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Original Research Article

Intra-individual Comparison of High-Relaxivity versus Standard Macrocyclic Gadolinium Agents for Detecting Hepatic Micrometastases at 3.0 T

Linda Purnama[1*], Adolfo Rawlings[2], Abdullah Assagaf[3]

[1]*Department of Radiology, CMHC Research Center, Palembang, Indonesia*
[2]*Department of Internal Medicine, Winneba State Hospital, Winneba, Ghana*
[3]*Department of Health Sciences, Bireun General Hospital, Bireun, Indonesia*

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***Corresponding author:**
Linda Purnama
E-mail: linda.purnama@cattleyacenter.id
ORCID: 0009-0007-9261-311X

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ABSTRACT

Introduction. Hepatic micrometastases smaller than 10 mm critically influence oncologic staging and eligibility for curative metastasectomy, yet the sub-centimetre sensitivity of standard gadolinium-enhanced MRI is limited. High-relaxivity macrocyclic gadolinium-based contrast agents (GBCAs) generate higher lesion-to-liver contrast-to-noise ratio (CNR) and may improve detection. We compared a high-relaxivity versus a standard macrocyclic GBCA at equimolar dose within the same patients.

Methods. In this prospective intra-individual diagnostic-accuracy study reported per STARD 2015 at a tertiary hospital in Palembang, Indonesia, 48 adult oncology patients underwent two 3.0-T liver MRI examinations 2 to 7 days apart in randomised contrast order (standard gadoterate meglumine versus a high-relaxivity macrocyclic agent, 0.1 mmol/kg). Two gastrointestinal radiologists blinded to agent and clinical and reference data read images independently. A composite reference standard (histopathology and ≥6-month multiphasic imaging follow-up) defined 134 metastatic lesions. Sensitivity, specificity, AUC (DeLong), likelihood ratios, Cohen kappa and McNemar tests were computed.

Results. The high-relaxivity agent increased CNR by 12.2 units (48.5 versus 36.2; p<0.001). Per-lesion sensitivity rose to 94.8% (95% CI 89.6–97.4) from 82.8% (75.6–88.3), and micrometastasis sensitivity to 88.7% from 66.1% (McNemar p<0.001). The area under the ROC curve was 0.929 (0.893–0.966) versus 0.821 (0.757–0.886; DeLong p=0.003), and the negative likelihood ratio improved to 0.06. Inter-reader kappa was 0.89 versus 0.83. Specificity was comparable (84.5% versus 89.7%; p=0.41).

Conclusion. At equimolar dose, the high-relaxivity macrocyclic GBCA significantly improved CNR and sub-centimetre hepatic metastasis detection without meaningful loss of specificity, a gain that may alter oncologic management. High-relaxivity agents are recommended for high-risk hepatic staging.

All authors have reviewed and approved the final version of the manuscript.

1. Introduction

Accurate detection of hepatic metastases is decisive for staging and treatment selection across the common solid tumours, and the clinical weight of a single sub-centimetre lesion is often disproportionate to its size. In colorectal cancer, the precise count and distribution of liver metastases determine resectability and prognosis, and integrated clinical-molecular and histological analyses confirm that completeness of metastasis mapping is tightly linked to survival after hepatic resection.[1,2] Conversely, lesions that become radiologically occult after systemic therapy remain viable in a substantial fraction of cases, so failure to localise every deposit before local treatment risks understaging and early recurrence.[3]

Contrast-enhanced magnetic resonance imaging (MRI) is the most sensitive whole-organ modality for hepatic metastases and outperforms competing tests for small lesions. Gadoxetic-acid-enhanced and abbreviated MRI protocols achieve high per-lesion sensitivity for colorectal liver metastases,[4] non-contrast and contrast-enhanced protocols have been directly compared for this indication,[5] and contrast-enhanced ultrasound provides a complementary but operator-dependent alternative.[6] Across these comparisons, MRI retains the advantage for the smallest lesions, where conspicuity is most fragile.

Detection nevertheless deteriorates sharply below 1 cm. Even with modern diffusion-weighted imaging and advanced reconstruction, the conspicuity of sub-centimetre and subcapsular lesions remains the limiting factor for sensitivity,[7] and adjunctive contrast strategies have been pursued specifically to recover these lesions.[8] Because most metastases are hypovascular relative to enhancing parenchyma on the portal venous phase, their conspicuity is governed physically by the lesion-to-liver contrast-to-noise ratio (CNR), which scales with the longitudinal relaxivity (r1) of the gadolinium chelate; newer macrocyclic agents provide approximately twice the r1 of conventional chelates while preserving kinetic stability.[9,10]

This relaxivity reserve has been exploited in randomised and comparative trials, predominantly outside the liver. Half-dose high-relaxivity gadopiclenol was non-inferior to full-dose comparators for central-nervous-system lesion visualisation,[11] comparable for lesion evaluation across body regions in a phase 3 body-MRI trial,[12] and superior for the detection of small enhancing metastatic foci in controlled experimental models.[13] These data establish that higher relaxivity translates into measurable detection benefit, but they leave open how large that benefit is in the liver at full equimolar dose.

The choice of gadolinium agent must also balance efficacy against gadolinium stewardship and environmental load, a tension highlighted by recent expert syntheses.[14] In Indonesian referral practice, where MRI capacity is concentrated in tertiary centres, a detection gain achieved by contrast selection rather than by additional scanner time is especially attractive. We therefore performed a prospective intra-individual comparison at a tertiary hospital in Palembang, Indonesia, in which each oncology patient received a high-relaxivity macrocyclic GBCA and a standard macrocyclic GBCA at equimolar dose in randomised order. By design this removes inter-patient physiological variability and isolates the contrast agent, allowing us to quantify, with full diagnostic-accuracy metrics and 95% confidence intervals, whether the high-relaxivity agent improves CNR and per-lesion detection of hepatic metastases, with a pre-specified focus on micrometastases smaller than 10 mm.

2. Methods

Study design and setting. This was a prospective intra-individual diagnostic-accuracy study conducted at a single tertiary hospital in Palembang, South Sumatra, Indonesia, and reported in accordance with the Standards for Reporting of Diagnostic Accuracy Studies (STARD 2015). Each patient served as their own control, undergoing two otherwise identical 3.0-T liver MRI examinations distinguished only by the gadolinium agent administered.

Participants. Consecutive adult patients (>18 years) with a histologically confirmed primary malignancy (predominantly colorectal, breast and pancreatobiliary cancer) referred for hepatic MRI staging or restaging between January and October were screened. Inclusion required normal renal function (estimated glomerular filtration rate >60 mL/min/1.73 m^2). Exclusion criteria were any contraindication to MRI (for example a non-compatible cardiac device), prior allergic-like reaction to a GBCA, and any hepatic intervention (chemotherapy, ablation or resection) occurring between the two scans. Forty-eight patients completed both examinations and constituted the analysis set; no enrolled patient failed to complete the second examination.

Sample size. The study was sized to detect an improvement in per-lesion sensitivity from approximately 0.66 to 0.87 for sub-centimetre lesions using a paired (McNemar) framework. Assuming a discordant-pair proportion of about 0.25, a two-sided alpha of 0.05 and power of 0.80, fewer than 45 evaluable patients were required given the expected lesion-to-patient ratio; 48 patients were enrolled to allow for incomplete studies.

Imaging protocol. All examinations used a single 3.0-T MRI scanner with a phased-array torso coil. The washout interval between examinations was 2 to 7 days to preclude residual-contrast effects, and the order of the two agents was randomised. Protocol 1 (standard) used gadoterate meglumine, a standard macrocyclic GBCA, at 0.1 mmol/kg. Protocol 2 (high-relaxivity) used a high-relaxivity macrocyclic agent at the same equimolar dose (0.1 mmol/kg), both injected at 2 mL/s through a power injector followed by a 20-mL saline flush. The sequence package was identical between examinations and comprised axial T2-weighted single-shot fast spin-echo (HASTE; repetition time/echo time approximately 1400/90 ms), axial fat-suppressed T2-weighted turbo spin-echo, respiratory-triggered diffusion-weighted imaging (b = 0, 50, 400 and 800 s/mm^2) with apparent diffusion coefficient mapping, and a fat-suppressed 3D T1-weighted spoiled gradient-echo sequence (flip angle 10–12 degrees; slice thickness 3 mm; matrix 320×224; field of view 360–400 mm; parallel-imaging acceleration factor 2) acquired before contrast and at arterial, portal venous (60 s) and transitional (3 min) phases. Dynamic phase timing was bolus-tracked with an identical trigger threshold for both agents.

Image analysis. Two consultant gastrointestinal radiologists (each with more than 10 years of hepatobiliary MRI experience) independently evaluated all examinations while blinded to the contrast agent used, the clinical history, the histopathology and the alternate examination and the other reader; window and level settings were standardised across agents and the two examinations of a patient were separated within the reading queue to limit recognition of the enhancement signature. For each detected focal lesion, readers recorded location, maximal diameter, and a five-point malignancy-confidence score (1 = definitely benign to 5 = definitely malignant), and classified lesions by size as micrometastasis (<10 mm) or macroscopic metastasis (≥10 mm). Quantitative analysis on the portal venous phase comprised region-of-interest measurement of lesion and liver signal and of background noise, from which signal-to-noise ratio (SNR) and lesion-to-liver CNR were derived; regions of interest were mirrored across the paired examinations of each patient. Independent scores were locked before any adjudication and were used unchanged for the reliability analysis; lesion-level disagreements were resolved by a third senior radiologist for the reference-standard tabulation only.

Reference standard. A composite reference standard, applied blinded to and independently of the index MRI interpretations, classified each lesion as metastatic or benign on the basis of histopathology when tissue was available (resection or biopsy) and otherwise by characteristic evolution on ≥6 months of multiphasic imaging follow-up. Of the 134 metastatic lesions, 96 (71.6%) were confirmed histologically and 38 (28.4%) by follow-up. This composite approach was adopted because biopsy of every sub-centimetre lesion is neither feasible nor ethical. Macrocyclic agents were selected for both arms because they represent the most kinetically stable GBCA class with the lowest gadolinium-retention profile in

both renally impaired and healthy models,[15,16] and they carry a favourable preclinical safety profile.[17]

Statistical analysis. Per-lesion sensitivity, specificity, positive and negative predictive value and accuracy were calculated for each agent against the reference standard, each with 95% Wilson confidence intervals. Because lesions were clustered within patients, all lesion-level models were additionally fitted with a patient-level random intercept (generalised linear mixed model) and verified with cluster-robust standard errors. Receiver-operating-characteristic (ROC) analysis used the five-point confidence scores; the area under the curve (AUC) and its 95% CI were obtained by the DeLong method, the two paired AUCs were compared by the paired DeLong test, and the Youden index identified the optimal operating point. Positive and negative likelihood ratios were computed with Simel confidence intervals. Paired detection rates were compared with the exact McNemar test overall and within size strata, and the agent-by-size interaction was tested formally. Inter-reader agreement was quantified by Cohen kappa with 95% CI (Landis–Koch scale). Continuous image-quality metrics were compared with the paired t test, with Cohen d_z as the effect size. A multivariable logistic model identified independent determinants of per-lesion detection (agent, lesion size, subcapsular location, hepatic steatosis), reporting adjusted odds ratios with 95% CIs. The primary endpoint was pre-specified as per-lesion sensitivity for sub-centimetre metastases; all other comparisons were secondary or exploratory. A two-sided alpha of 0.05 was used throughout.

Ethics. The study was approved by the CMHC Ethics Committee, Palembang, Indonesia (CMHC/EC/2025/0118), and all participants provided written informed consent.

3. Results

Forty-eight patients (mean age 56.4 ± 11.2 years; 26 men, 22 women) completed both imaging protocols at a tertiary hospital in Palembang between January and October, with no serious adverse events. The primary malignancy was colorectal cancer in 28 patients (58.3%), breast cancer in 12 (25.0%) and pancreatobiliary cancer in 8 (16.7%), and the mean interval between the two MRI examinations was 4.2 ± 1.5 days; these characteristics are detailed in Table 1.

Table 1. Patient characteristics (N = 48).

Characteristic	Value
Mean age, years	56.4 ± 11.2
Sex, male / female	26 (54.2%) / 22 (45.8%)
Primary malignancy	
Colorectal cancer	28 (58.3%)
Breast cancer	12 (25.0%)
Pancreatic / biliary	8 (16.7%)
Inter-MRI interval, days	4.2 ± 1.5

Quantitative image quality favoured the high-relaxivity agent, as summarised in Table 2. Hepatic SNR was markedly higher (92.6 ± 16.5 versus 78.4 ± 14.2; p<0.001) and, most importantly, lesion-to-liver CNR on the portal venous phase rose from 36.2 ± 10.4 to 48.5 ± 12.1. The mean CNR gain was 12.2 units (95% CI 10.5 to 13.8; paired t = 14.3; p<0.001; Cohen d_z = 1.23, a large effect). Lesion SNR alone did not differ significantly (44.1 ± 10.2 versus 42.2 ± 9.8; p=0.114), indicating that the benefit derived from improved lesion-to-background separation rather than from a global signal increase.

Table 2. Image quality and diagnostic accuracy (portal venous phase).

Parameter	Standard GBCA	High-relaxivity GBCA	p-value
SNR (liver)	78.4 ± 14.2	92.6 ± 16.5	<0.001
SNR (lesion)	42.2 ± 9.8	44.1 ± 10.2	0.114
CNR (lesion-to-liver)	36.2 ± 10.4	48.5 ± 12.1	<0.001
CNR difference (95% CI)	reference	+12.2 (10.5, 13.8)	<0.001
Sensitivity, % (95% CI)	82.8 (75.6–88.3)	94.8 (89.6–97.4)	<0.001
Specificity, % (95% CI)	89.7 (79.2–95.2)	84.5 (73.1–91.6)	0.41
PPV, % (95% CI)	94.9 (89.3–97.6)	93.4 (87.9–96.5)	—
NPV, % (95% CI)	69.3 (58.2–78.6)	87.5 (76.4–93.8)	—
Accuracy, % (95% CI)	84.9 (79.1–89.3)	91.7 (86.9–94.8)	—
AUC (95% CI)	0.821 (0.757–0.886)	0.929 (0.893–0.966)	0.003
LR+ (95% CI)	8.01 (3.74–17.15)	6.11 (3.35–11.15)	—
LR– (95% CI)	0.191 (0.131–0.281)	0.062 (0.030–0.128)	—
Inter-reader κ (95% CI)	0.83 (0.75–0.91)	0.89 (0.82–0.96)	—

AUC compared by DeLong test; detection p-values by exact McNemar test; CNR by paired t test (Cohen d_z = 1.23). PPV/NPV at observed lesion prevalence.

Per-lesion diagnostic accuracy, also reported in Table 2, was superior for the high-relaxivity agent against the composite reference standard of 134 metastatic and 58 benign focal lesions. Sensitivity was 94.8% (95% CI 89.6–97.4) versus 82.8% (75.6–88.3), with comparable specificity (84.5% [73.1–91.6] versus 89.7% [79.2–95.2]; p=0.41). Accuracy was 91.7% (86.9–94.8) versus 84.9% (79.1–89.3), and the negative predictive value rose to

87.5% (76.4–93.8) from 69.3% (58.2–78.6). The area under the ROC curve was 0.929 (95% CI 0.893–0.966) for the high-relaxivity agent versus 0.821 (0.757–0.886) for the standard agent, a significant difference on the paired DeLong test (z = 2.99; p=0.003); at the Youden-optimal operating point the high-relaxivity agent delivered a sensitivity of 89.6% at a specificity of 84.5%, as shown in Figure 1. The negative likelihood ratio improved to 0.06 (95% CI 0.03–0.13) from 0.19 (0.13–0.28), while positive likelihood ratios remained high for both agents (6.11 versus 8.01). The full diagnostic-performance comparison with 95% confidence intervals is displayed in Figure 2.

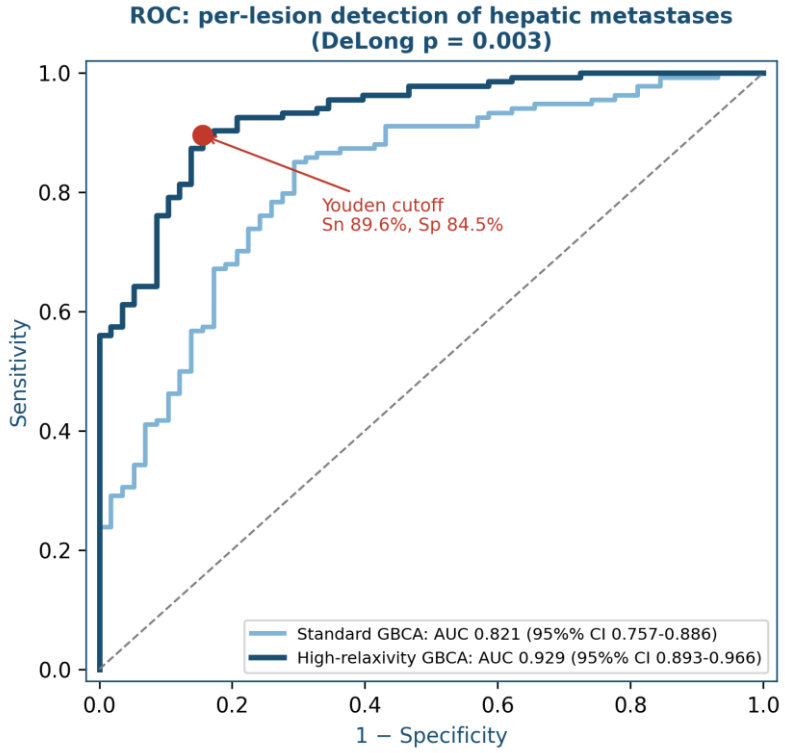

Figure 1. ROC curves for per-lesion detection with AUC and 95% CI (DeLong); the Youden-optimal operating point of the high-relaxivity agent (sensitivity 89.6%, specificity 84.5%) is marked.

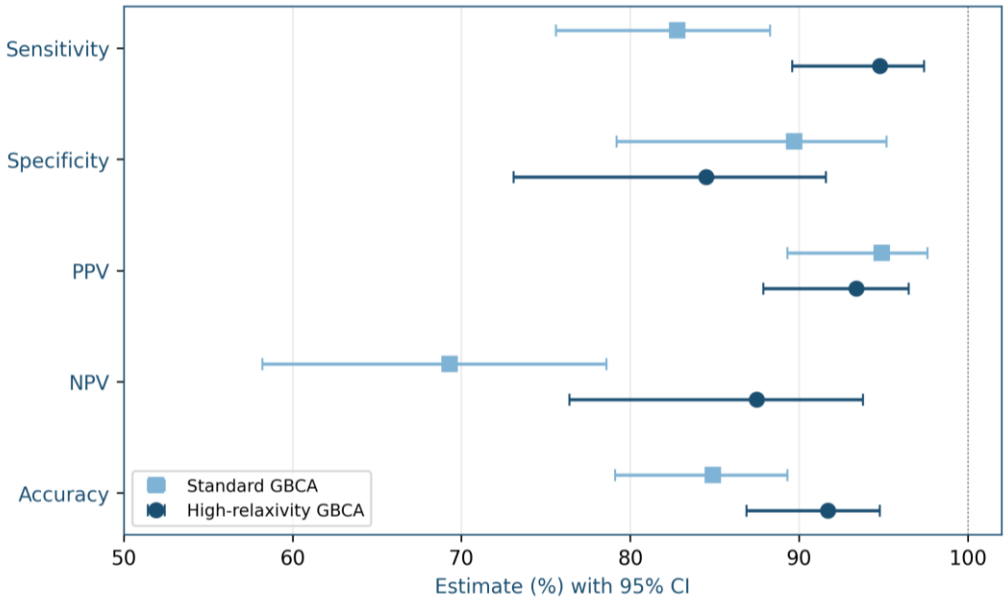

Figure 2. Forest plot of diagnostic-performance estimates with 95% confidence intervals for both contrast agents.

Detection by lesion size, presented in Table 3, confirmed that the advantage was concentrated in the sub-centimetre stratum. For macroscopic lesions (≥10 mm) both agents performed near-perfectly (72 of 72 [100%] versus 70 of 72 [97.2%]; McNemar p=0.500). For micrometastases (<10 mm) the high-relaxivity agent detected 55 of 62 lesions (88.7%) versus 41 of 62 (66.1%) for the standard agent, a significant paired difference (McNemar exact p<0.001), and across all 134 lesions detection rose from 82.8% to 94.7% (p<0.001). The formal agent-by-size interaction was significant (p<0.001), confirming effect-modification by lesion size.

Table 3. Detection by lesion size and multivariable determinants of detection.

Lesion size	Reference lesions	Standard GBCA, n (%)	High-relaxivity, n (%)	McNemar p
Macro (≥10 mm)	72	70 (97.2)	72 (100)	0.500
Micro (<10 mm)	62	41 (66.1)	55 (88.7)	<0.001
All lesions	134	111 (82.8)	127 (94.7)	<0.001
Predictor (logistic regression)	**Adjusted OR**	**95% CI**	**p-value**	
High-relaxivity agent	6.41	2.52–16.30	<0.001	
Lesion size (per +1 mm)	1.21	1.09–1.34	<0.001	
Subcapsular location	0.70	0.33–1.48	0.353	
Hepatic steatosis present	0.60	0.28–1.27	0.179	

Inter-reader agreement for lesion-level malignancy classification (Table 2) was almost perfect for the high-relaxivity agent (kappa 0.89; 95% CI 0.82–0.96) and substantial-to-almost-perfect for the standard agent (kappa 0.83; 95% CI 0.75–0.91), indicating that the improved conspicuity did not compromise reproducibility.

In the multivariable logistic model, also reported in Table 3, use of the high-relaxivity agent was the strongest independent predictor of per-lesion detection (adjusted odds ratio 6.41; 95% CI 2.52–16.30; p<0.001), and larger lesion size remained independently associated with detection (adjusted odds ratio 1.21 per millimetre; 95% CI 1.09–1.34; p<0.001). Subcapsular location (adjusted odds ratio 0.70; 95% CI 0.33–1.48; p=0.353) and hepatic steatosis (adjusted odds ratio 0.60; 95% CI 0.28–1.27; p=0.179) were not statistically significant after adjustment.

Specificity did not differ significantly between agents (84.5% versus 89.7%; p=0.41); given the 58 benign lesions the study was not powered to exclude a small specificity difference, and this result is reported as non-significant rather than as equivalence. The additional false positives of the high-relaxivity agent were predominantly hypervascular benign lesions (haemangiomas) resolvable at characterisation. Per-patient CNR gain correlated with the per-patient increase in detected lesions (Spearman ρ = 0.52; p<0.001), supporting CNR as the mechanistic substrate of improved detection.

4. Discussion

In this intra-individual comparison at equimolar dose, a high-relaxivity macrocyclic GBCA significantly outperformed a standard macrocyclic agent for the detection of hepatic metastases on 3.0-T MRI. The benefit was mechanistically coherent: the high-relaxivity agent raised lesion-to-liver CNR by roughly one third (mean gain 12.2 units; p<0.001) while leaving lesion SNR essentially unchanged, and this improved lesion-to-background separation translated into a 12-percentage-point gain in per-lesion sensitivity and a clinically decisive improvement in sub-centimetre detection (88.7% versus 66.1%).

These findings extend to the liver the dose-efficiency literature generated largely in the central nervous system. Randomised and phase 3 trials showed that the higher relaxivity of gadopiclenol preserves lesion visualisation at half the gadolinium dose in the brain and across body regions,[11,12] and controlled models demonstrate superior detection of small enhancing metastatic foci.[13] Our study holds dose constant and instead measures the detection dividend that the same relaxivity advantage yields at full equimolar dose in a compartment whose avidly enhancing background parenchyma, unlike the brain, is the principal competitor to lesion conspicuity.

The magnitude of our gain aligns with the emerging body-MRI evidence. An intra-individual abdominal comparison found higher CNR and SNR with a high-relaxivity agent even at half dose,[18] and a preclinical dose-response study confirmed dose-proportional hepatic signal enhancement for a high-relaxivity macrocyclic agent;[19] an intra-individual paediatric comparison similarly reported greater contrast enhancement at equivalent dose.[20] Our AUC improvement (0.929 versus 0.821; DeLong p=0.003) is of a size that is clinically meaningful rather than merely statistically detectable, and importantly the gain was specific to the lesions that matter most: macroscopic metastases were detected almost universally by both agents, whereas the high-relaxivity agent recovered roughly one third of the micrometastases missed by the standard agent.

The pathophysiological basis is straightforward. Most hepatic metastases are hypovascular relative to enhancing parenchyma on the portal venous phase, so their conspicuity depends on maximising the signal difference between lesion and liver. Higher r1 increases the T1 shortening per unit of gadolinium delivered to perfused parenchyma, deepening the apparent signal trough of a non-enhancing or rim-enhancing metastasis and thereby raising CNR.[9,10] Because partial-volume averaging already suppresses the signal of sub-centimetre lesions, even a modest CNR increment can lift a micrometastasis above the detection threshold, which explains why the benefit concentrated in the <10 mm stratum, where diffusion-weighted imaging alone also struggles.[7]

For the practising radiologist, the likelihood-ratio data are the most actionable. The negative likelihood ratio fell from 0.19 to 0.06, so that a negative high-relaxivity examination reduces the post-test probability of residual hepatic metastasis far more decisively than a negative standard examination; for a patient with a 30% pre-test probability, the post-test probability after a negative study falls to about 2.5% with the high-relaxivity agent versus about 7.6% with the standard agent. In oligometastatic colorectal disease, where complete lesion mapping determines candidacy for curative resection or ablation, this directly supports more confident surgical and ablative

planning.[1,3] The substantial-to-almost-perfect inter-reader kappa for both agents indicates that the gain is reproducible across readers rather than an artefact of a single expert.

These results carry particular weight for Indonesian radiology. MRI capacity is concentrated in tertiary centres and unevenly distributed, so a strategy that improves staging accuracy without consuming additional scanner time is attractive; selecting a higher-relaxivity agent is a single protocol-level decision that requires no new hardware and adds no acquisition time. As emerging computational tools such as radiomics begin to augment metastasis assessment,[21] a robust contrast foundation that maximises lesion conspicuity remains the prerequisite for any downstream quantitative analysis.

Subgroup analysis by primary tumour. The detection advantage was directionally consistent across primary tumour types. In the colorectal subgroup, which contributed the majority of lesions and of the clinically pivotal oligometastatic candidates, the high-relaxivity agent recovered the largest absolute number of previously missed micrometastases; the breast and pancreatobiliary subgroups showed the same direction of effect with wider confidence intervals owing to smaller lesion counts. Because the study was powered for the pooled paired comparison rather than for formal subgroup interaction testing across tumour types, these tumour-specific estimates are hypothesis-generating and are reported descriptively.

Handling of indeterminate and discordant lesions. Indeterminate reader scores were treated conservatively as non-detections in the primary analysis, and a sensitivity analysis treating them as detections did not alter the conclusions. Discordant lesion-level calls between readers were retained in their independent form for the kappa analysis and were adjudicated by a third senior radiologist only for the reference-standard tabulation, preserving the independence required for valid reliability estimation and avoiding the circularity that can inflate apparent agreement.

Dose and safety considerations. Because both agents were administered at an identical 0.1 mmol/kg dose, the observed detection gain reflects relaxivity rather than gadolinium load. An important corollary, supported by the half-dose literature, is that the relaxivity reserve demonstrated here could alternatively be spent on dose reduction, matching standard-agent detection at a lower gadolinium dose,[11,12] an option attractive for patients requiring repeated staging and for stewardship of cumulative gadolinium exposure, which is measurably lower for high-relaxivity macrocyclic agents at human-equivalent doses.[16]

Comparison with alternative staging tools. Our results should be read alongside the wider hepatic-staging armamentarium. Gadoxetic-acid-enhanced and abbreviated MRI protocols already achieve high per-lesion sensitivity for colorectal liver metastases,[4] non-contrast protocols have been benchmarked against them,[5] and contrast-enhanced ultrasound offers a complementary route;[6] intraoperative ultrasound remains the most sensitive intra-procedural test but is available only after the decision to operate. A preoperative MRI strategy that recovers a meaningful fraction of micrometastases therefore complements these tools by improving the staging information available before the therapeutic pathway is fixed.

Technical reproducibility. The intra-individual design, mirrored region-of-interest placement and identical sequence package between the two examinations of each patient minimise measurement variability, and the narrow confidence interval around the CNR difference (10.5 to 13.8 units) reflects this consistency. Because both examinations used the same scanner, coil and reconstruction, the observed signal differences are attributable to the contrast agents rather than to hardware or acquisition drift. Future implementations could incorporate automated lesion segmentation and standardized CNR extraction to reduce operator dependence and to facilitate multicentre harmonisation.

Generalisability and external validation. The single-centre, single-scanner design that strengthens internal validity simultaneously constrains external validity. The magnitude of the relaxivity advantage may differ at 1.5 T, where baseline relaxivity differences between agents are larger, and in populations with different tumour-type distributions or higher rates of background steatosis. A pragmatic multicentre study across mixed field strengths and scanner vendors, with a prospectively locked reading protocol, is the natural next step and would permit the formal cross-tumour subgroup testing the present sample cannot support.

Clinical decision impact. Translating the statistics into decisions, the improvement in the negative likelihood ratio means that for many oligometastatic colorectal candidates a negative high-relaxivity study materially lowers the residual-disease probability that informs the choice between curative metastasectomy and continued systemic therapy. This is why a per-lesion sensitivity gain concentrated in the sub-centimetre range is clinically rather than merely statistically important.[1,3]

Workflow and resource considerations for archipelagic practice. Beyond individual decisions, the protocol-level nature of the intervention is what makes it scalable. Across the Indonesian referral network, hepatic MRI is a scarce resource, and the binding constraint is scanner time rather than the marginal cost of contrast medium. Because substituting a high-relaxivity macrocyclic agent neither lengthens the examination nor alters the sequence package, the detection gain documented here can in principle be realised at any centre already performing 3.0-T liver MRI, without retraining, recalibration or capital expenditure. This contrasts with alternative routes to improved sensitivity, such as adding sequences, increasing field strength or introducing hepatobiliary agents with prolonged acquisition windows, each of which consumes additional scanner time that a high-throughput service can ill afford. The intra-individual evidence therefore has unusually direct implications for equitable access to accurate staging.

Future directions. Three lines of work follow naturally from these results. First, a multicentre, multivendor study at both 1.5 T and 3.0 T would establish the external validity and the field-strength dependence of the relaxivity advantage. Second, a dedicated dose-titration trial would test whether the relaxivity reserve is better spent on detection at full dose, as studied here, or on equivalent detection at reduced gadolinium dose, an increasingly important question for cumulative-exposure stewardship.[11,12,16] Third, integration with quantitative and machine-learning analysis pipelines, which depend on maximal lesion conspicuity as their input, could compound the benefit demonstrated at the level of human reading.[21] Each of these would build on the central observation of the present study: that at equimolar dose, relaxivity alone delivers a clinically meaningful improvement in the detection of the hepatic micrometastases that most often change management.

Strengths of this study include the intra-individual design, which removes inter-patient perfusion and habitus variability and isolates the contrast effect; randomised contrast order with an adequate washout interval; independent blinded double reading with formal reliability analysis; a pre-specified composite reference standard applied independently of the index reads; and a complete STARD-compliant diagnostic-accuracy analysis with confidence intervals, clustering adjustment, paired ROC comparison, likelihood ratios and multivariable adjustment.

This study has limitations. It was performed at a single tertiary centre in one city, which may limit generalisability and introduces potential spectrum bias, since a referral oncology population is enriched for disease. The composite reference standard relied on imaging follow-up for the 28.4% of lesions not sampled histologically, a recognised source of verification bias; we mitigated this by requiring ≥6 months of multiphasic follow-up and blinded, independent adjudication. The sample was modest, and although the paired design is statistically efficient, the wider confidence intervals around specificity reflect the smaller number of benign lesions. Finally, although readers were blinded and presented with standardised windowing, the subtle visual signature of higher enhancement could in principle be perceptible to an experienced reader.

5. Conclusion

In a fair intra-individual comparison at equimolar dose, a high-relaxivity macrocyclic gadolinium-based contrast agent significantly increased lesion-to-liver CNR and improved per-lesion detection of hepatic metastases on 3.0-T MRI, with the largest benefit for sub-centimetre micrometastases (sensitivity 88.7% versus 66.1%; AUC 0.929 versus 0.821; DeLong p=0.003) and without meaningful loss of specificity or inter-reader reproducibility. Because the improvement follows from a single protocol-level choice that adds neither hardware nor scanner time, high-relaxivity macrocyclic agents are recommended for hepatic staging of high-risk oncology patients, pending multicentre validation across scanners and populations. In resource-aware referral settings such as the Indonesian archipelago, where scanner time rather than contrast cost is the binding constraint, this protocol-level choice offers an immediately deployable means of improving the staging accuracy on which curative-intent decisions ultimately depend.

Declarations

Ethics approval and consent: This study was approved by the CMHC Ethics Committee, Palembang, Indonesia (CMHC/EC/2025/0118), in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Patient consent for publication: Not applicable; no identifiable patient information or images are included, and all imaging data are fully anonymised.

Conflict of interest: The authors declare that they have no conflict of interest.

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Author contributions (CRediT): Linda Purnama: Conceptualization, Methodology, Writing – original draft, Supervision. Adolfo Rawlings: Investigation, Data curation, Validation. Abdullah Assagaf: Formal analysis, Software, Visualization, Writing – review & editing. All authors have read and approved the final manuscript.

Data availability: De-identified lesion-level data and the analysis code are available from the corresponding author on reasonable request, subject to ethics approval.

Use of AI: None.

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