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EDITORIAL

Selective internal radiation therapy segmentectomy: A new minimally invasive curative option for primary liver malignancies?

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Abstract

Transarterial radioembolization or selective internal radiation therapy (SIRT) has emerged as a minimally invasive approach for the treatment of tumors. This percutaneous technique involves the local, intra-arterial delivery of radioactive microspheres directly into the tumor. Historically employed as a palliative measure for liver malignancies, SIRT has gained traction over the past decade as a potential curative option, mirroring the increasing role of radiation segmentectomy. The latest update of the BCLC hepatocellular carcinoma guidelines recognizes SIRT as an effective treatment modality comparable to other local ablative methods, particularly well-suited for patients where surgical resection or ablation is not feasible. Radiation segmentectomy is a more selective approach, aiming to deliver high-dose radiation to one to three specific hepatic segments, while minimizing damage to surrounding healthy tissue. Future research efforts in radiation segmentectomy should prioritize optimizing radiation dosimetry and refining the technique for super-selective administration of radiospheres within the designated hepatic segments.

Key Words: Transarterial radioembolization; Selective internal radiation therapy; Radiation

segmentectomy; Hepatocellular carcinoma; Primary liver malignancies; Personalised dosimetry

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Core Tip: Transarterial radioembolization (TARE), with the concept of radiation segmentectomy, is undergoing a paradigm shift in its role in treating primary liver malignancies, particularly hepatocellular carcinoma. This editorial delves into the emerging applications of TARE and explores the rationale, technical aspects, and future perspectives in the field of radiation segmentectomy.

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INTRODUCTION

Transarterial radioembolization (TARE), synonymous with selective internal radiation therapy (SIRT) and radioembolization, represents a minimally invasive modality for localized cancer therapy, entailing the percutaneous, intra-arterial administration of radioactive microspheres directly into the tumor vasculature[1]. Pioneering work by Ariel[2] in 1965 described a technique for the intrahepatic infusion of yttrium-90 (Y-90) bonded to ceramic microspheres, delivered *via* the celiac artery, in four patients with hepatocellular carcinoma (HCC), achieving symptomatic improvement. In 1968, Simon *et al*[3] proved the efficacy of Y-90, in treating five symptomatic patients with neuroendocrine liver metastases. Subsequent decades witnessed numerous studies investigating the use of TARE for both primary and secondary hepatic malignancies. These studies, employing both resin[4,5] and glass microspheres[6-8], demonstrated the efficacy and safety profile of TARE in selectively delivering high tumoricidal radiation doses while minimizing adverse effects. Data from these investigations supported regulatory clearances. The Food and Drug Administration granted a humanitarian device exemption for glass microspheres in 1999, in patients with unresectable HCC. Subsequently, in 2002, premarket approval was obtained for resin microspheres targeting colorectal cancer liver metastases[9]. Historically employed as a palliative intervention for hepatic malignancies, TARE has undergone a significant therapeutic transformation in the last decade. The advent of radiation segmentectomy (RS) has fundamentally reshaped the treatment paradigm for TARE, with the potential for reclassification as a curative locoregional modality.

PHYSICAL PROPERTIES

Three commercially available microsphere types currently exist for therapeutic applications: Y90-resin microspheres (SirSpheres, Sirtex Medical Ltd., Sydney, Australia), Y90-glass microspheres (TheraSphere, Boston Scientific, Boston, MA, United States) and 166Ho-poly-L-lactic acid microspheres (QuiremSpheres, Quirem Medical B.V., Deventer, The Netherlands)[10].

Y-90 is the most common radioisotope used in TARE. This pure β-emitter exhibits a 64.2-h half-life, and approximately 90% of its β-rays are emitted within 7 d, with a maximum β-ray energy of 2.27 MeV and a mean of 0.93 MeV. B-rays emitted from microspheres achieve a mean tissue penetration depth of 2.5 mm, with a maximum depth of 11 mm. The two commercially available Y-90 microsphere types exhibit distinct physical characteristics and Y-90 binding methods, leading to important clinical implications[11-14].

There is an important clinical impact about the use of microspheres, due to the difference in specific gravity (75 Bq for resin *vs* 2500 Bq for glass). To achieve a desired level of activity, a larger quantity of resin microspheres is required compared to glass spheres, resulting in a potentially greater embolic effect, which may be advantageous in certain clinical scenarios. On the other hand, glass microspheres might be the preferred choice, due to their lower embolic effect, when avoiding early blood stasis or reflux is critical. This could be particularly relevant in situations such as HCC with portal vein invasion or when planning for very high radiation dose administration[11].

MECHANISM OF ACTION

All local intra-arterial therapies are based on the principle that liver tumors are preferentially supplied by the hepatic arteries due to neo-angiogenesis, whereas the liver parenchyma is mainly supplied by the portal vein[15]. Although TARE and transarterial chemoembolization (TACE) are similar in terms of the technical aspects of the procedure, as both require selective catheterization of the tumor-feeding vessels, there are substantial differences between the mechanisms of

action[16]. In TACE, chemotherapeutic-loaded microparticles occlude tumor-feeding vessels, ensuring a stagnant flow and an ischemic microenvironment, maximizing exposure to cytotoxic drugs, and promoting ischemic necrosis. Conversely, TARE, leverages β-particles to generate free radicals in the presence of oxygen, inducing DNA damage to one or both DNA strands, ultimately leading to tumor cell apoptosis. Optimal tumor blood flow is therefore imperative for TARE. Furthermore, sufficient microsphere distribution throughout the tumor nodule is required to achieve maximum radiation effect and to avoid a low total radiation dose within the tumor[10,17]. Consequently, TARE procedures typically utilize smaller particles compared to those employed in TACE (25-35 μm *vs* 75-300 μm in diameter, respectively)[16].

INDICATIONS

TARE treatment is indicated for patients with HCC, metastatic liver lesions, and cholangiocarcinoma. Notably, the therapeutic role of TARE has evolved beyond its use as a primarily palliative intervention, with increasing application in recent years for curative or locoregional control[12,18]. The recent revision of the BCLC HCC treatment algorithm incorporates TARE as a curative treatment option in selected cases[19]. Of particular interest, for patients classified within BCLC stages 0 and A, TARE performed with the intent of achieving segmentectomy-like outcomes is considered therapeutically equivalent to established local ablative methods. This approach assumes particular importance in clinical scenarios where surgical resection or conventional ablative techniques are deemed unfeasible. Currently, TARE is recommended in single nodules < 8 cm, based on the results of the LEGACY study[19-21]. In large tumors, radiation lobectomy (RL) by TARE may be considered when future liver remnant (FLR) is small; moreover, TARE (as well as ablation and TACE) may be considered for bridging in liver transplant candidates with a waiting time of > 6 months. On the other hand, the BCLC 2022 update does not endorse TARE for patients classified as BCLC-B or BCLC-C, due to negative outcomes reported in phase III trials[20]. Nevertheless, encouraging data from various authors suggest potential benefits of TARE in patients with portal vein invasion, warranting further investigation to establish its role in this specific patient population[1].

The latest ESMO Clinical Practice Guidelines for Cholangiocarcinoma assert that intra-arterial therapies, such as TARE, may be considered in combination with chemotherapy to improve response and disease control in patients with liver-limited intrahepatic cholangiocarcinoma (iCCA)[22]. Several studies have shown encouraging results involving the use of RS in unresectable iCCA[23,24], but no randomized data are available to date. Ness and Molvar[25] stated that TARE has the potential to improve survival while exhibiting a favorable safety profile with minimal side effects, and downstage selected patients, allowing curative resection, especially when used in conjunction with chemotherapy.

RATIONALE OF SEGMENTECTOMY

TARE encompasses three primary techniques: Sequential lobar palliative radioembolization or lobar dosing, RL, and RS. The initial approach has been primarily performed with palliative intent in advanced-stage disease not amenable to surgical resection, transplantation, thermal ablation, or TACE. It is noteworthy that TARE, due to its microembolic effect, has historically been a viable treatment option for patients presenting with portal vein thrombosis, a contraindication for TACE[18]. RL involves the lobar administration of Y90, inducing atrophy of the treated liver lobe and compensatory hypertrophy of the untreated lobe, thereby potentially facilitating subsequent surgical resection in HCC patients with a limited FLR at presentation. The average lobar radiation dose for RL using glass microspheres generally ranges from 120 to 150 Gy[18,26,27].

RS, first described in 2011[28], represents a more selective approach that aims to deliver very high radiation doses within one to three liver segments. The primary objective is to achieve a high tumoricidal dose within the targeted tumor itself, while concurrently establishing an adequate zone of necrosis to eradicate potential adjacent satellite lesions[29]. The high radiation dose maximizes the cytotoxic effect, while the focused delivery minimizes the risk of collateral injury to the surrounding healthy liver parenchyma[18,29].

Since RS is based on high-dose delivery, most studies concern glass microspheres because they accommodate a higher specific activity with a concomitantly lower particle count, reducing the embolic effect and the risk of early stasis associated with resin microsphere (2500 Bq per glass microsphere *vs* 75 Bq per resin microsphere)[30]. Pathologic evaluation of explanted livers from patients undergoing liver transplantation following downstaging with RS provided compelling evidence for the efficacy of high-dose TARE[31]. A tumor-absorbed dose > 190 Gy was demonstrated to achieve a higher rate of complete pathologic necrosis (CPN) on liver explants, compared to a tumour absorbed dose < 190 Gy, resulting in longer time to progression and overall survival[32]. Moreover, Gabr *et al*[33] recently reported that a targeted dose of 400 Gy was well tolerated and resulted in CPN in all patients, compared to prior thresholds of 190 Gy (complete response of 100% *vs* 65% respectively). The extent of necrosis exhibited a positive correlation with the absorbed radiation dose, whereas tumor size did not appear to be a significant influencing factor[33].

RS is assuming an increasingly prominent role, particularly in HCC treatment, due to the continuously amassing published data, with a trajectory beginning from the first investigation in 2011[28], followed by the 2016 PREMIERE randomized trial[34], and culminating in the 2021 LEGACY milestone study[21], cited by the 2022 BCLC[19] and the latest RASER study, further supporting the ablative potential of RS[35]. The LEGACY study demonstrated the efficacy of Y90 radiation segmentectomy as a neoadjuvant strategy to liver transplantation, surgical resection, or as a standalone treatment for lesions up to 8 cm, supporting the use of a volume absorbed dose > 400 Gy as a "threshold" dose for an ablative effect with an objective response rate over 24 months of 88% and median response duration of 11.8 months[21].

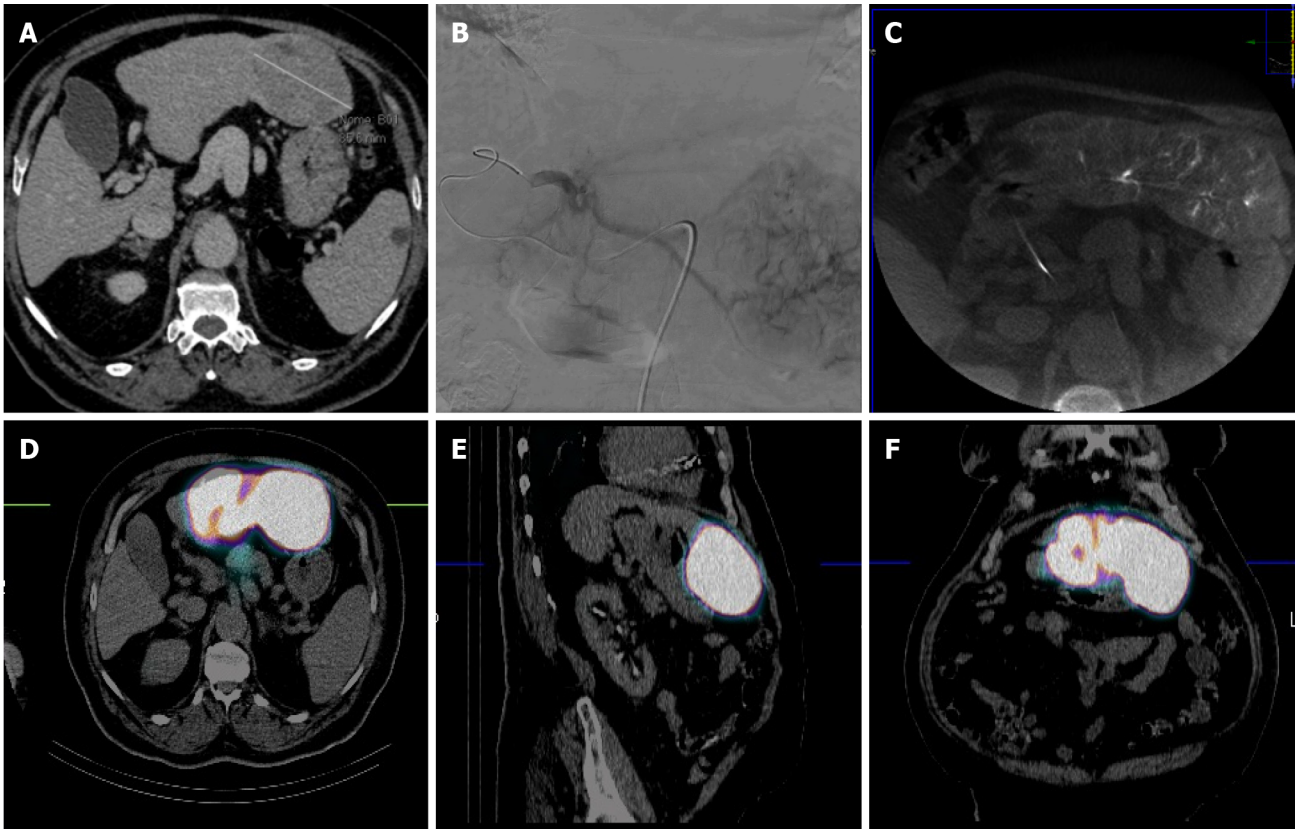

Figure 1 72-year-old man with hepatocellular carcinoma unfit for surgery due to comorbidities (alpha-fetoprotein 2235 ng/mL). A: Computed tomography (CT) showing large hepatocellular carcinoma nodule (7 cm) located in S3; B and C: Angiography and cone beam CT demonstrating superselective catheterization of the segmental S3 artery with perfused nodule; D-F: Single-photon emission tomography combined with CT showing 99mTc-MAA uptake into S3 without uptake in the remaining liver parenchyma or other organs.

Furthermore, results from the RASER study demonstrated 100% CPN rate following RS (mean delivered dose: 776.5 Gy) for HCC ≤ 3 cm[35].

RS may offer a potential curative approach for lesions not amenable to percutaneous ablation or surgical resection, due to anatomical constraints, significant comorbidities, or low functional liver reserve[36]. Unlike percutaneous therapies, RS has no risk of needle-track seeding, liver injury due to challenging anatomical locations, or development of arterioportal fistulas. While thermal ablation is generally accepted as a curative treatment option for lesions < 3 cm, RS demonstrates promise for achieving curative intent even in lesions up to 8 cm. Obviously, TARE carries a higher economic burden compared to ablation, and its efficacy may be limited in hypovascular tumors[36]. Compared to TACE, RS has been reported to be safer and more effective for patients with moderate liver dysfunction and advanced disease[37,38]. Recent important studies have investigated personalized and maximal dosing, transforming TARE to a local curative treatment comparable to surgical resection or percutaneous ablative options[21,33,39].

TECHNIQUE OF SEGMENTECTOMY

RS, as well as others RS techniques, entails a multi-step procedural approach, including pre-treatment angiography (with the possibility of embolization), followed by 99mTc-MAA administration, scintigraphy (Figure 1), dosimetry, Y90 treatment and post-treatment scintigraphy (Figure 2)[16,17,40]. As abovementioned, RS differs regarding dosimetry and extent of treated parenchyma. Personalised dosimetry is today routinely accepted and relies on mathematical models to estimate the absorbed radiation dose to target tissues, exploiting several different methods, each with its strengths and limitations. The Medical Internal Radiation Dose model assumes a uniform radiation distribution within the target liver volume, whilst the body surface area (BSA) method is based on a correlation between the BSA and liver size. Both do not take in account the difference in distribution between tumour tissue and the surrounding parenchyma. Partition model dosimetry, on the other hand, considers particle distribution ratio (tumour to normal, T:N ratio) between tumour and non-tumour compartments, as determined by software programs such as MIM (MIM Software, Beachwood, OH) and Simplicit90Y (Boston Scientific, Marlborough, MA). The T:N ratio is calculated from the 99mTc-MAA distribution in the target liver tissue or by evaluating tissue perfusion on intraprocedural cone beam CT[31].

Y90 treatment is performed by positioning the catheter within the selected arterial segment under fluoroscopic guidance and subsequently injecting the predetermined dose into the targeted perfused hepatic segment. TARE is typically confined to a maximum of two Couinaud hepatic segments to reduce the risk of radiation-induced complic-

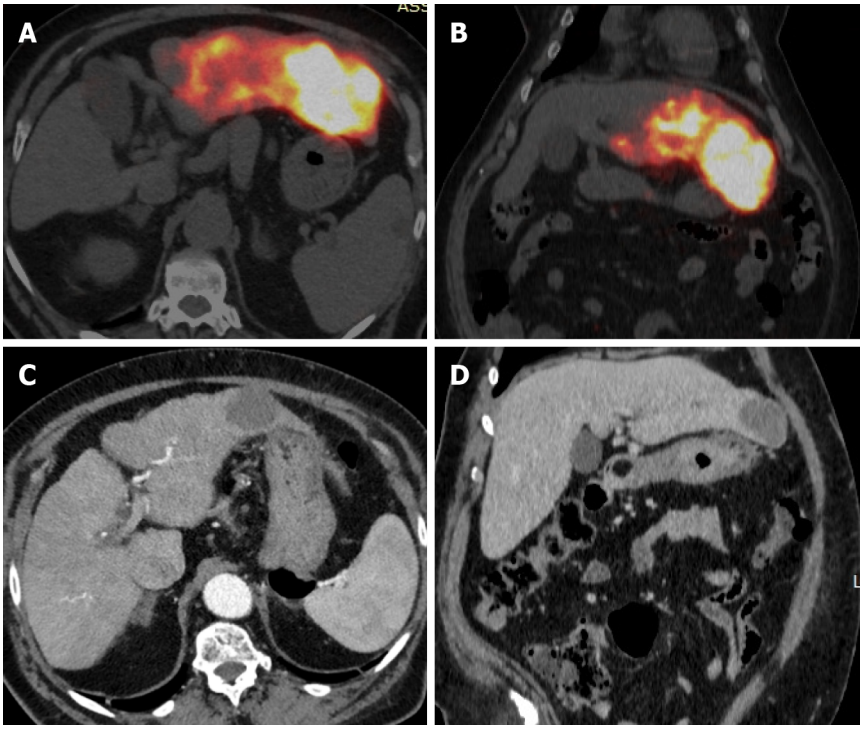

Figure 2 Same patient of figure 1. A and B: Post-transarterial radioembolization, axial and coronal positron emission tomography-computed tomography (CT) views of the Y-90 dose distribution demonstrating high uptake in the tumor without any nontarget activity; C and D: Four-months follow-up CT scan (axial and coronal view) showing necrotic nodule with segmental S3 atrophy (alpha-fetoprotein 7 ng/mL).

ations[30]. The delivery system for 90Y administration is projected to minimize radiation exposure for personnel involved in the procedure[16,41]. Glass microspheres are delivered in saline, whereas resin microspheres are often delivered in sterile water or a 5% dextrose solution[42].

CONCLUSION

Over the past decade, TARE has evolved from a palliative lobar treatment for liver malignancies not amenable to other surgical or local treatments, to a selective, segmental therapy with curative intent for both primary and oligometastatic liver disease[43]. The fundamental principle underlying RS lies in the concept that segmental administration of a high radiation dose achieves a targeted ablative effect on tumors[29]. The effectiveness of RS is directly linked to the safe delivery of the maximum tolerated dose in a super-selective manner, while sparing the surrounding liver parenchyma. Therefore, future investigations on RS should prioritize optimizing the dosimetry and refining the technique for super-selective administration of the radiospheres within the designated hepatic segment(s).

Personalized, accurate dosimetry is the cornerstone of successful modern radiotherapeutic modalities. The field of dosimetry is undergoing advancements through the development of novel and improved dosimetry software, as well as with the integration of 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT, facilitating the calculation of the metabolically active compound of the tumor, rather than the entire lesion visible on conventional axial imaging. Improvements in outcomes assessment, aiming for the prompt detection of recurrent disease are under investigation using 18F-FDG PET/CT protocols and the PERCIST criteria to evaluate the metabolic response[30]. Only recently, the dose limit for RS has been revisited and doses over 1000 Gy have been reported to be safe and effective in the treatment of HCC using glass microspheres[44].

State-of-the-art guidance using Angio-CT systems and fusion imaging, as well as novel anti-reflux catheter technology are currently under rigorous investigation for potential near-future incorporation into routine clinical practice, holding promise for optimizing targeting accuracy, achieving super-selective catheterization and enhancing delivery efficacy during RS[45,46].

Patient selection remains a critical determinant of treatment success and the influence of genetic factors, such as KRAS mutations and HCC genotypes, should be explored to provide a robust evidence base for personalized treatment regimens, incorporating combinations of different systemic and local treatments and aiming to further improve clinical outcomes[47,48].

The field of TARE microsphere technology is undergoing continuous development, as evidenced by the accumulating body of clinical data. ^{166}Ho microspheres have obtained the CE mark, with initial clinical data published[49], while ^{88}Re - Rhenium microspheres (30 μm) are currently under investigation, offering the significant advantage of immediate availability *via* a dedicated Rhenium generator[50]. Finally, increasing experience, alongside the establishment of

standardized protocols for catheterization and procedural planning, has the potential to propel widespread adoption and application of this promising percutaneous, locoregional therapeutic option for liver malignancies.

FOOTNOTES

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