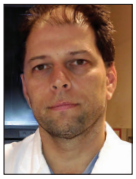
HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Selective Internal Radiation Therapy Using Yttrium-90 in Early and Intermediate Hepatocellular Carcinoma



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G&H How does selective internal radiation therapy using yttrium-90 work?

RS Selective internal radiation therapy (SIRT), also known as radioembolization, involves the intra-arterial injection of micron-sized radioactive yttrium-90 (Y90) particles. SIRT capitalizes on the physiology of liver tumors in hepatocellular carcinoma (HCC), which develop large blood vessels as they grow. This hypervascularity allows interventional radiologists to catheterize the vessels and infuse millions of microspheres that emit radiation. This method effectively delivers very high doses of radiotherapy from the inside out, as opposed to more classic techniques that deliver radiation from the outside in.

G&H What evidence supports the use of SIRT with Y90 in patients who have early or intermediate HCC?

RS There is now approximately 20 years of experience with the use of Y90 microspheres in HCC. The seminal LEGACY study demonstrated very high response rates as well as safe, curative intent in early disease in tumors up to 8 cm. These data led to premarket approval of this method, the first approval of its kind, by the US Food and Drug Administration (FDA) as well as incorporation into the recent Barcelona Clinic Liver Cancer (BCLC) guidelines. Furthermore, these data were validated by the RASER study, which showed in a prospective manner that the ability of radiation segmentectomy to deliver very high doses of radiation in small targets where the tumors are located is quite feasible and, in fact, curative. Hundreds of centers have replicated these data across Europe, the Middle East, Asia, and the United States supporting the notion that the technical feasibility of this method is reproducible. Doses can be administered in a safe and effective manner and can be applied across a wide spectrum of patients in the BCLC algorithm.

G&H How well does SIRT using Y90 work in subgroups of patients with early or intermediate HCC or in comparison with other techniques?

RS In terms of early disease, solitary tumors less than 8 cm are representative of the LEGACY clinical trial, which demonstrated excellent response rates and prolonged duration of response. Of course, the smaller the tumor, the better the outcome. SIRT using Y90 competes with, and in some cases outperforms, radiofrequency ablation in terms of curative intent in early HCC. In patients with multifocal disease that are within transplant criteria, SIRT with Y90 can also be used to bridge patients to liver transplant, in addition to being used in a curative manner.

When it comes to intermediate disease, many papers support the use of Y90 over chemoembolization, the current standard in the BCLC guidelines, given its very high response rates, safe technical aspect, and maintenance of

liver function. SIRT using Y90 has shown survival rates of 25 to 30 months in this patient population, matching guideline expectations of outcomes of treatment in the intermediate setting. Finally, the TRACE trial also showed the superiority of Y90 over drug-eluting beads in a randomized study.

It should also be noted that with other external beam techniques, treating the liver can be challenging because of motion artifact, respiration, and adjacency to other tissues. Those issues have not come up with Y90, which is why it has been adopted very rapidly. Also, in more than 90% of patients with early disease, Y90 is a onetime treatment.

G&H How safe and effective is the use of systemic therapy in combination with SIRT with Y90?

RS The reality is that patients go through HCC treatment algorithms in a complex, multidimensional manner, where they jump from treatment to treatment depending upon disease progression and tolerance. Investigators have long looked at the use of SIRT with Y90 in combination with systemic therapies, as these treatments are a very important standard of care in this patient population.

> … SIRT with Y90 can be performed safely and patients can be started on systemic therapies 3 to 5 weeks later with no adverse events from the combination.

Many doctors believe that it is important to apply the strongest HCC therapy available upfront and then use other therapies to maintain good response. That is why we always think about using a local therapy first and then a systemic therapy to maintain the response. We have seen in both retrospective and prospective manners that SIRT with Y90 can be performed safely and patients can be started on systemic therapies 3 to 5 weeks later with no adverse events from the combination.

G&H Could you expand on the safety of using SIRT with Y90 in this patient population?

RS Safety is an important component of radioembolization. The technical aspects to ensure safety have been at the forefront of training for Y90; thus, teaching sessions and manuscripts are important components to making sure providers learn the current state of the art. When patients have good liver function, lobar and segmental infusions can be performed without any problems, and liver functions will be maintained. When liver function is elevated but stable, selective SIRT with Y90 can be performed, and this will not adversely affect the liver because radiotherapy is being used in a very small area of the liver. Another good safety component is that Y90 treatment can be performed on an outpatient basis; patients can go home and do not need to be hospitalized.

In terms of adverse events, interventional radiologists try to avoid radiation-induced liver disease, which occurs when patients are selected improperly and whole-liver or very wide radioembolization is performed, thereby affecting much of the liver parenchyma. This is when adverse events develop.

G&H What are the main limitations or risks with this treatment approach?

RS As with any technical procedure, a skill set is needed. For example, liver transplant cannot be performed without skilled transplant surgeons. Thus, with SIRT using Y90, interventional radiologists are needed who are well versed in the technique, who have been properly trained, and who understand all of the components of the procedure, including its indication, liver functions, dosimetry, FDA approval, required imaging follow-up, and overall intent. Training and proctoring are integral components of Y90 treatment, which is growing at a very rapid rate.

In terms of risks, just like other procedures, if patients are selected improperly—for example, if they have abnormal liver function or excessive metastatic disease that should be treated with systemic therapy and not local regional therapy—they will not have a very good outcome. Thus, patient selection, particularly in terms of performance status, the degree of disease burden, and liver function, is very important for SIRT.

G&H Are randomized controlled trials still needed on the use of SIRT using Y90 for the treatment of early or intermediate HCC?

RS This is a controversial question, and the answer depends on who is asked. More randomized controlled trials (RCTs) would theoretically be good. The challenge is the feasibility of completing RCTs in the early setting. In fact, many of the current recommendations in the early setting are not based upon RCTs but phase 2 and cohort

studies because RCTs in this setting would require very long follow-up (5-9 years), hundreds of sites, and likely hundreds of millions of dollars for completion.

In addition, there is an ethical dilemma randomizing patients against treatments that are strongly established and have compelling data, of which there are many in early disease. An example would be performing an RCT against liver transplant, which is not feasible because of the very compelling outcomes and ethical implications of not transplanting someone who is potentially transplantable.

Thus, I would say that there is plenty of evidence to support the use of SIRT with Y90 in the early setting. The intermediate setting is potentially where randomized evidence might help doctors delineate which patient population does best. However, as discussed, these studies would require many years and thousands of patients, becoming a technical infeasibility.

G&H Why is the United States so Y90-focused, as opposed to Europe where guidelines give it a low score?

RS The United States is very Y90-focused because, in contradistinction to the rest of the world, we advocate for same-day and outpatient treatment. Discharging a patient on the same day is an important metric in the United States. It is not an important component of European guidelines. Some side effects of Y90, such as fatigue, can develop a number of days after the procedure; thus, doctors in Europe will admit patients for several days even if they feel fine, unlike in the United States.

As for some guidelines giving Y90 a low score, in general that is based upon the perceived level of evidence and experience with the therapy. Although it received a lower score than other therapies, Y90 received a score high enough to be included in the recently updated BCLC guidelines. Due diligence in terms of ranking levels of evidence will show a broad range of scores for data, but that does not mean that a therapy will not be included in the guidelines even with a low score. In general, surgery and transplant have moderate scores but can still be the number one treatment options; they have lower scores only because of the level of evidence. Their clinical utility is very high. All of this has to be taken into account.

G&H Does stereotactic body radiation therapy also have a role in early or intermediate HCC?

RS We believe in a multidisciplinary approach to the treatment of HCC. Y90 is radiotherapy delivered from an internal standpoint, whereas stereotactic body radiation therapy (SBRT) is radiotherapy from an external standpoint. Both involve radiation, and we know that Y90 and radiotherapy work for these types of tumors. What is needed next is a clear identification of which tumors are best treated with Y90 and which are best treated with SBRT, for example. Radiation oncology should be part of the multidisciplinary tumor board where the best treatment option for a patient is decided. Certainly, there are many areas of the liver where Y90 is challenging from a technical standpoint and SBRT may have a better role, and vice versa.

G&H Are there any common misconceptions in the medical community about SIRT with Y90?

RS One is that only a few centers can reproduce these outstanding outcomes. That is not true. SIRT with Y90 can be performed at many centers, and the data have been replicated in multiple, very prominent institutions with increasingly better outcomes because of improved patient selection.

Another misconception implies that patients develop hepatic dysfunction or liver function abnormalities after treatment. When proper patient selection is performed (ie, selecting patients with Child-Pugh A and some with Child-Pugh B7), liver functions remain steady, and patients are able to receive systemic therapy at disease progression.

Finally, there is a misconception that because of systemic therapy, Y90 should not be considered in patients with portal vein thrombosis. However, in patients with portal vein thrombosis and no metastases, Y90 has shown very good safety and efficacy. It is able to bridge patients to resection and transplant, which is new for this patient population because of the very strong cytotoxic effect of Y90 on the tumor and portal vein thrombosis. In the presence of portal vein thrombosis, many physicians opt to use Y90 prior to adding systemic therapy.

G&H What are the next steps in research regarding the use of SIRT with Y90 in early or intermediate HCC?

RS One of the next steps involves the combination of Y90 with systemic therapy when patients progress. For example, what happens when a patient receives Y90 but develops new tumors, and is not a candidate for transplant, ablation, or resection? Which systemic therapies are next? Systemic therapy has made major advances in HCC, but patients develop resistance at some point, or they develop 1 or 2 tumors that break through and progress, even though the patient is otherwise stable. This is where a local therapy such as Y90 can be used to solely treat the progressing lesion(s) all the while maintaining the patient on the systemic therapy that is doing well with

good tolerance. This minimizes premature discontinuation of systemic therapy, which is important because of the limited treatment options.

More research is also needed on the use of Y90 in patients with portal vein thrombosis. Some RCTs on Y90 tried to outperform the standard of care at the time, sorafenib, in patients with advanced disease who had portal vein thrombosis, but these were not successful in showing superiority. The DOSISPHERE study randomized standard dosimetry to high-dose Y90 in patients with portal vein thrombosis and large tumors. The study had a clever design in which randomization occurred after the diagnostic angiogram and the lung shunt fraction assessment. Overall survival was essentially increased by almost 150%, from approximately 11 months to 26 months. This was a compelling clinical trial that showed that despite the advent of systemic therapy, there is a role for Y90 in patients with portal vein thrombosis, particularly those with large tumors.

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This is a rapidly developing therapy with quick adoption by the marketplace, and there is excitement in its ability to combine with systemic therapy. There is hope that we can eventually achieve the ultimate goal in HCC, patient cure.

Disclosures

Dr Salem is a consultant for Boston Scientific, Cook, AstraZeneca, Eisai, Genentech, Roche, Autem, and Becton Dickinson.

Suggested Reading

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