The Year in Review and What's Ahead for Embolization Therapies

A brief review of the articles and headlines that helped advance embolotherapy in 2019 and a perspective on what the future may entail.

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Impact of Combined Selective Internal Radiation Therapy and Sorafenib on Survival in Advanced Hepatocellular Carcinoma

Ricke J, Klümpen HJ, Amthauer H, et al. J Hepatol. 2019;71:1164–1174.

In this palliative substudy of the prospective SORAMIC data, 424 patients with Barcelona Clinic Liver Cancer stages B and C hepatocellular carcinoma (HCC) and Child-Pugh scores A to B7 were randomized, with 216 patients receiving selective internal radiation therapy (SIRT) with yttrium-90 (Y-90) plus sorafenib and 208 patients receiving sorafenib alone. There was no significant difference in overall survival (OS) in intention-to-treat analysis, with a median OS of 12.1 months in the SIRT plus sorafenib arm versus 11.4 months in the sorafenib only arm (P = .95). Similarly, there was no difference in OS in the per-protocol population, with a median OS of 14 months in the SIRT plus sorafenib arm versus 11.1 months in the sorafenib only arm (P = .25). Subgroup analyses of the per-protocol population found a significant increase in OS in those treated with combination SIRT and sorafenib for patients aged ≤ 65 years (P = .046), noncirrhotic patients (P = .013), and patients with cirrhosis secondary to nonalcoholic etiology (P = .01). There was a significant increase in the total number of grade 3 and 4 adverse events in the SIRT plus sorafenib arm (P = .036).

The role of SIRT in the setting of advanced HCC remains largely unanswered. In this study, there was no significant improvement in median OS with the addition of Y-90 to sorafenib on either an intention-to-treat or per-protocol analysis, with an associated increase in grades 3 and 4 adverse events. A primary limitation of the study was the relatively large proportion of patients (47.2%) in the SIRT plus sorafenib group who did not receive SIRT and were excluded from the analysis due to major protocol deviations (inappropriate dosing, a delayed start to systemic therapy after SIRT), which may have contributed to the lack of statistical significance in OS between the two groups given the decrease in power. Despite being randomized to SIRT, it is becoming commonplace in randomized controlled trials (RCTs) for patients not to receive it, as demonstrated in the SARAH and SIRveNIB trials. A frequent bias in these studies is the delay in receiving SIRT, with a median time to start of 4 days and 22 days for sorafenib and SIRT, respectively. This may be due to the challenges of technical and scheduling approaches to SIRT and the lack of communication between the oncologist and interventionalist.

Despite the largely negative findings, the subgroup analysis of the per-protocol population showing significantly improved OS in young patients, noncirrhotics, and those with nonalcoholic HCC suggests that further studies evaluating patient selection are warranted.

TOP HEADLINES IN EMBOLIZATION

Mergers and Acquisitions Underscore Growing Industry Emphasis on Embolization

Boston Scientific Corporation finalized the acquisition of BTG, which firmly entrenches them in the interventional oncology and vascular disease market. This acquisition may provide enough economic backing and incentive to fund studies strengthening the role of TheraSphere radioembolic (Boston Scientific Corporation) in the setting of HCC. As a stipulation to this merger, Varian Medical Systems purchased the Boston Scientific embolic division, including Embozene and Oncozene; Varian also bolstered their interventional oncology portfolio with acquisitions of Endocare and Alicon.

Elsewhere, QXMédical purchased the exclusive rights to the resorbable and drug-loadable microspheres and hydrogels developed at the University of Minnesota that are made using organic materials, allowing controlled degradation rates and complete body resorption and, in theory, reducing vascular degradation or occlusion compared with nonabsorbable embolics on the market. It is still unclear if temporary embolics are significantly better tolerated and cost-effective compared with available permanent embolics. Nonetheless, it will be interesting to follow the development and potential clinical application of bioresorbable embolics as they continue to mature and reach the early trial phase.

Positive Data for Novel Applications Headline Annual Congresses

Data presented at various meetings, including the Society of Interventional Radiology and the Cardiovascular Radiological Society of Europe, and published in society journals showed that embolization is finding footing in various new(er) settings, such as for the treatment of OA and obesity. Additionally, more research emerged to support the use of PAE as an effective treatment option. Furthermore, mounting data continue to show not only the efficacy of uterine fibroid embolization but also improvements in cost-effectiveness and QOL.

Device Approvals Signal Continued Expansion for Embolization Use in Peripheral Interventions

Approval of new embolization devices and expanded indications in the United States and abroad, including various plugs, microspheres, and embolic assist devices, indicate the sustained commitment to enhancing physicians' armamentarium for embolic treatment across multiple disease pathologies.

Bariatric Embolization of Arteries for the Treatment of Obesity (BEAT Obesity) Trial: Results at 1 Year

Weiss CR, Abiola GO, Fischman AM, et al. Radiology. 2019;291:792–800.

In this prospective single-arm study, 20 patients underwent bariatric artery embolization (BAE) via transarterial embolization of the gastric fundus at two institutions. The primary endpoints were 30-day adverse events and weight loss at 12 months. Secondary endpoints included technical feasibility, health-related quality of life (QOL) (36-Item Short Form Health Survey [SF-36]), Impact of Weight on Quality of Life-Lite (IWQOL-Lite), and hunger/appetite using a visual assessment scale. The authors reported no major adverse events, with a total of 11 minor adverse events in eight patients. The mean excess weight loss at 1, 3, 6, and 12 months was 8.2%, 11.5%, 12.8%, and 11.5%, respectively. There was a significant increase in mean IWQOL-Lite score from 57 to 77 ($P < .001$) from baseline to 12 months. There was an initial significant improvement in QOL at 6 months (SF-36 score increased from 46 to 53; $P = .01$), which was not durable or significantly different from baseline at 12-month follow-up. The greatest change in hunger score was noted at 1 month, with a 51% decrease from baseline. After 1 month, there were sequential decreases in the percent change in hunger, with a 26% decrease in hunger from baseline at 12 months.

In this study of 20 patients, the authors demonstrated the safety and efficacy of BAE for clinically relevant weight loss, which is defined in the study as > 5%, per the FDA benchmark for devices and low-risk drugs. The authors suggest that BAE is not a replacement for bariatric surgery, which has an upwards of 30% postprocedural weight loss, but it may serve as an adjunct for patients who continue to struggle with weight loss despite lifestyle modification. Further investigations are necessary to better outline the degree of weight loss beyond 1 year, compare efficacy with and without alternative treatments, refine the patient selection, and elucidate the underlying metabolic effects after embolization.

Clinical Outcomes of Transcatheter Arterial Embolisation for Chronic Knee Pain: Mild-to-Moderate Versus Severe Knee Osteoarthritis

Lee SH, Hwang JH, Kim DH, et al. Cardiovasc Intervent Radiol. 2019;42:1530–1536.

In this retrospective study, 30 patients with mild-to-severe osteoarthritis (OA) refractory to conservative therapies underwent 71 geniculate artery embolization (GAE) procedures. The primary clinical endpoint was the change in the Visual Analog Scale (VAS) for pain at 1 day, 1 week, and 1, 3, and 6 months. Changes in the use of more conservative treatments, including nonsteroidal anti-inflammatory drugs, physical therapy, and intra-articular therapies, were also recorded at follow-up. Clinical success was defined as a decrease of ≥ 50% in VAS compared with baseline.

GAE was successfully performed in all patients. In the mild-to-moderate OA group, there was a significant decrease in mean VAS at 1 day (3.2), 1 week (3.1), 1 month (2.9), 3 months (2.2), and 6 months (1.9) compared with baseline (5.5; $P < .001$). Clinical success was achieved 3 months postprocedure and was maintained to the final 6-month postembolization follow-up exam. In patients with severe OA, VAS significantly decreased at 1 month compared with baseline (4.4 vs 6.3, respectively) but subsequently increased at 3- and 6-month follow-up (5.4 and 5.9, respectively). Significant clinical success was not achieved in the severe OA cohort.

GAE is a rapidly growing niche in interventional radiology (IR) with the potential to effectively treat a large number of patients with varying degrees of disability caused by OA. In addition to contributing to the promising findings detailed by Okuno et al in 2017,[1] the authors demonstrated the disproportionate benefit following embolization in patients with mild-to-moderate OA. Understanding the intricacies of patient selection is crucial in the design of future trials, especially for novel interventions with limited data, to ensure that inclusion criteria are optimized to include patients who are most likely to yield benefit from embolization.

CRITICAL QUESTIONS FOR THE FUTURE

The Role of Locoregional Therapy Versus Systemic Immuno-Oncology Therapy in Advanced HCC

Since the incorporation of sorafenib in the HCC treatment paradigm in 2008 after the SHARP trial, there has been a major pharmaceutical push into the space of advanced HCC.[2] Immuno-oncology, including multiple tyrosine kinase inhibitors (sorafenib, regorafenib, and lenvatinib ["-ibs"]) and checkpoint inhibitors (ipilimumab and nivolumab ["-mabs"]), is a growing field resulting in multiple large RCTs investigating their role in advanced, unresectable HCC. The looming question that was recently studied in three large RCTs (SARAH, SIRveNIB, and SORAMIC) is the survival benefit of locoregional therapy to systemic therapy. Although these studies demonstrated no significant OS benefit between SIRT and sorafenib, they showed improved tolerance of locoregional therapy to sorafenib. These studies also underscore the importance of IR to better standardize the approach and technique of delivering locoregional therapy. The lack of locoregional treatment uniformity and procedural experience in these studies, in addition to the lead-time bias in time to receive locoregional therapy compared with systemic therapy, can become a major confounder in the interpretation of these studies.[3] Therefore, a critical challenge in IR is the creation of a consistent protocol for locoregional therapy to deploy in these multicenter studies to better elucidate how liver-directed therapy compares with and, more importantly, complements systemic therapy, especially as novel immunotherapies become more widely applied in a clinical setting. With more RCTs investigating combination therapy, a true representation of technically appropriate locoregional therapy is vital to prove its worth in the treatment paradigm.

The Rise of PAE for BPH

Over the past few years, there has been increasing interest in incorporating PAE into the algorithm for symptomatic BPH. With studies beginning to demonstrate significantly fewer adverse events compared with surgical alternatives, the adoption of this minimally invasive treatment option is expected to become more widespread. This is exemplified by the growing approval of PAE in insurance coverage in the United States and the United Kingdom for patients with BPH and lower urinary tract symptoms. The growth of PAE as a valid treatment option further highlights the need for cooperative efforts with urology and a more clinically oriented interventionalist. In a broader sense, as IR physicians continue to provide alternatives to "gold standard" invasive surgical procedures, the critical task lies in the ability to own and understand the disease entities to the same degree as the specialists with whom we hope to collaborate, while maintaining our proficiency as imaging and procedural experts. Acquiring such clinical acumen will further solidify the role of IR as integral to the health care team.

Immune Activation Underlies a Sustained Clinical Response to Yttrium-90 Radioembolisation in Hepatocellular Carcinoma

Chew V, Lee YH, Pan L, et al. Gut. 2019;68:335–346.

The authors isolated tumor-infiltrating lymphocytes and peripheral blood mononuclear cells from 41 patients with HCC who underwent surgical resection with and without previous Y-90 SIRT at several intervals. Multiple analyses with time-of-flight flow cytometry and next-generation sequencing demonstrated enrichment of the tumor microenvironment with a variety of immunologic mediators and upregulation of genes related to innate and adaptive immune responses when compared with controls.

Patients with the sustained response after Y-90 had a significantly higher expression of tumor necrosis factor-α, a proinflammatory cytokine expressed on CD8 and CD4 T cells 1 month after SIRT, followed by an increase in antigen-presenting cells 3 months postprocedure. T cells specific to the sustained responders also showed higher expression of programmed cell death protein 1 and TIM-3 (exhaustion markers that accompany systemic immune activation) before and after Y-90 therapy, suggesting a higher level of peripheral T cell activation, which may partly facilitate sustained response to SIRT. Increased expression of chemokine receptors CCR5 and CXCR6 were also noted in sustained responders, implying increased recruitment of T cells to tumor sites. Using the differences in immunologic biomarker expression between nonresponders and responders, the authors also derived a model to predict response after SIRT with greater accuracy than tumor stage or multiplicity.

With the growing focus on immune modulation in oncology, the intersection between interventional procedures and novel medical therapies is an area of intense research. This investigation outlines elements of the sustained immune response following SIRT within the tumor microenvironment and peripheral blood, which may serve as a backdrop for future clinical studies evaluating the synergistic effects of combined locoregional and systemic immunologic approaches. Additionally, the authors characterized immunologic biomarkers that may predict which patients would have a sustained response to SIRT, both before and early after treatment.

Prostatic Artery Embolization for Benign Prostatic Hyperplasia: Prospective Randomized Trial of 100–300 µm Versus 300–500 µm Versus 100- to 300-µm + 300- to 500-µm Embospheres

Torres D, Costa NV, Pisco J, et al. J Vasc Interv Radiol. 2019;30:638–644.

In this prospective, single-center RCT, 138 patients underwent prostate artery embolization (PAE) for benign prostatic hyperplasia (BPH) with moderate to severe lower urinary tract symptoms, as defined by International Prostate Symptom Score (IPSS) ≥ 18 and QOL response ≥ 3. Patients were randomized to receive embolization with 100–300-µm (group A), 300–500-µm (group B), or 100–300-µm followed by 300–500-µm (group C) trisacryl gelatin microspheres (Embospheres, Merit Medical Systems, Inc.) to the angiographic endpoint of near stasis.

There was no significant difference in clinical success between the three arms at 18 months (76.7% for group A, 82.6% for group B, and 83.3% for group C; $P = .68$). Throughout the study period, all groups experienced a statistically significant decrease in IPSS, QOL, and prostate volume and a statistically significant increase in peak urinary flow. No significant difference was noted between the three groups in any clinical variable, with multiplicity adjusted $P > .99$ in all comparisons. There was a total of 137 reported adverse events, which were all mild in severity and self-limited. Of the 137 adverse events, 86% (37 of 43) occurred in group A, 41% (19 of 46) in group B, and 58% (28 of 48) in group C ($P < .001$).

This RCT not only confirms a previous study demonstrating no significant difference in outcomes between 300–500- and 100–300-µm microspheres but, more importantly, also notes an increase in mild adverse events with smaller particles.[4] Aside from demonstrating clinical efficacy, studies refining embolization techniques are important to optimize patient outcomes and limit adverse events. Compared with transurethral resection of the prostate, PAE has been shown to have significantly fewer adverse events, and additional efforts to lower complication rates will further establish its applicability in otherwise healthy patients seeking an efficacious and safe alternative.[5] ■

1. Okuno Y, Korchi AM, Shinjo T, et al. Midterm clinical outcomes and MR imaging changes after transcatheter arterial embolization as a treatment for mild to moderate radiographic knee osteoarthritis resistant to conservative Treatment. J Vasc Interv Radiol. 2017;28:995-1002.
2. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.
3. Sposito C, Mazzaferro V. The SIRveNIB and SARAH trials, radioembolization vs. sorafenib in advanced HCC patients: reasons for a failure, and perspectives for the future. Hepatobiliary Surg Nutr. 2018;7:487-489.
4. Gonçalves OM, Carnevale FC, Moreira AM, et al. Comparative study using 100–300 versus 300–500 µm microspheres for symptomatic patients due to enlarged-BPH prostates. Cardiovasc Intervent Radiol. 2016;39:1372-1378.
5. Abt D, Hechelhammer L, Müllhaupt G, et al. Comparison of prostatic artery embolisation (PAE) versus transurethral resection of the prostate (TURP) for benign prostatic hyperplasia: randomised, open label, non-inferiority trial. BMJ. 2018;361:k2338.

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