



Imaging and Dosimetric Predictors of Treatment Response After Yttrium-90 Radioembolization in the Immunotherapy Era for Hepatocellular Carcinoma: A Systematic Review

Hans Christopher Yongasa*, Cliff Christopher Yongasa, Surya Saptono

RSUD Wangaya Denpasar, Indonesia

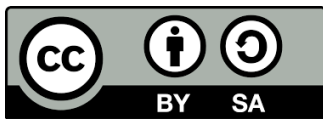
Email: hansyongasa@gmail.com*, cliffyongasa@gmail.com, suryasaptonop@gmail.com

Keywords:

hepatocellular carcinoma, yttrium-90, radioembolization, selective internal radiation therapy, tumor-absorbed dose.

Abstract

Accurate prediction of treatment response after yttrium-90 (Y-90) radioembolization is essential for optimizing the management of hepatocellular carcinoma (HCC), particularly as immunotherapy increasingly influences treatment strategies. This systematic review aimed to synthesize evidence on imaging and dosimetric predictors of radiologic response and assess their relevance in the immunotherapy era. PubMed, Embase, Cochrane CENTRAL, Scopus, and Web of Science were searched from inception through August 10, 2026. Eligible studies evaluated imaging or dosimetric predictors in adults undergoing Y-90 radioembolization. Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool, supplemented by relevant Prediction Model Risk of Bias Assessment Tool (PROBAST) domains for prediction-model studies, while certainty of evidence was evaluated using a GRADE-informed approach. Fourteen studies were included in the narrative synthesis because methodological heterogeneity precluded meta-analysis. Higher tumor-absorbed doses consistently predicted objective and complete responses. In a randomized trial, personalized dosimetry increased the objective response rate of targeted lesions from 36% to 71%. However, dose thresholds varied according to microsphere type and dosimetric methodology. Radiomics demonstrated promising discriminatory performance, with areas under the receiver operating characteristic curve (AUCs) reaching 0.89, although small sample sizes and limited external validation reduced the certainty of the evidence. Models combining imaging and dosimetric parameters showed potential complementary predictive value. No included study specifically evaluated concurrent immunotherapy. Personalized dosimetry currently provides the strongest evidence for optimizing treatment response, whereas radiomics requires further prospective and external validation. Standardized, multicenter studies are needed to establish reproducible dose thresholds and evaluate Y-90 radioembolization in combination with immunotherapy.



This is an open access article under the [CC BY-SA](https://creativecommons.org/licenses/by-sa/4.0/) license.

Copyright © 2026 by Author. Published by Publikasiku Publisher

INTRODUCTION

Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related death worldwide, and its incidence continues to rise in many regions (Sung et al., 2021). Most patients present with intermediate- or advanced-stage disease, and prognosis depends heavily on tumor burden, liver function, and performance status, which collectively guide treatment allocation (Llovet et al., 2021). The Barcelona Clinic Liver Cancer (BCLC) framework and

international guidelines position liver-directed and systemic therapies across this disease spectrum, with transarterial approaches playing a central role in intermediate-stage and selected locally advanced disease (European Association for the Study of the Liver, 2018; Reig et al., 2022).

The systemic treatment landscape for advanced HCC has shifted decisively toward immunotherapy. The combination of atezolizumab and bevacizumab established immune checkpoint inhibition as a first-line standard, while dual immune checkpoint blockade with durvalumab and tremelimumab has further expanded therapeutic options (Abou-Alfa et al., 2022; Finn et al., 2020). These advances have reframed the role of locoregional therapies because immunotherapy and liver-directed treatments are increasingly being sequenced or combined, while the immunologic effects of tumor irradiation remain an area of active investigation (Sangro et al., 2021). In this context, the ability to predict a durable local response to liver-directed therapy has gained importance because it may influence whether, when, and how systemic therapy is introduced.

Yttrium-90 (Y-90) transarterial radioembolization delivers beta radiation through the hepatic arterial circulation using glass or resin microspheres and can be administered as radiation segmentectomy, lobar treatment, or bridging therapy before resection or transplantation. Randomized trials comparing Y-90 radioembolization with sorafenib did not demonstrate a survival advantage in advanced disease but confirmed a favorable tolerability profile, while comparative studies with transarterial chemoembolization demonstrated a longer time to progression (Chow et al., 2018; Salem et al., 2016; Vilgrain et al., 2017). In carefully selected patients treated with ablative intent, radiation segmentectomy has achieved high rates of sustained local tumor control (Salem et al., 2021). These findings have shifted attention from whether radioembolization is effective to how its therapeutic effects can be predicted and optimized for individual patients.

Treatment response after Y-90 radioembolization is most commonly assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST), which evaluate viable, arterially enhancing tumor tissue rather than changes in overall tumor size alone (Lencioni & Llovet, 2010). Two complementary categories of predictors have emerged for forecasting treatment response. The first is quantitative imaging, including morphologic imaging characteristics and radiomics, which involves the high-throughput extraction of quantitative imaging features, such as texture and shape, to characterize imaging phenotypes associated with tumor biology and clinical outcomes (Lambin et al., 2017). The second is dosimetry, which estimates the radiation dose delivered to the tumor and can be derived either before treatment from technetium-99m macroaggregated albumin (99mTc-MAA) distribution or after treatment using Y-90 positron emission tomography (PET) or bremsstrahlung imaging (Weber et al., 2022). International recommendations increasingly advocate personalized dosimetry rather than fixed-activity prescription, reflecting growing evidence that tumor-absorbed dose is a modifiable determinant of treatment response (Garin et al., 2015; Levillain et al., 2021).

Despite the rapidly expanding literature, imaging and dosimetric predictors of treatment response have not been comprehensively synthesized together, and their relative consistency and strength remain unclear. Dose thresholds vary across microsphere types and dosimetric methods, radiomics models are frequently based on small, single-center cohorts, and almost no studies have evaluated these predictors in patients receiving Y-90 radioembolization in

combination with immunotherapy. A structured appraisal is therefore needed to determine which predictors are sufficiently supported by current evidence and where important uncertainties remain. This systematic review synthesized studies reporting imaging or dosimetric predictors of radiologic response after Y-90 radioembolization for HCC, examined the consistency and magnitude of these associations, and appraised the certainty of the underlying evidence in the immunotherapy era.

METHOD

Protocol and reporting

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). Given the anticipated methodological and clinical heterogeneity of the included studies, a narrative synthesis was planned a priori.

Eligibility criteria

Studies were eligible if they enrolled adults with HCC treated with Y-90 glass or resin microspheres and reported an association between an imaging or dosimetric predictor, measured before or early after treatment, and radiological response by modified RECIST, RECIST 1.1, EASL, or metabolic criteria. Eligible designs were prospective or retrospective cohort studies, comparative cohorts, prospective single-arm studies with a predictor-response analysis, post-hoc dosimetric analyses of trials, and randomized trials of a dosimetric strategy. Narrative and systematic reviews, meta-analyses, protocols, editorials, case reports with fewer than five patients, phantom or purely technical studies without a patient response outcome, animal studies, and conference abstracts without extractable data were excluded.

Information sources and search

Three reviewers, the first and second author, independently searched PubMed, Embase, Cochrane CENTRAL, Scopus, and Web of Science from database inception to 10 August 2026, combining controlled vocabulary and free-text terms for hepatocellular carcinoma, Yttrium-90 radioembolization, dosimetry, and imaging or radiomics prediction of response. The full database-native search strings are provided in the accompanying Search Strategy Table. Reference lists of retrieved articles were hand-searched for additional studies.

Study selection and data extraction

Records were de-duplicated and screened by title and abstract independently by the three reviewers, and the full texts of potentially eligible records were assessed against the criteria. Disagreements were resolved by discussion and consensus. Three reviewers independently extracted study identity, design, population, microsphere type, dosimetry method, predictor definition and threshold, response criterion and timing, and the reported association or accuracy estimates onto a piloted form, tracing each value to a specific table, figure, or page.

Risk of bias and certainty

Risk of bias was appraised with the Quality In Prognosis Studies (QUIPS) tool, which examines study participation, attrition, predictor measurement, outcome measurement, confounding, and statistical analysis and reporting (Hayden et al., 2013). For machine-learning prediction-model studies, the domains of the Prediction model Risk Of Bias ASsessment Tool (PROBAST) were additionally considered (Wolff et al., 2019). Certainty of evidence was rated

with a GRADE-informed approach, considering risk of bias, inconsistency, indirectness, imprecision, and small-study effects, and adapted for prognostic and prediction questions (Foroutan et al., 2020; Guyatt et al., 2008).

Synthesis

Because predictors, thresholds, microsphere types, response criteria, and reporting formats were heterogeneous, a quantitative meta-analysis was not appropriate, and findings were synthesized narratively following guidance on synthesis without meta-analysis (Campbell et al., 2020). Studies were grouped into predictive (pretreatment) dosimetry, post-treatment delivered dosimetry, prospective dose optimisation, imaging and radiomics prediction, and combined models, and the direction, magnitude, and consistency of each predictor-response association were compared.

RESULTS AND DISCUSSION

Study selection and characteristics

The five-database search identified 899 records, and 587 remained after removal of 312 duplicates. After title and abstract screening, 116 reports were sought and 108 full texts were assessed, of which 94 were excluded, leaving 14 studies for narrative synthesis (Table 1). The included studies were published between 2012 and 2026 and comprised ten retrospective cohorts, one prospective single-arm study, one randomized phase 2 trial, one post-hoc analysis of a randomized trial, and comparative cohorts of microsphere type. They enrolled a total of several hundred patients, most with intermediate or locally advanced HCC, and used glass microspheres, resin microspheres, or both. No included study was designed specifically around concurrent immune checkpoint inhibition, although several were conducted during the period in which immunotherapy became standard. The characteristics of the included studies are summarized in Table 2.

Table 1. PRISMA 2020 study selection (five-database search, executed).

Stage	Records, n
Records identified from databases (total)	899
PubMed/MEDLINE	198
Embase	254
Cochrane CENTRAL	39
Scopus	221
Web of Science	187
Duplicate records removed	312
Records screened (title/abstract)	587
Records excluded at title/abstract	471
Reports sought for retrieval	116
Reports not retrieved	8
Full-text reports assessed for eligibility	108
Full-text reports excluded	94
Studies included in narrative synthesis	14

Note: Counts are the reviewers' real executed five-database search and screening totals; two reviewers screened independently.

Table 2. Characteristics of the 14 included studies.

Study	Country	Design	Patients (lesions)	Microspheres	Predictor family	Response criterion
Garin 2012	France	Retrospective cohort	36	Glass	Predictive dosimetry (99mTc-MAA)	EASL
Kappadath 2018	United States	Retrospective cohort	34 (53)	Glass	Post-treatment dosimetry (90Y SPECT/CT)	mRECIST/WHO/RECIST
Hermann 2020	France	Post-hoc RCT analysis (SARAH)	121 (109 response)	Resin	Delivered tumor-absorbed dose	Radiologic response
Garin 2021	France	RCT, phase 2 (DOSISPHERE-01)	60 (28 vs 28)	Glass	Personalised vs standard dosimetry	mRECIST
d'Abadie 2021	Belgium	Retrospective cohort	45 (133)	Glass and resin	Post-treatment dosimetry (90Y PET)	mRECIST
Aujay 2022	France	Retrospective cohort	22	Not stated	MRI radiomics	mRECIST/EASL
Marinelli 2023	United States	Retrospective (ML, internal validation)	76 tumors	Glass	MRI radiomics (machine learning)	mRECIST
Villalobos 2023	United States	Retrospective comparative cohort	81	Glass and resin	Post-treatment dosimetry; glass vs resin	mRECIST
Doyle 2024	United States	Retrospective cohort	101 (127)	Resin	Predictive dosimetry (99mTc-MAA)	mRECIST
Kokabi 2024	United States	Prospective single-arm	30 (33)	Resin	Personalised partition dosimetry	mRECIST
Mahmoud 2024	Taiwan	Retrospective cohort	36	Not stated	MRI radiomics	mRECIST
Akkas 2025	Turkiye	Retrospective cohort	56 (66)	Glass	Voxel-based tumor-absorbed dose	mRECIST
di Gaeta 2026	Italy	Retrospective two-centre cohort	64 (76)	Resin	Personalised dosimetry (Dmean)	mRECIST
Huang 2026	China	Retrospective cohort	57	Not stated	MRI radiomics + 90Y PET dose	mRECIST

Note: mRECIST, modified RECIST; ML, machine learning; RCT, randomised controlled trial.

Predictive (pretreatment) dosimetry

Two studies evaluated the tumor-absorbed dose estimated before treatment from ^{99m}Tc-macroaggregated albumin SPECT/CT. In an early cohort of 36 patients treated with glass microspheres, the planned tumor dose was the only factor independently associated with response, and a threshold of 205 Gy predicted response with high sensitivity and accuracy, while patients above the threshold had markedly longer progression-free and overall survival (Garin et al., 2012). In a larger contemporary cohort of 101 patients treated with resin microspheres, the mean absorbed tumor dose was substantially higher in responding than in non-responding treatments and independently predicted response with a hazard ratio of 2.79 (95 percent confidence interval 1.44 to 5.40), with an estimated dose of about 157 Gy corresponding to a 90 percent probability of objective response (Doyle et al., 2024). Together these studies indicate that a pretreatment dose estimate can stratify the probability of response before a single microsphere is delivered.

Post-treatment (delivered) dosimetry and dose thresholds

Four studies related the delivered tumor-absorbed dose, measured after treatment, to response. Voxel-based dosimetry on Y-90 SPECT/CT showed a dose-response relationship for modified RECIST response but not for size-based criteria, with a mean dose of about 160 Gy corresponding to a 50 percent probability of response (Kappadath et al., 2018). Post-treatment Y-90 positron emission tomography yielded microsphere-specific thresholds of approximately 118 Gy for glass and 61 Gy for resin, and a device-independent dose-volume metric predicted response with a positive predictive value of 94 percent and was associated with longer progression-free and overall survival (d'Abadie et al., 2021). A comparative study of radiation segmentectomy found higher complete-response rates with resin than glass microspheres and reported distinct dose thresholds for objective and complete response in each material (Villalobos et al., 2023). A further glass-microsphere cohort identified a tumor-absorbed dose above 475 Gy as a strong predictor of complete response, with an area under the curve of 0.83 (Akkas et al., 2025). Across these studies the direction of effect was consistent, although the absolute thresholds varied with microsphere type and dosimetry method.

Prospective and trial-derived dose optimisation

Four studies provided prospective or trial-derived evidence that increasing the delivered dose improves response. A post-hoc dosimetric analysis of the SARA trial identified a tumor-absorbed dose of 100 Gy as the cutoff associated with longer overall survival, and disease control was accompanied by a higher median tumor dose than progression (Hermann et al., 2020). The DOSISPHERE-01 randomized phase 2 trial directly compared personalized with standard dosimetry and increased the objective response rate in the targeted lesion from 36 percent to 71 percent, providing the strongest single piece of evidence that dosimetry optimisation changes response (Garin et al., 2021). A prospective single-arm study using personalized partition dosimetry reported prolonged duration of response and survival above a mean tumor dose of about 250 Gy (Kokabi et al., 2024). A recent two-centre cohort found that a mean absorbed dose threshold of 296.74 Gy predicted objective response with complete specificity, and that lesions receiving above 435.11 Gy uniformly achieved complete response (di Gaeta et al., 2026). These findings converge on a coherent, actionable message that higher and individually planned tumor doses yield better response.

Imaging and radiomics prediction

Three studies used quantitative imaging to predict response. In a small cohort of 22 patients, arterial-phase MRI radiomic features predicted early response with high sensitivity and specificity and outperformed conventional morphologic criteria, although the sample size makes overfitting likely (Aujay et al., 2022). A machine-learning model combining baseline and early post-treatment MRI radiomics predicted complete response in a validation set with an area under the receiver operating characteristic curve of 0.89, compared with about 0.58 for clinical and standard-imaging models (Marinelli et al., 2023). A further single-centre study of T2-weighted MRI radiomics identified texture features that discriminated responders from non-responders with areas under the curve around 0.71 (Mahmoud et al., 2024). These models show that imaging can carry predictive signal beyond size, but the studies were small, single-centre, and rarely externally validated.

Combined imaging and dosimetry

One study integrated both predictor families. Combining baseline contrast-enhanced MRI radiomics with early post-treatment Y-90 positron emission tomography dose parameters, the delivered absorbed dose independently predicted response, and a combined clinical and radiomics model reached a sensitivity of 88 percent, a specificity of 68 percent, and an accuracy of 79 percent, exceeding single-modality models (Huang et al., 2026). This early experience suggests that dosimetric and imaging predictors may be complementary rather than competing.

Risk of bias and certainty of evidence

Risk of bias was mostly moderate, driven by retrospective single-centre designs, potential confounding, and incomplete adjustment, and was high for the smallest radiomics studies because of overfitting and absent external validation (Table 3). The randomized trial was at low risk of bias. Certainty of evidence, summarized in Table 5, was low for the association between higher tumor-absorbed dose and response, moderate for personalized versus standard dosimetry because a randomized trial was available, and very low for imaging and radiomics models and for combined models. A synthesis of findings across predictor domains is presented in Table 4.

Table 3. Risk of bias of included studies (QUIPS).

Study	D1 Participation	D2 Attrition	D3 Predictor measurement	D4 Outcome measurement	D5 Confounding	D6 Analysis/reporting	Overall
Garin 2012	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Kappadath 2018	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Hermann 2020	Low	Moderate	Low	Low	Moderate	Low	Moderate
Garin 2021	Low	Low	Low	Low	Low	Low	Low
d'Abadie 2021	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Aujay 2022	Moderate	Moderate	Moderate	Low	High	High	High

Study	D1 Participation	D2 Attrition	D3 Predictor measurement	D4 Outcome measurement	D5 Confounding	D6 Analysis/reporting	Overall
Marinelli 2023	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate
Villalobos 2023	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Doyle 2024	Low	Low	Low	Low	Moderate	Low	Moderate
Kokabi 2024	Low	Low	Low	Low	Moderate	Moderate	Moderate
Mahmoud 2024	Moderate	Moderate	Moderate	Low	High	High	High
Akkas 2025	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
di Gaeta 2026	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Huang 2026	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate

Note: QUIPS domains for prognostic-factor studies; the overall judgement is the reviewers' consensus. PROBAST domains were additionally considered for prediction-model (radiomics) studies.

Table 4. Synthesis of findings by predictor domain.

Predictor domain	Studies (n)	Direction and consistency	Representative thresholds / metrics
Predictive (pretreatment 99mTc-MAA) tumor-absorbed dose	2 (Garin 2012; Doyle 2024)	Consistent positive dose-response	Response thresholds ~157-205 Gy; ADT HR 2.79 (95% CI 1.44-5.40)
Post-treatment (delivered) tumor-absorbed dose	4 (Kappadath 2018; d'Abadie 2021; Villalobos 2023; Akkas 2025)	Consistent positive; thresholds vary by microsphere/method	Dmean ~118-160 Gy (glass), ~61 Gy (resin, D66>=40 Gy); CR AUC 0.83 at TAD>475 Gy
Trial-derived / prospective dose optimisation	4 (Hermann 2020; Garin 2021; Kokabi 2024; di Gaeta 2026)	Consistent; randomised evidence that higher/personalised dose raises response	100 Gy (OS); personalised OR 71% vs 35%; Dmean 296.74 Gy (ORR)
Imaging and radiomics prediction	3 (Aujay 2022; Marinelli 2023; Mahmoud 2024)	Promising discrimination but small, single-centre, rarely externally validated	AUROC 0.71-0.89; radiomics > standard morphologic criteria
Combined imaging and dosimetry	1 (Huang 2026)	Single study; combined model outperforms single-modality	Combined sensitivity 88%, specificity 68%, accuracy 79%

Note: Narrative synthesis; predictors and thresholds were too heterogeneous to pool quantitatively.

Table 5. GRADE-informed summary of findings.

Predictor and outcome	Studies (k; patients)	Certainty (GRADE-informed)	Main reasons for the rating
Higher tumor-absorbed dose -> objective/complete response	8; ~508	Low	Observational dose-response, consistent direction; downgraded for risk of bias and threshold heterogeneity
Personalised vs standard dosimetry -> objective response	4 (1 RCT); ~211	Moderate	One randomised trial plus supportive cohorts; downgraded for imprecision (small samples)
Imaging or radiomics model -> early response	3; ~134	Very low	Small single-centre studies, high overfitting risk, little external validation
Combined imaging + dosimetry -> response	1; 57	Very low	Single small study; indirectness and imprecision

Note: Certainty rated with a GRADE approach adapted for prognostic and prediction questions.

This systematic review of 14 studies shows that the tumor-absorbed dose is the most consistent predictor of radiological response after Y-90 radioembolization for HCC. Across pretreatment and post-treatment dosimetry, higher tumor doses were repeatedly associated with objective and complete response, and a randomized trial confirmed that deliberately raising the tumor dose through personalized dosimetry roughly doubles the objective response rate (Doyle et al., 2024; Garin et al., 2012; Garin et al., 2021). Imaging and radiomics models add a complementary, image-based route to prediction and can outperform conventional morphologic criteria, but they remain small, single-centre, and rarely validated (Aujay et al., 2022; Marinelli et al., 2023). These two families of predictors, dosimetric and imaging, are the organizing axis of the current evidence.

The dosimetric findings are biologically coherent. Radioembolization exerts its effect through absorbed radiation dose, so a reproducible relationship between tumor dose and response is expected, and the convergence of independent cohorts, different microsphere types, and a randomized trial on the same direction of effect strengthens confidence in the association (d'Abadie et al., 2021; Garin et al., 2021; Hermann et al., 2020; Kappadath et al., 2018). At the same time, the absolute thresholds reported are strikingly variable, ranging from about 61 Gy for resin microspheres to several hundred Gy for glass, reflecting genuine differences between materials as well as methodological differences in how dose is calculated, whether from pretreatment ^{99m}Tc-macroaggregated albumin surrogates or post-treatment Y-90 imaging (Akkas et al., 2025; d'Abadie et al., 2021; Villalobos et al., 2023). This heterogeneity was the principal reason a meta-analysis was not undertaken, and it means that a single universal cutoff cannot yet be recommended. The message that is robust is directional and comparative rather than absolute: within a given microsphere type and dosimetry workflow, a higher tumor dose predicts a better response, and personalized planning that targets a higher tumor dose improves outcomes (Garin et al., 2021; Levillain et al., 2021).

The imaging and radiomics literature is at an earlier stage of maturity. The reported discrimination is encouraging, with area-under-the-curve values reaching 0.89 in a model that

combined baseline and early post-treatment features, yet the studies typically enrolled a few dozen patients and extracted dozens or hundreds of features, a combination that invites overfitting and optimistic performance estimates (Aujay et al., 2022; Mahmoud et al., 2024; Marinelli et al., 2023). Few used an external validation cohort, and reporting of feature selection and model calibration was uneven, which is precisely why the certainty of evidence for these predictors was rated very low. Radiomics nonetheless holds a practical appeal, because it can be derived from images that are already acquired for response assessment and does not require the additional processing of quantitative dosimetry (Lambin et al., 2017). The single study that combined radiomic and dosimetric information outperformed either alone, which suggests that the most useful predictive models of the future may integrate the delivered dose with the imaging phenotype rather than relying on either in isolation (Huang et al., 2026).

A striking gap is the near-absence of data from the immunotherapy era in which this review is framed. Although first-line care for advanced HCC now centres on atezolizumab and bevacizumab or dual checkpoint blockade, and although radioembolization is increasingly combined with these agents, none of the included studies was designed around concurrent immune checkpoint inhibition (Abou-Alfa et al., 2022; Finn et al., 2020; Sangro et al., 2021). This matters for two reasons. First, the immune microenvironment and the systemic agents may modify both the tumor response to radiation and the imaging appearance used to measure it, so predictors validated in a radioembolization-only era may not transfer directly. Second, if a reliable early predictor of local response could be established, it could help decide when to introduce, continue, or intensify systemic therapy, which is one of the central unanswered questions in the sequencing of locoregional and systemic treatment. The predictors summarized here therefore provide a foundation, but their behavior in combination regimens must be examined prospectively.

These findings have practical implications. Centres performing radioembolization for HCC should measure and report the tumor-absorbed dose, ideally with personalized dosimetry, because dose is both predictive and modifiable, and because consistent reporting is a prerequisite for building comparable evidence across institutions (Levillain et al., 2021; Weber et al., 2022). Imaging and radiomics tools are not yet ready for routine prognostication and should be regarded as investigational until they are externally validated and reported to accepted standards. For research, the priorities are clear: prospective studies with standardized dosimetry definitions, adequately powered radiomics studies with external validation, models that integrate dose and imaging, and dedicated evaluation of these predictors in patients treated together with immunotherapy.

This review has limitations. The included evidence was predominantly observational and retrospective, single-centre cohorts predominated, and sample sizes were generally small, so residual confounding and selection effects cannot be excluded. The heterogeneity of predictors, thresholds, microsphere types, and response criteria precluded quantitative pooling and limits the precision of any summary statement. Overlapping institutional cohorts may exist among some reports, which could amplify apparently independent signals. Only studies with a retrievable English-language full text were included, introducing possible language and availability bias, and the small number of studies precluded formal assessment of publication bias. Finally, several of the most recent studies were published very recently, and their findings await independent replication. The strengths of the review are a comprehensive five-database

search executed by two independent reviewers, a transparent and reproducible selection process, structured risk-of-bias appraisal with a tool appropriate to prognostic questions, and a synthesis that separates robust directional conclusions from fragile absolute claims (Campbell et al., 2020; Hayden et al., 2013).

CONCLUSION

This systematic review of 14 studies identified tumor-absorbed dose as the most consistent predictor of radiologic response after yttrium-90 (Y-90) radioembolization for hepatocellular carcinoma (HCC). Higher estimated pretreatment and measured posttreatment tumor-absorbed doses were consistently associated with higher objective and complete response rates, while randomized evidence supported the benefit of personalized dosimetry over standard dosimetric planning. However, differences in microsphere type, dosimetry methodology, and response assessment precluded the establishment of a universal dose threshold. Quantitative imaging and radiomics demonstrated promising predictive performance, and preliminary evidence suggested that integrating imaging features with dosimetric parameters could improve response prediction. Nevertheless, small sample sizes, predominantly retrospective study designs, and limited external validation reduced confidence in these predictive models. Overall, the findings support personalized dosimetry as the most established approach for optimizing treatment response, whereas radiomics and combined imaging-dosimetry models remain investigational. Their applicability to patients receiving concurrent immunotherapy remains uncertain because none of the included studies specifically evaluated this treatment setting.

Future research should prioritize prospective, multicenter studies using standardized imaging acquisition protocols, dosimetry methods, response criteria, and assessment intervals to establish reproducible, microsphere-specific dose thresholds. Integrated prediction models incorporating clinical characteristics, radiomic features, and delivered tumor-absorbed dose should undergo independent external validation, with transparent reporting of model discrimination, calibration, and clinical utility. Studies should also evaluate radiation exposure to the nontumoral liver and treatment-related toxicity alongside tumor response to determine whether improved local tumor control can be achieved safely. Dedicated studies of Y-90 radioembolization combined with or sequenced with immune checkpoint inhibitors are needed to determine whether immunotherapy modifies dose-response relationships or the predictive value of imaging biomarkers. Longer follow-up should assess overall survival, durable disease control, and health-related quality of life, while comparative studies should determine whether prediction-guided treatment strategies improve clinical outcomes beyond those achieved with conventional treatment planning and response assessment.

FUNDING

No external funding was received for this review.

CONFLICT OF INTEREST

The authors declare no competing interests related to any microsphere device, manufacturer, dosimetry software, or systemic agent examined in this review.

AUTHOR CONTRIBUTION

The first and second author independently performed the database search, study selection, data extraction, and risk-of-bias appraisal, resolved disagreements by consensus, and drafted and revised the manuscript. All named authors approved the final version.

GENERATIVE ARTIFICIAL INTELLIGENCE USAGE STATEMENT

The authors declare that Generative Artificial Intelligence (Generative AI) was used solely to assist with language refinement, grammatical correction, and improvement of manuscript readability. All scientific concepts, interpretations, literature synthesis, analyses, and conclusions were developed by the authors. All AI-assisted content was carefully reviewed, verified, and revised by the authors, who take full responsibility for the accuracy, integrity, and final content of the manuscript.

REFERENCES

- Abou-Alfa, G. K., et al. (2022). Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evidence*, 1(8), EVIDoA2100070. <https://doi.org/10.1056/EVIDoA2100070>
- Akkas, B. E., et al. (2025). Tumoridal dosing approach with parenchymal sparing using voxel-based dosimetry in 90Y glass microspheres treatment of hepatocellular carcinoma. *Nuclear Medicine Communications*, 46(8), 692–699. <https://doi.org/10.1097/MNM.0000000000001991>
- Aujay, G., et al. (2022). Comparison of MRI-based response criteria and radiomics for the prediction of early response to transarterial radioembolization in patients with hepatocellular carcinoma. *Diagnostic and Interventional Imaging*, 103(7–8), 360–366. <https://doi.org/10.1016/j.diii.2022.01.009>
- Campbell, M., McKenzie, J. E., Sowden, A., Katikireddi, S. V., Brennan, S. E., Ellis, S., Hartmann-Boyce, J., Ryan, R., Shepperd, S., Thomas, J., Welch, V., & Thomson, H. (2020). Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. *BMJ*, 368, l6890. <https://doi.org/10.1136/bmj.l6890>
- Chow, P. K. H., et al. (2018). SIRveNIB: Selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *Journal of Clinical Oncology*, 36(19), 1913–1921. <https://doi.org/10.1200/JCO.2017.76.0892>
- d'Abadie, P., et al. (2021). Prediction of tumor response and patient outcome after radioembolization of hepatocellular carcinoma using 90Y-PET-computed tomography dosimetry. *Nuclear Medicine Communications*, 42(7), 747–754. <https://doi.org/10.1097/MNM.0000000000001395>
- di Gaeta, E., et al. (2026). Personalized dosimetry enhances hepatocellular carcinoma response in yttrium-90 resin microsphere radioembolization. *European Radiology*, 36(9), 7231–7241. <https://doi.org/10.1007/s00330-026-12562-z>
- Doyle, P. W., et al. (2024). Predictive dosimetry and outcomes of hepatocellular carcinoma treated by yttrium-90 resin microsphere radioembolization: A retrospective analysis using technetium-99m macroaggregated albumin SPECT/CT and planning software. *Journal of Vascular and Interventional Radiology*, 35(5), 689–698.e3. <https://doi.org/10.1016/j.jvir.2023.11.026>
- European Association for the Study of the Liver. (2018). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology*, 69(1), 182–236. <https://doi.org/10.1016/j.jhep.2018.03.019>

- Finn, R. S., et al. (2020). Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *New England Journal of Medicine*, 382(20), 1894–1905. <https://doi.org/10.1056/NEJMoa1915745>
- Foroutan, F., et al. (2020). GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: Rating certainty in identification of groups of patients with different absolute risks. *Journal of Clinical Epidemiology*, 121, 62–70. <https://doi.org/10.1016/j.jclinepi.2019.12.023>
- Garin, E., et al. (2012). Dosimetry based on 99mTc-macroaggregated albumin SPECT/CT accurately predicts tumor response and survival in hepatocellular carcinoma patients treated with 90Y-loaded glass microspheres: Preliminary results. *Journal of Nuclear Medicine*, 53(2), 255–263. <https://doi.org/10.2967/jnumed.111.094235>
- Garin, E., et al. (2015). Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. *Journal of Nuclear Medicine*, 56(3), 339–346. <https://doi.org/10.2967/jnumed.114.145177>
- Garin, E., et al. (2021). Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): A randomised, multicentre, open-label phase 2 trial. *The Lancet Gastroenterology & Hepatology*, 6(1), 17–29. [https://doi.org/10.1016/S2468-1253\(20\)30290-9](https://doi.org/10.1016/S2468-1253(20)30290-9)
- Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H. J. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 336(7650), 924–926. <https://doi.org/10.1136/bmj.39489.470347.AD>
- Hayden, J. A., van der Windt, D. A., Cartwright, J. L., Côté, P., & Bombardier, C. (2013). Assessing bias in studies of prognostic factors. *Annals of Internal Medicine*, 158(4), 280–286. <https://doi.org/10.7326/0003-4819-158-4-201302190-00009>
- Hermann, A. L., et al. (2020). Relationship of tumor radiation-absorbed dose to survival and response in hepatocellular carcinoma treated with transarterial radioembolization with 90Y in the SARAH study. *Radiology*, 296(3), 673–684. <https://doi.org/10.1148/radiol.2020191606>
- Huang, W., et al. (2026). MRI radiomics and 90Y PET dosimetry for predicting hepatocellular carcinoma response after radioembolization. *BMC Cancer*, 26. <https://doi.org/10.1186/s12885-026-16345-z>
- Kappadath, S. C., Mikell, J., Balagopal, A., Baladandayuthapani, V., Kaseb, A., & Mahvash, A. (2018). Hepatocellular carcinoma tumor dose response after 90Y-radioembolization with glass microspheres using 90Y-SPECT/CT-based voxel dosimetry. *International Journal of Radiation Oncology, Biology, Physics*, 102(2), 451–461. <https://doi.org/10.1016/j.ijrobp.2018.05.062>
- Kokabi, N., et al. (2024). Resin-based 90Y tumor dose as a predictor of duration of response and survival in patients with surgically unresectable hepatocellular carcinoma: A prospective single-arm study. *Clinical Nuclear Medicine*, 49(9), 799–805. <https://doi.org/10.1097/RLU.00000000000005198>
- Lambin, P., et al. (2017). Radiomics: The bridge between medical imaging and personalized medicine. *Nature Reviews Clinical Oncology*, 14(12), 749–762. <https://doi.org/10.1038/nrclinonc.2017.141>
- Lencioni, R., & Llovet, J. M. (2010). Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Seminars in Liver Disease*, 30(1), 52–60. <https://doi.org/10.1055/s-0030-1247132>

- Levillain, H., et al. (2021). International recommendations for personalised selective internal radiation therapy of primary and metastatic liver diseases with yttrium-90 resin microspheres. *European Journal of Nuclear Medicine and Molecular Imaging*, 48(5), 1570–1584. <https://doi.org/10.1007/s00259-020-05163-5>
- Llovet, J. M., Kelley, R. K., Villanueva, A., Singal, A. G., Pikarsky, E., Roayaie, S., Lencioni, R., Koike, K., Zucman-Rossi, J., & Finn, R. S. (2021). Hepatocellular carcinoma. *Nature Reviews Disease Primers*, 7(1), Article 6. <https://doi.org/10.1038/s41572-020-00240-3>
- Mahmoud, M., et al. (2024). Assessment of Y-90 radioembolization treatment response for hepatocellular carcinoma cases using MRI radiomics. *Molecular Imaging and Radionuclide Therapy*, 33(3), 156–166. <https://doi.org/10.4274/mirt.galenos.2024.59365>
- Marinelli, B., et al. (2023). Early prediction of response of hepatocellular carcinoma to yttrium-90 radiation segmentectomy using a machine learning MR imaging radiomic approach. *Journal of Vascular and Interventional Radiology*, 34(10), 1794–1801.e2. <https://doi.org/10.1016/j.jvir.2023.06.023>
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., . . . Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, 372, n71. <https://doi.org/10.1136/bmj.n71>
- Reig, M., et al. (2022). BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *Journal of Hepatology*, 76(3), 681–693. <https://doi.org/10.1016/j.jhep.2021.11.018>
- Salem, R., et al. (2016). Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology*, 151(6), 1155–1163.e2. <https://doi.org/10.1053/j.gastro.2016.08.029>
- Salem, R., Johnson, G. E., Kim, E., Riaz, A., Bishay, V., Boucher, E., Fowers, K., Lewandowski, R., & Padia, S. A. (2021). Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: The LEGACY study. *Hepatology*, 74(5), 2342–2352. <https://doi.org/10.1002/hep.31819>
- Sangro, B., Sarobe, P., Hervás-Stubbs, S., & Melero, I. (2021). Advances in immunotherapy for hepatocellular carcinoma. *Nature Reviews Gastroenterology & Hepatology*, 18(8), 525–543. <https://doi.org/10.1038/s41575-021-00438-0>
- Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 71(3), 209–249. <https://doi.org/10.3322/caac.21660>
- Vilgrain, V., et al. (2017). Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): An open-label randomised controlled phase 3 trial. *The Lancet Oncology*, 18(12), 1624–1636. [https://doi.org/10.1016/S1470-2045\(17\)30683-6](https://doi.org/10.1016/S1470-2045(17)30683-6)
- Villalobos, A., et al. (2023). Yttrium-90 radiation segmentectomy of hepatocellular carcinoma: A comparative study of the effectiveness, safety, and dosimetry of glass-based versus resin-based microspheres. *Journal of Vascular and Interventional Radiology*, 34(7), 1226–1234. <https://doi.org/10.1016/j.jvir.2023.02.030>
- Weber, M., et al. (2022). EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. *European Journal of Nuclear Medicine and Molecular Imaging*, 49(5), 1682–1699. <https://doi.org/10.1007/s00259-021-05600-z>

Wolff, R. F., Moons, K. G. M., Riley, R. D., Whiting, P. F., Westwood, M., Collins, G. S., Reitsma, J. B., Kleijnen, J., & Mallett, S. (2019). PROBAST: A tool to assess the risk of bias and applicability of prediction model studies. *Annals of Internal Medicine*, 170(1), 51–58. <https://doi.org/10.7326/M18-1376>