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Applying Evidence in Interventional Oncology

Interventional oncology is a rapidly growing field within interventional radiology that aspires to become one of the pillars of oncologic care, alongside surgical, medical, and radiation oncology. Technologic innovation and successful translation from bench to bedside brought about the birth and fast growth of interventional radiology.

The specialty continues to flourish with a new residency to train clinicians well equipped to manage all aspects of patient care. Our field is undoubtedly one of the most innovative, fast-paced specialties in medicine. In oncology specifically, exciting new horizons, such as immunotherapies, artificial intelligence, and image-guidance technologies, are expanding the breadth of therapeutic options. Despite the well-justified optimism, we continue to face challenges.

In times of an unparalleled, historic transformation of medical care and fiscal rationalization pressures, patient satisfaction and evidence-based practice will continue to be our most valid arguments in our struggle for recognition. We must continuously renew and broaden our knowledge of disease processes and speak the language of our sister disciplines, know national guidelines, and be familiar with the cutting-edge care in other fields. Therefore, understanding the respective literature and the therapeutic options they offer compared with our procedures are essential.

With this in mind, we devote this special issue of Endovascular Today to the topic of Oncology. We seek to present the readership with a rich variety of different perspectives from all interventional oncology pillars and opinions on available trial data dealing with the most commonly encountered conditions in our practice. We will further outline and highlight the novel horizons that will define the future of our profession in the next decade. It is with deep gratitude to our contributing expert faculty that we wish the readers to be enlightened and inspired by the content of this issue.

Nadine Abi-Jaoudeh, MD
Julius Chapiro, MD
Guest Chief Medical Editors
EXPANDING PATIENT CARE OPTIONS

Now FDA approved: the first off-the-shelf short neck EVAR solution

Endurant™ II/IIIs
AAA Stent Graft System
and
Heli-FX™
EndoAnchor™ System

Establish the strength of a sutured anastomosis† and avoid the need for renal stenting

Pre-case CT
No endoleak at 1-year post op

† Based on cadaveric study per Melas et al. JVS 2012;55(6):1726-33

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The Endurant™ II/Endurant™ IIs bifurcated stent grafts are indicated for the endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms. They may be utilized in conjunction with the Heil-FX EndoAnchor System when augmented radial fixation and/or sealing is required in particular. In the treatment of abdominal aortic aneurysms, the Endurant II/Endurant IIs Stent Graft System is indicated for use in patients with the following characteristics:

- Adequate iliac or femoral access that is compatible with vascular access techniques, devices, or access.
- Proximal neck length of:
  - ≥ 10 mm or
  - ≥ 4 mm and < 10 mm when used in conjunction with the Heil-FX EndoAnchor System (bifurcated stent graft only)
- Note: Neck length is defined as the length over which the aortic diameter remains within 10% of the infrarenal diameter.
- Infrarenal neck angulation of ≤ 60°
- Aortic neck diameters with a range of 19 to 32 mm
- Distal fixation length(s) of ≥ 15 mm
- Iliac diameters with a range of 8 to 25 mm
- Morphology suitable for aneurysm repair

Contraindications: The Endurant II/Endurant IIs Stent Graft System is contraindicated in:

- Patients who have a condition that threatens to infect the graft.
- Patients with known sensitivities or allergies to the device materials.

Warnings and Precautions:

- The Endurant II/Endurant IIs Stent Graft System has not been established. All patients should be advised that endovascular treatment requires lifelong, regular follow-up to assess the health and the performance of the implanted endovascular stent graft. Patients with specific clinical findings (e.g., endoleaks, enlarging aneurysms, changes in the structure or position of the endovascular graft, or less than the recommended number of EndoAnchors when used in short (≤ 4 mm) and/or < 10 mm) proximal necks) should receive enhanced follow-up. Specific follow-up guidelines are described in the Instructions for Use.

- The Endurant II/Endurant IIs Stent Graft System is contraindicated for use in patients with the following circumstances:
  - In patients with known allergies to the EndoAnchor implant material (MP35N-L T)
  - In conjunction with the Endologix Powerlink™* endograft

Adverse Events: Potential adverse events include (arranged in alphabetical order):

- Amputation: anesthetic complications and subsequent attendant problems (e.g., aspiration), aneurysm enlargement, aneurysm rupture and death, aortic damage, including perforation, dissection, bleeding, rupture and death; arterial or venous thrombosis and/or pseudoaneurysm; arteriogenous fistula; bleeding, hematoma or coagulopathy; bowel complications (e.g., fistula, ulcer, enteral ischemia, infarction); cerebral complications and subsequent attendant problems (e.g., arthromia, myocardial infarction, congestive heart failure, arrhythmia, hypotension, claudication, transient ischemia); death; endoankle; EndoAnchor (for infrarenal EVAR procedures using the Heli-FX EndoAnchor system): partial deployment, inaccurate deployment, fracture, dislodgement, embolization, and persistent endoankles may be required to undergo secondary interventions or surgical procedures.

- The Endurant II/Endurant IIs Stent Graft System is contraindicated in patients unable to undergo or who will not be compliant with the necessary preoperative and postoperative imaging and implantation studies as described in the Instructions for Use.

- Renal complications may occur: (1) From an excess use of contrast agents. (2) As a result of embolus or a misplaced stent graft. The radioopaque marker along the edge of the stent graft should be aligned immediately below the lower-most renal artery origin.

- Studies indicate that the danger of microembolization increases with increased duration of the procedure.

- The safety and effectiveness of the Endurant II/Endurant IIs Stent Graft System has not been evaluated in some patient populations. Please refer to the product instructions for Use for details.

MRI Safety and Compatibility:

- Non-clinical testing has demonstrated that the Endurant II/Endurant IIs Stent Graft is MR Conditional. It can be scanned safely in both 1.5T & 3.0T MR systems under certain conditions as described in the product Instructions for Use. For additional information regarding MRI please refer to the product Instructions for Use. The Aptus™ Heli-FX EndoAnchor System has not been evaluated in some patient populations. Please reference product Instructions for Use for MR safety status of the endograft system with which the EndoAnchor implants are being used.

Potential Adverse Events: Possible adverse events associated with the Heil-FX EndoAnchor include, but are not limited to:

- Aneurysm rupture
- Death
- EndoAnchor embolization
- EndoAnchors (Type III)
- Enteric fistula
- Failure to correct prevent Type I endoleak
- Infection
- Renal complications (renal artery occlusion/dissection or contrast-induced AKI)
- Stroke
- Vascular access complications, including infection, pain, hematoma, pseudoaneurysm, arteriogenous fistula
- Vessel damage, including dissection, perforation, and spasm

Please refer to product instructions for Use for more information regarding indications, warnings, precautions, contraindications and adverse events.

CAUTION: Federal (USA) law restricts these devices to sale by or on the order of a licensed healthcare practitioner. See package inserts for full product information.

CAUTION: EndoAnchor implant locations should be based upon a detailed examination of the preoperative CT imaging in cases involving regular or eccentric plaque in the intended sealing zone(s). EndoAnchor or implants should be implanted only into areas of aortic tissue free of calcified plaque or thrombus, or where such pathology is diffuse and less than 2 mm in thickness. Attempting to place EndoAnchor implants into more severe plaque or thrombus may be associated with implantation difficulty and suboptimal endograft fixation and/or sealing.

FTSOP113526-33 Rev. 1C
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- Reducing complications\(^1-3\)
- Improving procedural efficiencies\(^4\)
- Increasing patient satisfaction\(^5,6\)

References:

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INDUSTRY NEWS

Boston Scientific’s Eluvia Peripheral Drug-Eluting Stent Gains FDA Approval

September 24, 2018—Boston Scientific has announced US FDA approval of its Eluvia drug-eluting vascular stent system for use in peripheral artery disease. Earlier this week, results from the IMPERIAL trial were simultaneously published in The Lancet and presented at the Transcatheter Cardiovascular Therapeutics (TCT) conference in San Diego, California, and the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) congress in Lisbon, Portugal.

The IMPERIAL trial randomized treatment using Eluvia in a 2:1 fashion against Cook Medical’s Zilver PTX device, previously the only approved peripheral drug-eluting stent (DES) in the United States. As announced at TCT and CIRSE, Eluvia successfully met its noninferiority endpoint and showed superior results in the head-to-head trial. As summarized in the company’s announcement, patients treated with Eluvia saw a significantly greater 12-month primary patency rate of 88.5% compared to 79.5% for those in the Zilver PTX arm ($P = .0119$).

“In the IMPERIAL trial, the Eluvia stent demonstrated landmark vessel patency and freedom from target lesion revascularization rates, preventing more than 95% of patients from needing a reintervention after 1 year,” commented William Gray, MD, System Chief, Division of Cardiovascular Diseases and President, Lankenau Heart Institute at Main Line Health in Wynnewood, Pennsylvania, in Boston Scientific’s announcement. Dr. Gray is the Coprincipal Investigator of the IMPERIAL trial and presented the 1-year data at TCT. “The Eluvia stent is a breakthrough therapy that marks a significant step forward in the treatment of peripheral artery disease, and now with its approval and commercial availability, it has the potential to make an immediate impact on the quality and value of care that physicians can provide to their patients.”

FDA Approves Cook Medical’s 5-mm Zilver PTX Drug-Eluting Stent Diameter

September 24, 2018—Cook Medical announced FDA approval of a 5-mm diameter version of the Zilver PTX paclitaxel-eluting peripheral stent. Zilver PTX is now available with an indication to treat vessel diameters ranging from 4 to 7 mm.

The 5-mm diameter device is available in lengths up to 140-mm; in August 2018, Cook introduced its 6- and 7-mm diameters in 140-mm lengths. The company noted that the 5-mm diameter is the first peripheral DES approved in this size. During the 2018 CIRSE meeting, Prof. Kimihiko Kichikawa, MD, presented 5-year data from the company’s Japan Postmarket Surveillance Study. In this all-comers evaluation of Zilver PTX in Japan, the results included a freedom from target lesion revascularization rate of 74.2%.

Thirty-Day PLIANT Results Reported for Jotec’s E-liac System

October 2, 2018—Jotec GmbH, a fully owned subsidiary of CryoLife Inc., announced 30-day results of the PLIANT study of the E-liac stent graft system in patients with common iliac aneurysms. PLIANT was an observational, prospective, non-randomized, multicenter, international study conducted in 12 hospitals throughout Europe. The study enrolled 45 patients who were due to undergo implantation with the E-liac device.

According to the company, concomitant iliac artery aneurysms are a major anatomic challenge of endovascular aortic repair (EVAR) in patients with abdominal aortic aneurysms. They exacerbate the complexity of EVAR and increase the incidence of type Ib endoleak, iliac limb occlusion, and aneurysm rupture. Jotec’s E-liac stent graft system was introduced to address these issues and is indicated for patients with aortoiliac or isolated iliac aneurysms.
Treat More
With One DCB

The LUTONIX® 035 Drug Coated Balloon is now available in longer lengths up to 220 mm in diameters 4-7 mm.

LUTONIX® 035
Drug Coated Balloon PTA Catheter

Please consult product labels and instructions for use for indications, contraindications, hazards, warnings and precautions.

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The purpose of the study was to examine the clinical and technical success of the E-liac side branched stent graft system when implanted in accordance with the indications for use. Data were collected at pre-operative planning, intervention, before discharge, 30 ± 15 days, 12 ± 2 months, and 36 ± 2 months. All CT scans and final angiograms were analyzed by a core lab.

The primary endpoint was aneurysm exclusion (no type I, III, IV endoleak) with primary patency of the internal iliac artery (IIA) and external iliac artery (EIA) on the E-liac implantation side, which is equivalent to the definition of clinical and technical success. Technical success was assessed at 24 hours after the index procedure, whereas clinical success was determined at follow-up.

The investigators reported that the periprocedural primary patency rate of the IIA and EIA on the E-liac implantation side was 100%. Four patients had clinically relevant type Ia endoleak, three located in the infrarenal aorta and one in the common iliac artery. Two type Ia endoleaks were related to mismatch diameters of the graft and the respective landing zones.

Thirty-day clinical success was achieved in 43/45 (96%) patients and three successful endovascular reinterventions were performed within 30-day follow-up. Primary patency at 30 days was 100% for the IIA and 98% for the EIA with 100% primary assisted patency in the latter.

The investigators concluded that the high clinical success rate, low number of reinterventions (2%), and excellent patency rate demonstrate the safety and feasibility of the E-liac stent graft system. Long-term results of this study will be published when available, advised Jotec.

**CLOUT Registry Begins Enrollment for Inari’s ClotTriever Thrombectomy System**

September 27, 2018—Inari Medical, Inc. announced the enrollment of the first patient in the ClotTriever Outcomes Registry CLOUT using the company’s ClotTriever thrombectomy system.

According to the company, CLOUT is a 500-patient, prospective, multicenter, single-arm registry that will evaluate real-world outcomes after using ClotTriever to treat patients with thrombosis in the deep veins of the lower extremities. William Marston, MD, and Robert Beasley, MD, are CoPrincipal Investigators of the registry.

In the Inari announcement, Dr. Marston commented, “ClotTriever is an important new tool for venous thrombus. The acute outcomes measures will allow us to evaluate the safety profile of ClotTriever as a single session nonthrombolytic option. The 2-year follow-up will allow us to determine if significant clot removal improves symptoms and outcomes over the longer term.”

The ClotTriever system is designed to remove large clot volume from large veins via access sites as small as 6 mm without requiring the use of thrombolytic drugs. The ClotTriever thrombectomy system is 510(k) cleared by the FDA for the nonsurgical removal of thrombus from the peripheral vasculature, advised Inari Medical.

**BTG Launches the ICEfx Cryoablation System**

September 20, 2018—BTG plc announced the global launch of the ICEfx cryoablation system, which is an evolution of the company’s Visual ICE system. The company introduced the ICEfx cryoablation system at CIRSE 2018 held September 22–25 in Lisbon, Portugal.

According to the company, the compact console is designed for interventional radiologists to provide safe and efficient cryoablation procedures, facilitating precise and effective treatment without the need for surgery or repeat radiation treatments.

AJ Gunn, MD, commented in BTG’s announcement, “The ICEfx cryoablation system is a new, more compact design that simplifies the procedure through a set of user-friendly on-screen prompts. It is easy for my technicians to set up, operate, and shut down. Importantly, this updated version is designed to work with the current line of BTG cryoablation probes, meaning that physicians can still create the reliable ablation zones they have come to expect.” Dr. Gunn is an interventional radiologist at University of Alabama at Birmingham in Birmingham, Alabama.
At Terumo Aortic, we understand that no two aortas are alike. We are 100% focused on the aorta, from the arch to the iliacs. With a comprehensive surgical, endovascular and hybrid portfolio* of individualised and off-the-shelf solutions, we help you address your patients’ unique challenges — so no patient is left behind.

Visit us at the VEITH Symposium, booth 303, November 13-17 in NYC, to learn how we are delivering individualised solutions for every segment of every aorta.

* Hybrid portfolio does not currently include custom configurations
FDA Clears Contego’s Paladin Carotid PTA Balloon System With Integrated Embolic Protection

September 18, 2018—Contego Medical, LLC announced that the FDA has granted 510(k) clearance for its Paladin carotid percutaneous transluminal angioplasty (PTA) balloon system, which is a filter-based integrated embolic protection (IEP) device.

According to Contego Medical, the Paladin system is indicated for PTA in the carotid arteries for capture and removal of embolic material. The device is also indicated to postdilate self-expanding stents in the carotid arteries with capture and removal of embolic material. The diameter of the arterial site for filter deployment should be no more than 7 mm. The Paladin system with IEP should always be used in conjunction with an available embolic protection device.

The company noted that the Paladin system couples an angioplasty balloon and integrated 40-µm filter. The microembolic protection of the Paladin filter is designed for maximum capture efficiency and provides an added measure of protection and procedural flexibility in carotid stenting procedures. The system allows the physician to adjust the size of the embolic protection filter in vivo to suit each individual patient’s anatomy.

The Paladin system has received CE Mark approval. The company announced the European launch of the device in January 2016. Contego announced the completion of enrollment in a European postmarket registry. The system has been studied in 106 registry patients undergoing carotid artery stenting with a variety of stents, including open-cell, closed-cell, and mesh-covered designs, with no procedural strokes and a 30-day risk of death, stroke, and myocardial infarction of 0.9%, stated Contego Medical.

Guerbet’s Lipiodol Ultra Fluid Approved for New Indication in cTACE

September 18, 2018—Guerbet LLC announced that it has been granted approval for a new indication for the company’s Lipiodol Ultra Fluid in Belgium, Ireland, Portugal, Hong Kong, and the Philippines, for selective hepatic intra-arterial injection for visualization, localization, and vectorization during conventional transarterial chemoembolization (cTACE) of tumors in adults with known, intermediate-stage hepatocellular carcinoma (HCC).

In the cTACE procedure, Lipiodol Ultra Fluid mixed with an anticancer drug is injected transarterially in the liver as a locoregional targeted chemotherapy for unresectable HCC. Lipiodol Ultra Fluid acts as a contrast agent, a drug-eluting vehicle, and a dual arterioportal transient embolic.

According to the company, cTACE and HCC imaging indications are now approved in Austria, Belgium, Czech Republic, France, Germany, Hungary, Iran, Ireland, the Netherlands, Portugal, Turkey, Cambodia, Hong Kong, Japan, Mongolia, New Zealand, Philippines, South Korea, Taiwan, Thailand, Vietnam, Canada, the United States, Argentina, Brazil, Mexico, and Peru. Other registrations are ongoing in Asia and in Europe. The approved indications for Lipiodol Ultra Fluid may vary according to countries; users should refer to the local summary of product characteristics for further information.

Vesalio NeVa Neurothrombectomy Platform Launched in Europe

September 18, 2018—Vesalio announced that it initiated the full commercial European launch of its NeVa neurothrombectomy platform at the 10th annual congress of the European Society of Minimally Invasive Neurological Therapy held in September in Nice, France.

With the conclusion of the controlled launch in the European Union, Vesalio will now expand the number of NeVa centers in Europe while establishing its distributor network in the Asia-Pacific, Middle East & Africa, and Americas regions. According to the company, Vesalio’s flow model was utilized to simulate the navigation and deployment of NeVa’s Drop Zone and Smart Marker technology. The NeVa platform was designed to improve first-pass success with all clot types, including hard and organized clots.
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AngioDynamics to Acquire RadiaDyne

September 13, 2018—AngioDynamics, Inc. announced an agreement to acquire RadiaDyne, a privately held medical diagnostic and device company that designs and develops patient dose monitoring technology to improve cancer treatment outcomes. This transaction expands AngioDynamics’ growing oncology business by adding RadiaDyne’s early stage OarTrac real-time radiation dose monitoring platform and other oncology solutions, including the IsoLoc/ImmobiLoc and Alatus balloon stabilizing technologies. According to AngioDynamics, RadiaDyne recently launched the OarTrac system, which provides precise, real-time measurement via an intracavitary device. The system delivers critical dose feedback to medical and radiation oncologists, providing customized adaptive radiotherapy, reduced side effects, and improved clinical outcomes across all forms of radiation and photon beam therapy.

Other RadiaDyne products include the IsoLoc/ImmobiLoc endorectal technology, which removes transient rectal gas using a patented gas-release tip and reliably reduces prostate motion and radiation toxicity. RadiaDyne’s Alatus vaginal balloon packing system provides physicians with an improved method for optimal dosimetry protection and decreased complications.

European EXCeL Postmarket Study Begins for Gore’s Excluder Conformable AAA Device

September 17, 2018—Gore & Associates announced the first European patient implantation of its Excluder conformable abdominal aortic aneurysm (AAA) endoprosthesis with Active Control system. Gore’s next-generation endovascular aneurysm repair (EVAR) device is indicated to treat the broadest range of AAAs in patients with challenging anatomies. The Excluder conformable AAA endoprosthesis with Active Control system received European CE Mark approval for patients with proximal aortic neck angles of up to 90° with a minimum 15-mm aortic neck length or in patients with proximal aortic neck angles of up to 60° with a 10-mm minimum aortic neck length. The patient was the first enrollment in the EXCeL investigator-initiated postmarket European registry of the device. The EXCeL registry will enroll 150 patients at up to 11 European sites. Data from the registry will assess safety and treatment success of the Excluder conformable AAA device for the treatment of infrarenal AAAs in a broad range of anatomic presentations. In January, the company announced the beginning of enrollment in a United States pivotal investigational study of the Excluder conformable AAA endoprosthesis with Active Control system.

Cook Medical Resolves 2014 FDA Warning Letter

September 11, 2018—Cook Medical announced it has received a close-out notification from the FDA, resolving the warning letter issued to the company in September 2014. The warning letter pertained to device manufacturing processes at Cook’s Bloomington, Indiana, facility, but it ultimately led to widespread changes throughout the company. “Receiving critical feedback from the FDA in 2014 was tough, but beneficial,” commented Pete Yonkman, President of Cook Group and Cook Medical, in the announcement. Providing more details on the resolution and its effects at Cook to Endovascular Today, Mr. Yonkman explained how the FDA’s warning letter spurred the company to examine all of its processes from top to bottom. “It was an opportunity for us to reflect and make sure we were on the right path to where we wanted to be as a company, to make sure we served our customers and their patients,” said Mr. Yonkman. Some internal systems had become dated, he continued, and with new facilities and departments being added over the years, the company needed a clearer look at how all of its divisions fit together.

While working to address the issues cited by the FDA, Cook’s management team began soliciting feedback from its own employees as to which company practices needed to change and which needed to be preserved—
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engaging approximately 10,000 employees in the exercise. Coupling this feedback with that of its customers, Cook then initiated a 5-year "transformation" plan, a core component of which was clearing the FDA warning letter. Another key element of the plan was a major reorganization that saw 10 business units converted into two primary divisions—MedSurg and Vascular—earlier this year.

Mark Breedlove, Vice President of the Vascular division, noted that a key restriction levied under the FDA warning letter is that no premarket approval applications for class III devices could be approved until the company satisfactorily resolved the concerns cited by the agency. With the resolution in place, Cook’s Vascular group aims to move forward with premarket approval applications for two devices.

In the wake of the warning letter, Cook reassigned some of its engineering teams to help with the transformation, and the R&D teams have now been realigned and a new Vice President of R&D brought in. The company is focusing on new ways to partner with other companies, including acquiring new technologies, in addition to its internal product development and innovation efforts.

**CONFERENCE COVERAGE**

**Data Presented for In.Pact Admiral DCB as a Primary Treatment of Complex, Real-World Patient Populations**

September 22, 2018—Medtronic announced that data reinforcing the safety, durability, and consistency of the company's In.Pact Admiral drug-coated balloon (DCB) in real-world patients with peripheral artery disease (PAD) were presented at CIRSE 2018 and TCT 2018.

At CIRSE, Professor Gunnar Tepe, MD, presented 3-year, real-world, fully adjudicated results from the full clinical cohort of the IN.PACT Global Study, showing durability of treatment effect in a real-world population with challenging and complex lesions. The study included adjudication of events by an independent clinical events committee.

As summarized by Medtronic, the freedom from clinically driven target lesion revascularization (CD-TLR) rate calculated using Kaplan-Meier survival estimates was 76.9% in a real-world patient cohort with a mean lesion length of 12.09 ± 9.54 cm, an 18% rate of in-stent restenosis, 35.5% occluded lesions, and 39.9% of patients had diabetes. Additionally, the proportion of patients undergoing repeat procedures were low through 3 years: 0.8% major target limb amputations and 23.5% CD-TLR (n = 1,406).

In comments to *Endovascular Today* at CIRSE, Prof. Tepe said that these data are valuable because they reflect the clinical reality, contrasting the nature of the study with the narrow inclusion criteria necessary for many randomized controlled trials. “Randomized trials are very important for the comparative data they yield,” said Prof. Tepe. “But in some trials, only one out of every 10 patients screened might be eligible, so we do not always learn the capabilities of the technologies in daily practice. Although not head-to-head, the Global Study data show that this DCB works, and that three-quarters of patients did not require TLR within 3-year follow-up.”

At TCT, 1-year overall imaging and propensity-matched imaging data from the Total IN.PACT Pooled Analysis were presented by Mehdi Shishehbor, DO. The analysis is seeking to enhance the understanding of PAD patient treatment algorithms by characterizing the clinical performance of In.Pact Admiral in a large and diverse study population. The delta in patency rates demonstrates the DCB’s persistent superiority to standard percutaneous transluminal angioplasty (PTA), advised Medtronic.

According to the company, Total IN.PACT combined independently adjudicated data from a total of 1,837 patients treated with the In.Pact Admiral DCB from all In.Pact Admiral randomized clinical trials and real-world studies from 147 sites across 28 countries.

The analyses presented at TCT specifically looked at two different groups: a core laboratory–adjudicated imaging cohort and a propensity-matched imaging cohort. The data showed that the In.Pact Admiral DCB demonstrated consistently superior patency and freedom from CD-TLR rates compared to standard PTA alone.

The imaging cohort, which evaluated 926 DCB and 143 PTA subjects, demonstrated a patency rate of 88.8% for In.Pact Admiral compared to 53.9% for PTA (P < .001) and a freedom from CD-TLR rate of 94.3% compared to 80.2% for PTA (P < .001). Additional safety and effectiveness outcomes from the DCB arm also included low rates of thrombosis (2.4%) and CD-TLR (5.8%) and no occurrences of major target limb amputation at 1 year.
The propensity analysis (a subset of the imaging cohort) matched one PTA patient with up to four In.Pact Admiral DCB patients based on baseline variables (136 PTA patients and 466 DCB patients).

The propensity-matched analysis showed a patency rate of 90.5% for the In.Pact Admiral DCB as compared to 53.8% for PTA \( (P < .001) \) and a freedom from CD-TLR rate of 96.9% compared to 80.7% for PTA \( (P < .001) \). Additional safety and effectiveness outcomes from the DCB arm also included low rates of thrombosis (1.6%) and CD-TLR (3.3%) and no occurrences of major target limb amputation at 1 year.

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**Boston Scientific’s Eluvia DES Evaluated for Femoropopliteal Lesions in IMPERIAL Trial**

September 22, 2018—Boston Scientific announced 12-month data from the IMPERIAL trial evaluating the company’s Eluvia paclitaxel-eluting vascular stent system versus the Zilver PTX paclitaxel-eluting peripheral stent (Cook Medical) in patients with symptomatic peripheral artery disease (PAD). The results were presented during a late-breaking clinical trial session at TCT 2018 and CIRSE 2018. The clinical findings were published online by William A. Gray, MD, et al in *The Lancet*.

According to Boston Scientific, IMPERIAL is the first head-to-head trial comparing two different drug-eluting stent systems for the treatment of PAD. The global, multicenter, randomized controlled trial includes 465 patients with superficial femoral artery and proximal popliteal artery lesions up to 140 mm in length. The Eluvia stent exhibited superior rates of primary patency and higher rates of freedom from target lesion revascularization (TLR) at 1 year when compared to those treated with Zilver PTX.

Key 1-year findings from the IMPERIAL trial for Eluvia versus Zilver include:

- Primary patency rate (88.5% vs 79.5%; \( P = .0119 \))
- TLR rate (4.5% vs 9%)
- Freedom from major adverse events (95% vs 91%)

The Eluvia stent system received European CE Mark approval in February 2016 and FDA approval in September 2018.

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**SFA and ISR Data From BIOLUX P-III Registry Presented for Biotronik’s Passeo-18 DCB**

October 2, 2018—Biotronik announced that results from the BIOLUX P-III Registry evaluating the company’s Passeo-18 Lux drug-coated balloon (DCB) were presented at CIRSE 2018. BIOLUX P-III is a large real-world registry composed of 882 patients who were enrolled across 47 study sites. Data presented included the 24-month outcomes of the superficial femoral artery (SFA) subgroup and 12-month results for the in-stent restenosis (ISR) subgroup.

At CIRSE, Prof. Christoph Binkert, MD, presented the data from the SFA subgroup \( (n = 441) \). The findings demonstrated 91.7% freedom from clinically driven target lesion revascularization (CD-TLR) and 78% primary patency at 24 months. These outcomes are “particularly noteworthy given the complex patient cohort, with 42% of included lesions classified as moderately or heavily calcified,” stated the company. Prof. Binkert is from Kantonsspital Winterthur in Winterthur, Switzerland.

Prof. Marianne Brodmann, MD, presented the ISR subgroup of treatment of infrainguinal arteries \( (n = 103) \), including SFA, popliteal, and below-the-knee lesions. The 12-month data showed 90.1% freedom from CD-TLR and 77.3% primary patency, with 88.8% of patients without any major adverse events.

Prof. Brodmann commented, “You can’t treat ISR like a de novo lesion—naturally, the presence of a stent from a previous intervention complicates the procedure. In these cases, a DCB is an important treatment option to minimize the burden on the vessel. These results show that we can treat ISR effectively while leaving nothing behind.” Prof. Brodmann is from Medical University of Graz in Graz, Austria.
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Study Explores Impact of Severe Calcification on Outcomes Following Stellarex DCB

September 27, 2018—Fabrizio Fanelli, MD, EBIR, shared results from a study seeking to determine the impact of severe calcification and 12-month outcomes of femoropopliteal disease treatment using the Stellarex drug-coated balloon (DCB) (Philips) during the late-breaking trials session at CIRSE 2018. Key among the results were similar outcomes when using the device in severely calcified lesions versus those without severe calcium.

Dr. Fanelli is Director of the Vascular and Interventional Radiology Department at Careggi University Hospital in Florence, Italy, and a leading expert in the study of the effects of calcium in peripheral artery disease (PAD) and its treatment. At CIRSE, he detailed the nature of calcification and its demographic prevalence, as well as early findings regarding DCB efficacy in these lesions. Despite the research to date and rise in the use of DCBs, the impact of calcium on their performance is still not fully defined and understood, Dr. Fanelli noted. Additionally, multiple publications studying the effects of calcium in PAD (including his own 2014 paper) each define its severity in different ways, making comparisons and pooling challenging.

Dr. Fanelli presented a post hoc pooled analysis of 571 patients from two prospective studies involving the Stellarex DCB—ILLUMENATE Global and ILLUMENATE Pivotal. Both studies included independent core lab and clinical event adjudication with prospective definitions of severe calcification.

The pooled 12-month outcomes of the studies showed similar rates of freedom from the primary safety event, which was defined in this study as a composite of freedom from device- and procedure-related death through 30 days postprocedure and freedom from target limb major amputation and clinically driven TLR through 12 months postprocedure (93% for nonseverely calcified vs 93% for severely calcified, respectively), 12-month major adverse events (7.3% vs 7.8%), clinically driven target lesion revascularization (TLR) (7% vs 7%), and all TLR (8% vs 8.3%). Primary patency rates by Kaplan-Meier analysis were similar, although higher in nonseverely calcified patients (82.9% vs 80%).

Procedurally, longer predilatation pressures and durations were seen in the severely calcified group (9.5 atm/lesion; 3.9 min/lesion vs 8.8 atm/lesion; 3.4 min/lesion, respectively). The rate of bailout stenting was also similar, but lower in the severely calcified group (12.7%) than the nonseverely calcified group (13.5%).

Dr. Fanelli summarized the results of the analysis as demonstrating similar 12-month outcomes using the Stellarex device in severely and nonseverely calcified lesions. The study also confirms previous understanding regarding the patients in whom severe calcium is most likely to be present: those with diabetes, hypertension, hyperlipidemia, coronary artery disease, and renal insufficiency. Success in treating severe calcification requires “longer and stronger” inflation, which in this study enabled similar rates of bailout stenting between the two cohorts, concluded Dr. Fanelli.

Five-Year Data From Cook Medical’s Japan Postmarket Zilver PTX Registry Presented

September 22, 2018—Kimihiko Kichikawa, MD, presented 5-year follow-up data from a Japanese postmarket surveillance study of Cook Medical’s Zilver PTX paclitaxel-eluting stent at CIRSE 2018.

The all-comers registry enrolled 904 patients with 1,080 lesions, in which 1,877 Zilver PTX stents were placed. Five-year data were collected for 411 of the enrolled patients. Notable among the baseline patient characteristics were higher patient age, more diabetics, and more renal failure compared to the Zilver PTX randomized controlled trial, which had narrower inclusion criteria. Given the real-world nature of the study, the lesions were also longer (14.6 ± 9.6 cm) and more complex, with higher rates of total occlusions and fewer patent runoff vessels, as well as a higher incidence of critical limb ischemia.

Prof. Kichikawa showed a freedom from target lesion revascularization (TLR) rate of 74.2% in the registry, and clinical benefit (a composite endpoint including TLR, claudication, rest pain, change in Rutherford class by 2 or more, gangrene, ischemic ulcers, and amputation) was maintained in 68.2%. Clinical improvement was also maintained over time, with a 5-year average ankle-brachial index of 0.83 ± 0.18 (versus 0.63 ± 0.18 at baseline).
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*2% PE recurrence at one year

8mg tPA dose

23–26% reduction RV/LV ratio

2% PE recurrence at one year

2% mortality at one year

35% improved PE QOL score at one year
InspireMD’s CGuard EPS PARADIGM-Extend Trial Evaluate Clinical Trial

The study includes a number of subgroup analyses, of which the results in diabetic patients were presented at CIRSE. Of the 904 patients enrolled, 532 had diabetes. The freedom from TLR rate in this group was 72.2%, compared with 77% in nondiabetics.

The total stent fracture rate was 1.9%, with the majority having occurred in the first year (1.5%). Between years 1 and 3 and between years 3 and 5, the stent fracture rate was 0.8% in both intervals.

Summarizing the findings, Prof. Kichikawa concluded that the 5-year Japan postmarket surveillance study results are consistently good despite the all-comer study population’s high incidence of diabetes, renal failure, long lesions, in-stent restenosis, limited runoff, and critical limb ischemia. Prof. Kichikawa is with the Department of Radiology at Nara Medical University Hospital in Kashihara, Japan.

SoundBite Medical Solutions Completes Pivotal PROSPECTOR Clinical Trial

September 25, 2018—SoundBite Medical Solutions Inc. announced the completion of the pivotal PROSPECTOR trial using SoundBite’s shock wave energy system. In the study, 15 patients with peripheral artery disease with chronic total occlusions (CTOs) were treated at two sites in Montreal, Quebec and Ottawa, Ontario.

The company advised that there was a clinical success rate of 93% and no serious adverse events. The results were reported at TCT 2018. Eric Therasse, MD, who is the Principal Investigator of the PROSPECTOR trial, presented the study. Dr. Therasse is Professor at the Department of Radiology, Radio-Oncology, and Nuclear Medicine at the University of Montreal.

According to the company, the results of the 15 patients in the PROSPECTOR study were pooled with the 37 patients of the first-in-man study for a combined group of 52 cases presenting an average CTO length of 10 cm and a fairly even distribution of mild, moderate, and severe calcifications. SoundBite Medical noted that these pooled results will be presented to regulatory authorities in Canada and the United States.

Preliminary 3-Year Data From PARADIGM-Extend Trial Evaluate InspireMD’s CGuard EPS

September 27, 2018—InspireMD, Inc. announced that preliminary cumulative 3-year follow-up safety, efficacy, and stroke prevention durability data from the PARADIGM-Extend trial of the company’s CGuard MicroNet-covered embolic prevention system (EPS) were presented in a poster at TCT 2018.

PARADIGM-Extend is the continuation of PARADIGM, an investigator-led clinical study evaluating the use of the company’s CGuard EPS in patients with symptomatic or asymptomatic carotid artery stenosis with increased stroke risk.

According to the company, overall cumulative data showed no stroke or stroke-related deaths between 24 and 36 months and the absence of any device-related events.
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related issues in the first 93 of the 251 patients in the PARADIGM-Extend cohort. The company advised that 2-year follow-up data on 251 patients from PARADIGM-Extend were reported at EuroPCR 2018 held in May. Additional 3-year data from PARADIGM-Extend will be presented at the 45th annual VEITHsymposium to be held on November 13–17 in New York, New York.

REGULATORY AND REIMBURSEMENT

PAD Task Force and Lawmakers Call for Policies to Reduce Amputations

September 19, 2018—The Society for Cardiovascular Angiography and Interventions (SCAI) announced that members of the newly formed Peripheral Artery Disease (PAD) Task Force commended Congressman Erik Paulsen (MN-3) and Congressman Donald Payne (NJ-10) for sponsoring a Capitol Hill briefing on September 5 to raise awareness about the risks of PAD and the need for policies to reduce preventable amputations. In addition to SCAI, the PAD Task Force includes the Association of Black Cardiologists, CardioVascular Coalition, and Preventative Cardiovascular Nurse Association. The PAD Task Force, which was formed to collectively advance a comprehensive strategy that combines increased public awareness and robust screening with nonamputation treatment measures and multidisciplinary care, seeks the following:

• For the Administration to convene an intragovernmental workgroup to develop a standardized model for amputation reduction and raise awareness on the issue. The model could be designed like existing programs such as the Department of Veterans Affairs’ Preventing Amputations in Veterans Everywhere program.

• For lawmakers to urge the Centers for Medicare & Medicaid Services (CMS) to prevent cuts of 30% or more to revascularization procedures used to treat PAD included in the 2019 Physician Fee Schedule Proposed Rule. Stakeholders are concerned the cuts stem from CMS’ proposal to update equipment and supply pricing data in the Medicare Physician Fee Schedule database based on inaccurate and incomplete data.

SCAI advised that, earlier this year, 32 members of the US House of Representatives, led by Congressmen Paulsen and Payne, urged the US Department of Health and Human Services and the Veterans Health Administration to adopt a national strategy to reduce nontraumatic amputations through increased awareness of PAD, increased screenings for at-risk populations, and improved access to multidisciplinary care.

For full coverage of these stories along with the most recent news, visit the News section of our website at evtoday.com/news

CORRECTION

In Table 1 in the article “Transforming Open to Endo: Percutaneous Bypass as an Option for Long-Segment SFA Disease” by Dr. Joye, which appeared in our September 2018 issue (2018;17:85–86, 88–89), the manufacturer for Lutonix was incorrectly noted as Medtronic. This should have read BD Interventional.
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WITH ELIAS KASSAB, MD, AND PHIL HEMSTREET, MD

Outpatient locations, such as office-based labs (OBLs), have seen rapid growth in recent years and continue to facilitate a shift for doctors and patients alike away from traditional hospital settings. With the advent of more sophisticated technology coupled with a drive for increased physician control and autonomy, more OBLs are breaking ground. The shift has resulted in improved health outcomes, better patient experiences, and reduced costs per procedure.

Patients are seeking solutions that simplify health care. From turnkey procedures to effective time management during a visit, patients and physicians are enjoying efficiencies while benefiting from improved care delivery. Providers are relishing the fact that they spend more time in the office, see more patients, and connect more often with patients through the care process to ensure a continuum of care pre- and postprocedure. Physicians believe that by focusing exclusively on the clinical aspects of the procedure, fewer complications occur.

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PHYSICIAN INSIGHTS ON PHILIPS SYMPHONY SUITE

Like a conductor in a symphony, preparation, instruments, and cadence are critical for practice success. Philips provides the tools and resources so physicians can focus on improved, orchestrated patient care. We recently sat down with two thought leaders in the interventional cardiovascular space who have adopted the office interventional suite model and are using Philips SymphonySuite in their OBL. Their hands-on perspective gives insight into the outpatient model in practice.

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- Examine and treat patients in one location
Describe the community you serve.

Dr. Kassab: In the greater Dearborn area, we have a population of 650,000. Although we do serve a variety of patients, Dearborn has one of the largest Middle Eastern communities in the country.

Dr. Hemstreet: We are in Tuscaloosa, Alabama, about 55 miles south of Birmingham. Although the population is 100,000, we draw approximately 400,000 from surrounding areas.

What factors impacted your decision to open an OBL?

Dr. Kassab: After 30 years in the business, I have a clear understanding of what works in terms of patient care and time management. The OBL model frees physicians from layers of bureaucracy and opens the door to efficient and effective workflow. For both practice and patient, it is better to manage care under one roof and build a team of in-house experts including physicians, technicians, nurses, and mid-level extenders who are focused on a continuum of care for each patient.

Dr. Hemstreet: I agree with Dr. Kassab’s perspective. One of our primary challenges in interventional cardiology is an increasing number of patients to serve and a limited number of resources. By opening the OBL, we wanted to expedite care with advanced technology and service, keeping patients as priority number one. OBLs solve for that and increase patient care and efficiency. Through a partnership with Philips, we were able to develop a lab in a timely basis, providing patients with a better experience. Clearly, medical economics plays a role as well, and we are seeing favorable responses to the evolving role of OBLs.

What drives a successful OBL?

Dr. Hemstreet: Any interventional cardiologist will tell you, time is of the essence. Providing quality care and delivering it in a timely, efficient manner is key to our success. Philips has helped us ensure that paradigm. For both equipment and business services, we have one point of contact who assists in making complex decisions. Philips SymphonySuite is a one-stop shop for the OBL, freeing physicians to do what they do best—treat patients.

Dr. Kassab: In addition to Dr. Hemstreet’s feedback, I believe there are three factors that drive a successful OBL—quality, cost, and compliance. Within a hospital system, your identity can be lost. As a stand-alone OBL, we have more control. We purchase our own equipment and have chosen the best in SymphonySuite, and we surround our patients with knowledgeable physicians and staff who are respective of their time and care. That combination has delivered almost 100% patient satisfaction. When you surround yourself with the right people, the best equipment, and unprecedented service, you enhance patient care.

How do OBLs change the patient experience?

Dr. Kassab: The patient experience is simplified. Patients do not have to drive to multiple doctors and complete a variety of paperwork. OBLs offer a one-stop shop, one signature, and they are taken care of. The OBL model provides much less bureaucracy, easier access to the system, and better human interaction with the patient.

Dr. Hemstreet: Since our inception, we have had nothing but outstanding patient reviews. Philips was an equal partner in that. With quality equipment, we are better able to diagnose and treat in one setting. Through centralized care, grounded in long-term relationships with the same physician and staff, patients are in and out and on with their lives.
What challenges did you face when deciding to open an OBL?

Dr. Hemstreet: Philips can work with any scenario and help customize our technology based on our situation. For instance, we needed the lab to be associated with the clinic itself, so we were limited by the footprint of our office. Equipment is flexible and adaptable without compromising patient comfort, workflow, and excellence—we still see superior image quality.

Dr. Kassab: That’s a good point, Dr. Hemstreet. Another nuance for us was financing. Financing is a significant challenge and making smart investments upfront is key; you don’t want to invest too much, too soon. Philips SymphonySuite allows you to scale the lab based on your practice’s individual needs. Philips works with you to build a lab that works for your office. It’s not a cookie-cutter approach. We add technology as needed.

Why did you choose Philips SymphonySuite as your OBL provider?

Dr. Kassab: I was very impressed with the Philips team and their commitment to my success. Their scalable approach to setting up labs—small, medium, and large—demonstrates their flexibility to physician needs. But it’s not only the equipment, it’s the full package of services, including engineering, site identification, and financing, that would otherwise be unavailable to physician entrepreneurs. Physicians can regain independence while minimizing risk.

Dr. Hemstreet: We were also extremely impressed with the Philips team. We were faced with several challenges in deciding on an OBL. Beyond high-quality imaging, we needed a partner who could help us navigate the overwhelming process of opening an OBL and the financial aspect of an investment of this size. Philips was equally invested in the project and had solutions at every turn. The combination of exceptional technology, service offerings, and personalized care nurtured a trusting relationship that has grown into a smart investment.

How does Philips support your success?

Dr. Kassab: I agree with Dr. Hemstreet wholeheartedly. Philips SymphonySuite supported our ability to operate, partner, and adjust our practice model. My Philips representative is in contact with me on a regular basis, more than once a week, and sometimes several times a day, discussing practice challenges and solutions. That relationship, in sync with the Philips SymphonySuite approach, has grown substantially and supported our success.

How valuable is it to have a system that works together seamlessly?

Dr. Kassab: Having a reliable, affable company in your court is a game-changer. It has liberated us from the responsibilities of day-to-day management and the last-

**Diversified Portfolio Designed for the OBL**

Philips SymphonySuite offers a comprehensive range of products designed for the OBL and ambulatory surgery center ranging from patient monitoring, ultrasound, x-ray, and diagnostics to therapeutic devices. We are uniquely positioned to support all of your OBL cases. The portfolio includes:

**Capital Equipment**
- Mobile C-arms
- Fixed imaging systems
- Physiomonitoring systems (Hemo)
- Ultrasound
- Contrast injectors
- Ancillary equipment
- Patient monitors

**Devices**
- Intravascular ultrasound imaging
- Hybrid and laser atherectomy*
- Atherectomy guidewires
- Chronic total occlusion crossing catheters
- Drug-coated angioplasty balloon
- Scoring balloon
- Crossing catheters
- Aspiration catheters

*Hybrid atherectomy refers to the Phoenix family of products. The 2.4-mm deflecting catheter is the only device with directional cutting ability.
minute items that inevitably interrupt a physician’s day. Philips SymphonySuite works seamlessly, and support is available when needed.

**Dr. Hemstreet:** I’m sure Dr. Kassab agrees, we will only use products that deliver excellence. We want to be able to see everything the way it is represented. Philips’ training gave me and the staff an unparalleled level of confidence. Philips has been truly accommodating in making sure that we have the foresight, planning, flexibility, and structure we needed.

**For complex patients, do you refer to a hospital setting for the procedure?**

**Dr. Hemstreet:** We’re a full-service interventional cardiology practice. We practice both interventional cardiology from a coronary perspective as well as a peripheral perspective. Our peripheral procedures are performed here in the OBL. Although there will always be patients who require care in a hospital setting, sophisticated technology like the Philips SymphonySuite and a trained and experienced staff open the door to seeing more and more patients in the OBL.

**Dr. Kassab:** I get this question a lot. My answer leans on two items similar to Dr. Hemstreet’s perspective. It truly comes down to experience and quality. An experienced team, partnered with quality devices and technology, can perform any procedure, complex or simple, in an OBL setting.

**What does the future look like for your practice?**

**Dr. Kassab:** I like crystal balls and my crystal ball is predicting that we will open an ambulatory surgery center in the near future. We will partner with Philips to provide cath labs and equipment and all the ingredients necessary to showcase a superior outpatient vascular center. Because of our robust partnership with Philips, I’m no longer nervous about the future. I don’t need that crystal ball.

**Dr. Hemstreet:** Although I don’t own a crystal ball, I do know peripheral artery disease continues to grow and the number of patients who need our help increases. We’ll remain focused on exceptional care and improve awareness of treatment options. The OBL provides safe and efficient care in a very comfortable outpatient-based setting. In partnership with Philips, we’ll continue to explore innovations that improve the quality of life for our patients.

**WE BRING THE FINELY TUNED INSTRUMENTS, YOU CONDUCT THE SYMPHONY. LET’S HARMONIZE.**

We set you up for long-term success with customized OBL training programs, resources, and services to support every step of your OBL life cycle. As part of our industry-leading solutions, we have developed a comprehensive program called Philips SymphonySuite, which includes a robust set of tools to support your efforts in opening, growing, and maintaining an OBL. An experienced device team, tools for educating patients, physicians, and staff and a broad offering of physician-led training programs are just some of the ways Philips can support your practice’s evolving needs, allowing you to focus on priority number one: your patients.

**CONTACT US**

Philips is the only company able to uniquely offer a full range of services and a comprehensive portfolio of products to open your OBL. Learn more at Philips.com/OBL.

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**PROVIDING A COLLECTIVE SUITE OF OBL SERVICES**

Philips SymphonySuite offers an ensemble of instruments and services working in concert to assist you with building, opening, and generating momentum for your OBL.

**SPECIFIC SERVICES INCLUDE:**

- Construction
- Dimensional laboratory renderings tailored to your lab; beneficial for site planning
- Practice workflow education with Philips Deep Venous Summit
- Marketing tools
- Equipment service contracts
- Product training
- Capital financing through Philips Medical Capital*  

*Philips Medical Capital determines eligibility and not all customers will qualify. Certain credit requirements must be met.
VASCULAR LITERATURE HIGHLIGHTS

One-Year Findings Published From Long Lesion Imaging Cohort of Medtronic’s IN.PACT Global Study

October 4, 2018—The 12-month follow-up findings from the IN.PACT Global study’s long lesion imaging cohort were published online in Circulation: Cardiovascular Interventions by Dierk Scheinert, MD, et al. The IN.PACT Global study investigators concluded that the In.Pact Admiral drug-coated balloon (DCB; Medtronic) was safe and highly effective at 12 months after treatment in a rigorous independently adjudicated analysis of real-world patients with lesions ≥15 cm in the superficial femoral arteries (SFAs) and/or popliteal arteries (P1–P3).

The investigators explained that the IN.PACT Global study was an international, prospective, single-arm clinical trial to evaluate the safety and effectiveness of the In.Pact Admiral DCB in the treatment of atherosclerotic disease of the SFA and/or popliteal arteries (P1–P3) in patients with intermittent claudication and/or rest pain. Prespecified patients were selected for core laboratory–adjudicated duplex ultrasound imaging, including a subcohort with long lesions (≥15 cm). Patients were followed for 12 months.

The primary safety endpoint was a composite of freedom from device- and procedure-related mortality through 30 days and freedom from major target limb amputation and clinically driven target vessel revascularization through 12 months. An independent clinical events committee adjudicated all adverse events.

As summarized in Circulation: Cardiovascular Interventions, the primary effectiveness endpoint was primary patency at 12 months, as determined by duplex ultrasound. The long lesion imaging cohort included 157 patients (164 lesions). Mean lesion length was 26.40 ± 8.61 cm. Provisional stents were implanted in 39.4% (63/160) of lesions.

Primary patency by Kaplan-Meier estimate was 91.1%, and freedom from clinically driven target lesion revascularization was 94.2% at 12 months. The primary safety composite endpoint was achieved by 94% (126/134) of patients. The investigators reported that there were no device- or procedure-related deaths or major target limb amputations.

The In.Pact Admiral DCB was first approved by the FDA to treat SFA and popliteal arteries in December 2014.

On April 23, 2018, Medtronic announced FDA approval for the device to treat long SFA lesions up to 360 mm. Approval for the expanded indication was based on clinical data from the complex lesion imaging cohorts of the IN.PACT Global study, including long lesion in-stent restenosis and chronic total occlusion groups with lesion lengths >180 mm. Across these groups, investigators analyzed a total of 227 patients with mean lesion lengths of 28.7 ± 7.1 cm. Data showed a 1-year patency rate of 89.1% by Kaplan-Meier estimate at day 360 and a clinically driven target lesion revascularization rate of 7.1%.

On June 15, 2018, Medtronic announced FDA approval for 200- and 250-mm lengths of the In.Pact Admiral DCB to treat long SFA lesions.

Results Published From Pivotal WISE-LE Trial of Gardia Medical’s Wirion EPS in Lower Extremity Atherectomy


The multicenter study, which was conducted in the United States and Germany, was designed to assess the clinical performance of the Wirion EPS in patients undergoing lower extremity atherectomy for
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the treatment of peripheral artery disease.

As summarized in JACC: Cardiovascular Interventions, the primary endpoint was freedom from major adverse events (MAEs) occurring within 30 days postprocedure and was compared with an objective performance goal derived from historical atherectomy trials. MAE was defined as a serious adverse event that resulted in death, acute myocardial infarction, thrombosis, pseudoaneurysm, dissection (≥ grade C), or clinical perforation at the filter location, clinically relevant distal embolism, unplanned amputation, or clinically driven target vessel revascularization.

The study also included a histopathologic analysis of debris captured by the filter during the procedures.

The investigators reported that the study protocol specified enrollment of 153 patients with the primary endpoint successfully met if ≤ 18 (12%) MAEs occurred. A prespecified interim analysis performed after 103 patients revealed only two MAEs, and the study was stopped because it had met its predetermined metric for success.

A lesion deemed not accessible by the Wirion EPS occurred in seven patients. Debris that were < 1 mm, 1 to 2 mm, and > 2 mm in diameter were found in 98%, 22%, and 9% of patients, respectively.

The Wirion EPS is safe and non-inferior to the prespecified performance goal in capturing debris in the majority of patients and with the use of a broad range of atherectomy systems, concluded the WISE-LE study investigators in JACC: Cardiovascular Interventions.

In September 2017, Gardia Medical announced that the clinical results from the WISE-LE study, which was conducted under an FDA investigational device exemption, would support an anticipated application for 510(k) clearance to market the Wirion EPS in the United States with a label that covers use with all atherectomy devices (ie, orbital, rotational, directional, laser) in lower extremity atherectomy.

The Wirion device is currently cleared by the FDA for use during carotid artery stenting. It is also approved for marketing in Australia for the carotid indication. In Europe and Israel, it is approved for use for all cardiovascular indications.

The Wirion EPS is indicated to provide protection from blood clots and emboli that occur during catheterization. The system’s locking mechanism allows the physician to use any guidewire throughout the procedure and place the filter in any location on the guidewire. The Wirion system’s catheter allows for retrieval of the filter after placement of the stent.

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**EVAR Outcomes in Patients With Large Neck Diameters Studied**

October 4, 2018—Patients with abdominal aortic aneurysm (AAA) with large neck diameters have a higher risk of type la endoleaks and aneurysm rupture after standard endovascular aneurysm repair (EVAR), according to a study published online by Nelson F.G. Oliveira, MD, et al in Journal of Vascular Surgery (JVS). The study investigated the outcomes of EVAR in patients with neck diameters ≥ 30 mm in the prospectively maintained Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE).

This retrospective study compared patients with neck diameters ≥ 30 mm with patients with neck diameters < 30 mm. The primary endpoint was type la endoleak. Secondary endpoints included secondary interventions to correct type la endoleak, aneurysm rupture, and survival.

As summarized in JVS, the study included 1,257 patients (mean age, 73.1 years; 89.4% men) observed for a median of 4 years (interquartile range, 2.7–4.8 years). A total of 97 (7.7%) patients had infrarenal neck diameters ≥ 30 mm and were compared with the remaining 1,160 (92.3%) patients with neck diameters < 30 mm.

At baseline, there were no differences between groups regarding demographics and comorbidities other than cardiac disease, which was more frequent in the ≥ 30-mm neck diameter group (P = .037). There were no significant differences between the groups regarding neck length, angulation, thrombus, or calcification. Mean preoperative AAA diameter was 64.6 ± 11.3 mm in the ≥ 30-mm neck diameter group and 60.0 ± 11.6 mm in the < 30-mm neck diameter group (P < .001).

Stent graft oversizing was significantly less in the ≥ 30-mm neck diameter group (12.2% ± 8.9% vs 22.1% ± 11.9%; P < .001).

The investigators found that five (5.2%) patients in the ≥ 30-mm neck diameter group and 30 (2.6%) patients with neck diameters < 30 mm developed type la endoleak, yielding a 4-year freedom from type la endoleak of 92.4% versus 96.6%, respectively (P = .09).

Oversizing was 21.8% ± 13.0% for patients developing type la
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endoleak and 21.3% ± 12.4% for the remaining cohort (P = .99).

In adjusting for neck length, AAA diameter, and device oversizing, patients with neck diameter ≥ 30 mm were at greater risk for development of type Ia endoleak (hazard ratio [HR], 3.0; 95% confidence interval [CI], 1.0–9.3; P = .05).

Secondary interventions due to type Ia endoleak did not differ between groups (P = .36).

AAA rupture occurred in three patients with neck diameter ≥ 30 mm (3.1%) and in eight patients with neck diameter < 30 mm (0.7%; HR, 5.1; 95% CI, 1.4–19.2; P = .016); two cases were type Ia endoleak related in each group.

At 4 years, overall survival was 61.6% for the ≥ 30-mm neck diameter group and 75.2% for the < 30-mm neck diameter group (P = .009), which remained significant on correcting for sex and AAA diameter (P = .016).

“In this study, patients with infrarenal neck diameter ≥ 30 mm had a threefold increased risk of type Ia endoleak and fivefold risk of aneurysm rupture after EVAR as well as worse overall survival. This may influence the choice of AAA repair and underlines the need for regular CT-based imaging surveillance in this subset of patients. Furthermore, these results can serve as standards with which new, possibly improved technology, such as EndoAnchors (Medtronic), can be compared,” concluded the investigators in JVS.

Reliable New Risk Scoring Tool Developed to Guide Decisions for rAAA Patients

September 28, 2018—The Society for Vascular Surgery (SVS) announced that an accurate new scoring tool using only preoperative metrics can predict whether patients with a ruptured abdominal aortic aneurysm (rAAA) are likely to survive surgery. The study that developed the practical preoperative risk score to predict mortality after repair of rAAA was published by Brandon T. Garland, MD, et al in Journal of Vascular Surgery (JVS; 2018;68:991–997).

SVS noted that recent advances including endovascular aneurysm repair (EVAR) therapies, multidisciplinary protocols, and regionalization of aortic care have improved the survival of patients presenting with rAAA. However, previous risk scores that have been suggested to help guide decision-making between the practitioner, the patient, and the family are based on older information collected before the advent of EVAR for rAAA or rely on intraoperative information only.

The utility of guides becomes progressively important as the potential for mortality increases. As reported in JVS, the investigators retrospectively studied the outcomes of 303 patients presenting with rAAA between 2002 and 2013 who underwent either open repair or EVAR.

In the study, 70% of patients underwent open repair; however, after 2007 when an EVAR-first policy was adopted, this rate dropped to 53%.

The four risk factors found to be most predictive of mortality were:
- Systolic blood pressure < 70 mm Hg (odds ratio, 2.70; 95% CI, 1.46–4.97)
- Age > 76 years (odds ratio [OR], 2.11; 95% confidence interval [CI], 1.47–4.97)
- Creatinine > 2.0 mg/dL (odds ratio, 3.66; 95% CI, 1.85–7.24)
- pH < 7.2 (odds ratio, 2.58; 95% CI, 1.27–5.24)
- Neck diameter ≥ 30 mm (3.1%) and in eight patients with neck diameter < 30 mm (0.7%; HR, 5.1; 95% CI, 1.4–19.2; P = .016)

Limitations of the study include that it was conducted during a period of changing paradigms for care, it may not be applicable to institutions with low-volume AAA care, and it studied only patients who had already survived transport.
The BTG Sentry Bioconvertible IVC Filter is designed to provide immediate PE protection in patients at transient risk of PE and then bioconvert following that risk period, leaving a patent, unobstructed lumen.\(^1\)

The 12-month data from the prospective multicenter SENTRY study demonstrated a high level of safety and effectiveness with 100% freedom from new symptomatic PEs and no tilting, migrating, fracture or perforation.\(^1\)

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The BTG Sentry IVC Filter is indicated for the prevention of recurrent Pulmonary Embolism via percutaneous placement in the inferior vena cava in patients at transient risk of PE, in the following situations: pulmonary thromboembolism when anticoagulants are contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive PE where anticipated benefits of conventional therapy are reduced. Product availability varies by country. Prior to use, please refer to the applicable Instructions for Use (IFU) for complete product indications, contraindications, warnings, and precautions.

Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician.

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Neurointerventional Societies Outline New Criteria for Stroke Centers

September 7, 2018—The Society of NeuroInterventional Surgery (SNIS), with 12 other international neurointerventional societies, have released new guidelines outlining the criteria for level 1, 2, and 3 stroke centers that provide acute ischemic stroke interventions. The standards, published by Laurent Pierot, MD, et al, are available online in the Journal of NeuroInterventional Surgery.

SNIS noted that acute ischemic stroke caused by emergent large vessel occlusion (ELVO) is the leading cause of adult disability in the world. Recent studies have shown that neuroendovascular stroke surgery significantly improves outcomes in ELVO patients, especially if the patient receives the surgery in a timely fashion.

For the first time, the societies have specified criteria for level 1, 2, and 3 stroke centers—terminology they believe will help health providers and the public better understand the capabilities of stroke treatment facilities.

The guidelines recommend:
- Level 1 centers need to offer the full spectrum of neuroendovascular services, including neuroendovascular stroke surgery.
- Level 1 centers need to treat a minimum of 250 stroke patients per year and perform a minimum of 50 thrombectomies per year, in addition to other requirements.
- Level 2 stroke centers should see a minimum of 100 stroke patients per year and perform a minimum of 50 thrombectomies per year.
- Each neurointerventionalist in a level 2 center should perform a minimum of 15 acute intracranial thrombectomies per year.

According to SNIS, the guidelines recognize the challenges that newly created level 2 stroke centers could face in meeting the minimum volume criteria for procedures. They allow for these centers to operate below the minimum threshold numbers as long as they expect to hit their volumes within 12 to 24 months.

The purpose of these guidelines is not to serve as a substitute for existing national and regional guidelines, but rather to outline the best recommendations based on expert opinions and the most current evidence available in stroke care around the world, stated the society.

Adam Arthur, MD, President of SNIS, commented in the announcement, “ELVO patients should be taken to level 1 stroke centers. Establishing guidelines for level 2 stroke centers gives patients a chance at the best possible outcome in underserved regions. These guidelines, issued by this eminent group of organizations, will help facilities around the world maintain the highest standard of care for stroke patients.”

Meta-Analysis Evaluates Effects of Cerebral Hyperperfusion Syndrome After CAS


The investigators concluded in EJVES, “CHS is a serious and frequent complication in patients undergoing carotid angioplasty with stenting and is most likely to occur in the very early postprocedural period.” They advised, “Future studies are encouraged to investigate the effect of intensive hemodynamic monitoring, including blood pressure control and assessment of cerebral blood flow, on the incidence of stroke caused by CHS after CAS.”

For the study, a systematic search on incidence rates of CHS after CAS was conducted of the MEDLINE, EMBASE, and Cochrane databases. A metaregression analysis on CHS was performed to explain heterogeneity and determine the impact of potential risk factors on observed CHS. The Cowley criteria were used to assess the methodologic quality of the studies. The study evaluated data from 33 studies, which were composed of 8,731 CAS patients. In EJVES, the investigators reported:
- The pooled CHS risk was 4.6% (3.1%–6.8%).
- The stroke rate was 47% in CHS patients, of which 54% were fatal or disabling.
- The average time from procedure to symptoms was 12 hours (interquartile range, 8–36 hours).
- Impaired cerebrovascular reserve was associated with a higher risk of CHS after CAS.
- Symptomatic status was associated with a lower risk of CHS.
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*The AVeVA Clinical Study was a prospective, non-randomized, single arm multi-center study of the COVERA™ Vascular Covered Stent used to treat stenoses at the anastomosis of an arteriovenous graft and outflow vein. 110 patients were treated with the COVERA™ Vascular Covered Stent at 14 investigational sites in the US. Target Lesion Primary Patency (TLPP) of 71%, defined as the interval following the index intervention until the next clinically-driven reintervention at or adjacent to the original treatment site or until the extremity was abandoned for permanent access. AVeVA Clinical Study. Data on File. Bard Peripheral Vascular Inc., Tempe AZ. Complications and Adverse Events associated with the use of the COVERA™ Vascular Covered Stent may include the usual complications associated with endovascular stent and covered stent placement and dialysis shunt revisions. Please consult product labels and package inserts for indications, contraindications, hazards, warnings, cautions, and information for use. © 2018 BD. BD, the BD logo and all other trademarks are property of Becton, Dickinson and Company. Illustrations by Mike Austin. All Rights Reserved. BPV/SGF2/0618/0124
Calcium: Why It Matters

By Fabrizio Fanelli, MD, EBIR

Vascular calcification, traditionally known as ossification of the arteries, is a progressive accumulation of calcium and phosphate within the arteries that is associated with mineral deposits both in the intima and media layers of the vessel wall. Its physiological development and clinical treatment remain active areas of research. Chronic kidney disease and diabetes mellitus are the main causes of vascular calcification; however, vascular calcification is a pathologic process that occurs in response to dysregulated or inappropriate environmental stimuli and an atherogenic risk profile that includes advancing age, atherosclerosis, dyslipidemia, and genetic diseases. Besides the vasculature, where calcium contributes to atherosclerotic disease, calcium can accumulate in other organs such as the spleen, liver, and kidney.

ETIOLOGY AND PATHOPHYSIOLOGY
Vascular calcification is the pathologic response to toxic stimuli involving metabolic substances and/or inflammatory cells. Similar to the process of bone formation, vascular calcification consists of a complex, intracellular molecular process that includes the differentiation of macrophages and vascular smooth muscle cells into osteoclast-like cells. Vascular calcifications are divided into intimal and medial (Mönckeberg medial sclerosis) morphologies. Intimal calcification is associated with atherosclerotic plaques and is thought to result from modified lipid accumulation, proinflammatory cytokines, and apoptosis within the plaque that induces osteogenic cell differentiation. The most recognized function of intimal calcification is isolation and interruption of the abnormal cellular process, thus protecting healthy adjacent intima. Medial calcification is considered to be more widespread in the lower abdominal region. Associated with peripheral artery disease, medial calcification results from the osteogenic differentiation of smooth muscle cells within the medial layer of the vessel wall. Although medial calcification is generally not linked to luminal obstruction, the decrease in wall elasticity and compliance of the arterial vessel can ultimately lead to atherosclerosis and reduced perfusion.

WHY CALCIUM MATTERS
Calcium is a well-known enemy of endovascular procedures. Underdiagnosed and underestimated by angiography, calcium makes a vessel resistant to dilatation and susceptible to recoil and embolism. Importantly, calcium is significantly responsible for the occurrence of dissections. In fact, 71% of flow-limiting dissections occur within a calcified vessel because the presence of calcium dramatically reduces the arterial wall elasticity and the vessel cannot be compliant when a balloon is inflated. This problem has gained renewed attention with the introduction of drug-coated balloons (DCBs), especially when optimal balloon angioplasty is required to reduce the number of stents implanted. Moreover, calcified lesions present numerous challenges, including responding poorly to balloon angioplasty, requiring frequent use of stents, exhibiting a high incidence of angiographic complications, and limiting the effectiveness of DCBs.

Several technical advantages of DCBs have been described in their mode of action, such as the ability to achieve a uniform distribution and release of drug on
the arterial surface, and ultimately their ability to achieve arterial patency with provisional use of stents. However, even in the era of drug elution, calcium is still a potential barrier to optimal drug absorption after the use of DCBs. In particular, circumferential distribution of calcium, as opposed to longitudinal extension of calcium, appears to be a strong predictor of patency loss. These results have rendered primary stenting the preferred strategy in these settings. Nonetheless, once the stent is deployed, calcium continues to cause further challenges, with risks of malapposition, suboptimal expansion, and an increased likelihood of stent fractures.

ADDRESSING CALCIUM

To increase the efficacy of the endovascular approach in the presence of calcification, vessel preparation with atherectomy or a debulking system is very promising. These techniques can improve vascular remodeling, enhance drug diffusion in the vessel wall, and promote the antiproliferative drug effect. Physiologically, the results are reduced stenosis and improved tissue perfusion, while the clinical benefits include increased walking distance in claudicants, accelerated wound healing, and improved limb salvage in patients with critical limb ischemia.

CONCLUSION

In summary, vascular calcification associated with atherosclerotic disease is a progressive pathologic process that affects arterial wall compliance and elasticity and subsequently impairs tissue perfusion. Well-known risk factors, such as chronic kidney disease and diabetes mellitus, exacerbate the condition of vascular calcification, and clinically, this condition is associated with decreased walking distance, impaired wound healing, and reduced limb salvage. As a barrier to both traditional mechanical endovascular approaches, such as balloon angioplasty, as well as drug-eluting therapies, like DCBs, vascular calcification deserves special attention from vascular specialists charged with treating patients exhibiting this difficult lesion morphology.

Recommended Reading


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Disclosures: Consultant, speaker, and advisory board member for Medtronic, Cook Medical, Bard Peripheral Vascular, Boston Scientific Corporation, Shockwave Medical, and Spectranetics Corporation.

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Tumor Boards in Interventional Oncology

A multidisciplinary discussion of the approach to treatment for four patients with cancers of varying origins and severities.

CASE 1

WITH DIMITRIS FILIPPIADIS, MD, PhD, EBIR; ALEXIS KELEKIS, MD, PhD, EBIR, FSIR; AND MAUREEN P. KOHI, MD, FSIR

A 35-year-old woman with a past medical history of ductal breast cancer (R0M0) resected 1 year ago followed by chemotherapy (12 cycles of paclitaxel) and initially disease-free on positron emission tomography (PET)/CT now presents with three new nodules in the right liver lobe segments 4A, 5, and 6. The largest lesion measures 1.7 cm on MRI.

Drs. Kelekis and Filippiadis: Our recommendation is percutaneous ablation using either radiofrequency or, even better, microwave energy. Advantages of microwave ablation over radiofrequency ablation include the ability to achieve temperatures over 100°C and the ability to produce larger ablation volumes in a shorter time that are less affected by the heat sink effect and any kind of impedance-driven performance. According to published data, oligometastatic breast cancer patients treated with curative intent may remain disease free for a long period of time. Percutaneous thermal ablation of breast cancer metastases is a safe, efficacious, and feasible treatment option. Negative prognostic factors include a tumor burden > 4 cm and triple-negative histologic subtypes. The survival rates in selected patients with breast cancer liver metastases treated with percutaneous thermal ablation are comparable to those achieved with surgery.1

Three metastatic lesions, all confined in the right liver lobe and each with a diameter < 2 cm, constitute an ideal oligometastatic candidate for percutaneous thermal ablation. Curative intent in terms of complete lesion ablation along with a safety margin of 1 cm should be the therapeutic goal. For oligometastatic breast cancer patients who present with fewer than five lesions, like the patient in this case, percutaneous thermal ablation combined with systemic chemotherapy and specific hormone therapy can play an important role in the management of patients with a limited number and sites of metastases.2,3

Another approach that has not been extensively studied is to combine percutaneous thermal ablation with transarterial chemoembolization (TACE). In a recent comparative study, Wang et al suggest combining percutaneous ablation with TACE for statistically significant better outcomes.4

Dr. Kohi: In the absence of randomized, comparative data, my recommendation is entirely based on my clinical experience. However, it should be noted
that my experience and the available data are almost exclusively in women with chemorefractory, progressive liver metastases from breast cancer. It would be very unusual to see such a patient in my practice, as she would likely be treated with another line of systemic chemotherapy or other targeted therapies. However, should she choose locoregional therapy, I would offer intra-arterial therapy as opposed to ablation. I would discuss with her the procedural steps, risks, and benefits of TACE using drug-eluting beads (DEB-TACE) and transarterial radioembolization (TARE). Ultimately, I would recommend TARE. Although there is no comparative data between DEB-TACE and TARE in women with liver metastases from breast cancer, in my experience, TARE has been associated with lower rates of toxicity and higher tolerability.

Several studies have evaluated the use of TARE in women with liver-dominant breast cancer metastases. Bangash et al treated 27 women with glass beads and reported an objective response rate of 39.1% and a median overall survival (OS) of 6.8 months. The authors reported 11% grade 3 toxicity.5 Cianni et al treated 52 women with resin beads and reported a median OS of 11.5 months with a disease control rate of 91.4%. Toxicities occurred in < 4%.6 Saxena et al treated 40 women with resin beads and demonstrated a median OS of 13.6 months with a disease control rate of 71.1%. Grade 1 and 2 toxicities were noted in 40% of the patients.7 Additional studies exist that support the use of TARE for liver metastases from breast cancer.

If the patient does not desire TARE or is not a suitable candidate, I would proceed with DEB-TACE. Martin et al treated 40 women with doxorubicin-eluting beads (100–300 µm) and reported a median OS of 47 months with a tumor response rate of 57.5%. The authors also reported a 17% rate of grade 3 and higher toxicity.8 Lin et al treated 23 women with doxorubicin-eluting beads (70–150 µm) and reported a median OS of 17 months and a disease control rate of 83%. Grade 3 or higher toxicity was observed in 45% of the patients.9

Overall, the data regarding TARE and DEB-TACE include heterogeneous cohorts, varying techniques, and different response criteria, all reported in a retrospective manner without a control arm. In my practice, I have observed similar outcomes, with more women complaining of postembolization syndrome after DEB-TACE compared to TARE. Although thermal ablation is an alternative therapy for hepatic metastases from breast cancer, I would be inclined to use this approach in the setting of a solitary lesion.

CASE 2
WITH GHASSAN K. ABOU-ALFA, MD, AND ROBERT J. LEWANDOWSKI, MD, FSIR

A 67-year-old man with a past medical history of compensated alcoholic cirrhosis and type 2 diabetes mellitus and no symptoms is diagnosed with three arterial hypervascular lesions of the right liver lobe on recent MRI. The largest lesion measures 6 cm and demonstrates segmental portal vein invasion. The patient’s Eastern Cooperative Oncology Group performance score is 0, and his liver function status is Child-Pugh A.

Dr. Abou-Alfa: Considering the size of the lesions and the portal vein involvement, curative surgical resection and liver transplant are inappropriate options in this case.¹ Local therapy may be appropriate. Chemoembolization or embolization may be possible, although in view of the vascular involvement, certain experts may argue against this. Radioembolization could be considered as well. Unfortunately, the latest study of yttrium-90 (Y-90) radioembolization did not lead to any significant improvement in OS versus sorafenib in patients with hepatocellular carcinoma (HCC).² Thus, the use of systemic therapy would be appropriate and justified. The options include sorafenib and lenvatinib, pending the approval of the latter.³⁴

Dr. Lewandowski: Recent prospective randomized trials on locoregional versus systemic therapy for patients with “advanced” HCC failed to meet their primary endpoint of an OS advantage of radioembolization over sorafenib.⁵ Although not powered for noninferiority, these trials are consistent with current published literature revealing similar OS outcomes for these therapies in this patient population. Both published studies have significant limitations. In the SARAH trial,⁷ 22% of patients who were randomized to radioembolization did not receive this therapy; 45% of patients had previous chemoembolization in which hepatic arteries were embolized, potentially limiting efficacy of future embolotherapies; 18 more days elapsed between randomization and initiation of therapy with radioembolization than with sorafenib; 34% had main portal vein tumor thrombosis (PVTT), which is a relative contraindication to radioembolization; and treatment centers had limited experience with radioembolization, an operator-dependent procedure. In the SIRVENIB trial,⁵ 29% who were randomized to radioembolization did not receive this therapy and again there was limited experience with radioembolization at many centers, which included Myanmar and Mongolia.

Both studies revealed better tumor response rates and higher quality of life with radioembolization versus sorafenib. Of note, neither study utilized higher-dose glass microsphere radioembolization.⁶ The question regarding optimal treatment for patients with locally advanced HCC should not be locoregional versus systemic therapy. Rather, the question should be how to optimally combine these therapies for synergistic effect. The treatment approach advocated by our multidisciplinary tumor board for locally advanced HCC patients with preserved liver function/performance status is liver-directed therapy with radioembolization, followed by systemic therapy (historically sorafenib). We have had success with this treatment paradigm, downstaging several patients to liver resection and/or liver transplant after sustained tumor response and demonstration of good tumor biology. Radioembolization offers well-tolerated outpatient therapy with high tumor response rates and competitive survival outcomes, especially in Child-Pugh A patients with PVTT not extending to the main portal vein. Adjuvant systemic therapy offers the promise of reducing local/systemic disease progression. By themselves, systemic therapies are limited by poor tumor response rates and tolerability. The role of this combination therapy (radioembolization plus sorafenib) is currently being studied in the STOP-HCC trial (NCT01556490).

Although sorafenib is the gold standard systemic agent for locally advanced HCC patients based on a 2- to 3-month survival advantage over placebo,⁹ it might not be the ideal systemic agent for combination/adjuvant therapy given negative results from prospective randomized trials of sorafenib plus chemoembolization,⁷ as well as a recent negative trial of sorafenib in the adjuvant setting.⁸ There is tremendous enthusiasm for immunotherapy in this patient population. Our current treatment approach to the patient proposed in this scenario would be to enroll him in a clinical trial with radioembolization plus nivolumab (NCT02837029). Although nivolumab has been...
The steerable microcatheter that allows for positioning and re-direction within the vessel without the need for a guidewire.

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shown to promote long duration of tumor response, it is limited by poor tumor response rates. There is promise in using a locoregional therapy such as radioembolization to improve local tumor response rates and present antigen, enhancing innate tumor surveillance and tumor destruction.


Dr. Ziv: The International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society introduced a new classification of lung adenocarcinoma in 2011, dividing lung adenocarcinoma into five histologic subtypes: lepidic, acinar, papillary, micropapillary, and solid. This classification has important prognostic and predictive utility in the setting of early stage lung adenocarcinoma. The histologic subtypes can be identified on core needle biopsy, and therefore, the first question that needs to be addressed is whether a core biopsy was performed, and if so, which histologic subtypes were identified on the specimen.

Micropapillary and solid components are well-established indicators of worse outcomes. This includes higher local recurrence rates after surgery, ablation, and stereotactic body radiation therapy (SBRT). The presence of micropapillary and/or solid histologic subtype in clinically N2-negative patients was predictive of occult N2 lymph node metastasis, suggesting that radical lymph node dissection was necessary in these subgroups. Indeed, in patients with stage IA lung adenocarcinoma with micropapillary subtype, recurrence rates were lower if patients underwent lobectomy rather than limited resection. Therefore, if micropapillary or solid components are identified in the biopsy specimen, the most appropriate treatment for this patient is lobectomy with hilar and mediastinal lymph node dissection.

No randomized controlled trials exist to compare ablation and minimally invasive surgery. Comparisons between prospective trials are limited, as they are not stratified for the most important prognostic indicators—histologic subtype and KRAS mutation status. However, despite similar overall survival rates compared with surgery, local recurrence rates for lung ablation are high. Therefore, in a
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INFLATED AT RBP

RBP = Rated Burst Pressure

1 Average foreshortening calculated for the 18 similar diameter/length combinations between the respective product offerings. Data on file. Bard Peripheral Vascular, Inc. Tempe, AZ. Drawings are not to scale. For illustrative purposes only.

2 Foreshortening based upon the respective product’s IFUs and labeling information of comparable sizes at rate burst pressure. Bench tests may not be indicative of clinical performance. Different test methods may yield different results. Please consult package insert for detailed safety information and instructions for use.
patient with no medical comorbidities and no contraindica-
tions to surgery, surgical resection is the most appropri-
ate treatment. In a nonsmoker with presumably normal
pulmonary and cardiac function, I would recommend sur-
gical resection (lobectomy or limited resection based on
the histologic subtype). At present, ablation for primary
lung adenocarcinoma should be reserved for patients who
are not surgical candidates.

Drs. Saffarzadeh, Blasberg, and Detterbeck: To usefully
frame the discussion, we will assume this is a peripheral,
mostly solid lesion (not ground-glass) and that the patient
has normal pulmonary function, no significant comorbid-
ties, and there is no evidence of metastasis. We assume
that she is at a high-volume center that frequently per-
forms both minimally invasive lobectomy as well as SBRT
and ablation.

We need to ground decision-making on available evi-
dence and then use clinical judgment to individualize
the approach based on nuances of tumor-, patient-, and
setting-related factors. To date, there is no adequately
powered randomized evidence regarding lobectomy ver-
sus ablation or SBRT in fit, healthy patients with clinical
stage I non–small cell lung cancer (NSCLC). With respect
to ablation, there is minimal evidence on the long-term
outcomes of ablation for fit, healthy patients. Early data
from the ACOSOG Z4033 trial of 54 medically inoperable
patients with stage IA NSCLC treated with radiofrequency
ablation showed 40% local recurrence rate at 2 years,8
which is higher than the established recurrence rates for
lobectomy or sublobar resection. If we are to ground deci-
dion-making on available evidence, the use of ablation for
healthy individuals with stage I NSCLC cannot be routinely
recommended over surgery at this time.

For comparisons of surgery versus nonsurgical ther-
api es, we can also look at nonrandomized studies between
surgery and SBRT. Nonrandomized comparisons are
prone to confounding, but if a study can adjust for virtu-
ally all possible confounding factors, it can be viewed as
a “possibly only slightly confounded” comparison.10 Such
a study does exist; using the National Cancer Database,
limited pulmonary reserve or comorbidities that signifi-
cantly increase perioperative mortality. The role of abla-
tion is still to be determined. Age or comorbidities that
limit life expectancy have less impact on the relative role
of surgery versus nonsurgical therapy and mostly impact
whether any treatment is warranted. Finally, although it
is ultimately the patient’s decision, patient preference is
a valid reason only when unrealistic fears or expectations
have been addressed and short- and long-term outcomes
can be rationally weighed.

At the current time, we view surgery and nonsurgical
therapies such as SBRT and ablation as complementary,
not competitive. We place the patient first and find that
the most effective decision-making occurs during a joint
consultation between thoracic surgery, other treatment
providers, and the patient and his/her family. This allows
an open, honest discussion and a decision supported by all
parties, which avoids having the patient feel that they are
pitting one provider against another.

Drs. Yoshida and Lam: Our first recommendation in
the management of this patient would be completion of
her workup, including pulmonary function testing, fluoro-
deoxyglucose PET/CT, consideration of additional molecu-
lar evaluation (epidermal growth factor receptor [EGFR],
ALK, ROS1, BRAF, programmed death ligand-1), and dis-
cussion of pathologic mediastinal lymph node evalua-
tion. Importantly, she should be assessed by a thoracic surgical
oncologist for possible resection.

If further workup does not reveal regional or distant
disease, the patient would be staged with IIA NSCLC,
and the preferred treatment based on current National
Comprehensive Cancer Network guidelines is surgical
resection with or without adjuvant therapy. If the patient
is deemed medically inoperable or refuses surgery, an
alternative local therapy, such as SBRT, is indicated. SBRT
is generally composed of up to five high-dose radia-
tion treatments delivered to a small volume. Advanced
technology is required to plan and deliver a conformal
radiation dose to the tumor while minimizing dose to sur-
rounding normal tissue.

Prospective trials of definitive SBRT for medically inop-
erable, early stage, localized NSCLC have demonstrated
excellent local control of approximately 95% and rea-
sonable OS rates of approximately 60% at 3 years.16-18
Although multiple randomized trials comparing surgery
and SBRT for operable NSCLC have been initiated, all
were stopped early due to slow accrual. A pooled analysis of two trials (STARS and ROSEL) randomizing patients to SBRT versus lobectomy demonstrated a 3-year OS of 95% versus 79% in favor of SBRT (hazard ratio [HR], 0.14; \( P = 0.037 \)) despite similar recurrence-free survival rates of 86% versus 80% (HR, 0.69; \( P = 0.538 \)). Although one large population-based study comparing SBRT and surgery found a survival decrement associated with SBRT, prospective randomized trials (SABRTOOTH, POSTILV, STABLE-AMTES) comparing SBRT and surgery are anticipated to answer this question.

Due to the small size and peripheral location of this tumor, there are several acceptable dose and fractionation treatment paradigms. Commonly used in the United States, 54 Gy delivered in three fractions of 18 Gy allows treatment completion in 1.5 to 2 weeks. This strategy’s safety and efficacy were established in RTOG 0236, a phase 2 trial for medically inoperable patients with T1/T2 (< 5 cm) NSCLC. At 3 years, the primary tumor control rate was 97.6%. Grade 3 to 4 toxicity was reported in 15% of patients, and no grade 5 adverse events were reported.16

A 51-year-old man with no past medical history of cancer was recently diagnosed with adenocarcinoma of the descending colon and synchronous bilobar metastatic disease of the liver with at least 30% tumor burden and liver replacement. There is no sign of extrahepatic metastases on staging CT.

**Dr. Hickey:** The presence of synchronous liver metastases and lack of extrahepatic metastases indicate stage IV colon cancer with M1 metastatic disease. The most important question to answer when a patient presents with this stage of disease is whether the hepatic metastases would be eligible for curable treatment, meaning that all hepatic disease could be eliminated with surgical resection and/or ablation. Surgical resection remains the preferred treatment for resectable disease, but ablative therapies may be used alone or in conjunction with surgical resection provided that all sites of disease can be addressed. Resection and/or ablation can be performed in conjunction with removal of the primary tumor, either prior to or after a course of systemic chemotherapy, or hepatic resection can be staged to follow both removal of the primary tumor and a course of adjuvant systemic chemotherapy.

However, considering that this patient has bilobar metastases replacing approximately 30% of the liver volume, he is likely not a candidate for curative resection and/or ablation. In this circumstance, the patient should be treated with systemic chemotherapy consisting of FOLFOX (folinic acid [leucovorin], fluorouracil, and oxaliplatin), CAPEOX (capecitabine and oxaliplatin), or FOLFIRI (folinic acid, fluorouracil, and irinotecan) with or without bevacizumab. Panitumumab or cetuximab may be used in place of bevacizumab if the tumor expresses the wild-type KRAS/NRAS gene. The patient should be evaluated for conversion to resectability or ablative therapy every couple of months while on systemic therapy.

**Drs. Shah and Hochster:** Hepatic metastases are present in two-thirds of patients with colon cancer. In patients with isolated liver lesions, several liver-directed options are available in combination with systemic chemotherapy as a route to possible cure. The combination of surgery with systemic therapy is the only potentially curative treatment, with 5-year survival rates of 20% to 50% in multiple retrospective series. Initial resectability and recurrence due to persistence of micrometastases after liver surgery are major concerns. In this case, anatomic issues related to bilobar involvement, location of the specific metastases, and the extent of local resection may influence the approach. Multidisciplinary consultation on the best approach and possible need for portal vein embolization and timing are essential. We generally favor perioperative chemotherapy as the approach most likely to reduce the size and number of metastases, render them more easily resectable, and improve survival based on controlled trials.

In patients with synchronous disease that is amenable to resection, perioperative chemotherapy has been used to assess disease trajectory and chemotherapy responsiveness, thereby enhancing patient selection for surgery. EORTC 40983, a phase 3 randomized controlled trial, compared the use of perioperative chemotherapy (FOLFOX4, 3 months pre- and postsurgery) with surgery versus surgery alone for patients with liver metastases in 364 patients. At a median follow-up of 8.5 years, the trend for median OS (61.3% vs 51.2%) and 5-year progression-free survival (38% vs 30%; HR, 0.81; P = .068) favored the combined...
modality arm. Although the study did not meet statistical significance for the intent-to-treat population, when those ineligible for surgery were excluded from the analysis, the difference was significant and similar to the effect of adjuvant chemotherapy in the setting of stage III colon cancer. Additionally, 83% and 84% of patients were successfully resected in the combination group and the surgery alone group, respectively, indicating that perioperative chemotherapy did not render patients ineligible for surgery due to delay. Finally, the overall mortality rate was not affected even though postoperative complications were higher in the chemotherapy group. It should be noted that this trial was limited to patients with four or fewer metastases and clearly resectable disease. If these lesions are clearly resectable, this patient would meet that definition.

Additional progress has been made with chemotherapy. Emerging evidence shows that aggressive three-drug first-line chemotherapy can improve progression-free survival and resection rates in those with isolated liver metastases. The phase 3 randomized TRIBE study evaluated the combination of bevacizumab with FOLFOXIRI or FOLFIRI. It showed a significant advantage in OS for triplet therapy of 29.8 versus 25.8 months (HR, 0.8; \( P = .030 \)) and an objective response rate of 65% in favor of triplet therapy versus 53% \( (P = .006) \) with more liver resections. Moreover, the combination of FOLFOXIRI with an anti–EGFR agent in RAS and BRAF wild-type tumors has demonstrated remarkable anti-tumor activity and high subsequent resection rates of 28%, as in the randomized phase 2 MACBETH study. However, the addition of anti-EGFR agents to a triplet backbone significantly increases toxicity, as evidenced by the EPOC study of perioperative FOLFOX and cetuximab, which conversely decreased progression-free survival. We generally favor FOLFIRINOX with a targeted agent such as bevacizumab or anti-EGFR antibody (for RAS wild-type, left-sided tumors) prior to surgical resection, followed by metastectomy and resection of primary tumors (often as staged procedures).

We do not favor other means of hepatic-directed therapy in this potentially curable situation. For potential cure, surgery with R0 resection in conjunction with aggressive chemotherapy and targeted agents remains the gold standard treatment.

Drs. Jutric and Wolf: Previous criteria for offering surgery to patients with colorectal liver metastases were based on the number of tumors and tumor size. Considerable experience with more potent chemotherapy and modern surgical techniques has allowed for more inclusive criteria for resectability, with emphasis on the size and blood supply of the future liver remnant (FLR).

Patients are now considered resectable if the surgery will yield adequate liver volume in the remnant liver with remaining two contiguous liver segments (out of eight normally present), preserved vascular inflow/outflow, and intact biliary drainage. A minimum of 30% total liver volume standardized to body surface area is required for safe resection in a patient who has undergone preoperative chemotherapy. Ideally, no more than four to six cycles of preoperative chemotherapy should be administered, as the risk of postoperative liver failure increases after 2 months of chemotherapy.

Patients with bilateral disease, such as the case patient, are candidates for potentially curative surgical resection. We only consider radioembolization in cases in which an adequate FLR cannot be achieved even after preoperative portal vein embolization yields hypertrophy or when inflow/outflow cannot be preserved. Alternatively, if the patient’s underlying medical comorbidities preclude aggressive resection, systemic or liver-directed therapies would be considered, in part to lengthen progression-free survival in the liver.

The strategies used for resection are:

- Single-stage hepatectomy (ie, multiple wedge resections), which is used when bilateral liver
metastases are present in a diffuse but mostly peripheral distribution. The focus is on preservation of liver parenchyma.

- Two-stage hepatectomy, which includes limited hepatectomy to remove disease in the FLR as a first stage, followed by a major hepatectomy to clear the remainder of the disease.

- Combination of resection and ablation strategies, which are used to manage bilateral disease, but in cases in which the FLR has a single lesion that is deep within the liver parenchyma. Provided that there are adequate liver volumes, this can be done as a single stage.

With respect to this patient with bilateral metastases and 30% of the liver replaced by tumor, we would suggest four cycles of preoperative FOLFOX chemotherapy, followed by a two-stage hepatectomy, given that an outflow hepatic vein and inflow to the liver can be preserved.

The first stage can be performed laparoscopically at the same time as removal of the primary tumor. This stage also allows for visual and ultrason sound assessment of the planned liver remnant for unsuspected additional tumor burden or cirrhosis. Pathologic assessment of the tumor necrosis can be informative to prepare for the second stage hepatectomy. If there is concern for volume based on laparoscopic assessment during the first stage or by liver volumetrics used to calculate volumes, then portal vein embolization should be done in between the two stages. The ability to hypertrophy is the best predictor of FLR function postoperatively.15

In general, systemic therapy is offered to all eligible patients at high risk of recurrence, such as this patient, given that modest benefit is demonstrated in similar patients undergoing chemotherapy in lower-risk settings.16

In the case presented, we recommend an additional eight cycles of chemotherapy postoperatively. Using successful implementation of this strategy, OS of near 60% at 5 years can be expected.1 Figures 1 through 3 demonstrate our experience with this strategy: a patient with 70% liver replacement by tumor (Figure 1), successful downstaging with modern chemotherapy (Figure 2), followed by R0 resection (Figure 3). The patient remains alive without disease currently.}

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COMMENTARY

Staying on Course

Obtaining the highest level of evidence in interventional oncology requires that we stay on course and strive for positive prospective randomized trials.

BY NADINE ABI-JAOUDEH, MD

Between 2008 and 2016, most oncology prospective randomized trials pertaining to hepatocellular carcinoma (HCC) failed. None of the many trials demonstrated improvement in overall survival (OS) or progression-free survival (PFS). Oncologists kept trying different strategies and different molecules until, lo and behold, they succeeded and different molecules until, lo and behold, they succeeded and different molecules until, lo and behold, they succeeded and different molecules until, lo and behold, they succeeded and different molecules until, lo and behold, they succeeded. \(^1\) Several other therapeutic strategies are also expected to yield positive results. In fact, some trials are now aiming to compete with transarterial chemoembolization (TACE). During the decade of negative results, the oncology community did not decide that registries were the best option nor did they move away from patient-centered significant endpoints such as OS or PFS. In an investigational device exemption application in which I was involved, the FDA requested that we choose patient-centric endpoints (ie, OS, PFS). During our application, the FDA rejected time to embolization failure and time to progression as primary endpoints, and they are generally not accepted in the oncology community.

Several arguments have been leveled against performing prospective randomized trials, let alone with a survival endpoint, including the fact that several surgical practices were integrated/approved without level I evidence. Indeed, transplantation was approved with level IIA evidence and metastectomy of lung tumors was integrated based on surgical registry data. However, the latter remains controversial, and in both cases, any trial with level I evidence will supplant these therapies. In the end, the group with the level I evidence will get the patients.

Prospective randomized trials are hard and expensive to conduct; however, nothing of value is easily obtained. It may not be possible to obtain level I evidence, but that should always be the goal. Registries reflect population data and are more realistic than the artificial environment of a prospective trial. Registry data should be used to choose the appropriate target population for prospective randomized trials but cannot be the ultimate level of evidence of our specialty. The National Cancer Institute and Oxford Centre for Evidence-Based Medicine developed the level of evidence to define evidence-based medicine.

Finally, one additional argument against prospective trials with a survival endpoint is that patients with intermediate HCC have a prolonged life expectancy. Indeed, the results from studies by Llovet et al\(^2\) and Lo et al\(^3\) cannot be replicated. A prospective randomized trial with OS for intermediate HCC may not be logical, but PFS is an excellent surrogate.

Oncologists learned from their failed trials, and we must learn from their experience. A positive trial requires an effective agent and an appropriate target population. In the regorafenib trial, patients had to have tolerated sorafenib to be enrolled.\(^4\) The appropriate target population is key. For instance, if the yttrium-90 (Y-90) studies were performed in patients with rightsided colorectal cancer, the outcome may have been very different. Registries are an excellent way to narrow down the target population.

We also need to understand the pathophysiology effects of our procedures. Why is it that certain patients respond to TACE or Y-90, while others do not? When we understand the elements affecting the response, we can choose the right patients and also work on countering the factors preventing the desired response. A focus on basic science research is pivotal, even if it does not profit one particular entity, as it will benefit all of us.

TACE has demonstrated survival benefit for HCC, but several systemic therapies may dethrone TACE with prospective randomized data on PFS and OS.

In the “Tumor Boards in Interventional Oncology” article in this issue of Endovascular Today, we involved surgeons, oncologists, and radiation oncologists to raise awareness about novel surgical and radiation oncology therapeutic options (ie, aggressive surgeries for colorectal carcinoma that may limit the role of locoregional therapies). Our specialty should be aware of upcoming oncology and surgical therapeutic options so that we know where we stand.

Finally, prospective randomized trials were chosen to be the best level of evidence for a reason. Ultimately, lowering our standards will only hurt our specialty. We must stay our course, and if it takes 20 years to get another positive trial, 2022 is just around the corner.

Weighing Evidence Quality in Interventional Oncology

The importance of understanding the levels of evidence related to IO therapies and areas for future research.

BY DEREK BIEDERMAN, MD, AND EDWARD KIM, MD

Providing evidence-based medicine is vital to the delivery of premium patient care without exorbitant costs or undue patient harm. If data are the currency of evidence-based medicine, perhaps interventional radiology can be likened to a proverbial technology startup—tremendous upside potential but a little short on cash. Throughout history, innovation has been constant, rapid, and intertwined within the fabric of the specialty. Although the pace of innovation has undoubtedly been an advantage to interventional radiology, it has also created predictable challenges relating to data accrual and clinical trial design.

WEIGHING THE EVIDENCE FOR IO THERAPIES

In an ideal scenario, clinical decisions would be solely based on level IA evidence—randomized controlled trials (RCTs) with mortality as the primary endpoint. If level IA evidence were able to be rapidly obtained at a low cost, then this ideal scenario would likely mimic reality. However, for many important clinical questions, this is not the case. Understanding the levels of evidence is a critical component to providing the best possible patient care and acting as an informed participant in a tumor board. Hickey et al published an informative review on this topic for interventional oncologists.1,2

In reviewing the evidence supporting specific therapies in interventional oncology (IO), it is logical to begin with the initial prospective RCTs showing a survival benefit for chemoembolization over supportive therapy.3,4 These landmark studies provide the foundation for the level IA recommendation for the use of chemoembolization as a first-line therapy in Barcelona Clinic Liver Cancer (BCLC) stage B patients, and these studies changed the paradigm in the newly burgeoning field of IO. As such, in intermediate-stage patients, chemoembolization has been established as the standard of care, and thus trial designs need to have chemoembolization as the control arm. However, using overall survival as the primary endpoint for a phase 3 RCT in this patient population with a median overall survival of 20 months can be difficult, and surrogate endpoints such as objective response, progression-free survival, and duration of response have been more cost-effective in phase 2 studies, such as PRECISION V.

It is interesting to note the difference in the level of evidence supporting chemoembolization (level IA) and the level of evidence supporting transplantation as first-line therapy in patients who are not candidates for resection (level IIA).5 This is by no means to proclaim the superiority of interventional radiology in practicing evidence-based medicine, but to illustrate how level I evidence, the highest level of evidence that can be generated through good clinical trial design, is not the be-all and end-all of decision-making in clinical practice.

The clinical impact of the choice of delivery vector for chemoembolization in the treatment of hepatocellular carcinoma (HCC) was studied in the PRECISION V trial, which provided level I evidence of improved toxicity of drug-eluting beads over conventional chemoembolization.6 Level I evidence also exists for radiofrequency ablation in the treatment of HCC < 3 cm, with data showing similar survival rates compared to resection.7 An informative prospective randomized study comparing chemoembolization combined with ablation versus chemoembolization alone by Peng et al demonstrated a survival benefit for combination therapy compared to monotherapy.8
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Radioembolization, an increasingly used intra-arterial therapy for primary and metastatic liver tumors, has been the topic of several recent high-profile studies. Compared to standard medical therapy alone, resin-based yttrium-90 (Y-90) therapy in the treatment of colorectal cancer showed the initially encouraging result in the SIRFLOX study of improved progression-free survival in the liver when combined with standard medical therapy. However, this result did not translate into a direct overall survival benefit in the subsequent combined analysis of the FOXFIRE, SIRFLOX, and FOXFIRE Global trials.

A potential topic of further study is the difference in survival seen between patients with right-sided and left-sided colon cancers, with a significant survival benefit for radioembolization seen in the latter group. Recently, the SARAH trial and the SIRVeNlb trial, two randomized prospective trials comparing patients with advanced-stage HCC treated with resin-based radioembolization versus sorafenib, did not demonstrate significantly different survival between the two treatment arms. Notably, quality-of-life outcomes were more favorable in the radioembolization treatment arms in both studies. Outcomes from two prospective studies on glass-based radioembolization in the treatment of HCC, the STOP HCC trial (NCT0155649) and SORAMIC trial (NCT0126645), are eagerly awaited. A recent RCT performed by Salem et al provided level I efficacy data favoring Y-90 therapy over conventional chemembolization in BCLC stage A/B patients.

AREAS FOR FUTURE RESEARCH

Despite the steady progress in IO research over the past 2 decades, numerous unanswered questions remain. Niche applications of radioembolization, such as radiation segmentectomy, have garnered interest based on several promising retrospective studies. Duplicating these results in a prospective fashion can be challenging given the longer median survival of patients with early and intermediate-stage HCC. Prospective studies comparing radiation segmentectomy to ablative therapy or resection using progression-free survival as an endpoint is a more realistic near-term goal, as progression-free survival have a favored endpoint and surrogate of survival in this patient population because these patients are Child-Pugh A with a diminished risk of the confounding variable of death from natural progression of cirrhosis.

Tailoring treatment options and decisions based on tumor biology is another area that is ripe for further exploration in IO, which mirrors a trend across all of medicine and is currently a topic of active study in the field of medical oncology. Knowing which patients stand to benefit most from interventions could be transformative for IO because it could markedly improve patient outcomes, while avoiding the patient risk and financial cost of treatments that are unlikely to provide a significant benefit. An additional possibility is that knowledge of tumor biology could be utilized in a manner to improve study design. As previously mentioned, in the combined analysis of the FOXFIRE, SIRFLOX, and FOXFIRE Global trials, treatment with radioembolization did not appear to have a significant impact on survival across the entire cohort of patients. During subgroup analysis, a subpopulation of patients with right-sided colon tumors treated with radioembolization had a significant survival benefit. Although this study was not powered to analyze this subgroup of patients, this may provide a signal for further investigation and trial design in this patient population, such as potential differences in the tumor biology and responsiveness to radiation therapy. It may be possible to test therapies in vitro on different tumors of varying genetic composition, enabling smaller studies to be conducted with patients who have molecular tumor profiles known to be highly susceptible to the proposed therapy. Even a modest understanding of how genetic differences in tumors may influence the response to therapy could help tailor the design of eventual prospective studies.

Immuno-oncology is a rapidly burgeoning sector of oncologic medicine, which also remains understudied in IO. Unlike surgical oncology, where the tumor is physically removed from the body, IO therapies kill tumor cells, releasing intracellular contents within the body. This intracellular material contains numerous antigens, which could theoretically potentiate a cellular immune response awakening and activate the body’s own intrinsic cancer-fighting mechanisms.

CONCLUSION

The pace of innovation and growth in IO necessitates that careful attention be paid to making clinical decisions using the highest-quality evidence possible. Having a robust understanding of the levels of evidence is a critical aspect of providing high-quality patient care and is also important when engaging skeptical clinicians from other oncologic-based specialties. Many IO treatments are supported by level I evidence. However, there are important questions that are either incompletely answered or have yet to be studied. A greater understanding of tumor biology and its potential impact on the efficacy of therapies and the potential synergistic interplay of IO and immuno-oncology are exciting topics for further study.


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Interventional oncology (IO) is a subspecialty of interventional radiology (IR) that has added a number of therapeutic options for cancer patients, with a positive impact on survival demonstrated in certain conditions. The treatment of hepatocellular carcinoma (HCC), either as destination therapy or as a bridge to liver transplantation, is the most widely accepted intra-arterial IO intervention. However, the relative role of IO in metastatic disease is less defined. This article reviews the state of evidence for IO in the management of metastatic liver disease, primarily focusing on arterial therapy.

DIFFERENCES IN TREATING PRIMARY AND METASTATIC DISEASE

HCC is increasing in incidence and remains chemo-resistant. More than 50% of patients with HCC will undergo transarterial chemoembolization (TACE) during the course of their treatment. Significant improvement in overall survival (OS) has been demonstrated in separate randomized controlled trials in 2002, as well as in a later meta-analysis. Further technical refinements such as use of C-arm CT, development of better microcatheters, and referrals of advanced patients for sorafenib or hospice have continued to improve survival. As a result, OS to 4 years for patients treated with destination therapy is being increasingly reported, with some studies showing even longer OS rates. TACE is well represented in guidelines from a variety of organizations, including the National Comprehensive Cancer Network (NCCN) and the American Association for the Study of Liver Diseases.

In contrast, virtually all unresectable hepatic metastatic disease is principally treated with combinations of chemotherapy, biologic therapy, and immunotherapy. These therapeutic decisions are a result of large-scale, prospective, randomized trials that developed well-defined algorithms for a number of tumor types. An example of this approach is the addition of oxaliplatin or irinotecan to the previous standard therapy for colorectal cancer, 5-fluorouracil and leucovorin. OS nearly tripled following development and evaluation of these agents. Similarly powered prospective randomized trials had not been performed using arterial-directed therapy for metastatic disease until recently. As a result, most interventional radiologists treat metastatic disease from colon cancer, breast cancer, or most other metastatic tumors after systemic therapy options are exhausted or limited. The lone exception has been neuroendocrine tumors (NETs), in which embolotherapy of lower-grade tumors has been the standard of care.

COLORECTAL CANCER

In contrast to the previously described medical oncology trials, IO research has been largely retrospective, single-center reviews of 100 patients or fewer. Two of the largest prospective randomized clinical trials in IO were published in 2016 and 2017, respectively. Both studies centered on the addition of yttrium-90 (Y-90) to standard first-line chemotherapy for metastatic colorectal cancer. The SIRFLOX study compared the addition of Y-90 resin microspheres to standard first-line oxaliplatin-based chemotherapy (FOLFOX) plus or minus bevacizumab versus chemotherapy alone, with a primary endpoint of progression-free survival (PFS). In total, 530 patients were randomized. Although hepatic PFS was superior in the study group (20.5 months vs 12.5 months for controls; P = .002), overall PFS was not improved with the addition of Y-90 (10.2 months vs 10.7 months for...
controls; \( P = .43 \)). Toxicities were evaluated using the National Cancer Institute Common Toxicity Criteria, version 3.0. Complications directly attributable to Y-90 (gastric/duodenal ulcer and ascites) were significantly more common in the study group (\( P < .05 \) for both). Treatment-associated mortality was similar between groups.

OS results from SIRFLOX were combined with two other similarly structured prospective randomized phase 3 trials (FOXFIRE and FOXFIRE Global). All trials completed 2 years of patient follow-up with 1,103 total patients. In the combined cohort, 549 patients received FOLFOX and 554 received FOLFOX plus Y-90. There was no increase in median OS with the addition of Y-90 to first-line chemotherapy (22.6 months vs 23.3 months in the control group; \( P = .61 \)). The absence of an increase in OS was despite complete or partial responses in 72% of Y-90 recipients versus 63% in the chemotherapy only arm (\( P = .012 \)). Mirroring the SIRFLOX PFS outcomes, patients receiving Y-90 plus chemotherapy had a lower incidence of initial intrahepatic progression (31% vs 49% in the chemotherapy alone arm). Despite the hepatoprotective effect of adding Y-90, initial progresive disease outside the liver was more common in the Y-90 plus chemotherapy group (54% vs 36% of the control group). Grade 3 or greater toxicities in the Y-90 arm were significantly higher than the chemotherapy control group (54% vs 36% of the Y-90 plus chemotherapy group; \( P < .05 \)).

NEUROENDOCRINE TUMORS

Embolization has been a mainstay treatment for patients with liver-dominant neuroendocrine metastases with symptoms related to hormone production or bulk secondary to large-volume disease distending the liver capsule. A variety of embolic techniques have been successfully used, including Y-90, chemoembolization with Lipiodol (Guerbet LLC) or drug-eluting beads, and bland embolization using particles alone. Direct prospective comparison of these techniques has not been performed. A multicenter retrospective study included patients receiving Y-90, Lipiodol chemoembolization, and bland embolization. Among the three groups, there was no significant difference in hepatic PFS or OS. Bland embolization resulted in significantly more grade 3 toxicity from pain, whereas Y-90 resulted in more hepatic dysfunction.

Potential issues with liver dysfunction in long-term survivors with NETs treated with Y-90 have been retrospectively evaluated in two articles. Su et al reported on 54 patients with > 2 years of follow-up, with 39 patients undergoing bilobar treatment. In the bilobar therapy group, 22 patients had imaging findings suggestive of cirrhosis and eight patients developed clinical signs of hepatic decompensation. Although the Y-90 treatment may have contributed, six of the eight patients had progressive liver disease with more than 50% volume replacement and/or had received hepatotoxic chemotherapy. Another study by Tomozawa et al evaluated 93 patients with NETs who underwent Y-90 radioembolization. In this group, 45 patients had bilobar treatment. A total of 52 patients underwent imaging and completed more than 1 year of follow-up, including 29 patients from the bilobar Y-90 cohort. Of these patients, five (17%) had ascites, six (21%) had hepatic surface nodularity suggesting cirrhosis, six (21%) had splenomegaly, and two (7%) had varices.
Patients with low-grade mid-gut NETs can live more than 10 years from the time of initial locoregional therapy. This patient group is distinctly different compared to the majority of patients referred for Y-90. In salvage treatment of many other types of metastatic disease, 1 year of survival is considered a benchmark of clinical success. Postprocedural recovery from Y-90 is easier than from chemoembolization and embolization. However, the cirrhotic-like changes identified years after Y-90 therapy raise questions about the appropriateness of this therapy in patients with expected multiyear survival.

Another issue with the use of Y-90 in patients with NETs is when peptide receptor radionuclide therapy with lutetium-177 (Lu-177) dotatate is being considered. This agent is FDA approved in the United States for mid-gut NETs and is administered intravenously four times at 1-month intervals.8 The long-term effects and toxicities of Lu-177 remain to be defined in patients with survival exceeding 10 years. Some practitioners may use Lu-177 after failure of conservative measures to avoid hepatic toxicity. In our practice, patients with mid-gut NETs who may be eventual candidates for Lu-177 referred for arterial bridging therapy are currently being treated with Lipiodol chemoembolization to avoid potential toxicity from Y-90 and the postembolization pain of bland embolization. Additionally, this leaves the liver radiation naive to facilitate Lu-177 at a later time. In patients with a significant disease burden who are older or otherwise frail, we still consider using Y-90.

ACQUIRING BETTER DATA

The published literature for other metastases is not impactful enough to merit inclusion in the NCCN guidelines. Regarding arterial therapy, IR is fairly represented for HCC and NET. The only representation of interventional therapy in any NCCN guideline is for treatment of metastatic colorectal carcinoma, but it is mentioned as a footnote after 10 pages of systemic chemotherapy options. Currently, IR treatment is not mentioned in the guidelines for breast, melanoma, sarcoma, pancreatic, or lung cancer. Most interventional radiologists have treated these types of cases, albeit in small numbers, and anecdotal successes are frequently discussed. These experiences do not translate to impactful publications. Additionally, on a case-by-case level, getting insurance preapproval is frequently challenging, leading to issues in treating patients in a timely manner.

Prospective trials are expensive, difficult to design and recruit patients to, and have no guarantee of success. To improve trial success, a more cost-effective strategy gaining traction is the collection of registry data as a preliminary determination of efficacy and target population. In such a setting, individual sites can enroll, treat, and follow patients using local guidelines. Imaging response and toxicity are pooled among the centers. Another reason is that the cost-effective research data enable more centers to participate in some aspects of research, as many lack the resources for a prospective trial.

RESIN Liver Tumor Registry

Launched in 2015, the RESIN liver tumor registry includes 40 sites and continues to grow. Driven by real-world evidence, community and academic centers are nearly equally represented. This approach is unique in IR research given that approximately 80% of operators self-identify as community or private practice physicians, whereas most research is driven by the smaller number of practitioners in academic centers. RESIN also includes 10 of 27 NCCN and 16 of 49 National Cancer Institute comprehensive cancer centers. As of August 2018, over 1,100 patients have been enrolled. To date, enrollment is split nearly equally by community and nonuniversity hospital centers. Given the broad cross-section of included practitioners, RESIN will provide insight into areas of IR practice that have not previously been studied.

Of the 1,100 enrolled patients, nearly two-thirds have metastatic disease. Within this subpopulation, approximately two-thirds remained on systemic therapy while undergoing Y-90 treatment. These data will be an area of great interest moving forward—a key to acceptance of IO therapies by other cancer specialists will include incorporation of locoregional therapies into existing paradigms. When Y-90 or chemoembolization is used as monotherapy for salvage at the end stage of disease, patients frequently have declining performance status, a predictor of short survival. A principal use of Y-90 for metastatic colorectal cancer is after failure of first- and second-line therapy. A number of patients have been treated with Y-90 while on biologic therapies. Identifying combinations of Y-90 and biologic or immunotherapies with clinical benefit and low toxicity will provide valuable background data to identify prospective future trials. Indeed, several trials are currently exploring combination therapies involving immunotherapy and transarterial embolization.

CONCLUSION

Intra-arterial therapy continues to be used for patients with liver-dominant metastatic disease that is refractory to systemic therapy. The EPOCH trial may potentially identify an earlier role for Y-90 in colorectal cancer patients. With the approval of Lu-177 for NETs,
treatment options for these patients before receiving radionuclide therapy are evolving. Our current practice is shifting back toward Lipiodol chemoembolization to maximize long-term therapeutic options. Other tumors have less robust data. Hopefully, the RESIN registry will provide useful data identifying optimal treatment scenarios for these malignancies.

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RECENT MAJOR CHANGES

Indications and Usage (1) 4/2014
Doseage and Administration, Dosage Guidelines (2.1) 4/2014
Contraindications (4) 4/2014
Warnings and Precautions (5) 4/2014

INDICATIONS AND USAGE

Lipiodol is a prescription oil-based radiopaque contrast agent indicated for:
• hysterosalpingography in adults
• lymphography in adult and pediatric patients
• selective hepatic intra-arterial use for imaging tumors in adults with known hepatocellular carcinoma (HCC)

DOSAGE AND ADMINISTRATION

Use a glass syringe to draw and inject Lipiodol. (2)
• Hysterosalpingography
  Inject increments of 2 mL of Lipiodol into the endometrial cavity until tubal patency is determined; stop the injection if the patient develops excessive discomfort. Inject with radiologic monitoring.
• Lymphography
  Inject Lipiodol into a lymphatic vessel with radiologic monitoring.
  Adults:
  • unilateral lymphography of the upper extremities: 2 to 4 mL
  • unilateral lymphography of the lower extremities: 6 to 8 mL
  • penile lymphography: 2 to 3 mL
  • cervical lymphography: 1 to 2 mL
  Pediatric patients:
  • Inject a minimum of 1 mL to a maximum of 6 mL according to the anatomical area to be visualized. Do not exceed 0.25 mL/kg.
• Selective Hepatic Intra-arterial Use
  Inject 1.5 to 15 mL of Lipiodol slowly under continuous radiologic monitoring. Do not exceed 20 mL total dosage.

DOSAGE FORMS AND STRENGTHS

Each mL of Lipiodol contains 480 mg Iodine organically combined with ethylesters of fatty acids of poppy seed oil. (3)

CONTRAINDICATIONS

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• Lipiodol Selective Hepatic Intra-arterial Injection is contraindicated in: the presence of dilated bile ducts unless external biliary drainage was performed before injection.

WARNINGS AND PRECAUTIONS

• Pulmonary and cerebral embolism: avoid use in patients with severely impaired lung function, cardiorespiratory failure or right-sided cardiac overload (5.1)
• Hypersensitivity reactions: avoid use in patients with a history of sensitivity to other iodinated contrast agents, bronchial asthma or allergic disorders because of an increased risk of a hypersensitivity reaction to Lipiodol (5.2)
• Exacerbation of chronic liver disease (5.3)
• Thyroid dysfunction (5.4)

ADVERSE REACTIONS

Adverse reactions caused by Lipiodol include hypersensitivity reactions, pulmonary embolism, pulmonary dysfunction, exacerbation of liver disease, procedural complications, abdominal pain, fever, nausea, vomiting, and thyroid dysfunction. (6)

To report SUSPECTED ADVERSE REACTIONS, contact GUERBET LLC at 1-877-729-6679 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch (6)

Nonsurgical Local Therapies for Lung Metastases and Non–Small Cell Lung Cancer

Clinical data examining the use of available treatment options for selected lung cancer cases.

BY THIERRY de BAERE, MD

Today, nonsurgical local therapies are available for patients with non–small cell lung cancer (NSCLC) and oligometastatic lung disease from various cancers. The two most common approaches are thermal ablative therapies delivered through percutaneously inserted applicators under imaging guidance or stereotactic ablative radiotherapy (SABR) delivered via external beam radiation. Various thermal ablation technologies, such as radiofrequency (RF) ablation, microwave (MW) ablation, and cryoablation, are used for the treatment of pulmonary tumors.1-7 The lung has some organ-specific differences favoring thermal ablation, including insulation and low electric conductivity due to the lung tissue around the tumor,3 which necessitates a larger volume of ablation in the lung than in subcutaneous tissues or the kidneys for a given quantity of RF current.8

RF ablation before resection demonstrated 100% necrosis at histopathology for nine of nine lung metastases treated.9 Lung RF ablation for NSCLC and lung metastases demonstrated a median rate of complete ablation of 90%, with a variability from 38% to 97% in a review of 17 of the most recent publications.10 Selecting tumors that measure < 2 cm provides a 78% to 96% rate of complete ablation.3,11-14 Safety margins matter, as demonstrated by a 96% complete ablation rate when the ratio is ≥ 4 in between the area of RF ablation-induced ground-glass opacity and the targeted tumor.3 Ground-glass opacity margins receiver-operator characteristic analysis confirmed the ablation zone as a predictor of recurrence, with an estimated cutoff of 4.5 mm for a specificity of 100% (ie, no local recurrence).15

In addition to RF ablation, MW ablation, cryoablation, and electroporation have become available for lung ablation. MW ablation has not demonstrated clear superiority over RF ablation in clinical practice,16 even though it works at higher temperatures with lower convective cooling close to large vessels, as demonstrated in animal studies.17,18 Electroporation is a nonthermal ablation process that has shown excellent preservation of vulnerable lung structure in animals,19,20 but the local recurrence rate was a disappointing 61% in a multi-institutional study of 20 patients with lung metastases.21 Cryoablation utilizes multiple probe treatments in which the tip of the probe creates ice crystals that destroy the tissue/tumor. Reports on cryoablation of lung metastases demonstrated a promising 94.2% local tumor control rate at 12 months in a phase 2 multicenter study that included 40 patients with 60 metastases.22

CLINICAL RESULTS

Lung Metastases

Local treatment of lung metastases with surgical resection has been accepted since the late 1990s, with actuarial 5-, 10-, and 15-year survival rates of 36%, 26%, and 22%, respectively, reported in an international registry.23 However, the evidence for surgical metastasectomy remains controversial because the practice has never been subjected to a randomized trial, carries a risk of permanent loss of function, and has major cost implications.24 RF ablation for oligometastatic lung disease was evaluated in studies by both Lencioni et al and de Baere et al, which included 61 and 566 patients with 15 months and 35.5 months of follow-up, respectively.14,25 Lencioni et al reported 1-year local efficacy in 88% of patients. The study by de Baere et al was one of the largest reports to date of lung RF ablation for metastases, evaluating 566 patients with 1,037 lung metastases, including 52% with primary tumors of the colon or rectum and tumors at a median diameter of 15 mm...
(range, 4–70 mm). Four-year local efficacy was 89%. Overall survival (OS) rates at 1, 2, 3, 4, and 5 years were 92.4% (standard error [SE], 1.2), 79.4% (SE, 1.9), 67.7% (SE, 2.4), 58.9% (SE, 2.8), and 51.5% (SE, 3.3), respectively. Location of primary disease, disease-free interval, size > 2 cm, and metastases ≥ 3 were associated with OS in multivariate analysis.

A low complete local treatment rate of 37.5% in 32 tumors measuring up to 3.5 cm was achieved when RF ablation was guided by peroperative manual palpation during thoracotomy without any imaging guidance. This result emphasizes the pivotal role of CT guidance and multiplanar reconstruction imaging due to the high contrast ratio related to the air density of the lung parenchyma, tissue density of the target tumor, and metallic density of the RF needle, which allows for optimal visualization and likely improved accuracy in targeting treatment delivery.

The 62-month OS rate reported in a large series of RF ablation for lung metastases is within the range of the best results obtained by surgical resection, with the same predictive factors for OS. Surgical resection of lung metastases resulted in a 5-year OS rate of 53.5% in a multicenter registry by Iida et al.4 and between 27% and 68% in a meta-analysis by Pfannschmidt et al.5 In lung metastatic patients, the challenge of disease control is more linked to the occurrence of new metastases distant from the ablation site as opposed to local recurrences. This was demonstrated with a 4-year progression-free survival rate of 13.1%, a 72.4% rate of patients who showed progression in the lungs, and retreatment up to four times with RF ablation in 24% of initially treated patients, resulting in a 4-year control rate of lung metastatic disease of 44.1%.6 Thermal ablation is well tolerated and spares the lung parenchyma, as demonstrated by absence of post-RF ablation lung changes in respiratory function testing, which allows for high feasibility of retreatment when needed.7,8

Repeatability is definitively higher with thermal ablation than with any other local treatment, including surgery or SABR. Drawbacks of SABR are difficulties in treating several metastases in the same region with overlapping irradiation fields and near impossibility of retreatment with SABR for local progression after a previous SABR treatment. Reports of large series of SABR for lung metastases are scarce. One available large series that included 321 patients with 587 metastases (201 colorectal cancer metastases) treated with SABR over 13 years reported a median OS of 2.4 years (95% confidence interval [CI], 2.3–2.7) with 80%, 39%, 23%, and 12% OS at 1, 3, 5, and 7.5 years, respectively.9 Three deaths were possibly procedure related. Of note, SABR is considered a noninvasive technique even though some complications are directly related to the treatment, but they are often difficult to attribute to SABR because they usually occur late after treatment, with as most postradiation toxicity. Moreover, it has been reported that placement of a fiducial marker was needed for SABR in 105 patients with tumors in the lung, resulting in 33.3% pneumothoraces (major, 13.3%; minor, 20%), 30.5% small peritumoral alveolar hemorrhage, and 2.9% of major bleeding,10 which makes SABR invasiveness close to that of RF ablation in terms of pneumothoraces.

Non–Small Cell Lung Cancer

In NSCLC, surgical resection is the current standard of care for patients with stage I or II disease due to the benefit of associated lymphadenectomy. However, imaging-guided ablation and radiation therapy are increasingly offered as alternative therapies in nonsurgical candidates.11-15 Impressive 1-, 3-, and 5-year OS rates of 97.7%, 72.9%, and 55.7%, respectively, have been reported in 44 consecutive patients treated with RF ablation for 51 recurrent NSCLC after surgery (mean diameter, 1.7 ± 0.9 cm).16 The 1-, 3-, and 5-year OS rates were 100%, 79.8% (95% CI, 61.8%–97.8%) and 60.5% (95% CI, 32.5%–88.4%) in patients with tumors measuring < 3 cm. However, nearly 50% of reported deaths during follow-up of NSCLC treated with RF ablation were not related to cancer progression but rather comorbidities.17,18

Recent results of local ablation challenge surgery for stage IA and IB lung cancer combined with MW ablation showing similar therapeutic effect compared with lobectomy for stage I NSCLC but with fewer complications and less pain in a propensity-matched analysis.19 Although randomized studies are needed, they will be difficult to complete due patient refusal to be randomized. Indeed, two independent, randomized, phase 3 trials of SABR in patients with operable stage I NSCLC (STARS and ROSEL) ended early due to slow enrollment. Pooled data from these trials, including 58 patients with T1/T2a (< 4 cm)N0M0, operable NSCLC who were randomly assigned in a 1:1 ratio to SABR or lobectomy with mediastinal lymph node dissection or sampling, showed an estimated 3-year OS of 95% (95% CI, 85%–100%) in the SABR group compared with 79% (95% CI, 64%–97%) in the surgery group (hazard ratio, 0.14; 95% CI, 0.017–1.190; log-rank P = .037).20

Of note, Lam et al reported findings from a the National Cancer Database analysis of RF ablation versus stereotactic body radiation therapy (SBRT) in stage IA and IB NSCLC.21 The two cohorts were composed of 4,454 SBRT cases and 335 RF ablations and reported equivalent OS both for the unmatched groups and in
the propensity score–matched groups, with 1-, 3-, and 5-year OS rates of 85.5%, 54.3%, and 31.9% in the SBRT group versus 89.3%, 52.7%, and 27.1% in the RF ablation group (P = .835), respectively.

Pre- or postablation systemic therapy might improve outcomes of thermal ablation, and combination therapy has reported favorable outcomes.22-44 The excellent tolerance of thermal ablation might render such a combination highly feasible, while only 70% of patients who undergo perisurgical systemic therapies are able to complete the scheduled regimen after lung surgery due to the long recovery time.45

CONCLUSION

Thermal ablation for lung tumors is gaining popularity because the rate of complete ablation is close to 90% for tumors up to 2 cm. Thermal ablation allows for excellent short- and long-term tolerance, which is an asset in metastatic disease that will likely recur and need retreatment as well as in NSCLC, which is often seen in patients with comorbidities that prevent surgery. The clinical data examining the use of available treatment options for lung metastases cannot favor surgery over thermal ablation for tumors < 2 cm.  

25. de Baere T, Auperin A, Deschamps F, et al. Radiofrequency ablation is a valid treatment option for lung metastasis in patients with comorbidities that prevent surgery. The clinical outcomes of thermal ablation, and combination therapy has reported favorable outcomes.22-44 The excellent tolerance of thermal ablation might render such a combination highly feasible, while only 70% of patients who undergo perisurgical systemic therapies are able to complete the scheduled regimen after lung surgery due to the long recovery time.45

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Treatment options for localized renal cell carcinoma (RCC) include radical nephrectomy (RN), partial nephrectomy (PN), thermal ablation (TA), and active surveillance. There is a lack of randomized controlled trials (RCTs) comparing these different RCC treatments. This article reviews current guidelines and supporting evidence behind treatment recommendations, with a particular focus on treatment of stage T1a RCC (tumors ≤ 4 cm and confined to the kidney).

**AMERICAN UROLOGICAL ASSOCIATION GUIDELINE UPDATE**

TA for RCC has gained recognition as a viable treatment alternative to PN. In 2017, the American Urological Association (AUA) published updated guidelines stating that “physicians should consider TA as an alternate approach for management of cT1a renal masses < 3 cm in size.” The AUA guidelines further stated that a percutaneous approach to TA is preferable to a surgical approach (including laparoscopic and open) to minimize complications. Limitations of existing studies underlying the recommendations were acknowledged. Other notable statements regarding TA from the updated AUA guidelines included recognition of cryoablation and radiofrequency (RF) ablation as equivalent, the recommendation that renal biopsies should be performed prior to ablation to provide pathologic diagnosis and guide surveillance after TA, and the recommendation that patients be counseled prior to ablation regarding an increased chance of residual disease or local recurrence after primary ablation compared with PN and that a recurrence or residual disease can be treated with repeat ablation.

The primary support for TA as a treatment for stage T1a RCC in the updated 2017 AUA guidelines is a meta-analysis by Pierorazio et al. This analysis of interventions to manage renal masses that were suspected localized RCC included 107 studies and provided strength of evidence for each comparison, ranging from moderate or low to insufficient. A total of 60 studies provided data on one or more oncologic outcome: cancer-specific survival (CSS), metastasis-free survival, or local recurrence-free survival (LRFS). The majority of the studies were cohort studies and the single RCT did not address ablation. The median follow-up time was 48.6 months for the ablation groups and 60 months for RN and PN. The majority of tumors in the analysis were T1, and no ablations were performed on T2 tumors. The median tumor size was 2.9 cm for PN and 2.5 cm for TA. CSS was between 95% and 100% for all treatment modalities; however, the strength of evidence for comparing PN and TA for T1 RCC was rated as “low,” with high inconsistency and many limitations in the available studies.

Overall survival (OS) was lower in patients who underwent TA versus PN; however, this was attributed to patients in the TA group being older and having more comorbidities. TA patients were median age of...
66.6 years versus 60.1 years for PN and had significantly lower mean glomerular filtration rates before treatment. Metastasis-free survival ranged from 90.5% to 100%, with no difference between PN and TA (moderate strength of evidence). There was a statistically significant difference in LRFS between PN and TA with a moderate strength of evidence. A median of 99.4% of PN patients were recurrence free at the end of follow-up versus a median of 89.3% in TA patients; however, this difference was not significant after patients underwent a second TA treatment. TA had superior perioperative outcomes when compared with PN with moderate strength of evidence. TA was associated with decreased median hospital length of stay and decreased median blood loss. The rates of urine leak, acute kidney injury, and other urologic complications were higher in PN versus TA (median percentage urine leak and acute kidney injury was 0% for both in TA and 2.6% and 2.1% for PN, respectively). Renal function outcomes were similar between PN and TA with low strength of evidence. Compared with PN, TA offers similar CSS with fewer complications for stage T1a RCC.

**SEER CANCER REGISTRY**

Two studies based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) cancer registry have been published to date. Zhou et al published a SEER study comparing TA and PN in stage T1a RCC with a primary outcome of OS and secondary outcome of CSS.3 Patients diagnosed with stage T1a RCC from 2004 to 2013 were identified. Of 4,592 patients treated for stage T1a RCC, 809 (18%) underwent TA and 3,783 (82%) underwent PN. OS was inferior with TA compared with PN both in the pooled and propensity-matched populations, although the difference in OS was less in the matched population. Patients treated with TA were an average of 10 years older than patients treated with PN (mean age, 67.7 years vs 57.2 years), and the mean tumor size was larger with TA compared with PN (24.6 mm and 23.7 mm). After propensity matching, there was no statistically significant difference in CSS with TA as compared with PN. Limitations of the study included the limitations of the SEER database such as nonreporting of potentially confounding variables including histologic subtype, number of tumors, tumor location, tumor proximity to adjacent structures, other medical conditions, as well as other treatment complications.3

Talenfeld et al used the SEER data to compare TA with PN and RN for stage T1a RCC.4 Patients ≥ 66 years of age with stage T1a RCC treated between 2006 and 2011 were included. The patients were followed for a median of 42 months for RCC-specific survival. Compared with PN and RN patients, TA patients were older and sicker and had higher baseline renal insufficiency and increased cardiovascular disease. These differences were less significant between the TA and RN groups than between the TA and PN groups, confirming that similar to other analyses, patients chosen for PN tended to be healthier overall. Five-year OS was inferior with TA compared with PN (77% vs 86%), but differences in absolute survival with TA and PN were not substantial (95% vs 98%). Despite confounding variables, there was no statistically significant difference in CSS between TA and PN (although there was a trend toward significance). Five-year CSS was similar between TA and RN. As seen in other analyses, perioperative outcomes were worse in the PN group. Patients who underwent PN had statistically significant higher rates of acute renal failure and other nonurologic complications in the first 30 days after the procedure. Acute renal failure occurred in <3% of patients undergoing TA and 7% of patients undergoing PN. Nonurologic complications, which included pulmonary embolism, deep vein thrombosis, noncardiogenic shock, respiratory failure, pneumonia, hematoma, and abscess, were 29% in PN group and 6% in TA group.4

**AMERICAN SOCIETY FOR CLINICAL ONCOLOGY GUIDELINES**

The 2017 American Society for Clinical Oncology (ASCO) guidelines on the management of small renal masses reflects the increasingly recognized role of TA.5 Although the ASCO guidelines recommend PN for patients in whom treatment is indicated and tumor is appropriate for PN, the guidelines also state that “percutaneous TA should be considered for patients who possess tumors such that complete ablation will be achieved.” As with the AUA guidelines, biopsy is recommended before or at the time of ablation to guide surveillance. The ASCO recommendation was backed by “intermediate-quality” evidence and given as a “moderate” strength recommendation.5

One of the studies cited is a large cohort study by Thompson et al that analyzed 1,803 patients in the Mayo Clinic Renal Tumor Registry treated for stage T1 RCC between 2000 and 2011.6 There were 1,424 stage T1a patients. Of these, 1,057 underwent PN, 180 underwent RF ablation, and 187 underwent cryoablation. OS at 3 years for PN, RF ablation, and cryoablation was 95%, 82%, and 88%, respectively. There was no statistically significant difference in 3-year LRFS by treatment type (98% for all three groups). Five-year metastasis-free survival was excellent for all three treatment
groups (93%–100%). Limitations of the study included that it was a retrospective analysis; had heterogeneous patient follow-up, which was more robust for PN; and the median imaging after TA was < 3 years. As with other studies, selection bias of younger and healthier patients for PN was noted.6

CONCLUSION

There has been accelerated use of TA in the management of stage T1a RCC in the last decade, which is reflected by improved treatment outcomes and recognition of TA as a reasonable treatment option by AUA and ASCO guidelines. TA is associated with better perioperative outcomes and fewer complications when compared with surgery. Although local recurrence rates appear to be higher in patients treated with TA, this can be overcome with repeat TA treatment. Patients who undergo PN tend to have better OS; however, this effect may be attributable to PN patients being younger and healthier at baseline.

To date, there are no RCTs comparing TA with the established surgical treatments for stage T1a RCC. As a result, the level of evidence for TA for treatment of stage T1a RCC ranges from moderate to insufficient. In general, the paucity of level 1 data is an acknowledged weakness of interventional oncology. With respect to RCC, ongoing clinical trials are focused on biological agents and drugs, stereotactic radiation/radiosurgery, ablation-assisted surgery, gene- and protein-expression analysis, and assessment of other biomarkers. There is need for level 1 data directly comparing TA, PN, RN, and active surveillance with assessment of OS in addition to other clinical and cancer outcomes, with attention to histologic subtype, tumor location, tumor proximity to adjacent structures, and ablation modality.

The 2017 AUA guidelines, which support consideration of TA as an alternative to PN for cT1a RCC < 3 cm in size, have created the opportunity for an RCT. Based upon the data to date, it is expected that such a study could be pivotal for TA. Only once inherent biases in patient selection are eliminated and the treatments and their outcomes can be fully assessed will the role of TA in the management of stage T1a RCC be clearly established and accepted by the larger oncology community.


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Metastatic Osseous Disease: Current Interventional Oncology Treatment Options

Minimally invasive therapies such as embolization, thermal ablation, and consolidative therapy can be used for locoregional control and pain palliation or can be combined for a synergistic effect.

BY STEVEN YEVICH, MD, MPH

The musculoskeletal system is the third most common site of metastatic disease after the liver and lung, with > 50% of cancer patients developing osseous metastases.1–4 The associated morbidity with bone metastases includes pain, pathologic fracture, hypercalcemia, and neurologic deficits.5–7 Minimally invasive therapies can relieve pain or provide locoregional control that translates into improvements in quality of life, decreased opioid dependence, improved mobility, and lower overall health care costs.7–11 Treatment challenges can be attributed to the high variability in disease presentation. For example, the etiology of pain may be a result of structural bone instability, lost integrity of muscle and tendon insertions, cytokine-mediated tumor-associated inflammation, increased intraosseous pressure caused by tumor growth or increased vascularity, periosseous stretching, or extrinsic pressure on adjacent nerves and muscles.3,12 To meet these challenges, multiple interventional oncology (IO) techniques have been developed.

Common IO procedures used to treat osseous metastases include tumor embolization, thermal ablation, vertebral augmentation, and cementoplasty.13 In addition, image guidance software has expanded the capability to stabilize pathologic fractures with percutaneous placement of cannulated screws. The procedural approach is often tailored to individual tumor biology, location, vascularity, and size. This article reviews the current IO treatment options for osseous metastases. Supportive literature and potential future research directions are discussed for each treatment separately.

EMBOLIZATION

Embolization can be an effective treatment for hypervascular tumors as a presurgical adjunct to facilitate resection or as an independent pain palliative measure.

Figure 1. A 55-year-old man with metastatic RCC of the right iliac and sacral bones (arrows) (A, B). Initial treatment with particle embolization resulted in improvement in resting pain (C). After embolization, mechanical pain with weight bearing persisted. Consolidative treatment with percutaneous screw fixation and cementoplasty significantly relieved mechanical pain (D–F).
Pain palliation occurs through impedance of locoregional osteolysis and reduction of tumor volume, which in combination, downregulates cytokine-mediated tumor-associated inflammation, decreases intraosseous pressure and periosteal stretching, and relieves tumor compression on surrounding tissues and neurovascular structures. Multiple embolic materials can be used, including embolic beads, gelatin sponge, coils, or liquid agents such as ethanol, glue, or Onyx (Medtronic). Microsphere or microparticulate embolization is typically performed to achieve distal occlusion, although the choice of embolic agent depends on operator experience, degree of tumor vascularity, tumor-feeding artery size, presence of arteriovenous shunting, and amount of collateral blood flow to the surrounding musculoskeletal tissue.

Several retrospective reviews support embolization as a pain palliative treatment, with most studies examining treatment of renal cell carcinoma (RCC) and thyroid metastases. A small case series of nine patients with metastatic RCC reported mild to marked immediate pain relief that lasted 1 to 6 months in all patients. A more recent case series of 21 patients with metastatic RCC treated with embolization reported a > 50% decrease in narcotic use after treatment at 36 of 39 sites with a mean duration of 5.5 months. In another study, embolization of 41 vascular thyroid metastases improved clinical symptoms in 59% (24/41) of treated lesions for at least 1 month without tumor progression. To the author’s knowledge, the largest retrospective review examined 309 embolization procedures in 243 cancer patients with painful bone metastases from renal, thyroid, breast, and lung cancer, reporting a > 50% reduction in Visual Analog Scale (VAS) and decreased analgesic use in 97% of procedures for a mean duration of 8.1 months. Onset of pain relief occurred within 2 weeks of embolization for all studies.

Limitations and challenges exist in the current IO literature. The type of embolic agent employed is highly variable, as are the tumor types and subtypes. Subtle embolization outcome may be affected by the degree of vascularity, the amount of collateral circulation, or presence of intratumoral arteriovenous shunting. Furthermore, the location and size of osseous metastases may present confounding variables when assessing palliative outcome. For example, large lytic tumors located in weight-bearing bone may continue to cause pain due to structural instability from bone erosion. Lastly, the use of other treatments such as radiation therapy or chemotherapy combined with embolization is not uniformly reported. The combination of embolization and concomitant external therapy may have synergistic effects. For example, Eustatia-Rutten et al noted an increased mean duration of pain palliation from 6 to 15.5 months in patients with thyroid cancer who underwent embolization combined with either radioiodine or external irradiation therapy. A similar finding was seen in a smaller cohort of five patients with metastatic thyroid carcinoma treated with embolization and concomitant radioiodine treatment.

Future embolization studies may benefit from a prospective design with a larger patient cohort, considering the aforementioned limitations and challenges in study design. In addition, the value of chemoembolization has not been thoroughly evaluated for osseous metastases. Koike et al evaluated the palliative treatment effect of either chemoembolization or bland embolization for 24 bone metastases from multiple different primary tumor types in 18 patients, although no direct comparison was offered. Recent successes in the treatment of multiple cancer types with systemic or intratumoral injection of immunotherapy raise the question of whether concomitant treatment with embolization or endovascular injection plus embolization might augment local treatment or initiate an abscopal effect.

THERMAL ABLATION

Thermal ablation encompasses a variety of percutaneous technologies that deliver energy within a defined ablation zone to achieve irreversible tumor cellular death. The main thermal energy sources for ablation are radiofrequency, microwave, and cryotherapy (Figure 2). Thermal ablation can be used for pain palliation regardless of tumor size, although ablation of the interface between tumor and bone is usually sufficient to engender some symptomatic relief. The mechanism of pain relief is thought to occur through the destruction of sensory fibers supplying the periosteum, decompression of tumor volume, eradication of cytokine-producing tumor cells, and inhibition of osteoclast activity. In addition, thermal ablation may provide an effective means for local control. The selection of ablation modality depends on physician experience, patient comorbidities, and tumor location and size.

Prospective trials have evaluated the effect of radiofrequency ablation and cryoablation on pain palliation of metastatic osseous disease. In a multicenter clinical trial for treatment of painful bone metastases, percutaneous radiofrequency ablation was found to decrease the worst pain score from 7.9 to 1.4 out of 10 at 24-week follow-up. A subsequent single-arm prospective trial in 55 patients with a single painful bone metastasis demonstrated significant decrease in pain intensity and improved mood at 1- and 3-month
follow-up.\textsuperscript{30} Evaluation of percutaneous cryoablation for the treatment of 69 painful bone metastases from multiple different primary cancers performed in a multicenter observational clinical trial reported significant pain relief in 75% of patients, with overall mean worst pain score decreasing from 7.1 to 5.1 out of 10 at 1 week and to 1.4 out of 10 at 6 months.\textsuperscript{31} No significant difference was found when comparing palliative response in patients who underwent radiation prior to ablation. Across the majority of retrospective and prospective reports, patients can expect to have a lasting 2- to 3-point reduction in worst VAS pain score within the first week following ablation, regardless of the modality.

In comparison, the majority of studies that have evaluated the application of percutaneous thermal ablation for the local control of bone metastases are retrospective with small patient cohorts. Cryoablation of metastatic RCC to the bone in seven patients with 13 bone lesions (mean tumor size, 4.8 cm) demonstrated local control in 12 of 13 lesions with a median follow-up of 16 months.\textsuperscript{32} A more recent retrospective cryoablation study in 40 patients with 50 RCC metastases (mean tumor size, 3.4 cm) reported an overall local control rate of 82% (41/50 lesions) with a median follow-up of 35 months.\textsuperscript{33} A single-institute retrospective study of cryoablation of 40 patients with 52 tumors from multiple primary cancer types with a median size of 2 cm (range, 0.6–7.5 cm) reported local control in 87% (45/52 lesions) at a median follow-up of 21 months and with a median disease-free survival of 7 months.\textsuperscript{34} The largest retrospective cohort evaluated 89 patients treated for 122 metastatic lesions of multiple primary cancer types with either radiofrequency ablation (74 lesions) or cryoablation (48 lesions), reporting a 1-year local control rate of 67% after a median follow-up of 22.8 months.\textsuperscript{35}

Future studies of thermal ablation should include further evaluation of local control across different tumor types. The effects of ablation on sclerotic metastases by ablation modality should be assessed, as sclerotic lesions may be more responsive to cryoablation. In addition, the role of thermal ablation in oligometastases should be examined, as should the potentiation of palliative effects with radiation therapy.\textsuperscript{36}

Recent advances in imaging can be further explored to improve procedural safety and efficacy. Ablation margins may be difficult to accurately identify using CT, regardless of the modality employed, because of the high density of osseous structures. Advanced CT capabilities, such as metal artifact reduction algorithms and dual-energy CT, may help delineate the ablation margins or provide a means to facilitate computer-assisted detection. Further development of MRI-compatible bone needles may expand the potential for MRI-guided cryoablation.\textsuperscript{38-40}

**CONSOLIDATIVE TECHNIQUES**

Consolidative techniques for pain palliation include vertebral augmentation, cementoplasty, and percutaneous screw fixation. Vertebral augmentation and cementoplasty reinforce structurally weakened or fractured bones with the injection of bone cement through a percutaneously placed needle. The physical properties of bone cement (typically poly[methyl methacrylate] [PMMA]) provides resistance to the axial compressive forces experienced during weight-bearing activities. Vertebral augmentation encompasses the treatments of vertebroplasty and kyphoplasty,\textsuperscript{31} while cementoplasty or osteoplasty applies the same techniques outside of the spine.\textsuperscript{41} Percutaneous screw fixation...
OsteoCool™

The OsteoCool™ RF Ablation System is cooled radiofrequency ablation technology. OsteoCool™ offers simultaneous, dual-probe capabilities for the treatment of bone tumors, letting you treat patients confidently and consistently.

OptiSphere™

OptiSphere™ embolization spheres allow you to experience reliable hypervascular tumor embolization with the benefit of resorbable spheres. OptiSphere™ offers patients an alternative embolic with comparable results to a permanent embolic.

1. Based on animal testing, data on file. Pre-clinical studies are not indicative of human clinical outcomes.

Indications and Risks

The OsteoCool™ RF Ablation System is intended for the palliative treatment in spinal procedures by ablation of metastatic malignant lesions in a vertebral body. It is also intended for coagulation and ablation of tissue in bone during surgical procedures, including palliation of pain associated with metastatic lesions involving bone in patients who have failed or are not candidates for standard therapy.

Risks of the system include damage to surrounding tissue through iatrogenic injury as a consequence of electrosurgery; pulmonary embolism; nerve injury including thermal injury, puncture of the spinal cord or nerve roots potentially resulting in radiculopathy, paresis, and paralysis. The OsteoCool™ bone access kits are indicated for percutaneous access to bone.

Risks of embolization procedures may include non-target embolization and post-embolization syndrome.
describes the minimally invasive placement of metallic screws across a bone lesion to stabilize or prevent a pathologic fracture. The addition of metallic screws improves resistance to torque and tension stresses and provides a complement to the compression resistance of PMMA. Although the basic principles of internal fixation have been developed in surgical subspecialties, advanced IO imaging capabilities and expertise have driven a paradigm shift to extend this valuable palliative treatment option to nonsurgical candidates.

**Vertebral Augmentation**

Vertebral augmentation has been extensively supported for the treatment of metastatic disease. The selection of vertebroplasty versus kyphoplasty is at the preference and discretion of the physician operator and based on operator experience, degree of vertebral body compression, and presence of tumor extension through the posterior vertebral body into the epidural space. In evaluating vertebroplasty results in 868 patients treated for vertebral body compression fractures of both metastatic and osteopenic etiology, patients with metastatic disease reported satisfactory pain results and decreased opiate analgesic dose requirements (83% vs 78%). A multicenter randomized controlled trial of 134 patients with malignant vertebral compression fractures that compared kyphoplasty versus nonsurgical management reported a significant decrease in pain score in the treated group, without any significant change in the nontreated group.

Future directions to improve the effects of vertebral augmentation include evaluation of combination treatment with thermal ablation to potentiate pain palliative effects. Current small cohort reports remain inconclusive. A recent study has suggested that combination treatment improves safety by decreasing complications from cement leakage.

**Cementoplasty**

Cementoplasty has shown a sustained palliative effect in patients with extraspinal metastatic bone disease (Figure 3). A retrospective review of the use of cementoplasty for 65 lesions in the pelvis or extremities demonstrated a significant decrease in VAS pain score from 8.19 to 3.02 at 3-month follow-up. In a retrospective review of cementoplasty for 140 painful metastatic bone lesions outside of the spine in 105 patients, a significant pain reduction was seen in 91% of patients with a mean VAS pain score improvement from 8.7 to 1.9 after a median follow-up of 9 months.

Future directions to improve the effects of extraspinal cementoplasty also include broader evaluation of the combination of a locoregional control method and cementoplasty. Several small case series have evaluated the feasibility of combination ablation and extraspinal cementoplasty, although to the author’s knowledge, no direct comparison has been performed to evaluate pain palliative outcomes between combination treatment and cementoplasty alone.

**Percutaneous Screw Fixation**

Percutaneous screw fixation is predominantly performed for pain palliation or prevention of pathologic fractures in the pelvic ring or femoral neck (Figure 1). A recent retrospective review reported significant pain relief in the treatment of 20 pathologic fractures with mean VAS pain score improvement from 8 to...
2.5 out of 10.43 In addition, the same study supported the application for the prevention of impending pathological fracture with the treatment of 45 locations in the pelvis and femoral neck.44 Similar results have been confirmed in other small retrospective reviews.44–46,44,96

Future studies should continue to collect data on longer-term outcomes. In addition, the role for preventive treatment of potential impending pathologic fractures outside of the femoral bones may prove beneficial for patients with large painful metastases that have yet to result in fracture. Lastly, combination treatments that include locoregional therapies such as thermal ablation or embolization may synergistically extend the duration of pain relief.

CONCLUSION

Multiple valuable IO techniques have been advanced for the treatment of osseous metastases. Clinical success often relies on a tailored approach to address the challenges posed by the wide variability in metastatic tumor biology, location, size, and vascularity. The treatments can provide either locoregional control or pain palliation and may be combined for synergistic effect. Future research to cement the role of IO in bone relies on the continued collection of prospective large-cohort data.

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Pancreatic Cancer Interventions: The End of the Beginning?

Experts weigh in on the current roles of various therapeutic options for pancreatic cancer.

Current Evidence for IRE and Other Minimally Invasive Options

BY GOVINDARAJAN NARAYANAN, MD; THOMAS SCAGNELLI, MD; AND MEHUL DOSHI, MD

The diagnosis of pancreatic cancer carries a dismal prognosis with an 8% overall 5-year survival rate, and there is a desperate need for viable treatment options to improve the survival and quality of life for these patients. Due to the vague nature of the symptoms, nearly 80% of patients present with stage III locally advanced pancreatic cancer (LAPC) or stage IV metastatic pancreatic cancer (MPC) at the time of diagnosis. In patients who have undergone potentially curative resection, the 5-year survival is only 20%.1

The combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil (5-FU), and leucovorin (FOLFIRINOX) is first-line therapy for LAPC and MPC patients with an Eastern Cooperative Oncology Group performance status score of 0 or 1 and a median overall survival (OS) of 11.1 months.2 In patients with MPC, combination therapy of gemcitabine and nanoparticle albumin-bound (nab)-paclitaxel is considered a standard therapy based on the results of the MPACT trial.3

The lack of significant improvement in the OS in pancreatic cancer poses a challenge in identifying additional treatment options. Over the years, several minimally invasive options such as radiofrequency (RF) ablation, microwave (MW) ablation, and cryoablation, as well as noninvasive options including high-intensity–focused ultrasound, stereotactic body radiation therapy (SBRT), magnetic resonance (MR)–guided linear accelerator, and photodynamic therapy have been added to the list of treatment options. Irreversible electroporation (IRE) is the newest ablation technology that has been used in the treatment of pancreatic cancer with promising results. Although surgery and chemotherapy continue to be the current standard of care depending on the presentation of the disease, the following sections present a brief review of IRE and a few other minimally invasive treatment options for pancreatic cancer.

RADIATION TREATMENT

The role of radiation for both resectable pancreatic cancer and LAPC remains controversial. Two randomized European studies (EORTC4 and ESPAC5) concluded that radiation therapy offers no benefit after pancreatic cancer surgery. Currently, a trial sponsored by the National Cancer Institute (NCT01013649) is studying the role of adjuvant radiotherapy in addition to gemcitabine versus gemcitabine alone after resection. For LAPC, the LAP07 trial did not show a survival advantage when radiotherapy was added after a 4-month chemotherapy induction period.6

The benefit of chemotherapy versus chemoradiotherapy was also addressed in the phase 3 FFCD-SFRO study from France, in which patients with LAPC were randomly assigned to receive either gemcitabine alone...
or an intensive induction regimen of chemoradiotherapy with 5-FU plus cisplatin followed by gemcitabine maintenance treatment. In this study, gemcitabine alone was associated with a significantly increased OS rate at 1 year compared with chemoradiotherapy (53% vs 32%; hazard ratio, 0.54; 95% confidence interval [CI], 0.31–0.96; *P* = .006). This study was stopped before the planned accrual, because an interim analysis revealed that patients in the chemoradiotherapy arm had a lower survival rate.

Thus, the role of upfront chemoradiotherapy in the setting LAPC is still undefined. The role of SBRT following gemcitabine monotherapy in patients with LAPC has been examined in phase 2 trials. This regimen was associated with low toxicity and favorable rates of freedom from local disease progression.

**ABLATION THERAPIES**

RF ablation in pancreatic cancer has been mostly used in an open surgical approach. Early clinical applications in the pancreas were associated with unacceptably high rates of morbidity (0%–40%) and mortality (0%–25%). One of the largest prospective series of 100 patients with pancreatic cancer treated by RF ablation was reported by Girelli et al. The median OS from the date of diagnosis was 20 months. In this study, half of the patients were first treated with RF ablation and then with chemoradiotherapy, systemic or intra-arterial chemotherapy, or a combination of these. In the other half of the patients, RF ablation was performed after other primary treatments, leading to possible selection bias.

Data on cryoablation and MW ablation are limited. Lygidakis et al reported on the feasibility, safety, and efficacy of MW ablation in 15 patients with LAPC. Partial necrosis was achieved in all patients, with no major procedure-related morbidity or mortality.

**PERCUTANEOUS IRE OF THE PANCREAS**

IRE is a predominantly nonthermal ablative technique that uses high-voltage DC current to cause irreversible nanoscale defects in the cell membrane, disrupting homeostasis and leading to cellular apoptosis. The role of IRE in the pancreas was initially studied in a swine model by Charpentier et al and was concluded to be a safe method for pancreatic tissue ablation.

Narayanan et al established the feasibility of treating pancreatic cancer percutaneously in the first human series, which included data on 14 patients treated with IRE using a percutaneous technique. This was followed by a retrospective review of 50 patients with LAPC treated with percutaneous IRE. The primary objective was safety and the secondary objective was OS. All 50 patients had previous chemotherapy and 30 (60%) had previous radiation therapy. There were no treatment-related deaths and no 30-day mortality. Median OS was 27 months from the time of diagnosis (95% CI, 22.7–32.5 months) and 14.2 months from the time of IRE (95% CI, 9.7–16.2 months). Patients with tumors < 3 cm had a significantly longer OS than those with tumors > 3 cm (33.8 vs 22.7 months from the time of diagnosis and 16.2 vs 9.9 months from IRE). The study concluded that percutaneous IRE was safe in the treatment of pancreatic cancer.

The survival results of this study are similar to surgical data on IRE from Martin et al. This study reported results from a cohort of 200 patients with stage III LAPC treated with IRE. In this cohort, 150 patients underwent IRE alone and 50 had pancreatic resection plus IRE for margin enhancement. All patients underwent induction chemotherapy, and 52% received chemoradiation therapy as well for a median of 6 months (range, 5–13 months) before IRE. Median OS was 24.9 months (range, 4.9–85 months). This study concluded that for patients with LAPC (stage III), the addition of IRE to conventional chemotherapy and radiation therapy results in substantially prolonged survival compared with historical controls. These results suggest that ablative control of the primary tumor may prolong survival.

The prospective PANFIRE study reported a 12-month median time to local progression after percutaneous IRE (95% CI, 8–16 months). The median OS was 11 months from IRE (95% CI, 9–13 months) and 17 months from diagnosis (95% CI, 10–24 months). The study included patients with a median tumor size of 4 cm, and 52% underwent chemotherapy prior to IRE. Leen et al published their experience with the use of IRE for LAPC in 75 patients. Median OS and progression-free survival after IRE were 27 and 15 months, respectively, and 30 months from the time of diagnosis.

**DISCUSSION**

Percutaneous IRE of the pancreas is minimally invasive and usually only requires a single treatment with a short hospital stay compared to other local treatment options. It is not limited by the heat sink effect of thermal ablation and its nonthermal nature makes it safe for use near vasculature. Although IRE is a relatively new ablation modality, it has been shown to be safe and effective in the treatment of pancreatic cancer, and the similarity of the results from several studies from different centers seem to suggest a survival benefit. Although many of these studies are single-center retrospective studies, this is a positive signal that requires further confirmation.
attention. The ongoing CROSSFIRE trial (NCT02791503) is a randomized controlled phase 3 trial comparing the outcome of FOLFIRINOX plus IRE with FOLFIRINOX plus MR-guided SBRT on OS for patients with LAPC. Given the dearth of treatment choices in pancreatic cancer, this randomized controlled trial (RCT) and future multicenter registries will help further define the impact of IRE in the management of pancreatic cancer.


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STEREOSPECTACTIC BODY RADIATION THERAPY FOR LOCAL CONTROL AND TREATMENT

BY SHALINI MONINGI, MD; MAUREEN ALIRU, PHD; AND JOSEPH M. HERMAN, MD, MSC, MSHCH, FACR

Pancreatic carcinoma is one of the most lethal cancers in the United States and is currently the fourth leading cause of cancer death in both men and women. Although the only curative option is complete surgical resection, only selected patients are eligible at the time of presentation, leading to a 5-year survival rate of < 10%.

Recent advances in technology have led to multiple therapeutic options with improved clinical outcomes. Given the natural history of the disease, the best management for patients with pancreatic cancer occurs at the multidisciplinary level with collaboration between gastroenterologists, oncologists, pathologists, surgeons, radiologists, radiation oncologists, dieticians, palliative care experts, and social workers.¹

RADIOTherapy

A recent autopsy series showed that approximately 30% of patients with pancreatic cancer die from local disease, emphasizing the importance of local treatment, such as radiotherapy, for these patients.² Radiotherapy has hist-
torically been part of the multimodality treatment, along with chemotherapy and possible surgical resection for patients with pancreatic cancer. The goal of radiotherapy is to improve local control of disease, delay progression to distant metastatic disease, and alleviate symptoms secondary to obstruction from the tumor (eg, pain).

External beam radiotherapy has been traditionally delivered to the tumor and surrounding lymph nodes at risk in a long-course fashion over 5 to 6 weeks at doses ranging from 50 to 54 Gy. Recent advances in imaging and radiotherapy have allowed for improved treatment planning and dose escalation techniques. This has led to the development of SBRT, which allows for more precise delivery of radiation to the target tumor. SBRT has become the standard of care in several malignancies such as lung, brain, spine, and liver cancer1 and has shown promise in treating intra-abdominal tumors, including pancreatic cancer.4

**ADVANTAGES OF SBRT**

SBRT has multiple advantages and is becoming widely adopted in the United States for patients with pancreatic cancer. This type of treatment allows for dose-escalated radiation to be aimed precisely at the tumor while minimizing dose to surrounding, radiosensitive organs at risk (eg, the duodenum).

SBRT allows for shorter treatment times (3–5 days vs 25–30 days) with standard radiotherapy techniques. These allow for quicker implementation of systemic treatment options, milder side effects, and deposition of higher biologically effective doses within the tumor that result in improved tumor control.5 Additionally, it has been shown to improve pain while preserving quality of life and increasing the likelihood of a margin-negative resection due to the ability to escalate dose near the tumor vessel interface.6 SBRT also result in less lymphopenia than conventional radiotherapy and can be more easily combined with systemic therapy and immunotherapy.7,9

The delivery of SBRT requires close monitoring and advanced technological measures to properly and safely deliver an escalated dose to pancreatic tumors. Image guidance for treatment typically includes the placement of gold fiducial markers prior to treatment and a four-dimensional CT simulation scan with management of respiratory motion for treatment planning and imaging, along with cone-beam CT scans during treatment delivery. Advanced treatment planning allows for some heterogeneity in plans and modification of dose to successfully minimize dose to surrounding organs such as the duodenum and stomach.

**OTHER LOCAL THERAPIES**

Due to the importance of local control, other types of therapies have emerged recently for patient with localized pancreatic cancer. Recent studies have investigated endoscopy-driven therapeutic options for treatment of pancreatic cancer such as endoscopic ultrasound-guided RF ablation, cryo/thermal ablation, photodynamic therapy, ethanol ablation, high-intensity focused ultrasound, and brachytherapy.10 As in the case of fiducial placement for SBRT, the endoscopist can deliver brachytherapy or ablate the tumor directly under endoscopic guidance. Although a number of studies have demonstrated the potential of this technique,11 RCTs are still needed to establish treatment benefit and survival. There is current pilot study evaluating the safety and tolerability, along with efficacy as secondary endpoint, of an implantable radioactive phosphorus source that locally deposits dose to the tumor.12

**CONCLUSION**

SBRT and techniques that allow for enhanced local dose deposition show potential for treatment and local control of pancreatic tumors. Due to their localized nature, these techniques allow for additional treatment modalities to control systemic disease without added toxicity usually encountered with chemoradiation. SBRT can be used to palliate pain and allow for treatment breaks from systemic chemotherapy, leading to improvements in quality of life for patients with localized and oligometastatic disease.13,14

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Advances in Surgical Treatment

BY JORDAN M. CLOYD, MD, AND TIMOTHY M. PAWLIK, MD, MPH, PhD

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related mortality in the United States, with only 9% of patients alive 5 years after diagnosis.¹ A major reason for this dismal prognosis is that the vast majority of patients are diagnosed with metastatic disease and median survival at this stage is typically < 1 year. Clearly, earlier diagnosis and advances in systemic therapies are needed to improve the outcomes of these patients. However, even patients with localized PDAC who are able to undergo curative-intent therapies will likely experience local or distant relapse and ultimately die of cancer-related recurrence.²

The poor outcomes of these patients suggest that surgery is necessary (the long-term survival rate of patients with PDAC who do not undergo resection is negligible) but not sufficient for curative-intent treatment. Indeed, several large RCTs have confirmed that patients who undergo systemic chemotherapy³-⁵ and possibly chemoradiotherapy⁶ after resection of PDAC experience improved OS compared to those who do not. These observations have led to a renewed focus on multimodality therapy as part of a multidisciplinary treatment strategy for PDAC. As innovations in systematic treatments, radiation protocols, and interventional techniques continue to occur, these therapies will likely be complementary to, not in lieu of, surgical resection. Given the recent advances that have occurred in the surgical care of patients with PDAC, surgery will continue to play an important role in its multidisciplinary management.

PERIOPERATIVE OUTCOMES

One of the most important advances in the surgical care of patients with PDAC has been significant improvements in perioperative outcomes. Indeed, although morbidity rates have remained high, largely due to postoperative pancreatic fistula and delayed gastric emptying, rates of 30- and 90-day mortality have significantly decreased over the past several decades.⁷,⁸ The reasons for these marked improvements are likely multifactorial and include better patient selection and preoperative optimization, advances in biliary stenting and nutritional intervention, centralization of patients to high-volume institutions, improvements in surgical technique and minimization of intraoperative blood loss, as well as advances in perioperative care and enhanced recovery after surgery protocols. However, one of the most important developments in the perioperative care of patients undergoing pancreatectomy has been the ability to “rescue” patients who experience major complications. Advances in endoscopic, interventional, and medical therapies have enabled the safe resolution of complex postoperative complications at experienced centers. The rates of “failure to rescue” have declined in recent years, which has been considered a major contributor to improved postpancreatectomy outcomes.⁹

MINIMALLY INVASIVE APPROACHES

Over the past 2 decades, improvements in technology, training, and surgeon experience have facilitated the expansion of minimally invasive approaches to pan-
creatic surgery. In general, this has allowed for the traditional benefits of minimally invasive surgery, including the use of smaller incisions, reduced postoperative pain, and shortened recovery time, to be extended to patients with pancreatic neoplasms. Minimally invasive approaches (ie, laparoscopic or robotic) for left-sided pancreatic tumors (ie, distal pancreatectomy) have become well accepted.\(^{10}\) Given the equivalence in short-term (ie, margin status, lymph node yield) and long-term oncologic outcomes between open and minimally invasive approaches, there are no absolute contraindications to minimally invasive distal pancreatectomy, including its use for PDAC.\(^{13}\)

The recently published LEOPARD trial was the first RCT to compare minimally invasive versus open distal pancreatectomy (21.3% had PDAC) in a patient-blinded fashion and found less blood loss, increased operative time, reduced length of hospital stay, and faster functional recovery among patients who underwent minimally invasive surgery.\(^{14}\)

Minimally invasive pancreatoduodenectomy (MIPD) for tumors in the head of the pancreas are more challenging, and a significantly greater learning curve exists. In fact, early nationwide analyses demonstrated a significantly higher postoperative mortality rate among patients undergoing MIPD, although this difference seemed to be driven by low-volume hospitals performing MIPD early in their experience.\(^{15}\) More recent studies limited to high-volume centers suggest similar perioperative and short-term oncologic outcomes.\(^{16}\) Nevertheless, as the currently available literature is limited to highly selected retrospective series, more research is needed, especially on long-term outcomes. Importantly, the LEOPARD-2 trial will randomize patients with pancreatic tumors requiring pancreatoduodenectomy to either a minimally invasive or open approach.\(^{17}\)

NEOADJUVANT THERAPY

Because multimodality therapy is known to benefit all patients with PDAC and yet the rate of receipt of adjuvant chemotherapy following pancreatectomy is relatively low, an alternative approach is to administer nonsurgical therapies prior to pancreatectomy. Theoretical benefits of this approach include the early treatment of micrometastatic disease presumed present in nearly all patients, facilitation of a margin-negative resection, selection of a physiologically robust population of patients with biologically favorable tumors, and assurance that all patients who undergo surgery will receive all intended components of therapy. On the other hand, some worry about local progression occurring during neoadjuvant therapy, which may preclude an opportunity to resect the primary tumor. Other disadvantages include the potential for toxicity and deconditioning prior to pancreatectomy and the logistical challenges of obtaining durable biliary decompression, confirming a tissue diagnosis, and coordinating multidisciplinary care.

Regardless of the advantages and disadvantages, neoadjuvant therapy is increasingly utilized\(^{18}\) and is now established in practice guidelines for both borderline-resectable\(^{19}\) and resectable cancers.\(^{20}\) Multiple studies have confirmed that neoadjuvant chemotherapy or radiation therapy does not worsen postoperative outcomes, and in fact, preoperative chemoradiation may actually lead to a lower rate of postoperative pancreatic fistula.\(^{21}\) Although RCT data supporting the use of neoadjuvant therapy are still lacking, a recent intention-to-treat meta-analysis found that neoadjuvant therapy was associated with improved OS compared to upfront surgery for patients with resectable and borderline-resectable PDAC.\(^{22}\) In addition, a 25-year review of outcomes from a single institution that routinely administers preoperative therapy prior to pancreatectomy has demonstrated consistently improved long-term outcomes over time.\(^{23}\)

LOCALLY ADVANCED PDAC

Perhaps one of the most important advances in the surgical treatment of patients with PDAC has been the ability to offer surgical resection to more patients. Because the pancreas has an intimate relationship with retroperitoneal structures, locally advanced cancers often abut or even invade critically important vasculature such as the superior mesenteric vein, superior mesenteric artery, or branches of the celiac axis. Historically, vascular involvement, whether diagnosed radiographically prior to surgery or at the time of laparotomy, was considered a contraindication to surgical resection; these patients were then treated solely with chemotherapy and radiation. However, over the past several decades, developments in cross-sectional imaging, preoperative staging, and vascular surgical techniques have led investigators to again consider the merits of vascular resection at the time of pancreatectomy. In fact, pancreatectomy with venous resection now comprises a substantial proportion of operations for PDAC at high-volume centers, and a large series suggests no worse survival in patients who underwent margin-negative resection.\(^{24}\)

Equally important has been the observation that with the increased use of neoadjuvant chemotherapy and radiation therapy, margin-negative resections are
attainable in a significant proportion of patients with locally advanced cancers that were previously deemed to be unresectable. This is important because a large series suggests that arterial resections in the setting of pancreatectomy for PDAC are associated with poor short- and long-term outcomes. Therefore, utilizing nonsurgical therapies in a neoadjuvant fashion in order to sterilize the surgical margins has been an important breakthrough in increasing the number of patients who are surgical candidates.

The management of patients with locally advanced and truly unresectable PDAC remains controversial, especially following an extended period of systemic chemotherapy that has ensured the absence of progressive metastatic disease. The LAP07 trial randomized such patients to ongoing systemic chemotherapy versus chemoradiation and found no difference in OS but improved local control in those who underwent radiation. An alternative surgical option is IRE, which is a form of nonthermal ablation typically delivered at the time of surgery for unresectable tumors, although it can also be utilized for margin accentuation as well. Although the evidence for IRE remains limited, results from select centers suggest acceptable morbidity rates and the potential for improved local control and possibly OS compared to nonoperative treatments.

CONCLUSION

The incidence of PDAC is increasing in the United States while improvements in the survival durations of patients diagnosed with PDAC are occurring slowly. Future improvements in patient outcomes will likely require disruptive advances in systemic therapies based on an enhanced understanding of tumor biology. Technologic developments enabling earlier detection and improved delivery of novel therapies will likely be required. Nonetheless, for patients with localized cancers, the delivery of safe and timely surgical resection will remain a critical component of multimodality cancer care. Further improvements in patient selection, surgical technique, and perioperative care should only increase the number of patients who are candidates for curative-intent resection as well as enable their expedited return to intended oncologic therapies following surgery. Ongoing advances in minimally invasive approaches, vascular reconstruction techniques, and ablative strategies will expand the surgical options for patients with PDAC.

Literature Review of Current Novel and Combination Therapies

BY MOHAMMAD ALASKER, MD, AND DAVID K. IMAGAWA, MD, PHD, FACS

Pancreatic cancer remains a very challenging disease to treat. It is the second most common gastrointestinal malignancy and fourth most common cause of cancer deaths in the United States.1 Surgical resection offers the only chance for cure. Unfortunately, fewer than one-fifth of patients have resectable disease at the time of diagnosis; as many as 30% present with stage III LAPC. By definition, these tumors are unresectable if they involve the celiac trunk, the superior mesenteric artery, or both. With the difficulty in surgical resection of these tumors, novel techniques such as RF ablation, MW ablation, cryoablation, and IRE have been developed in an attempt to reduce tumor burden and increase survival as well as quality of life. Historically, LAPC patients are expected to survive 6 to 11 months from the time of diagnosis with standard chemotherapy and/or radiotherapy treatment.3 Recent trials have demonstrated improvement in survival using ablative techniques.

RF ABLATION
RF ablation has been used in multiple organs with a successful track record with solid tumors such as the liver, kidney, and bone.4 However, the soft, friable nature of the pancreas discouraged many physicians from attempting the procedure for pancreatic tumors. Elias et al treated two patients with metastatic kidney tumors of the pancreas.5 Both patients died of necrotizing pancreatitis after RF ablation. Hadjicostas et al successfully performed the procedure in four LAPC patients; all four patients were alive at the 12-month follow-up, suggesting an improvement in survival.6 Additionally, one patient who was on long-term morphine for intractable pain reported significant pain relief postprocedure.

MW ABLATION
MW ablation is a technique that induces excitation of water molecules with electromagnetic waves of frequencies between infrared and radio waves to produce coagulative necrosis. Compared to RF ablation, MW ablation can produce larger areas of ablation more quickly and with fewer applications.7,8 Vogl et al demonstrated the therapy’s feasibility in a study on 20 patients in which they achieved a mean ablation volume of 7.8 cm³ with only two cases of mild complications involving postablation pain.8 Carrafello et al evaluated the procedure in 10 patients, and although they observed both improved quality of life and a 1-year survival of 80%, minor complications included one case of mild pancreatitis, one case of pancreatic pseudocyst, and one gastroduodenal pseudoaneurysm.9

CRYOABLATION
Cryoablation has a few advantages over the other ablation techniques including visibility of the ice ball on ultrasound, allowing precise control of the ablation zone both intraoperatively and percutaneously, as well as its ability to preserve cellular architecture.7 Xu et al treated 49 patients with LAPC using combined cryotherapy and I¹²⁵ seed implantation. Six patients suffered acute pancreatitis, although all cases were controlled with medical management.10 Twenty patients underwent repeat procedures; however, the authors concluded that because the procedure was minimally invasive and median survival was 16.2 months, cryotherapy with I¹²⁵ seed implantation should be the recommended therapy of choice for LAPC.

NEOADJUVANT AND INTRAOPERATIVE THERAPY
Massachusetts General Hospital completed two prospective studies exploring the possibility of aggressive neoadjuvant therapy in borderline-resectable pancreatic cancer and LAPC. In the borderline-resectable setting, patients received a combination of the FOLFIRINOX regimen for eight cycles followed by chemoradiation and surgery. At the time of resection, those with close or positive margins received 10 Gy of radiation; patients who remained unresectable received 15 Gy. At 2 years, 72% of patients who underwent resection were still alive; 56% of patients across both groups were alive at 2 years posttreatment, suggesting favorable survival.

In the second trial, losartan was added to FOLFIRINOX in the hopes of improving chemotherapy delivery and improving resectability of otherwise unresectable LAPC. After neoadjuvant therapy, 52% of patients underwent R0 resection and 91% of those patients were alive at 2 years; across all patients, 2-year survival was 65%. The results of these two trials suggest that early, intensive, neoadjuvant therapy can improve resectability in LAPC, and intraoperative radiotherapy is a feasible option to prolong survival in patients whose tumors remain unresectable. The University of California, Irvine Medical Center will soon be conducting a phase 3 trial for intraoperative radiotherapy in pancreatic cancer.
IRREVERSIBLE ELECTROPORATION

IRE is the newest technique in the treatment of LAPC and unresectable pancreatic tumors. It is a nonthermal technique that uses high-voltage DC energy to permanently destabilize cell membranes and induce apoptosis of cells adjacent to an electrode. Although some heat is generated by the pulse of electrical energy, it is not enough to destroy surrounding structures such as ducts and blood vessels. From 2009 to 2011, Martin et al performed a pilot evaluation of the use of IRE in the treatment of LAPC. Thirty-six patients were treated with IRE by an open approach and one was treated percutaneously. At 90 days, there was one mortality from complications related to portal vein thrombosis on postprocedure day 25, and no patient showed signs of pancreatitis or fistula formation. Nine patients experienced mild complications associated with the surgical approach. No patients developed local recurrence.

Additional multiple large-scale trials of IRE-based treatment of LAPC combined with the current standards of care have succeeded in demonstrating the procedure’s survival benefit. Huang et al combined gemcitabine or titanium-silicate-1-based chemotherapy and radiofrequency ablation for patients suffering from pancreatic cancer. The procedure’s survival benefit. Huang et al combined gemcitabine or titanium-silicate-1-based chemotherapy and radiofrequency ablation for patients suffering from pancreatic cancer.

INTROOPERATIVE RADIATION AND OTHER NOVEL SURGICAL TECHNIQUES

Novel ablative and neoadjuvant techniques have only just begun to see widespread adoption in the treatment of LAPC. IRE in particular has already demonstrated promise, perhaps beyond that of other techniques in only its first decade of study. As the technology progresses and these techniques become more integrated into the standard current medical management, as well as other novel therapies such as gene therapy, there is great potential for prolonged survival and positive outcomes for patients suffering from pancreatic cancer.
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Technical Dos and Don’ts of Radiation Segmentectomy and Same-Day Y-90 Treatment

Contemporary radioembolization techniques and the approaches to avoid.

BY AHMED GABR, MD; ROBERT J. LEWANDOWSKI, MD, FSIR; RIAD SALEM, MD; AND AHSUN RIAZ, MD

Over the past 15 years, yttrium-90 (Y-90) radioembolization has emerged as an effective locoregional treatment for hepatocellular carcinoma (HCC) and hepatic metastases. The PREMIERE trial demonstrated a significantly longer time to progression in HCC patients treated with radioembolization when compared to conventional transarterial chemoembolization (> 26 vs 6.8 months, respectively). As technologies evolve, it is important to optimize clinical efficacy, cost, and patient comfort/convenience. Radiation segmentectomy is one such advancement and is now considered an ablative tool that is potentially curative. Same-day radioembolization is a concept that serves to minimize the number of procedures, reduce cost, and maximize patient convenience. This article discusses the dos and don’ts of radiation segmentectomy and same-day Y-90.

RADIATION SEGMENTECTOMY

Radiation segmentectomy involves superselective administration of a high (ablative) dose (≥ 190 Gy) of radiation to the segmental or subsegmental arterial branch feeding the tumor-bearing segment. Studies have shown that the clinical efficacy of radiation segmentectomy can be considered potentially curative.

Dos of Radiation Segmentectomy

• Do select appropriate patients and understand the goal of therapy (eg, definitive, bridge to resection, bridge/downstage to liver transplantation, curative, palliative).
  – Solitary HCC: Solitary HCC with tumor size < 8 cm and/or sparing one or two adjacent segments may be amenable to radiation segmentectomy.
  – Unilobar multifocal HCC (modified radiation lobectomy): Patients with multifocal unilobar tumors can undergo radiation segmentectomy to the index (largest) lesion while lobar or subselective Y-90 can be administered to the rest of the tumors. This may allow the patient to become a resection candidate with treatment of unilobar disease and hypertrophy of the contralateral lobe. Multiple treatment sessions may be needed to achieve this effect.
  – Bilobar multifocal HCC: Treatment of bilobar multifocal HCC is difficult. Radiation segmentectomy may still have a role, and definitive treatment may have to be split into multiple treatment sessions.
  – Metastatic disease: Selective treatment can be considered for hypervascular metastatic disease (metastatic neuroendocrine tumors, cholangiocarcinoma). Given the nature of metastatic colorectal cancer (hypovascular and presence of micrometastatic disease), lobar infusions may be necessary. Liver dysfunction in the setting of hepatic metastatic disease is associated with poor survival and in most cases excludes patients from locoregional therapeutic options. The concept of radiation segmentectomy needs to be further studied in the setting of metastatic disease.
  – Hyperbilirubinemic patients: Because superselective radiation segmentectomy spares the normal non–tumor-bearing parenchyma, it can be performed in hyperbilirubinemic patients whose bilirubin has remained relatively stable in the month(s) leading to treatment. This selective treatment can allow patients to be bridged or downstaged to liver transplantation.
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• Do meticulous mapping to confirm that the tumor is being supplied by the vessels that supply the tumor-bearing segment(s), and do cone-beam CT to confirm enhancement of all the tumor(s) within the segment(s). Consider interrogating alternate supply if this is not the case.
  – Planning angiography should identify an angiographically isolatable tumor with two or fewer hepatic segments being perfused at the intended catheter position.
  – Prophylactic coil embolization is rarely performed in patients undergoing radiation segmentectomy using Y-90 glass microspheres, given their low rate of reflux in addition to the selectivity of the method of administration.\(^{12}\)
  – A cone-beam CT run during planning angiography is essential to provide a three-dimensional (3D) delineation of the perfused liver tissue bearing the tumor.\(^{13}\)
  – Macroaggregated albumin (MAA) administration for lung shunt fraction (LSF) estimation is preferably done by lobar injection, either within the right hepatic artery or left hepatic artery,\(^{14}\) to minimize catheterization of the segmental artery.

• Do plan treatment after understanding the vascular anatomy and degree of subselection.
  – Y-90 vials are administered either in the artery supplying the two tumor-bearing segments (eg, anterior right hepatic for tumors located at segments 5/8 or posterior right hepatic artery for segment 6/7 tumors) or the segmental arterial branch feeding the tumor-bearing segment.\(^{6}\) Sometimes further selection of a subsegmental branch clearly supplying the tumor is also possible.
  – Radiation segmentectomy implies applying a target dose of > 190 Gy to the HCC-bearing segment (doses > 190 Gy were associated with higher rates of complete pathologic necrosis).\(^{15}\) Administered doses to the tumor-bearing segment can be as high as 500 to 1,000 Gy depending on the volume of the injected segment(s).
  – Comparing pretreatment cone-beam CT to posttreatment cross-sectional imaging can help identify incomplete tumor targeting.\(^{13}\)

• Do recognize that multiple vessel catheterizations may be necessary to perform radiation segmentectomy for segment I (caudate) tumors.\(^{16}\)

**Don’ts of Radiation Segmentectomy**

• Don’t give very high doses to tumors around the porta hepatitis. Segment IVb radiation segmentectomy may incur risk of biliary injury.
  
• Don’t forget to interrogate extrahepatic parasitized vasculature, such as internal mammary arteries or inferior phrenic arteries, if dome tumor(s) do not respond on the follow-up imaging.

**SAME-DAY RADIOEMBOLIZATION**

Same-day Y-90 is where planning angiography, technetium-99m MAA scanning, and Y-90 treatment are performed in a single-day session.\(^{17,18}\) Same-day Y-90 can be performed in patients with solitary or multifocal disease. However, patients who are candidates for radiation segmentectomy are the best candidates for same-day Y-90, provided that MAA results are consistent with the pretreatment estimates of LSF. Advantages of same-day Y-90 include convenience for the patient and the care team. Additional reasons to consider this approach include:

• Selected patients who initially present with borderline T2/T3 tumors would benefit from immediate treatment in order to be listed for transplant or maintain their status on the transplant waiting list.\(^{18}\)
  
• The hepatic artery is difficult to access (eg, abdominal aortic dissection requiring complex access)
  
• General anesthesia is required for the procedure because the patient is unable to tolerate moderate sedation
  
• The patient lives a long distance and cannot come twice for treatment (eg, international patients)

**Dos of Same-Day Y-90**

• Do meticulous pretreatment imaging review and clinical workup. Reviewing recent high-quality cross-sectional abdominal imaging (multiphasic CT or preferably MRI) is essential. After identifying the best treatment approach for the detected tumor(s) (typically solitary tumors are the best candidates for same-day Y-90), 3D images of the tumor-bearing parenchyma are reconstructed from the delayed venous phase. These images are used to estimate the hepatic volume that will be receiving treatment.

• Do perform dosimetry, keeping various treatment options in mind. Target dose is estimated by the nuclear physicist using volumetric data obtained from the 3D reconstruction of baseline cross-sectional imaging. As a precaution, all HCC patients are considered to have an LSF of 10%, while liver...
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metastases would have an LSF of 5%. Based on those estimates, a provisional lung dose can be calculated, and accordingly, multiple Y-90 vials can be ordered for the specific treatment day with the desired dose. Ordering multiple vials ensures: (1) on-site adjustment of doses in the event of any surprisingly elevated LSF values, (2) an effective strategy in treating watershed tumors for which a single vial will result in incomplete treatment (residual tumor), and (3) possible treatment of multiple vessels (in cases of tumors having supply from different arteries).

- Do plan the details of the treatment day.
  - Patients are prepped only once, and the femoral sheath remains in place until the end of the treatment session.
  - Planning angiography is performed and tumor-perfusing blood vessels are identified, followed by a cone-beam CT that confirms the volume of perfused liver parenchyma and tumor. Coil embolization of any aberrant blood supply can be performed in this session as well. Only 5% of patients who undergo same-day Y-90 also receive coil embolization in the setting of glass microspheres. 
  - Once target vessels have been identified, a small dosage of 2 mCi of MAA is administered and then the patient is transferred to nuclear medicine for LSF assessment. It is important to note that patients who receive same-day Y-90 only undergo planar scintigraphy. Single-photon emission CT is not performed for these patients given its lengthy duration.
  - Accompany the patient to nuclear medicine and make sure access site sterility is maintained and the sheath is minimally manipulated during transportation. The nurse, technologist, and physician should accompany the patient to nuclear medicine for monitoring.
  - Ensure proper coordination between the interventional radiology and nuclear medicine departments, which allows both accurate dosimetry planning as well as quick patient transport between both departments on the treatment day. Therefore, minimal time is lost in the transition phases between the three sessions of same-day treatment (eg, planning angiography, nuclear scan, and Y-90 treatment).
  - Once planar scintigraphy determines the actual LSF, just-in-time dosimetry adjustments are done. The patient is then transported back to interventional radiology to undergo the planned Y-90 treatment. By the time the patient returns to the angiography suite, the LSF should have been determined and final dosimetry adjustments made.
  - Patients are maintained on continuous conscious sedation throughout the entire same-day Y-90 session. Sedation is stopped only after treatment is complete. The entire duration of the same-day Y-90 treatment takes an average of 2.5 hours from the time the patient enters the interventional radiology room for angiography until he/she leaves the room after treatment. 

Don’ts for Same-Day Y-90
- Don’t select the wrong patients for this approach. Patients with complex history or advanced disease are not ideal candidates for same-day Y-90 treatment.7 Examples of these patients include:
  - Patients with malignant vascular invasion, especially hepatic vein thrombosis, because they usually have high LSF
  - Patients with infiltrative tumors or tumor burden > 50% of entire hepatic volume, which has been associated with high LSF
  - Patients with a poor glomerular filtration rate not on dialysis, as there is a risk of using a lot of contrast for the diagnostic and treatment angiograms

- Don’t maintain access to the hepatic artery when the patient is being transferred to nuclear medicine (unless it is a very difficult hepatic arterial access, which will require a second pressure bag). It is preferable to leave an angled 5-F catheter in the abdominal aorta.

CONCLUSION
Radiation segmentectomy has demonstrated high safety and efficacy in treating liver malignancies. This approach may be considered “curative” in a select group of HCC patients. Proper patient selection and a thorough understanding of both segmental/subsegmental vasculature and ablative doses lead to successful treatment. Same-day Y-90 is convenient for patients and can save both costs and time (an average 2.5-hour door-to-door time). Careful patient selection and coordination with nuclear medicine are key to implementing same-day Y-90.


(Continued on page 107)
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Prostate cancer is the second most common cancer in men and the fifth leading cause of cancer death in men worldwide.1,2 In the United States, approximately 165,000 new cases of prostate cancer will be diagnosed and 29,000 patients with prostate cancer will die in 2018. Approximately 80% of all men will develop prostate cancer in their lives, so effective diagnosis and treatment are immensely important goals for our health care system.1

Unfortunately, the detection of prostate cancer can be challenging, and once it is detected, the indolent nature of the disease can make management decisions difficult. With any cancer screening, the risks of overdiagnosis and overtreatment play a prominent role in decision-making, and overly aggressive treatment of prostate cancer has been shown to expose patients to significant risk.3 Once significant suspicion for prostate cancer is raised, patients typically undergo a biopsy. Classically, this is a random ultrasound-guided transrectal needle biopsy, which is prone to sampling error, but some centers offer MRI-guided prostate biopsies that improve detection rates of clinically relevant cancers.

CURRENT PROSTATE CANCER TREATMENT PARADIGM AND ITS CHALLENGES

After prostate cancer is detected, a complex individualized management decision must be made based on the severity of the detected disease, the health and life expectancy of the patient, and the potential risks and side effects of any proposed treatment strategy. Patients are stratified into risk groups based on prostate-specific antigen (PSA) level, biopsy specimen pathologic grading, and disease extent. Patients with localized, unfavorable, intermediate- or high-risk disease are offered definitive radical prostatectomy or radiation therapy, and those with localized very high-risk disease or locally advanced disease may be offered extended lymph node dissection with surgery or androgen deprivation therapy (ADT) with radiation.4 Patients with metastatic disease are offered ADT and possibly radiation. However, patients diagnosed with localized, favorable, intermediate- or low-risk cancer are offered active surveillance in addition to definitive treatment options, and for patients with very low-risk cancer, active surveillance is the primary recommendation.5 Active surveillance consists of repeat PSA level testing every 6 months, repeat digital rectal exam yearly, and yearly follow-up biopsy or possibly MRI to rule out any new or previously missed higher-grade disease.

For lower-risk patients, the binary choice between active surveillance and definitive therapy is currently the best we can do to fit patients with a spectrum of disease into the two available management “bins,” a strategy which, unfortunately for many patients, risks mismatching the relative severity of their disease with a chosen level of treatment. A certain proportion of undertreating or overtreating patients is tolerated so as to strike an optimal overall therapeutic balance for the population as a whole. This is where the minimally invasive image-guided endovascular techniques of interventional radiology could play a major role, to perhaps bring about a paradigm shift in prostate

Prostatic Artery Chemoembolization: The Next Frontier in Prostate Cancer Therapy?

Transarterial embolization techniques for treating liver malignancy are ready for adaptation to prostate cancer applications.

BY RAJ AYYAGARI, MD
cancer treatment by offering more intermediate treatment options.

**LOCOREGIONAL THERAPY MODEL: MORE GRANULAR TREATMENT OPTIONS**

For many years, imaged-guided transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) techniques have played a dominant role in the management of hepatocellular carcinoma (HCC). For cancers too large, diffuse, or difficult to ablate percutaneously or resect surgically, TACE and TARE procedures have shown great success in providing significant improvement in overall survival, disease-free survival, and recurrence rates. Although TACE and TARE are not considered curative, such interventions are often quite successful at bridging a patient to definitive liver transplantation. These procedures are the mainstay of the locoregional therapy model that provides a granular array of treatment options that can be readily tailored to an individual patient’s disease severity and overall health. Furthermore, such procedures are widely available and technically straightforward, are performed on an outpatient or overnight stay basis with short recovery times and minimal side effects, and can be easily and safely repeated as needed.

Can a locoregional therapy model be successfully applied to prostate cancer to provide less invasive, better-tailored, lower-risk treatment options for those with lower-grade disease or those too sick to tolerate more aggressive treatments? Prostate cancer is a fundamentally multifocal disease, so existing focal percutaneous ablative therapies designed to treat discrete lesions characterized by MRI have limitations—no imaging modality can reliably detect all foci of bona fide histopathologic disease. Interestingly, more aggressive tumors have been shown to be more susceptible to ischemia that disrupts their metabolism. This observation has led many to wonder if transarterial embolization could play a role in treating prostate cancer as it does in HCC.

**PROSTATIC ARTERIAL EMBOLIZATION: FOR BPH OR PROSTATE CANCER?**

Perhaps the most exciting advances foretelling such a paradigm shift in prostate cancer treatment have been in the realm of prostatic artery embolization (PAE), which has to date been used to treat symptoms related to benign prostatic hyperplasia (BPH). The procedure works by causing irreversible necrosis of prostatic adenomatous tissue, which causes the gland to shrink and soften, especially in the central periurethral tissue, thereby relieving pressure on the prostatic urethra and diminishing obstruction to urinary outflow. PAE was initially described in 2000 to treat severe prostatic arterial bleeding in a patient with massive BPH. Subsequently, pioneering groups led by Dr. João Pisco in Portugal and Dr. Francisco Carnevale in Brazil forged forward with numerous studies demonstrating safety and remarkable efficacy of the PAE technique for treating BPH. Many more groups throughout the world have since built upon this foundation, replicating their results, comparing PAE with transurethral prostate resection, and making numerous refinements in the technique and how it can be used to manage lower urinary tract symptoms, urinary retention, and hematuria.

Interestingly, some authors have proposed adjunctive roles for PAE in the setting of prostate cancer treatment. Embolization used to shrink large glands prior to radical prostatectomy could allow for less blood loss during resection and perhaps allow for a smaller cystotomy, which could contribute to improved urinary continence after resection. PAE has also been successfully used to control prostatic bleeding after radiation therapy. Of course, the true paradigm shift would be the successful development of a transarterial embolization procedure capable of directly treating prostate cancer. Such a procedure would need to be technically feasible, safe, and effective at palliating or treating some subset of prostate cancer patients.

![Figure 1. Coronal angiogram showing right inferior vesicular artery contrast injection with readily visualized collaterals to bilateral superior vesicular, inferior vesicular, and internal pudendal arterial branches. These collaterals need to be identified and excluded for safe and effective PAE.](image-url)
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Technical Feasibility: Arterial Anatomy and Tumor Distribution

Although the PAE procedure is technically challenging, its fairly steep learning curve is surmountable with training and experience. To safely embolize the prostate gland and avoid nontarget embolization, many periprostatic arterial shunts and collateral connections must be protected by coil occlusion, excluded with an occlusive balloon-tipped microcatheter, or carefully avoided by taking advantage of competitive inflow and shifting flow dynamics (Figure 1).

Another potential feasibility issue for transarterial prostate cancer therapy is that approximately 80% of prostate cancers arise in the peripheral zone of the prostate gland, whereas the gland infarction seen when PAE is performed to treat symptomatic BPH is primarily in the central periurethral tissues, as demonstrated by postembolization imaging studies (Figure 2). However, the degree of tissue penetration with an embolic agent is significantly affected by the diameter of the embolic particle. Most studies have looked at images obtained from glands embolized with 300–500-µm Embosphere microspheres (Merit Medical Systems, Inc.), whereas TACE procedures performed in the liver typically employ LC Bead particles (BTG International) as small as 70–150 µm or a liquid embolic agent (Lipiodol, Guerbet LLC). Furthermore, it is not certain that the infarction seen in the central parts of the gland after PAE would be necessary to treat a cancer in the peripheral zone, particularly if the injected particle were not just a simple embolic agent, but rather a vehicle for a chemotherapeutic or brachytherapeutic agent. Images acquired from a prostatic perfusion mapping study by Abele et al, as well as the standard cone-beam CTA images routinely acquired during a PAE procedure (Figure 3), demonstrate that injected agents uniformly reach and reside in the periphery of the gland.

Safety and Efficacy

Dozens of studies reporting on thousands of patients over the past decade have demonstrated that we can safely embolize the prostate gland in an outpatient setting with minimal complications and adverse side effects in patients of all relevant ages with a wide range of medical comorbidities. Regarding the safety of TACE or TARE to treat malignancy, the scientific literature is replete with thousands of reports demonstrating the safety and efficacy of these techniques when treating tumors in the liver.

Recently, a preliminary demonstration of the technical feasibility and safety of prostatic artery chemoembolization (PACE) to treat prostate cancer was reported by Pisco et al. Twenty patients with prostate cancer underwent PACE. Their mean Gleason score range was 6 to 10, and their staging was T2N0M0. PACE was performed with a combination of Chelidonium.
Subsequently, Mordasini et al reported on 12 patients with prostate cancer who underwent PAE using 100-µm Embozene microspheres (Boston Scientific Corporation) and then radical prostatectomy 6 weeks later. On pathologic evaluation of the resected specimens, two patients had complete necrosis of their index lesions, and five patients had partial necrosis of their lesions. Of note, all 12 patients had previously undetected secondary foci of viable disease. There were few adverse events.

FUTURE DIRECTIONS: PROSTATE EMBOLIZATION AS AN ANSWER TO ACTIVE SURVEILLANCE

We know that PAE is technically feasible and safe, and studies are beginning to show safety and some efficacy of chemoembolization in the treatment of prostate cancer. These pioneering studies are paving the way for more expansive and systematic trials that will further explore this potentially game-changing approach. Perhaps someday soon, we might even be able to use TARE as another means to deliver brachytherapy to the gland, if a radioisotope with favorable dosimetry parameters could be developed and appropriately packaged. Furthermore, any agents that might be developed to sensitize prostate cancers to radiation or chemotherapeutic treatments could be theoretically delivered in a transarterial fashion directly to the prostate gland.

Although these transarterial embolization techniques may never demonstrate equivalent efficacy to surgical or ablative procedures in treating prostate cancer, they show great promise in treating patients with localized lower-grade disease who may never need those more invasive procedures. Such techniques may provide sufficiently effective treatment options for patients who would otherwise have to live with the anxiety of active surveillance or the risks and side effects of definitive treatments such as urinary incontinence, erectile dysfunction, and radiation proctitis or cystitis. Moreover, these embolization procedures would still preserve a patient’s options to transition to more definitive treatments as appropriate.

CONCLUSION

Endovascular techniques have tremendous future potential to bring about a revolutionary paradigm shift in the treatment of prostate cancer.
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early 9.6 million people worldwide and 600,000 Americans die from cancer each year. In the near future, cancer-related deaths are projected to overtake heart disease as the leading cause of death in America.\textsuperscript{1,2} Progress has been made over the last several years to stem the tide of cancer mortality by diagnosing cancers earlier and curing early stage cancers before progression. Among the most revolutionary and successful approaches have been in the fields of immuno-oncology and interventional oncology (IO). Both of these fields have inspired new hope in treating incurable cancers and in improving tolerability and adverse event profiles for oncotherapies. Perhaps the most intriguing aspect regarding these approaches is their potential interplay in augmenting efficacy, further personalizing therapy, and broadening the scope for treatable cancers.

**IMMUNO-ONCOLOGIC THERAPIES**

Immunotherapeutics are a heterogeneous class of antineoplastic agents that aim to harness the existing infrastructure of a patient’s immune system to cause direct or indirect cell death. The approach is predicated on a few key recognitions. First, the immune system is equipped with an antitumor mechanism, known as “cancer immunoediting,” which malignancies must subvert to become pathologic and restoration of which may allow for the treatment of a tumor.\textsuperscript{3} Secondly, the specific microenvironment, or niche, of a tumor is a key factor in tumor response to any therapy and its constituent elements of effector cells, such as CD4+, gamma delta (γδ), and CD8+ T cells (tumor-infiltrating lymphocytes), play a key role in regulating the antitumor response. Ultimately, every immuno-oncologic therapy uses these pathways to harness the native immune system against malignancies. The different techniques used in immunotherapy include monoclonal antibodies against cell surface markers, oncolytic and cancer vaccines, polysaccharides, cytokines, and chimeric antigen receptor T (CAR-T) cells (Table 1).

The most well-known and successful immunotherapy to date is checkpoint inhibition with monoclonal antibodies targeted against the programmed death receptor-1/programmed death ligand-1 (PD-1/PD-L1) axis and cytotoxic T-lymphocyte associated protein 4 (CTLA-4). The PD-1 molecule is a transmembrane IgG protein that, when bound by its ligand PD-L1 in the context of major histocompatibility 1 stimulation, can decrease antitumor T cell proliferation, cytotoxicity, inflammatory mediator release, and self-tolerance.\textsuperscript{4,6} That is, the PD-1 axis can help tumor cells evade the immune system. Consequently, when a PD-1 axis inhibitor disrupts this chain, T cells may be able to detect, be primed by, and eliminate tumor cells.

The FDA has now approved PD-1/PD-L1 inhibitors for a broad range of indications including non–small cell lung cancer (NSCLC), metastatic melanoma, head and neck squamous cell cancer, urothelial cancer, gastric cancer, cervical cancer, hepatocellular carcinoma (HCC), and solid tumors with high microsatellite instability (MSI-H). Although lung cancer and metastatic melanoma are among the most common malignan-
cies, the approval to treat microsatellite instabilities offers tremendous potential in expanding the scope for checkpoint inhibition and personalizing future oncology research.

CTLA-4 is a T cell surface protein receptor that inhibits T cell activation after detection and activation against self-antigens. This pathway is among different immunoediting approaches that tumors such as melanoma have employed to evade the immune system.7 The only FDA-approved CTLA-4 inhibitor at present is ipilimumab (Yervoy, Bristol-Myers Squibb), although others (eg, tremelimumab, AstraZeneca) are close to approval. The indications for CTLA-4 inhibitors are narrower as compared with PD-1 axis inhibitors and are only approved in metastatic melanoma, renal cell carcinoma, and MSI-H tumors. However, combination therapy, particularly for melanoma, has shown tremendous promise, and studies for MSI-H tumors are ongoing.

Oncoviruses (ie, viruses with enhanced tumor tropism and decreased virulence for nonneoplastic host cells) are another form of immunotherapy that has shown efficacy in malignancies. These therapies directly induce cell lysis by either apoptosis or necrosis. The resultant immune cell recruitment coupled with neoantigen release enables regained function for immunosurveillance and tumor cell elimination. The other oncoviral approach is therapeutic vaccination by which a patient’s leukocytes are directly primed against a tumor antigen. The only FDA-approved oncovaccine therapy is sipuleucel-T (Provenge, Dendreon Pharmaceuticals LLC/Sanpower Group) for metastatic, hormone-resistant prostate cancer. Studies evaluating in vivo approaches for priming leukocytes against tumor cells are ongoing with the current approach requiring immune cells to be primed ex vivo via leukapheresis, followed by reinfusion.9

Clinical trials in multiple phases are presently underway not only to expand the number of checkpoint inhibitor and oncoviral therapeutics and their scope, but also to diversify mechanisms of action. Polysaccharides have been used in East Asia for antitumor immunogenicity for decades but are now under investigation in the United States for disrupting signaling pathways for tumorigenesis, upregulating proinflammatory cytokines, and vaccination. Peptides such as cytokines are also candidates for antitumor immunotherapy to stimulate and prime the immune system or disrupt other signaling pathways. Lastly, CAR-T cells, transformed T lymphocytes with recombinant antigen–binding and T cell–activating receptors specifically

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Abbreviations: CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1.
created against a tumor antigen, have shown tremendous promise in liquid tumors; however, research in solid tumors remains to be conducted.

**INTERVENTIONAL ONCOLOGY APPROACHES**

Immuno-oncology uses two main approaches, antibodies and antigens, to stimulate the immune system against diverse molecular targets. In contrast, IO uses diverse techniques to induce apoptosis or necrosis. The topics of chemoembolization, bland embolization, radioembolization, and ablation are familiar to this audience and are briefly discussed herein.

In the context of IO, the target is typically a tumor, and the smallest accessible feeding branches are typically selected to minimize the risk for nontarget embolization. Delivery platforms that can be used include particles, radionuclides, or chemotherapy.

Ablation is image-guided induction of direct tumor destruction by noxious stimuli. Ablation techniques can employ heat-based thermal mechanisms such as radiofrequency ablation, microwave ablation, and laser ablation or hypothermia-based thermal mechanism such as cryotherapy. Additionally, high-intensity focused ultrasound can be used via acoustic cavitation to cause coagulative necrosis. Irreversible electroporation uses a high voltage to destabilize cellular membranes and induce predominantly apoptosis as well as necrosis across the ablation zone.

**WHY USE IO x IO?**

IO and immuno-oncology (IO x IO) are both the “newest kids on the block” in their respective fields and have revolutionized and invigorated their fields and uniquely advanced the field of oncology. Although both fields continue to evolve, refine, and develop their present successes, a greater aspiration still remains. In particular, the hope is that the combination of these therapies is not simply additive but iterative or exponential. There are three main goals of IO x IO: to enhance the level of antitumor response, overcome resistance, and potentially induce a systemic immune resynchronization to treat metastatic cancers in addition to interventional targets (Figure 1).

Robust preclinical data have demonstrated efficacy of concomitant checkpoint inhibition and ablation. Moreover, clinical case reports and small series have demonstrated that concomitant administration of immunotherapeutics and IO treatments is safe and well tolerated, including cryotherapy with checkpoint inhibition in NSCLC and metastatic melanoma, yttrium-90 radioembolization with checkpoint inhibition in HCC, microwave ablation and checkpoint inhibition in metastatic colorectal cancer, and transarterial chemoembolization with checkpoint inhibition in small cell lung cancer. Moreover, a clinical trial combining ablation and anti-CTLA-4 for advanced HCC patients who had failed on sorafenib demonstrated an overall survival of 12.3 months and a time to progression of 7.4 months. Biopsies of the lesions demonstrated accumulation of intratumoral CD8+ cells.

Effects and modifications at the “niche” or tumor microenvironment is one of the potential explanations for how and why IO x IO therapies work. It has been proposed that ischemia and cell destruction caused by interventional techniques result in fundamental changes in peptide expression in nearby support cells (e.g., stromal cells) as
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well as recruit new naïve and programmable immune cells. These modifications may enhance susceptibility of tumor cells for the concomitant immunotherapy. The other prevailing hypothesis for how combination IO x IO therapies function involves the creation of neoantigens against which the immune system can be primed. This approach involves the use of tumor ablation that causes necrosis and releases potential antigenic peptide fragments while inciting an inflammatory response. Macrophages and other antigen-presenting cells then phagocytize these fragments to prime the immune system. Response to concomitant immunotherapy may then be induced (for resistant tumors) or enhanced.

**FUTURE DIRECTIONS**

The concept of IO x IO is an intriguing space for research given its potential impact on therapies for currently incurable cancers. However, despite significant enthusiasm, there are key limitations that must be addressed and critical questions that remain to be answered. With regard to limitations, the biggest barrier to widespread adoption of IO x IO techniques is the need for a robust large data set and carefully designed clinical trials. Until well-designed clinical trials are completed, there will remain a need for an empirically proven substantive improvement in clinical outcomes as well as consequent skepticism in the oncology community. Additionally, a major question that warrants further careful evaluation is what treatment protocols for the combined approach are the best; for example, which therapies (embolization and CTLA-4 inhibition, irreversible electroporation and oncolytic viruses, transarterial radioembolization and PD-L1 inhibition) are the most immunogenic and what host factors impact their outcomes.

To answer these questions, significant further basic and clinical research remains to be conducted to determine the mechanism(s) of action by which IO x IO therapies work, as well as to quantify the antitumoral effects of combination therapy via translational oncologic research. Research is underway to determine whether local delivery of immunotherapy offers benefit compared to oral or intravenous techniques. So far, hepatic arterial instillation of CAR-T cells has shown positive results in phase 1 trials, but it is unknown whether this translates to efficacy and whether other immunotherapies will show similar results. Lastly, the moonshot for IO x IO therapies is to use these treatments to induce positive immunologic responses in cancers otherwise not responsive to immunotherapy.

The concept of IO x IO is truly remarkable: using image-guided local treatments to create or augment therapeutic response to molecularly targeted immunogenic drugs. Yet, significant work remains, requiring collaboration both within and between both “IO” communities. This combination approach offers the potential to fundamentally change how advanced cancers are treated and offer hope to patients who presently have very few treatment options.

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Artificial intelligence (AI) is a computational approach to problem-solving commonly associated with human intelligence. Recently, AI has experienced a surge applied to many fields, including finance, transportation, and health care. Many studies have explored the application of AI in radiology. With AI's growing capabilities to analyze images, review large data sets, and constantly learn from new data, it has potential to transform interventional oncology (IO). The purpose of this article is to review the applications of AI in IO. Some of these applications have been tested and presented at meetings or published; other potential applications are inferred from application of AI in other fields.

DEFINITION OF ARTIFICIAL INTELLIGENCE

AI uses computing power to analyze data and perform complex tasks involving pattern recognition or problem-solving. A subset of AI is machine learning (ML), where a computer “learns” a task from data by automatically improving through repeated experiences. In contrast to other forms of AI, the ML system independently learns without explicit hard-coded “if-then” instructions.

Artificial neural networks (ANNs) are a specific type of ML that automatically learn relationships using “artificial neuron” layers. Deep learning involves the use of ANNs that have a large number of artificial neuron layers to learn more complex relationships. In the case of convolutional neural networks (CNNs), “convolutional” layers perform image analysis in a manner somewhat similar to the connectivity pattern of the retina and visual cortex. AI can be applied along the entire clinical continuum of IO, from research/outcome analysis to clinical applications for diagnosis, patient selection, order scheduling/workflow, and intraprocedural guidance.

RESEARCH WITH ARTIFICIAL INTELLIGENCE: BIG DATA AND OUTCOME REPOSITORIES

AI has potential to impact outcomes research in IO. The traditional paradigm for clinical research involves starting with a retrospective study, conducting prospective clinical trials that span several years, and forming clinical management guidelines (combining existing data from these trials with expert opinion and consensus). A limitation of this approach is that these efforts are often independent, resulting in the release of several conflicting management algorithms. Moreover, the current clinical research process is incremental, usually involving the manipulation of one clinical variable. In reality, several clinical variables may affect a particular outcome, and relationships may not be linear. Because the current process is time-consuming, expensive, and cumbersome for one variable alone, it is not usually feasible to simultaneously evaluate multiple variables.

Consider a different paradigm in which a standardized organized effort is made to collect multi-institutional pre-, intra-, and postprocedural data. This information can then be stored in centralized databases that can be continuously analyzed by ML systems. Clinical questions can be translated into ML prediction algorithms, which can eventually act as a substitute for retrospective studies. These trained models can be validated with prospective data, with a continuous cycle of prospective validation and model optimization. Unlike the incremen-
tal approach of single-variable studies, the entire clinical picture can be explored with inclusion of an unlimited number of variables. Management guidelines can then become more personalized, combining preset robust clinical variables prospectively validated by these ML systems and the output of a patient’s entire clinical picture fed through ML models.

**POTENTIAL CLINICAL APPLICATIONS IN INTERVENTIONAL ONCOLOGY**

In addition to impact on research, AI has potential to improve clinical care in IO. ML may be utilized to review preprocedural images for improved lesion detection and characterization and make assessments to predict the success of various IO procedures.

**Lesion Detection**

Earlier identification of tumors is important for improving care of IO patients, allowing for more curative-intent IO therapies (eg, ablation) to be utilized. In this manner, ML techniques can assist in diagnosing malignant lesions earlier. A recent study utilized CNNs to distinguish between different classes of liver masses on CT examinations. The study utilized select two-dimensional slices of three phases of contrast-enhanced CT as input to train a CNN model. “Ground truth” output consisted of labels for five categories of lesions, ranging from classic hepatocellular carcinoma to hemangiomas and cysts. Median lesion classification accuracy was 84% with an area under the receiver operating characteristic curve of 0.92 for malignant and benign/determinate lesion classification. Similar to this research, ML has also been used for breast cancer imaging and prostate cancer MRI.

**Lesion Characterization/Outcome Prediction and Radiomics**

Predicting tumor response to IO treatment options is critical to the future success of IO techniques. A recent study investigated the use of ML to predict tumor response to transarterial chemoembolization (TACE) using retrospective data from hepatocellular carcinoma patients. The goal was to predict responders versus nonresponders from baseline clinical, laboratory, demographic, and imaging data. Input data were prescreened by filtering out features demonstrating low variance and low contributions to the outcome. Logistic regression and random forest techniques were utilized for the ML model. Although this was a feasibility study in a small patient cohort with simple ML techniques, building upon this approach may eventually result in tools that optimize patient selection for TACE.

Another approach for outcome prediction is use of radiomics, which is the assessment of tumor biology aspects not readily discernible to the human eye on imaging. Radiomics analysis consists of extracting subvisual quantitative imaging features and assessing the correlation to patient prognosis and treatment response. Two small abstracts presented at the 2018 Society of Interventional Radiology (SIR) meeting showed that preablation radiomics improves survival prediction in patients with adrenal metastasis who underwent ablation. Further studies can utilize ML techniques to analyze preablation images and predict treatment success based on texture analysis correlated to follow-up imaging.

**Tumor Board Recommendations**

In the realm of interdisciplinary decision-making, ML can also be used to improve tumor board recommendations and help in triaging oncology patients to the appropriate treatments. A study presented at the 2017 SIR meeting utilized an ML approach to identify the relative importance of clinical and imaging features contributing to tumor board recommendations. Data involving a combination of clinical and imaging characteristics were collected from 76 training cases and presented to a multidisciplinary team consisting of specialists from interventional radiology, radiation oncology, medical oncology, surgical oncology, and transplant. Input data included the number of enhancing lesions, largest lesion size, Organ Procurement and Transplantation Network (OPTN) classification, model for end-stage liver disease score, and Child-Pugh score. The output for each data set was the tumor board treatment recommendation. A random forest algorithm model was utilized. The model found a set of highly predicted features, including lesion size, segments involved, enhancing lesions, patient age, and number of OPTN 5 lesions.

**Order Scheduling/Workflow**

Critical to a successful practice is the smooth transition of a patient through an interventional radiology department. ML tools are currently being used to enhance clinical decision support. They are also being applied for intelligent scheduling, with the goal of reducing missed patient appointments. Similarly, ML and predictive analytics are being used to identify patients at high risk for missing their radiology care appointments.

**Intraprocedural Planning**

Most directly relevant to the interventional oncologist is the application of AI to intraprocedural guidance—for both embolic and ablative therapies. Computational methods can be used to fuse images with registration...
Limitations and Challenges

Although the aforementioned studies and ideas lay the groundwork for integrating ML into IO, several important elements are necessary to bridge the gap between proof of concept and successful clinical translation. Due to limitations in data availability at single institutions, most currently published studies utilize small subsets of data that may not accurately simulate a realistic clinical practice environment. On the other hand, formation of large multicenter databases can allow for development of more robust algorithms that more closely simulate reality. In this setting, more heterogeneous data sets can be used to help models learn from cases with higher variability. Additionally, larger data sets allow for models that can technically accommodate multiple modalities, parameters, and time points as input, providing a more complete input set for decision-making.

In addition to employing large multicenter databases, a few other possible approaches can improve clinical applicability of AI systems. Although initial proof-of-concept algorithms could focus on including “ideal” data input, these models may break down when analyzing de novo information that does not follow simple classical patterns. Thus, it is important to eventually incorporate more “challenging” cases into training data sets, including atypical data and cases with artifacts or incomplete data.

Additionally, well-annotated data sets are crucial to the validity of any AI system. This can be accomplished by having multiple physicians assign labels, allowing for inter-reader variability to be compared to produce higher-quality “ground truths.” Moreover, techniques that utilize only one set of input data (eg, imaging data) may not provide a balanced global perspective; therefore, ML models can be optimized for clinical relevance by incorporating multiple input sources, including imaging, textual, and other clinical information. The creation of large data sets and defining standards that meet clinical practice guidelines are critical to the success of this approach. The National Cancer Institute’s Annotation and Image Markup model is an example used to standardize images.

From a more technical perspective, ML systems that function as a “black box” (ie, provide a prediction without explanation) are less likely to gain clinical acceptance, because they do not provide a mechanism for predicting technical mistakes. This can be remedied by developing algorithms that provide evidence for predictions and are capable of quantifying uncertainty. Finally, such models should be flexible and dynamic, easily adapting to the latest clinical guidelines and research findings for continuous improvement.

CONCLUSION

Despite the recent surge of AI in medicine, the application to IO is still in its infancy. An expanding body of data is increasingly demonstrating its potential to revolutionize the field. As described, AI has the potential to transform the entire clinical continuum of IO care. With an established pioneering history of blending technology with clinical care, interventional radiologists are ideally suited to lead these developmental and clinical translation efforts. In this manner, interventional radiologists can carve out a custom path for AI in IO, incorporating AI as their own tool to provide patients with optimal minimally invasive clinical care.

(Continued from page 90)

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Although interventional radiology (IR) has become integral in everyday practice in the United States and other developed nations, the majority of people around the world are left without access to these innovative and often life-saving procedures. According to the World Health Organization, up to 4 billion people lack access to medical imaging, and even more lack access to IR services. IR has grown exponentially in the United States over the past 50 years, raising the question of whether it could be possible to expand these practices to a broader population around the world. This would potentially give millions of people access to improved health care by offering new options for diagnosis and treatment for a wide range of diseases. Existing frameworks in global health outreach may prove useful in establishing goals and opportunities for IR in the global context.

RAD-AID INTERNATIONAL
RAD-AID International is a nonprofit organization with more than 9,000 volunteer members around the world and active outreach projects in radiology in nearly 30 countries. The goal of RAD-AID is to increase access to medical imaging around the world. Until recently, these efforts were primarily focused on diagnostic radiology. In 2017, an initial IR readiness assessment was performed in Tanzania, which demonstrated that there is not a single interventional radiologist in the country, but conditions are favorable for establishing IR. Based on the findings of this assessment, a strategy was developed for introducing IR to the Tanzanian health care system. This site will serve as the inaugural program for implementation of an IR training program in the low-resource setting. The strategy is focused on the following three key aspects: (1) practical training of fellows, residents, nurses, and technologists; (2) creation of a global IR curriculum for the resource-limited setting; and (3) establishment of sustainable procurement processes at partner institutions.

Tanzanian IR Training Project
The RAD-AID IR program focuses on fostering in-country educational opportunities and training programs. This strategy allows for trainees to learn in their own practice environment, ensuring application to local resources and disease patterns and increasing sustainability within institutions. Central to this approach is performing an assessment, creating an implementation plan, and organizing deployment teams. Considering the wide range of IR procedures available, multiple deployments to each site over the course of several years are required until local expertise is sufficient to provide teaching capacity for future trainees.

Ten teams are planned for deployment to Tanzania per year in 2-week blocks for the next 3 years, with the first trip in October 2018. Each deployment team includes an IR attending, nurse, and technologist. Trainees and medical students will accompany most teams. Similar to many IR training programs in the United States, the goal is to train three residents per class, and these trainees will form the first generation of interventional radiologists in Tanzania. The program aims to treat five to 10 patients per day or 50 to 100 per 2-week block, accounting for a total of 500 to 1,000 patients per year. Rather than achieving high case numbers, the goal is high-quality teaching with innovative approaches.
The first two trips in October and November 2018 are focused on training of four basic percutaneous IR procedures: core needle biopsy, cholecystostomy, nephrostomy, and drainage of abscesses and collections. In February 2019, this will be expanded to include bone biopsy, joint aspirations, and arthrograms. In each of the following months, additional procedures from the global IR curriculum will be added. The program will undergo continuous reassessment, allowing the program to evolve and focus on areas that demonstrate the highest impact in the country. The findings of these ongoing assessments will help guide future projects with expansion to other RAD-AID sites.

**Training schedule.** The practical training schedule is based on the global IR curriculum, which is a collaboration of the Society of Interventional Radiology residents, fellows, and students and RAD-AID. This provides a dynamic and open format focused on implementation of IR in the resource-limited setting. The curriculum is structured into core and advanced procedures that can be adapted according to local practices and available resources. For instance, if a given site has ultrasound and fluoroscopy but not CT, the curriculum can be tailored accordingly. The goal is to implement the curriculum at partner institutions according to institutional and national guidelines to achieve ways of accreditation and certification for local trainees.

**Equipment procurement.** Although procurement of required equipment by the local hospital system at the partner site provides the only long-term solution, some programs may initially also depend on outside contributions in the form of grants and donations. Once the IR service is established, the range of procedures offered and equipment used will adapt to allow sustainable local procurement. The global IR curriculum outlines a stepwise approach from percutaneous to endovascular to advanced procedures. This is reflected in the procurement process, which is initially focused on providing equipment needed for basic percutaneous procedures and aims to supply endovascular equipment by the second year of the program.

**SUMMARY**

The Tanzanian IR project is a collaboration of the RAD-AID IR program with academic centers in the United States and Europe. Methods established in Tanzania will be employed at additional RAD-AID sites, including Ghana, Kenya, Ethiopia, and Vietnam. RAD-AID aims to sustainably implement these practices and advances from our specialty to millions of people around the world who may tremendously benefit from the availability of the wide range of diagnostic and therapeutic options that IR can offer. We hope interventional radiologists, nurses, and technologists will consider the opportunity to support projects in resource-limited settings and create lasting global impact.


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Use of the MVP™ Micro Vascular Plug System as a Single Occlusion Device to Treat Pulmonary Arteriovenous Malformations

Real-world case reports demonstrating the unique benefits that this system offers to patients and operators.

BY BRIAN HOLLY, MD, AND SANJEEVA KALVA, MD

The ideal embolic device to treat PAVMs is easily deliverable, detachable, immediately occludes the feeding artery, and does not recanalize over time. At Johns Hopkins Division of Interventional Radiology, either detachable coils or detachable endovascular plugs are used to treat PAVMs. Once such device is the MVP™ micro vascular plug system (Medtronic). The MVP™ device is a nitinol plug that is partially covered with polytetrafluoroethylene (PTFE) and can be delivered through a microcatheter (MVP-3Q and MVP-5Q, Medtronic). The PTFE covering results in near-immediate occlusion of the feeding artery. The MVP™ device is detachable and can be resheathed up to three times if the operator is unsatisfied with the deployment (ie, if the plug is undersized or deployed in an undesired location). The MVP™ device comes in sizes that are large enough to treat vessels up to 9 mm in diameter, and it easily navigates tortuous anatomy, allowing for distal deployment in small PAVM feeding vessels. Long-term data regarding the recanalization rates of MVP™ devices for the treatment of PAVM have not been published.

Figure 1. Coronal (A) and axial (B) maximum intensity projection images from a contrast-enhanced CT scan of the chest demonstrate numerous, small, peripheral PAVMs (black arrows).
The cases that follow illustrate the advantages of the MVP™ device in the treatment of PAVMs.

CASE 1
A 46-year-old woman was incidentally found to have multiple pulmonary nodules on a noncontrast-enhanced CT scan during the workup of renal calculi. A repeat CT scan of the chest with contrast confirmed that the nodules were PAVMs. She was referred to interventional radiology for further evaluation of the PAVMs, and on screening, met 4 of 4 Curaçao criteria, confirming the diagnosis of HHT. Further review of the chest CT scan demonstrated at least eight separate PAVMs, most of which were located in the right lung (Figure 1). The decision was made to proceed with pulmonary angiography and embolization due to the large number of PAVMs.

During the first embolization procedure, eight separate PAVMs were identified and embolized within the right lung. The size and location of the feeding arteries necessitated the use of a microcatheter for embolization. A total of 10 MVP™ devices were used to occlude the feeding arteries (Figure 2). The patient returned approximately 2 weeks later for a second pulmonary angiogram and embolization, and five additional PAVMs were embolized, again with MVP™ devices. Several additional PAVMs were noted during these procedures but were too small to treat. The patient tolerated both procedures well.

She was seen for follow-up approximately 6 weeks after the second embolization procedure and a repeat CT scan was performed, confirming an excellent treatment response with improvement of nearly every visible PAVM. The patient continues to follow up and has noted improved exercise tolerance since the embolization procedures. She will undergo a repeat CT scan of her chest at 1 year postembolization.

This case illustrates the versatility of newer embolization devices and the ability to treat numerous PAVMs in a single treatment session.

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Disclosures: Royalties from Springer, Elsevier; consulting fees from GE Healthcare, Koo Foundation (Taipei), Medtronic; investor in Althea Health Inc.

CASE 2
A 34-year-old woman presented for evaluation of a suspected pulmonary arteriovenous shunt that was discovered on contrast-enhanced echocardiography during workup of a right posterior circulation stroke 6 months prior. She recovered well from the stroke with residual homonymous hemianopia and minimal left hemiparesis. She reported daily epistaxis and recurrent headaches and migraines but no breathlessness or previous history of hemoptyis.

Her family history was significant for hereditary hemorrhagic telangiectasia affecting her mother and mother’s siblings.

Clinical examination was unremarkable except for the residual neurologic deficit. Her oxygen saturation was 96% on room air. CT demonstrated multiple, simple PAVMs in both lungs (Figure 1). Three of these PAVMs were associated with a venous sac. Echocardiography and electrocardiography results were normal. Laboratory tests revealed microcytic anemia and a low ferritin level.

Figure 1. Three-dimensional volume-rendered CT pulmonary angiogram showing two PAVMs with associated venous sacs in the left lung.
Given her history of paradoxical embolism and stroke, the patient was offered embolization for treatment of these simple PAVMs. The procedure was performed under moderate sedation. Left pulmonary angiography demonstrated one small and three large PAVMs in the left lung (Figure 2). The left lower lobe segmental artery supplying the PAVM was selectively catheterized and angiography was performed. The feeding artery of the PAVM was occluded with a 9-mm-diameter MVP™ device deployed through a 5-F catheter (Figure 3). Similarly, the PAVM in the inferior lingular segment was occluded with a 7-mm MVP™ device (Figure 4) and the superior lingular PAVM was occluded with a 5-mm MVP™ device (Figure 5).

Postembolization left pulmonary angiography showed successful occlusion of all three large PAVMs (Figure 6).

The total fluoroscopy time was 30 minutes, with a cumulative air kerma of 1 Gy for the entire procedure. The smaller PAVM was later treated with a 3-mm MVP™ device that was deployed through a microcatheter (Figure 7).

This case illustrates the benefit of using MVP™ devices as the sole embolic material for treating PAVMs with feeding arteries of various diameters. Because these plugs allow easy and accurate deployment through a regular catheter and demonstrate immediate occlusion, multiple PAVMs can be treated during a single session with limited radiation exposure to the patient and the operator.

The Medtronic MVP™ micro vascular plug system is indicated to obstruct or reduce the rate of blood flow in the peripheral vasculature. This article is intended for US audience only.
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flow arrest and balloon guide catheter, thrombectomy devices choices and techniques), with the aim of achieving the most rapid and complete recanalization possible. However, it is worth noting that because our field is so dynamic and rapidly evolving, some of the recommendations will be outdated very soon, if not already.

Stroke care has recently absorbed much of the spotlight in the field of neurointervention, but other conditions and treatment options have also rapidly progressed in the past few years. Aside from ELVO, what research or developments are you most excited about?

Our field continues to evolve and mature. There is no question that endovascular mechanical thrombectomy has advanced tremendously and is in the spotlight of neurointervention; however, I am still very excited about the new technologies that continue to come out to improve aneurysm treatment, particularly devices addressing bifurcation aneurysms. In my practice, most of the treatments that I perform are aneurysm treatment (elective and urgent) and endovascular stroke treatment. I believe that this is true for most practitioners in the field, and therefore, it is only fair that these two disease processes share the neurointerventional spotlight. I am also very passionate and interested in the treatment of arteriovenous malformations, dural arteriovenous fistulas, and head and neck vascular malformations, in addition to new embolic materials, devices (such as microballoons), and new techniques to deliver the embolic agents.

With the seventh annual Miami Neuro Symposium approaching in November, what is the hot topic or main theme this year? What are you most looking forward to at this year’s meeting?

The Miami Neuro Symposium was conceived to update and educate our medical community on the recent advances in the management of neurological/neurosurgical/neuroendovascular problems. As such, the key components of the program will emphasize selection criteria for endovascular treatment of acute stroke and aneurysms, as well as provide updates on what has been the most important recent clinical evidence and technical advances in our field.

What path led you to radiology and, ultimately, neuroradiology?

My father is a radiologist back in Brazil, and because of that, I have been exposed to radiology since my early years during medical school. I was very intrigued by the technology and machinery involved in radiology and thought that it would be a career that I would enjoy. While I always enjoyed the aspect of the physician–patient relationship, it was only during my radiology residency that I had direct contact with neuroradiology as a separate subspecialty and subsequently interventional neuroradiology and neuroendovascular surgery. It was kind of love at first sight or, better put, first interaction. When I performed my first femoral access cerebral angiography and, as I progressed, first neuroendovascular treatment, I knew that God willing, that’s what I wanted to do for the rest of my life. Different than some of my other colleagues, I don’t see neuroendovascular surgery and interventional neuroradiology as just a group of techniques that I can use and offer to treat patients. Instead, I see this as my career. I knew from the beginning that it would be difficult, stressful, demanding, and would require long hours and extensive training, but so far, I have enjoyed every bit of it.

What is your favorite activity or pastime when you get a few hours or days with no on-call or hospital duties?

Because of the nature of what I do, when I am off, I try as much as possible to spend quality time with my family. You know, kids grow up fast, so every time that I can, I try to attend all of their school and sport events. My wife is an artist, so I do my best to attend her art exhibitions where she presents her paintings. When it comes to sports, being Brazilian, I really enjoy football (soccer) and playing tennis and, every once in a while, golf (which explains why I am a terrible golfer!). Now, one thing that I really love is playing guitar, so every time that I can, I try to get together with my band and play some music.

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INTENDED USE/INDICATIONS FOR USE: The ELUVIA Drug-Eluting Vascular Stent System is intended to improve luminal diameter in the treatment of symptomatic de-novo or restenotic lesions in the native superficial femoral artery (SFA) and/or proximal popliteal artery with reference vessel diameters (RVD) ranging from 4.0-8.0 mm and total lesion lengths up to 190 mm.

CONTRAINDICATIONS: • Women who are pregnant, breastfeeding, or plan to become pregnant in the next 5 years should not receive an ELUVIA Drug-Eluting Stent. It is unknown whether paclitaxel will be excreted in human milk, and there is a potential for adverse reaction in nursing infants from paclitaxel exposure. • Patients who cannot receive recommended anti-platelet and/or anti-coagulant therapy. • Patients judged to have a lesion that prevents proper placement of the stent or stent delivery system.

WARNINGS: • The delivery system is not designed for use with power injection systems. • Only advance the stent delivery system over a guidewire. • The stent delivery system is not intended for arterial blood monitoring. • In the event of complications such as infection, pseudoaneurysm or fistula formation, surgical removal of the stent may be required. • Do not remove the thumbwheel lock prior to deployment. Premature removal of the thumbwheel lock may result in an unintended deployment of the stent. • It is strongly advised that the treating physician follow the Inter-Society Consensus (TASC II) Guidelines recommendations (or other applicable country guidelines) for anti-platelet therapy pre-procedure to reduce the risk of thrombosis. Post-procedure dual anti-platelet therapy is required for a minimum of 90 days.

PRECAUTIONS: • Stenting across a bifurcation or side branch could compromise future diagnostic or therapeutic procedures. • The stent is not designed for repositioning. • Once the stent is partially deployed, it cannot be “recaptured” or “reconstrained” using the stent delivery system. • The stent may cause embolization from the site of the implant down the arterial lumen. • This product should not be used in patients with uncorrected bleeding disorders or patients who cannot receive anti-coagulation or anti-platelet aggregation therapy. • Persons with a known hypersensitivity to paclitaxel (or structurally-related compounds), to the polymer or its individual components (see details in Primer Polymer and Drug Matrix Copolymer Carrier section), nickel, or titanium may suffer an allergic response to this implant. • Persons with poor kidney function may not be good candidates for stenting procedures.

PROBABLE ADVERSE EVENTS: Probable adverse events which may be associated with the use of a peripheral stent include but are not limited to:

• Allergic reaction (to drug/polymer, contrast, device or other) • Amputation • Arterial aneurysm • Arteriovenous fistula • Death • Embolization (air, plaque, thrombus, device, tissue, or other) • Hematoma • Hemorrhage (bleeding) • Infection/Sepsis • Ischemia • Need for urgent intervention or surgery • Pseudoaneurysm formation • Renal insufficiency or failure • Restenosis of stented artery • Thrombosis/thrombus • Transient hemodynamic instability (hypotensive/hypertensive episodes) • Vasospasm • Vessel injury, including perforation, trauma, rupture and dissection • Vessel occlusion Probable adverse events not captured above that may be unique to the paclitaxel drug coating: • Allergic/Immunologic reaction to drug (paclitaxel or structurally-related compounds) or the polymer stent coating (or its individual components) • Alopeia • Arteritis • Gastrointestinal symptoms • Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia) • Hepatic enzyme changes • Histologic changes in vessel wall, including inflammation, cellular damage or necrosis • Myalgia/ Arthralgia • Peripheral neuropathy

There may be other potential adverse events that are unforeseen at this time. Eluvia is a registered or unregistered trademark of Boston Scientific Corporation or its affiliates. All other trademarks are property of their respective owners.

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In your opinion, where is the biggest current knowledge gap in endovascular stroke care?

I think we still need adjustments to our stroke systems of care. In my opinion, an important gap is that despite significant efforts from our professional societies, some of our patients are still being taken to facilities where intravenous tissue plasminogen activator (IV tPA) can be administered but endovascular care cannot be provided. Although it is important that IV tPA is given as quickly as possible, this should not be done at the expense of delaying endovascular care because, ultimately, that is what will make the difference for patients with large vessel occlusion (LVO). Data from the STRATIS registry support that the interhospital transfer process is onerous for the patient by delaying endovascular treatment and negatively impacting the outcome.1 In our community, as well as other cities, counties, and to a certain level, states, we have been working very hard along with emergency medical services and hospitals to provide endovascular stroke care in a streamlined process and pathway that will lead to faster door-to-groin times and, therefore, faster recanalization, and better outcomes for our patients.

In the past several years, we have seen the global standard of care for emergent LVO (ELVO) change entirely, followed relatively quickly by expansions of the time horizon in which mechanical thrombectomy is recommended as the first-line therapy in appropriate patients. What do you predict will be the next horizon in patient candidacy, whether based on timing or anatomy?

Endovascular treatment with mechanical thrombectomy is the first-line treatment for patients with LVO up to 24 hours from symptom onset, as per current scientific evidence independent of IV tPA eligibility. We have several trials now demonstrating the benefits of mechanical thrombectomy in this patient population with a number needed to treat of 3, making it one of the most powerful emergent treatments in medicine today. However, mechanical treatment is still only being performed in selected patients, and some would argue that we are overselecting patients, which explains the success of the treatment. New studies are being designed or are already underway to evaluate whether some patient groups not included in the current guidelines would benefit from endovascular treatment, such as those with low National Institutes of Health Stroke Scale scores and LVOs, distal occlusions, those already presenting with a large core—to mention a few. I think in the future we will be much more inclusive, which will decrease the overall rate of good outcomes, but it will also increase the total number of patients being helped.

What do you believe is the most significant update or takeaway from the Society of NeuroInterventional Surgery (SNIS) Standards and Guidelines Committee’s recommendations on neuroendovascular management of ELVO published earlier this year?

This type of document is very important in our field, because it provides guidance to the physicians who are involved in the endovascular treatment of acute stroke. The SNIS Standards and Guidelines Committee’s recommendations analyzed the published data not only from the major randomized controlled trials but also from other studies and registries to provide direction and recommendations regarding several technical aspects of the procedure (eg, the use of interarterial thrombolysis, sedation vs general anesthesia, access site, use of (Continued on page 117)
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