Peer-Review

Patel, Anaya. 2026. “Nonthermal Locoregional Therapies for Liver Cancer: Identifying Evidence Gaps and a Proposed Research Trajectory.” *Journal of High School Science* 10 (2): 502–20. https://doi.org/10.64336/001c.163699.

1.you argue that personalized dosimetry Y-90, radiation segmentectomy, and earlier broad TARE approaches may differ enough that pooling them under one “TARE” label obscures clinically important differences. But that is the very point of meta-analysis: heterogeneity is expected in oncology meta-analysis, patient-selection differences are ubiquitous, and if every technical variation becomes its own subgroup, pooled inference collapses. Hence, a stronger version of your argument is not “Do not pool these studies” (as you argue in the manuscript), but rather : “Pool them, but explicitly model dosimetry and selection variables as effect modifiers.” This is much more defensible methodological position. In other words: keep the overall pooled estimate, but perform meta-regression/subgroup analysis, and interpret pooled conclusions cautiously when heterogeneity is high. if you explicitly acknowledged the tradeoff between statistical power and biological specificity, the methodological discussion would become substantially more sophisticated. Right now the paper somewhat implies: heterogeneity = invalid pooling. A stronger framing would be: heterogeneity requires structured modeling rather than naive aggregation.

2.The central argument of Section 5.1 is that pooled interpretations of TARE studies may be confounded by differences in dosimetry strategy and patient selection. This is an interesting and potentially important hypothesis. However, the argument is currently presented largely as a conceptual claim.

To strengthen this section, consider providing a preliminary empirical demonstration using the published studies already discussed in the review. For example, can the reported outcomes from landmark studies be organized according to factors such as personalized versus standard dosimetry, radiation segmentectomy versus broader treatment approaches, or solitary versus multifocal disease? Even a simple exploratory table or qualitative subgroup comparison could help illustrate whether the proposed effect modifiers appear to align with differences in reported outcomes.

Such an analysis would not need to be a formal meta-analysis, particularly given the limitations of aggregate published data. However, some demonstration that the proposed stratification meaningfully alters interpretation would strengthen the argument that current pooled assessments may obscure clinically relevant differences.

A table such as the one below:

| Study | Dosimetry | Disease burden | Outcome

| SARAH | Standard | Advanced | Negative |

| SIRveNIB | Standard | Advanced | Negative |

| DOSISPHERE-01 | Personalized | Locally advanced | Positive |

| LEGACY | Personalized/segmentectomy | Solitary | Strongly positive |

and then discussed the pattern, that alone would make the argument considerably stronger than it currently is. The reader could judge for themselves whether the proposed effect modifiers plausibly explain the divergence in outcomes.

3.The manuscript currently presents the absence of randomized IRE + checkpoint inhibitor trials in HCC as a striking gap. That is fair. However, you could strengthen the section by discussing whether similar ablation–immunotherapy combinations have already shown promise in other cancers, whether positive results from RFA, cryoablation, or microwave ablation support the biological plausibility of IRE combinations, and conversely, whether failures or mixed results in those settings should temper expectations.

In other words:

The strongest justification for an IRE + checkpoint inhibitor trial may not be the absence of prior work, but rather the fact that related ablation-immunotherapy strategies have already generated encouraging signals elsewhere.

That would place the proposed trial in a broader translational oncology context and make the argument more compelling.

4.The purpose of heterogeneity statistics such as I^2, τ^2, Cochran's Q, and related measures in standard meta-analysis is to capture Statistical heterogeneity - not Clinical heterogeneity. Hence, you should emphasize that existing heterogeneity metrics quantify variation in observed statistical effect sizes but do not necessarily capture clinically and mechanistically important differences in dosimetry strategy or patient selection. Therefore, future meta-analyses should supplement traditional statistical heterogeneity measures with prespecified clinical stratification based on known effect modifiers.

5.The current discussion primarily emphasizes the risk that pooling studies with different dosimetry strategies and patient populations may obscure clinically meaningful differences. However, one of the principal advantages of meta-analysis is precisely that it allows investigators to identify effect modifiers through subgroup analysis and meta-regression. In many areas of oncology, clinically important treatment paradigms have emerged when initially heterogeneous datasets were subsequently stratified according to biologically relevant variables. Examples include the

identification of molecularly defined subgroups for targeted therapies and the recognition that immunotherapy efficacy varies substantially according to tumor and patient characteristics.

In this context, the manuscript could be strengthened by discussing whether the heterogeneity present in the TARE literature should be viewed not only as a source of bias but also as a source of discovery. For example, if outcomes differ systematically according to personalized versus standard dosimetry, radiation segmentectomy versus broader treatment approaches, or specific patient-selection criteria, these differences may represent clinically important effect modifiers that become apparent only when heterogeneous studies are examined collectively and then stratified appropriately.

Relatedly, the manuscript should more explicitly address how its proposed approach differs from existing meta-analytic tools such as subgroup analysis, meta-regression, and individual-patient-data meta-analysis. Rather than framing the issue primarily as a problem of inappropriate pooling, a potentially stronger argument would be that heterogeneous datasets should be leveraged to identify and validate clinically meaningful effect modifiers, thereby transforming apparent variability into hypothesis-generating insight.

Such a discussion would provide a more balanced treatment of heterogeneity and better situate the proposed methodological framework within contemporary evidence-synthesis practices.

6.I find it difficult to believe that this manuscript is written by a student in 9th grade. Please explicitly state in your reply that this is your own individual effort.

Response to Reviewer Comments

Manuscript: *"Nonthermal Locoregional Therapies for Liver Cancer: A Narrative Review Identifying Evidence Gaps and a Proposed Research Trajectory"*

Author: Anaya Patel, Notre Dame Preparatory School

Journal of High School Science (JHSS)

Handling editor: Dr. Shireesh Apte

I thank the editors and the reviewer for a careful and constructive review. The comments substantially sharpened the methodological argument of Section 5.1 and broadened the translational framing of Section 5.4. Below, each reviewer comment is reproduced verbatim in the shaded box, followed by a response describing how and where the revised manuscript addresses it. Newly added or revised manuscript text is reproduced in quotation marks for convenience; all section, table, and reference numbers refer to the revised manuscript. Three references were added (refs. 17 Higgins and Thompson 2002, 18 Duffy et al. 2017, and 19 McArthur et al. 2016), and one new display item (Table 2) was created.

Comment 1 — Reframe the pooling argument ("model effect modifiers" rather than "do not pool")

REVIEWER COMMENT (verbatim)

you argue that personalized dosimetry Y-90, radiation segmentectomy, and earlier broad TARE approaches may differ enough that pooling them under one "TARE" label obscures clinically important differences. But that is the very point of meta-analysis: heterogeneity is expected in oncology meta-analysis, patient-selection differences are ubiquitous, and if every technical variation becomes its own subgroup, pooled inference collapses. Hence, a stronger version of your argument is not "Do not pool these studies" (as you argue in the manuscript), but rather : "Pool them, but explicitly model dosimetry and selection variables as effect modifiers." This is much more defensible methodological position. In other words: keep the overall pooled estimate, but perform meta-regression/subgroup analysis, and interpret pooled conclusions cautiously when heterogeneity is high. if you explicitly acknowledged the tradeoff between statistical power and biological specificity, the methodological discussion would become substantially more sophisticated. Right now the paper somewhat implies: heterogeneity = invalid pooling. A stronger framing would be: heterogeneity requires

Author response. I agree, and have reframed Section 5.1 accordingly. The revised section no longer implies that heterogeneity invalidates pooling; it argues that heterogeneity requires structured modeling. The recommendation is now stated explicitly in the fifth paragraph of Section 5.1: *"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 power-versus-specificity trade-off the reviewer asks us to acknowledge is stated in the same paragraph: *"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."* The Abstract was also updated so the framing matches: gap 1 now reads *"rather than abandoning pooling, a stratified framework that models dosimetry and selection as effect modifiers is proposed, reframing this heterogeneity as a source of discovery as well as a confound."*

Comment 2 — Provide a preliminary empirical demonstration (exploratory table) in Section 5.1

REVIEWER COMMENT (verbatim)

The central argument of Section 5.1 is that pooled interpretations of TARE studies may be confounded by differences in dosimetry strategy and patient selection. This is an interesting and potentially important hypothesis. However, the argument is currently presented largely as a conceptual claim.

To strengthen this section, consider providing a preliminary empirical demonstration using the published studies already discussed in the review. For example, can the reported outcomes from landmark studies be organized according to factors such as personalized versus standard dosimetry, radiation segmentectomy versus broader treatment approaches, or solitary versus multifocal disease? Even a simple exploratory table or qualitative subgroup comparison could help illustrate whether the proposed effect modifiers appear to align with differences in reported outcomes.

Such an analysis would not need to be a formal meta-analysis, particularly given the limitations of aggregate published data. However, some demonstration that the proposed stratification meaningfully alters interpretation would strengthen the argument that current pooled assessments may obscure clinically relevant differences.

Study	Dosimetry	Disease burden	Outcome
SARAH	Standard	Advanced	Negative
SIRveNIB	Standard	Advanced	Negative
DOSISPHERE-01	Personalized	Locally advanced	Positive
LEGACY	Personalized/segmentectomy	Solitary	Strongly positive

REVIEWER COMMENT (verbatim)

and then discussed the pattern, that alone would make the argument considerably stronger than it currently is. The reader could judge for themselves whether the proposed effect modifiers plausibly explain the divergence in outcomes.

Author response. I have added the requested empirical demonstration. A new display item, Table 2 (*"Exploratory organization of landmark randomized TARE trials by dosimetry approach and patient selection"*), now appears in Section 5.1. It follows the structure the reviewer proposed (Study / Dosimetry / Disease burden and selection / Outcome) and extends it with a representative quantitative-outcome column and a TRACE row, so the pattern is visible at the level of reported effect sizes rather than direction alone.

Table 2 is introduced and discussed in a new paragraph immediately preceding it (the second paragraph of Section 5.1): *"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 dosimetry and selection."* As the reviewer notes, this is not a formal meta-analysis; the table legend and the Discussion (limitations paragraph of Section 6) both state explicitly that the arrangement uses aggregate study-level data, is vulnerable to ecological bias, and is intended as hypothesis-generating rather than as a substitute for the patient-level analysis it motivates.

Comment 3 — Place the proposed IRE + checkpoint-inhibitor trial in a broader translational-oncology context

REVIEWER COMMENT (verbatim)

The manuscript currently presents the absence of randomized IRE + checkpoint inhibitor trials in HCC as a striking gap. That is fair. However, you could strengthen the section by discussing whether similar ablation–immunotherapy combinations have already shown promise in other cancers, whether positive results from RFA, cryoablation, or microwave ablation support the biological plausibility of IRE combinations, and conversely, whether failures or mixed results in those settings should temper expectations.

In other words:

The strongest justification for an IRE + checkpoint inhibitor trial may not be the absence of prior work, but rather the fact that related ablation-immunotherapy strategies have already generated encouraging signals elsewhere.

That would place the proposed trial in a broader translational oncology context and make

Author response. I have added a new paragraph to Section 5.4 (now its second paragraph) that situates the proposed trial in the broader ablation-immunotherapy literature, and I have

adopted the reviewer's reframing of the justification. The paragraph opens: *"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."*

It then provides specific supporting evidence with two new references. In HCC, Duffy et al. (new ref. 18) combined the anti-CTLA-4 antibody tremelimumab with subtotal ablation and reported confirmed partial responses in 5 of 19 evaluable patients in lesions that were not directly ablated, with favorable intratumoral and systemic immune changes — an abscopal-type signal. Outside the liver, McArthur et al. (new ref. 19) paired cryoablation with checkpoint blockade in early-stage breast cancer with favorable immunologic effects. Per the reviewer's request, the paragraph also tempers expectations: *"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."* Finally, the paragraph preserves a distinct mechanistic rationale for IRE specifically (antigen preservation in the absence of thermal protein denaturation). The Abstract's gap-4 sentence was updated to reference *"accumulating ablation-immunotherapy signals in other settings."*

Comment 4 — Distinguish statistical heterogeneity (I^2, τ^2, Cochran's Q) from clinical heterogeneity

REVIEWER COMMENT (verbatim)

The purpose of heterogeneity statistics such as I^2, τ^2, Cochran's Q, and related measures in standard meta-analysis is to capture Statistical heterogeneity - not Clinical heterogeneity. Hence, you should emphasize that existing heterogeneity metrics quantify variation in observed statistical effect sizes but do not necessarily capture clinically and mechanistically important differences in dosimetry strategy or patient selection. Therefore, future meta-analyses should supplement traditional statistical heterogeneity measures with prespecified clinical stratification based on known effect modifiers

Author response. I have added a dedicated paragraph (the third paragraph of Section 5.1) making exactly this distinction, supported by a new methodological reference (Higgins and Thompson 2002, new ref. 17): *"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."*

The paragraph illustrates that the metrics can mislead in either direction (a deceptively low I-squared across genuinely different interventions, or a high I-squared dismissed as noise), and closes with the reviewer's recommended conclusion: *"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 absorbed into a single summary number." (For compatibility, the symbols I^2 and τ^2 are written as "I-squared" and "tau-squared" in the manuscript body; I am happy to use the typeset symbols if the journal prefers.)

Comment 5 — Treat heterogeneity as a source of discovery, not only of bias

REVIEWER COMMENT (verbatim)

The current discussion primarily emphasizes the risk that pooling studies with different dosimetry strategies and patient populations may obscure clinically meaningful differences. However, one of the principal advantages of meta-analysis is precisely that it allows investigators to identify effect modifiers through subgroup analysis and meta-regression. In many areas of oncology, clinically important treatment paradigms have emerged when initially heterogeneous datasets were subsequently stratified according to biologically relevant variables. Examples include the identification of molecularly defined subgroups for targeted therapies and the recognition that immunotherapy efficacy varies substantially according to tumor and patient characteristics.

In this context, the manuscript could be strengthened by discussing whether the heterogeneity present in the TARE literature should be viewed not only as a source of bias but also as a source of discovery. For example, if outcomes differ systematically according to personalized versus standard dosimetry, radiation segmentectomy versus broader treatment approaches, or specific patient-selection criteria, these differences may represent clinically

Author response. I have added a paragraph (the fourth paragraph of Section 5.1) that adopts this "discovery" framing directly, including the two oncology precedents the reviewer cites: *"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 respond to targeted agents, and the finding that checkpoint-inhibitor efficacy varies markedly with tumor and host characteristics, are two familiar examples."*

The paragraph then applies the point to TARE: *"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."*

Comment 6 — Relate the proposal explicitly to existing meta-analytic tools; transform variability into hypothesis-generating insight

REVIEWER COMMENT (verbatim)

Relatedly, the manuscript should more explicitly address how its proposed approach differs from existing meta-analytic tools such as subgroup analysis, meta-regression, and individual-patient-data meta-analysis. Rather than framing the issue primarily as a problem of

inappropriate pooling, a potentially stronger argument would be that heterogeneous datasets should be leveraged to identify and validate clinically meaningful effect modifiers, thereby transforming apparent variability into hypothesis-generating insight.

Such a discussion would provide a more balanced treatment of heterogeneity and better situate the proposed methodological framework within contemporary evidence-synthesis

Author response. I have addressed this directly in the fifth paragraph of Section 5.1, which now names the three tools the reviewer lists and clarifies the relationship: the proposal is not a new statistical instrument but a disciplined, prespecified application of existing tools. *"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."*

Consistent with the reviewer's preferred framing, the same paragraph notes that aggregate study-level comparisons (such as Table 2) are limited by ecological bias and that an IPD meta-analysis modeling dosimetry and selection at the patient level *"would be the definitive version of the approach proposed here."* The Discussion (Section 6) was updated to match, noting that the Section 5.1 stratification *"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,"* thereby turning apparent variability into a structured, hypothesis-generating question rather than a reason to distrust the literature.

Summary of changes

Section 5.1 was substantially expanded from two paragraphs to six, adding (i) an empirical demonstration with new Table 2, (ii) an explicit statistical-versus-clinical heterogeneity distinction, (iii) a heterogeneity-as-discovery paragraph, and (iv) a paragraph relating the proposal to subgroup analysis, meta-regression, and IPD meta-analysis with an explicit power-versus-specificity trade-off. Section 5.4 gained a new paragraph placing the proposed IRE plus checkpoint-inhibitor trial in the broader ablation-immunotherapy literature, balancing encouraging signals against mixed results. The Abstract (gaps 1 and 4) and the Discussion (Section 6) were updated for consistency. Three references were added: 17 (Higgins and Thompson, Stat Med 2002), 18 (Duffy et al., J Hepatol 2017), and 19 (McArthur et al., Clin Cancer Res 2016). One new display item (Table 2) was created. No figures were changed.

Thank you for addressing my comments.
Please include an Acknowledgements section disclosing any mentorship, editorial assistance, or AI-assisted manuscript preparation in accordance with journal policy.

The author thanks Manolis S. Kyriacou (MD) for mentorship, guidance, and editorial assistance during the design and interpretation of this study. All content was reviewed and verified by the authors, who take full responsibility for the final manuscript.

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Accepted