Current and Expanding Applications of Radiation Segmentectomy

A comprehensive review of radiation segmentectomy in *Radiology* journal prompts a discussion on its role versus other available therapies, dosimetry optimization, patient selection, future applications, and unanswered questions.

With Robert J. Lewandowski, MD, FSIR, and Beau Toskich, MD, FSIR

RADIATION SEGMENTECTOMY EVOLVING; FURTHER STUDY NEEDED ON LONG-TERM OUTCOMES, OPTIMAL PATIENT SELECTION, AND APPLICATIONS OUTSIDE THE LIVER

Initially a palliative therapy for patients with advanced liver cancer, transarterial radioembolization (TARE) with yttrium-90 (Y90) is now used as a potential curative ablative option for localized hepatocellular carcinoma (HCC). This evolution has been facilitated by techniques that provide the administration of high-radiation-dose microspheres to targeted hepatic segments, which limits radiation exposure of normal hepatic parenchyma, known as radiation segmentectomy.

With technologic advancements, including microcatheters and microwires, availability of glass and resin microspheres, imaging modalities such as cone-beam CT, and personalized TARE dosimetry, radiation segmentectomy continues to evolve.

In an article published in *Radiology*,[1] Lewandowski et al comprehensively review the concept of radiation segmentectomy and where it is most effective, the importance of TARE dosimetry, and the efficacy of Y90 TARE as compared with other treatment options for HCC (eg, thermal ablation and surgical resection). The potential of radiation segmentectomy for expanded applications, both within the realm of HCC, in metastatic disease, and outside the liver, are also briefly described.

ENDOVASCULAR TODAY ASKS…

Drs. Lewandowski and Toskich were asked to elaborate on key findings of their review, as well as overall thoughts on the evolving role of Y90 TARE and radiation segmentectomy, decision-making considerations, areas for future innovation, and more.

What are the most significant challenges in determining optimal patient selection for Y90 TARE?

With the evolution of Y90 TARE and the advancement of radiation segmentectomy as a curative-intent therapy for select patients with HCC, one of the challenges for multidisciplinary teams is determining best patient selection practices for surgical resection, thermal ablation, and radiation segmentectomy. From a technical standpoint, good candidates for radiation segmentectomy generally have tumor burden limited to a treatment angiosome, with an expendable volume of liver (usually < 25% for Child-Pugh A/ALBI [albumin-bilirubin] 1 and < 15% for Child-Pugh B/ALBI 2) and favorable arterial supply.[2] These parameters are evaluated with mapping angiography and cone-beam CTA, ensuring appropriate treatment targeting with adequate margin and the absence of nontarget arterial supply, such as enteric or biliary branches. Tumors can have multiple tumor-perfusing branches that require multisite dose administrations, and they can have extrahepatic perfusion (eg, from the cystic or phrenic artery) that requires thoughtful investigation to achieve a curative result. Occasionally, large tumors with high lung shunts may preclude ablative dosimetry. If blood supply is not favorable, the PREDATOR technique can be used for flow diversion with balloon microcatheters, gelfoam, particles, or coils.[3] Patients with hepaticojejunostomy or biliary stents can be at risk for posttreatment infection, and this should be discussed with the multidisciplinary team.

As noted in your *Radiology* article, radiation segmentectomy is currently a recognized treatment for Child-Pugh A patients with a solitary HCC < 8 cm and for metastases that cannot be resected or receive thermal ablation.[1] However, you mentioned that there is growing evidence showing similar effectiveness of radiation segmentectomy in smaller tumors as compared with thermal ablation. What is your opinion on its potential role in smaller tumors and benefits of use?

Retrospective, propensity score–matched, peer-reviewed publications have demonstrated comparable oncologic outcomes between thermal ablation and radiation segmentectomy, with radiation segmentectomy outperforming thermal ablation (microwave ablation [MWA]) for patients with HCC < 4 cm in terms of progression-free survival (57.8 months for radiation segmentectomy vs 38.6 months for MWA; $P = .005$).[4,5] The RASER study demonstrated that radiation segmentectomy is a suitable alternative to MWA, especially in patients in whom thermal ablation is not optimal (tumor positioned in a challenging location, such as near the portal triad or in the hepatic dome). The high tumor imaging response rates without local tumor recurrence in this prospective study coupled with the low adverse event rates demonstrate the potential role of radiation segmentectomy in lieu of thermal ablation for patients with small HCC.[6] In a multicenter study, radiation segmentectomy was compared to surgical resection and demonstrated comparable oncologic outcomes but higher adverse events in patients treated with surgery.[7] Radiation segmentectomy does not require advanced imaging software for navigation, fusion, or margin confirmation, and there is no requirement for general anesthesia or risk of tumor tract seeding. One drawback of radiation segmentectomy compared to thermal ablation is the necessity of two sessions: a mapping procedure and a treatment procedure. However, evolving published literature is challenging this concept, demonstrating small lung shunt fractions and subsequent low lung doses when treating small angiosomes for patients with early state HCC.[8,9] Ultimately, there is a population of patients not optimal for thermal ablation who have been treated via radiation segmentectomy with curative outcomes, and this is why radiation segmentectomy has been well adopted by the hepatobiliary oncology community.

Both glass (TheraSphere Y90, Boston Scientific Corporation) and resin (SIR-Spheres, Sirtex Medical) microspheres are now FDA approved for unresectable HCC. What key clinical and procedural considerations influence your choice between glass and resin microspheres?

Although both glass and resin microspheres now have FDA approval for treating unresectable HCC, most of the published radiation segmentectomy data are with glass microspheres. Glass microspheres are well-suited for this application because these microspheres have the highest specific activity at calibration through the first week of decay. They are also microembolic, which allows for reliable delivery of the prescribed dose and improved rates of complete pathologic necrosis compared to spheres with lower specific activity.[10]

The Sirtex FlexDose delivery program for resin microspheres is an advancement designed to allow for higher-specific-activity resin microspheres. Early resin radiation segmentectomy data using Flex 3 spheres have shown that vascular stasis is possible with resin microsphere radiation segmentectomy,[11] inhibiting the ability to deliver the entire prescribed dose. Radiation segmentectomy data with higher-specific-activity spheres, such as the recently released Flex 7 product, are developing and will likely require its own recommendations for best practice.

Dosimetry plays an important role in ensuring complete pathologic necrosis, with a

dose recommendation of > 400 Gy for solitary HCC ≤ 8 cm incorporated into National Comprehensive Cancer Network and Barcelona Clinic Liver Cancer guidelines. What is one of your top tips to optimizing dosimetry in HCC?

Common to both glass and resin microsphere radiation segmentectomy is the desire to provide curative intent through ablative dosimetry. The recommendation for delivering > 400 Gy to solitary HCC ≤ 8 cm is for glass microspheres based on the LEGACY study, and it is not translatable to resin microspheres.[12] However, 400 Gy can be achieved with multiple permutations of both specific activity and particle density. A recent publication with glass microspheres demonstrated that using particles with specific activity ≥ 570 Bq delivered improved explant complete pathologic necrosis (CPN), despite being prescribed ablative dosimetry; with lower-specific-activity microspheres, a total angiosome particle density ≥ 11.4 X 103/mL was needed to achieve CPN.[13]

Personalized dosimetry is increasingly being evaluated to improve patient-absorbed dose and potential hepatotoxicity, and voxel-based dosimetry is a relatively new concept for Y90 radioembolization treatment planning to help improve efficacy. Where do you stand on this, and where do you see this best used in clinical practice?

Personalized dosimetry is a very appealing concept for patients with advanced and/or multifocal disease. Further, personalized dosimetry allows more a more standardized dosimetry approach, and it is positioned to be a mandatory component for those with a radioembolization program. The reproducibility of personalized dosimetry can be limited by the inadequacies of macroaggregated albumin (MAA) as a microsphere surrogate and the ability to predict inhomogeneous particle distribution. However, most of the current radiation segmentectomy data are based on MIRD (medical internal radiation dosimetry), assuming homogeneous microsphere distribution throughout the perfused angiosome (tumor:normal = 1). This is an easy and reproducible approach, but it does not take tumor burden (eg, size and number) into consideration. Although there is an opportunity to improve the reproducibility of radiation segmentectomy outcomes with voxel-based dosimetry in larger tumors or those with intratumoral vascular variability, proving efficacy with this approach will be challenging given the current high rates of both imaging and pathologic complete response after radiation segmentectomy.

In your opinion, where does radiation segmentectomy show the most promise outside of its current use?

Radiation segmentectomy has proven its ability to offer curative radiation therapy where other standards have been limited. Enrollment was recently completed in the FRONTIER trial in which patients with refractory glioblastoma multiforme were treated with intracranially administered transarterial glass microspheres, known as NVRT (neurovascular radiotherapy). The ability to provide this therapy for challenging tumors, but with favorable blood supply, is an exciting and novel proposition for oncology that is currently being explored.

What are the gaps in knowledge that you would like to see answered in the next few years?

Over the past 10 years, radiation segmentectomy data for HCC have significantly moved the dial for this therapy as a curative-intent treatment. Standardization of patient selection, angiographic techniques, and advanced personalized dosimetry will make this therapy a more reproducible and appealing option. Of note, upcoming radiopathologic studies such as the COBRAS Consortium will further solidify radiation segmentectomy best practice for HCC. Over the next few years, we envision radiation segmentectomy without mapping angiography/MAA for small HCC, improving procedural efficiency and improving patient quality of life. Understanding how we can improve therapy delivery may be equally as important. Also, radiation segmentectomy is being increasingly applied to non-HCC liver tumors. More data, including radiopathologic studies aimed at determining threshold dosimetry to achieve CPN, will be needed. We are grateful for the excellent outcomes radiation segmentectomy has provided to our patients and are excited for its future advancements. ■

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