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Nonthermal locoregional therapies for liver cancer: identifying evidence gaps and a proposed research trajectory

Patel A

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Abstract
Liver cancer remains one of the most lethal malignancies worldwide, with a five-year relative survival rate of approximately 22 percent in the United States and fewer than 4 percent for patients with distant metastatic disease. Nonthermal locoregional therapies have emerged as important options for unresectable hepatocellular carcinoma (HCC) and liver metastases. This review examines four modalities—irreversible electroporation (IRE), pulsed electric field (PEF) ablation, transarterial chemoembolization (TACE), and yttrium-90 (Y-90) transarterial radioembolization (TARE)—and identifies four underappreciated gaps and assumptions in the current evidence base. First, TARE studies are frequently pooled as though they evaluate a single intervention, despite major differences in dosimetry and patient selection between negative trials (SARAH, SIRveNIB) and positive studies (LEGACY, DOSISPHERE-01); a stratified framework treating these factors as effect modifiers is proposed. Second, no randomized trial compares the EMERALD-1 regimen (TACE plus durvalumab plus bevacizumab) with personalized-dosimetry radiation segmentectomy for solitary unresectable HCC up to 8 cm, leaving a key first-line treatment question unresolved; a three-arm phase 3 design is proposed. Third, overall survival remains the dominant endpoint despite the growing use of locoregional–immunotherapy combinations; time to next systemic therapy and treatment-free interval may better reflect clinical benefit. Fourth, IRE is generally viewed as a purely ablative technique despite evidence of immunogenic cell death and emerging ablation-immunotherapy signals, yet no phase 2 or phase 3 trial has prospectively evaluated IRE plus checkpoint inhibition in HCC; such a study is proposed for perivascular lesions. Recent phase 3 data (EMERALD-1, LEAP-012) and the 2022 BCLC update are synthesized to support these arguments. Collectively, the field has advanced beyond asking which modality performs best in isolation and now faces questions of trial design, endpoint selection, and evidence synthesis that better reflect modern combination-based and selection-dependent practice.

Keywords
Hepatocellular carcinoma, Liver neoplasms, Yttrium-90, Radiation segmentectomy, Transarterial radioembolization, Transarterial chemoembolization, Irreversible electroporation, Immune checkpoint inhibitors, Personalized dosimetry, Clinical trial design

Anaya Patel, Notre Dame Preparatory School, 1300 Giddings Road, Pontiac, Michigan 48340, USA, anayapatel@ndpma.org

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1. Introduction

Cancer arises from the uncontrolled proliferation of abnormal cells and is among the leading causes of death worldwide. Solid tumors, including cancers of the lung, liver, and kidney, are traditionally treated with some combination of surgery, chemotherapy, radiation therapy, and immunotherapy. Liver cancer remains particularly difficult to manage. While the literature on thermal ablation of liver tumors is extensive, comprehensive narrative reviews of nonthermal locoregional options that explicitly analyze the methodological and conceptual gaps in the most recent randomized trial evidence are scarce. Existing reviews overwhelmingly summarize and collate findings without questioning the implicit assumptions that shape them. This review aims to fill that gap. Its central thesis is that the evidence base for nonthermal locoregional therapy has advanced sufficiently that the most clinically and scientifically consequential open questions are no longer which modality produces the highest response rate in a given trial, but rather how the field should design trials, choose endpoints, and structure meta-analyses to reflect the combinatorial and selection-dependent reality of modern practice. Four specific gaps and implicit assumptions are identified, developed, and addressed with concrete research proposals in Section 5.

Each established modality for treating solid tumors carries significant limitations. Systemic therapies, such as cytotoxic chemotherapy and immunotherapy, often produce substantial off-target toxicity because they cannot fully distinguish malignant from healthy cells. In a prospective cohort study of 441 patients with breast, lung, or colorectal cancer undergoing chemotherapy in New South Wales, Pearce et al. documented a high burden of patient-reported side effects across multiple symptom domains, including fatigue, nausea, and loss of appetite, underscoring how disruptive these toxicities remain even in modern practice (1). Tumors also acquire resistance over time, which further narrows the window of therapeutic benefit.

Liver cancer is particularly difficult to treat. According to American Cancer Society data derived from the Surveillance, Epidemiology, and End Results (SEER) program, the overall five-year relative survival rate for liver and intrahepatic bile duct cancer is ~ 22% (2). Survival varies sharply by stage: patients with localized disease have a five-year relative survival of ~ 37%, those with regional spread ~ 14%, and those with distant metastases only ~ 4% (2). Hepatocellular carcinoma (HCC) accounts for ~ 90% of primary liver cancers, and its incidence in the United States has risen over recent decades, driven in part by chronic hepatitis C infection, alcohol-associated liver disease, and metabolic dysfunction-associated steatotic liver disease (3).

Surgical resection and liver transplantation are the only widely accepted curative treatments for HCC, but most patients are ineligible at the time of diagnosis because of advanced stage, multifocal disease, inadequate hepatic reserve, or comorbidities. For this reason, locoregional therapies have assumed a central role in the management of unresectable liver cancer. These are image-guided, tumor-directed interventions that deliver treatment to the tumor while sparing most of the surrounding hepatic parenchyma,

and they can be broadly divided into thermal and nonthermal approaches.

Thermal ablation, including radiofrequency ablation, microwave ablation, and cryoablation, relies on extreme temperatures to destroy tumor tissue. These techniques are minimally invasive and effective for small tumors but are limited when lesions lie adjacent to bile ducts, major vessels, or other heat-sensitive structures, where collateral thermal injury is difficult to avoid. Nonthermal locoregional therapies were developed in part to address this gap. Electroporation-based techniques, such as irreversible electroporation (IRE) and pulsed electric field ablation (PEF), use high-voltage electrical pulses rather than heat or cold to permeabilize cell membranes. Transarterial approaches, including transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) using Yttrium-90 (Y-90), deliver chemotherapy or radioactive microspheres directly into the arterial supply of the tumor, achieving high local drug or radiation concentrations without thermal effects.

This review summarizes the current state of four nonthermal modalities used in liver cancer treatment: IRE, PEF, TACE, and TARE with Y-90 microspheres. For each modality, the mechanism of action, clinical indications, reported safety and efficacy data, and the most recent trial results are described. Section 5 then develops the central contribution of this review: an analysis of four specific gaps and implicit assumptions in the current evidence base, each paired with a concrete research proposal to address it.

2. Background

2.1 Patient selection for locoregional therapy

Locoregional therapy is generally most appropriate for patients with preserved liver function, good performance status, and tumor burden confined to the liver that is not amenable to surgical resection. A multidisciplinary tumor board typically evaluates candidacy by integrating tumor size, number, vascular involvement, hepatic reserve as measured by the Child-Pugh or albumin-bilirubin score, and overall functional status. The Barcelona Clinic Liver Cancer (BCLC) staging system, updated in 2022, is the most widely used framework for matching HCC patients to treatment options, including ablation, transarterial therapies, and systemic agents (4).

For tumors near critical structures such as the main hepatic vasculature or central bile ducts, surgical resection and thermal ablation both carry elevated risks of collateral injury. Widely metastatic disease is typically treated with systemic therapy because individual lesions cannot be locally controlled. Between these extremes lie patients with solitary unresectable tumors or oligometastatic disease, who are often the best candidates for nonthermal locoregional approaches because these methods deliver tumor-directed treatment while minimizing the systemic toxicity of chemotherapy and the morbidity of major surgery.

2.2 Thermal ablation as context

Among locoregional therapies, thermal ablation has historically been the most established. Radiofrequency ablation uses alternating electrical current to generate frictional heat

within tissue, producing coagulative necrosis. Microwave ablation employs higher-frequency electromagnetic energy to oscillate water molecules, creating larger ablation zones in less time and with reduced susceptibility to the heat-sink effect of nearby blood vessels. Cryoablation induces cell death through repeated freeze-thaw cycles and permits real-time imaging of the ice ball, which can be useful near sensitive structures but is associated with higher bleeding risk and rare complications such as cryoshock.

Despite widespread adoption, all thermal methods share the fundamental limitation that extreme temperatures damage tissue indiscriminately within the ablation zone. This creates particular risk when tumors are located near bile ducts, large vessels, the gallbladder, the diaphragm, or the bowel. The heat-sink effect, in which flowing blood dissipates thermal energy and leaves viable tumor cells near vessel walls, also contributes to local recurrence. These limitations have motivated the development and adoption of nonthermal alternatives.

2.3 Overview of nonthermal modalities

Nonthermal locoregional therapies can be grouped into two categories based on mechanism. The first category, electroporation-based ablation, encompasses IRE and PEF. These techniques use short, high-voltage electrical pulses to permeabilize the cell membrane, leading to cell death without thermal injury. Because electroporation targets the cell membrane rather than collagen-rich structures such as vessel walls and bile ducts, these techniques are particularly useful for tumors adjacent to critical anatomy.

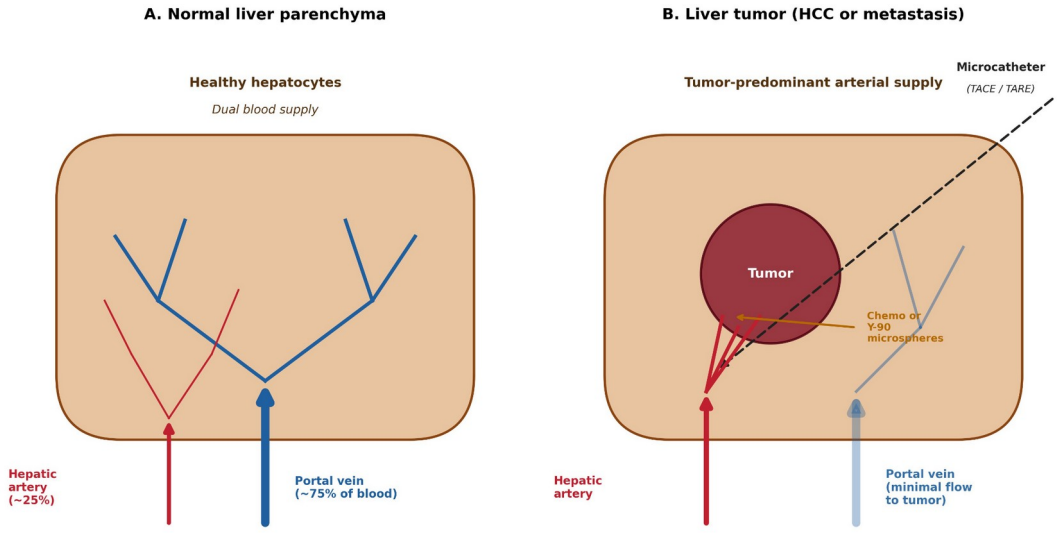

Figure 1. Blood supply of liver tumors

The second category consists of transarterial therapies, including TACE and TARE. These techniques exploit the preferential arterial blood supply of liver tumors: while normal hepatic parenchyma receives most of its perfusion from the portal vein, HCC and liver metastases are supplied primarily by the hepatic artery (Figure 1). By selectively catheterizing the tumor-feeding artery, interventional radiologists can deliver high concentrations of chemotherapy (TACE) or radioactive microspheres (TARE) directly to the tumor while sparing most of the surrounding liver. The following sections examine each modality in detail.

3. Methods

This review was prepared through a structured literature search conducted in PubMed, Google Scholar, and the Cochrane Library. Search terms included combinations of "hepatocellular carcinoma," "liver cancer," "locoregional therapy," "irreversible electroporation," "pulsed electric field," "transarterial chemoembolization," "transarterial radioembolization," "yttrium-90," "nonthermal ablation," and "survival." Inclusion criteria were peer-reviewed clinical studies, meta-analyses, systematic reviews, and randomized controlled trials published between 2010 and 2025 that reported on the use of nonthermal locoregional therapies for primary or metastatic liver cancer. Priority was given to randomized controlled trials, prospective cohort studies, and large multicenter series. Exclusion criteria included single case reports, studies focused on noncancer applications of these modalities, and articles not available in English. Reference lists of included articles were screened to identify additional relevant sources. Because this is not a formal systematic review, no PRISMA flow diagram was generated. The gap analysis in Section 5 was developed by comparing trial design, patient selection, and endpoint choices across the retrieved studies to identify inconsistencies and unexamined assumptions that have not been adequately addressed in prior reviews.

4. Results

4.1 Irreversible electroporation and pulsed electric field ablation

4.1.1 *Mechanism of action*

Irreversible electroporation uses brief, high-voltage direct current pulses, typically in the range of 1,500 to 3,000 volts per centimeter, delivered between two or more electrodes placed around the tumor. These pulses create nanoscale pores in the lipid bilayer of cell membranes. When the pores exceed a critical threshold, the cell cannot maintain ionic homeostasis and undergoes cell death through a combination of apoptosis and necrosis (5). Importantly, IRE preserves the extracellular matrix and the structural integrity of blood vessels, bile ducts, and nerves, because these structures are composed largely of collagen and elastin rather than cell membranes. This selectivity is the central advantage of electroporation-based techniques over thermal ablation.

Pulsed electric field ablation encompasses a broader family of related technologies, including high-frequency irreversible electroporation (H-FIRE) and nanosecond pulsed electric fields. Compared with

conventional IRE, newer PEF platforms use biphasic waveforms and can deliver ablation through a single electrode, which reduces muscle contractions and often removes the need for neuromuscular blockade. PEF also appears to induce immunogenic forms of cell death that may expose tumor antigens to the immune system (6). The ability of IRE and PEF to spare nonparenchymal structures makes them attractive options for tumors located in the hepatic hilum, near the inferior vena cava, or close to major biliary branches.

4.1.2 *Clinical outcomes in liver cancer*

Clinical data on IRE for liver tumors are sourced primarily from prospective single-arm trials and retrospective series. In the COLDFIRE-2 phase II multicenter trial, Meijerink et al. reported on 50 patients with 76 unresectable colorectal liver metastases treated with IRE; primary local tumor progression-free survival at one year was 68%, and overall survival at two years was ~ 65% (7). Complications were more common when lesions were large or abutted central biliary structures, but major biliary injury was rare. For hepatocellular carcinoma, systematic reviews report complete ablation rates ranging from 67 to 100%, depending on tumor size, with best outcomes achieved for lesions smaller than 3 centimeters (5).

Complications of IRE include cardiac arrhythmia related to the high-voltage pulses, transient elevation of liver enzymes, and, less commonly, pneumothorax or biliary stricture. Ruarus et al. reviewed the use of IRE in hepatopancreaticobiliary tumors and noted that overall procedure-related mortality was low, although morbidity rates of up to one-third have been reported in pancreatic applications; rates in liver applications are generally lower, reflecting the more favorable anatomy of most hepatic lesions (8). Recurrence after IRE remains a concern, particularly for larger tumors and for lesions in contact with major vessels, and careful electrode placement with intraprocedural imaging is essential to achieve complete ablation.

A potentially important secondary benefit of IRE is its capacity to release tumor antigens into the circulation after ablation. Preclinical and early clinical studies suggest that this release may stimulate an antitumor immune response, and ongoing trials are exploring the combination of IRE with checkpoint inhibitors (5, 6). Long-term efficacy data for PEF in liver cancer remain limited because the technology is newer, and most available evidence consists of preclinical models and early-phase human trials. The implications of these immunologic observations, and the striking absence of randomized data for IRE plus checkpoint inhibition in HCC, are developed in Section 5.4.

4.2 Transarterial chemoembolization

4.2.1 *Mechanism and technique*

TACE combines two mechanisms of tumor destruction. A microcatheter is advanced through the femoral or radial artery into the hepatic artery branch supplying the tumor. A chemotherapeutic agent, most commonly doxorubicin, is infused directly into the tumor bed, often emulsified with ethiodized oil (conventional TACE) or loaded onto drug-eluting beads (DEB-TACE). The procedure concludes with embolization of the feeding

artery using particles that block tumor blood flow. This dual action produces intense local cytotoxic exposure while inducing ischemic tumor necrosis. Because the normal liver receives most of its blood supply from the portal vein, hepatic arterial embolization typically spares noncancerous parenchyma (9).

4.2.2 *Clinical outcomes*

TACE is recommended by international guidelines for intermediate-stage (BCLC-B) HCC and is also used as a bridge to liver transplantation for patients meeting the Milan criteria. Large cohort studies and meta-analyses have reported one-, three-, and five-year survival rates of ~ 70 to 80%, 40 to 50%, and 25 to 30%, respectively, in well-selected patients with preserved liver function (9, 10). Common adverse events include post-embolization syndrome, characterized by transient fever, abdominal pain, and nausea; less frequent but more serious complications include hepatic abscess, biliary injury, and acute liver failure, particularly in patients with borderline hepatic reserve.

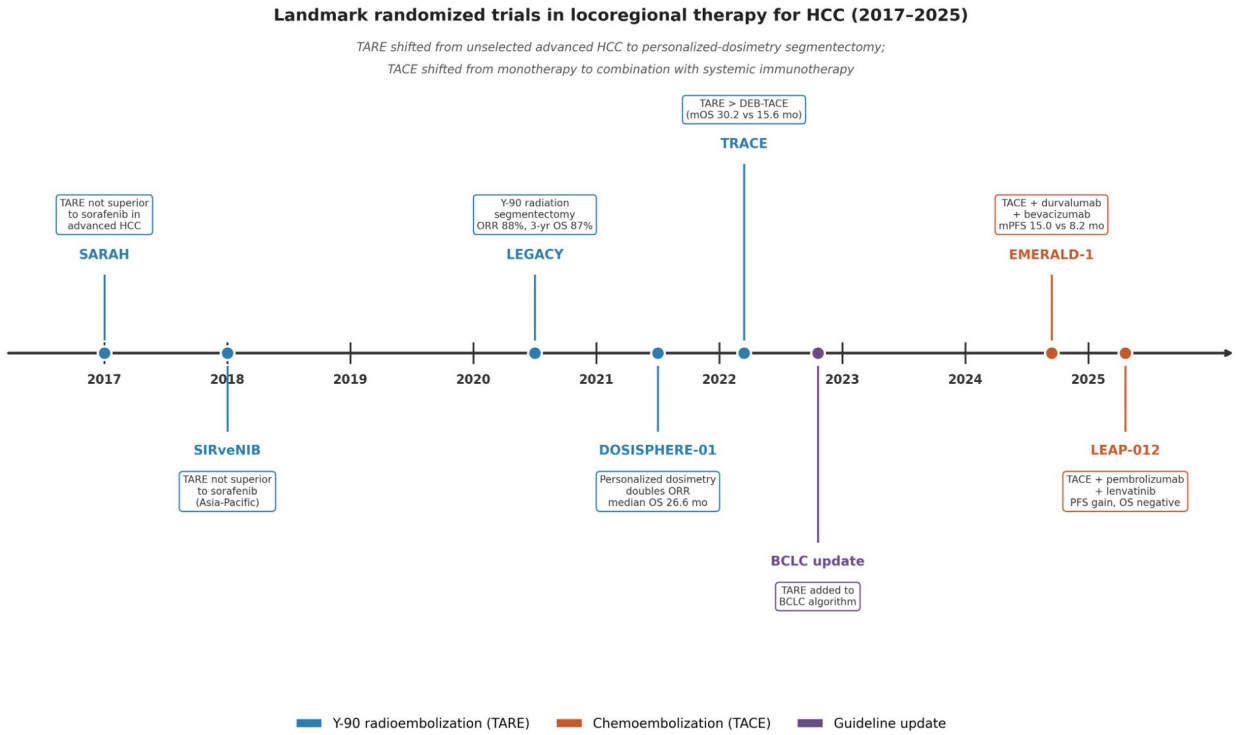

Figure 2. Landmark randomized trials in locoregional therapy for HCC (2017-2025)

The most significant recent development in the TACE field are the results from the EMERALD-1 phase 3 trial, shown alongside other landmark trials in Figure 2. Reported by Sangro et al. in 2025, EMERALD-1 randomly assigned 616 patients with embolization-eligible unresectable HCC in a 1:1:1 ratio to TACE plus durvalumab plus bevacizumab, TACE plus

durvalumab plus placebo, or TACE plus placebo. The primary comparison was the triplet regimen versus placebo plus TACE. Median progression-free survival improved from 8.2 months in the control arm to 15.0 months with the triplet (hazard ratio 0.77, 95% CI 0.61 to 0.98, P = 0.032), and median time to progression increased from 10.0 months to 22.0 months. The objective response rate, a secondary endpoint not formally tested for statistical significance under the trial's hierarchical testing plan, was higher at 43.6% with the triplet compared with 41.0% in the durvalumab plus TACE arm and 29.6% with placebo plus TACE. Grade 3 or 4 treatment-related adverse events occurred in 32.5% of patients in the triplet arm compared with 13.5% in the control arm, a trade-off that appears manageable given the efficacy gains (11). The LEAP-012 trial subsequently evaluated the combination of TACE with pembrolizumab and lenvatinib, and reported improved progression-free survival but did not meet its overall survival endpoint at planned interim analysis (12). Taken together, these results suggest that TACE monotherapy may become less central as a standalone strategy for many patients with intermediate-stage HCC; combining TACE with systemic immunotherapy is emerging as an important option when liver function and comorbidities permit.

4.3 Transarterial radioembolization with yttrium-90

4.3.1 *Mechanism and products*

Transarterial radioembolization, also known as selective internal radiation therapy (SIRT), delivers high-dose internal radiation directly to liver tumors using microspheres loaded with the radioactive isotope yttrium-90. Y-90 is a pure beta emitter with a half-life of 2.67 days and an average tissue penetration of ~ 2.5 millimeters, which allows concentrated radiation delivery while limiting damage to surrounding healthy parenchyma (13). Two FDA-approved products are in clinical use: TheraSphere, composed of glass microspheres approved for unresectable HCC, and SIR-Spheres, composed of resin microspheres approved for metastatic colorectal cancer to the liver. In March 2021, TheraSphere received a premarket approval expansion for HCC based on the LEGACY study (14).

As with TACE, the procedure relies on the preferential arterial supply of liver tumors. A diagnostic mapping angiogram is performed first, including a technetium-99m macroaggregated albumin scan to assess the degree of hepatopulmonary shunting and to identify any extrahepatic arterial branches that must be embolized to prevent nontarget radiation. Once mapping is complete, the Y-90 microspheres are infused via a microcatheter positioned in the tumor-feeding artery. The microspheres lodge in the distal tumor vasculature and deliver concentrated beta radiation over the ensuing two weeks.

4.3.2 *Clinical outcomes*

The LEGACY study, a multicenter retrospective analysis published by Salem et al. in 2021, evaluated 162 patients with solitary unresectable HCC up to 8 centimeters in diameter treated with Y-90 radiation segmentectomy using TheraSphere. The study reported an objective response rate of 88.3%, with 62.2% of responses sustained for at least

six months, and three-year overall survival of 86.6%, rising to 92.8% in patients who subsequently underwent transplantation or resection (14). LEGACY provided the evidence base for the 2021 FDA premarket approval of TheraSphere for HCC and established radiation segmentectomy as a potentially curative option for appropriately selected patients.

The DOSISPHERE-01 randomized phase 2 trial compared personalized dosimetry with standard dosimetry for locally advanced HCC. Garin et al. reported that personalized dosimetry ~ doubled objective response rates (71% versus 36%, P = 0.0074) and extended median overall survival from 10.7 to 26.6 months (15). Updated long-term analysis at five years confirmed sustained benefit and demonstrated that patients downstaged to resection after high-dose radioembolization achieved remarkably prolonged survival (15). These findings have shifted practice toward personalized treatment planning and higher tumor-absorbed doses.

The TRACE phase 2 randomized trial was the first head-to-head comparison of Y-90 radioembolization and DEB-TACE in patients with intermediate-stage unresectable HCC. Median time-to-progression was 17.1 months with TARE versus 9.5 months with DEB-TACE (hazard ratio 0.36, P = 0.002), and median overall survival was 30.2 versus 15.6 months (hazard ratio 0.48, P = 0.006). The trial was halted early for efficacy (16). Earlier phase 3 trials such as SARAH and SIRveNIB had not demonstrated survival superiority of TARE over sorafenib in advanced HCC, but they enrolled patients with more advanced disease and did not use the personalized dosimetry approach validated in DOSISPHERE-01. This apparent contradiction between the earlier negative and the more recent positive trials is the entry point for the technique-heterogeneity argument developed in Section 5.1. A timeline of these and other landmark trials is shown in Figure 2.

Y-90 radioembolization is generally well tolerated. Common side effects are mild and transient, including fatigue, mild abdominal discomfort, and temporary elevation of liver enzymes. Serious but uncommon adverse events include radioembolization-induced liver disease, radiation pneumonitis when hepatopulmonary shunting is inadequately assessed, and gastrointestinal ulceration from nontarget embolization. Most procedures are performed on an outpatient basis or require only a short hospital stay. Contraindications include inadequate hepatic reserve, excessive lung shunt fraction, and unavoidable nontarget vascular distribution (13).

4.3.3 *Choosing between TACE and TARE*

The choice between TACE and TARE depends on tumor burden, vascular involvement, liver function, and institutional expertise. Table 1 summarizes common clinical scenarios and the modality often favored in each. The table also makes visible the one scenario (solitary unresectable HCC up to 8 cm, embolization-eligible, preserved liver function) in which two strong but non-overlapping evidence bases now conflict and no head-to-head randomized data exist; this is the gap developed at length in Section 5.2.

Table 1. Selection between TACE and TARE for unresectable hepatocellular carcinoma.

Clinical scenario	Often favored	Rationale
Solitary unresectable HCC up to 8 cm	TARE (Y-90)	Radiation segmentectomy with personalized dosimetry yields high response rates and prolonged survival (LEGACY, DOSISPHERE-01) (14, 15). No head-to-head randomized comparison with the EMERALD-1 triplet exists; see Section 5.2.
Portal vein tumor thrombus	TARE (Y-90)	Microsphere delivery carries lower ischemic risk than bland embolization, and TARE has demonstrated activity in the setting of portal vein invasion (4, 13).
Intermediate-stage HCC with preserved liver function, embolization-eligible	TACE + durvalumab + bevacizumab	EMERALD-1 demonstrated nearly doubled progression-free survival compared with placebo plus TACE (11).
Marginal liver function or contraindications to systemic therapy	TACE (conventional or DEB)	Longer track record and more widely available; avoids bevacizumab-related bleeding risk.
Downstaging for transplantation	Either (case-by-case)	Both TACE and TARE have been used successfully; selection depends on tumor characteristics and local expertise.
Tumor adjacent to bile ducts or major vessels where thermal ablation is unsafe	IRE	Electroporation spares nonparenchymal structures and avoids heat-sink effects (5, 7).

5. Gap analysis and research trajectory

The preceding sections synthesized the current evidence on four nonthermal locoregional modalities. This section goes beyond synthesis to identify four specific gaps and non-obvious implicit assumptions in that evidence base, and to propose concrete research, trial, and methodological approaches to address each. These are the central contributions of the review.

5.1 The technique-heterogeneity confound in pooled TARE analyses

The HCC literature often treats TARE as a single intervention when comparing it with systemic therapy or TACE. Two phase 3 trials, SARAH in 2017 and SIRveNIB in 2018, failed to show survival superiority of Y-90 over sorafenib in advanced HCC, and these negative results continue to be cited as evidence that radioembolization is not a transformative technology. Yet the subsequent LEGACY and DOSISPHERE-01 studies, both published in 2021, reported favorable outcomes despite evaluating different patient populations and endpoints, including a three-year overall survival of 86.6% in LEGACY and a median overall survival of 26.6 months in DOSISPHERE-01 (14,15). The mechanistic explanation is that the earlier trials used single-compartment standard dosimetry and enrolled patients with advanced, often multifocal disease, whereas LEGACY used ablative-intent radiation segmentectomy for solitary tumors up to 8 centimeters, and DOSISPHERE-01 specifically tested personalized multi-compartment dosimetry. The recurring implicit assumption in pooled analyses is that technique and patient selection are interchangeable details rather than primary effect modifiers.

This argument has so far been advanced largely as a conceptual claim, and a preliminary empirical demonstration using the trials already discussed in this review helps to test it. Table 2 organizes the principal randomized TARE studies according to the two candidate effect modifiers, dosimetry approach and disease burden or patient selection, alongside a representative reported outcome and the overall direction of each trial. Although these are aggregate, study-level data rather than a formal pooled analysis, a clear pattern is visible: the trials that used standard dosimetry in advanced, often multifocal disease were negative, whereas those that used personalized dosimetry or ablative-intent radiation segmentectomy in more selected, lower-burden populations were positive, and in the case of TRACE superior even to drug-eluting bead TACE. The radioisotope and the microsphere class are held essentially constant across these studies; what varies, and what tracks with the direction of the result, is consistent with the hypothesis that dosimetry and selection act as effect modifiers. The reader can therefore judge directly whether the proposed effect modifiers plausibly explain the divergence in outcomes rather than taking the claim on assertion.

Outcomes are drawn from the studies summarized in Section 4.3 and Figure 2. This is a qualitative, hypothesis generating arrangement of study-level data, not a formal meta-analysis; aggregate comparisons of this kind are vulnerable to ecological bias and residual confounding and are intended only to illustrate the proposed effect modifiers. OS, overall survival; ORR, objective response rate; DEB, drug-eluting bead.

Table 2. Exploratory organization of landmark randomized TARE trials by dosimetry approach and patient selection.

Study (year)	Dosimetry approach	Disease burden / selection	Representative reported outcome	Direction
SARAH (2017)	Standard, single-compartment	Advanced HCC; often multifocal or with vascular invasion	No OS superiority versus sorafenib	Negative
SIRveNIB (2018)	Standard, single-compartment	Advanced HCC (Asia-Pacific)	No OS superiority versus sorafenib	Negative
DOSISPHERE-01 (2021)	Personalized, multi-compartment	Locally advanced HCC	ORR 71% vs 36%; median OS 26.6 vs 10.7 mo	Positive
LEGACY (2021)	Personalized; radiation segmentectomy	Solitary lesion up to 8 cm	ORR 88.3%; 3-yr OS 86.6%	Strongly positive
TRACE (2022)	Ablative-intent (vs DEB-TACE comparator)	Intermediate-stage HCC	Median OS 30.2 vs 15.6 mo (vs DEB-TACE)	Positive

It is important to be precise about what “heterogeneity” means in this context. The conventional heterogeneity statistics reported in meta-analyses, Cochran’s Q, the I-squared

statistic, and the between-study variance tau-squared, quantify statistical heterogeneity, that is, the extent to which observed effect sizes vary more than would be expected from sampling error alone (17). They do not, by themselves, identify the clinical or mechanistic sources of that variation, and they can mislead in both directions: a pooled TARE analysis could report a deceptively low I-squared while still averaging across fundamentally different interventions, or report a high I-squared that is treated as noise to be statistically accommodated rather than as a signal to be explained. The claim of this section is therefore not that heterogeneity statistics are invalid, but that they are insufficient on their own. Future meta-analyses of TARE in HCC should supplement traditional statistical heterogeneity measures with prespecified clinical stratification based on known effect modifiers, here dosimetry approach and anatomic selection framework, so that clinically meaningful variation is modeled rather than being absorbed into a single summary number.

Framed this way, the heterogeneity in the TARE literature is a threat to valid pooling but- when recognized as such- is also a potential source of discovery. One of the principal advantages of evidence synthesis is precisely that it allows investigators to identify effect modifiers that are invisible within any single underpowered trial. Oncology offers many precedents in which initially heterogeneous datasets yielded their most important insights only after stratification by a biologically meaningful variable: the recognition of molecularly defined subgroups that responded to targeted agents, and the finding that checkpoint-inhibitor efficacy varied markedly with tumor and host characteristics, are two familiar examples. By analogy, if TARE outcomes vary systematically with dosimetry and selection, that variation is itself the finding. It localizes where, how, and for whom the technology works, and apparent inconsistency in the pooled literature becomes a hypothesis-generating observation rather than merely a reason for caution.

This reframing also clarifies how the proposal relates to existing methods and what, specifically, is being recommended. The recommendation is not to abandon pooling, which would sacrifice statistical power and discard the central advantage of meta-analysis, nor is it to introduce a new statistical instrument. It is instead a disciplined application of tools that already exist, namely prespecified subgroup analysis, meta-regression, and, ideally, individual-patient-data (IPD) meta-analysis, directed by a specific, mechanistically grounded stratification rather than by post hoc data dredging. The contribution lies in the stratification framework itself and in the conceptual shift from treating heterogeneity as a reason to distrust the pooled estimate toward treating it as a structured question about effect modification. This involves an explicit trade-off between statistical power and biological specificity: finer stratification increases mechanistic interpretability at the cost of precision within each stratum, and analyses should be transparent about that balance and interpret sparsely populated strata cautiously. Aggregate published data of the kind arranged in Table 2 are themselves a limitation, because study-level subgroup comparisons remain vulnerable to ecological bias; this is exactly why an IPD meta-analysis, in which dosimetry and

selection are modeled at the level of the individual patient, would be the definitive version of the approach proposed here.

Concretely, meta-analyses of TARE in HCC should prespecify the stratification by dosimetry approach, distinguishing personalized multi-compartment from standard single-compartment, and by anatomic selection framework, distinguishing solitary lesions up to 8 centimeters from multifocal or advanced presentations. An individual-patient-data meta-analysis applying this stratification across the landmark trials summarized in Figure 2, especially if extended to include real-world registries such as TARGET and PROACTIF, would yield a fundamentally different and more clinically useful picture of what radioembolization can and cannot do. Without this correction, the field risks continued misattribution of technique failures to the underlying technology, and, just as importantly, risks overlooking the effect modifiers that a properly structured synthesis could reveal.

5.2 The unanswered first-line question: a three-arm trial proposal

For the specific patient profile most often encountered in modern practice, solitary unresectable HCC up to 8 centimeters, Child-Pugh A cirrhosis, ECOG 0 to 1, embolization-eligible, and not an immediate transplant candidate, two strong but non-overlapping evidence bases now exist. LEGACY and DOSISPHERE-01 support personalized-dosimetry Y-90 radiation segmentectomy as a potentially curative monotherapy with three-year overall survival approaching 87% (14, 15). EMERALD-1 supports TACE plus durvalumab plus bevacizumab, with median progression-free survival of 15.0 months versus 8.2 months for TACE alone (11). No randomized trial compares these two strategies head-to-head. Clinicians currently choose between them on the basis of indirect comparisons, local expertise, and tumor characteristics. This is an evidence gap with immediate clinical consequences.

A concrete trial design to address this gap would be a three-arm randomized phase 3 study with a target enrollment of ~ 600 patients. Eligibility would mirror the intersection of LEGACY, DOSISPHERE-01, and EMERALD-1: solitary HCC up to 8 centimeters, Child-Pugh A cirrhosis, ECOG 0 to 1, no extrahepatic disease, no portal vein tumor thrombus, and no macrovascular invasion. Randomization would be 1:1:1 across three arms: (a) personalized-dosimetry Y-90 radiation segmentectomy alone; (b) conventional or drug-eluting bead TACE plus durvalumab plus bevacizumab in the EMERALD-1 regimen; and (c) personalized-dosimetry Y-90 radiation segmentectomy plus durvalumab plus bevacizumab. A primary endpoint of 24-month recurrence-free survival would provide a clinically meaningful and statistically tractable signal, and would be less confounded by competing risks from cirrhosis than 5-year overall survival. Translational endpoints should include paired pre- and post-treatment biopsy for immune infiltrate characterization, circulating tumor DNA kinetics, and quantitative assessment of tumor-absorbed radiation dose. Such a trial would directly address the first-line question that clinicians now face every day in multidisciplinary tumor boards, and its third arm would also establish whether the benefits of

ablative radiation and systemic immunotherapy are additive or redundant.

5.3 Rethinking primary endpoints in the immunotherapy era

A second non-obvious assumption in the current literature is that overall survival and progression-free survival, evaluated as if locoregional therapy were a standalone treatment, adequately capture the value of these interventions. This was a reasonable assumption when first-line options were sparse and most patients who progressed on TACE received sorafenib or supportive care. It is no longer reasonable. Current and emerging systemic regimens for HCC include atezolizumab-bevacizumab, durvalumab-tremelimumab, nivolumab-ipilimumab, and a growing list of second-line agents. A locoregional therapy that achieves modest initial tumor control but preserves immune fitness for subsequent checkpoint blockade may ultimately be more valuable than one that produces a deeper initial response but compromises the tumor microenvironment. The implicit assumption that OS and PFS collapse these distinctions into a single number is a methodological limitation, not a feature.

Two alternative endpoints would better reflect modern practice. Time to next systemic therapy, which has gained traction in solid tumor oncology, directly captures the clinical benefit of durable local control without conflating it with death from competing causes such as cirrhosis progression. Treatment-free interval after initial locoregional response measures the ability of a therapy to keep patients off systemic treatment entirely, a patient-centered outcome that aligns with quality-of-life concerns and with the health-economics case for locoregional therapy. Both endpoints are tractable to collect, interpretable to clinicians, and aligned with patient-reported priorities. Future phase 2 and phase 3 trials of nonthermal locoregional therapy should prespecify these endpoints alongside conventional OS and PFS. Future work should evaluate whether such endpoints could be considered for regulatory use as primary measures when combination strategies are the control arm.

5.4 IRE as an immunomodulatory platform: an untested hypothesis in HCC

Preclinical and early clinical evidence that electroporation-based ablation releases tumor antigens and stimulates local and distant antitumor immunity has been discussed for more than a decade (5, 6). Despite this, IRE is still classified and trialed in hepatology as a purely mechanical ablative technique. No randomized phase 2 or phase 3 trial in HCC has prospectively tested IRE in combination with a checkpoint inhibitor, and published IRE series do not routinely report immune correlates. This is a striking omission given that the mechanistic rationale for combination is at least as strong for IRE as for the thermal modalities for which such trials are now underway.

The strongest justification for such a trial may lie less in the mere absence of prior IRE-specific work than in the accumulating evidence that ablation-immunotherapy combinations are biologically active across several tumor types. In advanced HCC itself, Duffy et al. combined the anti-CTLA-4 antibody tremelimumab with subtotal tumor ablation and reported not only

acceptable safety but confirmed partial responses in 5 of 19 evaluable patients in lesions that had not been directly ablated, together with favorable intratumoral and systemic immune changes, a clinical signal of abscopal, immune-mediated activity (18). Outside the liver, cryoablation, which, like IRE, avoids the protein-denaturing heat of thermal coagulation and may therefore preserve tumor antigens in a more immunogenic form, has been paired with checkpoint blockade in early-stage breast cancer, where the combination was safe and produced favorable intratumoral and systemic immunologic effects (19). These signals support the biological plausibility of combining nonthermal ablation with checkpoint inhibition and indicate that the rationale for an IRE plus checkpoint-inhibitor trial does not rest on theory alone. At the same time, the existing evidence should temper expectations: these studies are small and early-phase, several ablation-immunotherapy combinations in other settings have failed to convert immunologic signals into durable clinical benefit, and reported response rates remain modest. This mixed record is itself an argument for the translational immune correlates built into the proposed design, which are intended to establish whether IRE produces the hypothesized immunogenic effect in HCC, rather than to assume it. The distinctive and still untested rationale for IRE specifically is mechanistic: because electroporation kills cells without thermal denaturation of proteins, it may release tumor antigens in a more intact and immunostimulatory form than radiofrequency or microwave ablation, making it a particularly attractive partner for checkpoint inhibition in precisely the perivascular and perihilar lesions for which it is already the preferred ablative tool. A phase 2 trial of percutaneous IRE followed by durvalumab or pembrolizumab for perivascular or perihilar HCC lesions unamenable to thermal ablation would address this gap. The primary endpoint would be objective response rate at 6 months by mRECIST. Key secondary endpoints would include abscopal response rate in untreated lesions elsewhere in the liver, progression-free survival, and safety. Translational endpoints should include tumor-infiltrating lymphocyte density on pre- and post-ablation biopsy, T-cell receptor repertoire diversity, and peripheral immune cell profiling. Because the anatomic niche for IRE is tumors adjacent to structures where thermal ablation is contraindicated, such patients are already a defined clinical population with limited alternatives, and recruitment should be feasible at high-volume hepatobiliary centers. A positive result would reclassify IRE from a niche ablative tool into a platform therapy for combination immuno-oncology in HCC, with implications for every perihilar and perivascular lesion currently treated without the benefit of systemic priming.

6. Discussion

The nonthermal locoregional toolkit for liver cancer has expanded substantially over the past decade, and each modality now occupies a distinct niche. IRE and PEF provide ablation options for tumors adjacent to critical anatomical structures where thermal methods are unsafe, trading some recurrence risk for improved preservation of nearby tissues. TACE appears to be transitioning from a monotherapy benchmark toward a platform therapy that is increasingly combined with systemic immunotherapy. TARE with Y-90, particularly

when guided by personalized dosimetry, has matured into a treatment associated with potentially durable disease control in selected patients with solitary unresectable HCC.

The gap analysis in Section 5 reframes what the field should now prioritize. Rather than continuing to ask which modality wins in isolation, investigators and meta-analysts should examine how technique and patient selection interact within each modality, how combination strategies alter the meaning of traditional endpoints, and how untested mechanistic hypotheses, particularly around IRE and immunity, might unlock new treatment paradigms. The three-arm trial proposed in Section 5.2, in particular, is a discrete and feasible next step that would resolve what is currently the most consequential uncertainty in first-line locoregional therapy for solitary HCC up to 8 centimeters. The proposed methodological stratification in Section 5.1 could be implemented on existing data without any new clinical trial and, as the exploratory arrangement in Table 2 suggests, would likely change how guidelines interpret the pooled TARE-versus-sorafenib literature by treating dosimetry and selection as effect modifiers rather than averaging across them.

Several limitations of the current evidence base and of this review should be acknowledged. Many studies of IRE and PEF remain single-center series with small sample sizes and short follow-up, which limits conclusions about long-term durability. Most Y-90 and TACE trials enroll patients at high-volume academic centers, which may not reflect outcomes in community practice. The pace of change in systemic therapy also complicates locoregional trial design, because comparator arms can become outdated before trials complete enrollment. The proposed three-arm trial in Section 5.2 would be an ambitious undertaking requiring substantial funding and international coordination, and its feasibility depends on continued manufacturer interest in both TheraSphere and durvalumab-bevacizumab. Since this is not a formal systematic review, its gap analysis is therefore the author's structured interpretation of the literature rather than a quantitative synthesis. In particular, the subgroup pattern illustrated in Table 2 is based on aggregate, study-level data and is intended to be hypothesis-generating rather than to serve as a substitute for the patient-level analysis it is meant to motivate.

From a practical standpoint, the decision between modalities should be made in a multidisciplinary setting that incorporates tumor number and size, presence of vascular invasion, Child-Pugh and ALBI scores, performance status, and patient preference. For solitary tumors up to 8 centimeters that are not amenable to resection or ablation, radiation segmentectomy with Y-90 is supported by the strongest contemporary data, though the unanswered head-to-head question noted in Section 5.2 leaves room for reasonable clinical disagreement. For multifocal embolization-eligible intermediate-stage disease, TACE combined with durvalumab and bevacizumab is emerging as an important option. For lesions abutting critical structures where both thermal ablation and resection are contraindicated, IRE remains a valuable option and an underexploited immunotherapy platform. Ongoing trials combining locoregional therapy with immune

checkpoint inhibitors and emerging technologies such as histotripsy are likely to further refine this algorithm in the coming years.

7. Conclusion

Nonthermal locoregional therapies have moved from the margins to the center of liver cancer care. IRE and PEF provide safe ablation options for tumors adjacent to critical structures where thermal methods cannot be used without risk of major complications. TACE and TARE offer tumor-directed delivery of chemotherapy and radiation, respectively, and recent randomized trials have transformed how both are used. EMERALD-1 may help reshape treatment strategies for intermediate-stage HCC by combining TACE with durvalumab and bevacizumab, while LEGACY, DOSISPHERE-01, and TRACE together support personalized-dosimetry Y-90 radioembolization as a high-impact option with potentially long-term disease control for selected patients.

The central argument of this review, however, is that the field has matured enough that evidence synthesis alone is no longer sufficient. Four specific gaps and implicit assumptions now shape the literature and clinical practice: pooled TARE analyses that conflate technique and patient selection; the absence of a head-to-head trial between personalized-dosimetry radiation segmentectomy and the EMERALD-1 triplet; the continued reliance on OS and PFS endpoints that assume standalone operation of locoregional therapy; and the untested hypothesis that IRE is an immunomodulatory platform for HCC rather than a purely mechanical ablation. Each of these is addressed with a concrete research or methodological proposal in Section 5. Implementing even one of them would meaningfully advance care for patients who cannot undergo curative surgery.

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