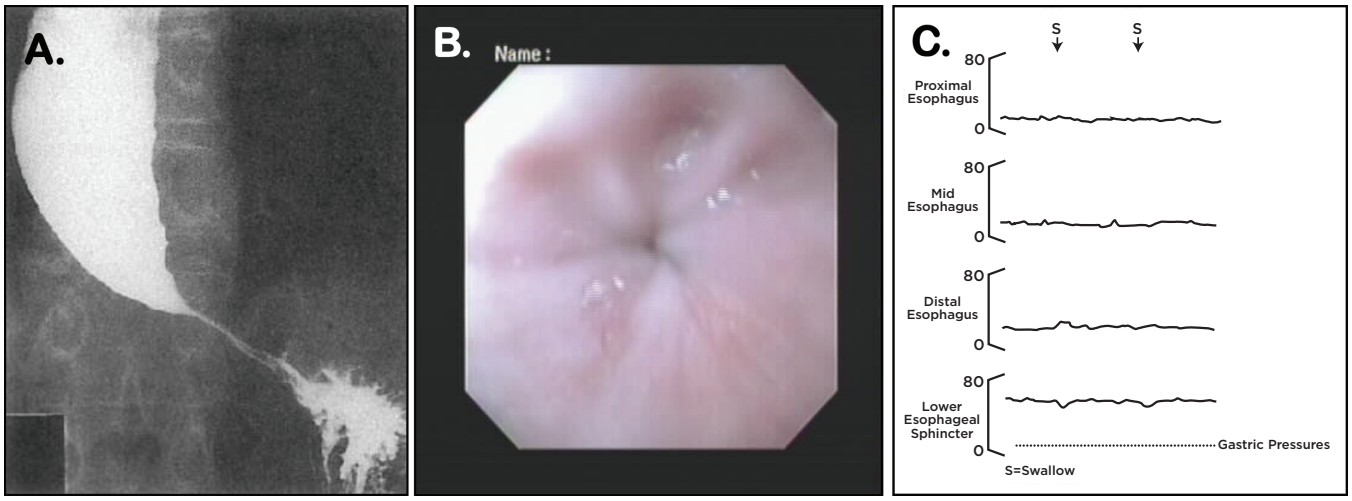

Figure 1. *Preoperative evaluation prior to POEM. A) Barium esophagram, showing typical bird's-beak anatomy. B) Upper endoscopy showing incomplete relaxation of the lower esophageal sphincter (LES). C) Manometry showing incomplete relaxation of the LES and the absence of coordinated peristalsis.*

visualization with an upper endoscopy to confirm the tight LES, and esophageal manometry to assess motor function and the ability of the LES to relax (Figure 1). To begin POEM surgery, we lay the patient supine, induce general anesthesia, and place a breathing tube. An endoscope is inserted through the patient's mouth, and all surgical instruments are sequentially introduced through the working channel of the endoscope. We irrigate the esophagus until it is clear of all debris and inject methylene blue dye into the mucosal-submucosal junction 10-15 centimeters above the LES to create a mucosal cushion and improve visualization of the esophageal layers. We then create a one-centimeter longitudinal mucosal incision (Figure 2A) and tunnel through the submucosa toward the LES and gastroesophageal junction (GEJ). During this procedure, we separate the submucosa from the circular muscle layer of the esophagus (Figure 2B). We tunnel across the GEJ and into the stomach. We then divide the circular muscle layer of the esophagus that is immediately adjacent to the submucosa using electrocautery (Figure 2C). We typically begin dividing the muscle fibers 10 to 11 centimeters above the GEJ, depending on the manometry findings. The muscle fibers spring apart, relieving constriction in the lower esophagus. We leave the outer, longitudinal muscle layer of the esophagus intact. After we withdraw the endoscope from the submucosal tunnel, we irrigate with antibiotics and close the hole in the esophageal mucosa with endoclips (Figure 2D). The day after surgery, we assess the results of the procedure with a barium esophagram, which should confirm that there are no leaks and demonstrate improved passage of barium from the esophagus, across the LES, and into the stomach. The channel in the esophageal submucosa created by the endoscopic tunneling heals quickly in the vast majority of cases. The endoclips slough off seven to 10 days after the procedure and pass uneventfully through the patient's digestive tract. We follow up with the patient in the clinic approximately 10 days after POEM.

POEM surgery is a good option for most patients with achalasia. The majority of patients do well during POEM and are typically very pleased with the results; 90% of patients experience immediate improvement of dysphagia. None of our patients have experienced clinically significant bleeding complications from a POEM procedure. We have not had to emergently convert to open surgery during any POEM operation, and there has been no mortality within the first 90 days after surgery. The team presented our initial POEM results at the 96th Annual Meeting of the American Association for Thoracic Surgery in May 2016. In our series of 28 patients, the mean dysphagia score improved from 5.6 prior to POEM to 0.4 after POEM. Approximately 30% of patients experienced gastroesophageal reflux postoperatively, which was managed with medication. None of our patients have needed a surgical antireflux procedure for gastroesophageal reflux after POEM.

It is important to note that the learning curve for completing POEM surgery effectively and safely can be quite steep. We chose to have a proctor present for our first eight cases. In addition, we have limited our surgical team to one main surgeon with dedicated first assistants. Similarly, efforts are made to engage the same nursing team for all cases. We stress that anyone considering performing a POEM operation should be well-versed in laparoscopic and open myotomy. Also, extensive endoscopic experience is a prerequisite. This experience reduces the likelihood of intraoperative and postoperative complications and is essential to manage complications that can occur, including gastric distension, pneumoperitoneum, pneumothorax, and small leaks of contrast into the endoscopic tract during the postoperative barium esophagram.

Laparoscopic surgical myotomy with partial fundoplication is still considered the standard of care for achalasia by many surgeons. However, when performed by an experienced surgeon, POEM appears to be a good option, especially for patients who are not good surgical candidates and may not otherwise tolerate an operation to correct achalasia. While further studies are needed to better determine the durability of symptom relief, side effects (particularly gastroesophageal reflux), and long-term outcomes, POEM is quickly emerging as a popular, effective, and less invasive alternative for the treatment of achalasia. Despite its straightforward design, POEM is not an easy procedure to conduct, and ideally should be performed by surgeons with extensive esophageal experience in high-volume centers of excellence, such as the Division of Thoracic and Foregut Surgery and the Esophageal and Lung Surgery Institute at UPMC.

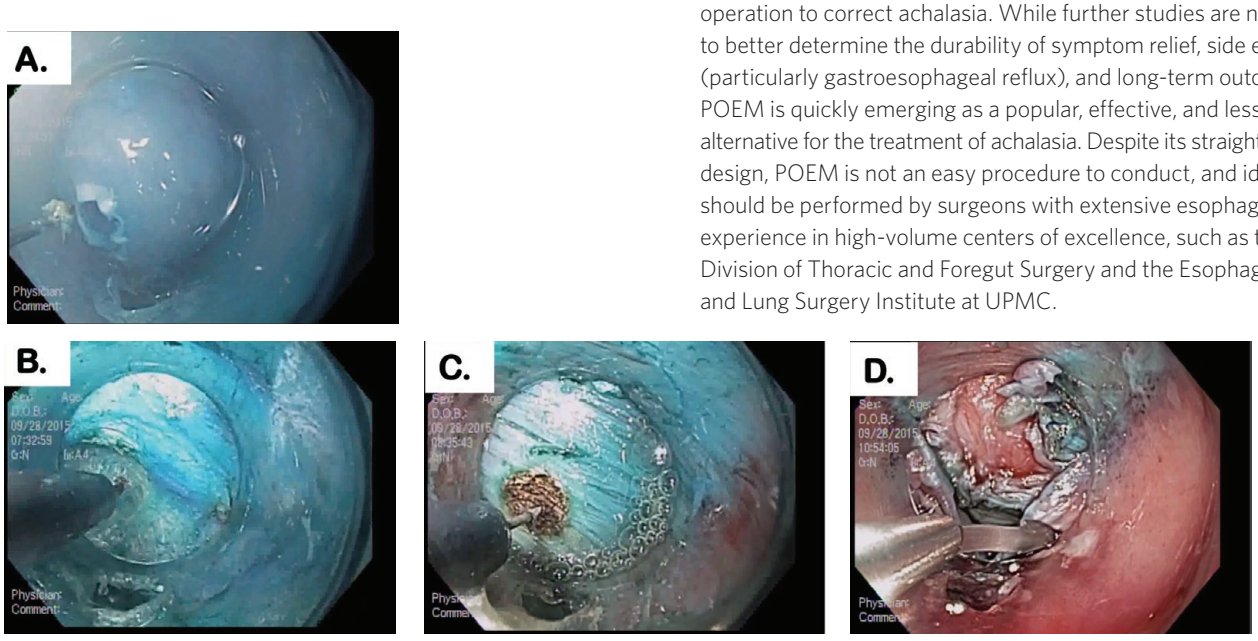

Figure 2. *Steps of the POEM procedure. A. Mucosotomy. B. Creation of submucosal tunnel. C. Circular muscle fiber division. D. Endoscopic closure of the mucosa with clips.*

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- National Mesothelioma Virtual Bank
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