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Review Article

Superselective transarterial radioembolization for the treatment of hepatocellular carcinoma

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A B S T R A C T

Superselective transarterial radioembolization (TARE) refers the delivery of Y90 at the tumor-feeding segmental or subsegmental arteries. The purpose of TARE would be delivering high dose in the tumor while saving as much normal parenchyma as possible. This concept is similar to the radiation segmentectomy. To identify all tumor feeders, thorough angiography and cone-beam computed tomography are essential. Reported target dose of radiation segmentectomy ranges 222.6–521 Gy. After superselective TARE, the treated segments can show persistent enhancement, and then atrophy combined with capsular retraction. Superselective TARE promises favorable outcomes. It's reported objective response rates range 64%–95% and toxicities are tolerable in most cases. In conclusion, superselective TARE is a very safe modality for the treatment of HCCs with favorable outcome close to the curative-intent treatments in selected patients.

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Keywords: Hepatocellular carcinoma; Radiation segmentectomy; Superselective approach; Transarterial radioembolization

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the second most common cause of cancer-related mortality.¹ Despite of the development of surveillance and early diagnosis, about half of patients are diagnosed in the intermediate or advance stage.² The Barcelona clinic liver cancer (BCLC) guideline recommends the transarterial chemoembolization (TACE) as a primary treatment for intermediate-stage HCC, and systemic treatment for advanced-stage HCC.³

Transarterial radioembolization (TARE) is a relatively novel treatment by a selective intra-arterial delivery of yttrium-90 (Y90)-loaded microspheres, which serve as sources of internal radiation. Recently, TARE has been considered as an alternative treatment option to TACE and sorafenib in patient with intermediate and advanced stage HCC. With the best optimism, two important randomized controlled trials (SARAH and SIRveNIB) had been conducted to compare efficacy and safety of TARE with those of sorafenib in locally advanced and inoperable HCC.^{4,5} Disappointingly, these trials failed to prove the superiority of TARE in survival. SARAH and SIRveNIB had included very heteroge-

neous patient group, and currently, many researchers are trying to refine the technique of TARE for the selected patients for the improvement of treatment outcome.

TARE is essentially a kind of radiation therapy and there are some limitations for the treatment of liver tumors: > 70 Gy are needed for the destruction of liver tumors,⁶ whereas the tolerance of normal liver tissue is only about 30 Gy⁷ to prevent hepatic dysfunction. Therefore, main considerations during planning and administrating Y90 delivery should be focused on giving as much doses as possible in as few liver volumes as possible.

The purpose of this review is to provide an overview on current status of superselective TARE. As this review is not performed systematically, it may be biased by the author.

Concept of Superselective Transarterial Radioembolization

Superselective TARE is not a well-established concept. Though there are few case series dealing with superselective TARE,^{8,9} this term is not frequently used in the literature yet. The term “superselective” is more commonly used in the literatures on TACE. Superselective TACE means that TACE at the distal portion of the

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tumor-feeding subsegmental hepatic artery.¹⁰ It is regarded as a standard technique for localized HCCs in Asian countries. If we introduce this concept for TARE, superselective TARE can be defined as the delivery of Y90 at the tumor-feeding (sub)segmental arteries, contrary to the conventional lobar treatment. A more frequently used term for a concept similar to this may be radiation segmentectomy. Radiation segmentectomy refers segmental TARE using intentionally ablative doses of Y90 microspheres, generally for two or fewer hepatic segments, which was first described by Riaz et al.¹¹ While radiation segmentectomy emphasize the purpose of the treatment-ablation of the treated segment for curative intention, superselective TARE can be said to be the term focused on the technique of delivering Y90 via multiple segmental and subsegmental tumor feeders to save the remaining ipsilateral segments from any radiation toxicity.

Indications

Patients with (1) small solitary tumor; (2) liver-confined disease; (3) tumor supplied by no more than two hepatic segments, who are not tolerated surgical resection, are considered as good candidates for radiation segmentectomy. Poor candidates for percutaneous thermal ablation due to unfavorable tumor location, such as in the hepatic dome area, or near the bowel, gallbladder, or porta hepatis also can get benefit of radiation segmentectomy (Fig. 1). For the patients with larger tumor involving three or more hepatic segments with marginal hepatic function, we can perform TARE more safely by superselective delivery of Y90 at the all identifiable segmental or subsegmental tumor-feeding arteries instead of at the lobar artery.

Planning Angiography and Dosimetry

Thorough angiography is very important for superselective

Fig. 1. Superselective transarterial radioembolization for hepatocellular carcinoma (HCC) close to the extrahepatic organs. (A) An arterial phase magnetic resonance (MR) image shows a 5-cm diameter HCC abutting the duodenum (arrows). (B) Coronal MR image shows the mass are also close to the gallbladder (arrowhead) and ascending colon (arrows). (C) Post-treatment positron emission tomography-computed tomography scan shows dense uptake of Y90 only in the tumor and adjacent hepatic parenchyma. (D) Follow-up computed tomography scan shows complete response of the tumor without any damage to the extrahepatic organs.

Fig. 2. With the analysis of multiplanar reformation images (A) and maximum intensity projection images (B) derived from cone-beam computed tomography, tumor-feeding arteries are clearly depicted.

TARE. Cone beam computed tomography (CBCT) from proper hepatic or lobar artery is mandatory for precise planning. According to Lee et al,¹² combined analysis of multiplanar reformation images and maximum intensity projection images derived from CBCT hepatic arteriography, confident detection and tracking of tumor feeders were possible in almost all patients (Fig. 2). If CBCT or CT hepatic arteriography are performed at the segmental branches responsible for the tumor perfusion, the volume and dose of the treated area can be calculated more precisely.¹³ If possible, it is better to administer Technetium-99m macroaggregated albumin (99mTc-MAA) at the target arteries to reflect the actual treatment.

Until now, almost all published studies on radiation segmentectomy or superselective TARE have utilized glass microspheres to treat HCC. Therefore, a two compartment (liver and lung) Medical Imaging Radiation Dose model is generally used. Target dose for superselective TARE in the published literatures ranges 222.6–521 Gy.^{8,9,11,14–16} For radiation segmentectomy with resin microspheres, an expert panel suggested simply prescribing enough activity to allow embolization to stasis.¹⁷

Delivery

Delivery technique is not different from that used for lobar infusion. However, there is a possibility of vascular spasm and wedging of microcatheter during superselection of the small feeding artery, so maintenance of antegrade blood flow should be confirmed before infusion of Y90. It is more important for resin microspheres delivery, because resin microspheres have much more spheres than glass microspheres, so it can cause an embolic effect in small vessels easily.

In our institution, nitroglycerin is administered intra-arterially before Y90 delivery for superselective TARE. However, the effectiveness of nitroglycerin during transarterial treatment has not

been established yet.^{18,19}

Imaging Findings after Superselective Transarterial Radioembolization

Typical imaging findings after superselective TARE includes wedge-shaped or nodular, persistent enhancement in the entire treated area (Fig. 3). This finding corresponds to the dark signal area which can be seen in the hepatobiliary phase of dynamic magnetic resonance imaging. It should not be misinterpreted as infiltrative hypervascular tumor progression.²⁰ Rim enhancement encircling tumor margin is also a benign finding related with capsular fibrosis suggesting a favorable response.²¹

Capsular retraction and atrophy of the treated segments follow the aforementioned findings (Fig. 3). These findings are explained by fibrosis and scarring of the treated tissue in addition to the tumor necrosis.²²

Outcomes

There are few reports focusing superselective approach of TARE. Therefore, we can only infer from the outcome of radiation segmentectomy. Data show promising results expecting curative-intent treatment for the selected patients (Table 1).^{8,9,11,14,16,23,24} Radiation segmentectomy was described first by Riaz et al.¹¹ Though this series included many patients with advanced HCCs or marginal hepatic function, 81% of the patients showed objective response (OR) and median overall survival (OS) reached 26.9 months. Vouche et al¹⁴ and Padia et al⁸ dealt with radiation segmentectomy for relatively small and early HCCs and reported complete response (CR) rates were 47% and 95%, respectively, while OR rates were 87% and 95%, respectively. Biederman et al^{23,24} had published two studies comparing radiation segmentec-

Fig. 3. Follow-up computed tomography (CT) scans after superselective transarterial radioembolization (TARE). (A) CT scan obtained 1 month after TARE shows wedge-shaped, persistent enhancement at the treated area (arrowheads). The tumor shows no remained vascularity. (B) Five-month post-TARE image shows atrophy of treated segment with capsular retraction (arrowheads).

Table 1 Results of Radiation Segmentectomy or Superselective TARE

Author (yr)	No. of patient	Tumor size (cm)	Median target dose (Gy)	ORR (%)	Median OS (mo)
Riaz et al (2011) ¹¹	84	N/A	521	81	26.9
Vouche et al (2014) ¹⁴	102	2.6	242	87	53.4
Padia et al (2014) ⁸	20	3.9	254	95	N/A
Biederman et al (2017) ²³	41	N/A	N/A	85*	30.8
Biederman et al (2018) ²⁴	55	N/A	N/A	82*	N/A
Kim et al (2020) ⁹	53	9.6	237	64	N/A
Salem et al (2021) ¹⁶	162	2.7	410	88	57.9

TARE, transarterial radioembolization; ORR, objective response rate; OS, overall survival; N/A, not available.

*Complete response rate.

tomy with TACE alone and TACE combined with microwave ablation (MWA). In these studies, radiation segmentectomy showed 82% to 85% of CR rates, which were superior to TACE alone and similar to TACE combined with MWA. Recently, Kim et al⁹ has reported a case series especially focusing on superselective approach of TARE, that is, multifocal delivery of Y90 mainly at the segmental and subsegmental branches using multiple (mean 3.36) vials of glass microspheres. Though this series included the patients with relatively large single HCC (median tumor size = 9.6 cm), the OR rate was up to 64%.

Recently, an important multicenter study on TARE for the treatment of solitary, unresectable HCC of 162 consecutive patients from three sites was published.¹⁶ Radioembolization was conducted as radiation segmentectomy in 58.6%, and as downsizing to surgery or bridge to liver transplantation in 24.7% of cases. Median 410 Gy of target dose was delivered and OR rate was 88% with median OS of 57.9 months.

Adverse Events

In all published literatures, radiation segmentectomy and superselective TARE have shown to be safe.^{8,9,11,14,16,23,24} Commonly reported toxicity included fatigue, abdominal pain, post-embolization syndrome, and benign biliary stricture. Biliary stricture is an adverse event associated with superselective TARE via caudate artery and may require unexpected additional treatments including antibiotic therapy and biliary drainage.¹⁵ Y90 uptake in the nontarget tissue or organ is less likely with superselective TARE than with lobar treatment, since Y90 is delivered at more distal branches, though there is no comparative study.

Conclusion

Superselective TARE is a technique giving as much doses as possible while sparing as much liver volumes as possible. It is closely associated with the concept of radiation segmentectomy. Superselective TARE is a very safe modality for the treatment of HCCs with favorable outcome close to the curative-intent treatments in selected patients.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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