AATS

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In this issue

Malcolm Gladwell delivers his Keynote Lecture on Monday

Pig-to-human heart transplant ushers in new era

In January of this year, Bartley Griffith and his team successfully performed the first xenotransplantation of a genetically modified pig heart in patient David Bennett. While the patient eventually passed away, the ripples from the procedure have been felt around the world, setting a precedence for a new era of organ replacement, and opening up a fresh perspective on what is achievable in the field of life-saving transplantation.

Dr. Griffith is a heart and lung transplant surgeon whose name is synonymous with innovation. He started out his career in Pittsburgh, since serving as vice chair in the Department of Surgery at the University of Pittsburgh School of Medicine. He was also chief of cardiothoracic surgery and founding director of the internationally recognized McGowan Center for Artificial Organ Development. Currently, he is a distinguished professor at the University of Maryland School of Medicine.

Dr. Griffith took to the podium on Saturday morning to share his perspectives from his groundbreaking work, offering lessons learned and future goals for an enthralled audience.

"We all start our surgical careers with visions or ideations about great grandeur and great success, but along the way there are significant bumps in the road," he began. "So, what gets us beyond healing patients? This is of course the reason we're all in this field, but cardiac surgery and thoracic surgery are difficult.

> "I walked away saying, 'This man has a pig's heart: it's just fantastical'."
>
> **Bartley Griffith**

"I can tell you that in the last five years, having become involved in the xenotransplantation project, it's really been fun to come to work. It's been fun to become a nascent virologist, immunologist, veterinarian, expert in non-human primate development and the size of pig hearts – I mean it's been quite amazing."

As he began to introduce Mr. Bennett's story, Dr. Griffith commented: "I would say with hubris, let's just declare success! At forty days into his postoperative course, other than infectious complications which we believed we had overcome, David was making slow and steady progress. I visited with him and my God, I walked away saying, 'This man has a pig's heart: it's just fantastical'."

Mr. Bennett had said that if the operation did not succeed, at least his experience could be learned from. "I promised David that we would continue to work, and even with his autopsy tissue, we continue to learn daily," said Dr. Griffith.

Overcoming earlier challenges

Dr. Griffith spoke of the challenges faced in transplants leading up to Mr. Bennett, most notably survival

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rates which – of 16 implantations in non-human primates between 2017 and 2019 – only three lived past two days. Despite implant times of 30 minutes or less, the team kept running into perioperative cardiac xenograft dysfunction, or PCXD. "The hearts would expire, inexplicably, and we didn't know whether there was something very odd in the metabolics and the energetics of what really was happening," he said.

In collaboration with Bruno Reichart and his team, they used the Steen XVIVO system for non-ischemic cardiac perfusion during the time where the pig heart had been removed ready for implantation. This dramatically changed results. "We then did not seem to have any problems," said Dr. Griffith.

He added: "We were able to make some progress, and we had to determine which genetic modifications might be best. The genetic implementations that occurred included gene knockouts – which primarily occurred to the sugar epitopes – and also a growth hormone knockout so we could limit the size of these pigs, many of whom would otherwise grow as big as 400 pounds. Having done that, we also added some human transgenes to affect complement- and coagulation regulation ... we also added inflammatory regulators to reduce inflammatory induced problems that we anticipated."

Lessons learned

After a while, it became clear that Dr. Griffith and his team were learning less and less from repeated non-human primate attempts, and felt ready to go for human implantation in the right candidate (i.e. someone who was out of options).

"My partner Dr. Mohiuddin were addressing the FDA for a traditional investigational new drug [IDE] application, but that wasn't going to be within the next two years. And in order to qualify, we would have to work with another six animals for three to five months, without alteration of their immune suppression."

He added: "So we thought we knew enough at least to try a patient if we had the right patient, but who would that be? That patient ended up being David Bennett, and actually he wasn't ideal."

Notably, Mr. Bennett had "striking" sarcopenia, among other issues, and Dr. Griffith reasoned that most people working in allotransplantation would have walked away from the patient. But, as Mr. Bennett did not qualify for human heart transplant, he did fit the criteria of someone without any further options.

Preparing for success

When embarking on the early stages of Mr. Bennett's journey, Dr. Griffith and his team started to think about how they would actually define success. "If the heart beats for an hour, would that be deemed a success? Would a day? How about a week, a month, or maybe six months? We just didn't know."

In terms of immunosuppression, the team had already learned in earlier work that B-cell suppression is the target of choice in xenotransplantation, as opposed to allotransplantation, where it is T cells. To that end, they utilized KPL-404, an anti-CD40 monoclonal antibody designed to reduce B-cell proliferation, along with some T-cell effects. It had never been used in a human case before, noted Dr. Griffith. Rituximab, a staple in lymphoma therapy, was given the day before implantation in order to mitigate CD20+ B cells.

> "It was actually thrilling. I couldn't wait for the echoes to come in ... it was a perfect heart for about 43 days."
>
> **Bartley Griffith**

Mr. Bennett was also given ATG 4 mg/kg, completed by Day 7, a C1 esterase inhibitor at Days -1 and 0, mycophenolate mofetil (MMF) 500 mg (although halted halfway through the postoperative course due to infection), and methylprednisolone 125 mg with rapid taper to 30 mg.

"The most important part of what we were trying to accomplish was to reduce antibodies," said Dr. Griffith, confirming that both anti-non-Gal IgG and IgM were dramatically decreased.

B-cell counts also went down dramatically at first, but a lymph node taken from the patient's chest on postoperative Day 4 showed a significant amount of B-cell activity. "We hadn't penetrated the lymph-bearing tissues enough," said Dr. Griffith, "so we had had the conversation about rituximab, and decided to give another dose on postoperative Day 8, with trepidation."

He proclaimed: "This pig heart was a rock star," commenting on the first postoperative days. "It was actually thrilling. I couldn't wait for the echoes to come in. The stress echo was remarkable, and anybody doing allotransplantation would be thrilled to see this. It was a perfect heart for about 43 days."

The good news continued, with a normal biopsy coming back from the lab, further cementing the hope and excitement that Dr. Griffith and his team were feeling. "Imagine this: now we have a guy who's heart looks great on echo, he's the world's first recipient of a pig heart, and now we have tissue proof that everything is looking pretty darn good!"

A rollercoaster ride begins

As time went on, the team continued with aggressive immunosuppression, "terrified" that the worst outcome might be around the corner: rejection. On postoperative Day 10, Mr. Bennett suffered an E. coli infection which, despite the immunosuppression, he was able to recover from. On Day 21, his white blood cell count dropped dramatically, at which point MMF was halted. "That scared us, because the MMF was an important kind of cofactor between the T cells and the B cells," said Dr. Griffith.

On Day 43, Dr. Griffith and the team started to notice a downturn in Mr. Bennett. He wasn't looking well, he wasn't functioning as well, and there were signs of sepsis. However, this was not confirmed. What was seen was a cytokine storm. He was given immunoglobulin to boost his levels, moved to a new antifungal and antiviral, and appeared to improve, looking well and sitting up four days later. "I thought maybe we had dodged another disaster," he said.

However, the next day Mr. Bennett began to decline. "He looked less well-perfused, and then really the car went off the track. He just got sicker and sicker, and we made a subjective decision for phoresis, thinking that perhaps we were in situation of antibody mediated rejection. We had nothing else really left to throw at him, so we went for an additional treatment with

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intravenous immunoglobulin.

"He went into acute diastolic heart failure. On Day 49, you could see that his heart looked thickened, stiffer, and was not relaxing well."

On biopsy, there was no positive complement staining, nor thrombosis or inflammation. supporting the notion that there was no antibody mediated rejection. He did have IgG and IgM staining throughout his capillaries, but this is not uncommon in allotransplantation patients, noted Dr. Griffith. What was striking, however, was the presence of extravasated red blood cells, suggesting capillary breakdown. On a third biopsy several days later, this had escalated to the point where the capillaries appeared to be lost.

Looking for answers

"Why was that happening?" asked Dr. Griffith. "We started detecting porcine cytomegalovirus [PCMV] in the patient's blood, and we were shocked by that because the animal and tested free of PCMV before transplantation.

"We know that the PCMV virus lives in monocytes and in capillary cells. You might in your own mind say, 'if you had evidence that it reactivated, maybe that's what happened to the capillaries in the face of intense immune suppression in the human? Maybe the virus infected its own heart, the porcine tissue?'. We have no evidence the patient himself had any organ [infection] with this virus. In other words, the patient didn't become infected, but it could have affected the heart. So, the hitchhiker became the driver.

> "I think we need to continue to be cautiously optimistic."
>
> **Bartley Griffith**

"We don't know this to be true yet. Every day we are still working additional details, but we're not afraid to mention it because in fact, we can fix this [in the future]."

Back to the future

Framing his next steps for the audience, Dr. Griffith began by asking all in attendance to encourage him to keep going. "We need to dig for the cause of the demise," he said. "We don't know the relative roles of the intravenous immunoglobulin that we gave him, which included human anti-pig antibody in those lots of intravenous immunoglobulin. We tested those lots and found them to be non-sidolytic, but it could have prompted something.

"In terms of PCMV, we now know we transplanted it with the heart. We've learned that from autopsy. Antibody mediated rejection? We don't know."

He continued: "We need to qualify screening tools for the latent virus, probably PCR, but maybe also serologic testing, and that is under way. Donor animal care is also important ... the plan is to remove the animals in their pathogen-free environments from being around herds of other animals that are free-ranging."

In his closing remarks, Dr. Griffith relayed that they now hope to approach the FDA for additional patients in their eIND pathway, and incorporate lessons into stronger multi-site INDs. "This will hopefully involve members of this august audience and society, as early as 2024," he said.

"We're on the way. I think we need to continue to be cautiously optimistic."

Plenary Session Ballroom ABC *Saturday 1:30 PM*

'Lung cancer surgeons need to do much more than cut and sew'

A tripartite combination of a molecular revolution in tumor biology, novel therapeutics, and technological advances from video-assisted to robotic surgery has changed the prognosis for lung cancer patients over the past century. This was the message during the David J. Sugarbaker Memorial Lecture: Lung Cancer Care: A Glance Back, a Look Forward, on Saturday afternoon.

"Lung cancer used to be cancer with a very poor prognosis. This is rapidly changing," said Valerie Rusch, esteemed thoracic surgeon from the Memorial Sloan Kettering Cancer Center, New York City, NY, USA, and Vice Chair for Clinical Research in the Department of Surgery.

The past 20 years has seen a raft of significant developments in the field and shows that lung cancer care is a very technology-driven specialty. "The progression of technology is going to continue at a very fast pace, and you need to exercise life-long learning to adopt and assess new technologies in a way that optimizes patient care," Dr. Rusch noted. "You need to be nimble and adaptable and have the humility to learn something that is actually entirely a new skill set."

The lecture is given in honor of the late David J. Sugarbaker, a thoracic surgeon of international renown, who pioneered the treatment of malignant pleural mesothelioma for nearly 30 years. Dr. Rusch is also a renowned specialist in mesothelioma, so there is a special resonance in her delivering this lecture.

Alongside a huge transition that has occurred in the world of molecular oncology with the molecular assessment of tumors, the use of precision medicine, and the constant stream of novel therapeutics becoming available, there is also a technological revolution in surgical management, and parenthetically a continuous improvement in radiotherapy planning and techniques, she pointed out.

"Surgeons are not just trained to cut and sew," she remarked. "To really manage the disease optimally, doctors need a knowledge base that includes a total understanding of the disease and all of the modalities involved. We have to understand this to be able to make optimal multidisciplinary decisions with our colleagues."

Dr. Rusch took the audience on a whistle-stop tour of the evolution of lung cancer knowledge and care from the 1920s to the early 21st century, including: the development of safe resection techniques; establishing a link to tobacco; clinical and surgical staging methods with computed tomography (CT) and positron emission tomography (PET), lymph node (LN) maps, staging systems and endobronchial ultrasound (EBUS); multimodality therapy beginning in the 1970s; lung cancer screening; pneumonectomy versus lobectomy versus sub-lobular resection through to minimally invasive techniques including video-assisted (VATS) and robot-assisted thoracoscopic surgery (RATS); more recently the molecular era of genetic markers and drugs; and since the 1940s the evolution in radiation techniques from cobalt to megavoltage, to conformal, to stereotactic body radiation therapy, to protons.

> "There's no question that there are going to be new technologies, month after month, and year over year, and they need to be evaluated and thoughtfully incorporated into treatment paradigms."
>
> **Valerie Rusch**

"Key areas of progress in the early 20th century were methods of staging, approaches to surgical resection with a marked reduction in surgical mortality," she said, adding that multimodality therapy was really the accomplishment of the last 25 years using cytotoxic chemotherapy and examination of the role of surgery versus radiation in the context of locally advanced cancer.

EGFR mutation – a watershed moment in molecular biology of lung tumors

A ground-breaking moment in the history of lung cancer care can be pinned on 2003, Dr. Rusch highlighted. "This was the identification of the epidermal growth factor receptor [EGFR] mutation as the target for a new class of oral chemotherapy agent." She added that they had struggled for years to understand lung cancer biology when this single event and the recognition that there were targetable mutations in many lung cancers transformed the field and the survival for certain patients with advanced lung cancer.

Patients with the EGFR mutation now had a new opportunity for treatment. "I always tell patients that the drugs will only work if they have a specific mutation, and that it's like selecting the key to fit the lock. If you don't have the correct key, you can't undo the lock."

Dr Rusch pointed out that it was necessary to do molecular profiling on all lung cancers. "The selection of treatment for patients with lung cancer is totally dependent on understanding individual tumor molecular composition," she said.

From 1999 to 2014, the molecular understanding of lung cancer evolved dramatically and has continued since. "From 1999 we went from having a single mutation that we knew had some prognostic impact, this was the KRAS mutation, to the discovery of other highly specific mutations for which we now have novel therapeutics."

She added that as a consequence of these advances in the molecular biology of lung tumors, they are now between only 25% to 30% of patients where a specific molecular target cannot be found in advanced disease.

"The new class of therapeutics developed on the back of the molecular advances have now been moved into patients who have localized disease. In particular, resectable lung cancer," said Dr. Rusch.

Rapid advances in technologies – VATS and robotics

In the early 90s, the technology for VATS was developed and transformed the field so suddenly surgeons were able to do what were conventionally open operations through a novel minimally invasive approach.

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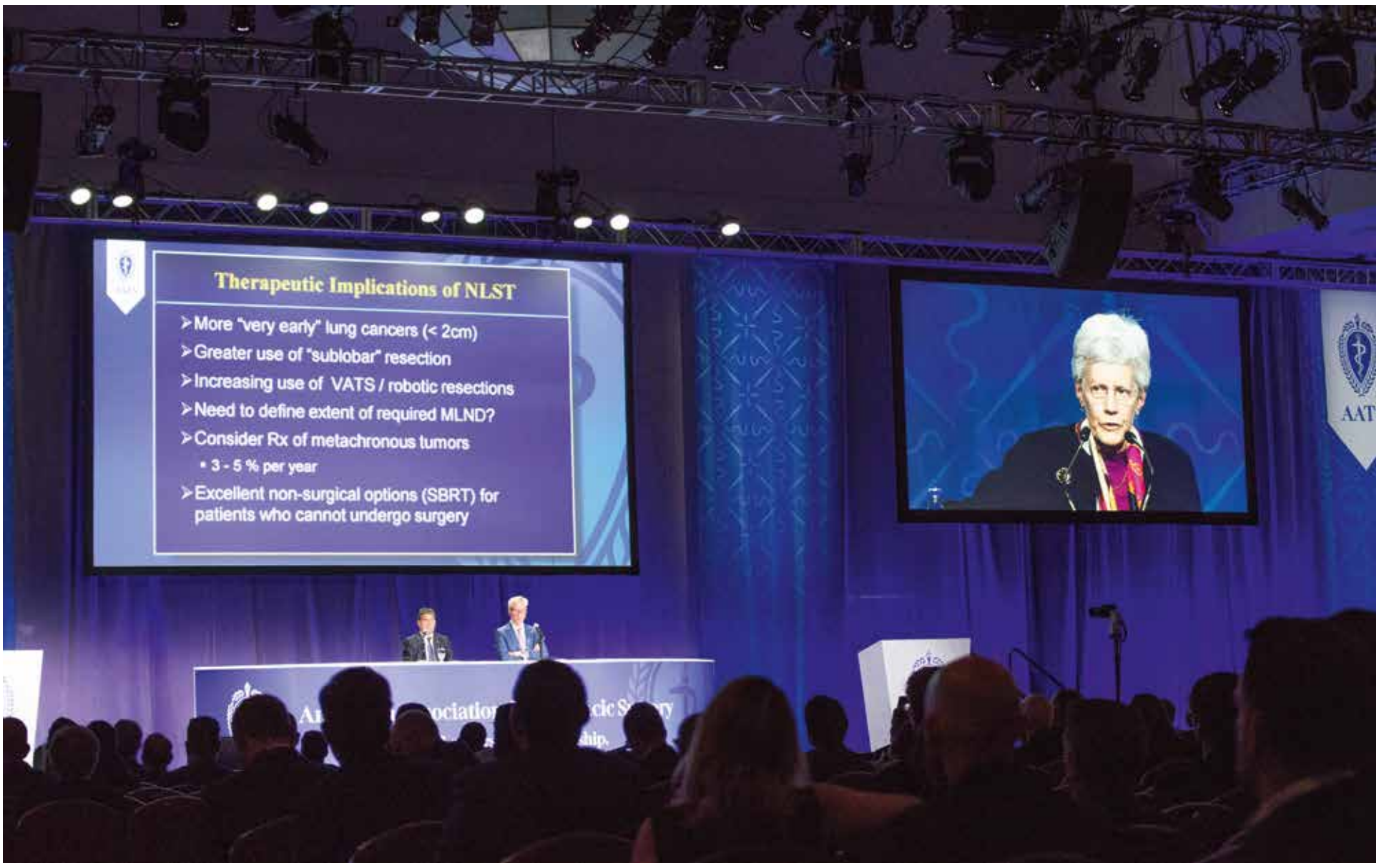

The recently published results of the VIOLET trial have finally provided the incontrovertible evidence of the superiority of VATS resections for stage one lung cancer, said Dr. Rusch. "This work came on the heels of many publications most of which were retrospective and done by single institution, suggesting that VATS would deliver superior outcomes. Now, the VIOLET trial has definitively established that."

Results, published in January this year, showed that at five weeks, physical function was better in VATS compared to open surgery patients. Patients who underwent VATS had fewer serious adverse events after discharge compared to those who had open surgery at 30.7% versus 37.8% respectively. No differences were seen in cancer progression-free survival or overall survival.[1]

After VATS, came the advent of robotic technology. "Surgeons of my generation who are trained on open procedures, that is thoracotomies, had to make the transition to VATS in the early 2000s, and then around seven years ago, I started doing robotic cases and that was a whole other skillset," recalled Dr. Rusch.

This technological advance not only affects early-stage patients, but it has now been moved into the treatment of patients who have more locally advanced disease. Dr. Rusch recalled that since being a high-volume VATS surgeon in recent years, and then moving into robotics, 90% of lung resections she does are conducted robotically. "It's a dramatic difference to what I was doing 10 or 20 years ago."

However, the degree to which more widespread use of VATS, and particularly robotics, will make a difference to patients with locally advanced tumors who receive multimodality therapy remains unknown, said Dr. Rusch: "We don't yet know how much that will actually change the landscape. VATS has improved physical function, reduced hospital stay, with essentially identical oncological outcomes, and if you can take these technological outcomes and apply them to patients with locally advanced disease, potentially they will have more rapid recovery, potentially they could resume adjuvant therapy more rapidly if needed, and have the same oncologic outcomes but with lower morbidity."

> "To really manage the disease optimally, doctors need a knowledge base that includes a total understanding of the disease and all of the modalities involved."
>
> **Valerie Rusch**

Currently, there are two trials testing the use of the checkpoint inhibitor immunotherapies on a heterogeneous group of patients with stages 1b to 3a lung cancer. A substantial proportion of patients in both of these trials – the Study of Atezolizumab as Neoadjuvant and Adjuvant Therapy in Resectable Non-Small Cell Lung Cancer (NSCLC) by the Lung Cancer Mutation Consortium (LCMC3), and the Checkmate 816 trial – had lung resections via by minimally invasive techniques either using VATS or robotic VATS, explained Dr. Rusch.

Tools of the trade: screening and molecular markers

In the US at least, there has been a decline in the incidence and mortality of lung cancer. However, this is not being seen across all racial and ethnic groups. "There are underserved minorities in this country, especially the African American population that still lag behind for a multitude of reasons and don't get lung cancer screening as they should."

This decline in incidence and mortality is multifactorial and probably related to earlier diagnosis, said Dr. Rusch. "I always tell people that CT screening is like the mammogram of the lung, so it is similar to the effect that mammography had on the earlier diagnosis of breast cancer."

She added that the impact of screening was significant, but that smoking cessation had had the largest effect. "This will probably be seen in a more delayed manner in Western Europe, because it lags behind the US in terms of public health-based smoking cessation programs."

In addition, there are many new therapies available, said Dr. Rusch, which for the most part do not cure lung cancer, but they extend life expectancy to a substantial degree. There are three broad categories of lung cancer drugs currently: the toxic chemotherapies that were standard for a long time; the targeted therapies from the early 2000s, namely the tyrosine kinase inhibitors; then the checkpoint inhibitor immunotherapies. "But none of these drugs are necessarily the right thing for all patients. Patient selection based on individual tumor biology is critical," she added.

"In one of the early immunotherapy trials they looked at the survival according to PD-L1 expression in the tumor. It has been validated repeatedly that if you have a high PD-L1 expression, when patients are more likely to respond to those drugs, and 3have a better outcome of progression-free survival."

However, this is not a totally reliable parameter to use for patient selection and there is still a need for a much clearer understanding of which patients will and will not respond to these drugs. "They are relatively less toxic overall than platinum-based chemotherapy but they are not toxicity free. You don't want to throw potentially toxic and very expensive drugs at patients were not going to benefit," explained Dr. Rusch.

The LCMC3 trial uses pre-operative immunotherapy only versus the Checkmate 816 trial which is chemotherapy plus immunotherapy. If the patient is given just two cycles of immunotherapy, 20% of patients will respond and have the complete pathologic response or a major pathologic response (10% or less viable tumor).

> "I assure the younger members of the audience that you will never have a dull moment coming up, because the field scientifically and intellectually is developing so rapidly."
>
> **Valerie Rusch**

"We need to develop a way to determine who he is going to respond and who is not, so we can de-escalate therapy if necessary. Giving platinum-based chemotherapy and immunotherapy is a lot of drug treatment, and if someone only needs one of those drugs then the patient should only be receiving that one," Dr. Rusch asserted. She also noted that it was necessary to understand the impact of these drugs on the surgical management of the patient, and what is going to potentially make surgical resection either technically more complicated or higher risk.

Finally, circulating tumor DNA (liquid biopsy) was the last aspect of lung cancer care referred to by Dr. Rusch. "We need to be able to measure what is happening, but we don't yet have a good way to do that."

The technology around circulating tumor DNA is still in its nascent phase, she added. "There are different platforms, and gene panels, and these are not necessarily standardized in a way that provides a commercial product available to all institutions at a low price and that you know is highly reliable."

Also, explained Dr. Rusch, it is not possible to measure circulating DNA in every patient, because those with early-stage disease, so stage one tumor, are less likely to have material that is measurable in a blood sample compared to those with advanced disease.

And, with that, Dr. Rusch ended her overview of lung cancer care over the past century. "There's no question that there are going to be new technologies, month after month, and year over year, and they need to be evaluated and thoughtfully incorporated into treatment paradigms. This demands that we be nimble and flexible to adopt new surgical techniques into a practice and evaluate them carefully.

"I assure the younger members of the audience that you will never have a dull moment coming up, because the field scientifically and intellectually is developing so rapidly that it is dynamic and ever-exciting."

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Using Technology to Impact Patient Centered Perioperative Care Room 206 *Monday 7:30 AM*

Machine learning for real-time and early prediction of acute kidney injury after cardiac surgery

The use of technology to improve patient care took center stage on Monday morning, with speakers offering insights into their cutting-edge work. In his talk, Christopher Ryan (Baylor College of Medicine, Houston, TX, USA) introduced the concept of machine learning (ML) for real-time prediction of acute kidney injury (AKI), taking the audience through early results, as well as the ultimate goals for the technology at the bedside.

Speaking to *AATS Daily News*, Dr. Ryan underlined the difficulty in sifting through countless parameters to try and predict the risk of AKI after cardiac surgery using clinical judgment alone. "The problem is, current diagnosis relies on findings that can be significantly delayed from the actual kidney insult," he began. "Changes in serum creatinine and mean urine output typically occur 48 to 72 hours later. But what we were hoping to do is detect the actual insults themselves to get some lead time on that, and allow earlier intervention to mitigate, or even prevent that injury."

Given the myriad parameters involved in the early-stage identification of AKI, it begs the question as to what aspects to prioritize. "It's a good problem to have – having lots of data is certainly better than the opposite – but it does require a different approach."

As such, Dr. Ryan and colleagues have been working on an ensemble ML model that incorporates patient characteristics, operative details, and intensive care unit time series data to predict AKI before conventional clinical identification. Part of the impetus of the project, he notes, is to recognize that there's so much data in electronic medical records which is never really utilized for either research or clinical care.

"That is one of the benefits of the ML strategy: it can use a lot more variables effectively than traditional logistic regression or related strategies, and you don't necessarily have to go through the variable selection process before, because that can be automated within the training of the model."

Most risk scores currently rely on preoperative or intraoperative factors, noted Dr. Ryan, for instance the Society of Thoracic Surgeons risk score, which includes an AKI component. However, the score does not update after surgery, despite the postoperative environment being dynamic.

"So, knowing a patient's risk preoperatively doesn't necessarily help you guide their management postoperatively, particularly when they've already had other complications or issues, and you have to adjust their risk."

In this stage of development for the ML model, Dr. Ryan and colleagues are focusing mainly on predictive accuracy, but the next part will be to try to make it a so-called 'explainable model'. "This means that it can actually tell you which factors are behind predictions of elevated risk, and the hope would then be that some those factors would be modifiable," explained Dr. Ryan. "Some of the most obvious modifiable ones would be hemodynamic parameters such as cardiac output or blood pressure, as well as nephrotoxic medications."

In terms of how a model would be trained to better predict AKI in different centers, Dr. Ryan underlined the importance of using retrospective data, in conjunction with collaborators. After all, given that the sample size of cardiac surgery patients even at bigger centers is still relatively small in the grand scheme of things, he is keen to coordinate larger data sets from multiple centers to help build the model.

Then, to operationalize the model in clinical practice, there is the hurdle of gaining access to real-time streaming of electronic medical data. "The Food and Drug Administration currently regulates software such as that, as it's actually going to be used for clinical decision making," he said. "You essentially have to get approval of the software as if it were a device.

"So that is our long-distance thinking: we want to take that process and actually do a trial to see if it works."

In any case, results with the ML model thus far have been promising, having been shown to predict development of AKI from currently collected electronic medical record data with high accuracy and specificity. With incorporation of time series ICU hemodynamic and pharmacologic data, he added that ML predicted development of AKI earlier than conventional clinical identification.

"Having lots of data is certainly better than the opposite – but it does require a different approach."

Christopher Ryan

"But we don't want to build a model just to show how successful it can be at predicting AKI ... we're coming from the very beginning with the mindset of actually putting it to clinical use. We chose AKI as the initial thing to focus on, but we're hoping it may be expandable to other conditions. We want to be careful to make sure that it's actually helping improve practice."

A burning question in some people's mind might be whether the model is being designed to validate clinical judgment, or possibly step in when there is insufficient expertise on hand? Certainly, the COVID-19 pandemic has thrown staffing issues into sharp focus, and the arena of intensive care – where some of the data comes from – has looked at ways to help less experienced members of clinical teams validate diagnoses and treatment choices.

Dr. Ryan commented: "With that in mind, I think it does make sense to use this model as a 'backstop'. Maybe it could at least alert people earlier [to the risks], so that important interventions aren't missed. I don't think expert clinicians are going to have their own decisions overridden, but it is one of the reasons why we're focusing on the explainable part next."

Delving deeper, Dr. Ryan said that in order to get clinician buy-in, there will have to be clear face-value validity of what's driving the predictions. In other words, clinicians will need to be able to understand the behavior of the model, not least because it will then also help them to determine why the model came to a conclusion they disagree with. "For instance, the expert clinician would be able to say, 'I see why it made that conclusion, but I think it's wrong for this particular patient'," said Dr. Ryan. "I don't think this is ever going to override ultimate clinical decision making, nor should it."

Offering his concluding remarks, Dr. Ryan commented: "We see that the usage and access of electronic medical record data is feasible – there's a wealth of information out there, and with some assistance I think it's definitely a treasure trove that we haven't accessed fully. In time, we hope to really start to dig into it to help drive and improve patient care."

"We don't want to build a model just to show how successful it can be at predicting AKI ... we're coming from the very beginning with the mindset of actually putting it to clinical use."

Christopher Ryan

Monday's session, An Executive Roundtable on Bringing Discoveries to the Bedside.

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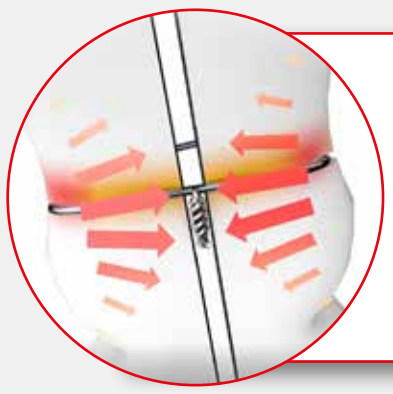

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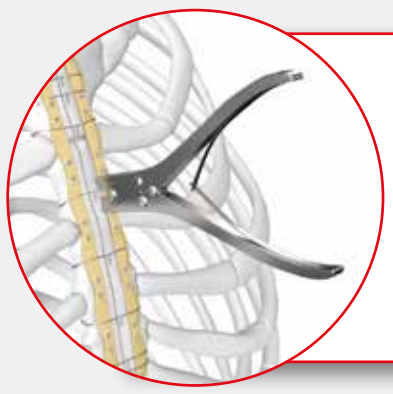

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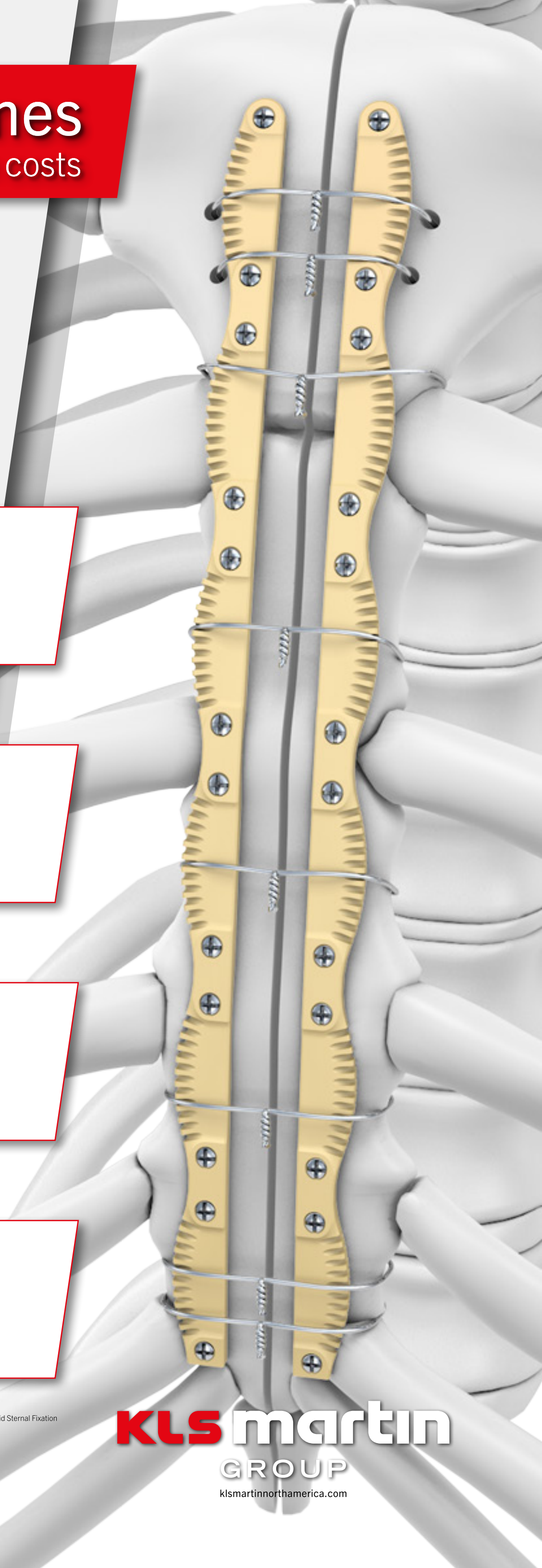

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Rescuing and Failing to Rescue the Postoperative Patient Room 206 *Tuesday 8:00 AM*

Do METs help turn the tide on 'failure to rescue'?

An investigation into the effects of medical emergency teams (METs) on failure to rescue (FTR) rates in cardiac surgery patients will be the focus of an interesting talk by Andrew Young, a third-year research resident in general surgery at the University of Virginia (UVA), Charlottesville, VA, USA.

Dr. Young will talk about a retrospective study, conducted at UVA Hospital in Charlottesville, looking at FTR in more detail: "The concept of FTR – defined as mortality following a complication – is relatively new as a metric in cardiac surgery," he said, noting its gaining popularity. "People have started writing on it and trying to identify ways of reducing it or what contributes to it. And we noted that at our institution, we have a MET or a rapid response team who check on patients who they think are having issues."

Therefore, the idea was to see whether, when this team came into existence, it helped reduce FTR rates and other complications. "The biggest step we were curious about is basically triaging people who might need to go to the ICU earlier, and whether or not that helps," he explained.

Dr. Young said that rapid response teams, like the one at UVA, are not ubiquitous in the US, but are becoming more common. When a patient reports a particularly high blood pressure, or experiences tachycardia or bradycardia, the hospital system will send an alert to the team – something which is known as 'activation'. "The person who's taking care of the patient will be notified, the team will come and asses the patient, and then will provide ICU care where necessary," he explained. Crucially, the team is comprised a group of critical care nurses that anybody – including family members – can activate if there are concerns.

Dr. Young spoke of sample data of patients at UVA hospital, where the MET began in 2007. From a sample of about 17,000 patients, Dr. Young and colleagues then proceeded to risk-adjust the data, because patients in different years will have different outcomes. "That's because of theoretical improvements in how we take care of patients over time," he explained.

Dr. Young used the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD), a clinical outcomes registry for adult cardiac surgery for data pertaining to UVA. Launched in 1989, the database contains more than 7.5 million cardiac surgery procedure records, and currently has nearly 3,800 participating physicians, including surgeons and anesthesiologists.

> "The establishment of the rapid response team is clearly associated with decreased rates of failure to rescue."
>
> **Andrew Young**

"So, in the ACSD, they have predicted risks and mortality, such as the risks of renal failure," he said. "These models were created based on years of data to say how likely a person is to have certain complications."

From this data, Dr. Young used propensity score matching: "That is where you try to balance two groups of patients. One is the control group, one is the exposed group, and you try to make them look as similar as possible to try and determine if what you're doing is what's causing a difference rather than other differences in their baseline characteristics."

Therefore, the matched groups both have about the same risk of mortality. "So, if there's a difference between the two groups, it's hopefully because of the intervention. You can never say for sure, because this is retrospective data, but you can say that there's an association, and then try to remove as much bias and confounding aspects as possible."

After propensity score matching, there were about 3,500 patients in each group, originating from 10 years before the team was created in 2007, to 10 years after. In those two groups, Dr. Young's team looked for rates of FTR – i.e., mortality after a major complication, such as renal failure, prolonged postoperative ventilation, stroke, and re-operation.

The results were interesting, noted Dr. Young. In patients within a major morbidity subgroup – those with complications – the difference in figures were startling. Before (or without) the MET, the rate of mortality was 20.2%, yet after introduction of the MET it was 11.6% (this is a smaller subset of patients who had only those specific complications in the cohort). In the overall cohort, before the MET, the hospital reported a 3.5% rate of mortality, versus 2% after their introduction (odds ratio for FTR 0.47; confidence interval 0.32–0.68; p<0.001).

The UVA study is of interest, said Dr. Young, because most other studies looking at changes in FTR rates have focused on medical patients rather than surgical ones. That being said, he stressed that more granularity in the data would glean more information on reasons for FTR. However, such data may be beyond the scope of the ACSD for now. "The database contains pretty broad complications – things like renal failure – but I think that once it gets to that point, you're a little too late. And in terms of things that can be done to improve the team, it's tough to say with the data that we have."

Ultimately Dr. Young believes that it would be great to capture further data within the ACSD, such as whether a person has a rapid response after activation. "It's a great outcomes database because it has all this detailed data, it's well maintained, and has good validation," he said. "But sometimes we identify new quality metrics."

Activation of the MET (when an alert is initially sent) isn't collected by the STS currently, thus Dr. Young reasoned that to be clinically applicable, it'd be interesting to look more and see at systems that help identify these patients. "For example, if a patient has a trigger, how long before they received a response, and how did that impact the outcome? Knowing whether a center has a rapid response team, and whether a patient received rapid response, is something I think is worth looking into."

Ultimately, Dr. Young said the MET is a positive addition to the surgical department. "While we cannot say definitively that FTR was decreased, the establishment of the rapid response team is clearly associated with decreased rates of FTR," he said. "For institutions that don't have such a system in place, it's worth considering a rapid response team."

Liesle Zühlke delivers her lecture on eradicating the global burden of rheumatic heart disease

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Noted abstracts at the AATS 102nd Annual Meeting

Therapeutic Approaches for Locally Advanced Cancer Room 312 *Tuesday 8:00 AM*

LB11. Safety and Tolerability of Adjuvant Atezolizumab Following Chemo in Patients With Stage II-IIIA Non-Small Cell Lung Cancer Who Had Pneumonectomy or Bilobectomy: Results From the IMpower010 Trial

Abstract presenter **Jay Lee** *UCLA*
Invited discussant **Uma Sachdeva**
Massachusetts General Hospital

Abstract

Objective: IMpower010 (NCT02486718) established adjuvant atezolizumab as standard of care after chemotherapy in resected stage II-IIIA PD-L1 TC≥1% non-small cell lung cancer (NSCLC). However, the safety/tolerability of checkpoint inhibitors in pneumonectomy or bilobectomy patients is unclear. We investigated adverse events (AEs), time to adjuvant treatment and atezolizumab treatment withdrawal and duration by surgery type.

Methods: IMpower010 enrolled patients with completely resected stage IB (tumors ≥4 cm)-IIIA NSCLC (AJCC/UICC v7) and ECOG PS 0/1. Patients received up to four 21-day cycles of cisplatin-based chemotherapy (enrollment phase) and were subsequently randomized 1:1 to receive atezolizumab 1200 mg every 3 weeks (up to 16 cycles) or best supportive care (BSC; randomization phase). Investigator-assessed disease-free survival (primary endpoint) was tested hierarchically in the PD-L1 TC≥1% (SP263) stage II-IIIA population, then the all-randomized stage II-IIIA population, and then the ITT population (stage IB-IIIA). This exploratory analysis evaluated AEs and clinical characteristics by surgery type (pneumonectomy/ bilobectomy [P-BL] vs lobectomy/ sleeve lobectomy [L]).

Results: Overall, 1280 patients were enrolled; 1269 received adjuvant chemotherapy; 1005 were randomized and 871 with stage II-IIIA NSCLC were included in the safety population. Within the safety population, 148 patients had pneumonectomy, 47 had bilobectomy, 667 had lobectomy and 7 had sleeve lobectomy. In the atezolizumab arm, 87% of the P-BL patients vs 95% of the L patients had any AE. Grade 3/4 AEs occurred in 21% (P-BL) and 23% (L) of patients; serious AEs occurred in 13% (P-BL) and 19% (L). Atezolizumab withdrawal occurred in 32% of P-BL patients vs 35% of L patients. The median atezolizumab treatment duration in both groups was 10.4 months. The median time from surgery to adjuvant atezolizumab was 5.1 (P-BL) vs 5.2 (L) months. Incidence of hospitalizations related to any AE was 13% (P-BL) vs 17% (L). The median time from surgery to adjuvant chemotherapy and chemotherapy duration were similar in both groups.

Conclusions: In IMpower010, AE profiles after adjuvant chemotherapy and atezolizumab were similar in P-BL and L patients. There were no differences in discontinuation and duration of atezolizumab treatment or time from surgery to adjuvant chemotherapy/atezolizumab. In P-BL patients, adjuvant atezolizumab had no new safety signals and was well tolerated.

Pushing the Boundaries with Technology in Thoracic Surgery Room 312 *Tuesday 10:00 AM*

LB13. Robotic-Assisted Lobectomy for Early-Stage Lung Cancer Provides Better Patient-Reported Quality of Life Compared to Video-Assisted Lobectomy: Early Results of the RAVAL Trial

Abstract presenter **Waël Hanna** *McMaster University*
Invited discussant **Robert Cerfolio** *NYU Langone Health*

Abstract

Objective: The primary objective of Phase A of this international prospective blinded randomized controlled trial comparing robotic-assisted lobectomy (RTS-Lobectomy) to video-assisted lobectomy (VATS-Lobectomy) for early-stage lung cancer is to determine the difference in patient-reported health-related quality of life (HRQOL) between the two arms at 12 weeks after surgery and incremental cost per quality-adjusted life year (QALY) at 12 months after surgery.

Methods: Patients with early-stage lung cancer who were candidates for minimally invasive lobectomy were enrolled from January 2016 to July 2020 at 4 academic sites in the US, Canada, and France. Participants were randomized in a 1:1 ratio to either RTS-Lobectomy (intervention) or VATS-Lobectomy (control). Patients were assigned to surgeons before randomization and all surgeons performed the operations per protocol. Patients were blinded to the type of surgery until the 12-month follow-up. EQ-5D-5L and other HRQOL questionnaires were administered at baseline, postoperative day 1, weeks 3, 7, 12, and months 6, and 12. Data is presented as mean (SD) and median (range). Direct and indirect costs were tracked using standard methods. Seemingly Unrelated Regression was applied to estimate the cost effect, adjusting for baseline characteristics and stratification factors (surgeons) and baseline health utility. The incremental cost effectiveness ratio was generated by 10,000 bootstrap samples using bias-corrected and accelerated method, with multivariate imputation by chained equations for missing data in QALY. Continuous variables were compared using Student's t-test, and categorical variables using Chi-square test.

Results: Of 406 patients screened, 45.81% (186/406) were randomized (RTS n=92; VATS n= 94). At final eligibility review (protocol deviations, withdrawal, loss to follow-up), 82 were analyzed in the RTS arm and 83 in the VATS arm. All patients were followed for at least 12 months. Mean age was 67.36 (9.82) and 66.67% (110/165) were women. There were no significant differences in the body mass index, comorbidities, pulmonary function, smoking status, location of tumor, tumor size, or disease stage between arms. The mean 12-week health utility score was 0.85 (0.10) for the RTS arm and 0.80 (0.19) for the VATS arm [mean difference (MD) 0.05, 95% Confidence Interval (CI) 0.01, 0.09; p=0.02]. Significantly more lymph nodes were sampled [10 (8-13) vs 8 (5-10); p=0.003] in the RTS arm. The incremental cost per QALY of RTS-Lobectomy was $14,925.62 (95% CI $6,843.69, $23,007.56) at the 12-month time horizon.

Conclusions: Early results of the RAVAL trial suggest that RTS-Lobectomy is a cost-effective intervention which is associated with better patient-reported HRQOL when compared to VATS-Lobectomy within 12 months of surgery. RTS-Lobectomy is also associated with superior lymph node sampling. Long-term oncological and HRQOL outcomes will be analyzed in later phases of the ongoing RAVAL trial.

High Performance Cardiothoracic Surgery in the Digital Age* Room 309 *Tuesday 10:00 AM*

LB14. Heart Rate Variability Correlates with Emotional Exhaustion in Thoracic Surgery Trainees

Abstract presenter **Lauren Barron** *Barnes Jewish Hospital*
Invited discussants:
Mara Antonoff *Anderson Cancer Center*
Andrew Goldstone *NYP-Columbia*

Abstract

Objective: Physician burnout is defined as a reaction to chronic job-related stress marked by emotional exhaustion, depersonalization, and decreased sense of personal accomplishment. It is widespread in surgery with 40%-69% of attending surgeons and >50% of thoracic surgery trainees endorsing symptoms of burnout. This study sought to determine whether burnout could be correlated with physiologic data in thoracic surgery trainees and whether burnout would correlate with performance.

Methods: This was a prospective study of thoracic surgery trainees in a 4+3 or standard 5+2 training program over a 5-month period ending January 2022. Participants were evaluated with a wearable biometric device and the Maslach Burnout Inventory. Demographic data (sex, ethnicity, marital status and number of children), academic data (clinical training year, training focus and ACGME milestones report) and physiologic data (resting heart rate, heart rate variability, and sleep) were collected. Burnout and physiologic data were analyzed using regression analysis or chi-squared test. Resident performance was quantified using ACGME milestones (scale, 1 to 5) normalized to target where target is 3 for ≤ PGY-6 and 4 for PGY-7.

Results: The cohort consisted of 71% females (5 of 7) with 86% of trainees having 1 or more children. High levels of emotional exhaustion (median: 30 [IQR: 20,36] where < 19 is low and > 26 is high) and high levels of depersonalization (16 [14,22] where < 6 is low and > 12 is high) were common. Personal accomplishment was uniformly high (43 [41,46] where 38 is high). There was no significant relationship between gender (p>0.69), number of children (p>0.08), sleep (p>0.4), training track (p>0.16) and any dimension of burnout. There was a significant correlation between heart rate variability and emotional exhaustion (r(12)=.65, p=0.01, Figure 1A) but not depersonalization (p=0.28) or personal accomplishment (p=0.24). Depersonalization and personal accomplishment did not correlate with resident performance (p=0.12 and p=0.75, respectively); however, increased emotional exhaustion showed a significant correlation with higher resident performance scores (r(6)=.76, p=0.047, Figure 1B).

Conclusions: Dynamic measurement of resting heart rate variability may offer an objective measure of burnout in thoracic surgery trainees. Thoracic surgery trainees who report high levels of burnout maintain the ability to meet the ACGME milestones at or above the level expected of their post graduate year. Further multi-institutional studies investigating the sources of burnout and potential interventions are essential to optimize training in thoracic surgery.

Esophagectomy: Improving Outcome Room 311 *Tuesday 10:45AM*

Regionalization a must for better outcomes

The concept of ensuring that patients with complex medical needs are treated in those hospitals better equipped to provide complex care, i.e. regionalization, will be discussed today by Daniel J. Boffa, Professor & Chief and Division of Thoracic Surgery at Yale School of Medicine (CT, USA). A general thoracic surgeon with a clinical interest in esophageal cancer, Professor Boffa has conducted health policy and outcomes research for the past several years. His team has looked at regionalization from multiple stakeholder perspectives including patients, hospitals, and payers.

Regionalization assumes three critical things, explained Professor Boffa. First, a meaningful gap in quality or safety must exist between subsets of hospitals. "If the gap is too small, then the benefit of redirecting patients will be small," he explained. The second assumption is that there is a way to predict which hospitals would provide care at the extremes of the gap – between the safest and least safe. "In other words, quality and safety assessment of a hospital must reflect the current status of care," said Professor Boffa. Finally, the benefit of having surgery at a destination hospital (that might be further away) must be important enough to the stakeholders to justify the additional investment of time, effort and expense.

> "Ultimately, these studies have shown that hospitals can be stratified into cohorts that have meaningful gaps in safety and effectiveness."
>
> **Daniel J. Boffa**

Professor Boffa said that a large number of studies have consistently demonstrated variability in the safety and effectiveness of complex cancer surgery across hospitals in the United States. "Several methods have been used to stratify hospitals into extremes in terms of patient outcomes," he noted. Health policy research giants such as John D. Birkmeyer of Sound Physicians (NH, USA) have, for example, established the relationship between low annual volumes of complex procedures and a higher likelihood of lethal complications.[1]

"Some, including Alex Chiu from our team, have used safety performance,[2] rather than annual volume to stratify hospitals," he said. Others still have used reputation as a predictor of patient outcomes. "Ultimately, these studies have shown that hospitals can be stratified into cohorts that have meaningful gaps in safety and effectiveness."

But the factor relating to benefit versus stakeholder investment appears to be the most important driver guiding where patients have surgery, said Professor Boffa. "This explains why regionalization is still a hypothetical discussion in 2022," he explained. The fact is, despite the complexity of, say, esophagectomy, less than 400 patients die each year from lethal complications of this procedure. In contrast, models of regionalization predict that less than 100 deaths would be preventable each year by regionalization. "That raises the inevitable question of would the effort be worth it to realign patients?" said Professor Boffa.

> "Most hospital network affiliates – though not all – achieve inferior short and long-term outcomes after cancer surgery."
>
> **Daniel J. Boffa**

Importantly, if the focus is not exclusively on esophagectomy, this may tip the balance. His team's research indicates that many more lives could be saved when looking more generally at complex cancer surgeries. "Regionalization would likely cover a wider range of complex cancer surgeries," he explained. "We have estimated regionalization in complex cancer surgeries could save around 1,000 lives each year. That should resonate with payers and hospitals. Patients appear to value the safety of their hospitals."

Therefore, addressing the barriers to this additional investment is key. One survey performed by his team[3] indicated that over 90% of respondents would travel an hour to reduce their surgical mortality rate, but three out of four had a barrier that would prevent them from doing so. "Many of these barriers could be facilitated or mitigated by a low-cost intervention, such as free parking or a ride," said Professor Boffa. Importantly, the reputation of a hospital matters, as Alex Chiu's survey study suggested. "Most patients would prefer to have complex surgery at a hospital that was top ranked," said Professor Boffa. "This is a critical piece of the puzzle, as patient-driven realignment toward safer hospitals is key in health systems such as the United States, and patients would require a relatable source of hospital status."

However, hospital networks seem to represent both a significant barrier and provide the greatest hope for regionalization in the United States, said Professor Boffa. Prior work from his group has demonstrated that the public incorrectly perceives network status to correlate with hospital quality, particularly in the networks that form around top-ranked hospitals. "More than half of survey respondents feel the safety and effectiveness of complex cancer surgery is the same when performed at top-ranked hospitals or their affiliates," he said.

> "We have estimated regionalization in complex cancer surgeries could save around 1000 lives each year."
>
> **Daniel J. Boffa**

"In fact, an affiliation between their local hospital and a top-ranked hospital would decrease their willingness to travel for complex cancer surgery." However, studies from the Medicare database and the National Cancer Database suggest this is not necessarily a true assumption, he said. "Most hospital network affiliates – though not all – achieve inferior short and long-term outcomes after cancer surgery," he said. "On the other hand, several networks have demonstrated how effectively regionalization can be handled, with complex cancer surgeries being preferentially performed at certain hospitals within the network."

In many ways, the network model is the perfect answer to the benefit versus stakeholder investment conundrum, said Professor Boffa. "The connectivity across hospitals would bring stakeholders into more alignment and lessen several financial and administrative barriers to regionalization," he said. "There may also be greater accountability across the network which could justify investments to mitigate those barriers that remain."

Professor Boffa added that cancer leaders such as American College of Surgeons' Heidi Nelson and Tim Mullet, a thoracic surgeon who leads the Commission on Cancer, are committed to optimizing quality in networks. "I suspect this is the beginning of the end of the era of hypothetical regionalization," he concluded.

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Plenary Session Ballroom ABC *Saturday 1:30 PM*

Conduction mapping during complex congenital heart surgery – when to expect the unexpected

Injury to the conduction system remains a significant problem in congenital heart surgery, thus there is great potential in using conduction mapping techniques to better identify where conduction runs in any given patient, the audience heard on Saturday afternoon in the Ballroom.

Speaking during Saturday's plenary session, Eric Feins from Boston Children's Hospital, MA, USA, introduced his work in conduction mapping, beginning with a snapshot of the dangers and impact of operating on congenital cases without knowledge of the conduction system's exact location.

"If you look at the literature across the whole spectrum of congenital heart surgery, the risk of injury to the conduction system, which can lead to heart block and a child requiring a pacemaker for the rest of their lives is actually around 1%, but it's an oversimplification to just say that heart block is rarely a problem in congenital heart surgery," he said.

Indeed, Dr. Feins stressed that the rate of heart block is much higher in more complex congenital heart defects that require more extensive surgeries. In a double switch operation, for example, which is an established yet complicated technique, the risk of heart block exceeds 15%. In children with heterotaxy syndrome, the risk of heart block requiring a pacemaker may be as high as 25%.

Heart block and pacemaker implantation also carry with them a host of subsequent problems, noted Dr. Feins, with a significant amount of data pointing toward failure with pacing leads or generators, infections, and the need for reinventions in some patients. "There is an increased mortality risk across the board for children who have suffered heart block and received a pacemaker," he said.

> "It's an oversimplification to just say that heart block is rarely a problem in congenital heart surgery."
>
> **Eric Feins**

Of course, the solution to avoiding heart block lies in navigating effectively around the conduction system, avoiding making incisions or tissue damage within its path. "As surgeons, we are kind of tiptoeing around it," said Dr. Feins.

For certain congenital heart defects, there is prior knowledge of where the conduction system is likely to lie thanks to decades of histopathological data. "That is why rates of heart block are not high in all patients: we do kind of know where the conduction system will be in many of these patients," noted Dr. Feins, adding: "But there is variation, especially in more complex patients, and that's why our rates of heart block are not zero."

As such, there is still relative uncertainty when embarking on a congenital heart operation, thus there is a great desire to provide surgeons will the tools to confidently map where the conduction system is in any given patient.

To that end, in a collaboration with the electrophysiology group at

Boston Children's hospital, Dr. Feins and colleagues have been introducing routine use of intraoperative His bundle mapping via the placement of multielectrode catheters along the endocardial surface. This allows the surgeon to see real-time electrograms on screen which pinpoint the conduction system.

Typically, after 5 or 6 minutes of scanning, there will be enough information to map out where the conduction areas are, at which time the surgeon is able to proceed with the rest of the operation. "The metaphor I always use is, if you are on a plot of land and someone tells you to just walk around and not step on the landmines, and all you are relying on is what people have told you from prior studies of where they might be, that is risky. But, if you have a metal detector, you can check where those landmines are, and make a roadmap of where is safe to go."

Over the course of two years, Dr. Fein's center has mapped around 180 patients, the first 100 of which he presented during the session on Saturday afternoon. As he described, median age and weight were 2.1 years (range: 0.2–35.4) and 10.9 kg (range: 3.5–85.2), respectively. Conduction was identified in 95/100 patients, and median mapping time was 6 minutes (range: 2–33).

One of the key conclusions that came out of the work was that a significant percentage of patients with complex congenital heart disease have an unexpected location of their conduction system. Particularly, L-looped ventricles, heterotaxy syndrome, atrial situs inversus and L-malposed great vessels were seen to be anatomic predictors of unexpected conduction location. As such, Dr. Feins emphasized that surgeons must account for this when performing intracardiac repair in these complex anatomies.

"In this particular cohort, we found about 27% of patients had what we called 'looping discordance'," said Dr. Feins. "In other words, with L-looped ventricles, we thought conduction would run inferiorly, but actually it ran superiorly, and vice versa."

All in all, this discordance between expected and actual location of the conduction system re-emphasizes the need to not oversimplify, nor be overconfident, based on lessons learned from the past. While not 100% perfect, mapping offers a vastly improved understanding of where conduction lies beneath the endocardial surface.

> "We do kind of know where the conduction system will be in many of these patients, but there is variation, especially in more complex patients, and that's why our rates of heart block are not zero."
>
> **Eric Feins**

Turning to how the data generated in his center can now be used, Dr. Feins stressed that one aspect will be just to exemplify the difference between presumption and reality of the conduction system's location. "Basically, when to expect the unexpected," he said.

In addition, he also touched upon the burning question of how to predict the unexpected, based on anatomical features. "For that we performed a classification and regression tree analysis. That looks at which variables have the greatest power in discriminating between conduction running in one place vs. another. It creates a sort of decision tree that you can plug your patient's data into and say, 'Okay, I have a patient with this and that anatomic factor, and we know that 20% of the time the conduction for these patients runs here,' etc. Basically, we're trying to create a predictive model."

For example, breaking down which patients had conduction running superiorly, these can then be further stratified by those with atrial situs solitus, revealing different location-based data which can guide future surgeries. "As we gather more mapped patients, it'll inform the model more, and we further refine it and get better at prediction," said Dr. Feins.

Importantly, if the predictive model continues to refine to the point where surgeons will be able to have better understanding of where conduction lies, the question remains of wouldn't it still be best to continue mapping in real time for every patient? "The short answer is yes," said Dr. Feins. "If there is a 95% chance that it's in one place, that sounds great, but if I then tell you there's a 5% chance you will injure the conduction system, we're kind of back to where we are now."

In addition, Dr. Feins notes that, currently, the mapping of conduction is still a little "crude", detailing *fairly* closely where it can be found, but not with the kind of precision that would ultimately be beneficial. That's why he and his team and very keen on the next stage of development to be focused on not only refining the technology to make it higher resolution, but also making it easier to wield and use.

"Rather than using tools originally developed for the electrophysiology or cath lab, we'd like to have tools designed for these specific procedures," he said. "That is something we are actively working on right now. The easier and simpler it is to use these techniques and this technology, the more likely it is that people are going to use it, and the threshold to use it is going to be lower."

He concluded: "If all of a sudden we have ... a surgical instrument with electrodes on the end that can be very easily put on the heart, and doesn't require a lot of setup and adaptation, then why wouldn't you use it in every child?"

C. Walton Lillehei Resident Forum Winner

Congratulations to Gregory Kennedy (Perelman School of Medicine at the University of Pennsylvania) for their work, L1. Single-Cell Optical Detection of Lung Cancer in Real Time by Targeted Near-Infrared Confocal Laser Endomicroscopy Imaging

Atrioventricular Valves Room 210 *Tuesday 8:00 AM*

Improving outcomes in infant mitral valve replacement

Clinical insights on mitral valve replacement in infants will be provided this morning by David Overman, Chief of the Division of Cardiovascular Surgery at the Children's Minnesota, Minneapolis, MN, USA. Dr. Overman will review data on clinical experience with different surgical strategies, and advise on operative techniques to facilitate successful mitral valve replacement.

In discussion with *AATS Daily News*, Dr. Overman set the scene by highlighting the difficulties surrounding this surgery in infants. "Infant mitral valve replacement is a challenging clinical problem with outcomes that are suboptimal," he began. "Space constraints involving hypoplasia of the mitral annulus, small left atrial chamber size, and the proximity of pulmonary venous orifices all pose challenges for replacement."

Given these challenges, Dr. Overman explained that preservation of native valve anatomy (via valve repair) is always preferred over replacement when possible. "In neonates and infants, however, anatomic substrates can present challenges to achieving an effective repair," he said. "This means replacement is necessary in some cases and this presentation addresses the surgical challenges encountered in that scenario."

The most common approach for replacement is the implantation of a mechanical mitral valve prosthesis, but the lack of available implants of less than 15 mm diameter is a well-recognized constraint when patients have a small annulus. Dr. Overman ran through various operative techniques to help address this problem, the first of which was the implantation of the valve in a supra-annular position.

Supra-annular implantation allows the use of a larger valve, but concerns have been raised over the risks of complications resulting from altered hemodynamics and higher left atrial pressures. Studies have yielded varying results as regards outcomes, with one 2021 retrospective study finding that supra-annular implantation in young children was associated with an increased risk of reoperation as compared to annular implantation (sub-hazard ratio 3.1, 95% CI 1.003–9.4, p=0.049) but that there was no effect on the risk of postoperative heart block.[1] However, the authors acknowledged that an earlier study found supra-annular implantation to be associated with worse survival than annular implantation, despite a lower risk of operative complete heart block.[2]

In his talk, Dr. Overman will provide his insights on supra-annular implantation, as well as other techniques to facilitate mechanical mitral valve replacement in infants. These include the implantation of an aortic mechanical prosthesis in an inverted position, and the use of the 'chimney technique' in which a mechanical prosthesis is mounted on a Dacron graft.

Looking more broadly at outcomes of mechanical mitral valve replacement, Dr. Overman drew attention to a multi-institutional study evaluating predictors of prosthesis survival, growth, and functional status after valve replacement in children under five years old (n=102). On multivariate analysis, shorter prosthesis survival was predicted by a younger age at the time of first mitral valve replacement (odds ratio 7.7, 95% CI 2.6–22.7) and a smaller prosthesis size (odds ratio 6.8, 95% CI 2.6–18.2). Other factors associated with shorter prosthesis survival on univariate analysis included a lower weight, a higher ratio of prosthesis size to body weight, the presence of Shone's syndrome, and the use of an implant other than the St. Jude Medical (USA) prosthesis.[3]

Dr. Overman will evaluate data on the 15 mm St. Jude prosthesis in particular in his talk. Giving a brief overview of the literature in this area, he noted a recent multicenter cohort study evaluating early and long-term outcomes with this valve. Amongst 17 infants, there was one early cardiac death and one late non-cardiac death. The median freedom from prosthesis replacement for outgrowth was found to be 3.5 years, and thromboembolic complications were rarely observed.[4]

> "The stented bovine jugular venous valved conduit is a very important addition to the surgical armamentarium for infant mitral valve disease."
>
> **David Overman**

After reviewing the data on clinical experience with mechanical prostheses, Dr. Overman moved on to consider the use of the stent-mounted bovine jugular vein valve (Melody valve, Medtronic, USA). While there is less long-term data available on the use of this valve, Dr. Overman believes that it provides a useful alternative to mechanical prostheses, especially given the size limitations of available mechanical valves. One particular advantage of the Melody valve, Dr. Overman explained, is the potential for enlargement to adjust for patient growth.

"The stented bovine jugular venous valved conduit is a very important addition to the surgical armamentarium for infant mitral valve disease," he stated. "The ability to re-dilate the valve as the patient grows is a very attractive, though still largely untested, attribute of this valve."

Reviewing the available evidence on the Melody valve, Dr. Overman highlighted a multicenter retrospective cohort study evaluating outcomes amongst infants and children who underwent either mitral (n=59) or tricuspid (n=9) replacement with this valve. As regards early outcomes, the valve was competent in the immediate postoperative period in all patients, with low gradients observed. Twelve months after surgery, cumulative incidence analysis indicated that 55% of patients were expected to be free from death, structural valve deterioration, valve replacement, or heart transplantation. The authors concluded that the Melody valve is a feasible surgical option, but noted the need to refine device design and implantation techniques to improve durability and reduce the rate of complications.[5]

In his talk, Dr. Overman will delve into this topic, providing advice on implantation techniques for the Melody valve. In particular, he will emphasize the avoidance of left ventricular outflow tract obstruction as well as left atrial augmentation.

Looking towards the future, Dr. Overman recognizes that we need more data on the Melody valve in order to facilitate clinical decision-making. "We need long-term outcome data on the device, as well as larger cohort studies of infant mechanical mitral valve replacement, in order to fully understand the different treatment strategies and their respective roles," he observed. "Only then can patient factors such as anatomy and physiologic condition be optimally matched to surgical strategy."

> "We need long-term outcome data on the Melody valve, as well as larger cohort studies of infant mitral valve replacement."
>
> **David Overman**

Another area in which Dr. Overman identified a need for further research is the timing of surgery. "We must consider the potential impact of the timing of mitral valve replacement on outcomes," he stated. "The question is: when is the right time to abandon a failed repair or a dysfunctional native anatomy and replace the infant mitral valve?"

More research on both these issues is key to improving outcomes, Dr. Overman believes. "To improve the outlook for infants requiring mitral valve replacement, emphasis should be placed on understanding the impact of timing of surgery, as well as contrasting long-term outcomes after replacement with the Melody valve versus mechanical prostheses," he concluded.

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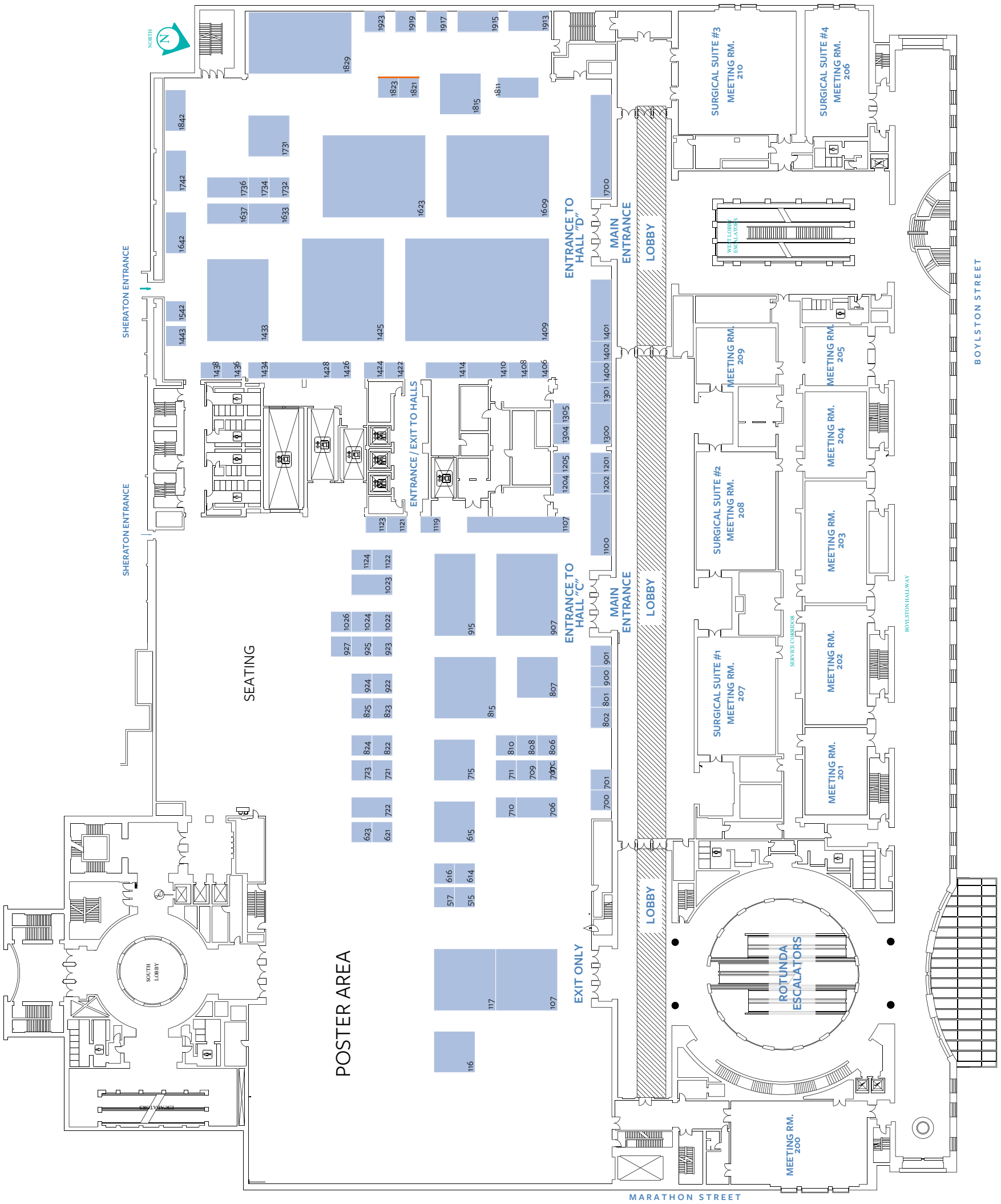
AATS 2022 Floor plan



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Acumed, LLC	**706**
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