Building the Evidence on Embolization

Gaps in existing data, key trends in clinical study endpoints, the role of registries and potential drawbacks, and the importance of patient-centric endpoints.

With Nadine Abi-Jaoudeh, MD, FSIR

First, what do you see as the biggest gaps in existing data regarding embolotherapy?

It really depends on the embolotherapy indication. In general, there is only a rudimentary understanding in pathophysiologic mechanisms of embolotherapy for geniculate artery embolization, prostate artery embolization, and oncologic embolization. There are many questions left to be answered. One big gap common to most embolotherapies is our inability to predict which patients will respond to therapy. It is unclear why some patients respond to transarterial chemoembolization (TACE) while others do not. We have recently discovered the importance of dosimetry in radioembolization, but we still don't know the ideal dose for complete tumor kill while avoiding risks recently described in several case reports, as well as the misunderstood effects on the tumor microenvironment.

Where is the data support currently the strongest?

Oncologic embolization has the strongest data (randomized controlled data and animal studies) and the largest number of randomized controlled trials (RCTs). Unfortunately, it is also the area with the most gaps and questions that remain to be answered. It started with trials by Llovet et al and Lo et al, both published in 2002, comparing TACE to standard of care for hepatocellular carcinoma.[1,2] Since then, there has been a slew of trials. In chemoembolization, several trials have compared drug-eluting beads (DEBs) to bland beads or DEBs to conventional TACE. None of these trials met their endpoints of superiority of DEBs. In colorectal cancer, the SIRFLOX, FOXFIRE, and FOXFIRE Global trials were all RCTs exploring the addition of yttrium-90 (Y-90) to first-line chemotherapy in metastatic colorectal cancer with liver-only or liver-dominant disease.[3-5] The trials did not meet their endpoint of improved overall survival (OS) with the addition of Y-90; however, improvements in hepatic progression-free survival (PFS) were observed. Recently, the EPOCH trial met its primary endpoint of improved PFS with the addition of Y-90 for patients beyond first-line chemotherapy with metastatic colorectal cancer. Interestingly, despite improving PFS, the EPOCH trial did not find that Y-90 improved OS.[6] The DOSISPHERE-01 study was a prospective randomized trial and showed improved objective response rate with personalized dosimetry versus standard dosimetry in patients with hepatocellular carcinoma.[7] Numerous large, prospective, randomized trials are currently underway exploring the combination of systemic and locoregional therapies.

What are some key trends you've seen in how clinical study endpoints for embolotherapies have evolved in recent years?

This is very broad question. For oncologic applications, OS has been replaced by PFS or overall response rate. In some areas, such as uterine fibroid embolization and other pelvic conditions, we're seeing the creation of endpoints and surveys around quality of life (QOL). The main thing I have noticed in our specialty is a move away from imaging or technical endpoints to patient-centric endpoints, whether survival or QOL endpoints because they are more clinical.

What are the unique benefits or capabilities of large registries in studying embolotherapies? What are some of the potential drawbacks of registries?

The main gap is our inability to predict responders to therapy. Registries like the VIRTEX registry might help narrow down subpopulations that may benefit from a specific intervention. Then, more rigorous trials can be designed with those subpopulations.

The highest quality of evidence is meta-analysis of RCTs. RCTs eliminate the most biases, and several RCTs with the same conclusion affirm the highest level of truth. This is fact even if it is not convenient and expensive. Real-world data can never replace that. If anyone has doubts that this is true, take what happened with hormone replacement therapy (HRT) and cardiovascular risk in women in the 1990s. Observational, real-world studies in 1990 on > 100,000 women determined that HRT for menopausal women would decrease risk of heart attacks, and theoretically, it made sense. Two small, randomized trials found evidence that this may not be true. This led to two large National Institutes of Health trials, which were both halted prematurely because they found that HRT in menopausal women increased the risk of breast cancer, deep venous thrombosis/pulmonary embolism, stroke, and even heart attacks depending on the HRT regimen.

From a practical standpoint, what advice do you have for first-time trialists? And for first-time principal investigators specifically?

Get trained before you embark on your first protocol. The science may come naturally to us, but the legal aspects of research are difficult. About 70% of principal investigators who are audited by the FDA never do another trial even though most audits by the FDA are routine. Several organizations provide courses into research performance, such as the Society of Clinical Research Associates. Certified clinical research professionals can help investigators understand the basic regulations, know responsibilities of when to report adverse events and how fast, the requirements for consent, and investigational drug and device accountability. For example, I learned that shipping labels of investigational products must be kept along with the trial documents. Who even looks at shipping labels? It is important to keep them in trial settings in case of a recall of an investigational product.

When determining optimal endpoints, how vital is the importance of incorporating patient needs and feedback? How can investigators ensure they are incorporating these elements into their studies?

QOL endpoints are essential and have gained even more importance in recent years. Investigators must integrate QOL metrics in their studies. If QOL surveys/questionnaires for a specific disease state are not available, then I would say to follow the lead of an interventional radiology pioneer, Dr. Jim Spies, and create one just as he created one for uterine fibroid embolization. ■

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