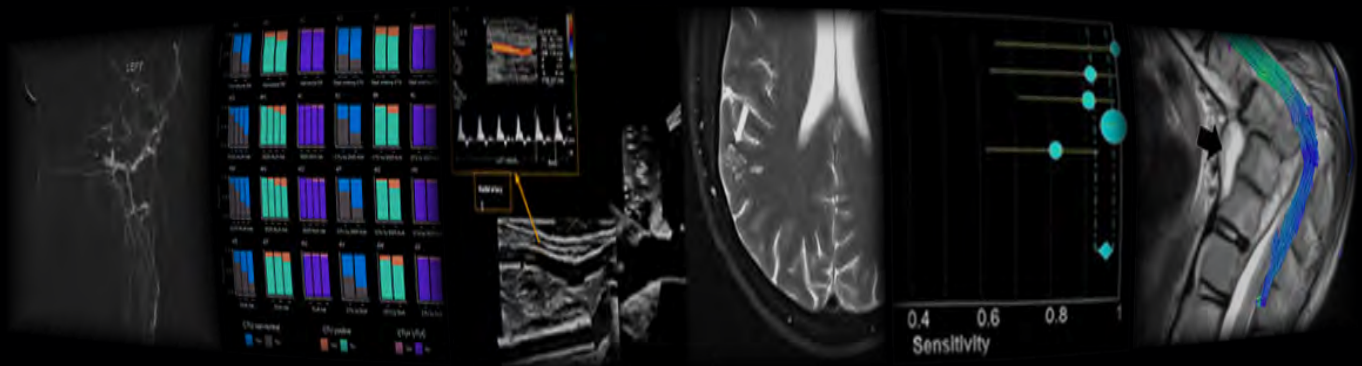


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The Journal of Practical Medical Imaging and Management

2025 Leaders on the Horizon Radiology Residents Program



From Signals to Signs:
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Fiber Tractography of Spine
in Predicting Neurological
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FOREWORD

We are pleased to present the *2025 Leaders on the Horizon Residents Program Special Edition of Applied Radiology*, featuring the winning articles from this year's program. Leaders on the Horizon is supported by an unrestricted educational grant from Bracco Diagnostics, whose continued commitment to education and to the future of medical imaging plays an essential role in the success and longevity of this initiative.

The Leaders on the Horizon program offers radiology residents from around the world the opportunity to submit original manuscripts for consideration in two categories: Clinical Research and Clinical Review. Each submission is evaluated by a distinguished panel of radiology professionals, ensuring a rigorous and thoughtful peer-review process. The program continues to reflect the global nature of today's radiology community and the high caliber of work being produced by residents early in their careers.

This Special Edition highlights the first-, second-, and third-place winning authors in each category for the 2025 program. In the Clinical Research category, we recognize Meemansa Jindal, MBBS, MD (first place); Daniel Veyg, DO (second place); and Ian Rumball, MD (third place). In the Clinical Review category, honors are awarded to Paula Elena Hernández Quiroz, MD (first place); Meagan Bechel, MD, PhD (second place); and Luis Lorenzo A. Chan, MD (third place). Their articles, published in full in this issue, exemplify the clinical relevance, intellectual curiosity, and scholarly rigor that define emerging leaders in radiology.

Beyond publication, Leaders on the Horizon is designed to recognize excellence and encourage professional development. Program winners receive an educational grant and are honored annually at a special reception held during the Radiological Society of North America (RSNA) meeting each November. This event provides an opportunity for residents to be recognized by peers, mentors, and industry leaders in an international setting.

Anderson Publishing and *Applied Radiology* are proud to host the Leaders on the Horizon program and to provide radiology residents with a platform to share their work with a global audience. For more than two decades, this initiative has supported the next generation of radiology professionals by encouraging academic excellence and fostering meaningful engagement within the imaging community.

On behalf of *Applied Radiology*, I extend my congratulations to this year's award recipients and my sincere appreciation to Bracco Diagnostics for their ongoing support of this important educational program.

Sincerely,



Kieran N. Anderson
Group Publisher, *Applied Radiology*

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RESEARCH

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**Daniel Veyg, DO**

Hofstra University Zucker School
of Medicine and Northwell Health
Hempstead, New York

**Ian Rumball, MD**

Medical College of Wisconsin
Milwaukee, Wisconsin

REVIEW

**Paula Elena Hernández Quiroz, MD**

Department of Radiology, Instituto
Nacional de Ciencias Médicas y
Nutrición Salvador Zubirán
Mexico City, Mexico

**Meagan Bechel, MD, PhD**

Emory University
Atlanta, Georgia

**Luis Lorenzo A. Chan, MD**

St. Luke's Medical Center
Quezon City, Philippines

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Anderson Publishing, Ltd
180 Glenside Avenue,
Scotch Plains, NJ 07076
Tel: 908-301-1995
Fax: 908-301-1997
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Special Edition: 2025 Leaders on the Horizon Residents Program

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Kieran N. Anderson, Group Publisher

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Nina S. Vincoff, MD, is the editor-in-chief of *Applied Radiology*. She is the Executive Medical Director of the Radiology Care Division at Prisma Health and Clinical Associate Professor of Radiology at the University of South Carolina School of Medicine Greenville. She can be reached at nina@appliedradiology.com

Leaders on the Horizon: A Glimpse into Radiology's Future

Nina S. Vincoff, MD

In this issue of *Applied Radiology*, we are proud to share the work of our Leaders on the Horizon award winners. First launched in 2001, this program celebrates the scholarship of radiology residents from around the world. Each year, Leaders on the Horizon reminds us how fortunate we are to welcome new voices into our specialty—voices that reinvigorate us with their fresh ideas, curiosity, and sense of purpose.

This year's winning manuscripts reflect both innovation and insight, demonstrating not only technical advances but also a thoughtful understanding of radiology's evolving role in clinical practice. As a group, the 2025 winners show how emerging leaders are advancing precision medicine while maintaining a strong commitment to value-based care, safety, and the patient experience.

In the research category, Daniel Veyg, DO, presents evidence that geniculate artery embolization can provide meaningful pain relief for cancer patients with severe knee osteoarthritis, offering a minimally invasive option for individuals who are not candidates for surgery. Meemansa Jindal, MBBS, advances our understanding of spinal tuberculosis by demonstrating that diffusion tensor imaging and tractography detect microstructural spinal cord changes that correlate with neurologic impairment—information that may allow earlier or more targeted intervention. Ian Rumball, MD, examines the impact of evolving hematuria risk-stratification guidelines on the diagnostic yield of CT urography, raising important considerations around high-value imaging and responsible resource use.

The review article winners further underscore the importance of quality, value, and patient-centered practice in everyday radiology. Meagan Bechel, MD, PhD, offers a well-structured pictorial review that clarifies the complex differential diagnosis of glioneuronal tumors and provides practical guidance for radiologists. Paula Elena Hernández Quiroz, MD, presents a systematic US approach for evaluating arteriovenous fistula complications in the emergency setting, emphasizing rapid, safe imaging that supports timely clinical decision-making and enhances the patient experience. Luis Lorenzo Chan, MD, contributes a comprehensive meta-analysis showing that artificial intelligence- and radiomics-based models hold significant promise for predicting chemotherapy response in colorectal liver metastases.

As I reflect on the work of these six residents, I am reminded of why this program matters. It shows us where radiology is going and introduces us to the thoughtful and collaborative leaders who will shape its progression through their ingenuity, discipline, and genuine commitment to improving care. Our field is in very good hands.

From Signals to Signs: Diffusion Tensor Imaging and Fiber Tractography of Spine in Predicting Neurological Impairment in Spinal Tuberculosis

Meemansa Jindal, MBBS, MD; Alpana Manchanda, MBBS, MD; Anjali Prakash, MBBS, MD; Sumit Sural, MBBS, MS

Abstract

Purpose: To evaluate the utility of diffusion tensor imaging (DTI) and fiber tractography (FT) in spinal tuberculosis (TB) by assessing its correlation with neurological status.

Materials and Methods: This cross-sectional study comprised 30 patients (mean age: 33.7 ± 16.7 years) with clinically suspected spinal TB above L1 (adults) and L3 (children) vertebral levels, who underwent 3.0T MRI with DTI before initiation of treatment. Neurological status was assessed using the Japanese Orthopaedic Association (JOA) score. DTI parameters, including fractional anisotropy (FA), apparent diffusivity coefficient (ADC), and radial diffusivity (RD), were measured at the site of cord compression and one level above it. Parameters were assessed as mean values, absolute differences (Δ), and percent changes ($\Delta\%$), calculated as per

$$\Delta FA = FA(Above) - FA(At) \quad (1)$$

$$\Delta ADC \text{ or } \Delta RD = ADC \text{ or } RD(At) - ADC \text{ or } RD(Above) \quad (2)$$

$$\Delta FA\% = \frac{FA(Above) - FA(At)}{FA(Above)} \times 100 \quad (3)$$

$$\Delta ADC\% \text{ or } \Delta RD\% = \frac{ADC \text{ or } RD(At) - ADC \text{ or } RD(Above)}{ADC \text{ or } RD(Above)} \times 100 \quad (4)$$

Conventional MRI metrics, including T2 hyperintensities and spinal canal encroachment (SCE), were also recorded. FT was qualitatively graded into types I-IV (types I, III: no disruption of fibers; types II, IV: with disruption of fibers). Statistical analysis included paired *t*-tests, Spearman correlation, receiver-operating characteristic (ROC) curve analysis, and Fisher exact test.

Results: A significant decrease in FA and increase in ADC and RD were seen at the site of compromise ($P < .001$). A SCE threshold of 74.4% predicted neurological deficit with 62% sensitivity and 83% specificity [area under the curve (AUC) = 0.74]. ROC analysis identified $\Delta FA\%$ ($\geq 13.6\%$) as the strongest predictor of neurological deficit (AUC = 0.77, sensitivity 100%, specificity 62%). $\Delta RD\%$ (cutoff: $\geq 45.3\%$) showed 76% sensitivity and 56% specificity for both T2 hyperintensity (AUC = 0.60) and fiber disruption (AUC = 0.67). Fiber disruption, as seen in type II and IV FT patterns, was significantly associated with JOA < 13 (odds ratio 7.5, $P = .0318$) and correlated negatively with JOA scores ($r = -0.621$, $P < .0013$).

Conclusion: DTI-derived metrics, particularly $\Delta FA\%$ and $\Delta RD\%$, along with fiber tractography, demonstrate strong correlation with clinical impairment and may provide early indicators of neural damage.

Keywords: diffusion tensor imaging, spinal cord, tuberculosis, tractography, MRI

Affiliations: Department of Radio-diagnosis, Maulana Azad Medical College, New Delhi, India (Jindal, Manchanda, Prakash). Department of Orthopedics, Maulana Azad Medical College, New Delhi, India (Sural).

Disclosures: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

Ethics approval. This study was approved by the Institutional Ethics Committee of Maulana Azad Medical College (MAMC), New Delhi [F.1/IEC/MAMC/MD/MS(96/02/2023)/No. 301], and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Human Ethics and Consent to Participate: Written informed consent/assent was obtained from all participants or their parents/guardians, as applicable.

Introduction

Spinal tuberculosis (TB) constitutes approximately 2% of all TB cases and commonly arises as a complication of pulmonary or abdominal TB, spreading via arterial or venous routes. MRI is the modality of choice due to its superior soft-tissue contrast (sensitivity of 100% and specificity of 80%) and effectively identifies contiguous and skip lesions, paraspinal collections, and epidural extension.

Diffusion tensor imaging (DTI) evaluates the magnitude and direction of water diffusion, thereby providing insight into axonal and myelin integrity. It has demonstrated clinical utility in cervical spondylotic myelopathy and traumatic spinal cord injury, often detecting microstructural alterations before they are apparent on conventional MRI. However, the application of DTI in spinal TB remains underexplored, despite its potential to quantify subtle intramedullary changes resulting from infection or compression. Recognizing this gap, the study aims to bridge the limited understanding of diffusion behavior in spinal TB by correlating DTI-derived metrics with clinical and tractographic findings. This approach not only highlights the role of diffusion parameters in assessing functional impairment but also offers a new perspective on cord pathology in tuberculous myelopathy.

The objectives of this study were to:

1. Compare the DTI values “At” and “Above” the site of cord compromise to find out the changes in DTI parameters at the site of cord compromise.
2. Correlate these changes with the neurological status of patients.
3. Determine the cutoffs for various DTI parameters at which significant neurological deficits can be expected.
4. Describe the tractography findings in these patients.

Methodology

Study design

The study comprised 30 patients (15 males, 15 females; mean age: 33.7 ± 16.7 years, range: 6-71 years) with suspected spinal TB. All patients underwent MRI of the spine between July 2023 and October 2024 before initiation of treatment. Neurological impairment was assessed using the Japanese Orthopaedic Association (JOA) score (Keller et al modification 1993), which evaluates motor, sensory, and bladder function on a scale of 0-17 (0 being most severe and 17 being normal).¹ Based on the JOA score, patients were categorized as

Normal (16-17)
Grade I (12-15)
Grade II (8-11)
Grade III (0-7)

All patients included in the study had MRI findings consistent with spinal TB, with or without altered signal intensity changes in the spinal cord. Patients with spinal TB showing cord involvement, either due to epidural abscess or intraspinal tuberculoma, were included. Patients with cord compression due to nontuberculous causes (eg, degenerative disease, neoplasm, trauma) were excluded. Differentiation between “intrinsic” and “extrinsic” tuberculous cord involvement was not attempted, as imaging cannot reliably establish this distinction without histopathologic confirmation.

Since the spinal cord ends at the lower border of L1 vertebra in adults and at the upper border of L3 vertebra in children, patients having spinal TB with involvement below these levels were excluded. Other exclusion criteria included a history of spinal surgery, stroke, or any contraindications to MRI.

MRI and DTI Protocol

MRI was performed on a 3T scanner (MAGNETOM Skyra, Siemens

Healthineers, Germany) using a phased array coil for spine imaging. Precontrast sequences included sagittal T1WI (TR/TE: 550/9.5 milliseconds), sagittal and axial T2WI (TR/TE: 4000/82 milliseconds), and coronal STIR sequence. All sequences were acquired with the field of view ranging from 22 to 32 cm, matrix size between 220×180 and 350×350 , slice thickness between 2 and 4 mm, and a consistent flip angle of 160° .

DTI was acquired precontrast using axial single-shot spin-echo echo-planar imaging covering the lesion and one vertebral level above. Parameters: TR/TE: 5500/78 milliseconds, flip angle 120° , slice thickness 5 mm, 2 mm interslice gap, 25 slices, matrix 220×220 , 10 noncollinear directions, b-values: 0 and 700 s/mm^2 . The imaging plane was perpendicular to the spinal cord. Total acquisitions: 2 (one pretreatment and one after 6 months of treatment). The total scan time was 25-30 minutes for conventional MRI sequences, including pre- and postcontrast imaging, and an additional 5-8 minutes for DTI sequences.

Contrast-enhanced sequences included fat-suppressed T1 Dixon (TR/TE: 550/11 milliseconds) and 3D VIBE (TR/TE: 6.68/2.46 milliseconds), following intravenous administration of gadopentetate dimeglumine (0.1 mmol/kg) via 22G (adults) or 24-26G (children) cannula.

Image Processing and Data Analysis

All the images were processed on a dedicated advanced workstation (Syngo.via, Siemens Medical Solutions). Conventional MRI images were analyzed to classify the level of the disease into cervical, cervicodorsal, upper dorsal (D1-D4), mid-dorsal (D5-D8), lower dorsal (D9-D12), and dorsolumbar (with involvement of L1 vertebra). Patterns of involvement were classified as either typical (paradiscal, anterior, posterior, central) or atypical (including isolated sacral involvement, craniovertebral junction involvement, posterior element

involvement, skip lesions, intraspinal tuberculomas, solitary vertebral disease, and tubercular arachnoiditis), as described in literature.^{2,3}

The degree of spinal canal compromise was quantified by calculating the percentage of spinal canal encroachment (SCE) at the site of maximal narrowing using the following formula:

$$\% \text{ Spinal Canal Encroachment (SCE)} = \frac{A}{B} \times 100 = \frac{B-C}{B} \times 100 \quad (1)$$

where

B: area of the canal (calculated by taking average of spinal canal areas one vertebral segment above and one below)

C: area occupied by the spinal cord

A: area occupied by CSF, A=B-C

A value of 100% represented a normal canal with complete CSF preservation, whereas 0% indicated complete CSF effacement and spinal canal stenosis.

Post-acquisition DTI processing included generation of fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) maps. Regions of interest (ROIs) were manually placed at the site of maximal spinal cord compression ("At") and one level above ("Above") using standardized circular ROIs (0.12-0.20 mm²), encompassing both gray and white matter while excluding surrounding CSF. To minimize sampling bias, each measurement was repeated at least 3 times and averaged.

Tractography was performed to visualize directional diffusion, with tractography in different planes depicted by different colors: craniocaudal (blue), anteroposterior (red), and transverse (green). Tractography reconstructions were manually refined to exclude background noise and motion artifacts, including those from swallowing and respiration. Based on the classification by Abdelgawad et al, tractography patterns were categorized as follows: type I (no displacement or disruption), type II (disruption without displacement), type III (splaying without disruption), and type IV (splaying or displacement with disruption).⁴

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics software (version 25.0, IBM Corp., Armonk, New York) and Google Colab (Python 3.9 environment). Normality of continuous variables was assessed using the Shapiro-Wilk test, and nonparametric tests were applied for parameters that were not normally distributed.

DTI parameter mean values "Above" the site of cord compromise were taken as control, and those "At" the site of cord compromise were taken as case and were compared using paired *t*-test (normal distribution) or Wilcoxon signed-rank test (non-normal distribution). A significance threshold of *P* < .05 was used for these tests.

Differences between the values of DTI parameters "Above" and "At" were calculated according to Equations (2)-(4) and represented as ΔFA, ΔADC, and ΔRD, respectively.

$$\Delta FA = FA (\text{Above}) - FA (\text{At}) \quad (2)$$

$$\Delta ADC = ADC (\text{At}) - ADC (\text{Above}) \quad (3)$$

$$\Delta RD = RD (\text{At}) - RD (\text{Above}) \quad (4)$$

Further, to normalize the differences in baseline DTI parameter values, ΔFA, ΔADC, and ΔRD values were divided by "Above" values to calculate the rate of change and percentage decrease in these parameters according to Equations (5)-(7), represented as ΔFA%, ΔADC%, and ΔRD%, respectively.

$$\Delta FA\% = \frac{FA (\text{Above}) - FA (\text{At})}{FA (\text{Above})} \times 100 \quad (5)$$

$$\Delta ADC\% = \frac{ADC (\text{At}) - ADC (\text{Above})}{ADC (\text{Above})} \times 100 \quad (6)$$

$$\Delta RD\% = \frac{RD (\text{At}) - RD (\text{Above})}{RD (\text{Above})} \times 100 \quad (7)$$

Receiver-operating characteristic (ROC) curve analysis was performed on percentage SCE as well as on mean, Δ, and %Δ values of DTI parameters to find out cutoffs/thresholds. The optimal threshold values were determined using the Youden index, with sensitivity, specificity, and area under the curve (AUC) reported. Bivariate Spearman correlation analysis [reported as correlation coefficients (ρ)] was used to assess the correlation of SCE,

T2-hyperintensities, and DTI parameters with JOA scores.

Results

Following the clinical and neurological evaluation for the 30 patients with suspected spinal TB (cervical, dorsal, and dorsolumbar regions), baseline conventional MRI and DTI of the spine were performed. All patients had fever, anorexia, night sweats, and weight loss at presentation. A majority of the patients had localized complaints of lower back pain (73.4%), followed by upper back pain (23.3%) and neck pain (3.3%). Disseminated TB was seen in 50%, predominantly pulmonary (26.7%) and intracranial (20%). A history of exposure to TB was reported in 76.7%. Neurological deficits were present in 86.7%, most commonly JOA grade II (40%), followed by grade III (26.7%) and grade I (20%), with a mean JOA score of 10.04.

Conventional MRI Findings

Dorsal spine (83.3%) involvement, predominantly the lower dorsal segments (D8-D12), was most commonly seen, followed by cervical and cervicodorsal spine (16.7%), with 60% showing contiguous vertebral disease. Most patients (76.7%) showed typical involvement patterns, primarily paradiscal (70%). Among atypical forms, intraspinal tuberculomas (13.3%), skip lesions (6.7%), and CV junction involvement (3.3%) were observed. Pre-/paravertebral abscesses were seen in 86.7% of patients, with epidural extension in 73.3%. Severe (>75%) SCE was seen in 50% of patients, all of whom had cord T2 hyperintensity and significant deficits (mean JOA: 8.1). Overall, T2 hyperintensity was seen in 70% of patients, and moderate (>50%) canal compromise in 83.3% (Table 1).

ROC curve analysis demonstrated that a canal stenosis threshold of 74.4% best predicted significant neurological deficit

Table 1. Patient Distribution Characteristics, Based on JOA Score, Altered Cord Signal Intensity, and Percentage Spinal Canal Encroachment

CANAL ENCROACHMENT RANGE (%)	TOTAL NUMBER OF PATIENTS IN THE CATEGORY	PATIENTS WITH T2 HYPERINTENSITIES	PATIENTS WITH SIGNIFICANT NEUROLOGICAL DEFICITS (JOA SCORE < 13)	MEAN JOA SCORE
0-25	2	0	0	14.5
26-50	3	0	1	13
51-75	10	6	7	11.3
76-100	15	15	14	8.1
JOA, Japanese Orthopaedic Association.				

Table 2. DTI Parameters “Above” and “At” the Site of Cord Compromise

DTI PARAMETERS	ABOVE	AT	P VALUE
Mean FA	0.67	0.51	Paired t-test: $P < .001$
Mean ADC ($\times 10^{-6}$ mm ² /second)	1123.52	1552.68	Paired t-test: $P < .001$
Mean RD ($\times 10^{-6}$ mm ² /second)	741.21	1318.56	Wilcoxon signed-rank test: $P < .001$
ADC, apparent diffusivity coefficient; DTI, diffusion tensor imaging; FA, fractional anisotropy; RD, radial diffusivity.			

(JOA < 13), yielding a sensitivity of 62% and specificity of 83% (AUC = 0.74).

DTI Findings

Of the 30 patients, 4 showed discrete intramedullary tuberculomas, while the remaining had varying degrees of cord compression and edema secondary to epidural abscesses or vertebral collapse. As the mechanisms often overlapped and the diffusion abnormalities likely represented combined compressive, ischemic, and inflammatory changes, the entire cohort was analyzed together for DTI and tractography correlation with clinical findings. The mean FA, ADC, and RD values “Above” and “At” the site of cord compromise are summarized in Table 2. There was a significant decrease in FA and a significant increase in ADC and RD values “At” the site of cord compromise compared with “Above” (P value < .001 for all).

ROC/characteristic curve analysis of mean FA, ADC, and RD; Δ FA, Δ ADC, Δ RD; and Δ FA%, Δ ADC%, and Δ RD% values was performed to determine thresholds (T) and their respective sensitivity (SE), specificity (SP), and AUC for

1. Significant neurological deficits (JOA score < 13): Parameters showing good discriminatory power (AUC ~ 0.7) included Δ FA (AUC = 0.74) and Δ FA% (AUC = 0.77). Δ RD% also demonstrated moderately good performance (AUC = 0.66).
2. Presence of T2-hyperintense altered signal intensity in spinal cord: Only Δ RD% showed comparatively good discriminatory power (AUC = 0.60).
3. Disruption of fibers on tractography (seen in tractography patterns type II and IV): Δ RD% (AUC = 0.67) and Δ ADC (AUC = 0.59) showed the best performance, followed by RD (At) and Δ RD (AUC = 0.58).

These are summarized in Table 3 and Figure 1.

Tractography Findings

The most common tractography pattern in the study was type IV (67%), followed by type I (16.7%), type III (13.4%) and type II (3.3%). Of patients who had type IV tractography pattern, 85% had significant neurological deficit (JOA score < 13) (Table 4).

There was a significant association between tract disruption, seen in patterns II (3.3%) and IV (67% patients), and the presence of neurological deficit (JOA < 13), with an odds ratio of 7.5 ($P = .0318$, Fisher exact test).

Figures 2-5 depict the conventional MRI, DTI, and tractography findings in a few cases of spinal TB.

Correlation Analysis

There was a significant negative correlation between JOA scores and both percentage canal encroachment ($\rho = -0.59$, $P = .0005$) and the presence of T2-hyperintensity in the spinal cord ($\rho = -0.49$, $P = .0065$). Correlation analysis between DTI parameters and JOA score using Pearson and Spearman correlations was performed. Higher FA values correlated with higher JOA scores ($\rho = 0.13$, $P = .50$), while RD values negatively correlated with JOA scores ($\rho = -0.11$, $P = .55$). Both Δ FA and Δ RD showed negative correlation with JOA scores ($\rho = -0.336$, $P = .07$ and $\rho = -0.16$, $P = .41$, respectively). Only Δ FA% showed statistically significant negative correlation with JOA score ($\rho = -0.374$, $P = .04$). Mean ADC, Δ ADC, Δ ADC%, and Δ RD% showed minimal correlations with JOA scores. There was a significant negative correlation between fiber disruption on tractography (seen in type II and IV patterns) and JOA scores ($\rho = -0.621$, $P = .0003$), indicating that disrupted fibers were associated with worse neurological status.

Discussion

In the evaluation of 30 patients with spinal TB, this study highlights the importance of conventional MRI findings such as pre- and paravertebral abscesses with epidural extension, SCE, altered cord signal intensity, and DTI parameters, by drawing statistically significant correlations and diagnostic cutoffs.

A SCE threshold of 74.4% optimally predicted significant neurological deficit, with an AUC of 0.74, sensitivity of 62%, and specificity of 83%. There was a

Table 3. ROC Curve Analysis Results for Mean, Δ , and % Δ Values

PARAMETER	SIGNIFICANT NEUROLOGICAL DEFICIT (JOA SCORE < 13)				T2 HYPERINTENSITIES IN CORD				DISRUPTION OF FIBERS ON TRACTOGRAPHY			
	T	SE (%)	SP (%)	AUC	T	SE (%)	SP (%)	AUC	T	SE (%)	SP (%)	AUC
FA (At)	≤ 0.68	95	38	0.55	≤ 0.25	14	100	0.42	≤ 0.2	05	100	0.29
ADC(At) ($\times 10^{-6}$ mm ² /second)	≥ 2384	10	10	0.3	≥ 1700	38	78	0.51	≥ 1272	81	44	0.57
RD (At) ($\times 10^{-6}$ mm ² /second)	≥ 930	73	38	0.44	≥ 708	95	22	0.45	≥ 738	67	67	0.58
Δ FA	≥ 0.12	86	62	0.74 ^a	≥ 135	67	56	0.56	≥ 100	95	22	0.49
Δ ADC ($\times 10^{-6}$ mm ² /second)	≥ 380	55	50	0.39	≥ 365	62	56	0.52	≥ 377	62	67	0.59
Δ RD ($\times 10^{-6}$ mm ² /second)	220	95	38	0.52	≥ 152	10	22	0.5	≥ 393	67	67	0.58
Δ FA%	≥ 13.6	10	62	0.77 ^a	≥ 13.6	90	33	0.5	≥ 12.2	95	22	0.38
Δ ADC%	≥ 62.5	36	75	0.41	≥ 33.2	43	78	0.53	≥ 62.5	43	89	0.55
Δ RD%	≥ 45.3	77	62	0.66 ^a	≥ 45.3	76	56	0.6	≥ 45.3	76	56	0.67 ^a
<i>Parameters with AUC ~0.5 and ≤ 0.5 suggest no discrimination power.</i>												
<i>^aAUC ~0.7 suggests good discrimination power, which tends to increase as the AUC approaches 1 (ideal).</i>												
<i>ADC, apparent diffusivity coefficient; AUC, area under the curve; FA, fractional anisotropy; JOA, Japanese Orthopaedic Association; RD, radial diffusivity; ROC, receiver-operating characteristic; SE, sensitivity; SP, specificity; T, threshold.</i>												

significant negative correlation between JOA scores and both canal encroachment ($\rho = -0.59$, $P = .0005$) and T2 hyperintensity ($\rho = -0.49$, $P = .0065$), supporting the combined role of mechanical and intrinsic cord pathology in determining neurological status. Spinal TB can cause cord compromise by 2 processes: external compression by epidural abscesses or intrinsic compromise due to intraspinal tuberculomas and myelitis. More often than not, in clinical and imaging practice, these processes often coexist along a pathophysiologic continuum, and the actual results are a mixture of the 2. The altered diffusion and signal characteristics within the spinal cord due to compression by epidural abscesses externally can be a result of direct dissemination of bacteria into the cord, inflammatory or ischemic cord changes, and not just a mere consequence of canal compromise and impingement.

Since the true differentiation can be made only via biopsy, a strict distinction between “intrinsic” and “extrinsic” cord involvement would have been misleading and therefore was not the goal of this study. The present work instead focuses on assessing how diffusion tensor metrics and tractography reflect the overall degree of cord compromise and functional impairment in spinal TB, irrespective of the exact mechanism of cord involvement.

Compression of the spinal cord leads to altered membrane permeability, extracellular edema, and ischemic injury, resulting in increased ADC and RD and reduced FA. RD is particularly sensitive to myelin integrity, with higher values reflecting demyelination.⁵⁻⁸

In our patients, we observed significant changes “At” the site of cord compromise compared to “Above.” FA decreased from 0.67 to 0.51, while ADC and RD increased from 1123.522 to 1552.68 $\times 10^{-6}$ mm²/

second and 741.21 to 1318.56 $\times 10^{-6}$ mm²/second, respectively ($P < .001$ for all). These reflect reduced anisotropy and increased extracellular diffusion due to microstructural damage. Few studies have reported similar decreased FA and increased MD at and below the level of cord compromise in their patients with spinal TB, although MD changes were not significant between groups with and without neurological deficits, highlighting FA's superior sensitivity.⁹

Among all evaluated DTI parameters, Δ FA% demonstrated the best diagnostic performance for identifying significant neurological deficit (JOA < 13), with AUC 0.77, sensitivity 100%, and specificity 62%. Δ FA performed similarly (AUC 0.74), followed by Δ RD% (AUC 0.66, sensitivity 77%, specificity 62%). ROC analysis for predicting T2 hyperintensity and fiber disruption showed Δ RD% had the best combined sensitivity and specificity (76%

Figure 1. Receiver-operating characteristic (ROC) curves for mean, Δ , and $\%$ values of fractional anisotropy (FA) (A), apparent diffusivity coefficient (ADC) (B), and radial diffusivity (RD) (C).

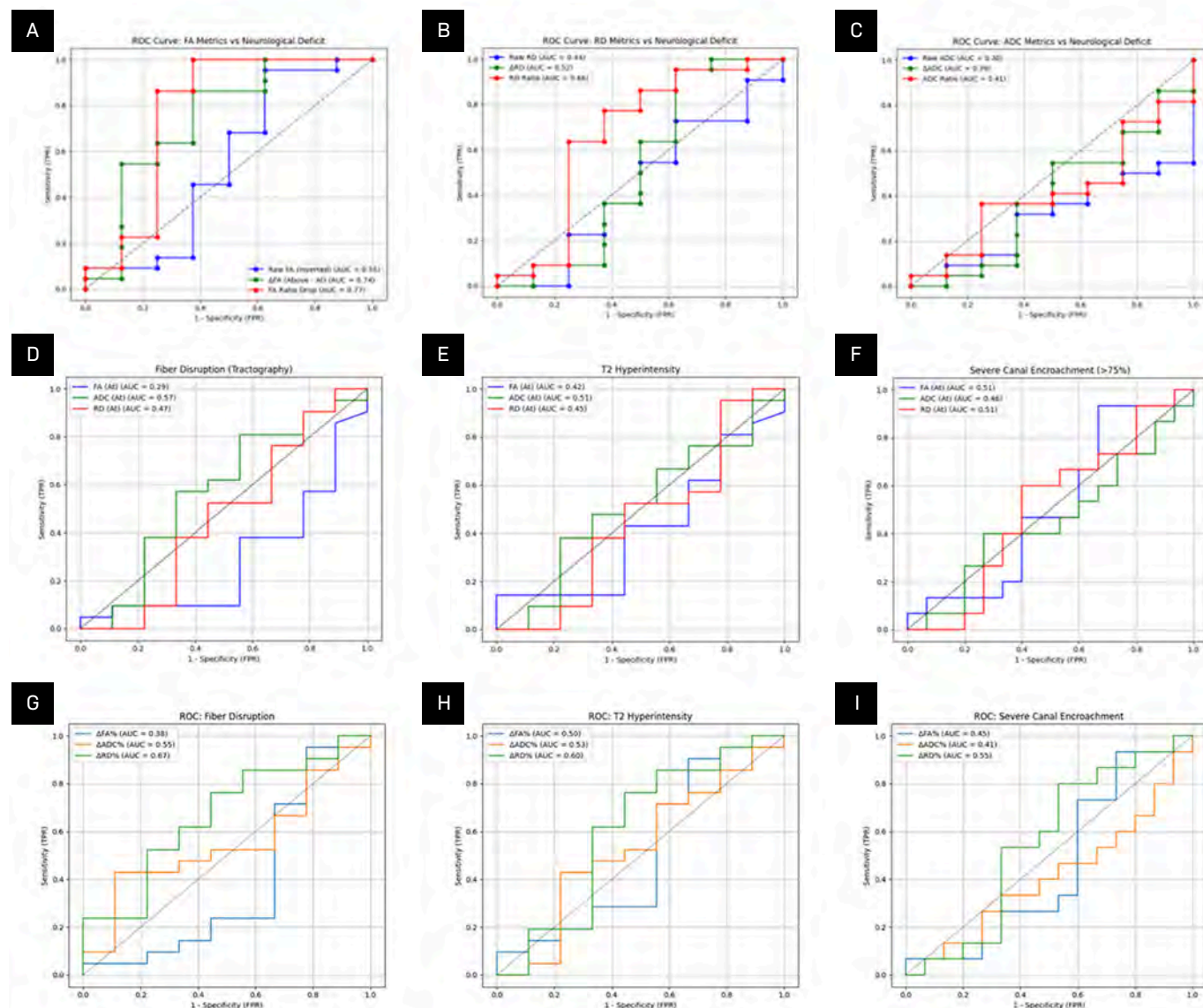
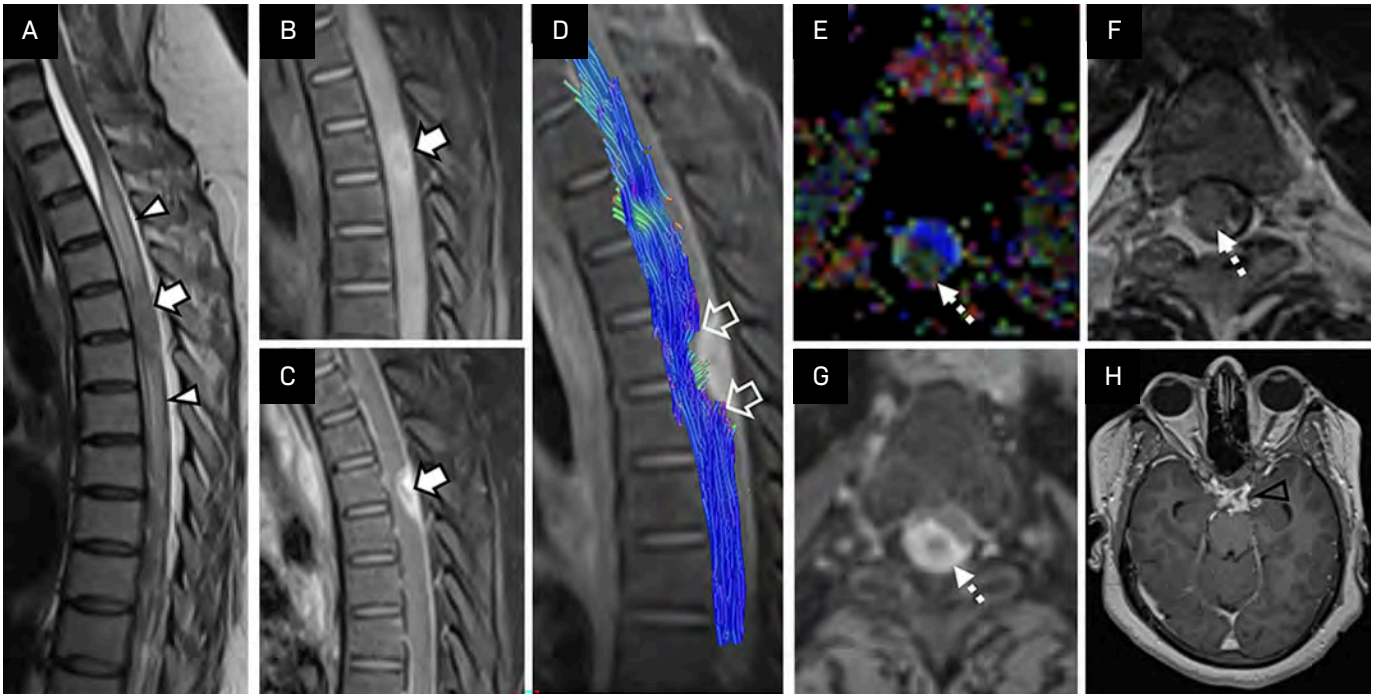


Table 4. Distribution of Various Tractography Patterns in Patients with and Without Significant Neurological Deficits

TRACTOGRAPHY PATTERN	TOTAL NUMBER OF PATIENTS	NO SIGNIFICANT DEFICIT (JOA $\geq$ 13)	SIGNIFICANT DEFICIT (JOA < 13)
Type I (no displacement or disruption)	5	3 (60%)	2 (40%)
Type II (disruption without displacement)	1	0	1(100%)
Type III (splaying without disruption)	4	2 (50%)	2 (50%)
Type IV (splaying/displacement with disruption)	20	3 (15%)	17 (85%)
JOA, Japanese Orthopaedic Association.			

Figure 2. A 44-year-old woman with complete paraplegia with urinary retention (Japanese Orthopaedic Association score 5) and seizures. T2W-sagittal (A), pre- and postcontrast T1W fat-saturated sagittal (B, C), tractography (D), colored fractional anisotropy (FA) map (E) with corresponding T2W-axial (F) and postcontrast T1W-axial (G) images at the same level show a well-defined enhancing T2-hypointense lesion within the cord (white solid arrows in A-C), measuring 20 × 7 mm at D4-D5 vertebral level, with surrounding myelitis from D1-D7 level (white arrowheads in A) displacing the cord anteriorly and left laterally, causing disruption of fibers (hollow arrows in D) without any significant displacement, typical of the type II tractography pattern. There is an alteration of signal on colored FA map at the level of the lesion (dashed arrows in E-G). Postcontrast T1W section of brain (H) shows enhancing exudates in the basal CSF cisterns with few ring-enhancing lesions in the left temporal lobe (hollow arrowhead in H), consistent with the diagnosis of craniospinal tuberculosis.



and 56%, AUC = 0.60-0.67), suggesting its potential as a surrogate marker for myelin damage.

To our knowledge, there is limited literature on sensitivity and specificity of DTI parameters in spinal TB. Prior studies have reported FA and MD cutoffs differentiating pyogenic and tuberculous spondylitis, but these were measured within vertebral bodies and not the cord.¹⁰ Our findings extend DTI analysis to cord-level pathology and define thresholds with functional correlation.

Similar results have been reported in other compressive pathologies. Lee et al identified FA, MD, RD, and AD cutoffs in cervical spondylotic myelopathy (FA: 0.475; RD: $0.749 \times 10^{-3} \text{ mm}^2/\text{second}$) and showed that FA combined with RD or AD is superior to FA or MD alone. Likewise, prior studies have shown FA's superior specificity and sensitivity (100% and 73.3%) over ADC and T2WI in detecting neurological

impairment due to various causes of cord compression. Nischal et al demonstrated that FA (87.5%) outperformed ADC (75%) and T2 hyperintensity (25%) for early myelopathy detection.¹¹ These findings reinforce FA's role in identifying early microstructural injury, while RD indicates myelin disruption.¹²

Among DTI metrics, only $\Delta\text{FA}\%$ demonstrated a statistically significant negative correlation with JOA score ($\rho = -0.374$, $P = .04$). While ΔFA showed a moderate negative trend ($\rho = -0.336$, $P = .07$), other parameters, including mean FA, ADC, RD, and their respective Δ and $\%\Delta$ values, showed weak and nonsignificant correlations. Few studies have highlighted that preoperative motor scores in patients with spinal TB correlated positively with FA ($P < .001$) and negatively with canal compromise and ADC ($P \leq .05$), suggesting that FA is a better marker for preserved motor function. In contrast, sensory scores correlated weakly with

canal compromise and moderately with ADC, possibly explaining why JOA score (which encompasses both motor and sensory components) showed a diluted association with ADC in our analysis.¹³

There is evidence suggesting that in patients with spondylotic myelopathy, FA showed strong negative correlation and ADC showed moderate positive correlation with Nurick clinical scores at the stenotic level.⁷ In patients with mild to moderate cervical spondylotic myelopathy, FA and RD were significantly correlated with severity of stenosis and mJOA scores, with RD indicating myelin disruption.⁸

In this study, tractography findings showed that 67% of patients had type IV pattern (disruption with splaying/displacement), among whom 85% had significant neurological deficits (JOA < 13). There were significant associations (odds ratio of 7.5, $P = .0318$, Fisher exact test) and significant negative correlations ($\rho = -0.621$, $P = .0003$) of fiber disruption (seen

Figure 3. A 60-year-old man with paraplegia without bowel-bladder involvement (Japanese Orthopaedic Association score 10). T2W-sagittal (A), region of interest plotting on T2W-axial sections “At” and “Above” the level of cord compromise (B), postcontrast T1W-sagittal (C), tractography (D), colored fractional anisotropy (FA) map (E) with corresponding T2W-axial (F) and postcontrast T1W-axial (G) images at the same level show subligamentous T2-hyperintense peripherally enhancing prevertebral abscess (black solid arrows in A, C, F, G) at D5-D8 level and anterior epidural abscess (white arrowhead in C), measuring ~13 mm in thickness at D6-D7 vertebral level, resulting in T2-hyperintense signal within the cord (white solid arrow in A) with posterolateral displacement of cord (black dashed arrows in F, G) and disruption of fibers (hollow arrows in D), typical of type IV tractography pattern. There is an alteration of signal within the spinal cord on colored FA map at the level of the lesion (white dashed arrow in E).

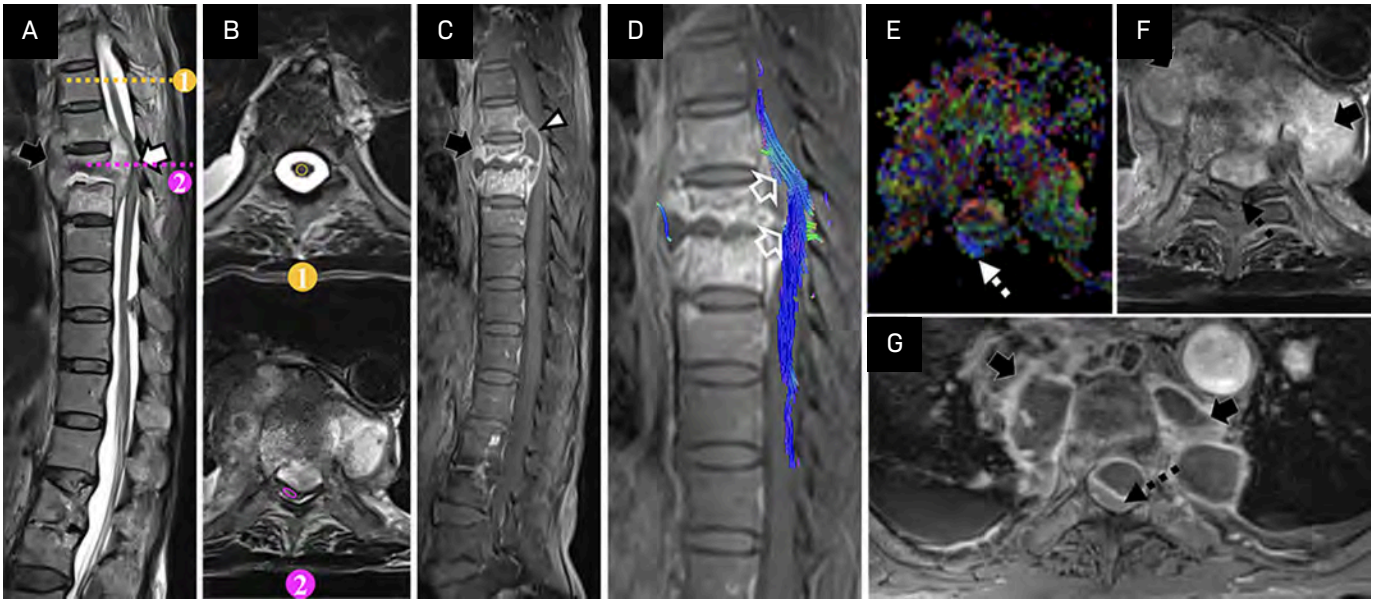


Figure 4. A 20-year-old woman with complete paraplegia and urinary retention (Japanese Orthopaedic Association score 4) and seizures. T2W-sagittal (A), precontrast T1W-sagittal (B), postcontrast T1W-fat saturated sagittal (C), tractography (D), colored fractional anisotropy (FA) map (F) with corresponding T2W-axial (E) image at the same level show destruction and anterior wedge collapse of D4, D5, and D6 vertebrae with subligamentous T2-hyperintense peripherally enhancing prevertebral abscess (black solid arrows in A, C, D, E) and anterior epidural abscess (white arrowheads in C), measuring ~5.8 mm in thickness at D1 to L1 vertebral levels causing gibbus deformity and posterior displacement of cord without any disruption of fibers, typical of the type III tractography pattern; however, no T2-hyperintense signals were noted within the cord. There is signal alteration of the cord on colored FA map at the level of the lesion (dashed arrow in F). Postcontrast T1W image of the brain (G) shows few ring and nodular enhancing lesions in the left frontal lobe (hollow arrow in G), suggesting disseminated CNS tuberculosis.

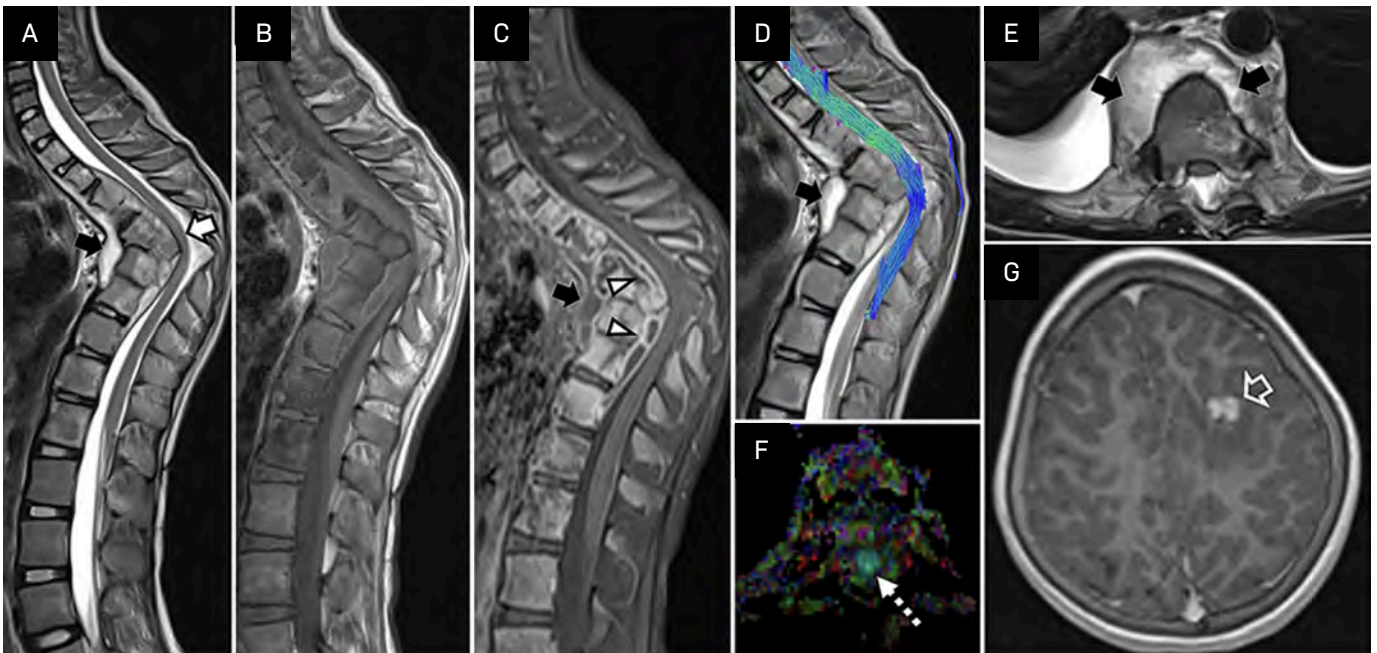
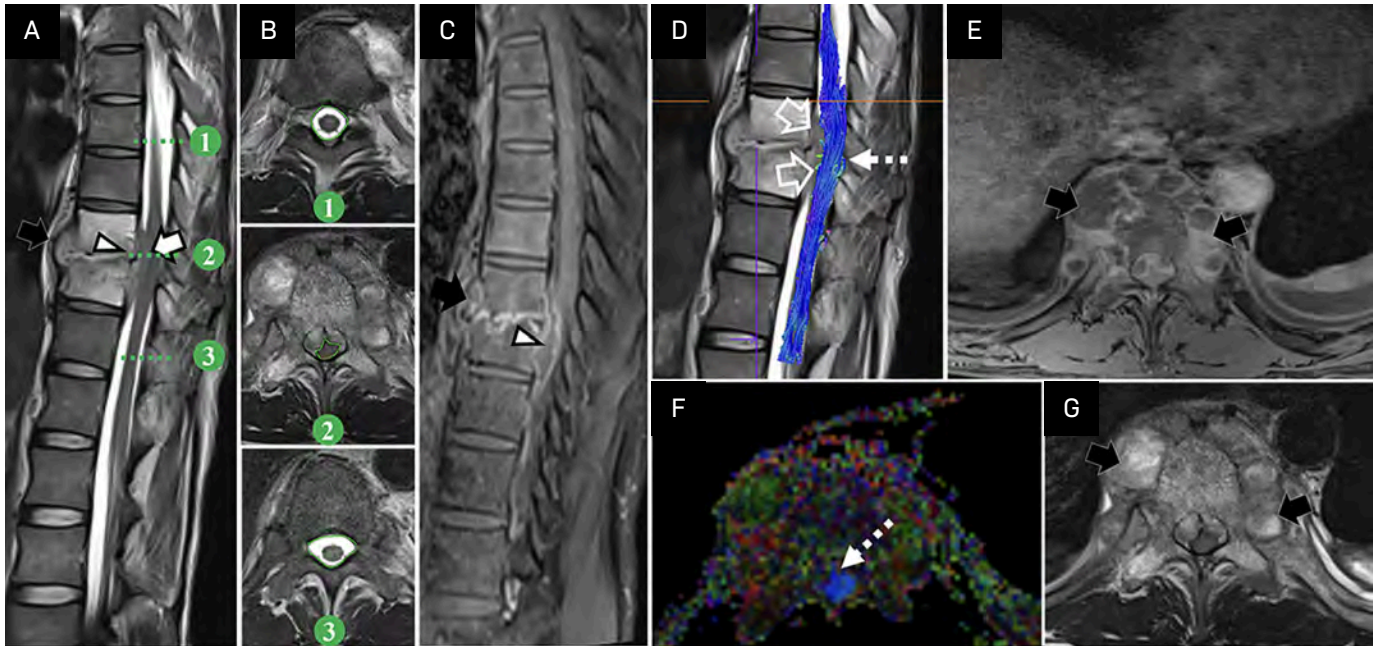


Figure 5. A 50-year-old man with paraplegia and severe bowel-bladder dysfunction (Japanese Orthopaedic Association score 9). T2W-sagittal (A), T2W-axial images taken above, at, and below the site of cord compromise for estimation of spinal canal encroachment (B), postcontrast T1W-sagittal (C), tractography (D), colored fractional anisotropy (FA) map (F) with corresponding postcontrast T1W (E) and T2W-axial (G) images at the same level show typical paradiscal pattern of spinal TB with subligamentous T2-hyperintense peripherally enhancing prevertebral abscess (black solid arrows in A, C, E, G) and anterior epidural abscess (white arrowheads in A, C) measuring ~8 mm in thickness at D8-D11 vertebral levels with T2-hyperintensity within the cord at D9-D10 level causing posterior displacement of cord and disruption of fibers (hollow arrows in D), typical of the type IV tractography pattern. There is a mild alteration of signal on tractography and colored FA map at the level of the lesion (dashed arrows in D, F).



in patterns II and IV) with neurological impairment, indicating its association with lower JOA scores and worse neurological status. Quantitative analysis of fiber tractography in a few studies of compressive spondylotic myelopathy has shown that there is a decrease in the length of fibers, track, and voxel counts with loss of long fiber tracks compared with normal healthy spinal cord.¹⁴ A few studies have shown that while disruption of fibers may not have a direct bearing on the clinical severity of myelopathy, it is associated with poor neurological recovery.^{9,15,16}

Limitations

This study had certain limitations. The sample size was modest ($n = 30$), limiting statistical generalizability and precluding subgroup analysis by spinal level. Its cross-sectional design did not allow longitudinal evaluation of DTI metrics or functional recovery. Manual ROI placement in the narrow spinal

cord may have introduced operator bias, and susceptibility or motion artifacts could have affected quantitative accuracy, particularly in markedly compressed segments. Tractography interpretation was occasionally limited by cord distortion or signal dropout. Finally, although we included patients with cervical, dorsal, and cervicodorsal involvement, region-specific analysis of DTI metrics could not be performed due to small numbers in the various subgroups.

Conclusion

This study demonstrates the utility of DTI as a valuable adjunct to conventional MRI in the evaluation of spinal TB. We observed that parameters such as Δ FA, Δ FA%, and Δ RD% showed strong correlation with neurological deficits and tract disruption, with Δ FA% emerging as the most robust

predictor of neurological impairment. ROC curve analysis further highlighted the diagnostic potential of DTI-derived metrics, particularly in identifying significant cord compromise and altered signal intensity. Tractography patterns also showed significant association with neurological outcomes, emphasizing the importance of assessing fiber integrity in addition to morphologic changes. While our findings support the role of DTI in assessing the severity and functional impact of spinal TB, larger studies with longitudinal follow-up are warranted to validate its prognostic value and establish standardized thresholds for clinical use.

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Geniculate Artery Embolization in Enhancing Quality of Life for Patients with Cancer

Daniel Veyg, DO; Armaan Shah, MD; Audrey Soo, BS; Kadir Ozler, BS; Joe Khoury, DO, MBA; Mustafa Al-Roubaie, MD

Abstract

Geniculate artery embolization (GAE) is a safe, minimally invasive technique for managing refractory knee osteoarthritis (OA) pain. In patients with advanced malignancy who are not surgical candidates, it poses a valuable alternative in the OA management algorithm for otherwise nonoperable patients. This retrospective, multicenter study evaluated the safety and efficacy of GAE in 12 patients (mean age 75.8 years) with severe knee OA and active or recently treated cancer. All patients underwent successful unilateral GAE with no immediate or delayed complications. Mean baseline Western Ontario and McMaster Universities Osteoarthritis Index score was 64.8, which improved significantly to 42.7 and 42.6 at both 3- and 6-month follow-up, respectively ($P < .001$), reflecting sustained medium-term symptom relief. Kellgren-Lawrence scores remained stable, suggesting no radiographic progression. Procedures were completed on an outpatient basis with same-day discharge. These findings suggest that GAE offers a safe, effective alternative for pain relief in patients with limited options due to cancer-related comorbidities. GAE may play a valuable role in the palliative care setting by improving quality of life and functional outcomes in this complex population.

Keywords: embolization, pain management, GAE

Introduction

Knee osteoarthritis (OA) is a highly prevalent and frequently debilitating musculoskeletal disorder that imposes a substantial burden on the general population. In patients with cancer, OA complicates pain management, which is frequently multifaceted owing to the complex interplay between malignancy-related inflammatory changes and side effects from cancer therapies. Additionally, chemotherapy and radiation used to treat the malignancy can complicate musculoskeletal pain and contribute

to bone density loss, worsening joint health and complicating pain management.¹ Consequently, addressing pain in this patient population requires an approach that accounts for the underlying malignancy while targeting the joint pathology.

Palliative care is often employed in patients with advanced cancer. However, the complex nature of treatment-resistant pain requires alternative management strategies.^{2,3} Standard pharmacologic and surgical interventions are often limited by advanced disease, comorbidities, and active cancer treatment, requiring

exploration of alternative management. Intra-articular steroid injections, while safe, are usually of limited durability in advanced OA.⁴ Additionally, patients may also have concomitant higher opioid tolerances secondary to other chronic pain treatment, thus further complicating effectiveness.

Geniculate artery embolization (GAE) is a promising, minimally invasive technique for managing refractory knee OA pain, particularly in patients who are ineligible for total knee arthroplasty (TKA). By selectively targeting the hypervascularized geniculate arteries,

Affiliations: Hofstra University Zucker School of Medicine and Northwell Health, Hempstead, New York (Veyg, Shah, Soo, Ozler). Emory University School of Medicine, Atlanta, Georgia (Khoury). University of South Florida Morsani College of Medicine and Moffitt Cancer Center, Tampa, Florida (Al-Roubaie).

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Data. Clinical and procedural data were used in this study. The data contained within this series are not publicly accessible but are available upon reasonable request from the primary author.

Table 1. Patient Characteristics, Baseline WOMAC, and K/L Scores

PATIENT	CANCER DX	AGE	SEX	PRE-WOMAC	PRE-K/L	BMI
1	Lung	74	M	62	4	45
2	Lung	72	F	68	3	41
3	Lung	78	F	55	4	50
4	Lung	82	M	58	3	57
5	Colorectal	65	M	68	3	43
6	Colorectal	72	M	65	3	49
7	Colorectal	70	F	72	3	38
8	Melanoma	69	M	62	4	41
9	Melanoma	84	M	65	4	43
10	Sarcoma	82	M	58	3	28
11	Sarcoma	67	M	73	3	39
12	Lung	90	F	71	3	52

BMI, body mass index; Dx, diagnosis; F, female; K/L, Kellgren-Lawrence; M, male; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

GAE modulates synovial hypervascularity and inflammatory processes, key contributors to nociceptive pain.⁵ The ability to precisely target the affected vascular structures minimizes systemic effects while providing durable, localized pain relief, which is especially advantageous in frail patients. In the context of palliative oncology, these improvements can contribute not only to the patient's physical comfort but also to their psychological and emotional well-being.

In this study, we present a retrospective analysis of 12 patients with advanced cancer initially evaluated by orthopedic specialists, deemed unsuitable candidates for TKA due to oncologic diagnosis, and subsequently managed with conservative measures. Owing to their refractory symptoms, these patients were referred to interventional radiology for GAE.

Methods

Study Design and Patient Population

This study was conducted across 2 institutions from January 2023 to February 2025. The study cohort comprised 12

patients with an underlying malignancy, including 9 patients actively undergoing cancer treatment and 3 patients under imaging surveillance. Patient demographics, clinical characteristics, and treatment histories were extracted from electronic medical records. Those who were not surgical candidates for reasons other than treatment for active underlying malignancy or those who underwent GAE for other indications were excluded. Per the research protocol, institutional review board approval was not required.

Procedure

Unilateral GAE was performed successfully on all patients in an outpatient setting under intravenous sedation. Using a contralateral common femoral artery approach and standard angiographic techniques, the geniculate artery was catheterized, and embolization was performed with microspheres ranging from 100 to 300 μ in diameter. Postembolization angiography confirmed successful synovial hyperemia resolution and distal branch vessel pruning in all cases.

Data Collection and Analysis

Data collected included patient age, sex, cancer type and stage, procedural details, immediate outcomes, and 3- and 6-month clinical follow-up. Baseline, 3-month, and 6-month Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Kellgren-Lawrence (K/L) scores were also collected and analyzed. Descriptive statistics were used to summarize the data. Given the small sample size, statistical analyses were primarily descriptive, focusing on median values and ranges. Analysis of variance, paired *t*-tests, and Pearson *R* correlation were used to analyze variables from follow-up clinical data.

Results

Patient Characteristics

The mean age of the included cohort was 75.8 years (range: 65-90 years, SD 7.9, 75% male). 45% ($n = 5$) had a diagnosis of primary lung malignancy. The mean preprocedure WOMAC and K/L scores were 64.8 (SD 6.8) and 3.3 (SD 0.5), respectively (Table 1). 75% of patients ($n = 9$) had stage 4 disease at presentation for GAE.

Procedural Outcomes

Technical success was achieved in all embolization procedures and was defined by post-embolization angiography demonstrating vascular pruning and resolution of prior hyperemia without immediate complications (Figure 1). All procedures were completed on a same-day outpatient basis.

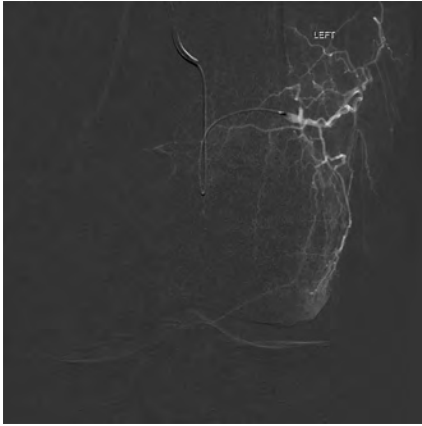
Safety and Complications

No immediate postprocedural complications were observed, nor were any observed during the mean follow-up period of 6 months.

Follow-Up

At 3-month follow-up, the mean WOMAC score was 42.7 (SD 6.5, $P <$

Figure 1. Superselected negative digital subtraction angiography of the left superior lateral geniculate artery demonstrating synovial hyperemia in the patient's reported area of concern.



.001), with a mean difference of -22.1 from preprocedural baseline. At 6-month follow-up, the mean WOMAC score was 42.6 (SD 5.9 , $P < .001$), with a mean difference of -22.2 from baseline (Table 2).

There was no change between pre- and postprocedural K/L score for any patients at 3- or 6-month follow-up. Additionally, no significant differences between WOMAC or K/L scores were observed when comparing 3- and 6-month follow-up data (Tables 3, 4; Table 5). There was no correlation between preprocedure body mass index and 3- or 6-month follow-up WOMAC scores in our cohort (Table 6).

Discussion

Although TKA remains the therapy of choice for osteoarthritic knee pain, numerous prospective studies have established GAE as a safe, effective, and minimally invasive alternative.⁵⁻⁷ To our knowledge, however, GAE has not been studied in patients with OA knee pain and concurrent advanced malignancy who are not candidates for surgical management. Thus, this population represents a uniquely vulnerable cohort warranting special consideration beyond other nonoperative TKA candidates.

Table 2. Follow-Up WOMAC and K/L Scores at 3 and 9 Months Postprocedure

PATIENT	3-MONTH WOMAC	3-MONTH K/L	6-MONTH WOMAC	6-MONTH K/L
1	38	4	40	4
2	42	3	42	3
3	44	4	38	4
4	34	3	38	3
5	35	3	35	3
6	47	3	45	3
7	50	3	50	3
8	35	4	38	4
9	52	4	50	4
10	38	3	42	3
11	42	3	42	3
12	55	3	51	3

All K/L grades remained unchanged (3 or 4) across time points, indicating no radiographic progression or improvement at 3 or 6 months.

K/L, Kellgren-Lawrence; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Unlike patients excluded from arthroplasty based solely on anesthetic risk, advanced age, or cardiopulmonary comorbidities, oncology patients face a distinctly complex pain syndrome, in which malignancy-related inflammation synergizes with degenerative joint disease, while chemotherapy and radiation undermine musculoskeletal integrity through accelerated bone demineralization and iatrogenic cartilage degradation.¹ A cycle then ensues in which cancer treatment exacerbates joint pathology while OA-related pain limits mobility and functional status. This has the potential to compromise oncologic outcomes during a critical treatment window.

Our findings support the incorporation of GAE into pain management algorithms for advanced OA in oncology patients, who face multiple challenges such as increased opioid tolerances, failure of steroid injections, and nonoperative status secondary to cancer treatment. For these patients, GAE offers a viable alternative intervention that directly addresses the vascular component without systemic toxicity, surgical morbidity, or interference with ongoing cancer

therapy. These advantages are particularly meaningful when every treatment decision carries heightened stakes and functional preservation impacts quality of life.

Integrating GAE requires careful consideration of patient-specific goals and alignment with the overall palliative approach. Differences in patient priorities, for example, achieving long-term survival versus maintaining quality of life, can impact treatment decisions that fulfill each goal.⁸ Discussing the potential outcomes of GAE with patients and their families is essential to shared decision-making and ensures that patient values are central to all therapeutic choices.⁹

Optimal patient outcomes require the collaboration of oncologists, interventional radiologists, pain specialists, orthopedic surgeons, and palliative care physicians. In so doing, GAE has the potential to relieve overwhelming OA-related pain, allowing patients to continue daily living activity with improved functionality.⁵

Our findings contribute to this growing body of evidence, demonstrating that GAE can be a safe and effective alternative for

Table 3. Descriptive Statistics of Patient Age, WOMAC, and K/L Scores

VARIABLE	N	MEAN	MEDIAN	SD	MIN	MAX	RANGE
Age	12	75.8	73.5	7.9	65	90	25
Pre-WOMAC	12	64.8	65	6.8	55	73	18
Pre-K/L	12	3.33	3	0.47	3	4	1
3-month WOMAC	12	42.7	42	6.5	34	55	21
3-month K/L	12	3.33	3	0.47	3	4	1
6-month WOMAC	12	42.6	42	5.9	35	51	16
6-month K/L	12	3.33	3	0.47	3	4	1

Age ranges from 65 to 90 years (mean 75.8).
 Pre-WOMAC (mean ~64.8) drops by ~22 points at both 3 and 6 months (means ~42.7 and ~42.6).
 K/L remains stable (3.3±0.47) across all time points.
 K/L, Kellgren-Lawrence; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 4. Mean Differences and ANOVA for WOMAC and K/L Scores

TIME POINT	WOMAC (MEAN ± SD)	MEAN DIFFERENCE FROM BASELINE	P VALUE VS BASELINE	K/L SCORE CHANGE
Pre (baseline)	64.8±6.8	–	–	–
3 Months	42.7±6.5	–22.1	<.001	No change
6 Months	42.6±5.9	–22.2	<.001	No change

WOMAC scores improve by ~22 points from pre to both 3 months and 6 months ($P < .001$).
 No further change between 3 and 6 months.
 K/L scores do not show any change at follow-up.
 ANOVA, analysis of variance; K/L, Kellgren-Lawrence; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

patients unable to undergo surgery due to malignancy-related comorbidities.

The limitations of our study include its small sample size and retrospective design. Further large-scale, randomized controlled trials are warranted to validate these findings and establish standardized protocols for patient selection and procedural techniques.

Conclusion

GAE represents a promising therapeutic option for knee OA pain in patients with active malignancy but who are not candidates for surgery. Its minimally invasive nature, coupled with a favorable safety profile and medium-term durability, positions GAE as a valuable

addition to pain management strategies in this patient population.

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Table 5. Comparison of Pre → 6-Month WOMAC Improvement by Baseline K/L Grade

GROUP	N	MEAN Δ (6 MONTHS – PRE)	SD(Δ)
K/L = 3	8	–23.5	5.95
K/L = 4	4	–19.5	4.2

Both K/L=3 and K/L=4 groups show a substantial negative Δ (ie, improvement of ~20+ points).
 The K/L=3 group's mean improvement is about ~23.5 points, and the K/L=4 group's is about ~19.5 points.
 Although the K/L=3 group's average improvement is numerically a bit larger, the difference is not statistically significant ($P = .21$), using Welch 2-tailed t-test, within this sample of 12 patients.
 K/L, Kellgren-Lawrence; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 6. BMI and WOMAC Correlations

COMPARISON	PEARSON R	P VALUE
BMI vs pre-WOMAC	–0.016	.96
BMI vs 3-month WOMAC	0.116	.72
BMI vs 6-month WOMAC	–0.06	.85

BMI does not appear to influence WOMAC scores at baseline or follow-up in this cohort (all $P > .05$).
 BMI, body mass index; K/L, Kellgren-Lawrence; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Impact of Hematuria Risk-Stratification Guidelines on CT Urography Detection of Upper Urinary Tract Malignancy

Ian Rumball, MD; Andrea A. Arenz, MS; Barbara A. Bennie, PhD; Jody Riherd, MD

Abstract

Objectives and Hypothesis: CT urography (CTU) is a preferred diagnostic modality in hematuria evaluation and has the highest sensitivity and specificity for upper urinary tract malignancy, including renal cell carcinoma and upper tract urothelial carcinoma. Recent guidelines offer differing approaches to risk stratification of patients with hematuria, which may affect malignancy detection and CTU use. We hypothesize that among CTUs obtained for hematuria, there will be increased diagnostic yield for upper tract malignancy for imaging obtained in accordance with recent risk-stratification guidelines.

Materials and Methods: This retrospective observational study assessed patients who underwent primary CTU for hematuria at a rural health system between January 1, 2021, and July 31, 2023. Cases were divided into microscopic and gross hematuria, and risk-stratified according to the 2020 American Urologic Association (AUA), 2023 Dutch Urological Association (DUA), and 2025 AUA guidelines. CTU, cystoscopy, and pathology reports were reviewed. Prevalence and diagnostic yield between subgroups were compared with appropriate statistical analyses.

Results: Among 969 patients (mean age 65 years), CTU detected pathologically confirmed upper tract malignancy in 28 (2.9%). Diagnostic yield was not significantly higher among CTUs performed in concordance with the 2020 AUA (3.2% vs 0%; $P = .4$), 2023 DUA (3.4% vs 2.2%; $P = .4$), and 2025 AUA (3.4% vs 0%; $P = .1$) guidelines. Of the 274 patients for whom CTU was not recommended by the DUA guidelines, 6 had pathologically confirmed upper tract malignancy, contrasted with none for the AUA 2020 and 2025 guidelines.

Conclusions: Application of risk-stratification guidelines did not significantly improve diagnostic yield of CTU detection for upper tract malignancy among patients presenting with hematuria. Despite this, risk-stratification approaches are likely warranted given poor yield in low-risk populations. Guidelines differed in the rate of recommended CTU use and the number of cases of potentially nonimaged upper tract malignancies.

Keywords: hematuria, urography, upper, tract, yield

Affiliations: Department of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin (Rumball). Department of Research Navigation, Gundersen Medical Foundation, La Crosse, Wisconsin (Arenz, Bennie). Department of Radiology, Emplify Health by Gundersen, La Crosse, Wisconsin (Riherd).

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Data availability. Data are available from the co-author, Andrea Arenz, who can be contacted at andrea.arenz@emplifyhealth.org or ORCID identifier 0009-0006-4223-4843. Access to the data is granted upon reasonable request and subject to approval to ensure compliance with ethical guidelines and participant confidentiality. Reuse of the data is permitted for research purposes only, under conditions that protect participant privacy and adhere to any applicable data use agreements. In addition to the de-identified data, supplementary materials such as study protocols and detailed statistical analysis plans are also available upon request.

Prior publication/Presentation: Presented at RSNA 2024. Rumball I, Arenz A, Bennie B, Riherd J. CT Urography for Hematuria: Impacts of Risk-Stratification. Poster presented at Radiological Society of North America Annual Meeting, December 2024, Chicago, IL.

Introduction

Hematuria is a common manifestation of a wide spectrum of processes affecting the kidneys, urinary tract, and reproductive organs, accounting for up to one-fifth of urologic assessments.¹ The condition may be characterized as macroscopically visible hematuria, also known as gross hematuria (GH) or microscopic hematuria (MH), defined as ≥ 3 red blood cells per high-power field. While it can be caused by a range of benign conditions, hematuria may signal urologic malignancy in up to 5% of patients with MH and 19% with GH.² CT urography (CTU) is often used to assess hematuria with its capability to characterize upper urinary tract malignancy, as well as urolithiasis, and is frequently performed alongside cystoscopy for evaluation of the lower urinary tract.^{3,4} Relative to other diagnostic modalities such as renal ultrasonography, CTU is the most sensitive for detection of renal cell carcinoma (RCC) and upper tract urothelial carcinoma (UTUC).⁵

Given the broad array of pathologies causing hematuria, societal guidelines have evolved to balance detection of aggressive or intervenable conditions with the harms of diagnostic evaluation and imaging. While American Urologic Association (AUA) guidelines from 2012 recommended that all individuals with GH and those aged ≥ 35 years with MH receive CTU and cystoscopy evaluation to minimize missed cases of genitourinary malignancy, other contemporaneous diagnostic algorithms promoted further risk stratification for patients with MH, as well as broader use of renal ultrasonography.⁶⁻¹⁰

More recent urologic society guidelines have continued this trend. The AUA's 2020 guidelines and 2025 amended guidelines suggest comprehensive evaluation with cystoscopy and upper urinary tract imaging only in cases of GH and high-risk MH, per their published criteria, which align with radiologic

society recommendations.^{4,11,12} Notably, the 2023 Dutch Urological Association (DUA) guidelines reserve recommendation of CTU for cases of GH in patients aged ≥ 50 years.¹³

Optimizing CTU use in hematuria evaluation may affect yield, cost, and adverse effects. In low-risk cohorts, existing literature has shown poor diagnostic yield of CTU, increased costs with broader CTU utilization, and limited benefit over alternative modalities while causing increased rates of secondary malignancy, false positives, and procedural complications.^{5,14-18} Conversely, increased selectivity of CTU use has demonstrated improvements in diagnostic yield and cost savings.^{14,19}

Given recent changes to diagnostic guidelines, and in the pursuit of high-value care, we sought to investigate the impact of recent societal recommendations on CTU's performance in detecting upper urinary tract malignancy. Existing literature has demonstrated higher diagnostic yield in stratification by risk factors such as age or smoking history. We hypothesize that among recent hematuria diagnostic guidelines, including the 2020 AUA, the 2023 DUA, and 2025 AUA guidelines, increased selectivity in CTU utilization will correspond with improved diagnostic yield for upper tract malignancy with minimal impact on the rate of nonimaged or missed malignancies.

Materials and Methods

Study Design and Patients

The Institutional Review Board approved the study and granted a waiver of informed consent. The study was conducted in compliance with the Health Insurance Portability and Accountability Act. We retrospectively reviewed electronic health records (EHRs) of all adult patients (≥ 18 years) who underwent CTU for hematuria in our health system from January 1, 2021,

through July 31, 2023. A total of 1136 consecutive CTUs for hematuria were performed during this period. For patients with multiple CTUs in the study interval, only the primary study was assessed. Patients whose EHR contained insufficient data for risk stratification, whose CTU was performed for an indication other than hematuria, and who had a prior known urologic malignancy were excluded from the study.

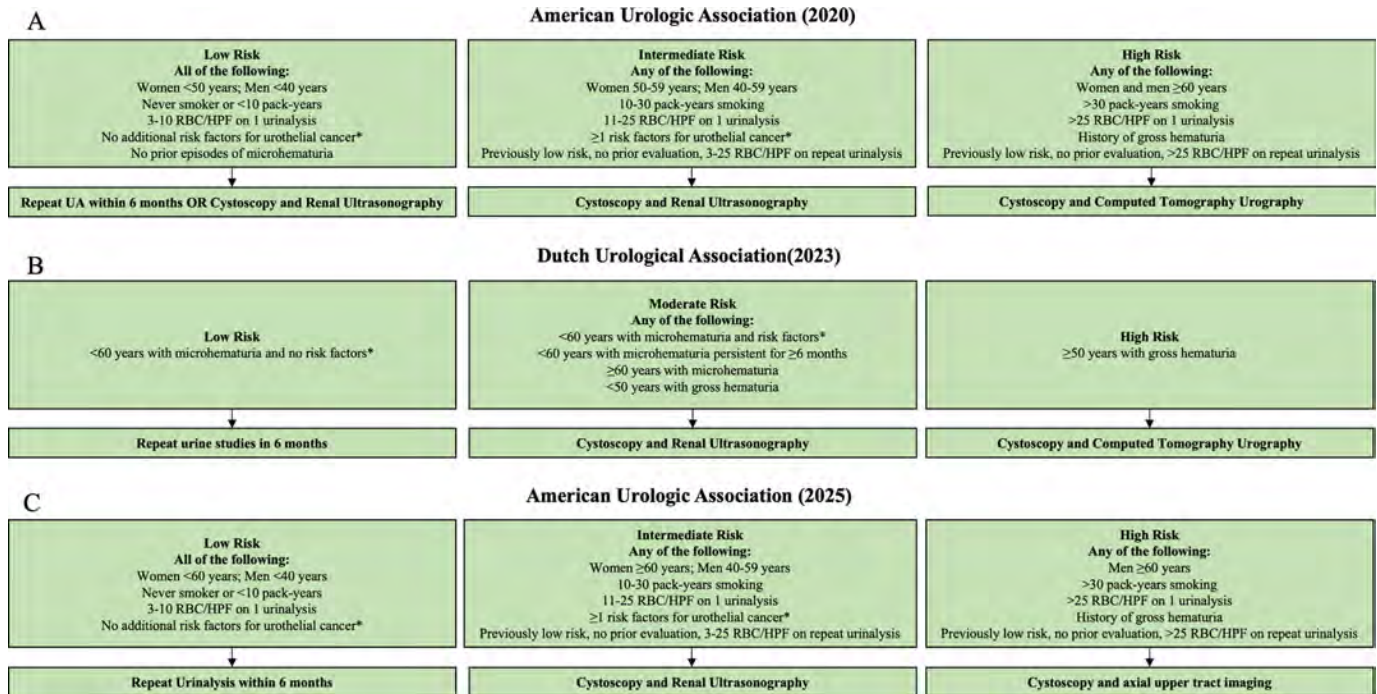
Pre-CTU Risk Assessment

Patient records were reviewed for demographic, clinical, and laboratory factors. Hematuria was classified as MH or GH based on listed indication, clinical documentation, and urine microscopy results. Patients were stratified into risk categories according to the 2020 AUA, 2023 DUA, 2025 AUA guidelines using age, smoking history, prior hematuria, urinalysis/urine microscopy features, and other urologic malignancy risk factors (Figure 1). For determining the presence of persistent MH for risk stratification, the initial urine study with MH obtained within the year preceding CTU was considered the primary sample, while subsequent urine studies obtained prior to CTU were considered repeat samples. Guideline familiarity or adherence by ordering providers was not accounted for, and guideline criteria were solely applied retrospectively.

CTU Protocol

Imaging was performed without oral contrast or bowel preparation using 128-multidetector CT scanner Siemens Somatom X.cite or 144-multidetector CT scanner (Siemens Naeotom Alpha). Patients were instructed to drink 1000 mL of water before arriving for their examination. A 3-scan CT protocol was used that consisted of: an unenhanced scan of the abdomen and pelvis; a nephrographic phase scan of the kidneys 90 seconds after intravenous administration of 150 mL nonionic

Figure 1. Summary of the initial diagnostic steps recommended by the (A) 2020 American Urologic Association (AUA), (B) 2023 Dutch Association of Urology, and (C) 2025 AUA guidelines for the evaluation of hematuria.



*Risk factors: smoking, irritative lower urinary tract symptoms, previous irradiation, previous cyclophosphamide or ifosfamide treatment, family history of urothelial carcinoma or Lynch syndrome, occupational exposure to benzene or aromatic amines, and chronic bladder catheterization.

iopamidol 300 mgI/mL (Isovue, Bracco Diagnostics) at 3 mL/s with a 30 mL normal saline flush; and an excretory phase scan of the abdomen and pelvis 10 minutes after contrast medium injection.

The parameters for scanning were 120 kVp, 0.6 mm collimation, 0.8 pitch, and tube current based on patient size. Images were acquired on inspiration, and patients were scanned in the supine position. If the ureters were incompletely visualized, then a prone scan was performed at the discretion of a radiologist. Axial, coronal, and sagittal reconstructions were obtained at 3 mm slice thickness. Excretory phase scans were also reconstructed in a maximum intensity projection of 3 mm slice thickness at 3 mm intervals. A 2-scan protocol was used in patients younger than 60 years. This protocol consists of an unenhanced scan of the abdomen and pelvis, followed by intravenous administration of 75 mL Isovue. After an 8-minute delay, a second dose of 75 mL Isovue was given. CT of the abdomen and pelvis was then performed with a 90-second scan delay. All images were

forwarded to the Picture Archiving and Communication System and subsequently interpreted by certified radiologists.

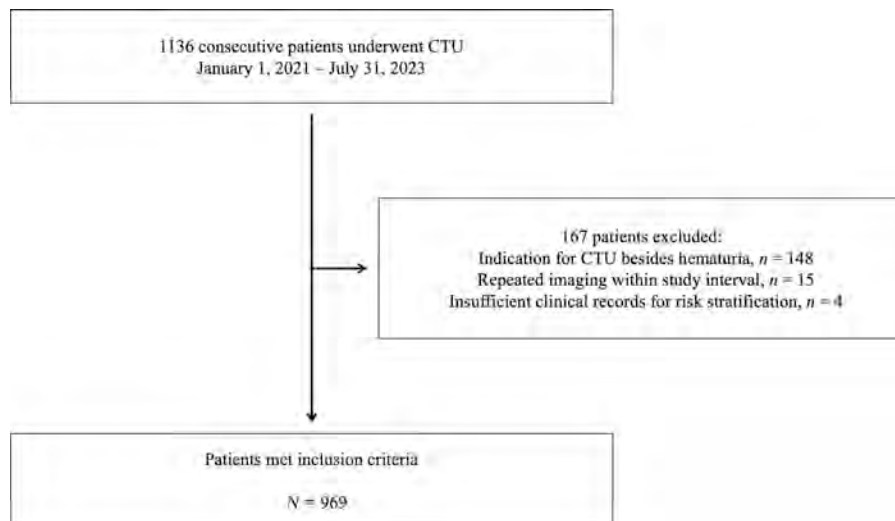
Report Review

CTU reports were assessed for mention of potential etiologies of hematuria using a methodology similar to that described by Fenwick et al.¹⁵ CTU results were assigned to 1 of 5 groups: (1) explicit mention of likely genitourinary malignancy, (2) other findings suggestive of malignancy as per Fenwick et al, (3) urolithiasis, (4) benign prostatic hyperplasia, and (5) all other benign genitourinary abnormalities potentially causing hematuria. Patients with more than one hematuria etiology were assigned to the numerically lowest category, as it likely represented the most relevant finding. Patients with findings suggestive of malignancy were also grouped by location—that is, whether findings were in the upper or lower urinary tract. We reviewed the health records of the study cohort for renal ultrasonography and cystoscopy performed within 1 year of the CTU; if present, these

reports were reviewed. Cystoscopy reports were reviewed for presence of (1) explicit mention of likely malignancy, (2) urolithiasis, (3) prostatic hyperplasia, and (4) other benign genitourinary abnormalities causing hematuria. For all patients, we reviewed pathology reports published within 1 year after CTU of the genitourinary system. Pathology results were classified as malignant or benign.

Statistical Analysis

The prevalence of CTU findings was calculated as the number of findings divided by the size of the study cohort or subgroup. Diagnostic yield and false referral rates were calculated according to the methodology described by Park et al.²⁰ Categorical variables were summarized using frequencies and percentages, while numeric variables were summarized using mean and standard deviation. Associations of patient diagnosis (GH or MH), ordering provider (urology or nonurology), and risk classification (AUA and DUA risk classifications) with CTU results were

Figure 2. Patient selection flow chart. CTU, CT urography.**Table 1.** Demographic Characteristics of Patients Who Had CT Urography for Hematuria (N = 969)

CHARACTERISTIC	VALUE ^A
Sex	
Women	369 (38.1)
Men	600 (61.9)
Race	
American Indian and Alaska Native	5 (0.5)
Asian	8 (0.8)
Black	6 (0.6)
Refused	2 (0.2)
White	948 (97.8)
Ethnicity	
Hispanic	12 (1.2)
Non-Hispanic/Non-Latino	952 (98.2)
Refused	5 (0.5)
Body mass index ^b : mean ± SD; median [IQR]	30±8; 29 [26–34]
Age, years: mean (SD); median [IQR]	65 (15); 67 [57–76]
^A Unless otherwise indicated, data are number of patients (%).	
^B Body mass index was calculated as patient weight in kilograms divided by patient height in meters squared.	
IQR, interquartile range.	

assessed using Pearson χ^2 or Fisher exact tests, as appropriate. A Bonferroni-adjusted significance level of $0.05/16 = 0.003$ was used for all statistical testing to control for the error of multiple comparisons. All analyses were completed using R statistical software.²¹

Results

A total of 969 patients met inclusion criteria (Figure 2), 600 (62%) of whom were men and 948 (98%) of whom were White. The mean age was 65±15 years (Table 1). GH was present in 778 (80%)

Table 2. Hematuria Types and Urologic Society Risk Groups Among Patients Who Had CT Urography for Hematuria (N = 969)

CHARACTERISTIC	NO. OF PATIENTS (%)
Hematuria diagnosis	
MH	191 (19.7)
GH	778 (80.3)
2020 AUA risk class (MH)	
Low	11 (1.1)
Intermediate	41 (4.2)
High	139 (14.3)
2025 AUA risk class (MH)	
Low	12 (1.2)
Moderate	84 (8.7)
High	95 (9.8)
DUA risk class	
Low	16 (1.7)
Moderate	266 (27.5)
High	687 (70.9)
AUA, American Urologic Association; DUA, Dutch Urological Association; GH, gross hematuria; MH, microscopic hematuria.	

of patients (Table 2). Per AUA 2020 and 2025 guidelines, MH was classified as high risk in 139 (14%) patients and 95 (9.8%) patients, respectively. Among CTUs obtained, 95% (917/969) would have been considered appropriate under the 2020 AUA guidelines compared with 90% (873/969) for the 2025 AUA guidelines and 71% (687/969) for the DUA guidelines. Within 1 year of CTU, cystoscopy was performed in 654 (68%) patients, and renal ultrasonography was obtained for 58 (6.0%).

CTU showed findings suggestive of upper tract malignancy in 73 (7.5%) patients (Table 3). Among patients with these findings, 33 (3.4%) had pathologic sampling, which confirmed malignancy in 28 (2.9%) patients: 23 (2.4%) cases of RCC and 5 (0.5%) cases of UTUC (Table 4). The diagnostic yield of CTU for upper tract malignancy was 3.0% (Figure 3). Comparing cases in which

Table 3. Prevalence of Hematuria Etiologies Stratified by Hematuria Type and Risk Groups

CTU RESULT	OVERALL	HEMATURIA TYPE		AUA RISK GROUP (MH)			DUA RISK GROUP					
				2020			2025					
		GH	MH	LOW	INTERMEDIATE	HIGH	LOW	INTERMEDIATE	HIGH	LOW	MODERATE	HIGH
		N = 969	N = 778	N = 191	N = 11	N = 41	N = 139	N = 12	N = 84	N = 95	N = 16	N = 266
Probable malignancy	102 (10.5)	96 (12.3)	6 (3.1)	0 (0)	0 (0)	6 (4.3)	0 (0)	0 (0)	6 (6.3)	1 (6.3)	13 (4.9)	88 (12.8)
Other findings suggestive of malignancy	90 (9.3)	74 (9.5)	16 (8.4)	0 (0)	2 (4.9)	14 (10.1)	0 (0)	4 (4.8)	12 (13.0)	1 (6.3)	17 (6.4)	72 (10.5)
Urolithiasis	269 (27.8)	229 (29.4)	40 (20.9)	1 (9.1)	8 (19.5)	31 (22.3)	1 (8.3)	14 (17.0)	25 (26.0)	3 (18.8)	75 (28.2)	191 (27.8)
BPH	119 (12.3)	106 (13.6)	13 (6.8)	0 (0)	2 (4.9)	11 (7.9)	0 (0)	2 (2.4)	11 (12.0)	0 (0)	15 (5.6)	104 (15.1)
Other GU tract abnormalities	78 (8.0)	64 (8.2)	14 (7.3)	1 (9.1)	4 (9.8)	9 (6.5)	1 (8.3)	8 (9.5)	5 (5.3)	0 (0)	17 (6.4)	61 (8.9)
Normal	311 (32.1)	209 (26.9)	102 (53.4)	9 (81.8)	25 (61.0)	68 (49.0)	10 (83.0)	56 (67.0)	36 (38.0)	11 (68.8)	129 (48.5)	171 (24.9)
Suspicious for upper urinary tract malignancy	73 (7.5)	63 (8.1)	10 (5.2)	0 (0)	1 (2.4)	9 (6.5)	0 (0)	2 (2.4)	8 (8.4)	1 (6.3)	14 (5.3)	58 (8.4)

Data are presented as number of patients (%). Percentages may not total 100 due to rounding.

AUA, American Urologic Association; BPH, benign; CTU, CT urography; DUA, Dutch Urological Association; GH, gross hematuria; GU, genitourinary; MH, microscopic hematuria.

Table 4. Observed Malignancies Among Patients Who Had CT Urography for Hematuria

DIAGNOSIS	NO. OF PATIENTS (%)
Bladder cancer	
Urothelial carcinoma	73 (7.5)
Adenocarcinoma (urachal)	2 (0.2)
Small cell carcinoma	1 (0.1)
Urothelial carcinoma in situ	1 (0.1)
Upper urinary tract cancer	
Renal cell carcinoma	23 (2.4)
Upper tract urothelial carcinoma	5 (0.5)
Other	
Prostatic adenocarcinoma	5 (0.5)
Colorectal adenocarcinoma	1 (0.1)
Penile squamous cell carcinoma	1 (0.1)

CTU was or was not recommended by risk-stratification algorithms, diagnostic yield was not significantly different for the 2020 AUA (3.2% vs 0%; $P = .4$), 2023 DUA (3.4% vs 2.2%; $P = .4$), and 2025 AUA (3.4% vs 0%; $P = .1$) guidelines. Of the 282 patients for whom CTU was not

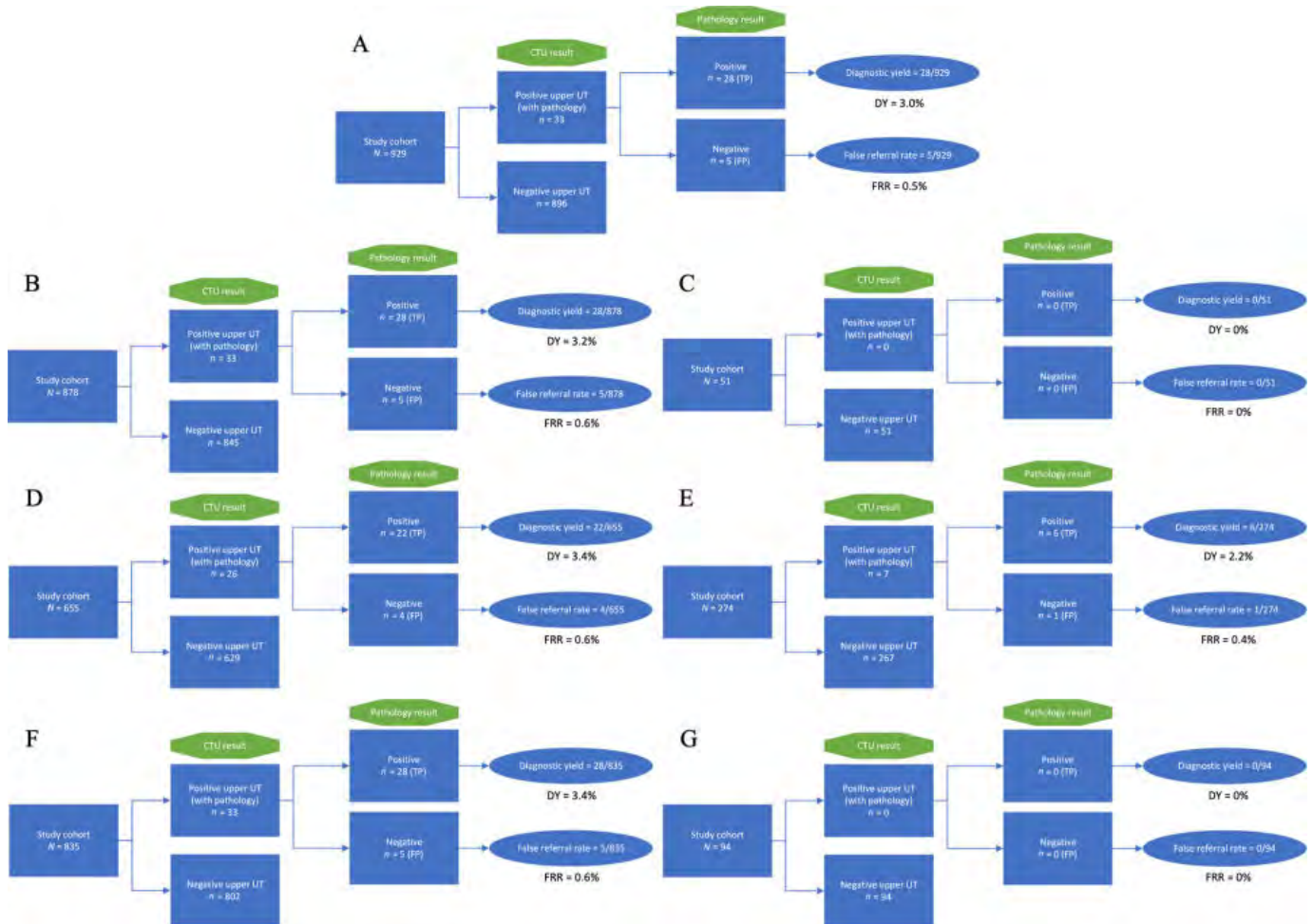
recommended by the DUA guidelines, 6 had pathologically confirmed upper tract malignancy compared with zero such cases for the 2020 and 2025 AUA guidelines.

No hematuria etiology was detected for 32% ($n = 311$) of patients. The rate of normal CTU findings was 53% ($n = 102$)

in cases of MH and 27% ($n = 209$) for GH. Increasing AUA and DUA risk categories were associated with increasing detection of a hematuria etiology (Figure 4). 192 (20%) studies were considered suggestive of any malignancy. Of the 134 patients for whom pathology was available, 112 had confirmed malignancies, with the most prevalent being urothelial carcinoma of the bladder (7.5%, $n = 73$). Benign hematuria etiologies, namely urolithiasis, benign prostatic hyperplasia, and all other genitourinary abnormalities, were found in 307 (32%), 190 (20%), and 258 (26.6%) cases, respectively.

Imaging performed for GH detected more abnormal findings (73%, $n = 569$ vs 47%, $n = 89$; $P < .001$) and findings suggestive of urologic malignancies (22%, $n = 170$ vs 12%, $n = 22$; $P = .001$) than CTU obtained for MH. CTUs ordered by a urology provider had a higher rate of detection for all hematuria etiologies (74%, $n = 373$ vs 61%, $n = 285$; $P < .001$), although not for malignant findings (22%, $n = 110$ vs 18%, $n = 82$; $P = .10$). Cases in which CTU was appropriate per

Figure 3. Flow diagrams demonstrating diagnostic yield and false referral rate of CT urography (CTU) for upper urinary tract malignancy for (A) all patients; those meeting (B) or not meeting (C) 2020 American Urologic Association (AUA) criteria for evaluation with CTU; meeting (D) or not meeting (E) 2023 Dutch Association of Urology (DAU) criteria; and meeting (F) or not meeting (G) 2025 AUA criteria. There were no significant differences in diagnostic yield between guideline-concordant and guideline-discordant imaging when applying the 2020 AUA, 2023 DAU, DAU, or 2025 AUA criteria. False referral rate is defined as cases with positive CTU result but benign pathology. Cases with CTU suspicious for upper tract malignancy and no pathology results ($n = 40$) are not reflected in these figures.



diagnostic criteria had increased detection of all hematuria etiologies and findings suggestive of malignancy, which was seen for the 2020 AUA (70%, $n = 640$ vs 35%, $n = 18$; $P < .001$ | 21%, $n = 190$ vs 2.8%, $n = 2$; $P < .003$), 2023 DAU (75%, $n = 516$ vs 50%, $n = 142$; $P < .001$ | 23%, $n = 160$ vs 11%, $n = 32$; $P = .001$), and 2025 AUA (72%, $n = 628$ vs 31%, $n = 30$; $P < .001$ | 22%, $n = 188$ vs 4.2%, $n = 4$; $P = .001$) guidelines.

Diagnostic yield for any urologic malignancy was increased with adherence to the DAU guidelines [14% vs 4.2%; odds ratio (OR) = 3.8, $P < .001$] and 2025 AUA guidelines (12% vs 1.1%; OR = 24.0, $P < .001$), but not with the

2020 AUA guidelines (12% vs 2.0%; OR = 6.7, $P = .04$). Applying this analysis to assess diagnostic characteristics of CTU for bladder cancer, CTU was found to have a diagnostic yield of 7.3% compared with 12% for cystoscopy.

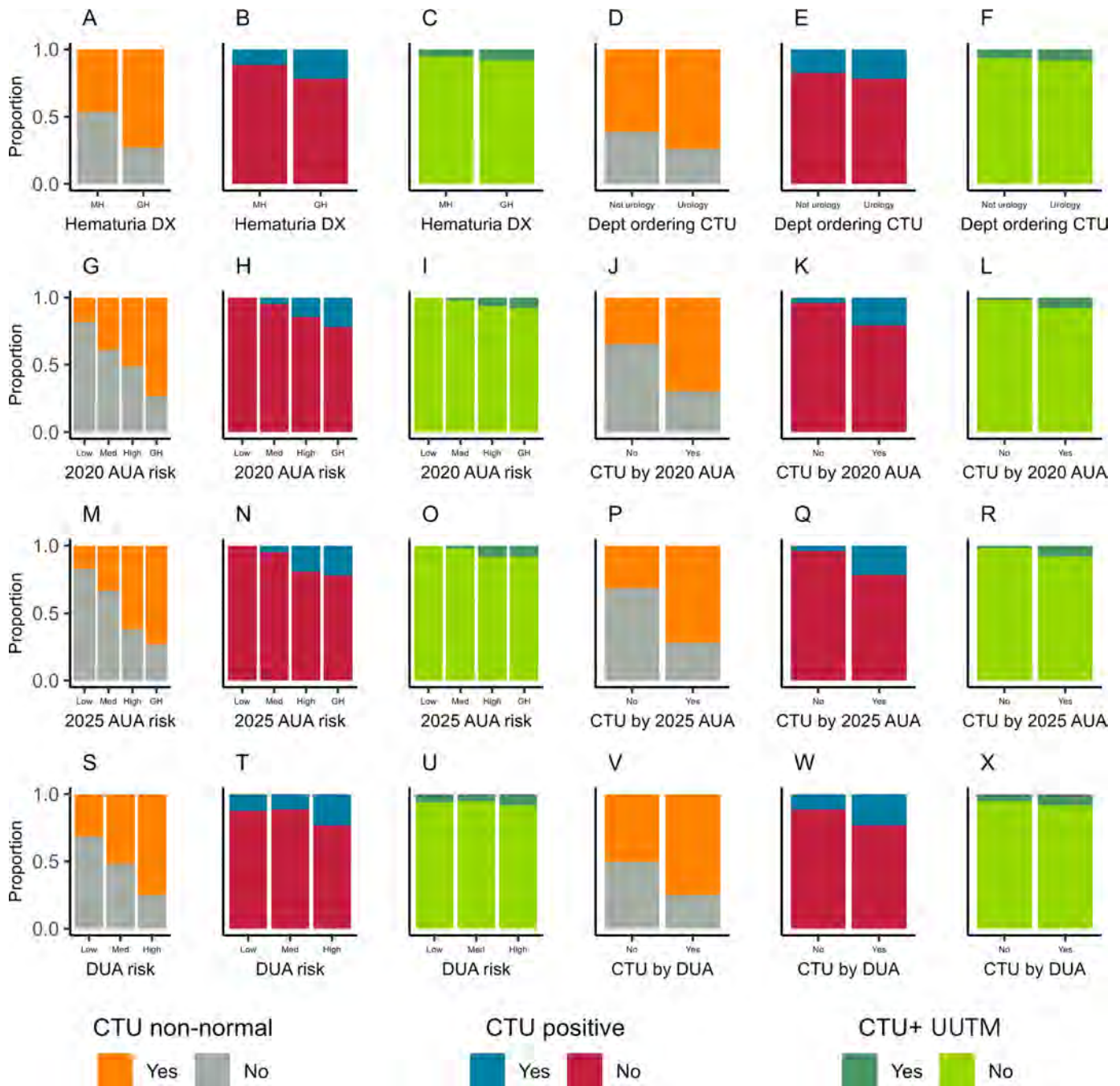
Discussion

In this retrospective analysis of 969 patients undergoing CTU for hematuria, application of recent hematuria risk-stratification guidelines did not significantly affect the diagnostic yield for upper urinary tract malignancy. While risk stratification would have

averted 52, 96, and 282 CTUs for the 2020 AUA, 2025 AUA, and DAU guidelines, respectively, 6 patients with confirmed upper tract malignancy would not have undergone cross-sectional imaging under the DAU recommendations, which reserve the procedure for GH patients over age 50 years. This is contrasted with no missed cases with either AUA guideline. The 2023 DAU and 2025 AUA recommendations both increased yield for detection of any urologic malignancy, though this includes bladder cancers likely to be found via cystoscopy.

All risk-stratification guidelines assessed offered similar diagnostic

Figure 4. Prevalence of all hematuria etiologies, findings suspicious for urologic malignancy, and findings suspicious for upper urinary tract malignancy (UUTM) on CT urography (CTU) stratified by (A-C) type of hematuria, (D-F) ordering provider, (G-I) 2020 American Urologic Association (AUA) risk category, (J-L) 2020 AUA guideline adherence, (M-O) 2023 Dutch Association of Urology (DAU) risk category, (P-R) DAU guideline adherence, (S-U) 2025 AUA risk category, and (V-X) 2025 AUA guideline adherence.



recommendations for low-, intermediate-, and high-risk patients but differed in their definition of these risk categories. While the 2020 AUA guidelines recommend cystoscopy plus CTU for the evaluation of

GH and MH patients with age ≥ 60 years, smoking history of ≥ 30 pack-years, or ≥ 25 red blood cells on urine microscopy, the 2025 amended guidelines consider age ≥ 60 years a high-risk factor only in men. This

change reflects lower rates of upper tract malignancy among women, particularly younger women.^{17,22}

The 2023 DUA guidelines recommend CTU only in GH patients ≥ 50 years

of age; this even more conservative recommendation led to 6 instances of upper tract malignancy that would not have received cross-sectional imaging in this cohort. All guidelines recommend that intermediate-risk patients undergo renal ultrasonography and cystoscopy, though renal ultrasonography was performed in only 58 patients and was not performed in the 6 patients referenced, limiting comparison with CTU in this cohort. Prior studies have shown highly variable results regarding the performance of renal ultrasonography in detecting upper tract malignancy, and future studies comparing these modalities may be useful.^{17,23-27}

Risk-stratifying hematuria patients prior to CTU may improve diagnostic performance and reduce costs and adverse effects. This study showed 95% concordance between ordered CTUs and the contemporaneous 2020 AUA guidelines, and an overall diagnostic yield of 3.0% for upper tract malignancy, higher than has been reported in the literature. For example, a yield of 0.6% was observed in a comparable Canadian cohort of 1046 patients, with similar findings reported in other studies.^{15,16,18,28} While our study did not demonstrate significantly increased diagnostic yield for CTU in upper urinary tract malignancy based on societal risk-stratification guidelines, a meta-analysis of 24,366 patients with MH found that retrospective application of simplified risk criteria (cohorts with median age ≥ 60 years, $> 50\%$ male sex, $> 50\%$ smoking history) resulted in increased diagnostic yield for CTU in UTUC from 0.1% to 0.5%.¹⁴ Regarding cost savings, an assessment comparing more selective use of CTU under the 2020 versus 2012 AUA guidelines led to a savings of \$40,000 per cancer detected in the workup of MH.¹⁸ Even for patients with GH, among lower-risk cohorts the risk of CTU-induced secondary malignancy from ionizing radiation may be up to 5 times greater than that of missing malignancy by using renal ultrasonography. This emphasizes the possible utility of pre-CTU risk stratification, CT protocols with

reduced radiation dose (eg, unenhanced CT or CTU with omission of unenhanced phase), or alternative imaging studies.¹⁷ Implementing any recommendation requires buy-in and participation of ordering providers, which has been shown to be limited in studies of prior guidelines.^{29,30}

Our study had several limitations. The retrospective and observational study design inherently fails to control for biases or failures that may be introduced in clinical documentation, image or procedure ordering or performance, and imaging or procedural documentation. Follow-up was limited to 12 months following primary CTU, potentially limiting detection of indolent malignancies. Use of renal ultrasonography was limited, as described. Our small sample of studies discordant with the AUA guidelines limited detection of differences in diagnostic yield for this guideline. Diagnostic yield assessment was limited to patients for whom pathology was available, which is a source of selection bias. Further, because CTU patients without findings suggestive of disease generally would not receive pathologic sampling, our results do not lend themselves to assessing other test characteristics and would be affected by verification bias. Finally, while the false referral rate was calculated, our study considered neither cost nor adverse effects of CTU, such as secondary malignancy, procedural or contrast-related complications, or other consequences of workup of false-positive results.

Conclusion

Applying risk-stratification guidelines did not significantly increase the CTU yield for upper urinary tract malignancy. Despite this finding, risk-stratification approaches are likely warranted given poor yield in low-risk populations. Guidelines differ in the rate of recommended CTU use and the number of cases of potentially

non-imaged upper tract malignancies. Future research should include large-cohort, prospective comparisons of the currently proposed risk-stratification criteria and their impact on the performance, cost, and harms of CTU, renal ultrasonography, and cystoscopy within their diagnostic frameworks.

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US Evaluation of Arteriovenous Fistula Complications in the Emergency Setting

Paula Elena Hernández Quiroz, MD; Verónica Espinosa Cruz, MD

Abstract

Arteriovenous fistulas (AVFs) are the preferred vascular access for hemodialysis, but they are prone to complications that frequently present in the emergency department. Timely recognition of these problems is essential to preserve access patency and avoid life-threatening events. Bedside US is uniquely suited to this setting because it is rapid, repeatable, and provides direct visualization of the access, surrounding soft tissues, and arterial and venous hemodynamics. This review offers a practical, stepwise US approach for the emergency evaluation of AVFs and for each major complication. We summarize key clinical presentations, high-yield B-mode and Doppler findings, common pitfalls, and typical management pathways. Illustrative cases, tables, and checklists highlight how integrating clinical information with standardized US techniques can help differentiate overlapping entities. By adopting a structured US protocol and recognizing these characteristic imaging patterns, emergency physicians and radiologists can improve diagnostic confidence, streamline consultation with nephrology and vascular surgery, and contribute to safer and more efficient care for patients with AVFs.

Keywords: hemodialysis, arteriovenous fistula, emergency US, Doppler US

Introduction

End-stage renal disease represents a substantial and escalating global public health challenge, consuming considerable health care resources worldwide. In 2023, the global point prevalence of kidney failure requiring replacement therapy was estimated at 4.59 million, with type 2 diabetes and hypertension together accounting for 40.6% of cases.¹ In this expanding hemodialysis population, the quality and durability of vascular access are key determinants of long-term outcomes.

The arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis owing to its lower complication rates and superior longevity compared with

arteriovenous grafts and central venous catheters.² Despite these advantages, AVFs remain susceptible to a substantial burden of dysfunction and failure. Early failure rates range from 20% to 60%,³ and, according to the United States Renal Data System, the cumulative incidence of primary unassisted patency loss 2 years after AVF creation is 48.8%, while losses of primary assisted and secondary patency are 18.6% and 2.7%, respectively.⁴ This frequency of failure, combined with the persistent requirement for maintenance interventions, generates a significant volume of acute clinical presentations to emergency departments.

Compared with CT or MR angiography, US is more widely available, cost-effective, and can be performed at the

bedside.^{5,6} In addition to its diagnostic role, US plays a critical part in preoperative planning, postoperative surveillance, and guiding interventional procedures. Duplex Doppler evaluation provides essential hemodynamic data, such as peak systolic velocity (PSV), PSV ratios across stenotic segments, and volumetric flow estimations. These parameters serve as reproducible markers of access dysfunction and help distinguish clinically significant from incidental findings. Consequently, comprehensive AVF ultrasonography is a core competency for radiologists in the emergency care pathway, and adherence to a standardized bedside protocol improves reproducibility and expedites specialty consultation.

Affiliation: Department of Radiology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), Mexico City, Mexico.

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Emergency Department Evaluation and Systematic Scanning Protocol

Proficiency in the imaging evaluation and characterization of hemodialysis access is essential for the radiologist, as accurate diagnosis directly guides clinical management, preserves the long-term functionality of this vital access, and associated morbidity.

Common emergency department presentations for suspected AVF complications include pain, swelling, erythema, a diminished or absent thrill, or bleeding at the access site.⁷

The examination should proceed in a logical sequence:

- During the initial patient encounter, a simple handshake is not only a gesture of courtesy but also a functional test. It allows for the assessment of distal hand temperature, sensation, and motor function, helping to identify signs of distal ischemia.⁸
- A systematic visual inspection of the skin and soft tissues overlying the AVF is imperative. This initial assessment serves to exclude superficial pathologies, such as cellulitis or skin ulceration, which may mimic or coexist with underlying access complications.
- Palpation and auscultation subsequently confirm a reduced or absent thrill or an abnormal bruit. The presence of warmth, tenderness, or drainage should be documented, as it may influence both management (antibiotic therapy) and the sonographic technique. Furthermore, a simple functional test like the Arm Elevation Test can confirm adequate venous outflow in AVFs if the access collapses upon elevation.⁹
- Adapt positioning to patient comfort and clinical status. For patients with kyphosis, orthopnea, or severe respiratory compromise, a semi-recumbent position is preferable.¹⁰ The presence of traumatic scars or neurological deficits may necessitate

examining the limb in pronation rather than the standard supination.

- Document the access side/type, date of creation, history of cannulation difficulties, and prior interventions.

A concise, stepwise summary of this bedside US approach for emergency evaluation of AVFs, highlighting key scanning phases and the main reportable items, is presented in Table 1. A representative Doppler sampling strategy and volume-flow measurement technique for a brachiocephalic AVF is illustrated in Figure 1.

Complications of Arteriovenous Fistula

The management of acute complications associated with AVFs in the emergency department relies heavily on rapid diagnostic imaging to inform immediate therapeutic decisions. US is considered the first-line imaging technique due to its noninvasive, repeatable, and cost-effective nature, serving as a critical diagnostic adjunct to the physical examination.¹⁴ Table 2 provides a rapid reference of each major AVF complication with its typical emergency department presentation, key diagnostic US findings, and reported incidence. Complications are commonly classified based on their time of occurrence and functional outcome: early events, or primary failure, refer to permanent access failure before it achieves suitability for hemodialysis (typically within 3 months) due to causes such as insufficient inflow or inappropriate remodeling, while late events, leading to secondary failure, occur in an access that previously met the criteria for successful dialysis.³

Thrombosis

Thrombosis is the most common acute event leading to access failure or loss of function. In approximately 75% of cases, it is associated with venous outflow

stenosis, with thrombophilia identified in approximately 9% of patients experiencing recurrent thrombosis episodes.³

Venous neointimal hyperplasia is the principal pathophysiological mechanism. Other factors include excessive access compression, persistent hypotension, hypovolemia, and coagulation anomalies related to chronic kidney disease. Clinically, patients present with acute pain, swelling, and loss of bruit or thrill. Prompt recognition is essential as salvage rates decrease rapidly with time.

On grayscale US, acute thrombi appear as hypoechoic or anechoic intraluminal material, while chronic thrombi become more echogenic. Doppler demonstrates absent flow within the affected segment, and compression confirms noncompressibility of the vein (Figure 2).

The thrombotic process typically involves the anastomotic region and the draining vein; arterial involvement is uncommon and generally suggests underlying atherosclerotic, iatrogenic, or inflammatory pathology. Surgical thrombectomy historically represented the standard management for thrombosed arteriovenous grafts and fistulas. In contemporary practice, percutaneous endovascular approaches have been increasingly employed.¹⁹

Stenosis

Stenosis is the most frequent underlying pathology that affects access. Pathogenesis involves a maladaptive vascular remodeling process, primarily driven by neointimal hyperplasia in response to abrupt changes in hemodynamic forces and wall shear stress. This process progressively manifests as luminal narrowing.²⁰

Patients may present with clinical indicators suggestive of access dysfunction, including difficult cannulation, prolonged bleeding after needle removal, or ipsilateral limb edema. Physical examination, however, demonstrates significant limitations in reliably identifying underlying stenosis.

Table 1. Emergency Arteriovenous Fistula US Quick Protocol: Stepwise Approach and Key Reportable Items

EXAM PHASE	KEY ACTIONS	REPORTABLE ITEMS
Pre-scan	- Use a high-frequency (7-12 MHz) linear array transducer for superficial segments of the fistula - Use a small-footprint curvilinear (5-8 MHz) or phased-array (2-5 MHz) probe to assess deep/central veins (eg, subclavian, brachiocephalic, superior vena cava) via a supraclavicular or sternal-notch window¹¹ - Optimize color settings (PRF, gain, box size) - Maintain a Doppler angle $\leq 60^\circ$	Access side/type, time of presentation, and brief chief complaint (pain/swelling/bleeding/loss of thrill)
(1) Venous survey	- Scan superficial and deep veins with and without compression; confirm respiratory phasicity - Obtain a comparative spectral trace from the contralateral subclavian	- Venous compressibility and phasicity - Presence/absence of intraluminal echogenic material; when present, document noncompressible echogenic material and its cephalic extent - Save one B-mode, one color, and one spectral image Goal: Starting with the venous survey is a high-yield strategy that addresses one of the most common complications (thrombosis or vein stenosis).
(2) Arterial survey	- Evaluate subclavian $\rightarrow$ brachial $\rightarrow$ radial/ulnar - Use color mapping to place spectral samples away from turbulence	- Near the anastomosis: low-resistance, high-velocity monophasic inflow - Distal (radial/ulnar): triphasic high resistance Goal: Rapidly confirm the expected pattern. Any loss of monophasic inflow proximally, absence of triphasic high-resistance distal, parvus-tardus or marked velocity asymmetry should raise suspicion for a significant lesion.
(3) Arteriovenous fistula functional assessment	- Perform grayscale, color, and pulsed-wave Doppler of the inflow artery, anastomosis, and outflow vein, with explicit annotation of each sampling site¹¹ - Keep Doppler angle $\leq 60^\circ$, center the gate, and avoid turbulent jets - Archive one labeled B-mode, one color, and one spectral image for each site (inflow, anastomosis, outflow)	- Peak systolic velocity at predefined sites (pre-, intra-, and post-anastomotic) and peak systolic velocity ratio across suspected lesions¹² - Flow directionality in distal arteries and in the outflow vein - Venous volume flow measured in a straight venous segment proximal to the anastomosis; average 3-5 samples with angle $\leq 60^\circ$; typical adequacy for mature arteriovenous fistulas: ~ 600-1200 mL/min¹³ Goal: Detect clinically significant arteriovenous fistula dysfunction (eg, reduced venous volume flow or abnormal inflow/outflow waveforms/directionality).

The sensitivity of physical examination for detecting arteriovenous graft stenosis is notably low, ranging from 36% to 57%.²¹

Digital subtraction angiography definitively diagnoses critical stenosis, defined as a luminal diameter reduction exceeding 50% relative to an adjacent normal vascular segment.³ Correspondingly, identifying a hemodynamically significant stenosis with sonography requires a multimodal approach encompassing morphological, hemodynamic, and functional parameters (Figure 3). This comprehensive assessment includes precise vessel lumen measurements, quantitative analysis of PSV, PSV ratio, and volumetric flow

quantification. The specific thresholds used to define hemodynamically significant stenosis are summarized in Table 3, and the most common sites of stenosis and their clinical implications are presented in Table 4. Treatment typically consists of percutaneous transluminal angioplasty to restore flow, although highly resistive lesions, such as juxta-anastomotic stenosis, may require surgical revision.

Vascular Steal Syndrome

Ischemic steal syndrome, also known as vascular steal syndrome, is defined as hand or finger pain caused by hypoperfusion (reduced blood flow) distal

to the AVF access. The incidence of symptomatic steal syndrome ranges from 0.25% to 20%, with incidence strongly correlated to anastomosis location. Forearm accesses demonstrate lower rates (0.25-1.8%) than brachial accesses (4-9%), where higher flow volumes predispose to ischemic complications and approximately 4% of patients require surgical intervention for steal syndrome following access creation.²² Key risk factors include diabetes, female sex, upper arm fistulas, peripheral arterial disease, and advanced age.

Patients may develop ischemic symptoms such as rest pain, paresthesia, digital ulcers, or even necrosis. On

Figure 1. Representative spectral Doppler assessment of a brachiocephalic arteriovenous fistula. (A) Spectral Doppler of key segments. The proximal brachial artery (inflow) shows a low-resistance waveform with persistent diastolic flow. The cephalic vein (outflow) is arterialized, with high-velocity signal and color turbulence. Distal radial and ulnar arteries retain the expected triphasic, high-resistance pattern of a resting limb. (B) Volume-flow quantification. The upper panel illustrates the measurement of venous outflow in a straight cephalic vein segment a short distance to the anastomosis, avoiding valves and branches. The lower panel demonstrates corroborative inflow assessment in the brachial artery proximal to the anastomosis. Average 3-5 samples and report site and value.

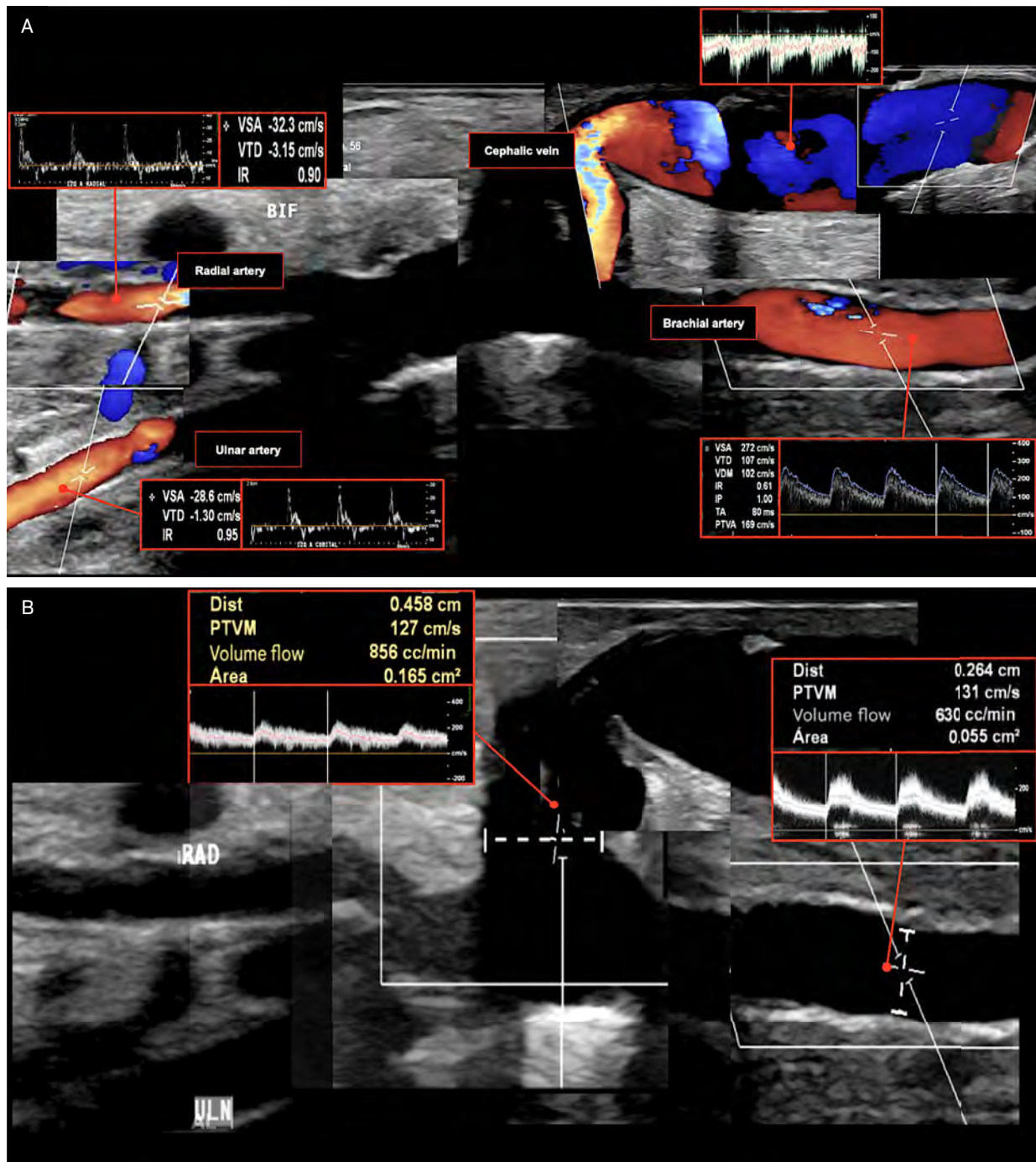


Table 2. Complications of Arteriovenous Fistulas: US Fast Guide

COMPLICATION	EMERGENCY DEPARTMENT CLINICAL PRESENTATION	KEY DIAGNOSTIC US FAST GUIDE FINDINGS	RATE/INCIDENCE
Thrombosis	- Sudden loss of thrill/bruit. - Inability to dialyze - Pain at the site of thrombosis	Absent or markedly reduced color Doppler flow within the fistula or graft; echogenic intraluminal thrombus; loss of normal spectral signal; and loss of compressibility in the involved segment	17-25% ⁶
Stenosis	- Gradual loss or change in thrill/bruit - Difficult cannulation, low dialysis flow, and prolonged post-dialysis bleeding - Arm or hand swelling in advanced cases	Focal luminal narrowing with color aliasing and post-stenotic turbulence; peak systolic velocity increases across the lesion with reduced flow distally	14-42% ⁶
High-output cardiac failure	Dyspnea, orthopnea, and peripheral edema	Markedly elevated access volume flow with very low-resistance arterial waveform in the feeding artery; large caliber of inflow and outflow vessels	12.2-17% ⁶
Aneurysm/pseudoaneurysm	- Palpable pulsatile mass along the access - Local pain, rapid enlargement, and overlying skin thinning or ulceration - Difficult cannulation	True aneurysm: fusiform dilatation of the access Pseudoaneurysm: saccular outpouching connected by a narrow neck showing "to-and-fro" waveform	4% ¹⁵
Steal syndrome	- Hand pain, coldness, and pallor, often worse during dialysis - Paresthesias or weakness of the hand - In severe cases, rest pain, tissue loss, or digital gangrene	High-flow, low-resistance waveform within the fistula with diminished, dampened, or even reversed flow in the distal artery	4% severe ischemia that requires reintervention 10-20% patients develop pain or paresthesias¹⁶
Infection	- Local erythema, warmth, swelling, and tenderness over the access - Purulent drainage from puncture sites - Fever, chills, or sepsis in severe cases	Hypoechoic or complex perivascular fluid collection around the fistula; thickened, heterogeneous vessel wall; increased soft-tissue vascularity on color Doppler; and possible gas with dirty shadowing or organized abscess	2-3% ⁶
Venous hypertension	- Painful, persistent arm and hand swelling - Dilated, tortuous superficial veins; skin discoloration or ulceration of the distal limb	Dilated outflow and collateral veins with sluggish, nonphasic flow	Uncommon 0.03 events per 1000 patient days¹⁷
Hemorrhage	- Acute external bleeding from puncture site or ruptured aneurysm - Expanding pulsatile hematoma - Hypotension, tachycardia, and signs of hemorrhagic shock in severe cases	Perivascular heterogeneous collection consistent with hematoma; focal wall defect with color Doppler jet extravasating into surrounding soft tissues	Uncommon The incidence of fatal vascular access hemorrhage episodes is reported to be less than 1 episode per 1000 dialysis patient-years¹⁸

Figure 2. Acute cephalic vein thrombosis in a radiocephalic arteriovenous fistula. A 29-year-old man presented with left upper-limb swelling after hemodialysis. Grayscale and compression US show noncompressible hypoechoic thrombus within the cephalic vein with absent color/spectral flow, extending proximally and ending 5 cm before the subclavian vein. Adjacent vessels, including the basilic and brachial veins, remain patent.

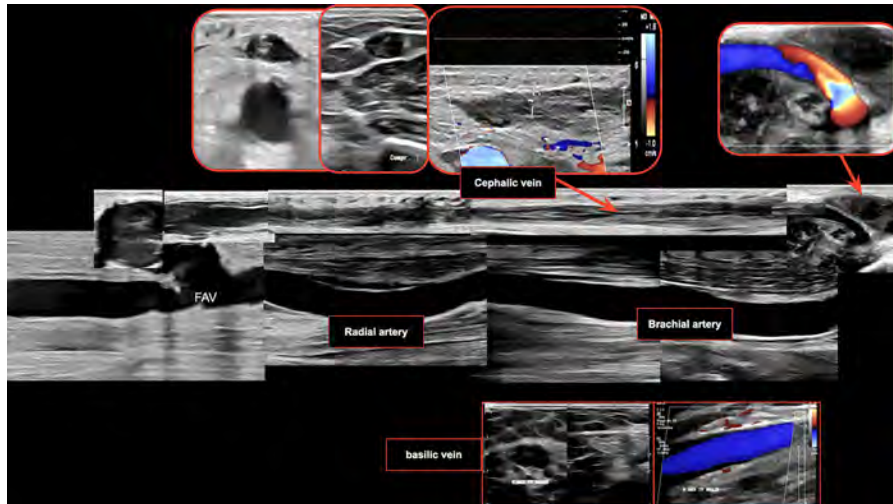
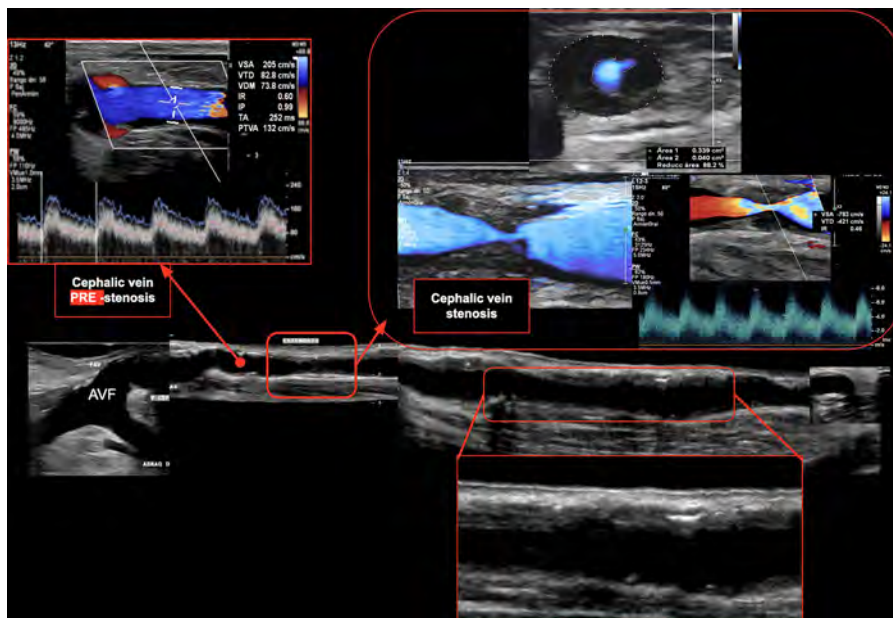


Figure 3. Stenosis in a brachiocephalic arteriovenous fistula. A 39-year-old man presented with a 1-month history of left upper extremity pain and edema. Color Doppler demonstrates significant luminal narrowing with aliasing in the mid-cephalic vein. Spectral analysis reveals a peak systolic velocity of 783 cm/s within the stenosis, with a pre-stenotic velocity of 205 cm/s, yielding a peak systolic velocity ratio of 3.7—consistent with significant stenosis. The sonographic appearance of intimal thickening with calcifications of the cephalic vein suggests chronic venous wall injury.



US, retrograde diastolic flow in distal arteries is the hallmark finding, which normalizes upon manual compression of the fistula (Figure 4).⁷ Flow volume allows differentiation between high-flow steal, in which a brachial-based arteriovenous access diverts an excessive volume of

blood away from the hand, and low-flow steal, in which distal hypoperfusion is driven by arterial inflow stenosis or severe peripheral small-vessel disease rather than excessive shunting. In high-flow steal, flow-reducing procedures such as revision using distal inflow (RUDI) (which

typically reduces access flow by about 50%) or proximalization of arterial inflow (PAI) are used to decrease access flow, while in low-flow steal the priority is to correct inflow disease (angioplasty or bypass).

High-Output Cardiac Failure

High-output cardiac failure (HOCF) secondary to an AVF occurs when the large amount of blood shunted through the access chronically increases venous return and ultimately exceeds the heart's compensatory capacity. Hemodialysis accesses usually consume about 20% of the cardiac output (CO), and AVF increases CO by 15% and end-diastolic ventricular pressure by 4% in most patients.⁸

HOCF is characterized by typical heart failure symptoms (dyspnea, orthopnea, peripheral or pulmonary edema, and reduced exercise tolerance), together with an elevated cardiac index and low systemic vascular resistance. Patients with pre-existing ischemic or valvular heart disease are particularly vulnerable, and symptoms often improve after flow reduction or obliteration of the access, underscoring the importance of a detailed history regarding the temporal relationship between access creation and symptom onset.

US reveals elevated venous flow volume and low-resistance arterial waveforms (Figure 5). The US should be used to determine the access volume flow (Qa) and the CO. An access flow > 2 L/min and a Qa:CO ratio > 25%⁸ are generally considered high and are associated with an increased risk of HOCF. Management focuses on reducing the hemodynamic burden on the heart while preserving dialysis access whenever possible. Surgical options include flow-reduction procedures such as RUDI, which typically decreases access flow by 50%,²³ banding techniques to create a controlled stenosis, and PAI. Ligation of the access is reserved for severe or refractory cases.

Aneurysm

An AVF aneurysm can be defined as a segmental dilatation of the arterialized

Table 3. US Criteria for Significant Stenosis (Practice Parameters and Technical Standards: ACR-AIUM-SRU Recommendations¹¹)

CRITERIA TYPE	VASCULAR ACCESS	THRESHOLD/VALUE
Morphological	- Luminal diameter reduction - Residual diameter (stenotic point) - Doppler spectral	≥50% reduction in transverse diameter compared with the uniform caliber segment upstream Diameter < 2-3 mm Parvus and tardus arterial waveforms are post-stenotic in the inflow artery
Hemodynamic	Peak systolic velocity ratio (anastomosis/artery 2 cm upstream) Absolute peak systolic velocity Peak systolic velocity ratio (narrowed draining vein/vein 2 cm caudally)	- Peak systolic velocity ratio (anastomosis/artery 2 cm upstream) > 3 may represent ≥50% stenosis within the anastomosis - Peak systolic velocity > 375 cm/s at the anastomosis or draining vein may represent ≥50% stenosis - Peak systolic velocity ratio (narrowed draining vein/vein 2 cm caudally) > 2:1 may represent ≥50% stenosis within the fistula
Functional (flow volume)	Arteriovenous fistula (inadequate flow)	Flow volume < 500 mL/min is predictive of access dysfunction

Table 4. Characteristic Locations and Clinical Relevance of Stenosis in Vascular Access

LOCATION	CLINICAL RELEVANCE
Juxta-anastomotic stenosis	The most common stenosis in native arteriovenous fistulas, affecting the first 2 cm of the draining vein immediately downstream of the anastomosis. It accounts for approximately 80% of all venous stenoses and is a frequent cause of early access failure. ³
Arterial inflow stenosis	Occurs proximal to the anastomosis and is present in up to 40% of dysfunctional arteriovenous fistulas. Etiologies include anastomotic narrowing from neointimal hyperplasia, technical surgical factors, or atherosclerotic disease in the feeding artery, the latter being more prevalent in elderly patients. ¹¹
Cannulation segment stenosis	A late complication typically resulting from the venous wall's fibrotic response to repeated needle trauma.
Central venous stenosis	Involves the central veins (eg, subclavian, brachiocephalic). Clinically, marked ipsilateral arm swelling often with a history of previous central venous catheterization.

vein involving all 3 wall layers, with a minimum diameter ≥18 mm, which corresponds to approximately a 3-fold enlargement of the recommended 6 mm diameter of a mature, usable fistula.²⁴ Its development is multifactorial and relates to degenerative changes triggered by repeated cannulation of

the same sites, recurrent endovascular dilatation of stenoses, and chronic hemodynamic stress.

Clinically, aneurysms present as localized, pulsatile, “ballooned” segments; they may progress to skin thinning, ulceration, infection, thrombosis, inability to puncture, or rupture with potentially

life-threatening hemorrhage.⁸ For this reason, the aneurysmal segment should be inspected at every dialysis session, with particular attention to rapid growth, shiny or translucent skin, necrotic patches, or bleeding; stable aneurysms without worrisome features can be monitored conservatively.

Duplex US is invaluable for assessing wall integrity and the extent of aneurysmal change. On B-mode imaging, the lesion appears as a fusiform or saccular venous dilation, sometimes partially filled by mural thrombus that may mask its true size angiographically. Color Doppler typically demonstrates slow, swirling flow within the cavity, generating the characteristic “Korean flag” or “yin-yang” appearance (Figure 6).³ True aneurysms may be associated with hemodynamically significant stenosis.⁸ When the overlying skin is compromised—thinned, ulcerated, or bleeding—surgical treatment is indicated.⁹

Pseudoaneurysm

A pseudoaneurysm (PSA) is a post-traumatic, perivascular blood collection that, unlike a true aneurysm, does not involve all 3 layers of the vessel wall. It has no true wall of its own; instead, it communicates with the parent vessel through a narrow neck and is contained

Figure 4. Hemodynamic characterization of steal syndrome in a brachiocephalic arteriovenous fistula. A 48-year-old man presented with pain, paresthesia, and numbness in the hand ipsilateral to a brachiocephalic arteriovenous fistula, associated with cyanosis and digital ulceration. Doppler US demonstrates bidirectional flow in the radial artery and reversed diastolic flow in the ulnar artery distal to the anastomosis. Manual compression of the arteriovenous fistula restores normal antegrade ulnar arterial flow and waveform morphology, confirming the diagnosis of hemodynamic steal syndrome.

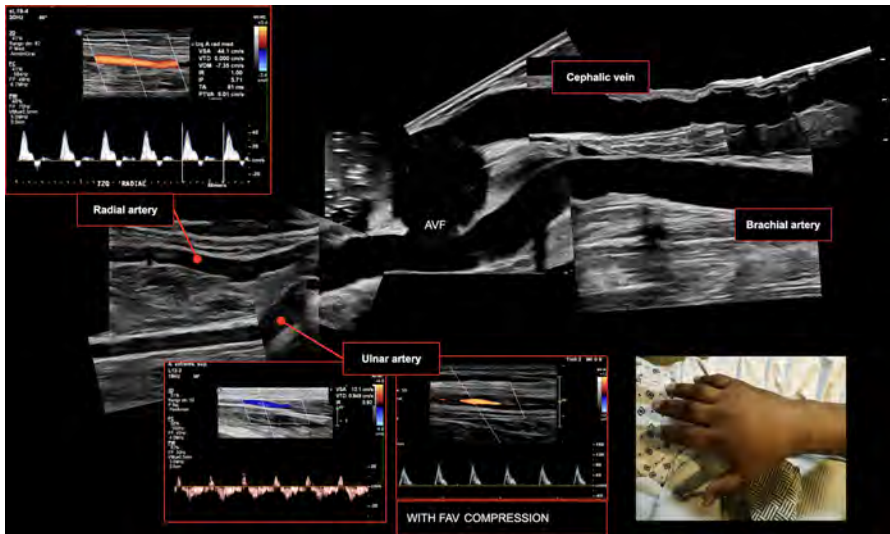
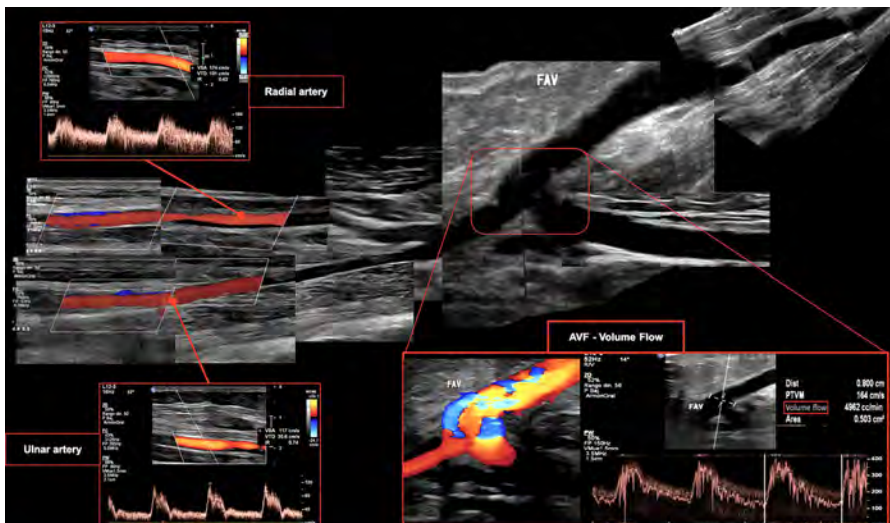


Figure 5. High-flow brachiocephalic arteriovenous fistula in a patient with dyspnea and edema, suggestive of high-output heart failure. A 50-year-old man with a left brachiocephalic arteriovenous fistula presented with generalized edema predominantly involving the left upper extremity and associated dyspnea. Quantitative Doppler assessment demonstrated markedly elevated access flow (4.9 L/min). Spectral analysis of the distal radial and ulnar arteries showed monophasic, low-resistance waveforms with loss of the normal triphasic pattern, consistent with substantial flow diversion into the fistula, reduced distal arterial perfusion, and a high-flow state predisposing to high-output cardiac failure.



by reactive fibrous tissue, which explains its higher risk of rupture compared with a true aneurysm of similar size. In the hemodialysis setting, PSAs occur most commonly in synthetic grafts and are usually related to cannulation mishaps,

repeated puncture of the same site, or extravasation after needle removal. Their formation typically requires a defect in the graft material combined with elevated venous pressure, often resulting from associated outflow stenosis. They may

involve the prosthesis, draining vein, or—less frequently—the feeding artery; anastomotic PSAs almost always warrant surgical repair.

Clinically, PSAs present as a pulsatile mass, and the overlying skin must be carefully inspected for thinning, scarring, ulceration, or spontaneous bleeding. Because of the high rupture risk, most require intervention, particularly when the sac exceeds twice the diameter of the adjacent graft or is larger than 1 cm with mural thrombus.

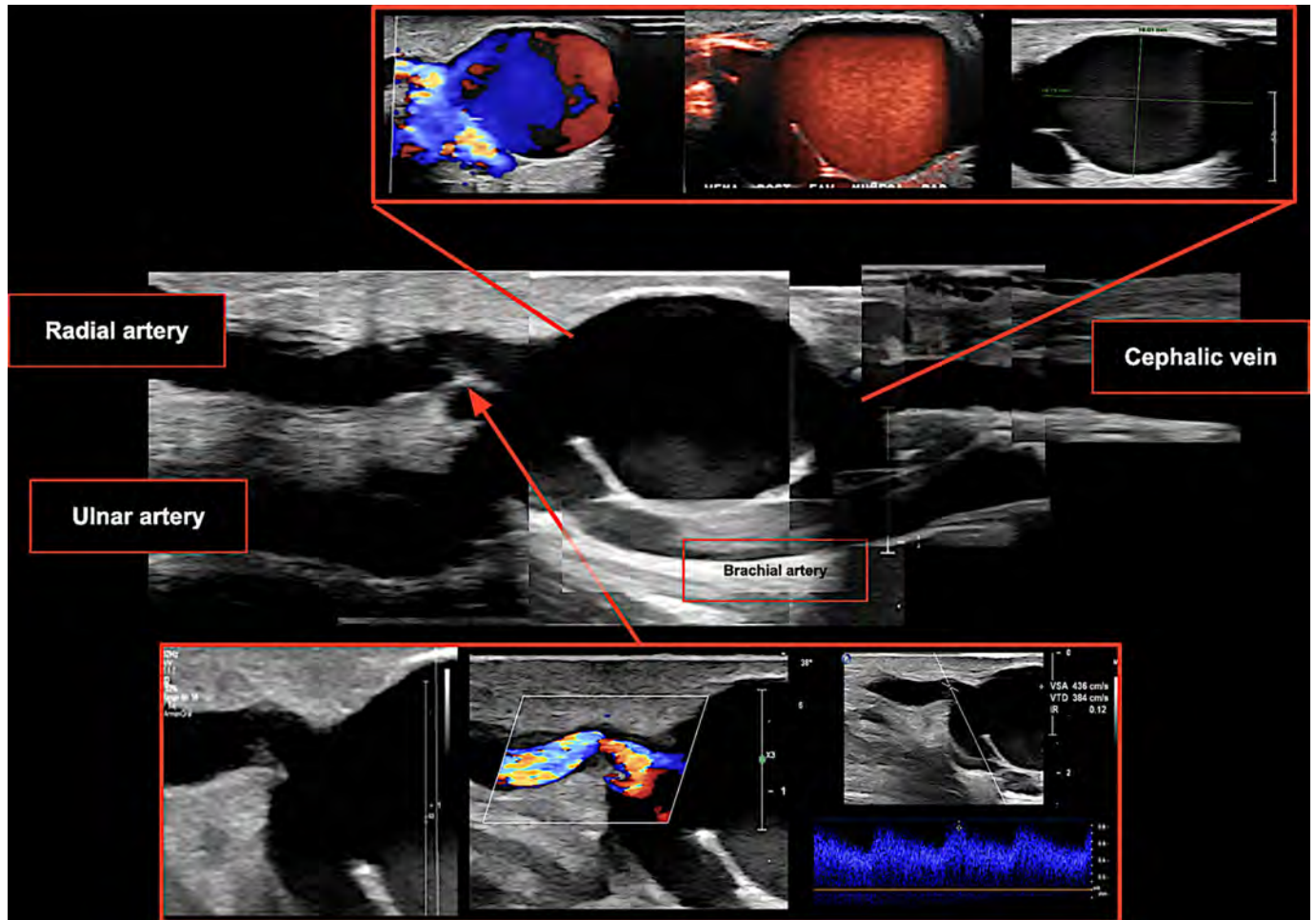
Duplex US is the first-line imaging modality and shows a perivascular anechoic collection with or without thrombus on B-mode. Color Doppler demonstrates swirling “yin-yang” flow within the sac, while spectral Doppler at the neck reveals the classic bidirectional “to-and-fro” pattern, sometimes with aliasing (Figure 7).³ Treatment options range from minimally invasive approaches—such as US-guided compression, percutaneous thrombin injection, or covered stent placement in selected graft lesions—to open surgical repair with resection and interposition graft.³

Hemorrhage

Hemorrhage is a rare but life-threatening complication, most often resulting from the rupture of a degenerated true aneurysm or a PSA, or from cannulation-related trauma.²⁵ The integrity of the overlying skin is critical: marked thinning with a shiny or translucent appearance, ulceration or necrotic patches, and any episode of spontaneous bleeding mandate urgent surgical evaluation.

Patients may present with external bleeding, expanding hematomas, or hypovolemic shock. On US, hemorrhage appears as heterogeneous perivascular collections with variable echogenicity depending on clot age. Color Doppler may demonstrate active extravasation of flow, which is diagnostic (Figure 8). When rupture risk is high or bleeding is ongoing, temporary endovascular stent graft placement may be considered as a bridge to definitive surgery, while in

Figure 6. True aneurysm in a brachiocephalic arteriovenous fistula with proximal radial artery stenosis. A 27-year-old woman with a right brachiocephalic arteriovenous fistula presented with progressive right upper extremity edema and difficult cannulation during hemodialysis. Grayscale and color Doppler US show a true aneurysm of the vein measuring 18.01×19.15 mm. Immediately distal to the aneurysm, the radial artery demonstrates a focal, high-grade stenosis with marked luminal narrowing, color aliasing, and elevated peak systolic velocities on spectral Doppler, consistent with flow-limiting stenosis and aneurysmal degeneration.



extreme cases, access ligation may be required, at the cost of losing the access.⁸

Infection

Infection of AVFs contributes substantially to morbidity, accounting for a significant proportion of access-related complications and predisposition to aneurysm, PSA, and hemorrhage through progressive vessel wall damage. Risk factors include poor patient hygiene, diabetes, older age, and history of bacteremia.²⁶

Staphylococcus aureus is the predominant pathogen, followed by *Staphylococcus epidermidis*. Most AVF infections are localized to the puncture sites and

present as perivascular cellulitis with erythema, swelling, and tenderness, but patients may also develop systemic manifestations such as fever, chills, or rigors, and deep infection or abscess formation should be suspected in cases involving fluctuance, purulent drainage, or compromised skin integrity. Because access infection can serve as a nidus for bacteremia and endocarditis, blood and local cultures are mandatory when infection is suspected. Transthoracic echocardiography is recommended in cases of *S. aureus* bacteremia to rule out septic emboli.

US demonstrates vessel wall thickening, perivascular edema, heterogeneous

periaccess collections, and hyperemia on color Doppler (Figure 9). The ability to identify abscesses is particularly useful for guiding drainage and monitoring treatment response. Surgical revision or excision is indicated when medical therapy fails, there is perivascular abscess requiring drainage, or the fistula becomes a source of recurrent septic emboli.²⁷

Venous Hypertension

Venous hypertension is a painful, nonthrombotic complication of AVFs caused by impaired venous outflow, most commonly resulting from stenosis. The condition presents with arm swelling, varicosities, pain, and ulceration. The

Figure 7. Multiple pseudoaneurysms in the draining vein of a left brachiocephalic arteriovenous fistula. A 31-year-old woman with a left brachiocephalic fistula and episodes of absent venous flow during hemodialysis was evaluated with US. Grayscale imaging demonstrates 3 sac-like dilatations along the draining vein, compatible with pseudoaneurysms, likely related to repeated cannulation, with preservation of fistula patency. Within the sacs, intraluminal echogenicity and circular swirling of blood are evident, reflecting marked flow deceleration. Color Doppler shows recirculating flow with a characteristic “yin-yang” appearance, while spectral Doppler at the pseudoaneurysm neck demonstrates a classic “to-and-fro” (bidirectional) waveform.

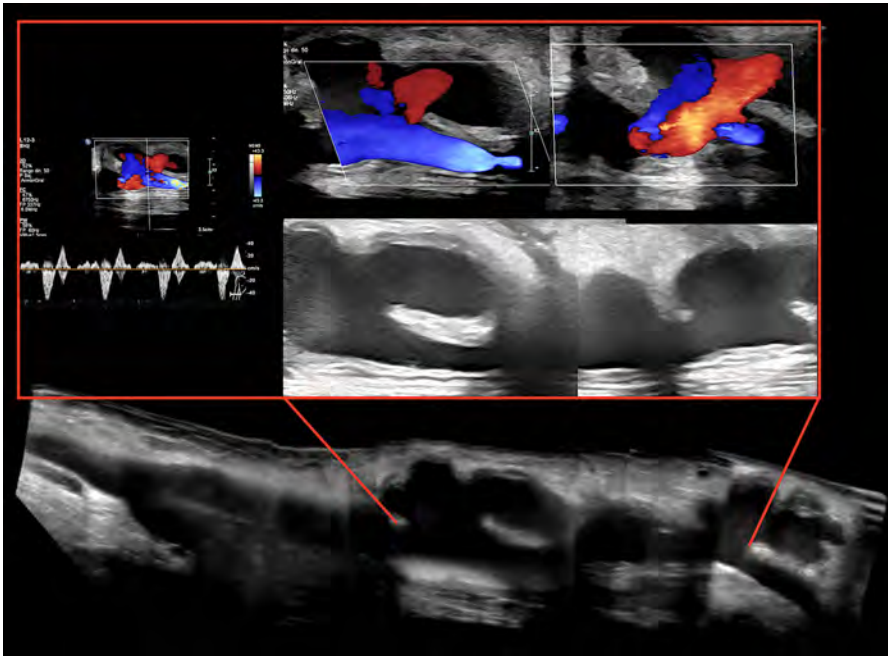
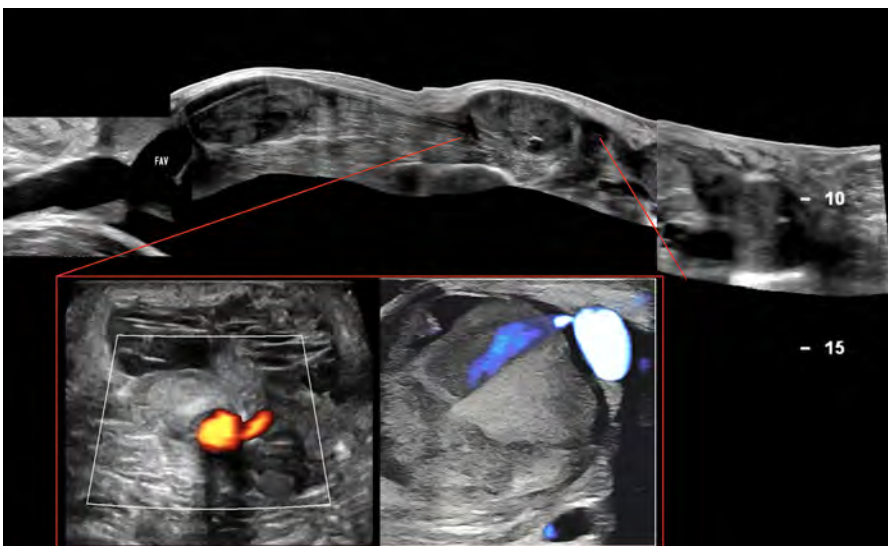


Figure 8. Acute hemorrhage from a radiocephalic arteriovenous fistula. A 39-year-old man with chronic kidney disease and a right radiocephalic arteriovenous fistula presented with rapidly progressive swelling and erythema of the ipsilateral upper extremity. Panoramic grayscale US shows an extensive heterogeneous hematoma along the draining vein. In the mid-third of the vein, color Doppler demonstrates a focal high-velocity jet breaching the fistula wall into the surrounding collection, indicating active extravasation.



most advanced stages of this complication can progress to marked discoloration of the affected limb and, in extreme cases, culminate in venous gangrene. Given its often insidious onset and potential misattribution to other causes of edema, this entity is likely under-recognized and under-reported.

US findings include venous dilatation, turbulent or reversed flow, and evidence of collateral circulation (Figure 10). Recognition is important, as untreated venous hypertension leads to progressive morbidity and functional impairment.

Management is primarily surgical, with selective ligation of the arterialized veins draining into the hand. When the deep venous system is arterialized, fistula closure is required. Only mild cases, usually limited to edema, can be managed conservatively with limb elevation and compression bandaging.²⁸

Conclusion

US has established itself as the first-line modality for AVF evaluation in patients undergoing hemodialysis. Its capacity to provide detailed anatomical and hemodynamic information makes it indispensable in routine surveillance and emergency settings. This review underscores the characteristic findings of the most common and uncommon complications. For radiologists, familiarity with these entities and adherence to standardized protocols are essential to ensure reproducibility and reduce interoperator variability.

Future developments, including the integration of advanced techniques such as contrast-enhanced US and elastography, may provide additional insights into vascular wall properties and flow dynamics. Artificial intelligence also holds promise for automating vessel segmentation and objectively quantifying flow, potentially reducing operator dependence.

Figure 9. Incipient abscess formation around a brachiocephalic arteriovenous fistula. A 54-year-old man with chronic kidney disease and type 2 diabetes presented with localized pain at the access site and 2 weeks of fever with elevated inflammatory markers. US demonstrates a small, hypoechoic, wall-forming collection adjacent to the inferior border of the fistula, measuring approximately 3.1×0.7×0.8 cm, without internal vascularity on color or power Doppler, and associated subcutaneous tissue edema along the lateral aspect of the forearm findings consistent with an incipient abscess. Unlike a hematoma, the collection shows a well-defined capsule and occurs in the setting of systemic infection, and in contrast to a pseudoaneurysm it shows no communication with the fistula lumen and lacks the characteristic “yin-yang” Doppler patterns.

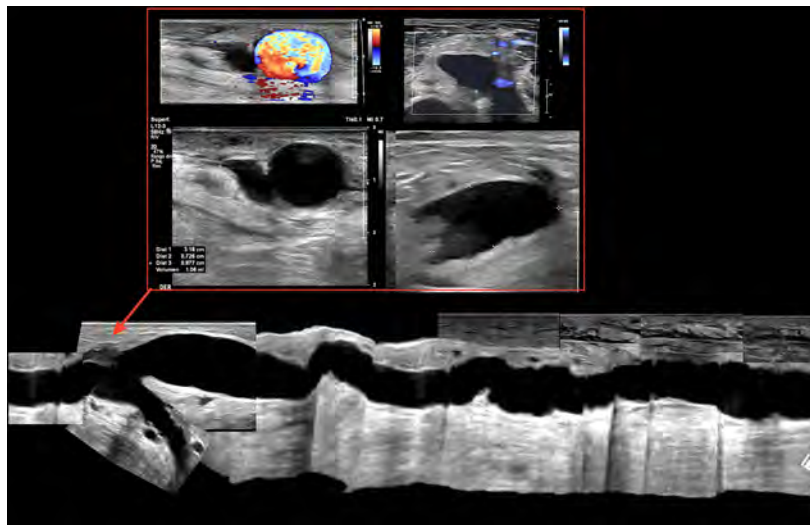
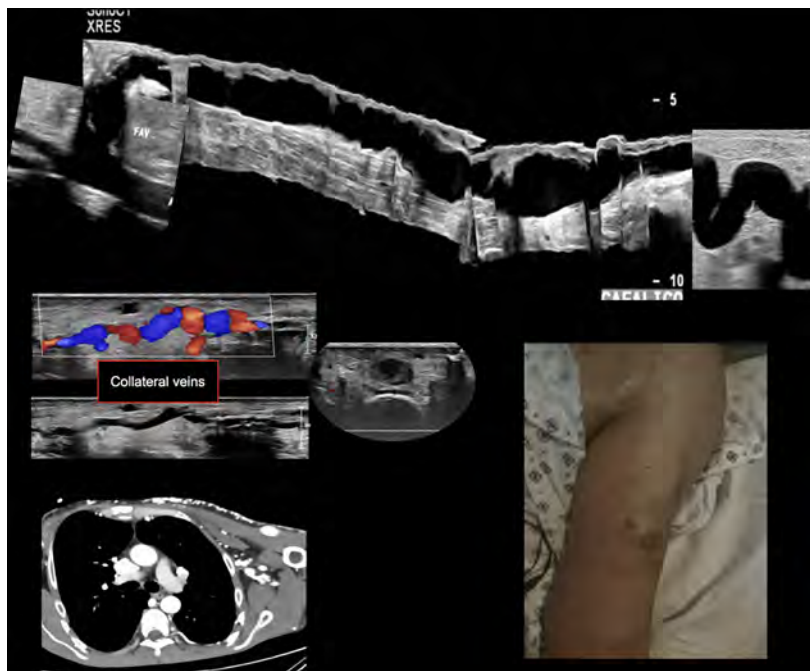


Figure 10. Venous hypertension in a left brachiocephalic arteriovenous fistula. A 47-year-old man with a left brachiocephalic arteriovenous fistula presented with progressive edema of the left upper extremity, limited mobility, skin hyperpigmentation, varicosities, and ulcerations. Long-axis US of the cephalic vein demonstrates marked venous dilatation with mural calcifications and turbulent flow. The superficial venous system of the left forearm is dilated with multiple varicose segments, some containing noncompressible echogenic material consistent with thrombosis. Contrast-enhanced CT confirms extensive collateral circulation through superficial intercostal and upper-extremity veins, supporting the diagnosis of chronic venous hypertension.



Ultimately, early detection and accurate characterization of AVF complications through US directly impact patient outcomes by preserving access patency, minimizing hospitalizations, and ensuring effective dialysis delivery. Radiologists, therefore, play a pivotal role in the multidisciplinary team managing vascular access, contributing not only to clinical decision-making but also to the overall efficiency and quality of care in this growing patient population.

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Glioneuronal Tumors: A Pictorial Review and Practical Approach

Meagan Bechel, MD, PhD; Saumya Gurbani, MD, PhD; Samia Sabir, BA, BS; Andres Brito, BS; Zofia Lasiecka, MD, PhD

Abstract

Many radiologists struggle to parse between glioneuronal tumors due to significant overlap in imaging, histology, and long-term behavior. However, most glioneuronal tumors have long, primarily benign courses, and therefore, it is not uncommon for imaging to be the primary source for clinical decision-making. In cases requiring resection, imaging features can inform preoperative risk and determine the need for adjuvant therapies. While these tumors are diagnostically challenging, specific imaging features have stronger diagnostic and prognostic associations. This review aims to provide an approach to navigating the glioneuronal tumor differential for practicing radiologists and radiology trainees. Through a set of representative cases, key imaging features are discussed that inform specific glioneuronal tumor diagnoses as well as subsequent clinical management.

Keywords: glioneuronal tumors, central nervous system tumors, neuroradiology, pediatric neuroradiology

Introduction

As their name indicates, glioneuronal tumors contain glial and neuronal cellular features. They typically exhibit low-grade behavior and do not fall into the molecular subtype of other brain tumors such as gliomas, oligodendrogliomas, and astrocytomas.^{1,2} Their clinical symptoms usually stem from mass effect and/or medically refractory seizures, and while they can occur across all age groups, they are often diagnosed in childhood or early adulthood.²

Advances in molecular pathophysiology have led the World Health Organization

to update its diagnostic criteria for brain tumors, switching from an imaging or histopathological approach to genetic and molecular categorization.¹ Nevertheless, radiologists play a key role in diagnosis and prognosis. MRI is the modality of choice for tumor characterization, with occasional use of advanced techniques such as MR perfusion and spectroscopy (MRS) for indeterminate cases.³

Here, we present an overview of glioneuronal tumors and typical imaging findings. We also present an approach to differentiating these tumors from other types based on key imaging features that can inform diagnosis and subsequent management.

Review of Tumors

Supratentorial: Cortical

Desmoplastic Infantile Astrocytoma and Ganglioglioma

Desmoplastic infantile gangliogliomas (DIGs) and astrocytomas (DIAs) occur most often in infants under age 24 months.⁴ DIGs demonstrate a slight male predominance (~60%) while DIAs have no gender predilection.^{4,5} In contrast to other glioneuronal tumors, DIG/DIA presents with seizures in a minority of cases.^{4,6} DIGs/DIAs are large tumors most often located within the superficial cortex in the frontal or parietal lobes (Figure 1).^{4,6}

Affiliations: Department of Radiology and Imaging Sciences, Emory University, Atlanta, Georgia (Bechel, Gurbani, Lasiecka). Emory University, Atlanta, Georgia (Sabir). Philadelphia College of Osteopathic Medicine, Philadelphia, Pennsylvania (Brito).

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Declaration on the use of AI. The authors of this manuscript declare that in the writing process of this work, no generative artificial intelligence (AI) or AI-assisted technologies were used to generate content, ideas, or theories. The authors declare that they did not utilize AI for the purpose of enhancing readability and refining language.

Figure 1. Desmoplastic infantile gangliocytoma imaging features. (A) T1 postcontrast image in a 9-month-old girl demonstrates a cortical-based tumor in the frontoparietal vertex. (B) T2 FLAIR postcontrast imaging in a 1-year-old boy demonstrates a cortical-based tumor in the sylvian fissure. These tumors are mixed cystic-solid masses with cystic components (white arrows) deep to avidly enhancing solid components (black arrows). Patient B demonstrates the most common metastatic site, with leptomeningeal enhancement (arrowheads) and experienced multiple subsequent recurrences requiring multiple resections. Patient B's solid component (black arrow) also encases the insular M2 middle cerebral artery and adjacent deep veins, which is easiest to appreciate when comparing to the flow voids on the contralateral side (white arrowhead).

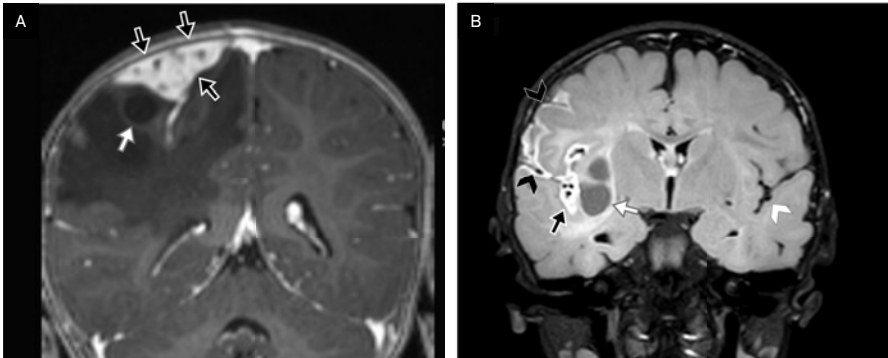
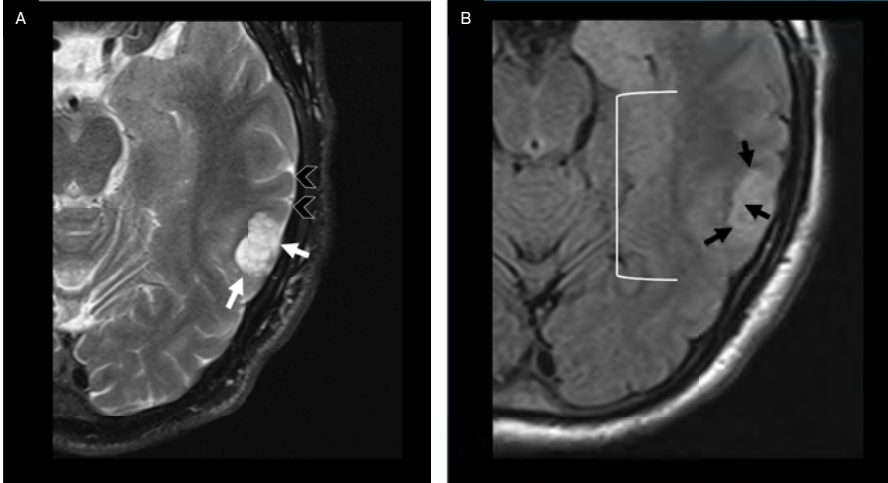


Figure 2. Dysembryoplastic neuroepithelial tumor. Axial T2 (A) demonstrates a T2-hyperintense multicystic lesion in the left temporal lobe (white arrows). On axial T2 FLAIR (B), the lesion demonstrates a hyperintense ring (black arrows), suggestive of the “FLAIR rim” sign. This tumor does not demonstrate features associated with higher grade tumors and worse outcomes. Specifically, there are no satellite lesions, which would most commonly be found along the medial aspect of the tumor (white bracket), and the adjacent cortex has no focal dysplasia.



Cystic components are found in most cases (>90%) and often located deep to solid components (Figure 1).⁶ The peripheral solid components enhance vividly.^{4,5} While these tumors are considered benign, they can demonstrate metastatic behavior; one case series has documented metastasis at presentation in 11.7% of cases (Figure 1B).⁷

The main differentials are pleomorphic xanthoastrocytoma (PXA), ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), and atypical teratoid/rhabdoid tumor (AT/RT). DIAs/DIGs typically present at younger ages and have stronger T2 hyperintensity compared with PXAs and gangliogliomas.⁴ In addition, DIAs and DIGs enhance more strongly than

DNETs.^{4,6} AT/RTs are more likely to calcify and hemorrhage than DIAs and DIGs; however, calcification and hemorrhage can be seen in DIA/DIG cases with acute clinical symptoms.^{4,5} Total resection is uncommon (27-30% of cases), and adjuvant therapy is recommended only in cases of documented tumor progression.⁶

Imaging offers a few key predictors of patient outcomes.⁶ The leptomeninges are the most common site of metastasis (Figure 1), but intracranial and spinal metastases have also been reported.⁶ Midline location is associated with more aggressive histological behavior, increased chance of recurrence, and increased intraoperative risk.^{4,6} Specifically, involvement of the hypothalamus should be reported, as it is associated with increased mortality secondary to postoperative respiratory compromise.⁴ Finally, the solid components of DIAs/DIGs usually encase vessels, which can help with diagnosis but can also limit surgical resection.⁶

Dysembryoplastic Neuroepithelial Tumors

Slow-growing and cortical-based, DNETs most commonly affect patients <20 years and are found in the temporal and frontal lobes.⁸

DNETs demonstrate a characteristic multicystic, “bubbly” lesion with high T2 and low T1 signal (Figure 2).⁸ Multicystic morphology is associated more with DNETs than with other cortically based lesions such as oligodendrogliomas and gangliogliomas.⁹ Most DNETs extend into the subcortical white matter, occasionally in a tapered fashion.⁹ The FLAIR rim sign has been suggested as a specific finding for DNET (82% specificity in one case series) (Figure 2B).¹⁰

Some DNETs will demonstrate peripheral contrast enhancement, may contain macroscopic calcification (~20%), and rarely contain intratumoral hemorrhage.¹¹ They frequently present with multiple satellite lesions, preferentially occurring along the medial

aspect of the primary lesion.⁸ Additionally, focal cortical dysplasia can be associated with higher-grade DNETs.¹²

Surgical resection provides effective seizure control. Persistent seizures have been seen in 46% of patients with satellite lesions but only 18% of patients without satellite lesions.¹³

Polymorphous Low-Grade Neuroepithelial Tumors of the Young

Polymorphous low-grade neuroepithelial tumors of the young (PLNTY) were previously considered a subtype of DNET, differentiated via mutations within the MAPK pathway.¹⁴ They are primarily seen in children and young adults,¹⁵ occurring only rarely in older adults.¹⁶ Typically, PLNTYs are cortically based, heterogeneous cystic or mixed solid cystic masses (Figure 3) classically with central calcification¹⁷ and mild, heterogeneous enhancement.¹⁸ A “transmantle”-like signal abnormality (linear increased T2 signal in the deep white matter extending peripherally) can be seen, with some mixed evidence around its postresection persistence for predicting poorer seizure control.¹⁸ Beyond seizure-associated morbidity, the tumor follows a benign course with minimal mass effect. There is low recurrence after total resection¹⁷; however, a recent meta-analysis reported that the extent of resection was not significantly associated with postoperative seizure control.¹⁹

Gangliogliomas

Gangliogliomas are the most common epilepsy-associated neoplasm, typically found in the temporal and frontal lobes.^{20,21} They can occur infratentorially, including in the spinal column. They occur in both pediatric and adult populations, with most pediatric cases diagnosed in those over the age of 10 years²¹ and adult cases at a median age of 32 years.²²

On imaging, gangliogliomas are typically superficial, well-circumscribed mixed cystic and solid tumors, but a diffuse infiltrative appearance is possible.

Enhancement is variable and associated with the solid components (Figure 4); infratentorial gangliogliomas are more likely to demonstrate “paintbrush” enhancement (dorsal predominant) compared with supratentorial tumors.²² Brainstem gangliogliomas are associated with older patient age (median of 30 years), peritumoral edema, higher solid proportion, and lower rates of calcification.²³

With their variable imaging appearance, the differential is wide, including PXA, PLNTY, and oligodendrogliomas. In general, PXAs enhance more vividly than gangliogliomas and very rarely calcify, while up to 50% of gangliogliomas calcify.²³ Finally, gangliogliomas have been reported to have higher normalized cerebral blood volume and lower normalized apparent diffusion coefficient compared with oligodendrogliomas.²⁴

Tumor locations associated with worse outcomes include the brainstem, cerebellopontine angle, spinal cord, and midline tumors.²² Brainstem involvement is often the defining factor for total vs subtotal resection.²¹ There is mixed evidence for the ability of resection extent to predict long-term outcomes.^{22,25,26} Finally, there have been rare case reports of malignant degeneration; in these cases, leptomeningeal involvement was common and MRS showed anaplastic features (increased choline, lipid, and lactate).²²

Cerebral Gangliocytoma

Cerebral gangliocytomas (CGs) are rare (<3% of CNS tumors), occurring most frequently in children and young adults.² These tumors typically arise in the cerebral cortex, most often in the temporal lobe (~75%) (Figure S1), though occasional exophytic and rare extra-axial presentations have been described.

Sometimes exhibiting variable imaging features, CGs can be difficult to distinguish from other tumors, particularly gangliogliomas. Meningioma is in the differential, given that CGs can be extra-axial and demonstrate a dural tail.^{2,27} MRS may be a helpful

diagnostic adjunct, as CGs demonstrate a highly elevated choline signal and reduced N-acetylaspartate, a pattern more typical of high-grade gliomas than other glioneuronal tumors such as ganglioglioma.²⁷ Diagnosis is ultimately based on histopathology.

Supratentorial: Intraventricular

Myxoid Glioneuronal Tumors

Previously known as “DNET of the septum pellucidum,”²⁸ myxoid glioneuronal tumors (MGTs) are now defined by a gain-of-function mutation in the PDGFRA gene.²⁹ Given their similar histology and patient populations, MGTs and DNETs are difficult to distinguish from each other; therefore, imaging and genetic testing play an important diagnostic role.

The pathognomonic finding of MGT is location within the septum pellucidum (Figure 5), but they have also been reported in the midbrain.²⁹ Other imaging characteristics are similar to DNETs, with a multicystic morphology with well-defined margins and variable enhancement.³⁰ Unlike DNETs, no macrocalcifications have been reported in histologically proven MGTs.²⁹

Central Neurocytoma

Originally classified as oligodendrogliomas, central neurocytomas (CNs) are now recognized as a distinct entity.^{31,32} These tumors present at a median age of 30-31 years and typically demonstrate no gender predilection.^{31,32}

Classically, CNs are found in the frontal horn of the lateral ventricles in close association with the foramen of Monro.^{31,32} Most are unilateral at presentation, with bilateral involvement more common in larger tumors.³² These tumors consist of mixed calcific, cystic, and solid tissue components, resulting in heterogeneous imaging characteristics (Figure 6). CNs may contain coarse “popcorn” calcifications on CT,^{31,32} while cystic components produce a “Swiss-cheese” or “soap bubble” appearance on T2 sequences.^{31,33} The solid tissue component

Figure 3. Polymorphous low-grade neuroepithelial tumor of the young. Axial T2 (A) MRI demonstrates a T2-hyperintense cortically based lesion in the right temporal lobe (white arrow) with central heterogeneous signal. This central signal demonstrates susceptibility artifact (black arrow) on susceptibility-weighted imaging (B), consistent with calcification.

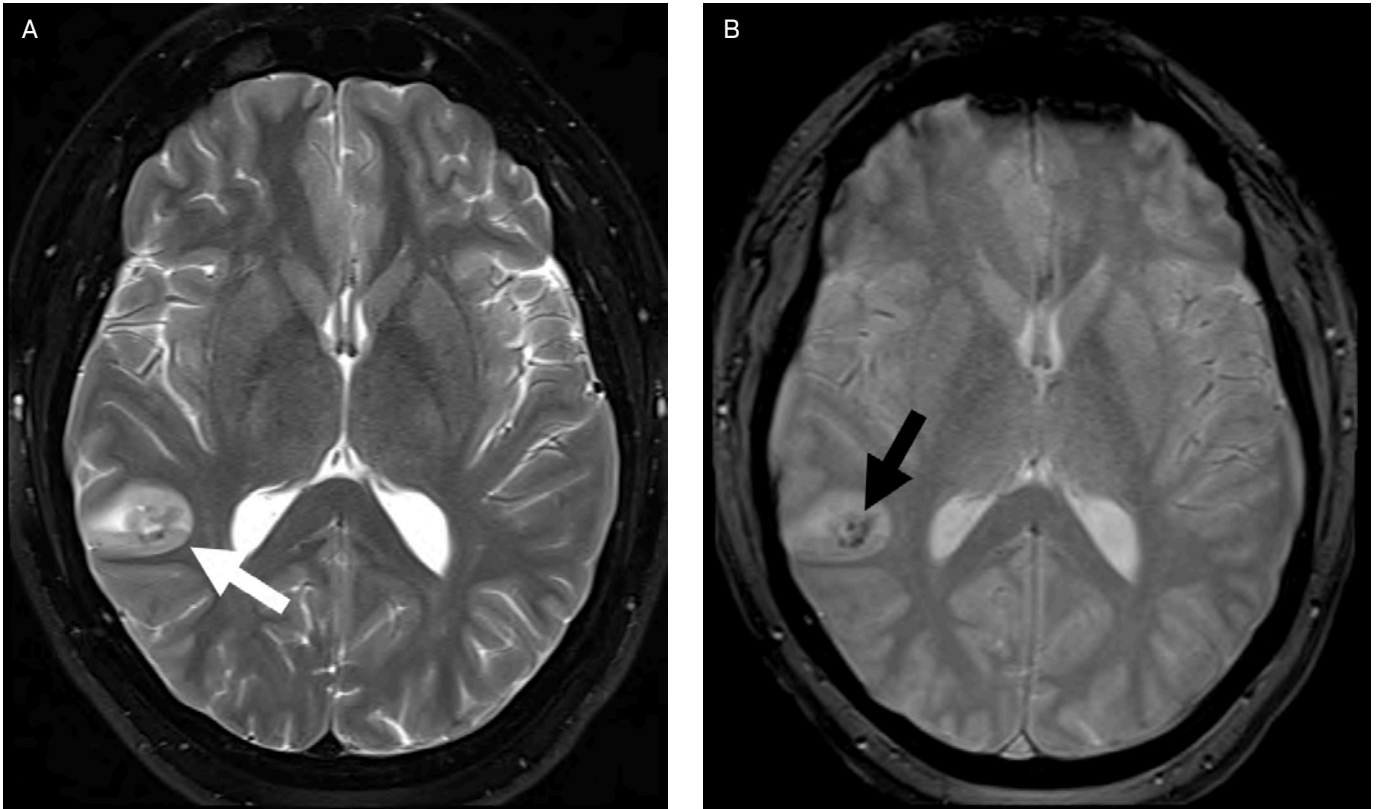


Figure 4. Variable imaging presentation of gangliogliomas. Ganglioglioma appearance can vary on imaging, owing to factors such as composition (cystic vs mixed cystic solid), borders (well-circumscribed vs infiltrative), and postcontrast enhancement. Two patients with pathology-proven gangliogliomas demonstrate this spectrum. Imaging of patient (A) shows a well-circumscribed, primarily cystic, tumor in the classic temporal lobe location with peripheral enhancement (white arrowheads) on T1 postcontrast imaging. Imaging of the second patient (B, C) demonstrates an infiltrative, mostly solid tumor with no enhancement (B, white oval), which is better visualized on T2 FLAIR (C, black arrowheads). Neither tumor had calcifications, which can occur in up to half of gangliogliomas. Given this variability, ganglioglioma is important to keep on the differential for cortical-based epilepsy-associated neoplasms.

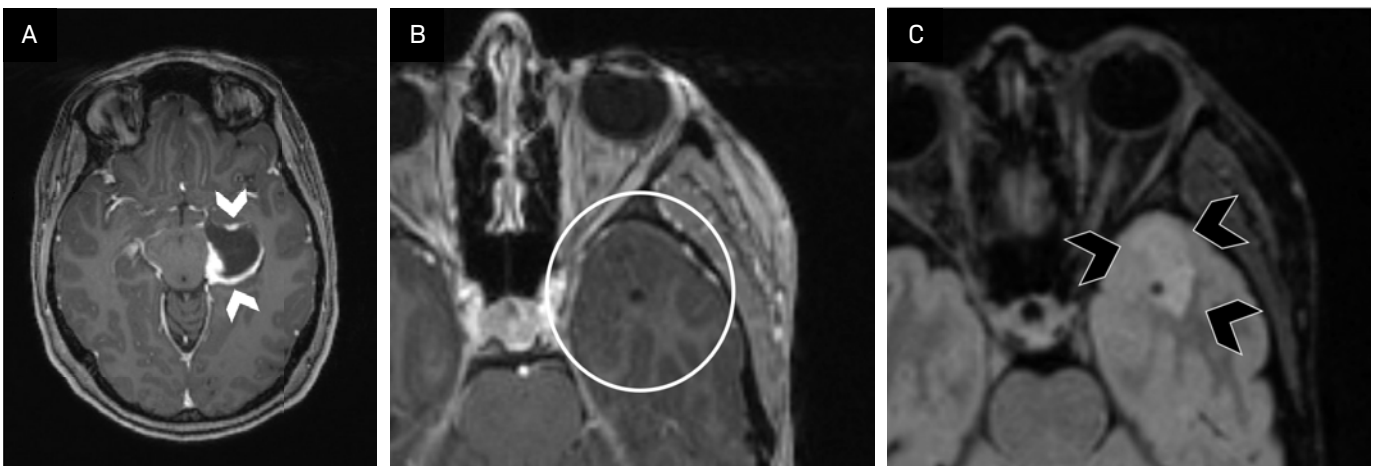


Figure 5. Myxoid glioneuronal tumor (formerly dysembryoplastic neuroepithelial tumor [DNET] of the septum pellucidum). Axial T2 FLAIR imaging (A) demonstrates a mass in the septum pellucidum (arrow) with imaging features similar to DNET: well-circumscribed with multiple hyperintense internal cystic structures. The mass is nonenhancing on axial postcontrast T1 image (B, arrowhead), consistent with the variable enhancement patterns of DNET. At biopsy, the mass was confirmed to contain histological characteristics of DNET of the septum pellucidum, which subsequently was classified as myxoid glioneuronal tumor. Genetic testing for PDGFRA was not performed for this patient owing to lack of testing availability but would be considered the gold standard for myxoid glioneuronal tumor diagnosis.

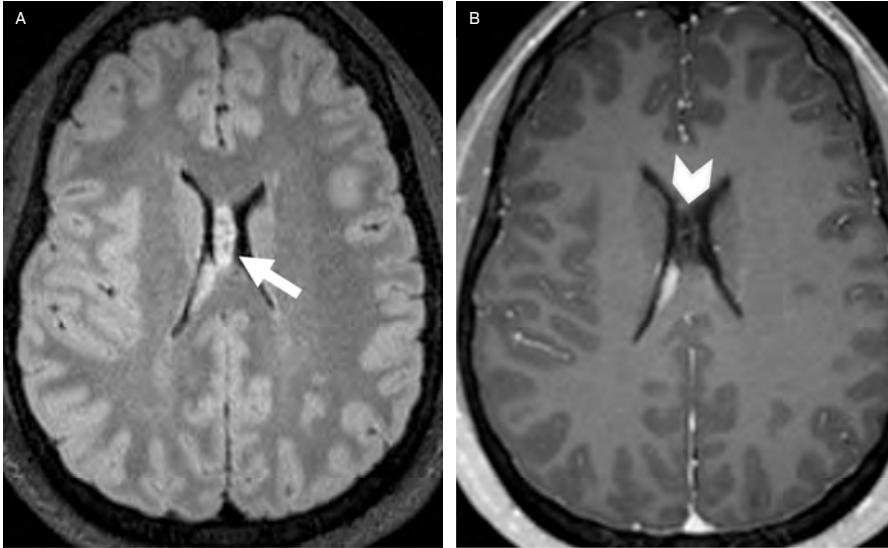
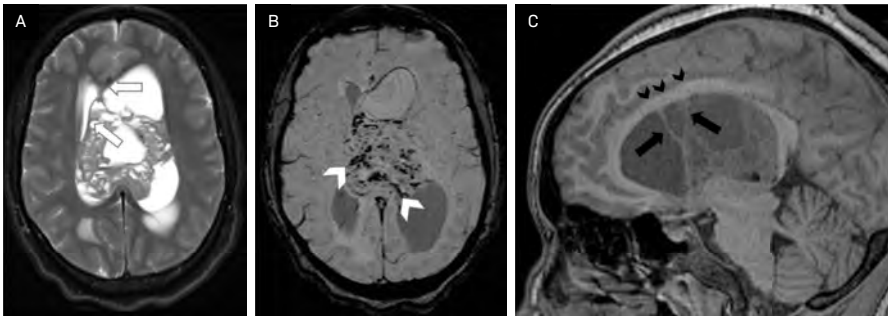


Figure 6. Central neurocytoma. Axial T2 (A) and susceptibility-weighted imaging (B) images show a mixed cystic solid mass with abutment and bowing of the septum pellucidum (white arrows). Susceptibility artifact (white arrowheads) from calcification and vascularity helps differentiate it from myxoid glioneuronal tumor. The “scalloping sign” is seen on sagittal T1 precontrast imaging (C) with peripheral cysts creating radial lines from their walls (black arrows) and a wavy appearance of the ventricular wall (black arrowheads).



dictates the degree of diffusion restriction and postcontrast enhancement, with the adjacent choroid plexus used for baseline enhancement comparison.^{31,33,34}

While the imaging appearance of CNs can vary, specific characteristics can assist with diagnosis and prognosis. These include a broad-based septum pellucidum attachment (Figure 6), peripheral cystic components, periventricular edema, and the “scalloping sign,” a wavy ventricular

wall with adjacent rows of cysts.^{12,15,16}

On MRS, CNs typically demonstrate elevated choline and reduced creatinine and N-acetylaspartate^{31,33}; elevated glycine is considered a sensitive but nonspecific finding for CN.³²

Total resection is the gold standard treatment for CNs; however, this is limited by the degree of vascularity and potential neurologic complications, the rates of which range from 30% to 70%.³³ Adjuvant

radiation is controversial in cases of subtotal resection but may be considered for tumors that demonstrate atypical and/or aggressive histologic features (~20% of CNs).^{31,32,35} Imaging findings associated with aggressive histologic features include enhancement, larger size, and the presence of irregular vessels.³⁶ Radiation is also considered for recurrent disease, which typically occurs 3-4 years post-treatment.^{31,35}

Supratentorial: Subcortical Tumors

Multinodular and Vacuolating Neuronal Tumors

Primarily occurring in adults, multinodular and vacuolating tumors (MVNTs) present at mean and median ages ranging from 38 to 45 years.^{37,38} They are benign tumors with very slow growth and do not typically require resection.³⁸

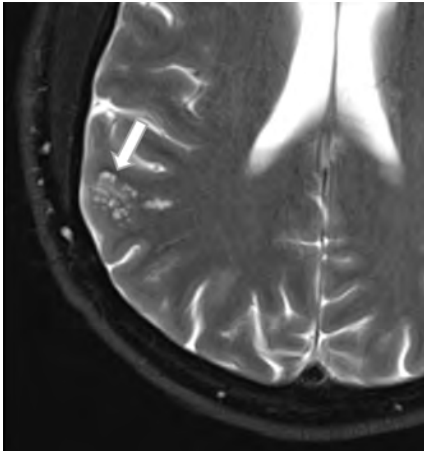
Their classic MRI appearance is a cluster of nonenhancing T2 and FLAIR hyperintense nodules centered at the cortical-subcortical junction, most commonly in the temporal lobe (Figure 7), without restriction.^{37,38} The differential is wide and includes other glioneuronal tumors and non-neoplastic processes such as prominent perivascular spaces or focal cortical dysplasia. The most appropriate follow-up MRI protocol for MVNTs continues to be debated.³⁸

Papillary Glioneuronal Tumors

Extremely rare entities, papillary glioneuronal tumors (PGNTs) primarily affect adults in their second decade.³⁹ There is no gender-based predilection.

The imaging features of these tumors are similar to those of other glioneuronal tumors, with a mixed solid cystic appearance. The 2 features suggestive of PGNT are location—80% are within or adjacent to the lateral ventricles—and septated cystic components, though these are not specific.⁴⁰ PGNTs are generally diagnosed histologically, genetically differentiated by the fusion of SLC44A1-PRKCA proteins.⁴¹ Treatment involves resection, which has a good prognosis.²

Figure 7. Multinodular and vacuolating neuronal tumor (MVNT). Axial T2 fat-saturated image demonstrates a cluster of juxtacortical hyperintense cysts (arrow) in the right parietal lobe, classic findings for MVNT. This lesion will typically not demonstrate enhancement on postcontrast images nor will it have diffusion restriction.



Posterior Fossa

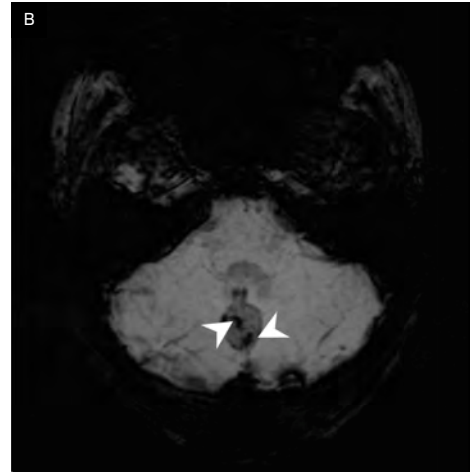
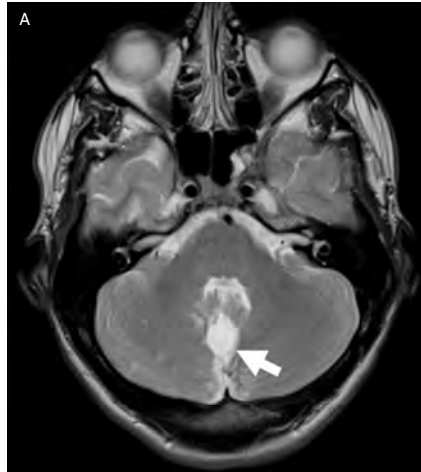
Rosette-Forming Glioneuronal Tumors

Rosette-forming glioneuronal tumors (RGNTs) are defined histologically⁴² and typically present in adults at a mean of 23 years, with a slight female predilection (1.36:1).⁴³ The classic location is adjacent to the 4th ventricle, with local parenchymal extension (Figure 8).² Less common sites include the cerebellum and spine.⁴³ Given their mixed solid-cystic composition, their imaging appearance is variable; thus, tissue sampling is required for diagnosis.

The main differential considerations are pilocytic astrocytoma and DNET. Most reported RGNTs are <3.0 cm,⁴³ with a diameter <3.5 cm being just over 3 times more likely for RGNT.⁴⁴ Calcifications in RGNTs are exceedingly rare, with only 2 cases reported,⁴³ while pilocytic astrocytomas and DNETs have reported calcification incidences of 17%⁴⁵ and 20%,¹¹ respectively. Microhemorrhage is common in RGNTs (Figure 8), and while pilocytic astrocytomas can hemorrhage, it is exceedingly rare for DNETs, reported in 3%.⁴⁶

While RGNTs are considered benign,² mass effect can be significant and require resection.⁴⁷ Pineal involvement is possible and should be reported, as

Figure 8. Rosette-forming glioneuronal tumor (RGNT). Axial T2 imaging (A) demonstrates a small (<3.0 cm) hyperintense lesion in the posterior fossa abutting the 4th ventricle (arrow). Susceptibility-weighted imaging (B) has susceptibility artifact (arrowheads) consistent with microhemorrhages. Susceptibility artifact from calcification would be exceedingly rare in RGNT and more consistent with a glioneuronal tumor or pilocytic astrocytoma.



it changes surgical approach.⁴⁸ Overall recurrence rates between total and subtotal resection of these tumors are similar, at about 10%⁴⁴; however, the recurrence/progression timeline for subtotal resection vs total resection is reported at an average of 2.9 and 6.2 years, respectively.⁴⁴ Additionally, there is evidence that a higher proportion of solid tissue within the tumor predicts higher recurrence risk and worse histological features.⁴³ Rarely, RGNTs can develop satellite lesions and CSF involvement, which can lead to drop metastases; thus, postcontrast series should be evaluated for leptomeningeal involvement.^{42,43} Finally, MRS usually shows elevated choline, reduced N-acetylaspartate, and absent lactate and lipid peaks²; deviations from this pattern should raise suspicion for malignant transformation.

Dysplastic Cerebellar Gangliocytomas

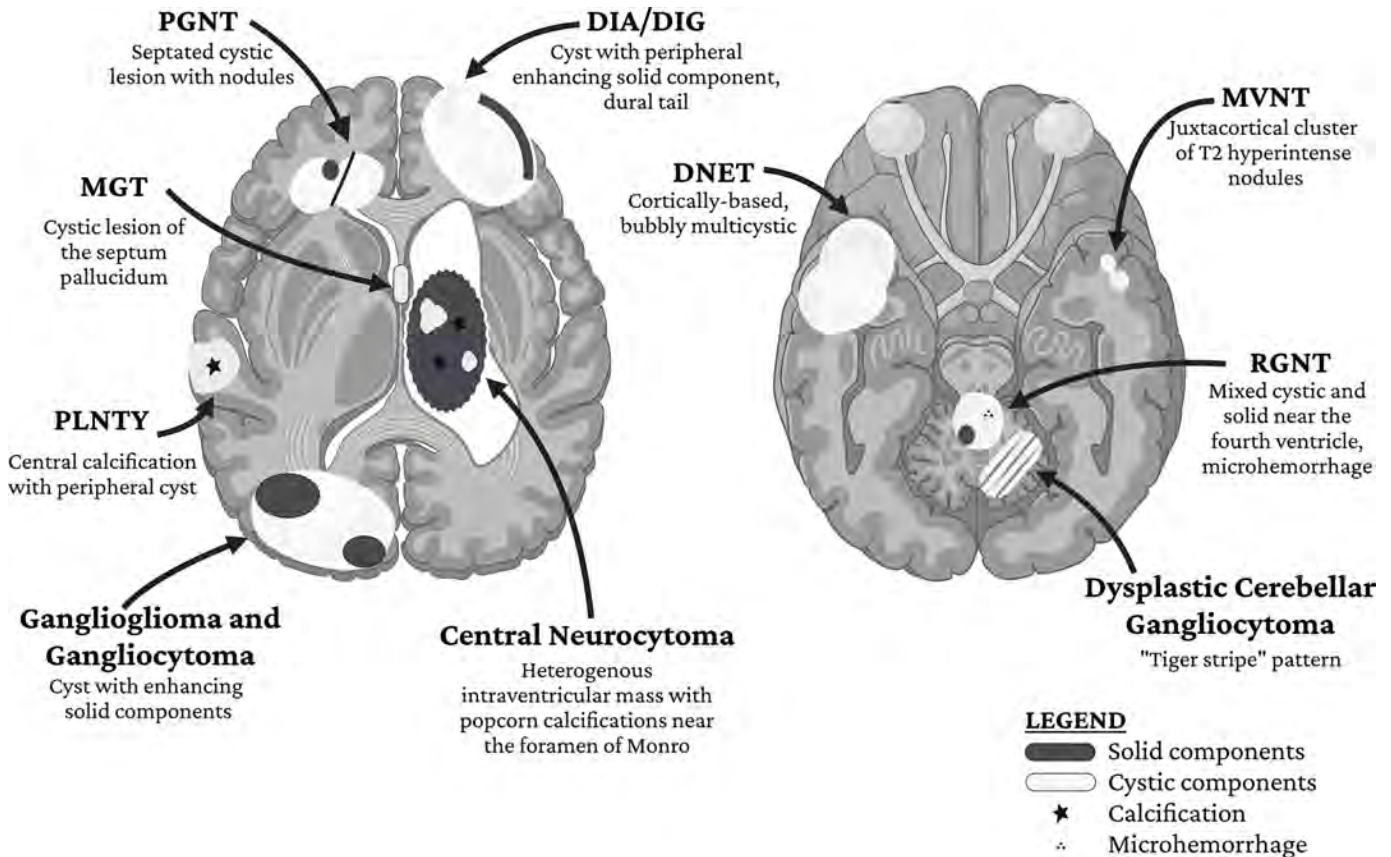
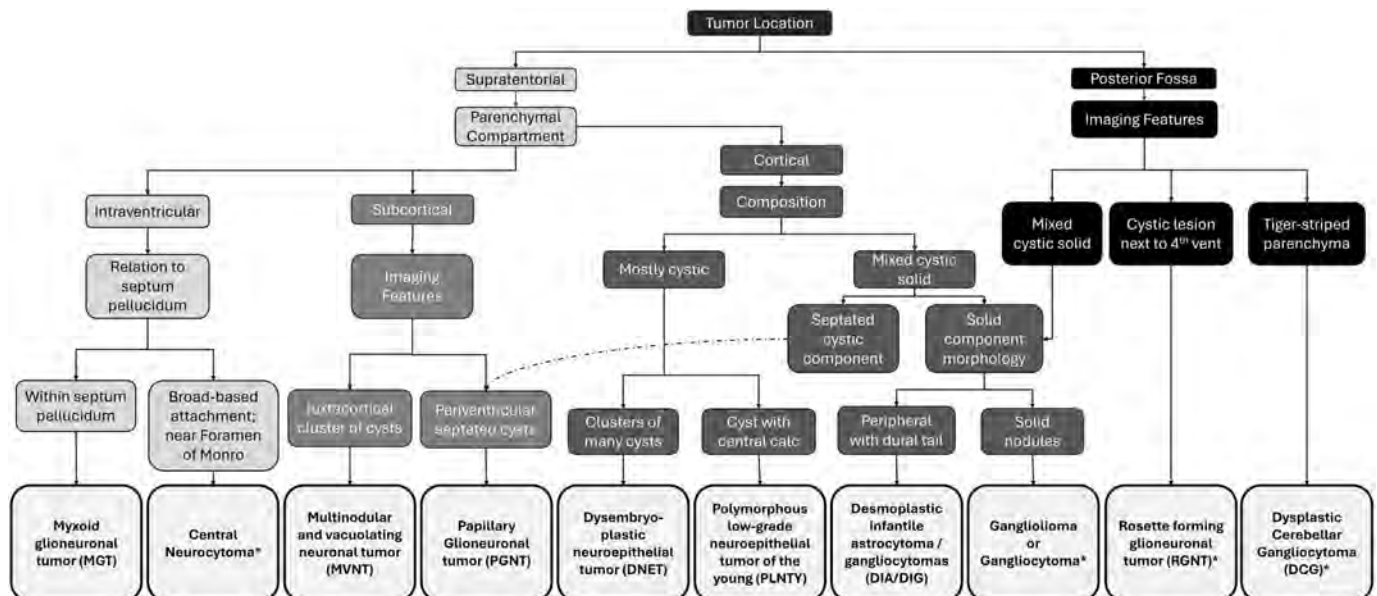
Also known as Lhermitte-Duclos disease, dysplastic cerebellar gangliocytomas are found primarily in patients with Cowden syndrome.⁴⁹ Arising in the cerebellum, they are benign, with no reported malignant transformation.⁴⁹ Surgical resection provides definitive treatment in acute cases; however, these tumors often do not require intervention.⁵⁰

MRI demonstrates a unilateral cerebellar parenchymal mass with T2 hyperintensity, no enhancement, and variable diffusion restriction. Widened cerebellar folia create the pathognomonic “tiger-stripe” pattern,^{49,50} which is primarily seen in adults.⁵¹ SWI and contrast-enhanced sequences can demonstrate prominent vascular structures within the folia (Figure S2),⁵² while MRS may reveal reduced choline and an inverted lactate peak.^{52,53} The differential is limited, but subacute infarct or cerebritis can be considered in patients with acute deterioration.

Discussion

Differentiating between glioneuronal tumors is challenging, owing to similarities in demographics, clinical presentation, and imaging appearance, as well as their overall low incidence, resulting in limited reports in the literature. In this paper, we propose a diagnostic approach to these tumors, present representative cases, and describe prognostic imaging features based on our review of the current literature.

Owing to their shared cellular origin, most glioneuronal tumors have a mixed cystic-solid composition (Figure 9).

Figure 9. Summary of classic glioneuronal tumor imaging findings.**Figure 10.** Approach to glioneuronal tumor differentiation. Glioneuronal tumors can overlap considerably in their imaging presentation. This flowchart shows the most prevalent presentations. Note that gangliogliomas are particularly variable in their imaging appearance and should be considered in the setting of an atypical cortical-based tumor. * indicates potential role for MR spectroscopy or MR perfusion.

Location and parenchymal compartment are most useful for initially narrowing the differential, followed by the morphology and arrangement of the specific tumor components (eg, peripheral vs septated cysts, calcification vs no calcification) (Figure 10). MR perfusion and spectroscopy may be helpful in some cases. Ultimately, many glioneuronal tumors require histopathology for definitive diagnosis, but some patients may choose to forgo biopsy, relying instead entirely on image-based diagnosis.

Radiologists have a great impact on the management of glioneuronal tumors, as the primary treatment consists of excision with continued surveillance. Preoperative reports should include features that could alter operative approach and risk, such as involvement of midline structures and their relationship to major vessels. Furthermore, specific imaging features are associated with more aggressive histopathology in certain glioneuronal tumors; these can inform care management discussions. While the evidence is mixed for several glioneuronal tumors on the relationship between resection extent and long-term outcomes, including seizure control, the presence of metastatic foci or recurrent tumor on imaging affects the decision whether to pursue adjuvant systemic therapy.

In conclusion, while differentiating between glioneuronal tumors is challenging, narrowing the differential diagnosis is possible with careful assessment of tumor location and relational morphology. Radiologists can provide useful evidence for clinical management, including surgical approach, operative risk, and the need for adjuvant treatment.

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Artificial Intelligence and Radiomics for Predicting Chemotherapy Response in Colorectal Liver Metastases: A Systematic Review and Meta-Analysis

Luis Lorenzo A. Chan, MD; Adrian Christopher A. Elio, MD

Abstract

Objective and Hypothesis: The emergence of artificial intelligence (AI) and radiomics in oncology has introduced new paradigms in disease characterization, risk stratification, and treatment monitoring. In patients with colorectal liver metastases (CRLM), the ability to noninvasively predict chemotherapy response using advanced imaging biomarkers could significantly influence therapeutic decision-making. This systematic review and meta-analysis evaluates the diagnostic performance of radiomics-based AI models in predicting treatment response in CRLM.

Methods: A systematic review of PubMed and Google Scholar was conducted for studies from January 2015 to April 2025 using radiomics-based AI models for CRLM chemotherapy response prediction. Eligible studies reported model performance against a reference standard (Response Evaluation Criteria in Solid Tumors version 1.1, histopathology, or survival). Meta-analysis using Review Manager 5.4 generated pooled area under the curve (AUC), sensitivity, and specificity. Subgroup analyses were performed by treatment regimen, AI model type, validation strategy, and outcome definition.

Results: 21 studies comprising 2769 patients were included. The pooled AUC for all studies was 0.86 (95% CI 0.79-0.94), with a sensitivity of 0.83 and specificity of 0.65. Chemotherapy-only cohorts showed AUC 0.85, sensitivity 0.78, and specificity 0.66, while cohorts receiving chemotherapy plus targeted therapy showed AUC 0.88, sensitivity 0.96, and specificity 0.63.

Conclusion: Radiomics-based AI models achieve robust predictive accuracy in chemotherapy response stratification for CRLM, particularly when biologic agents are used. These findings support AI integration as a noninvasive, scalable adjunct to treatment planning in precision oncology.

Keywords: artificial intelligence, radiomics, colorectal liver metastases, chemotherapy response, precision oncology

Introduction

Colorectal cancer (CRC) remains one of the most prevalent malignancies worldwide and a leading cause of cancer-related mortality.¹ A significant proportion of patients with CRC, which is approximately 25-50%, will develop liver

metastases either at the time of diagnosis or during the course of disease progression.^{1,2} These colorectal liver metastases (CRLM) represent a critical therapeutic challenge, as their presence significantly impacts prognosis, with 5-year survival rates remaining below 15% without intervention.³ The mainstay of

CRLM management includes systemic chemotherapy, targeted therapies, and surgical resection, with the latter being the only potentially curative option.² However, not all patients respond equally to systemic treatments, and early identification of responders versus nonresponders is essential for tailoring therapeutic

Affiliation: Institute of Radiology, St. Luke's Medical Center, Quezon City, Philippines.

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plans, minimizing toxicity, and maximizing survival benefit.⁴

Traditional methods of evaluating treatment response rely heavily on morphological criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.⁵ While RECIST provides standardized guidelines for assessing tumor shrinkage, it is inherently limited by its dependence on linear size measurements and its inability to capture subtle biological or functional changes within tumors.^{6,7} Consequently, there has been growing interest in more sophisticated tools that can quantify intratumoral heterogeneity and predict treatment outcomes beyond size-based assessments.

Radiomics refers to the high-throughput extraction of quantitative features from medical imaging data. These features, encompassing tumor shape, intensity, texture, and wavelet transformations, reflect underlying pathophysiological processes and can provide insights into tumor behavior, aggressiveness, and response to therapy.⁸⁻¹¹ When paired with artificial intelligence (AI) techniques such as machine learning (ML) and deep learning (DL), radiomics can be transformed into predictive models that recognize complex patterns and make data-driven predictions. ML algorithms can be trained on large, labeled datasets to distinguish between responders and nonresponders based on imaging-derived features, while DL approaches such as convolutional neural networks can autonomously learn hierarchical representations directly from raw imaging data.¹²

The application of AI and radiomics in CRLM has gained traction in recent years, driven by advances in computational power, access to large imaging datasets, and improvements in imaging standardization. Numerous studies have explored the use of radiomics-based signatures derived from CT, MRI, or PET/CT to predict histopathologic response or RECIST-based radiologic response in patients undergoing

chemotherapy. These studies vary widely in terms of patient population, treatment regimens, feature extraction methods, and validation approaches, necessitating a systematic synthesis to determine overall diagnostic performance.¹³⁻³³

This meta-analysis aims to address this gap by pooling data from studies using radiomics-based AI models to predict chemotherapy response in CRLM. In addition to evaluating overall accuracy, we assess model performance in key subgroups, particularly those receiving chemotherapy alone versus those receiving combination therapy with biologics such as bevacizumab or cetuximab.

Methods

Search Strategy and Data Extraction

A systematic search of the literature was conducted using PubMed and Google Scholar for relevant articles published between January 1, 2015, and April 1, 2025. The search utilized combinations of the following keywords: “artificial intelligence,” “radiomics,” “colorectal liver metastases,” “chemotherapy response,” “machine learning,” and “deep learning.” Only peer-reviewed studies published in English were included. 2 reviewers independently screened titles and abstracts, followed by full-text review to identify studies meeting the eligibility criteria. Data were extracted using a standardized form that included information on study design, patient characteristics, imaging modality, AI model type, radiomics feature sets, comparator, reference standard, and diagnostic performance metrics [area under the curve (AUC), sensitivity, and specificity].

Study Selection

Inclusion criteria required studies to involve patients with CRLM undergoing chemotherapy, utilize radiomics-based AI models as index tests, and compare results to a reference standard such as RECIST 1.1 or histopathology, with provided

extractable diagnostic accuracy metrics. Both retrospective and prospective studies were eligible. Exclusion criteria included case reports, reviews, conference abstracts, nonpeer-reviewed articles, and studies with incomplete data or high methodological bias.

Objectives

The primary objective was to evaluate the pooled diagnostic performance of radiomics-based AI models in predicting chemotherapy response in CRLM, specifically measuring AUC, sensitivity, and specificity. Secondary objectives were to compare performance by treatment regimen (chemotherapy alone vs chemotherapy with targeted therapy) and evaluate the impact of model heterogeneity (AI method), validation rigor (internal vs external), and outcome definition (RECIST vs pathology vs survival).

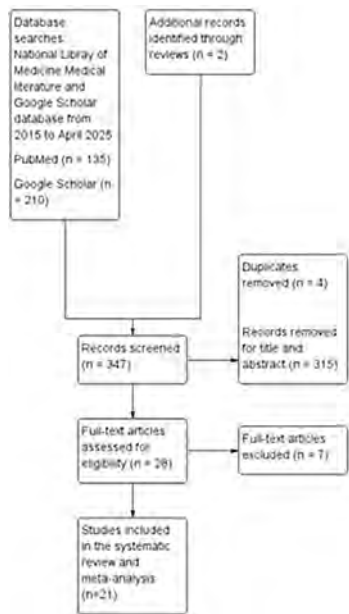
Assessment of Publication Quality

Methodological quality was evaluated using the QUADAS-2 tool. 2 reviewers assessed risk of bias across 4 domains: patient selection, index test, reference standard, and flow/timing. All included studies were rated as low risk of bias, indicating high methodological rigor. Validation rigor was additionally classified according to TRIPOD-AI³⁴ guidance as (1) internal validation only, (2) external validation using independent cohorts, or (3) temporal quasi-external validation.

Statistical Analysis

Meta-analysis was performed using Review Manager version 5.4. Pooled estimates for sensitivity, specificity, and AUC were calculated using random-effects models. Summary receiver operating characteristic curves were generated to visualize model performance. Subgroup analyses were performed for treatment regimen, AI method, validation rigor, and outcome definition subgroups. Heterogeneity was assessed using the chi-square statistic and interpreted alongside clinical variability.

Figure 1. Study flow diagram (based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses).



Ethical Considerations

This study was reviewed and approved by the St. Luke's Medical Center Institutional Ethics Review Committee. It was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013) and followed the International Council for Harmonisation–Good Clinical Practice guidelines.

As a systematic review and meta-analysis of published studies, no new patient data were collected or accessed. All extracted data were anonymized and publicly available, with data handling compliant with the Data Privacy Act of 2012.

Results

There are 21 studies included in this systematic review and meta-analysis. These were published between 2020 and 2025. Overall, there are 2769 patients included in this study.¹³⁻³³ All studies used radiomics-based or DL-based AI models to predict treatment response.

The literature search resulted in 347 total citations, with 135 from PubMed,

210 from Google Scholar, and 2 from further reviews (Figure 1). After removing duplicates and screening through the titles and abstracts, we screened 28 unique citations. During the full-text assessment phase, 7 articles were excluded as they did not meet the inclusion criteria. 21 articles were included in the final analysis.

Studies were grouped according to treatment regimen (chemotherapy alone vs chemotherapy plus targeted therapy), AI model type (radiomics-based ML, DL, or delta-radiomics), validation design (internal vs external), and reference standard (RECIST 1.1, histopathology, or survival-based response). A detailed summary of included studies is provided in Table 1.

Considerable methodological heterogeneity was observed across studies. 14 studies relied exclusively on internal validation strategies, including cross-validation and bootstrapping, while 5 studies used a form of temporal or internal-external validation. Only 2 studies employed independent external validation cohorts, and none achieved full TRIPOD-AI level 2b or 3 validation standards. The definition of treatment response also varied. 17 studies used RECIST 1.1 as the reference standard, 3 studies used histopathologic tumor regression grade, and 1 study defined response based on an overall survival threshold.

The pooled area AUC for all studies combined was 0.86 (95% CI 0.79 to 0.94) (Figures 2, 3), indicating excellent overall diagnostic performance. Among the 21 studies, 15 provided sufficient data for pooled sensitivity and specificity analysis. Sensitivity was 0.83 (95% CI 0.81 to 0.86) (Figure 4), demonstrating the model's strength in correctly identifying responders. Specificity was 0.65 (95% CI 0.62 to 0.68) (Figure 5), suggesting moderate capability in correctly identifying nonresponders.

Treatment Regimen Subgroup

Models applied to chemotherapy-only cohorts ($n = 14$) yielded a pooled AUC of 0.85 (95% CI 0.76-0.95) (Figure 6), with a sensitivity of 0.78 (95% CI 0.74-0.81)

(Figure 7) and specificity of 0.66 (95% CI 0.62-0.70) (Figure 8). Studies including targeted agents ($n = 7$) demonstrated the highest pooled diagnostic performance, with an AUC of 0.88 (95% CI 0.77-1.00) (Figure 9), markedly higher sensitivity at 0.96 (95% CI 0.93-0.98) (Figure 10), and comparable specificity of 0.63 (95% CI 0.57-0.69) (Figure 11).

AI Model Type Subgroup

Radiomics-based ML models ($n = 12$) produced a pooled AUC of 0.85 (95% CI 0.74-0.97), with a sensitivity of 0.74 (95% CI 0.68-0.79) and specificity of 0.74 (95% CI 0.68-0.80). DL approaches ($n = 6$) showed similar overall discrimination (AUC 0.84; 95% CI 0.71-0.97) but with higher sensitivity (0.88; 95% CI 0.85-0.90) and lower specificity (0.59; 95% CI 0.55-0.64). Delta-radiomics studies ($n = 3$) reported the strongest pooled AUC (0.91; 95% CI 0.77-1.05), although based on substantially fewer datasets.

Validation Strategy Subgroup

Internally validated models ($n = 15$) achieved a pooled AUC of 0.83 (95% CI 0.73-0.93), with a sensitivity of 0.86 (95% CI 0.83-0.88) and specificity of 0.67 (95% CI 0.63-0.71). Temporal or internal-external validation designs ($n = 4$) yielded the highest pooled AUC (0.92; 95% CI 0.80-1.04), with a sensitivity of 0.74 (95% CI 0.67-0.80) and specificity of 0.59 (95% CI 0.52-0.65). Independent external validation ($n = 2$) showed lower pooled AUC (0.82; 95% CI 0.55-1.09) but maintained a sensitivity of 0.86 (95% CI 0.73-0.94) and higher specificity (0.77; 95% CI 0.64-0.88).

Outcome Definition Subgroup

RECIST-based studies ($n = 17$) demonstrated a pooled AUC of 0.86 (95% CI 0.78-0.95), with a sensitivity of 0.77 (95% CI 0.74-0.81) and specificity of 0.67 (95% CI 0.63-0.71). Histopathology-based response studies ($n = 3$) produced a pooled AUC of 0.88 (95% CI 0.72-1.04) and very high sensitivity (0.98; 95% CI 0.95-0.99) but lower specificity (0.59; 95% CI 0.52-0.65). One study using a survival-based definition reported an AUC of 0.80 (95% CI 0.32-1.28).

Table 1. AI Analysis of the Response to Standard Chemotherapy Alone for Patients with Colorectal Metastasis

STUDY	YEAR	PATIENTS	DESIGN	CHEMOTHERAPY REGIMEN	AI (ML/DL)	SIGNATURE	IMAGE MODALITY	RADIOMICS FEATURES	COMPARATOR	REFERENCE STANDARD
<i>Chemotherapy only</i>										
Giannini	2022	57	Retrospective	FOLFOX	ML	Delta-radiomics	CT	CT scans at differential time points, 14 lesion shape-based 18 images intensity-based statistics, 75 images gray-level-based statistics	RECIST 1.1	RECIST 1.1
Wei	2020	192	Retrospective	Oxaliplatin or irinotecan	DL	Fusion radiomics	MDCT	CT scans at baseline; 583 radiomics features (traditional radiomics)	RECIST 1.1	RECIST 1.1
Nakanishi	2021	42	Retrospective	Oxaliplatin	ML	Radiomics	CT	CT scans at baseline; 1038 radiomics features	RECIST 1.1	RECIST 1.1
Defeudis	2022	92	Retrospective	FOLFOX or FOLFIRI	ML	Radiomics	CT	CT scans at baseline; 75 radiomics features	RECIST 1.1	RECIST 1.1
Chen	2024	85	Retrospective	XELOX, FOLFOX, FOLFIRI	ML	Radiomics	CT and MRI	MRI at baseline; 1786 radiomics features	RECIST 1.1	RECIST 1.1
Giannini	2020	95	Retrospective	FOLFOX or FOLFIRI	ML	Radiomics	CT	CT scans at baseline; 22 radiomics features	RECIST 1.1	RECIST 1.1
Karagkounis	2024	85	Retrospective	FOLFOX or FOLFIRI	ML	Radiomics	CT	CT scans at baseline; 21 radiomics features (19 texture features, contrast, and average gradient sum)	RECIST 1.1 and CT morphologic criteria	Histopathologic result
Rabe	2022	29	Retrospective	FOLFOX, FOLFIRI, FOLFOXIRI, CAPE-OX, CAPE-IRI, or capecitabine	ML	Radiomics	CT	CT scans at baseline; 175 radiomics features	RECIST 1.1	RECIST 1.1

Table 1. continued

STUDY	YEAR	PATIENTS	DESIGN	CHEMOTHERAPY REGIMEN	AI (ML/DL)	SIGNATURE	IMAGE MODALITY	RADIOMICS FEATURES	COMPARATOR	REFERENCE STANDARD
Su	2022	100	Retrospective	XELOX, FOLFOX, FOLFIRI	ML	Radiomics	MRI	MRI at baseline; 1688 radiomics features; used 10 single-classifier radiomics models and IVIM parameter images	RECIST 1.1	RECIST 1.1
Davis	2024	95	Prospective	5-FU with oxaliplatin and/or irinotecan	DL	Radiomics	CT	CT scans at baseline; used 2 DIM (ABMIL and MIL)	RECIST 1.1	RECIST 1.1
Gennaro	2025	84	Retrospective	Systemic chemotherapy	DL	Delta radiomics	CT	CT scans at baseline; 62 radiomics features	RECIST 1.1	RECIST 1.1
Piliposyan	2025	355	Retrospective	Systemic chemotherapy	DL	Radiomics + CNN	CT	CT scans at baseline; 107 radiomics features	RECIST 1.1	RECIST 1.1
Qi	2023	116	Retrospective	Irinotecan-based chemotherapy	ML	Radiomics	CT	CT scans at baseline; first-order, shape, and texture features from multiscale voxel sampling ($1 \times 1 \times 1$ to $5 \times 5 \times 5$ mm ³)	RECIST 1.1	RECIST 1.1
Ma	2021	102	Retrospective	FOLFOX	ML	Delta-radiomics	MRI	MRI at baseline; 396 radiomics features	RECIST 1.1	RECIST 1.1
<i>Chemotherapy with targeted therapy</i>										
Yoon	2024	17	Prospective	FOLFIRI, folinic acid fluorouracil, or irinotecan with bevacizumab or cetuximab	ML	Radiomics	CT and MRI	MRI baseline; 107 radiomics features	RECIST 1.1	RECIST 1.1
Zhu	2021	180	Mixed	FOLFOX, FOLFIRI, XELOX with bevacizumab or anti-EGFR antibody	DL	Radiomics	MRI	Used 3 DL models	RECIST 1.1 and histopathology	RECIST 1.1 and histopathology
Dercle	2020	129	Retrospective	FOLFIRI + cetuximab	ML	Radiomics	CT	CT scans at differential time	Overall survival > 17.7 months	Overall survival > 17.7 months

Table 1. continued

STUDY	YEAR	PATIENTS	DESIGN	CHEMOTHERAPY REGIMEN	AI (ML/DL)	SIGNATURE	IMAGE MODALITY	RADIOMICS FEATURES	COMPARATOR	REFERENCE STANDARD
								points, 1749 radiomics features, 8 rim specific features		
Maaref	2020	202	Retrospec tive	FOLFOX or FOLFIRI with bevacizumab	ML+ DL (DCNN)	Radiomics + DCNN	CT	CT scans at baseline; 14 textural features	Histopathology	Histopathology
Miyamoto	2024	150	Retrospec tive	FOLFOX or irinotecan with bevacizumab or anti-EGFR antibody	ML	Radiomics	CT	CT scans at baseline; 107 radiomics features	RECIST 1.1	RECIST 1.1
Zhou	2023	307	Retrospec tive	FOLFOX with bevacizumab	DL	Radiomics	PET/CT	PET/CT baseline; multimodal fusion	RECIST 1.1	RECIST 1.1
Qu	2023	76	Retrospec tive	FOLFOX/XELOX/ FOLFIRI with bevacizumab	ML	Radiomics	CT	CT scan baseline; used 5 models	RECIST 1.1	RECIST 1.1

Data are grouped according to chemotherapy-only and chemotherapy-with-targeted-therapy subgroups.
AI, artificial intelligence; CNN, convolutional neural network; DL, deep learning; ML, machine learning; RECIST, Response Evaluation Criteria in Solid Tumors.

At the study level, several methodological patterns recurred across higher-performing models. Approaches that incorporated temporal or multiphasic information such as delta-radiomics¹⁶ and dynamic radiomics,¹⁸ longitudinal MRI or multiparametric imaging,^{13,20,23,24} and DL-based feature extraction^{21,24-28} frequently achieved AUC values above 0.80-0.90. Models that incorporated peritumoral or microenvironmental features,^{17,19} or fused imaging with clinical and biologic data,²⁸⁻³² also tended to yield stronger performance.

Discussion

The findings of this systematic review and meta-analysis provide evidence that AI and radiomics-based models can play a significant role in predicting chemotherapy response in patients with CRLM. The pooled AUC of 0.86 for all studies supports the clinical utility of these tools in stratifying patients based

on their likelihood of responding to systemic therapy. Our findings are reinforced by multiple innovative radiomics strategies across included studies. Delta-radiomics¹⁶ and dynamic feature analysis¹⁸ offered superior early response prediction, aligning with the need for early identification of nonresponders to avoid unnecessary treatment and toxicity.³⁵ Su²⁰ and Yoon²³ demonstrated the power of serial and longitudinal MRI, highlighting the importance of capturing temporal changes in tumor characteristics.³⁶ Ensemble learning²⁰ and attention-based DL²⁵ showed performance advantages over traditional radiomics, supporting the impression that more sophisticated AI techniques can better extract and learn from complex imaging data.³⁶ Integration of tumor microenvironment,¹⁷ peritumoral features,²¹ and biologic markers²⁸ further improved prediction, underscoring the multifactorial nature of treatment response and the benefit of incorporating diverse data sources.

The particularly high sensitivity observed in the chemotherapy with targeted therapy subgroup is notable. This group included studies such as Zhou et al²⁸, who developed a multimodal model integrating PET/CT, clinical, and histopathological features (DERBY+), which achieved an AUC of 0.83. Similarly, Dercle et al demonstrated an AUC of 0.80 using a CT-based radiomics response signature in patients treated with anti-EGFR therapy.²⁹ Yoon et al further validated the potential of MRI radiomics, achieving an AUC of 0.857 in a longitudinal DL model predicting early response to biologic therapy.²³ Other key contributors to this subgroup include Zhu et al,²⁴ Maaref et al,³⁰ Miyamoto et al,²² and Qu et al,¹⁸ all of which underscore the value of integrating temporal and multiparametric imaging in biologic therapy response prediction. This finding may reflect the enhanced biological impact of agents like bevacizumab and cetuximab, which influence tumor vasculature and molecular expression profiles. These

Figure 2. Pooled under the curve (AUC) of radiomics-based artificial intelligence (AI) models predicting chemotherapy response in colorectal liver metastases. The pooled random-effects estimate (diamond) demonstrates excellent overall discrimination (AUC = 0.86, 95% CI 0.79-0.94). Values to the right of zero favor AI-based prediction over conventional assessment methods.

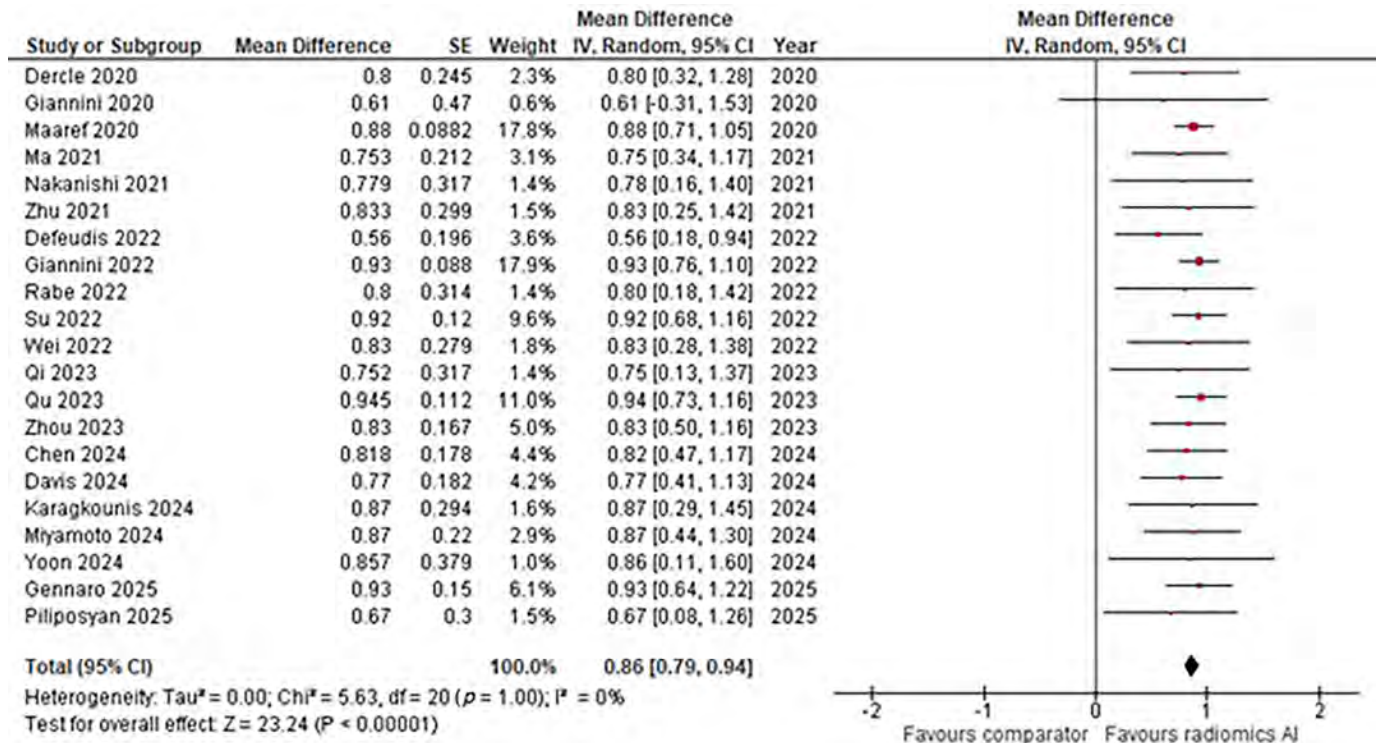
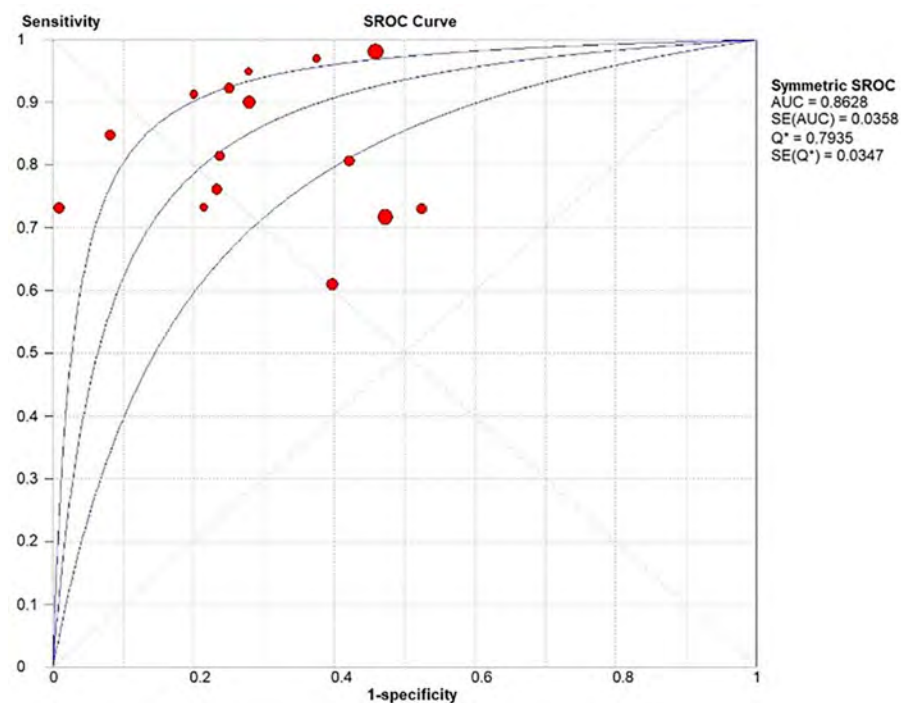


Figure 3. Summary receiver operating characteristic (SROC) curve demonstrating the diagnostic performance of radiomics-based artificial intelligence models versus standard comparators across all included studies. The pooled area under the curve (AUC) was 0.87, indicating good overall discriminative ability.



subtle changes are not always readily apparent through size-based RECIST criteria but may be detected through quantitative imaging biomarkers. AI models, especially those utilizing DL, are well-suited to capture these nuances due to their ability to learn hierarchical imaging features.³⁷

In contrast, the chemotherapy-only subgroup showed slightly lower sensitivity and similar specificity. However, several high-performing studies still emerged within this group. For instance, Chen et al achieved an AUC of 0.818 by incorporating hepatobiliary phase MRI radiomics,¹³ and Karagkounis et al reported an AUC of 0.87 with 100% sensitivity using post-treatment CT features from tumoral and peritumoral regions.¹⁷ These findings illustrate that even without adjunct biologic therapy, advanced radiomics frameworks can deliver high diagnostic accuracy. Additional models such as those by Su et al,²⁰ Rabe et al,¹⁹ and Giannini et al^{15,16} further support the feasibility of using imaging-based AI approaches,

Figure 4. Pooled sensitivity of radiomics-based artificial intelligence models. Sensitivity was 0.83 (95% CI 0.81-0.86). Heterogeneity ($I^2 = 86.8\%$) suggests performance differences across model types and patient cohorts.

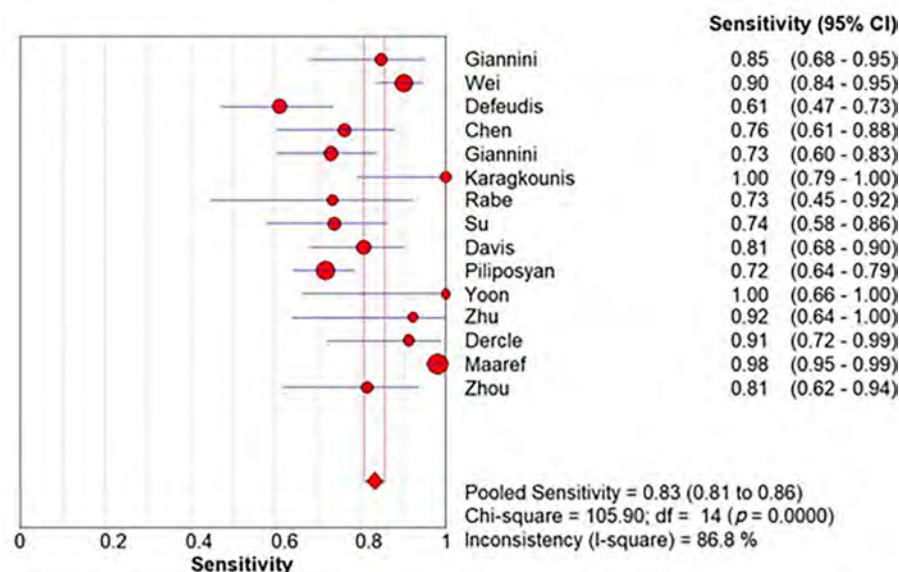
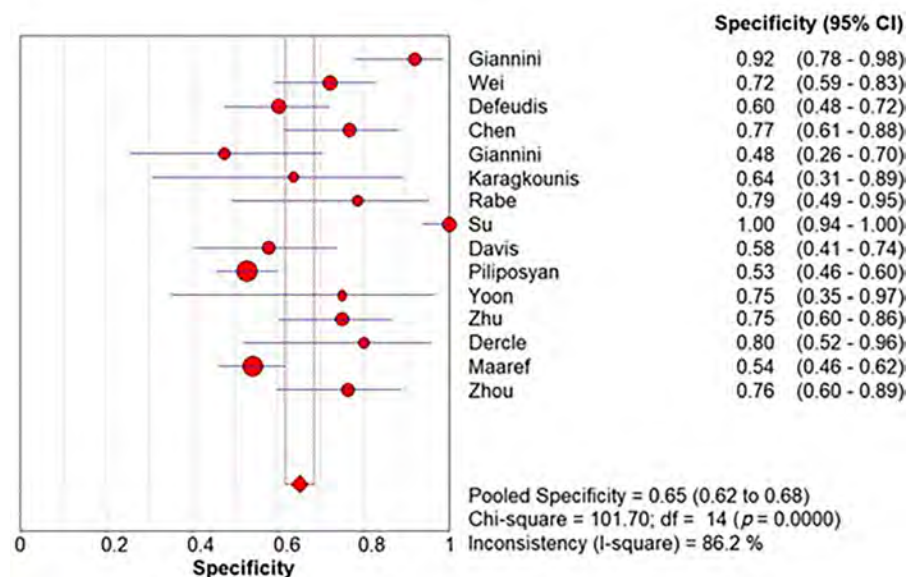


Figure 5. Pooled specificity of radiomics-based artificial intelligence models. The overall pooled specificity was 0.65 (95% CI 0.62-0.68), with substantial heterogeneity ($I^2 = 86.2\%$).



particularly those leveraging longitudinal analysis, lesion-level heterogeneity, and texture-specific features, for predicting chemotherapy response with strong clinical relevance.

The differential performance between chemotherapy-only and biologic-inclusive cohorts suggests that radiomics may be particularly sensitive to biologically targeted treatment effects. This supports

the notion that AI-derived imaging biomarkers can serve as noninvasive surrogates for molecular or histologic assessment.³⁸ The high AUCs seen in biologic-treated cohorts²⁸⁻³⁰ also validate AI's role in predicting response to agents with complex mechanisms beyond cytotoxicity.³⁹

Radiomics-based ML and DL models demonstrated comparable overall

discrimination, although DL models showed higher pooled sensitivity and lower specificity, indicating a tendency to favor responder classification at the expense of misclassifying nonresponders. Delta-radiomics models yielded the highest pooled AUC despite fewer included studies, maintaining a more balanced sensitivity-specificity profile. These findings suggest that models leveraging temporal or treatment-induced imaging changes may better reflect true biologic response than those relying solely on baseline tumor features. From a clinical standpoint, highly sensitive models may reduce the risk of prematurely halting effective therapy, whereas models with more balanced accuracy may better prevent continuation of ineffective regimens.

However, the observed performance must be interpreted in the context of nontrivial methodological limitations. A large majority of studies relied on internal validation only, with relatively few employing temporal or internal-external designs and very few using independent external cohorts. The attenuation in AUC observed across validation strata illustrates the risk of optimism bias when models are not tested on independent datasets. This pattern mirrors the broader AI and radiomics literature and emphasizes the need for robust, multicenter external validation and adherence to reporting standards such as TRIPOD-AI.

Outcome definitions also varied, with most studies using RECIST 1.1, some using histopathologic tumor regression, and one using survival-based endpoints. RECIST-based models dominated the pooled estimates but also carried the intrinsic limitations of size-based criteria, which may not fully reflect biologic response, especially in the setting of targeted therapies. Histopathology-based models showed numerically higher AUCs, suggesting that biologically grounded endpoints may yield more meaningful predictive signatures; however, they were fewer in number and often limited to resectable cohorts. Survival-based

Figure 6. Forest plot showing the pooled area under the curve (reported as mean difference) for radiomics-based artificial intelligence models in the chemotherapy-only subgroup. The pooled mean difference was 0.85 (95% CI 0.76-0.95; $I^2 = 0\%$).

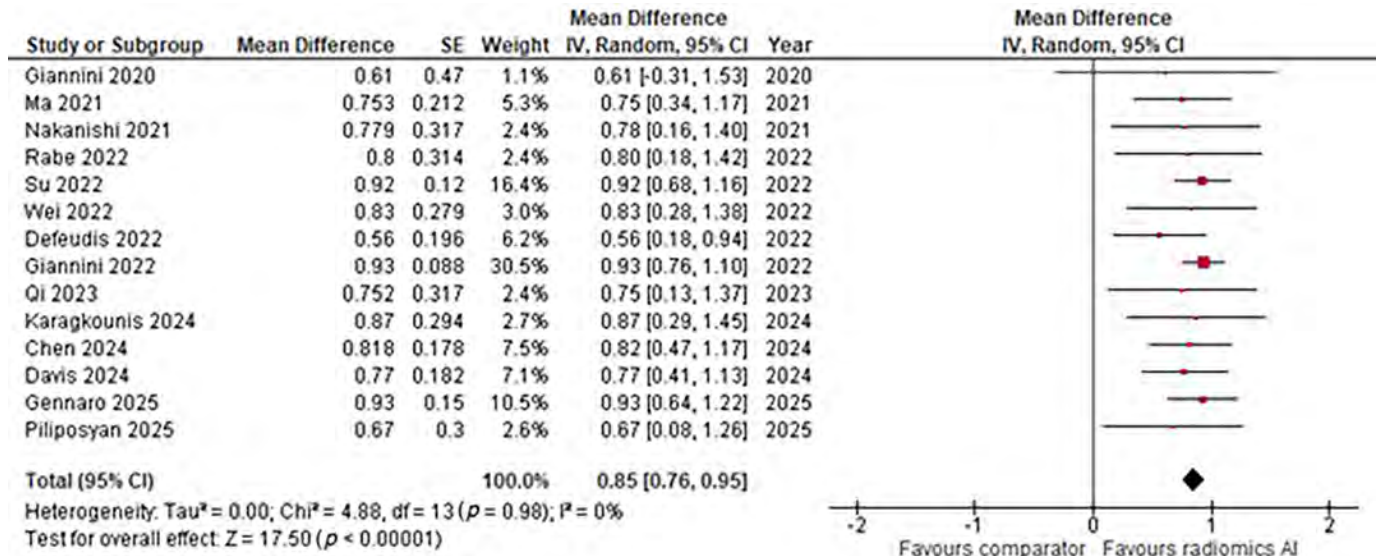
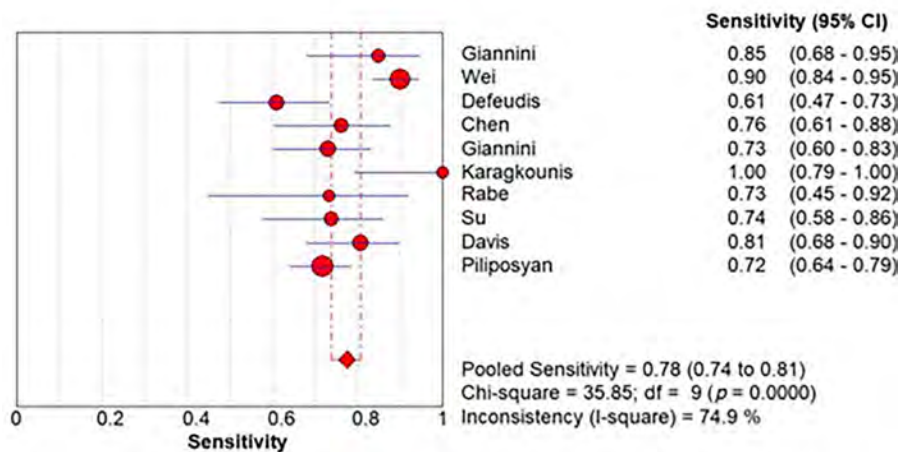


Figure 7. Forest plot showing the pooled sensitivity of radiomics-based artificial intelligence models in the chemotherapy-only subgroup. The pooled sensitivity was 0.78 (95% CI 0.74-0.81), with moderate heterogeneity ($I^2 = 74.9\%$).



models are conceptually attractive but more challenging to standardize and were underrepresented in the current literature. Collectively, this heterogeneity in outcome definitions complicates direct comparison between studies. A shift toward histopathologic endpoints, survival metrics, or composite response criteria incorporating functional imaging (eg, DWI, PET-CT) would enable more clinically meaningful prediction models.

While the pooled sensitivity of 0.86 across all studies, and 0.88 within the biologics subgroup, is encouraging, clinical applicability depends not only on

the ability to detect responders but also to accurately identify nonresponders. The observed specificity of approximately 0.65 suggests that a considerable proportion of patients may be misclassified as likely responders despite potentially limited benefit. This could lead to unnecessary exposure to chemotherapy-related toxicities or delay in transitioning to alternative therapies. One contributing factor may be the difficulty in distinguishing stable disease from partial response using imaging alone. These models, though highly sensitive to subtle image-derived changes, may lack access to

molecular or serum biomarkers that could refine response prediction. Therefore, future models must strike a balance between sensitivity and specificity to optimize treatment planning. Integrating genomic data or circulating tumor markers such as CEA, KRAS/NRAS status, or ctDNA levels may improve the discriminatory power of AI models and reduce false-positive rates.^{40,41}

Heterogeneity in imaging protocols, segmentation approaches, feature extraction pipelines, and model architectures further complicates generalizability. Most studies were single-center, used institution-specific imaging parameters, and applied heterogeneous feature engineering and selection strategies. This variability likely contributed to the statistical heterogeneity observed in pooled estimates and limits the immediate transferability of any single model into routine practice. Standardization efforts, such as harmonized acquisition protocols, robust feature harmonization pipelines, and transparent reporting of preprocessing steps, will be critical for translating radiomics models beyond the research setting.

For clinical integration, several practical barriers must be addressed. These include the computational requirements

Figure 8. Forest plot showing the pooled specificity of radiomics-based artificial intelligence models in the chemotherapy-only subgroup. The pooled specificity was 0.66 (95% CI 0.62-0.70), with high heterogeneity ($I^2 = 89.6\%$).

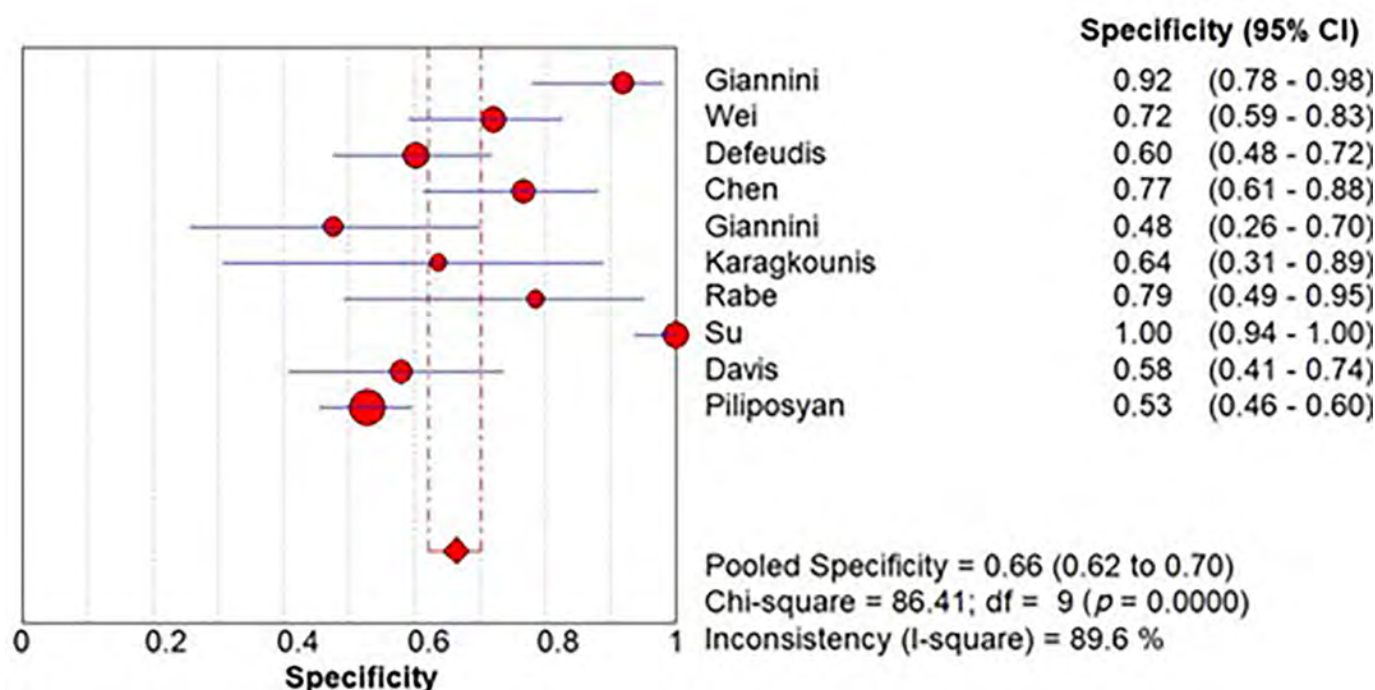
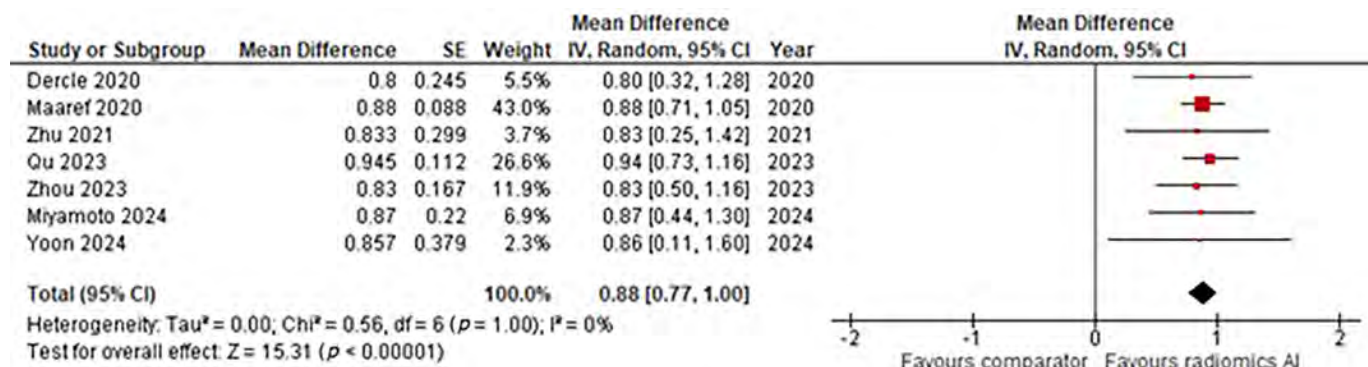


Figure 9. Forest plot showing the pooled area under the curve (expressed as mean difference) for radiomics-based artificial intelligence models in the chemotherapy plus targeted therapy subgroup. The pooled mean difference was 0.88 (95% CI 0.77-1.00).



of DL models, lack of interpretability (“black-box” nature), and the need for radiomics software validation.⁴² Explainable AI techniques, such as SHAP values, Grad-CAM, or attention heatmaps, may help bridge the gap between algorithm output and clinical trust.⁴³ Additionally, institutions with limited access to advanced imaging modalities or GPU infrastructure may face challenges in model deployment. Cost-effectiveness studies and integration into clinical decision support systems are needed to evaluate real-world feasibility.

Despite these limitations, the present analysis confirms that AI and radiomics have strong potential to augment traditional imaging criteria in CRLM, particularly for early response assessment and treatment stratification. The consistent signal of high AUCs across diverse models and settings suggests that quantitative imaging biomarkers can capture relevant aspects of tumor biology and therapeutic effect that are not readily visible to the human eye. For institutions seeking to adopt such tools, the current evidence supports prioritizing

models that incorporate longitudinal or multiphasic imaging, leverage DL or hybrid architectures, and have undergone at least some form of external validation.

Future research should focus on prospective, multicenter trials that incorporate harmonized imaging protocols, standardized radiomics workflows, and predefined validation plans. Studies that link radiomics signatures with molecular and genomic data, as well as with circulating biomarkers, may enable more comprehensive and biologically

Figure 10. Forest plot showing the pooled sensitivity of radiomics-based artificial intelligence models in the chemotherapy plus targeted therapy subgroup. The pooled sensitivity was 0.96 (95% CI 0.93-0.98), with moderate heterogeneity ($I^2 = 69.9\%$).

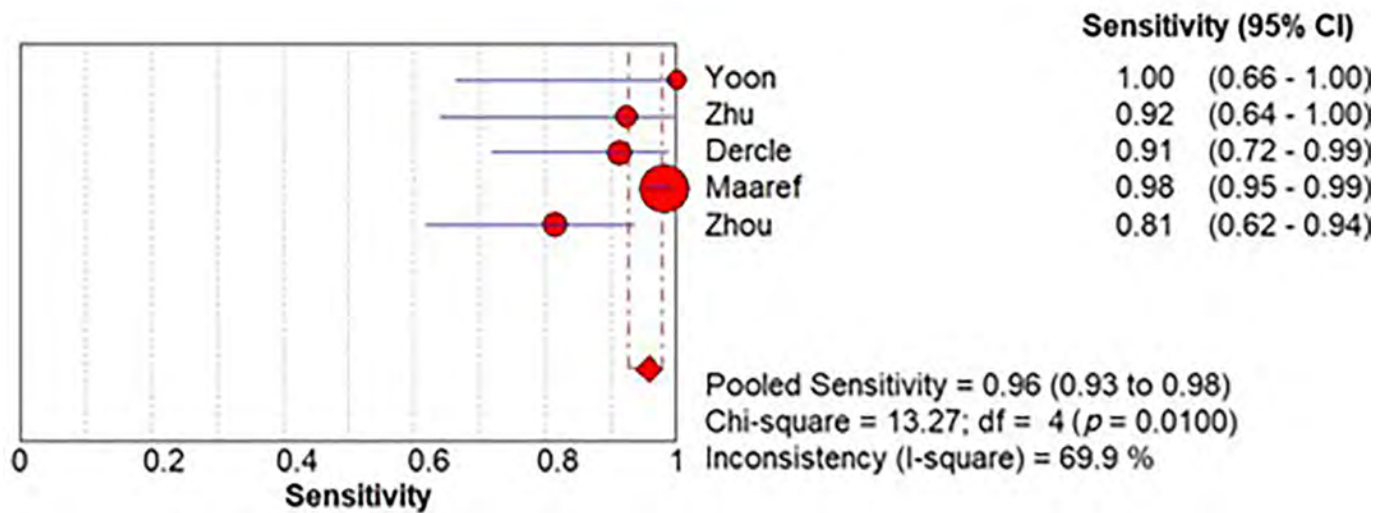
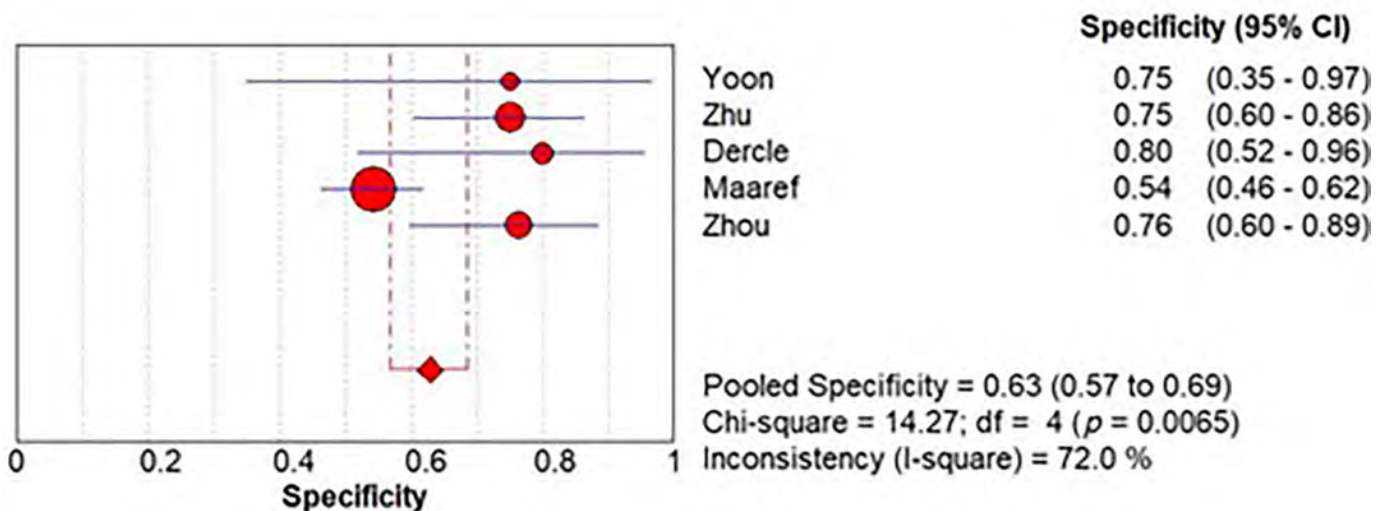


Figure 11. Forest plot showing the pooled specificity of radiomics-based artificial intelligence models in the chemotherapy plus targeted therapy subgroup. The pooled specificity was 0.63 (95% CI 0.57-0.69) with substantial heterogeneity ($I^2 = 72.0\%$).



grounded predictive models. In parallel, development and testing of explainable AI frameworks and formal cost-effectiveness analyses will be necessary to clarify how these tools can be safely and efficiently integrated into real-world oncologic decision-making.

Conclusion

This meta-analysis affirms the promising diagnostic value of

radiomics-based AI models in predicting chemotherapy response in CRLM. These models perform particularly well in patients receiving chemotherapy in combination with targeted therapy, reflecting the value of integrating biologically rich treatment data into AI frameworks. With continued refinement and validation, these technologies have the potential to revolutionize how oncologic imaging is interpreted and applied in treatment decision-making.

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Leveraging Illuccix's® Established Imaging Performance: An Intraindividual Comparison with Gozellix® PET

Leveraging Illuccix's® Established Imaging Performance: An Intraindividual Comparison with Gozellix® PET

Munir Ghesani¹, Harshad R. Kulkarni²

⁶⁸Ga-PSMA-11 (Illuccix®) has demonstrated safety and tolerability in numerous studies.¹ The recently FDA-approved Gozellix® ⁶⁸Ga-PSMA-11 kit offers a longer shelf-life, thereby increasing patient access to ⁶⁸Ga-PSMA-11 PET imaging by increasing the existing prostate-specific membrane antigen (PSMA) PET agent distribution network. Illuccix and Gozellix are both indicated for PET imaging of PSMA-positive lesions in patients with prostate cancer with suspected metastasis and candidates for initial definitive therapy or with suspected recurrence based on elevated serum prostate-specific antigen (PSA) levels.^{2,3}

Gozellix delivers the same clinical performance as Illuccix. Gozellix is formulated to support increased patient access, more scalable preparation, scheduling flexibility, and clinical throughput. This longer shelf-life allows for greater flexibility in patient scheduling and an improved transportation range for distributors who need to

transport the PET radiopharmaceuticals. Local hospitals and radiopharmacies can significantly improve clinical practice through increased patient access, more scalable preparation, scheduling flexibility, and clinical throughput. In addition to generators, Gozellix offers the option to use cyclotron ⁶⁸Ga, enabling greater flexibility and potentially reducing costs for imaging centers transitioning to new generator and cyclotron infrastructure.

Building upon Illuccix's established clinical imaging performance, we present a case series of patients who received both Illuccix and Gozellix PET/CT scans (within 1-6 days and with 55-65-minute uptake times) to demonstrate the similarity of biodistribution and lesion uptake as characterized by the average of SUV_{max} and SUV_{mean} across 3 readers. All patient cases demonstrate lesions detected on both scan types with similar maximum and mean standardized uptake values (SUV_{max} and SUV_{mean}, respectively) and concordance across both Gozellix and Illuccix scans (Table 1).

Table 1. Average of SUV_{max} and SUV_{mean} across 3 readers of intraindividual Illuccix and Gozellix PET/CT scans.

	Illuccix	Gozellix
Case 1: lymph node lesion on the left internal iliac		
SUV _{max}	49.62	47.30
SUV _{mean}	16.35	17.99
Case 2: right rib bone lesion		
SUV _{max}	46.78	57.98
SUV _{mean}	11.58	11.35
Case 3: mesorectal lymph node lesion		
SUV _{max}	15.55	13.93
SUV _{mean}	6.00	6.45

Conclusion

This case series highlights the similar biodistribution and SUV_{max} on Illuccix and Gozellix scans, which both utilize ⁶⁸Ga-PSMA-11 for PET/CT imaging. We demonstrate high image quality and comparable tracer uptake with both Illuccix and Gozellix among a range of tumor scores.

Affiliations: ¹United Theranostics, Princeton, NJ, USA; ²BAMF Health, Grand Rapids, MI, USA

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Case 1

A 67-year-old male was diagnosed with prostate cancer 2 months prior with a Gleason Score of 4+4, PSA 8.9 ng/mL, ISUP Grade 4, and tumor score TX. The patient underwent an Illuccix PET scan and, one day later, underwent a Gozellix PET scan. The patient had an evaluable left internal iliac lymph node lesion detected on both Illuccix and Gozellix PET images, with SUV_{max} of 49.62 and 47.30, respectively, and SUV_{mean} of 16.35 and 17.99, respectively (Figure 1).

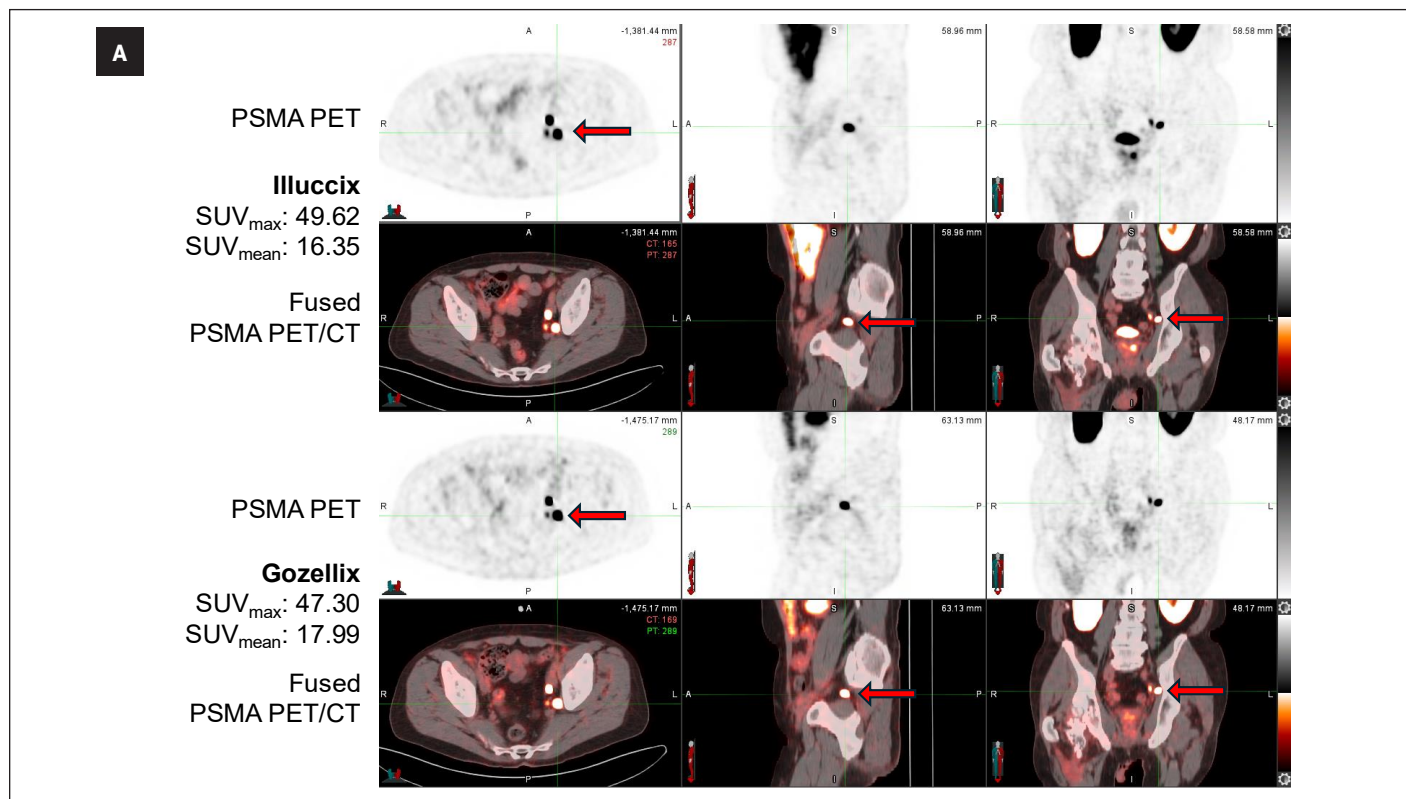
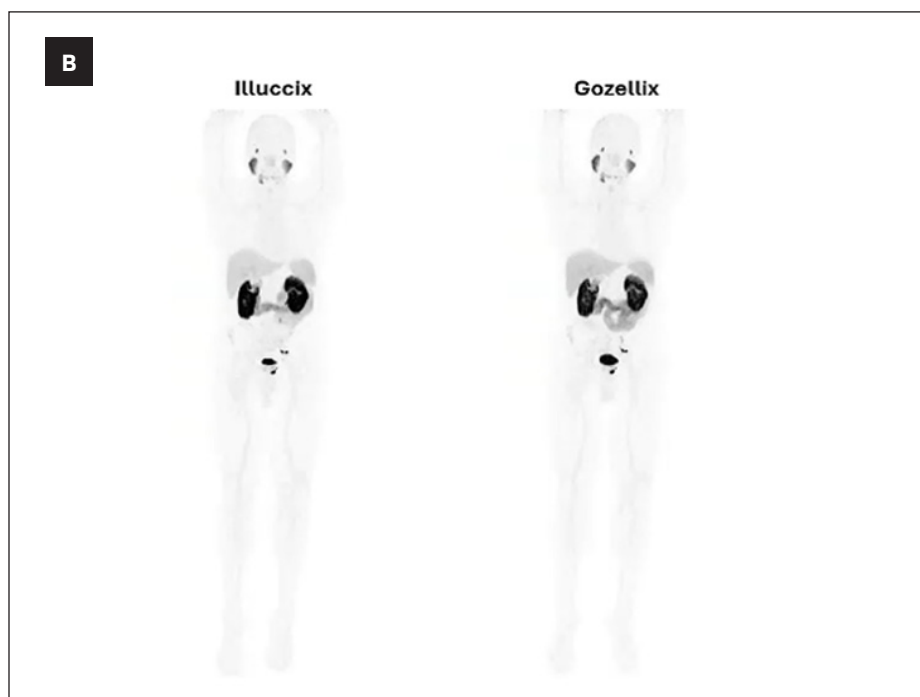


Figure 1. (A) Illuccix (top) and Gozellix (bottom) PSMA PET and fused PSMA PET/CT images of a 67-year-old male. Arrows indicate a lymph node lesion in the left internal iliac region. (B) MIP from Illuccix (left) and Gozellix (right).



Case 2

A 79-year-old male was diagnosed with prostate cancer 1 month prior with a Gleason Score of 4+4, PSA 7.9 ng/mL ISUP Grade 4, and tumor score T2b. The patient underwent an Illuccix PET scan, and, two days later, underwent a Gozellix PET scan. The patient had an evaluable right rib bone lesion detected on both Illuccix and Gozellix PET images, with SUV_{max} of 46.78 and 57.98, respectively, and SUV_{mean} of 11.58 and 11.35, respectively (Figure 2).

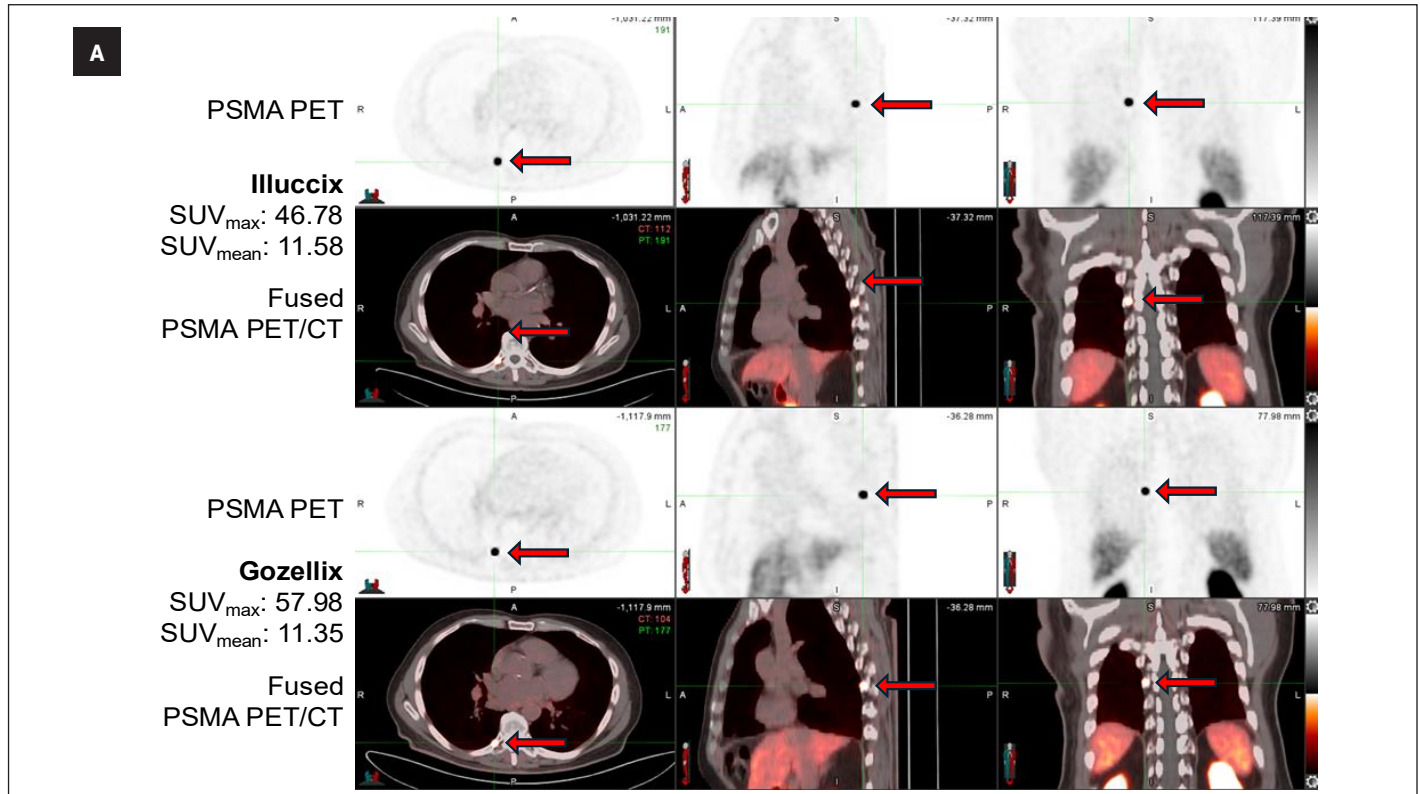
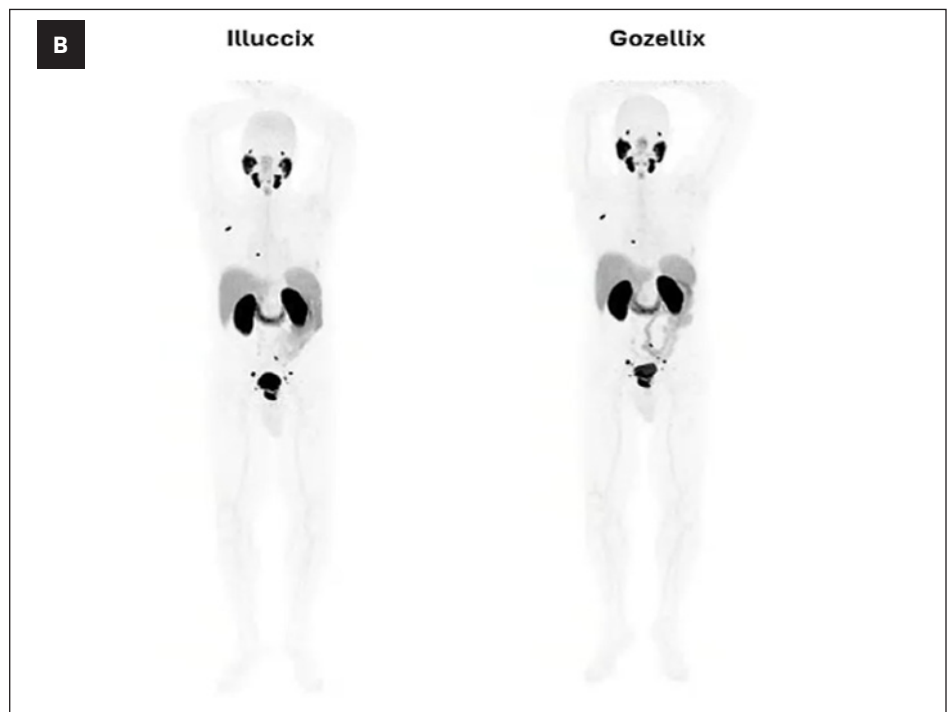


Figure 2. (A) Illuccix (top) and Gozellix (bottom) PSMA PET and fused PSMA PET/CT images of a 79-year-old male. Arrows indicate a right rib bone lesion. (B) MIP with Illuccix (left) and Gozellix (right).



Case 3

A 65-year-old male was diagnosed with prostate cancer 0.5 months prior with a Gleason Score of 9-10, PSA 12.1 ng/mL, ISUP Grade 5, and tumor score T3. The patient underwent an Illuccix PET scan, and, six days later, underwent a Gozellix PET scan. The patient had an evaluable mesorectal lymph node lesion on both Illuccix and Gozellix PET images, with mean SUV_{max} values of 15.55 and 13.93, respectively, and mean SUV_{mean} values of 6.00 and 6.45, respectively (Figure 3).

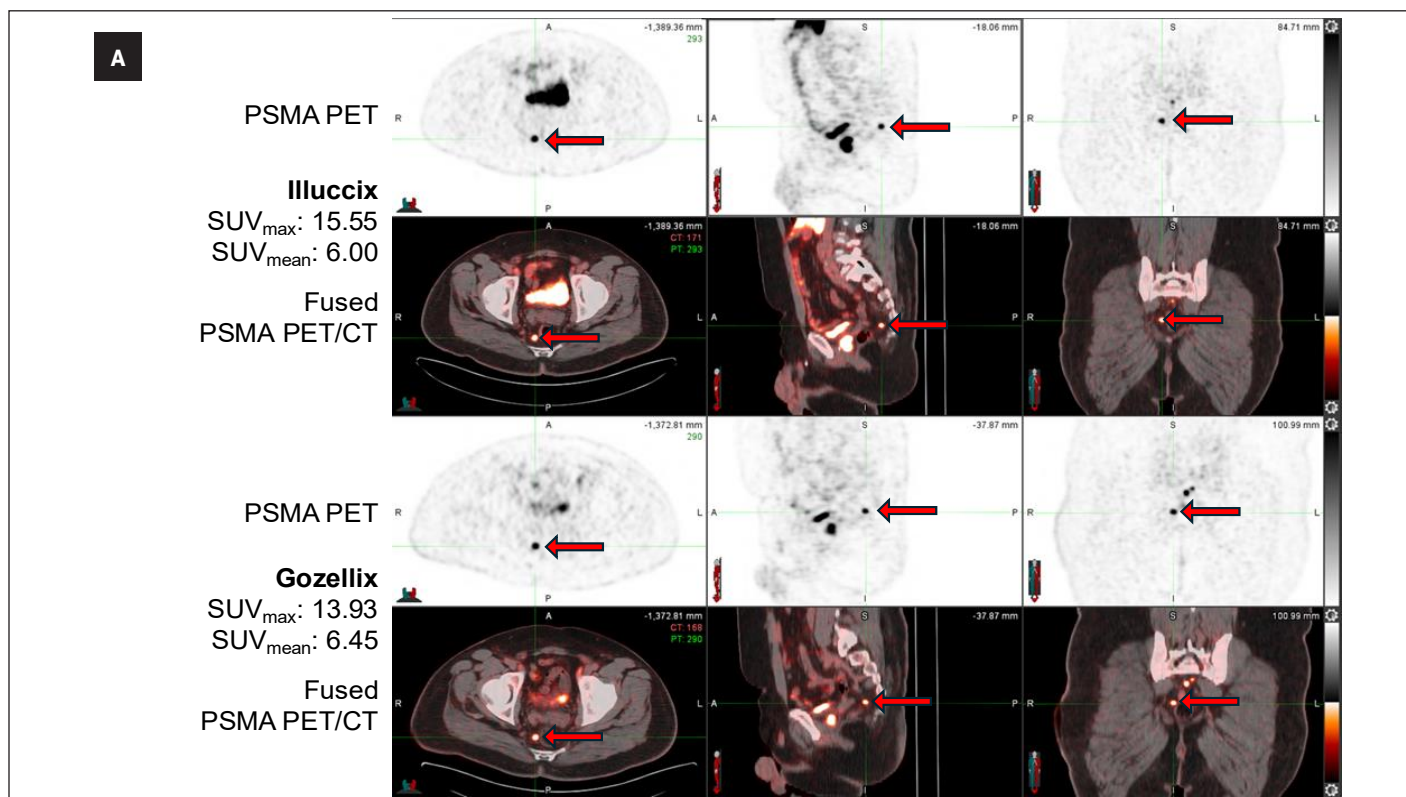


Figure 3. (A) Illuccix (top) and Gozellix (bottom) PSMA PET and fused PSMA PET/CT images of a 65-year-old male. Arrows indicate a mesorectal lymph node lesion. (B) MIP with Illuccix (left) and Gozellix (right)

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