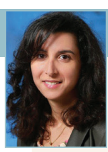
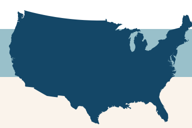
EXPANDING HORIZONS IN EMBOLIZATION

What Does the Future Hold for Interventional Radiologists?

EIGHT LEADERS IN THE INTERVENTIONAL RADIOLOGY FIELD SHARE THEIR THOUGHTS.





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Disclosures: None.

Interventional radiologists (IRs) are always searching for the next big thing into which to expand. In the past 5 years, IRs have explored prostate artery embolization, gastric artery embolization, and genicular artery embolization—even hemorrhoidal artery embolization.

The inventiveness of interventional radiology is one of the specialty's most attractive qualities. IRs' inherent desire to reduce morbidity and mortality by developing minimally invasive solutions is commendable as long as we are able to adequately demonstrate improved outcomes; just because we *can* embolize something does not mean that we *should*.

IRs should remain committed to perfecting what we have developed. Let's consider transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC). With the advent of microcatheters and advanced imaging, outcomes have improved over the past decades, but complete response rates (for intermediate-stage disease) are still low, and the overall response rate is 52%. Drug-eluting embolics (DEEs) are not as disruptive as we had hoped. However, did the DEE fail, or is it the drug we use? Doxorubicin is not very effective against HCC, yet we use it. We still do not know whether hypoxia, drugs, or both are responsible for the antitumoral effect. Moreover, a predominant hypothesis of TACE failure is the release of hypoxia-inducible factor 1-alpha and vascular endothelial growth factor (VEGF); however, all trials combining an anti-VEGF agent with TACE have failed. Clearly, our understanding of the actual mechanism of action and failure for TACE is deficient and needs to be corrected. Oncologic therapeutic options are expanding, and unless we improve our results, we will be outperformed by noninvasive infusions. That being said, better systemic options can be an opportunity for IRs to expand into new indications with better drugs.

The quantity of prospective randomized trials has significantly increased in our specialty, and IRs must remember to follow the evidence, even if it is not where we hoped it would lead—eventually, we will reach our goal.

Finally, a consistent message is that IRs have to be more clinical and keep patients as their top priority. Most understand that message, as IRs see patients before and after procedures and are involved in tumor boards. However, the desire for efficiency has to be replaced by the desire for efficacy. Indeed, cone-beam CT and superselective TACE have been shown to improve outcomes, but segmental or lobar TACE are still being performed for the sake of speed. Standardizing the technique to maximize outcomes is essential. With the new Medicare reimbursement centered on quality rather than fee for service, IRs are positioned to succeed.

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Liver embolization represents one of the primary effective localized therapies against cancer, thanks to the huge amount of data supporting its clinical value. Developed from the basic concept of producing ischemic damage to the cancerous environment, embolization is now increasingly considered as a platform for carrying and delivering therapies to the target. Following this concept, the future will see developments in new and more efficient carriers (eg, beads) and drugs against cancer cells. A deeper knowledge of tumor mechanisms will enhance the development of drugs that are effective for specific cancers.

It is now clear that every tumor has its own specific biological characteristics that define a certain sensitivity (and resistance) to some drugs. Eventually, anticancer molecules to the tumor will be selected according to their tested and proven effectiveness, as has occurred for some of the new systemic therapies. Hence, percutaneous biopsies of the target tumor will be a crucial step in planning embolization therapy.

Moreover, immunology seems to play an essential role in cancer therapy, and it is also related to the emerging concept of tumor-infiltrating lymphocytes. The mechanism of immune activation against cancer is based on the infiltration of tumor by lymphocytes, which damage the tumor mass in some way. Embolization, ablation, and radiation may cause tumor damage, which can activate the immune system against the same cancer cells, even if located in a distant organ or tissue. With embolization, beads could be loaded with certain molecules that could enhance this mechanism.

Last but not least, embolization will play a crucial role in therapy beyond the liver. As we know, every tissue needs blood for survival. The same blood feeders theoretically can be used to affect any organ or tissue. The only limit we have today is how to reach some targets due to the complexity of vascular anatomy. It is also well known in this field how improvements to imaging technology will allow delivery of embolics almost everywhere.

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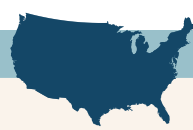


In 1972, Josef Rösch, MD, and colleagues reported the first case of catheter-based arterial embolization on a 43-year-old woman in hemorrhagic shock secondary to a bleeding gastric ulcer.[1] During the initial angiogram, active contrast extravasation from the right gastroepiploic artery was identified. After a failed arterial epinephrine infusion, 2 mL of the patient's venous blood was drawn and allowed to clot. This clot was then injected through the catheter in the right gastroepiploic artery, with subsequent resolution of the patient's hemorrhage.

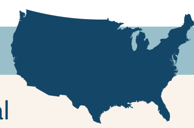
Since then, the field of embolization has flourished to encompass a wide range of indications with a profound impact on patient care. With the advent of smaller-caliber microcatheters and a wider variety of embolic devices, the field of embolization can now be used in a vast array of disease states. The primary intent of embolization has been to stop patients from ongoing hemorrhage. This includes the patient involved in significant trauma, when gelatin slurry or coils are deployed in the internal iliac artery for an unstable pelvic fracture. Coil embolization for diverticular hemorrhage, bleeding ulcers, or ruptured varices continues to play a major role for patients with gastrointestinal hemorrhage. Detachable coils and liquid embolics now allow us to perform embolization in potentially high-risk regions, with a wider margin of safety and greater degree of efficacy. Liver cancer therapy has advanced dramatically with the widespread use of radioactive and DEE agents. Due to these advances, liver-directed therapy for cancer has shifted to an outpatient therapy with vastly improved quality of life for patients.

Where do we go from here? The field of embolic agents will continue to expand down multiple paths. Currently, only two chemotherapy agents are actively used for DEEs. The development of novel and potentially more cytotoxic DEEs over the next several years may result in greater and more durable tumor response. The advent of smaller calibrated microspheres could potentially be used for more distal penetration into tumors, with eventual adoption of nanoparticle technology. Although the current embolic agents are typically permanent, biodegradable particles used for tumor therapy may maintain vessel patency for future interventions. A wider array of liquid embolics, perhaps with controlled polymerization rates, will allow more versatility in terms of treating both high- and low-flow lesions.

The advent of new embolic technologies will be coupled with potentially expanding applications for embolization. Although embolization for cancer has focused on the liver, malignancy in other organs, such as the pancreas, kidneys, and musculoskeletal system, may be candidates for catheter-directed embolization. Research is currently underway using particle embolization to treat inflammatory disorders, which could potentially change the treatment paradigm for these patients.

Although evolving technology always brings excitement to interventional radiology, our challenge is to tailor therapy for each individual patient. With this comes the increasing necessity of producing high-quality safety and outcomes data to prove the effectiveness of our therapy. Nevertheless, the future of embolization shows great promise for our patients.

1. Rösch J, Dotter CT, Brown MJ. Selective arterial embolization. A new method for control of acute gastrointestinal bleeding. Radiology. 1972;102:303-306.



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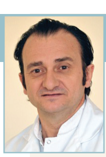
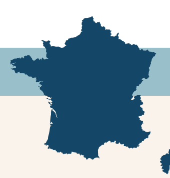
The future of embolization in the interventional radiology space is brighter than ever. This is bolstered by the advances in melding fluoroscopic and cross-sectional imaging, the leaps forward in catheter/wire technology, and the flexibility of use with newer detachable and liquid embolics. The latter is supported by several well-performed studies that have assessed recanalization rates for agents in certain clinical scenarios. These factors have led to substantial advancement in embolotherapy. Whether the vessel is large or small, or whatever the length of vessel occlusion, the progression in coil technology has also allowed for IRs to have a better understanding of what will occur to the tissue that this vessel is supplying, allowing for more predictable outcomes.

IRs, with their superior knowledge and understanding of the cross-sectional space, now have added liquid embolics to their armamentarium. Taking advantage of vessel flow dynamics, liquid embolics provide deeper penetration to the distal vessel, which is not always accessible by coils. However, this is still an area of intense research, as the ideal material has yet to be developed. We now have agents for any clinical scenario—large or small vessels or temporary or permanent occlusions.

The evolution of detachable coils, their materials, and the dynamics of their deployment have made vessel takedown significantly easier and more efficient. Plugs deployed in the right circumstances can hasten procedures and has made the learning curve a bit less steep for our trainees and more junior physicians. All of this has allowed IRs to not only treat more varied and complex medical conditions, but most importantly also has improved patient care.





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Disclosures: None.

Despite the enormous amount of progress made since the 1970s on embolic materials, the potential for future improvements remains infinite. Our research strategies must focus on one clear objective: to peacefully gain new territory through new arms. In recent years, after prostatic artery embolization, bariatric embolization, musculoskeletal pain embolization, emborrhoid, and other spaces, there remain unknown territories.

The development of new microcatheters and very precise guidance tools will enable us to reach these unknown territories. There will be an ability to catheterize very small vessels (< 300 µm) for ultraselective drug delivery, along with a less-invasive (< 3 F) arterial approach to improve patient safety and comfort.

I anticipate the toolbox of the future having custom-made embolic agents: beads loaded with specific molecules and coated with surface antigens, liquids with viscosity and cohesion that are modifiable according to the target, and embolic agents that are excitable and directed by external sources. Imagine, for example, a liquid embolic agent that becomes solid under the excitation of an external field focused on a target.

These technologies already exist in our imagination, and some already exist in our research laboratories. This exciting story of interventional radiology continues to evolve with embolization, and now is the time to think outside the box and reveal new clinical applications that are calling out to us. Embolization also protects IRs with its high technology that resonates with radiology.

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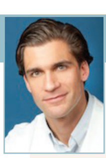
A wide variety of indications, techniques, and compounds for embolization have evolved over time. Beyond the long-established indications for controlling bleeding, various embolization techniques were developed to enhance transarterial tumor treatment. These therapies encompass both benign (eg, uterine fibroids, prostatic hyperplasia) and, perhaps on a larger global scale, malignant conditions, where embolization complements other tumor therapies for enhanced precision. When utilizing embolization technologies, IRs and oncologists could gain an important position in supporting hepatic treatments. Many questions regarding "which, when, and how" embolization techniques should be used are not answered comprehensively, and some answers are still not satisfying.

Inconsistent results remain a challenge with embolic therapies, leaving room for future improvements. Ongoing studies will provide more insight into the pathophysiologic effects of embolization techniques. A better understanding of the currently available embolic compounds and compositions (eg, loaded and unloaded particles, liquids, emulsions, suspensions, permanent or transient embolization) will help to enhance specific treatment needs. Consequently, interventional oncologists may be able to apply embolizing compounds more deliberately in terms of size and loadability. Moreover, because tumor perfusion and humoral (immunologic) parenchymal factors determine tumor growth and influence potential therapy response in the vast majority of tumors, this fuels expectations that the combination of highly precise, transvascular angiographic techniques and various embolization compounds, along with immunologic or targeted therapies, may enhance therapeutic efficacy, precision of addressing tumor tissue, and reduce side effects.

Based on an already existing substantial body of evidence, numerous oncologic guidelines have appreciated the role of embolization in complex treatment regimens, especially in primary and secondary hepatic tumors. This provides ground for a broader acceptance and further development of multimodality treatment, where the multifaceted nature of embolization will play an important role.



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Embolization procedures have been performed for many years by IRs all over the world. Compared to relatively old embolization techniques, we also have a wide variety of "younger" nonembolization techniques available to us, such as branched and fenestrated stent grafts for the treatment of abdominal aortic aneurysms, drug-eluting techniques for the treatment of peripheral artery occlusive disease, and ablation techniques for locoregional tumor treatment. Nevertheless, embolization techniques have shown a dramatic improvement in the last several years—the basis of this improvement is a huge variety of newly developed technical devices for different embolization procedures.

With high-quality devices such as microwires and microcatheters, almost every region of the human body can be reached, and with a variety of available embolization materials, different benign and malignant lesions can be treated. The treatment is, in most cases, minimally invasive with almost no side effects for the patient. In many fields of medicine, these techniques have become the standard of care and should be available in every state-of-the-art hospital.

New embolization therapies such as prostate artery embolization, bariatric embolization, or embolization of hemorrhoids have been developed recently by IRs. In cancer treatments, techniques such as radioembolization or embolization with drug-eluting beads are becoming more common—and I am sure this is not the end. With the upcoming development and evaluation of different new drugs including immunotherapy, new fields of minimally invasive therapies will open up for IRs.

The most important task for all IRs will be to produce good evidence based on randomized multicenter trials to make these new therapies valuable for our clinical partners. Moreover, it will be very important to take care of our patients not only during the interventional procedure, but also in the pre- and postinterventional setting. IRs should not only be excellent technicians in terms of the procedures they perform, but also excellent clinicians in taking care of their patients.

Last but not least, we have to work hard to stay at the forefront in modern hospitals. For that reason, IRs have to be a central part of tumor boards and other hospital decision-making institutions in order to promote our highly advanced diagnostic and therapeutic possibilities.

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Interventional radiology is a clinical specialty that combines correct clinical judgment and technical skills to use devices under imaging guidance to achieve expected patient outcome. Embolization as a therapeutic modality was introduced more than 40 years ago, but has had a revolutionary growth in terms of indications and success in the last decade. Embolization for fibroids, prostate, and some types of liver tumors, combined with chemotherapy or radiotherapy agents, have been recently introduced and have become standard of care in selected patients. Future improvement in technology, devices, and imaging quality will probably result in new indications of embolization and better patient outcomes in different diseases and territories. As the population is aging, an increased incidence of diabetes and obesity will further affect current and potential new interventional radiology treatments throughout the body.

Cancer care through interventional oncology foresees a great future with the development of new biologic drugs, radio sensitizers, immunotherapy, and other antitumor agents that could be easily delivered inside the tumor under imaging guidance. Longer survival of patients is turning cancer into a chronic disease; thus, secondary complications of cancer such as hemorrhage or vascular occlusions will further involve interventional radiology with oncology.

The future seems bright for those interventional radiologists who commit to patient care and are involved in both outpatient and in-hospital management and follow-up. Recognition of interventional radiology by patients, managers, and hospital administration as a clinical specialty and not as a technical service is a must to expand its horizons. As a minimally invasive discipline with short hospital stay and excellent results in appropriate candidates, IRs may have a great impact in value-based medicine. IRs should be encouraged to move from a simple technical specialty to becoming a well-recognized specialty aligned with other key stakeholders to deliver enhanced value to patients through quality, safety, efficiency, and patient satisfaction. ■

In the U.S., no embolic microspheres are FDA indicated for use as a drug-eluting microsphere.