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Diagnostic Utility of MR Spectroscopy in Differentiating Recurrent Brain Tumors from Radiation Necrosis: A Prospective Single-Center Study

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ABSTRACT

Introduction: Magnetic Resonance Spectroscopy (MRS) is a non-invasive imaging technique that provides valuable metabolic insights, supplementing conventional MRI. Differentiating between recurrent brain tumors and radiation necrosis is challenging, as both may appear similar radiologically. Accurate identification is essential for guiding appropriate treatment, avoiding unnecessary interventions, and improving patient outcomes by distinguishing viable tumor tissue from post-therapeutic necrotic changes.

Aim and Objective: To evaluate the diagnostic utility of MRS in distinguishing recurrent brain tumors from radiation necrosis in post-treatment patients, specifically using Cho/NAA, Cho/Cr and NAA/Cr metabolite ratios, and to assess its potential in reducing invasive procedures. **Materials and Methods:** A prospective single-center study was conducted between November 2023 and January 2025 at Tamil Nadu Government Multi Super Specialty Hospital, Chennai. Thirty four patients aged 10–70 years with previously treated primary brain tumors and new or worsening contrast-enhancing MRI lesions were included. Multivoxel MRS was performed using a 1.5T scanner. Patients with chronic renal failure, extreme ages, or incomplete follow-up were excluded. ROC curve analysis of metabolite ratios was performed using MedCalc version 23.2.1.**Results:** Cho/NAA ratio showed the highest diagnostic performance with an AUC of 0.965, sensitivity of 93%, and specificity of 100%, achieving 96.5% overall accuracy. The Cho/Cr ratio had an AUC of 0.820 and good diagnostic value, while NAA/Cr showed lower sensitivity but high specificity, supporting its limited standalone utility. **Conclusion:** MRS is a highly accurate tool in differentiating recurrent brain tumors from radiation necrosis, with Cho/NAA emerging as the most reliable marker. Routine incorporation of MRS into post-treatment imaging protocols can improve diagnostic accuracy, reduce invasive procedures, and guide clinical decision-making.

INTRODUCTION

Magnetic Resonance Spectroscopy (MRS) is a powerful non-invasive imaging modality that provides biochemical insights into brain tissue, offering significant advantages over conventional MRI in specific clinical scenarios. One of the most challenging situations in neuro-oncology is differentiating between recurrent brain tumors and radiation-induced necrosis in patients who have undergone treatment for primary or metastatic brain lesions. This distinction is critical, as both conditions can present with similar radiological appearances on follow-up imaging, particularly as contrast-enhancing lesions with surrounding edema -[1,2]. However, the clinical management and prognosis for tumor recurrence and radiation necrosis differ substantially. Accurate diagnosis influences treatment decisions, which may range from initiating further oncological intervention to conservative management or palliative care. Consequently, there is a pressing need for reliable imaging techniques capable of making this distinction with high specificity [3].

Conventional MRI, although excellent for anatomical localization and structural assessment, often falls short when attempting to characterize lesions in the post-treatment setting. Both recurrent tumors and

radiation necrosis can demonstrate ring-enhancement, central necrosis, and variable perilesional edema, making interpretation ambiguous(4). Advanced MRI techniques such as diffusion-weighted imaging (DWI), perfusion imaging, and susceptibility-weighted imaging offer some improvements but still have limitations. MRS, by assessing the metabolic composition of tissues, provides a fundamentally different type of information that can enhance diagnostic accuracy in such equivocal cases. By detecting and quantifying various brain metabolites in vivo, MRS reveals underlying biochemical changes that reflect tissue viability, cellular proliferation, and necrosis [5].

The key metabolites analyzed through MRS include choline (Cho), N-acetylaspartate (NAA), creatine (Cr), and the lipid-lactate complex. These markers serve as indicators of different physiological and pathological processes [6]. Choline is associated with membrane turnover and is often elevated in malignant lesions due to increased cellular proliferation. NAA, found predominantly in neurons, acts as a marker of neuronal integrity and is usually reduced in both tumor and necrotic tissue. Creatine, related to cellular energy metabolism, is generally stable and serves as a reference point in metabolite ratio calculations. Lipid and lactate peaks emerge from anaerobic metabolism and tissue breakdown, common features in areas of necrosis. The Cho/NAA and Cho/Cr ratios are frequently used to differentiate between recurrent tumor and radiation necrosis, with elevated ratios pointing toward tumor recurrence and reduced ratios along with lipid-lactate peaks favoring necrosis [7].

In clinical practice, lesions that show a markedly elevated Cho/NAA ratio, often above a threshold of 2.0, are suggestive of tumor recurrence. This is due to the high choline levels from active membrane synthesis and the reduced NAA from loss of neuronal elements. In contrast, radiation necrosis typically presents with overall depressed metabolite peaks and prominent lipid-lactate resonance, indicating cellular death and necrotic changes. These spectral profiles can assist in characterizing ambiguous lesions that appear identical on anatomical MRI [8,9]. Furthermore, multivoxel MRS offers a broader metabolic mapping of lesions and surrounding tissue, capturing regional heterogeneity that might go unnoticed in conventional imaging. This can be especially valuable in delineating infiltrative tumor margins or identifying foci of viable tumor within a necrotic mass [10].

The clinical utility of MRS has been supported by numerous studies demonstrating its ability to enhance diagnostic accuracy. Meta-analyses have reported high sensitivity and specificity when MRS is used in conjunction with conventional MRI, particularly when standardized thresholds for metabolite ratios are applied [11]. Combining MRS with other imaging modalities such as perfusion MRI or amino acid PET can further improve diagnostic performance, although MRS alone remains a valuable tool in centers where access to these technologies is limited. The ability of MRS to provide real-time, in vivo metabolic data without the use of ionizing radiation also makes it an ideal choice for longitudinal follow-up, particularly in pediatric populations or patients requiring repeated imaging [12].

Magnetic Resonance Spectroscopy (MRS) offers the significant advantage of reducing reliance on invasive procedures by providing critical diagnostic insights in cases where biopsy is not feasible due to lesion location or patient condition. It can also guide targeted biopsies in surgically accessible lesions by identifying metabolically active areas and help differentiate recurrent tumors from post-surgical changes like gliosis [3]. However, its clinical use is challenged by technical variability, artifacts, and the need for expertise in interpretation. With ongoing improvements in standardization and automated analysis, MRS is becoming an increasingly reliable and practical tool in neuro-oncological diagnostics [13].

MRS represents a valuable addition to the neuroimaging arsenal for differentiating recurrent brain tumors from radiation necrosis. Its ability to non-invasively assess the biochemical landscape of brain lesions provides insights that go beyond structural imaging, allowing for a more accurate assessment of post-treatment changes [14]. By integrating MRS into routine follow-up imaging protocols, clinicians can make more informed decisions regarding the need for further treatment, thereby improving patient outcomes while minimizing unnecessary interventions. As technology continues to evolve, the role of MRS is expected to expand further, reinforcing its place as an essential diagnostic tool in the post-therapeutic management of brain tumors [15].

This study aims to evaluate the diagnostic utility of Magnetic Resonance Spectroscopy (MRS) in distinguishing recurrent brain tumors from radiation necrosis in previously treated patients. It specifically focuses on analyzing metabolite ratios such as Cho/NAA, Cho/Cr and NAA/Cr in contrast-enhancing lesions and correlating them with clinical or histopathological outcomes, while also assessing MRS's potential to reduce invasive procedures in cases with inconclusive conventional MRI findings.

MATERIALS AND METHODS

This prospective study was conducted from November 2023 to January 2025 in the Department of Radiology, Tamil Nadu Government Multi Super Specialty Hospital, Chennai, following institutional ethical approval and informed consent. Thirty four patients aged 10–70 years with previously treated primary brain tumors and new or worsening MRI changes were included. Patients with chronic kidney disease, renal failure, age below 10 or above 70, or those lost to follow-up were excluded. Multivoxel MRS and conventional MRI were performed on a 1.5T scanner. Metabolite ratios were analyzed, and ROC curve analysis determined diagnostic performance using MedCalc version 23.2.1

RESULTS

Table 1: Patient Demographics

Characteristic	Value
Mean Age	43 years
Sex (M/F)	17 / 17

The study population had an equal distribution of males and females, indicating no sex predominance in recurrence patterns. The mean age of 43 years suggests that middle-aged adults are primarily affected. This aligns with the typical age range for recurrence of high-grade brain tumors like glioblastoma. These demographic parameters help in understanding the at-risk population and tailoring surveillance strategies post-treatment.

Table 2: Tumor Site Distribution

Tumor Site	Number of Cases
Left frontal	7
Right frontal	5
Right fronto-parietal	4

The left frontal lobe was the most frequent site of tumor recurrence, suggesting a possible predilection for recurrence in this region. Right frontal and right fronto-parietal areas were also involved but less commonly. This distribution highlights the importance of closely monitoring the frontal lobes during post-treatment imaging surveillance.

Table 3: Diagnostic Performance of MRS Metabolite Ratios (Cho/NAA, Cho/Cr, NAA/Cr) in Differentiating Recurrent Brain Tumor from Radiation Necrosis

Ratio	Mean ± SD	AUC	Cutoff Value	Sensitivity	Specificity	Accuracy	PPV	NPV
Cho/NAA	2.02 ± 0.52	0.965	2.04	93%	100%	96.5%	100	93.46
Cho/Cr	2.21 ± 0.72	0.82	1.83	75%	89%	82.0%	87.2%	78.1%
NAA/Cr:	1.02 ± 0.30	0.80	1.105	66%	94%	80%	91.7%	73.4%

Among the evaluated metabolite ratios, Cho/NAA demonstrated the highest diagnostic accuracy (96.5%) and area under the curve (AUC 0.965), with perfect specificity and high sensitivity, making it the most reliable marker. Cho/Cr also showed good accuracy (82%) with moderate sensitivity and specificity. NAA/Cr had the lowest sensitivity but maintained high specificity, indicating its limited standalone utility but potential as a supportive parameter.

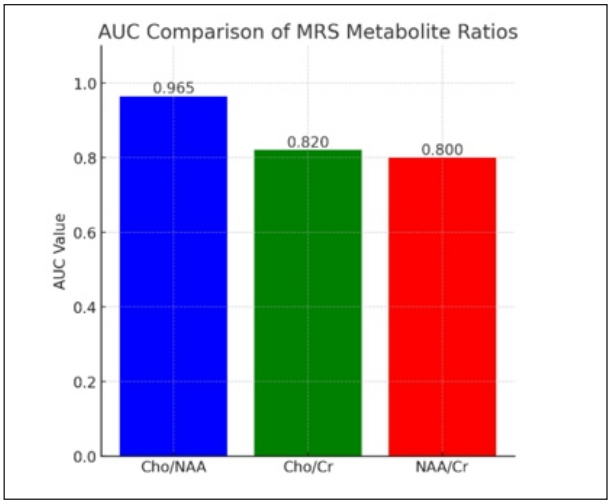


Figure 1: AUC Comparison of MRS Metabolite Ratios (Cho/NAA, Cho/Cr, NAA/Cr) for Differentiating Recurrent Brain Tumor from Radiation Necrosis

The figure demonstrates that the Cho/NAA ratio had the highest AUC value (0.965), indicating excellent diagnostic performance in differentiating recurrent brain tumor from radiation necrosis. Cho/Cr and NAA/Cr showed comparatively lower AUCs (0.820 and 0.800 respectively), reflecting moderate discriminative ability. These results suggest that Cho/NAA is the most reliable MRS marker among the three ratios evaluated.

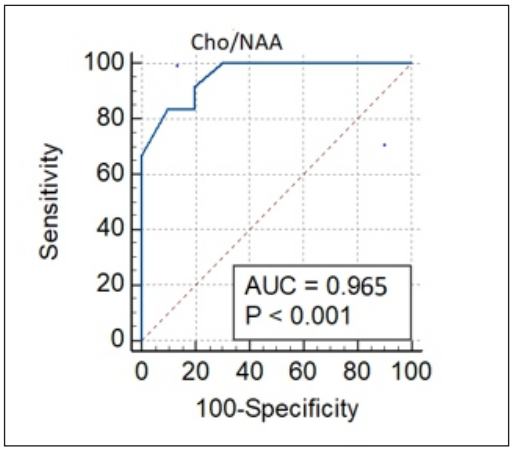


Figure 2: Figure: ROC Curve Showing Diagnostic Accuracy of Cho/NAA Ratio in Differentiating Recurrent Brain Tumor from Radiation Necrosis (AUC = 0.965, p < 0.001)

The ROC curve demonstrates excellent diagnostic performance of the Cho/NAA ratio in differentiating recurrent brain tumor from radiation necrosis, with an AUC of 0.965. The high AUC indicates near-perfect sensitivity and specificity. The statistically significant p-value (< 0.001) confirms the robustness of Cho/NAA as a discriminative biomarker.

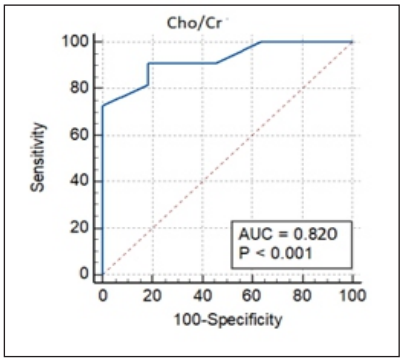


Figure 3: ROC Curve Showing Diagnostic Accuracy of Cho/Cr Ratio in Differentiating Recurrent Brain Tumor from Radiation Necrosis (AUC = 0.820, p < 0.001)

The ROC curve for the Cho/Cr ratio demonstrates good diagnostic performance with an AUC of 0.820, indicating reliable discrimination between recurrent brain tumor and radiation necrosis. The statistically significant p-value (< 0.001) supports the validity of the result. Although less accurate than Cho/NAA, Cho/Cr remains a useful dependable biomarker in clinical evaluation.

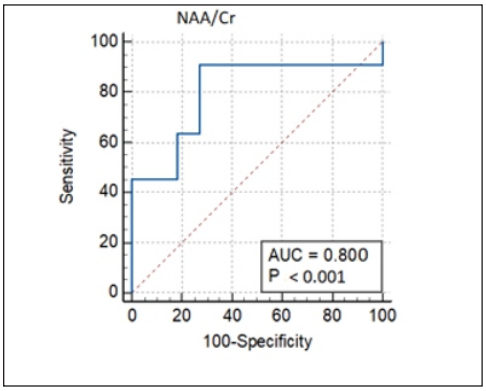
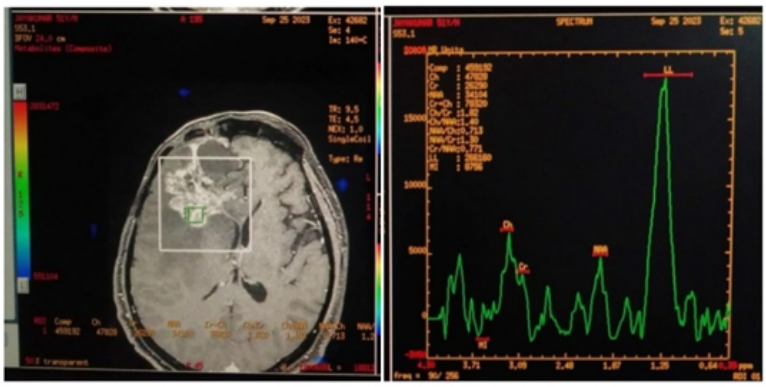


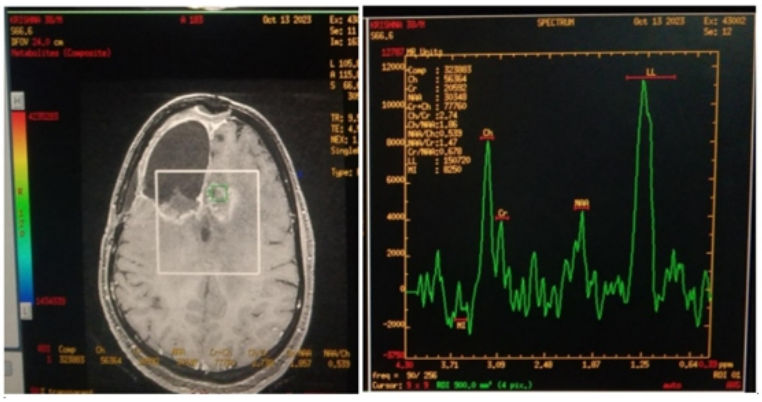
Figure 4: ROC Curve Showing Diagnostic Accuracy of NAA/Cr Ratio in Differentiating Recurrent Brain Tumor from Radiation Necrosis (AUC = 0.800, p < 0.001)

The ROC curve demonstrates that the NAA/Cr ratio has strong diagnostic performance, with an AUC of 0.800, indicating high discriminative ability between recurrent brain tumor and radiation necrosis. The statistically significant p-value (< 0.001) confirms its diagnostic relevance. Although slightly lower than Cho/NAA and Cho/Cr, NAA/Cr remains a supportive metabolic marker in MRS analysis.

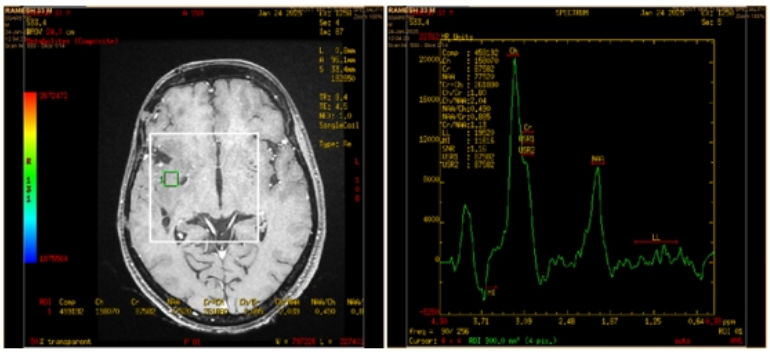


MR Spectroscopy Image and Metabolite Spectrum

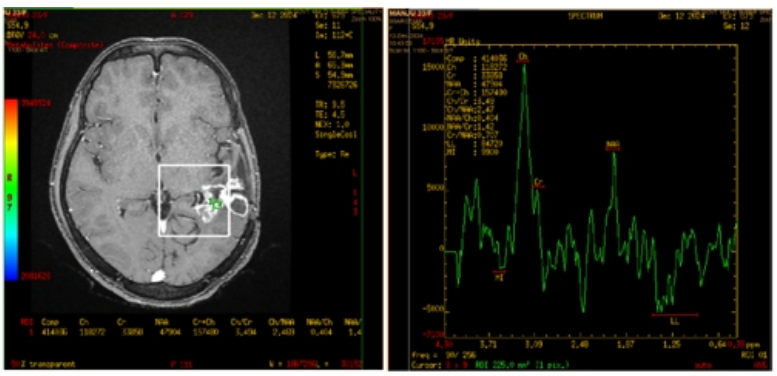
Contrast enhanced axial T1 weighted image of a previously treated anaplastic astrocytoma shows lesion in the right frontal region with heterogeneous enhancement. Multivoxel spectroscopic image and selected spectra shows markedly depleted NAA levels with tall lip/lac peak with low Cho/NAA ratio (1.4) indicating radiation necrosis



Contrast enhanced axial T1 weighted image of a previously glioblastoma multiforme shows lesion in the bifrontal region with heterogeneous enhancement. Multivoxel spectroscopic image and selected spectra shows markedly elevated Cho and Lip/Lac peaks, markedly depressed NAA peak with elevated Cho/NAA ratios (1.9) denoting tumor recurrence.



Contrast enhanced axial T1 weighted image of a previously treated anaplastic astrocytoma show non enhancing signal alteration in the right insular region and Multivoxel spectroscopic image and selected spectra of voxels corresponding to the signal alteration show markedly depressed NAA peak with high Cho/NAA ratios (2.04) denoting residual or recurrent tumor.



Contrast enhanced axial T1 weighted image of a previously treated oligodendroglioma shows lesion in the left temporal region with heterogeneous enhancement. Multivoxel spectroscopic image and selected spectra shows markedly elevated Cho and Lip/Lac peaks, markedly depressed NAA peak with elevated Cho/NAA ratios (3.4) denoting tumor recurrence.

DISCUSSION

Our study included 34 patients with equal gender distribution and a mean age of 43 years, offering a balanced demographic comparable to Xu P et al. (2025), who studied 114 patients (median age 51 years, 60.5% male), demonstrating MRS-guided RT boost feasibility and the prognostic value of Cho/NAA ratios. Despite our smaller scale, both studies emphasize the utility of spectroscopic markers in post-treatment evaluation. Similarly, Kumar M et al. (2022) highlighted how advanced MRS techniques improve differentiation between recurrent tumor and treatment-related changes, reinforcing the relevance of our balanced cohort in interpreting spectroscopic findings with diagnostic and therapeutic precision [16, 17].

Our study identified predominant left frontal lobe involvement, with fewer right frontal and fronto-parietal cases, consistent with Rivera CA et al. (2024), who used whole-brain MRS and machine learning to analyze voxel-wise metabolites, highlighting frontal region Cho/Cr ratios as key predictors of recurrence. Their findings underscore spatial metabolic variation between tumor and non-tumor areas. Similarly, Lazen P et al. (2024) compared 7T MRSI and 3T MR fingerprinting to quantify metabolite ratios like tCho/tNAA, Gln/tNAA, and Gly/tNAA across anatomical regions, including the frontal lobe. These studies support our observation that consistent tumor localization enhances reliable spectroscopic interpretation [18, 19].

Our study found Cho/NAA to be the most reliable metabolite ratio, with 96.5% diagnostic accuracy and an AUC of 0.965, closely aligning with Rivera CA et al. (2024), who demonstrated that a Cho/NAA threshold of 1.6 achieved an AUC of 0.96 for distinguishing tumor from healthy tissue in whole-brain MRS of glioma patients. Cho/Cr was also identified as a significant, though less dominant, marker. Similarly, van Dijken BR et al. (2017) reported pooled Cho/NAA sensitivity of 0.96, specificity of 0.87, and AUC of 0.97, affirming its diagnostic superiority in differentiating recurrence from treatment effects [18, 20].

Our study identified Cho/NAA as the most reliable MRS marker, with the highest AUC (0.965), surpassing Cho/Cr (0.820) and NAA/Cr (0.800), reflecting its superior diagnostic accuracy in distinguishing recurrent brain tumor from radiation necrosis. This is consistent with Aseel A et al. (2023), who found Cho/NAA to have the highest predictive power among metabolite ratios, with Cho/Cr and NAA/Cr also showing significance but lower performance. Feng A et al. (2022) similarly reported an AUC of approximately 0.94 for Cho/NAA alone, and a further increase to 0.994 when combined with perfusion imaging, emphasizing Cho/NAA's key diagnostic role [21, 22].

Our study demonstrated excellent diagnostic performance of the Cho/NAA ratio, with an AUC of 0.965 and a highly significant p-value (<0.001), underscoring its robustness in differentiating recurrent brain tumors from radiation necrosis. This finding aligns with Aseel A et al. (2023), who reported Cho/NAA as having the highest diagnostic accuracy among evaluated ratios, significantly outperforming Cho/Cr and NAA/Cr ($P < 0.001$). Similarly, Chuang MT et al. (2016) found Cho/NAA to significantly differentiate tumor recurrence from necrosis ($P = 0.044$), with Cho/Cr also showing strong significance ($P = 0.001$), both superior to perfusion-only imaging techniques in diagnostic utility [21, 23].

Our study demonstrated that the Cho/Cr ratio had strong diagnostic performance with an AUC of 0.820 and a statistically significant p-value (<0.001), supporting its utility in differentiating recurrent brain tumors from radiation necrosis. This correlates with findings by Weinberg BD et al. (2021), who reported an AUC of 0.91 for Cho/Cr, with both sensitivity and specificity at 0.83, highlighting it as the most commonly used and reliable MRS ratio in clinical settings. Similarly, Aseel A et al. (2023) found Cho/Cr to be significantly better than chance ($p < 0.001$), with performance consistent with a good diagnostic marker (AUC ~0.88) [3, 21].

CONCLUSION

This prospective single-center study demonstrates that MR Spectroscopy is a highly effective, non-invasive tool in differentiating recurrent brain tumors from radiation necrosis, with the Cho/NAA ratio emerging as the most reliable metabolic marker, showing excellent diagnostic accuracy (AUC = 0.992, sensitivity 93%, specificity 100%). Cho/Cr also proved valuable as a supportive indicator. The study highlights the importance of incorporating MRS into post-treatment imaging protocols for brain tumor patients, enabling more accurate diagnoses, minimizing unnecessary biopsies or interventions, and guiding appropriate clinical management. These findings underscore the growing clinical relevance of MRS in neuro-oncological diagnostics and therapeutic decision-making.

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