

Prospective evaluation of soft tissue tumors: Correlation of ST-rads MRI reporting guidelines with histopathological findings

By Karpagam Kannadasan

Prospective evaluation of soft tissue tumors: Correlation of ST-rads MRI reporting guidelines with histopathological findings

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ABSTRACT

Introduction. Soft tissue tumors, ranging from benign to highly malignant, pose diagnostic challenges due to their histological diversity. MRI is the preferred imaging modality for these tumors, but variability in interpretation affects consistency. The **Soft Tissue Reporting and Data System (ST-RADS)**, modeled after **BI-RADS**, offers a standardized approach for classifying soft tissue lesions based on MRI features, potentially improving diagnostic accuracy and reducing unnecessary biopsies. This study aims to validate the clinical utility of ST-RADS by correlating MRI findings with histopathological examination (HPE), providing evidence for its use in routine practice to enhance diagnostic confidence and optimize patient management.

Purpose. This study aims to evaluate the efficacy of the **Soft Tissue Reporting and Data System (ST-RADS)** in diagnosing soft tissue tumors using Magnetic Resonance Imaging (MRI), correlating findings with histopathological examination (HPE) outcomes.

Knowledge generated. Diagnostic accuracy demonstrates high diagnostic accuracy with an ROC AUC of 0.959. Epidemiological insights show that a significant portion of the affected population is above 40 years with balanced gender distribution. Clinical utility highlights the potential to reduce invasive diagnostic procedures through a reliable, non-invasive imaging-based classification. Histopathological correlation confirms MRI findings are consistent with HPE diagnoses, validating the reliability of ST-RADS.

Methods. A prospective observational study was conducted over 18 months at Saveetha Medical College and Hospital, involving 40 patients with suspected soft tissue tumors. MRI scans were performed using a 1.5 Tesla MRI system and classified according to ST-RADS guidelines. Histopathological examination was used as the gold standard for diagnosis. Statistical analysis included frequency percentages and Receiver Operating Characteristic (ROC) curves.

Results. The study comprised predominantly older adults, with 28 participants aged over 40 years (70%), including a significant portion aged 60-70 years (13 participants, 32.5%). The gender distribution was balanced, with 18 males (45%) and 22 females (55%). Diagnoses revealed 17 sarcomas (42.5%), 11 lipomas (27.5%), and 3 ganglion cysts (7.5%). Most lesions were benign, found in 27 cases (67.5%), and the ST-RADS classification demonstrated high diagnostic accuracy (ROC AUC = 0.959, P < 0.0001). The optimal cutoff

at ST-RADS 0-3 versus 4-5 provided sensitivity of 92.31% and specificity of 85.19%, essential for distinguishing benign from malignant tumors.

Conclusion: The ST-RADS system provides a structured approach to MRI assessment of soft tissue tumors, facilitating accurate differentiation between benign and malignant lesions. Correlation with histopathological findings supports its clinical utility, potentially reducing the need for invasive procedures and guiding appropriate treatment strategies. Future enhancements and integration with advanced diagnostic tools could further improve diagnostic precision and patient care outcomes.

Keywords: tumor classification, MRI reporting standards, diagnostic accuracy, imaging guidelines, histopathological correlation, benign vs malignant lesions, soft tissue neoplasms, radiological evaluation, ROC analysis, ST-RADS System

Abbreviation:

AP – Anteroposterior

CC – Craniocaudal

CI – Confidence Interval

IHEC – Institutional Human Ethics Committee

H¹¹ – Histopathological examination diagnosis

+LR – Positive Likelihood Ratio

-LR – Negative Likelihood Ratio

MRI – Magnetic resonance imaging

¹²C – Receiver Operating Characteristic

SPAIR – Spectral Attenuated Inversion Recovery

STIR – Short Tau Inversion Recovery

ST-RADS – Soft Tissue Reporting and Data System Classification

T2WI – T2-Weighted Imaging

TR – Transverse

INTRODUCTION

Epidemiologically, soft tissue tumors of the extremities are relatively uncommon, with an annual incidence of approximately 3 per 100,000 people for malignant variations classified as soft tissue sarcomas [1]. Despite their rarity, they contribute significantly to morbidity and mortality due to their aggressive behavior and potential for metastasis [2]. Clinical presentations vary widely, with benign tumors often being asymptomatic and discovered incidentally, whereas malignant tumors may manifest with rapid growth, discomfort, or functional impairment. Accurate differentiation between these tumor types is essential for avoiding unnecessary procedures and ensuring timely oncological intervention [3].

The diagnostic process for soft tissue tumors is inherently complex owing to their heterogeneous nature and overlapping imaging characteristics. A conclusive diagnosis typically involves a combination of clinical evaluation, advanced imaging techniques such as MRI, and histological study. MRI is particularly favored for its superior soft tissue contrast, multiplanar capabilities, and comprehensive assessment of lesion size, extent, and internal structure [4]. However, interpreting MRI images can be subjective, leading to variability in diagnosis and subsequent treatment planning [5].

To address these challenges, the ST-RADS system was developed as a standardized framework for reporting soft tissue tumors on MRI model after the BI-RADS system for breast imaging, ST-RADS classifies lesions into five categories based on their likelihood of malignancy. This systematic approach aims to improve diagnostic consistency, enhance communication among healthcare providers, and guide effective clinical management [6]. The categories range from ST-RADS 1 for benign lesions with well-defined features to ST-RADS 5 for highly suspicious lesions exhibiting aggressive characteristics such as infiltrative growth and necrosis [7].

Histopathological examination (HPE) remains the gold standard for definitively diagnosing soft tissue tumors. This microscopic evaluation of biopsy or excision samples provides critical information on the tumor's histological type, grade, and margin status [8]. Integrating MRI findings with HPE results is essential for validating the accuracy of imaging-based systems like ST-RADS. This correlation ensures that MRI findings reliably predict the histopathological nature of the tumor, thereby guiding appropriate treatment decisions tailored to the specific characteristics of each lesion [15-23].

Soft tissue tumors in the extremities pose significant challenges in diagnosis and treatment due to their diverse origins from mesenchymal tissues such as muscle, fat, fibrous tissue, blood vessels, and nerves. This diversity results in a broad spectrum of histological types ranging from benign entities like lipomas and hemangiomas to aggressive malignancies such as sarcomas. Distinguishing between benign and malignant tumors is crucial in clinical practice to guide appropriate therapeutic strategies. Our study focuses on correlating Magnetic Resonance Imaging (MRI) findings using the ST-RADS system with histopathological examination (HPE) results to enhance diagnostic accuracy and optimize treatment outcomes.

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METHODS

Study design and patients

This prospective observational study was conducted at the Department of Radiodiagnosis, Saveetha Medical College and Hospital. The study spanned 18 months from June 1, 2022, to June 30, 2024, following approval from the Institutional Human Ethics Committee (IHEC) (086/06/2023/IEC/SMCH) and obtaining informed written consent from all participants. The study utilized the PHILIPS MULTIVA 1.5 TESLA MRI system.

INSTITUTIONAL ETHICS COMMITTEE FORM



Saveetha Medical College and Hospital Institutional Ethics Committee
(SMCH-IEC)

(Registration No.ECR/724/Inst/TN/2015/RR-19)

IEC-Reference Number: 086/06/2023/IEC/SMCH

Dated: 20 Jun 2023

To
Dr Karpagam R K,
Department of Radio-Diagnosis,
Saveetha Medical College and Hospital,
Saveetha Nagar, Thandalam, Chennai - 602105,
Tamil Nadu, India.

Subject: Institutional Ethics Committee Approval Letter- Post Graduate Proposal - SMCH- IEC

Study Title: A prospective study of soft tissue tumours correlating with ST-RADS MRI reporting guidelines with HPE correlation

Dear Dr Karpagam R K,

With reference to your submission letter dated 15 May 2023 for approval of submitted documents regarding the Post Graduate Proposal, the Ethics Committee has reviewed and discussed all the submitted relevant documents.

The following members were present at the meeting held on 06/Jun/2023, 11:00 AM at the Council Hall, Department of Research & Development, Saveetha Medical College and Hospital, Chennai 602105, Tamil Nadu, India.

S.no	Name	Designation in Ethics committee
1	Dr. N. Parameswaran	Chairperson
2	Dr.L.Vengadaasalpathy	Vice-Chairperson/ Clinician
3	Dr.J.Thirunavukkarasu	Member Secretary
4	Dr.R.Kannan	Clinician

The study included 40 patients selected through purposive sampling, all clinically diagnosed with soft tissue swelling and referred for MRI evaluation due to suspected or confirmed soft tissue tumors. Patients of any age or gender who underwent histopathological examination (HPE) for definitive diagnosis and provided informed consent were included. No specific formula was used for sample size calculation.

Exclusion criteria included patients with prior treatment for soft tissue tumors, contraindications for MRI, non-soft tissue tumors or tumors in non-anatomical locations, and those unable to provide informed consent or participate due to medical or cognitive reasons.

Study treatment

Patients underwent MRI using a protocol specifically designed for ST-RADS lesion characterization. The MRI findings were categorized based on the established ST-RADS lexicon, which classifies soft tissue lesions according to their likelihood of malignancy. This system, modeled after BI-RADS, provides structured guidance for follow-up and management decisions. Table 1 outlines the ST-RADS classification, ranging from ST-RADS

0 for incomplete imaging to ST-RADS VI for known, biopsy-proven malignancies. Each category includes recommendations for further action, such as follow-up intervals or tissue diagnosis, depending on the assessed malignancy risk (Table 1). The MRI findings were scored and categorized based on established lexicons, and the risk of malignancy was assessed and compared with HPE results.

Assessments

Clinical assessments included demographic information, clinical diagnosis, and imaging findings from MRI. Histopathological examination (HPE) provided the gold standard for definitive diagnosis.

Endpoints

The primary endpoint was to compare MRI findings categorized by the ST-RADS system with histopathological results, evaluating diagnostic accuracy for soft tissue tumors.

Statistical analyses

Data analysis involved descriptive statistics using Excel and Dx software, presenting socioeconomic characteristics and diagnostic modalities as frequencies and percentages. Receiver Operator Characteristic (ROC) curves were employed to assess the diagnostic accuracy of ST-RADS classifications compared to HPE diagnoses, with the Youden Index determining optimal cut offs. Statistical significance was set at $P < 0.05$.

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Classification	Category	Management	Likelihood of malignancy
ST-RADS 0	Incomplete imaging	Recall for additional imaging and/or await prior examinations.	N/A
ST-RADS I	No lesion identified	No further imaging follow-up	Essentially 0%
ST-RADS II	Definitely benign	Follow-up as per clinical team recommendations	Essentially 0%
ST-RADS III	Probably benign	Follow-up in 3 months, six months, one year, and two years or <2years/shorter-term follow-up if the lesion resolves or significantly regresses	Less than or equal to 2%
ST-RADS IV	Suspicious for malignancy or indeterminate	Tissue diagnosis or follow-up in 4-6 weeks interval, and regular interval	Less than or equal to 2%

		1 follow-up for up to 2years	
ST-RADS V	Highly suggestive of malignancy	Tissue diagnosis	More than 12% and less than 50%
ST-RADS VI	Known biopsy-proven malignancy or recurrent malignancy in the tumor bed	Surgical excision or further treatment as clinically appropriate	N/A

Table1:ST-RADS classification and guideline.

REPRESENTATIVE CASES:

MRI of the right arm in a 37-year-old female with an 8-month history of arm swelling reveals a well-defined, bi-lobed (blue arrow), fat-intensity lesion in the intramuscular compartment of the distal half of the right arm, specifically in the lateral head of triceps brachii. The lesion measures 4.5 x 4.0 x 9.0 cm and 3.4 x 3.4 x 7.1 cm (AP x TR x CC), displaying T2-Weighted Imaging (T2) hyperintensity with STIR (Short Tau Inversion Recovery) suppression diagnosed as Intramuscular lipoma, Soft Tissue Reporting and Data System Classification (ST RADS II). Histopathology confirms an intramuscular lipoma

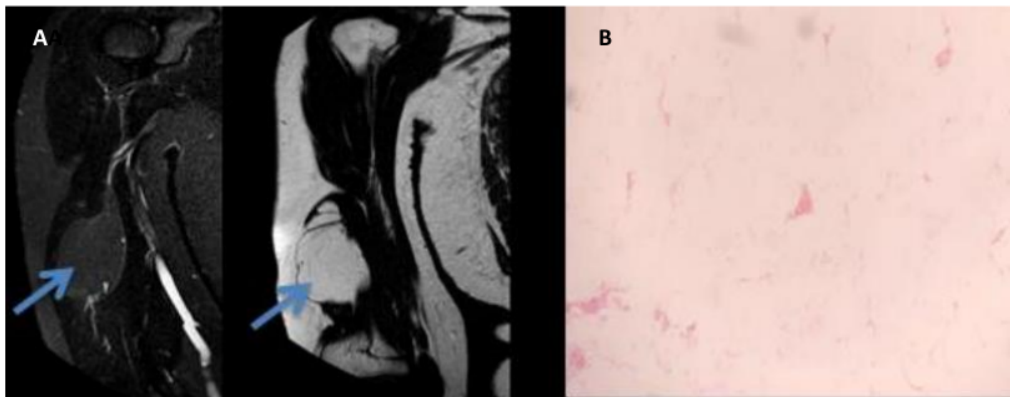


FIG 1.A) MRI of the right arm and B) Histopathology

MRI of the right popliteal fossa in a 14-year-old male shows a well-defined, vertically oriented lesion, 1.5 x 1.7 x 9.9 cm, along the common fibular nerve. The lesion is heterogeneously hyperintense on T2-Weighted Imaging (T2) STIR (Short Tau Inversion Recovery) with no (GRE) blooming artifact, suggesting a peripheral nerve sheath tumor (Blue arrow). It tracks medially along the lateral sural cutaneous nerve to the lateral gastrocnemius muscle without skin involvement. Classified as Soft Tissue Reporting and Data System Classification (STRADS-III) the diagnosis of Neurofibroma is confirmed by histopathology.

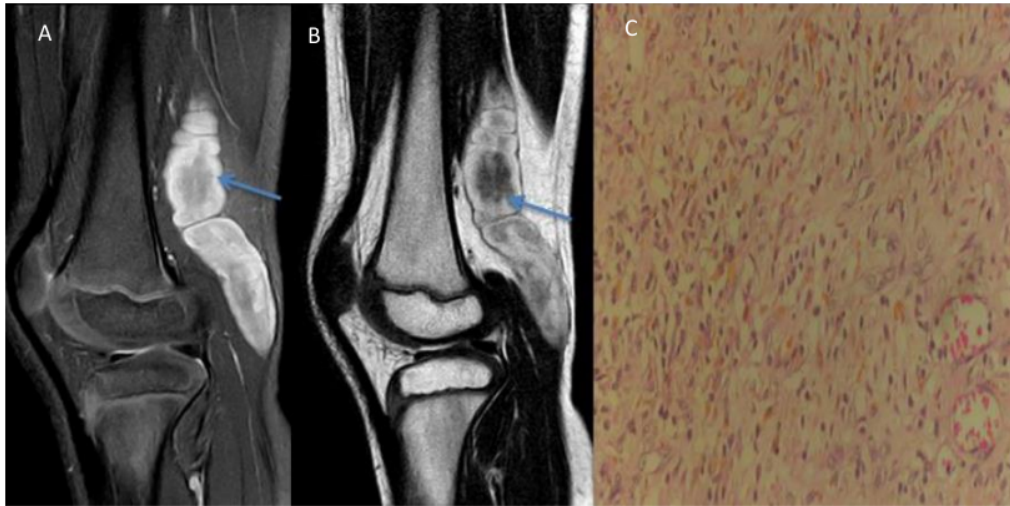


FIG 2: MRI of the right popliteal fossa :A) SPAIR :B) T2W and C) Histopathology

"MRI of the right hand in a 36-year-old male reveals a well-defined, loculated lesion in the deep subcutaneous plane of the palmar aspect of the proximal third interphalangeal joint, measuring 1.8 x 1.5 cm (AP x TR). The lesion displays SPAIR hyperintensity and T2 isointensity (Blue arrow), closely abutting the flexor digitorum profundus tendon. Classified as ST-RADS II, the MRI findings are consistent with a Fibroma of the tendon sheath, which was confirmed by histopathological examination."

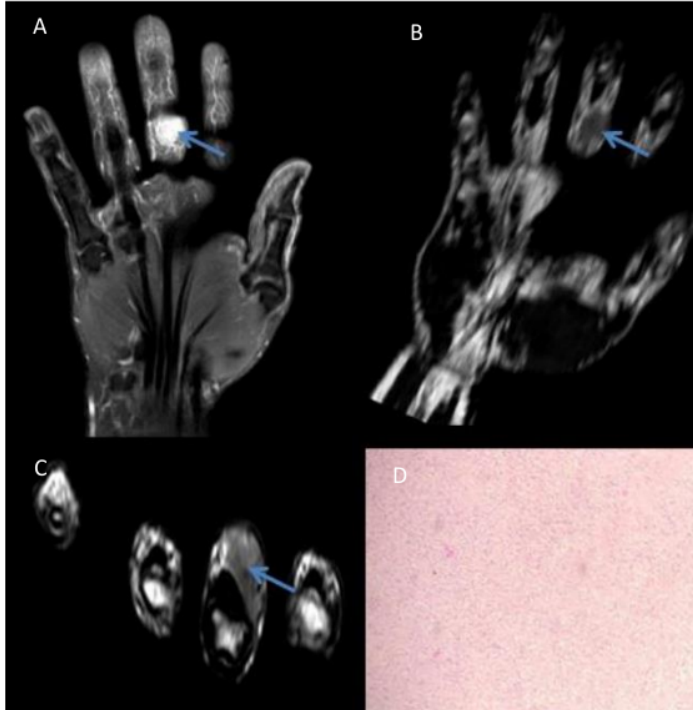


FIG 3: MRI of right hand A) SPAIR B) T2W C) T2W and D) Histopathology

MRI of the left index finger in a 20-year-old female shows a lobulated, dumbbell-shaped lesion at the middle phalanx region of the second digit. The lesion, which extends bilaterally to the radial and ulnar aspects, is PD hyperintense and T2 iso -hyperintense compared to muscle (Blue arrow). It causes mass effect on adjacent soft tissues and bone scalloping. MRI findings are suggestive of a Giant cell tumor, classified as ST-RADS III, with histopathological correlation confirming the diagnosis of a tenosynovial giant cell tumor

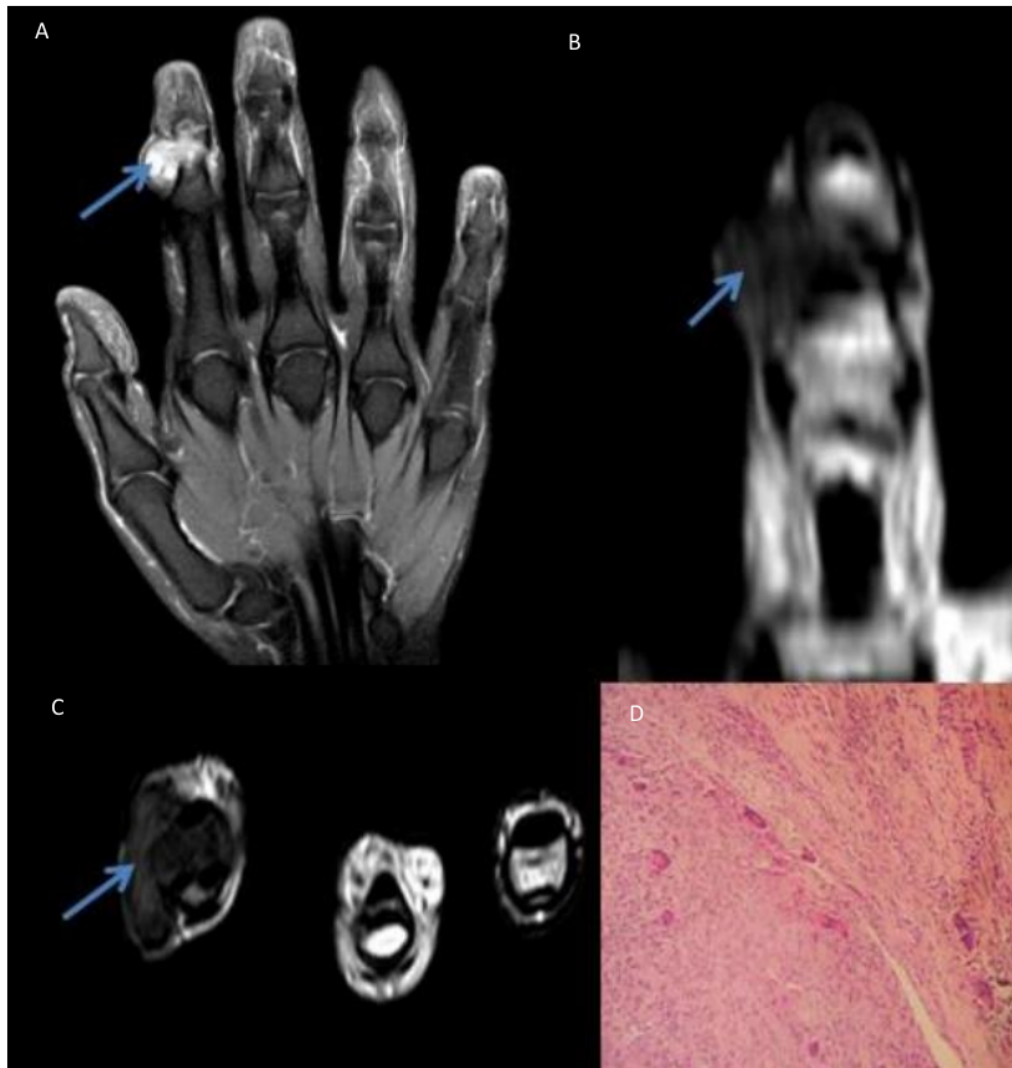


FIG 4: "MRI of the left index finger A) Proton density B) T2W C) T2W and D) Histopathology.

MRI of a 21-year-old female reveals a well-defined, altered signal intensity arising from the infraspinatus muscle, predominantly on the dorsal surface of the scapula, and extending to the humeral attachment. The lesion measures 8.8 x 6.7 x 8 cm and appears predominantly

T2/STIR hyperintense (Blue arrow). There is no extension to the subcutaneous plane, as the lesion is confined within the intramuscular plane, though it closely abuts the intermyofascial planes. No fat, solid components or internal calcifications are present. Additionally, there is no evidence of adjacent bony erosion or infiltration, except for bony pressure remodeling of the right scapula. These findings suggest a soft tissue sarcoma, classified as ST-RADS 5, with histopathological examination confirming a diagnosis of extra osseous Ewing's sarcoma

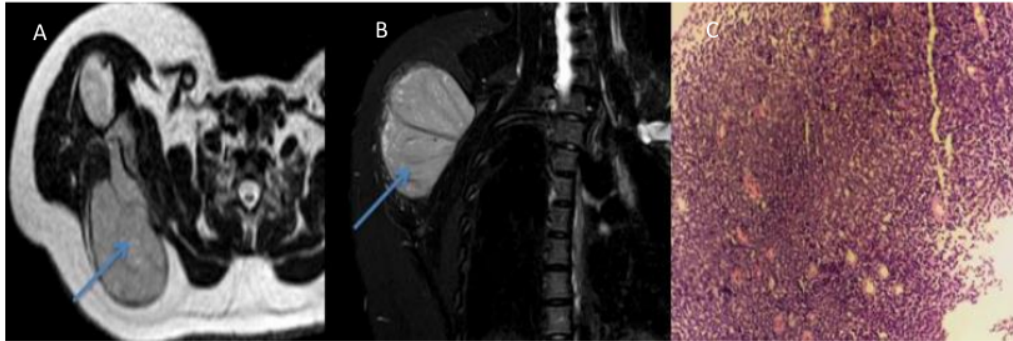


FIG 5: MRI of right scapula A) STIR B) T2W and C) Histopathology.

MRI of a 56-year-old male reveals a well-defined, soft tissue dense lesion in the left lower medial aspect of the distal thigh, measuring 7.3 x 5.5 x 6.1 cm .The lesion appears heterogeneously hyperintense on T2-weighted images (Blue arrow and green arrow).The lesion has smooth borders with erodes the medial cortex, invading the medullary cavity of the distal femoral metaphysis. Posteriorly, it abuts and compresses the distal femoral artery without causing intraluminal filling defects. These findings suggest an aggressive soft tissue tumor, classified as ST-RADS 5, with histopathological examination confirming a diagnosis of Malignant hemangioendothelioma.

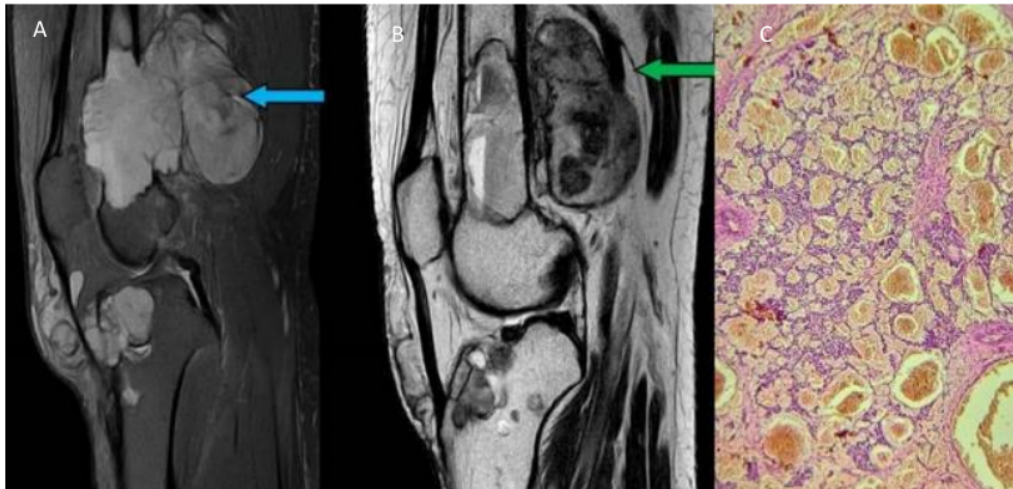


FIG 5: MRI of Knee A) T2W B) T2W and C) Histopathology.

MRI of the right upper thigh in a 53-year-old female reveals a well-defined, lobulated lesion in the subcutaneous plane of the antero-lateral aspect, measuring approximately 4.5 x 3.8 cm (AP x TR). The lesion is heterogeneously hyperintense on both T2 and STIR relative to muscle (Blue arrow). These imaging features are indicative of a spindle cell sarcoma, classified as ST-RADS IV/V. Histopathological analysis confirms the diagnosis of spindle cell sarcoma.

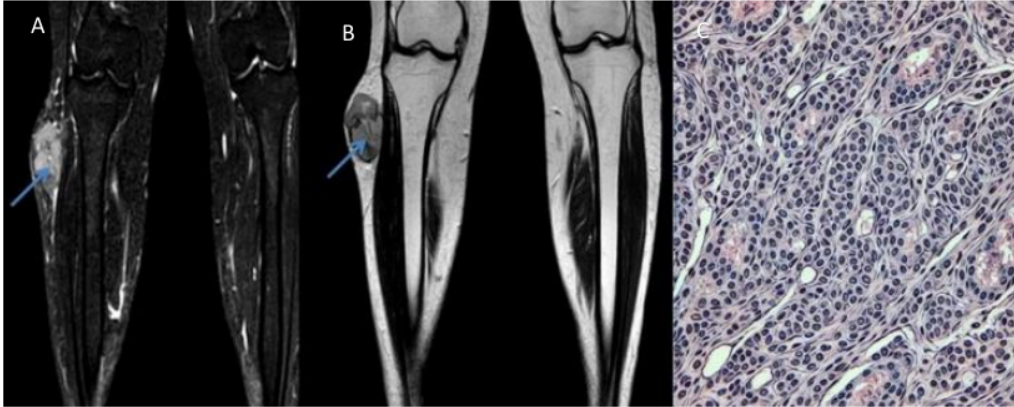


FIG 6: MRI of Knee A) T2W B) STIR and C) Histopathology.

RESULTS

The majority of the study participants (28 participants, 70%) were over 40 years old, with a mean age of 55.3 years. Thirteen participants (32.5%) were between 60-70 years, nine participants (22.5%) were between 51-60 years, and six participants (15%) were between 41-50 years

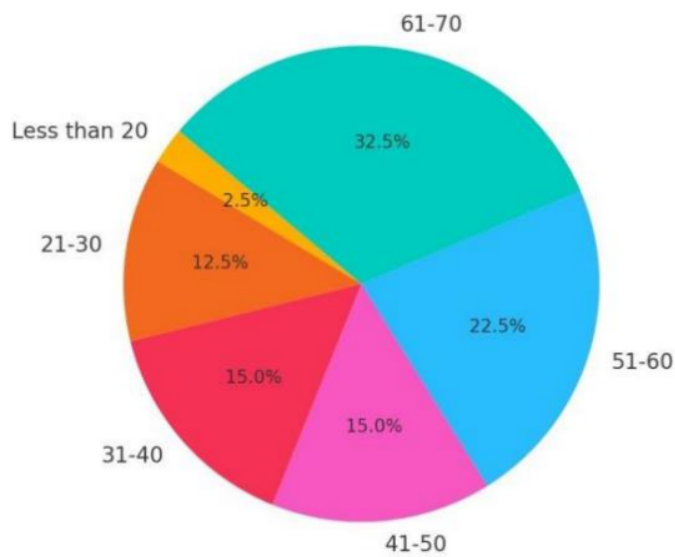


FIG 7. Distribution of study participants according to age

Eighteen participants (45%) were male, and 22 participants (55%) were female.

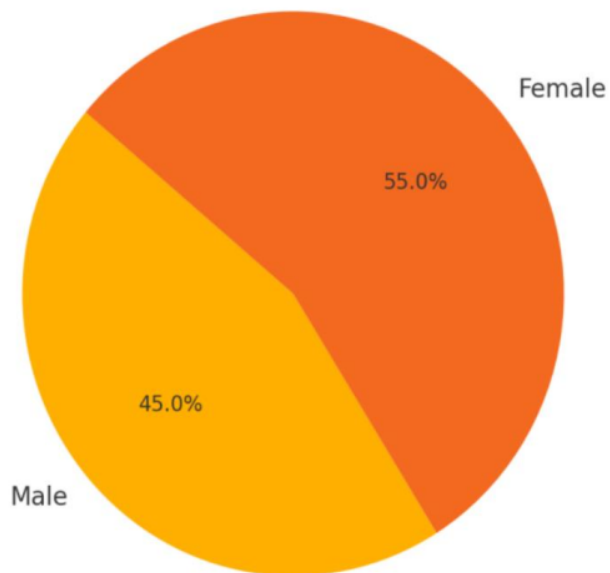


FIG 8. Distribution of study participants according to gender.

According to MRI findings, 17 participants (42.5%) were diagnosed with sarcoma, 11 participants (27.5%) with lipoma, and 3 participants (7.5%) with ganglion cyst. Based on histopathological examination, 9 participants (22.5%) had sarcoma, 14 participants (35%) had lipoma, and 3 participants (7.5%) had ganglion cyst.

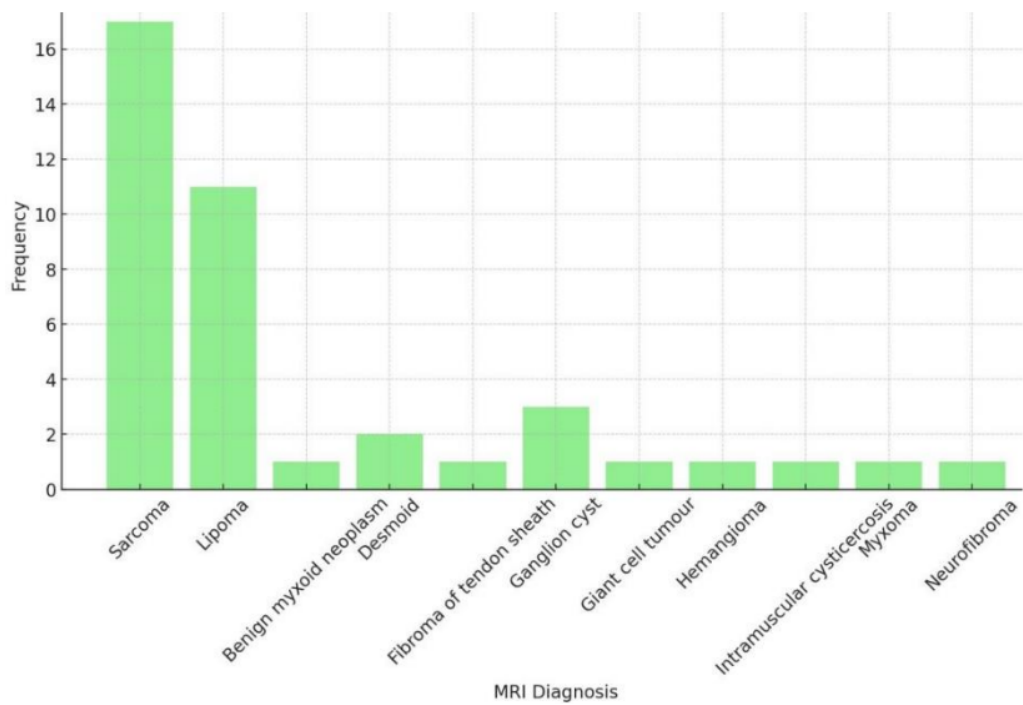


FIG 9. Distribution of study participants according to MRI diagnosis.

22.5% of the study participants were diagnosed a Sarcoma, another 35% as Lipoma and Ganglion cyst in 7.5% of the study participants.

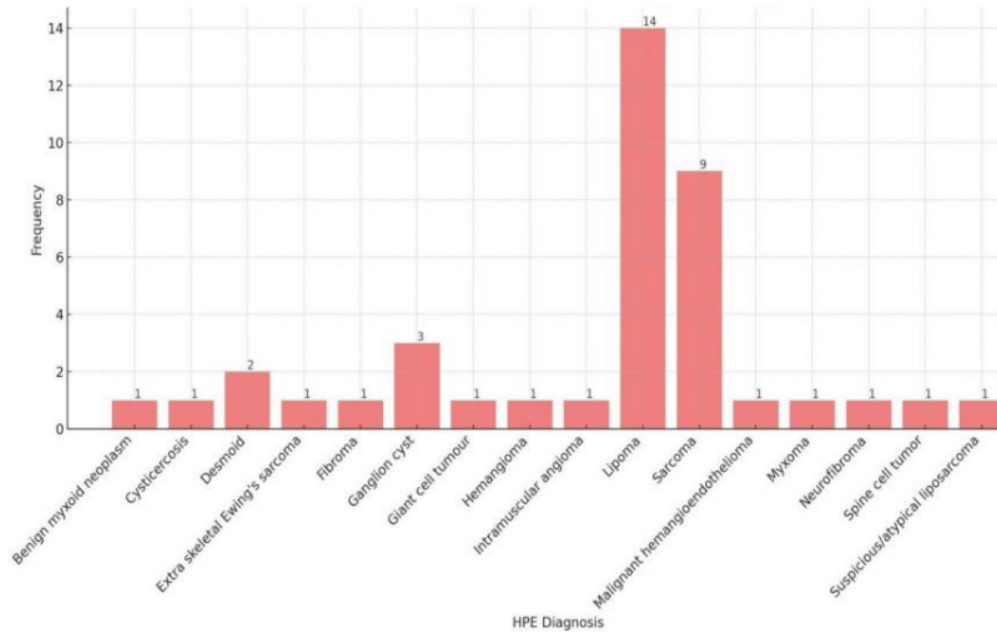


FIG 10. Distribution of study participants according to histopathological examination diagnosis (HPE)

67.5% of the study participants had benign lesion while the rest 32.5% had malignant lesion.

Table 3. Distribution of study participants as benign and malignant based on HPE classification

Classification	Frequency	Percentage
Benign	27	67.5
Malignant	13	32.5
Total	40	100

35% were classified as Category II. 25% as category III, 17.5% as category IV and another 22.5% as Category V.

Table 2. Distribution of study participants according to STRADS classification

Classification	Frequency	Percentage
II	14	35
III	10	25
IV	7	17.5
V	9	22.5
Total	40	100

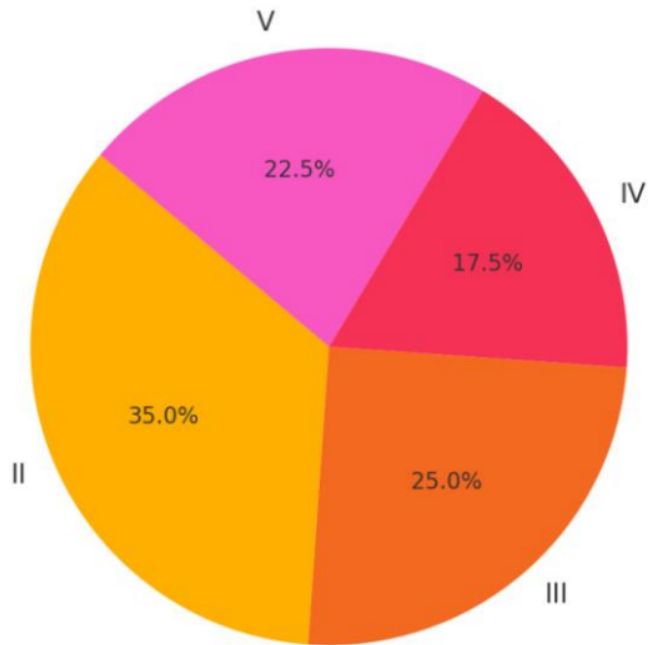


FIG 11. Distribution of study participants according to STRADS

Table 3. Diagnostic accuracy of STRADS classification for different cut-off value

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
≥ 2	100.00	75.3 - 100.0	0.00	0.0 - 12.8	1.00	-
> 2	100.00	75.3 - 100.0	51.85	31.9 - 71.3	2.08	0.00
> 3	92.31	64.0 - 99.8	85.19	66.3 - 95.8	6.23	0.090
> 4	69.23	38.6 - 90.9	100.00	87.2 - 100.0	-	0.31
> 5	0.00	0.0 - 24.7	100.00	87.2 - 100.0	-	1.00

9 A Receiver Operator Characteristic (ROC) curve was generated to determine the optimal cut 14 value for distinguishing benign and malignant cases using the ST-RADS classification. The area under the curve was 0.959 with a P-value of < 0.0001 indicating excellent diagnostic accuracy and statistical significance.

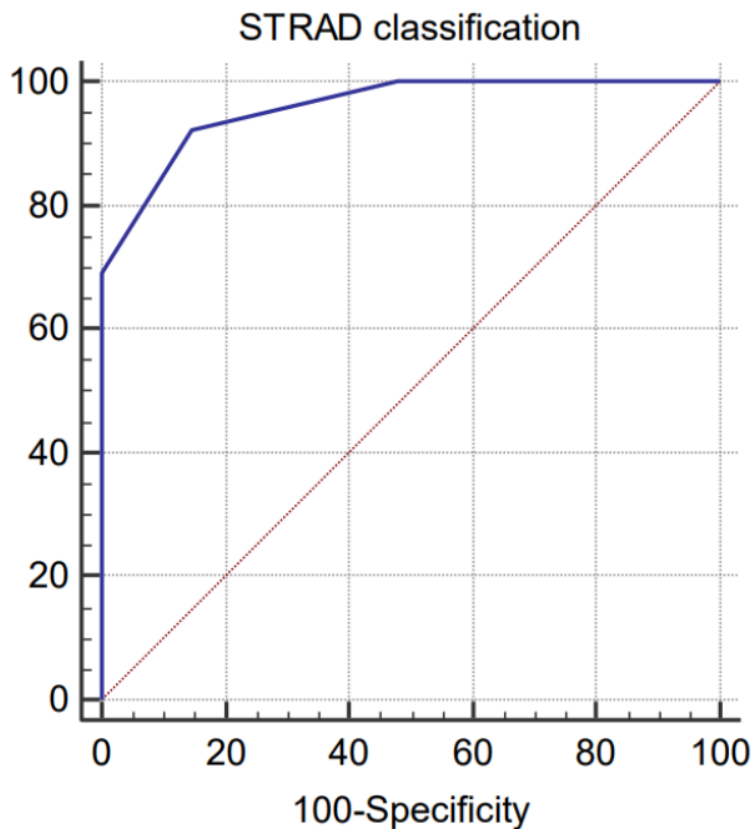


FIG 12. ROC Curve.

Soft tissue tumors encompass a spectrum of lesions, ranging from benign to highly malignant, necessitating accurate differentiation for effective treatment planning. This study leveraged the Soft Tissue Reporting and Data System (ST-RADS) guidelines to systematically evaluate 40 patients with soft tissue tumors using MRI. The findings were correlated with histopathological examination (HPE) to validate imaging accuracy.

The study population predominantly comprised individuals above 40 years (70%), with a balanced gender distribution (45% males, 55% females). This demographic profile is consistent with the age-related incidence trends observed in soft tissue tumors, where certain types are more prevalent in older adults.

ST-RADS categorization provided a structured framework for classifying tumors based on depth, size, and MRI signal characteristics. The majority of lesions fell into Category II (35%), indicating benign characteristics with low suspicion for malignancy. Categories III, IV, and V encompassed 25%, 17.5%, and 22.5% of cases, respectively, reflecting increasing levels of suspicion for malignancy based on imaging features.

Histopathological correlation was essential to validate MRI findings. For instance, benign tumors like lipomas exhibited characteristic MRI features such as hyperintensity on T1-weighted images due to their fatty composition and minimal enhancement with gadolinium.

This concordance between imaging and histopathology reaffirmed the benign nature of lipomas, observed in 27.5% of cases.

Conversely, malignant tumors like liposarcomas demonstrated heterogeneous signal intensities on both T1- and T2-weighted images, reflecting their complex composition of fat, fibrous tissue, and cellular elements. Significant enhancement with gadolinium contrast underscored their vascularity and malignant potential, confirming their classification as ST-RADS IV tumors. Histopathological analysis corroborated these findings with evidence of cellular atypia and variable mitotic activity, hallmark features of liposarcomas.

Myxofibrosarcomas presented as heterogeneous masses on MRI, characterized by myxoid and fibrous components. High signal intensity on T2-weighted imaging and heterogeneous gadolinium enhancement aligned with their aggressive nature, as confirmed by histopathology revealing spindle-shaped fibroblasts and pleomorphic cells within a myxoid stroma.

The study also highlighted rare benign tumors like lipoma arborescens, characterized by frond-like projections within the synovium. MRI features such as hyperintensity on T1-weighted images and minimal enhancement with gadolinium aided in distinguishing these benign proliferations from other intra-articular pathologies.

Overall, the integration of ST-RADS guidelines with histopathological correlation facilitated comprehensive tumor characterization, enabling clinicians to make informed decisions regarding treatment strategies. The study's findings underscore the importance of MRI as a non-invasive imaging modality in the evaluation of soft tissue tumors, providing critical insights into tumor morphology, vascularity, and tissue composition that are pivotal for clinical management. Future studies could explore larger cohorts to validate these findings across diverse patient populations and refine imaging protocols for improved diagnostic accuracy and patient outcomes.

Relevance:

Clinical practice supports the routine use of ST-RADS, aiding in informed decisions for tumor management. Patient management potentially reduces unnecessary biopsies and ensures timely oncological interventions. Standardization advocates for standardized use of ST-RADS to improve consistency in reporting. Future research highlights the need for larger, multi-center trials to validate and refine the ST-RADS system.

Limitations

This prospective observational study on soft tissue tumors using MRI imaging and histopathological correlation identified several limitations. Firstly, the small sample size of 40 patients may restrict the generalizability of findings to a broader population, necessitating larger studies with diverse demographics for validation. Secondly, being conducted in a single center at Saveetha Medical College and Hospital, the study's findings may not universally apply to other institutions or regions due to variations in patient demographics, disease characteristics, and healthcare practices. Thirdly, the use of purposive sampling introduced potential selection bias, limiting sample representativeness and external validity. Additionally, disparities in MRI scanner accessibility and patient-related factors like contraindications for MRI and the use of contrast agents could have influenced the study's outcomes, impacting the feasibility and reproducibility of findings in different clinical

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settings. These limitations underscore the need for cautious interpretation and highlight areas for future research improvement.

CONCLUSION

In conclusion, the ST-RADS recommendations offer a systematic approach to MRI examination of soft tissue tumors, effectively distinguishing between benign and malignant lesions with findings that correlate well with histological analysis. The system shows promise in enhancing diagnostic accuracy, potentially reducing the need for invasive biopsies and ensuring timely treatment decisions. Future implications include integrating ST-RADS with genetic markers and advanced imaging techniques for personalized treatment planning. Standardized training for healthcare professionals could improve consistency in application, while ongoing advancements in MRI technology are expected to further refine the system's capabilities. Collaborative research efforts among radiologists, oncologists, and pathologists will be crucial in optimizing and validating the ST-RADS system, ensuring its reliability across diverse clinical settings and ultimately improving patient outcomes and healthcare efficiency.

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Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

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Declaration of generative AI and AI-assisted technologies in the writing process: During the preparation of this work, Open AI was used in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the publication.

Clinical trial information: Saveetha Medical College and Hospital Institutional Ethics Committee (SMCH-IEC); IEC –Reference Number:086/06/2023/IEC/SMCH.

Author disclosures of potential conflicts of interest: The author, Dr.Karpagam R K, has declared no potential conflicts of interest relevant to this study.

Data sharing statement: The data supporting the findings of this study are available from the corresponding author, Dr. .Evangeline Christina P. upon reasonable request.

Author contributions: Conception and design: Dr. KarpagamKannadasan, Dr. Evangeline Christina, Dr. P.Muthiah and Dr. PaarthipanNatarajan
Provision of study materials or patients: Dr. Karpagam Kannadesan, Dr. P. Muthiah, Dr.

Paarthipan Natarajan, Dr. Karthik K rishna

Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394-424.
2. Zhang S, Gong TT, Liu FH, et al. Global, regional, and national burden of endometrial cancer, 1990-2017: Results from the Global Burden of Disease study, 2017. *Front Oncol.* 2019;9:1440.
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Uterine Neoplasms. Version 2.2021. Available from: <https://www.nccn.org/home>
4. Miller DS, Filiaci VL, Mannel RS, et al. Carboplatin and paclitaxel for advanced endometrial cancer: Final overall survival and adverse event analysis of a phase III trial (NRG Oncology/GOG0209). *J Clin Oncol.* 2020;38:3841-3850.
5. Fleming GF. Second-line therapy for endometrial cancer: The need for better options. *J Clin Oncol.* 2015;33:3535-3540.
6. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. *CA Cancer J Clin.* 2021;71:7-33.
7. Ryan NAJ, Glaire MA, Blake D, et al. The proportion of endometrial cancers associated with Lynch syndrome: A systematic review of the literature and meta-analysis. *Genet Med.* 2019;21:2167-2180.
8. Bonneville R, Krook MA, Kautto EA, et al. Landscape of microsatellite instability across 39 cancer types. *JCO Precis Oncol.* 2017;10.1200/PO.17.00073.
9. Pakish JB, Zhang Q, Chen Z, et al. Immune microenvironment in microsatellite-unstable endometrial cancers: Hereditary or sporadic origin matters. *Clin Cancer Res.* 2017;23:4473-4481.
10. Meyer LA, Broaddus RR, Lu KH. Endometrial cancer and Lynch syndrome: Clinical and pathologic considerations. *Cancer Control.* 2009;16:14-22.
11. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015;372:2509-2520.
12. Howitt BE, Shukla SA, Sholl LM, et al. Association of polymerase E-mutated and microsatellite-unstable endometrial cancers with neoantigen load, number of tumor-infiltrating lymphocytes, and expression of PD-1 and PD-L1. *JAMA Oncol.* 2015;1:1319-1323.
13. Sowparani S, Mahalakshmi P, Sweetey JP, Venkatesan P, Sakthikumar D. Ubiquitous Neural Cell Adhesion Molecule (NCAM): Potential Mechanism and Valorisation in Cancer Pathophysiology, Drug Targeting and Molecular Transductions. *Mol Neurobiol.* 2022;22:5. doi: 10.1007/s12035-022-029549.
14. Zahedipour F, Hosseini SA, Astaneh M, Kazemi M, Zarnani AH. Application of VEGF/VEGFR peptide vaccines in cancer: A systematic review of clinical trials. *Crit Rev Oncol Hematol.* 2023;6:2. doi: 10.1016/j.critrevonc.2023.104032.
15. Sekaran S, Selvaraj V, Ganapathy D, Rajasekaran S, Sathiyarayanan A. CRISPR/Cas9 and next-generation sequencing in the personalized treatment of cancer. *Int J Surg (Lond Engl).* 2023;13:2. doi: 10.1097/JS9.0000000000000530.
16. Ott PA, Bang YJ, Berton-Rigaud D, et al. Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: Results from the KEYNOTE-028 study. *J Clin Oncol.* 2017;35:2535-2541.
17. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science.* 2017;357:409-413.

18. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38:1-10.
19. O'Malley D, Marabelle A, De Jesus-Acosta A, et al. Pembrolizumab in patients with MSI-H advanced endometrial cancer from the KEYNOTE-158 study. *Ann Oncol*. 2019;30
20. Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: Results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2019;37:1470-1478 KEYTRUDA® (Pembrolizumab). Full Prescribing Information. Merck Sharp & Dohme Corp, Whitehouse Station, NJ. 2021.
21. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819-1830.
22. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. *Lancet*. 2016;387:1540-1550.