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Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
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E-mail: info@galenos.com.tr/yayin@galenos.com.tr
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Original Article

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Hotspots and Research Trends in Machine Learning for Prostate Cancer: A Bibliometric Analysis and Visualization (1997-2025)

Tunahan Ateş[1], Nezih Tamkaç[2], İbrahim Halil Şükür[3], Fesih Ok[3], İsmail Önder Yılmaz[4], Mutlu Değer[4], Volkan İzol[4]

[1]*Defne State Hospital, Clinic of Urology, Hatay, Türkiye*
[2]*Hatay Mustafa Kemal University Faculty of Medicine, Department of Urology, Hatay, Türkiye*
[3]*University of Health Sciences Türkiye, Adana Training and Research Hospital, Department of Urology, Adana, Türkiye*
[4]*Çukurova University Faculty of Medicine, Department of Urology, Adana, Türkiye*

Abstract

Objective: This bibliometric analysis examines the evolution of prostate cancer (PCa) research and evaluates the impact of machine learning and artificial intelligence (AI) on its diagnosis, classification, and treatment.
Materials and Methods: Articles published between 1997 and 2025 were analysed using the Web of Science Core Collection database. VOSviewer and Bibliometrix software was utilized for bibliometric analysis. Terms such as "PCa", "machine learning (ML)", "deep learning" and "AI" were included in the search strategy. The number of publications, the most cited studies, author collaborations and country collaborations, thematic trends, and citation networks were visualised.
Results: A total of 3,277 articles were analysed. The in augural article was published in 1997. Over the past five years, there has been a significant increase in the number of articles published. The United States and China are the countries with the highest number of publications, and the most influential authors and institutions are concentrated in these countries. A marked upward trend has been observed in ML applications for PCa diagnosis, risk stratification, and treatment planning.
Conclusion: The use of AI and ML in PCa research has grown significantly over the last 20 years. However, most of the existing models have been tested with retrospective data, and more multicenter and prospective studies are needed for clinical applications. Comprehensive clinical validation is essential before AI-based systems can be reliably implemented.
Keywords: Prostate cancer, machine learning, artificial intelligence, bibliometric analysis, scientific trends

Introduction

Prostate cancer (PCa) ranks as the second most prevalent cancer among men globally and constitutes a substantial proportion of cancer-related mortality (1). This disease is particularly common in older men and may progress aggressively, with a high risk of metastasis if not detected early (1). Currently, the standard diagnostic methods for PCa include the prostate-specific antigen (PSA) test, multiparametric magnetic resonance imaging (mpMRI), and biopsy (2). Nevertheless, conventional diagnostic methods are not consistently definitive, and instances of false negatives or false positive results may occur (3). In this context, machine learning (ML) techniques offer innovative and promising approaches for the diagnosis and treatment of PCa, encompassing areas such as medical imaging analysis and biomarker discovery (3).

ML is a subset of artificial intelligence (AI) that enhances clinical decision-making support through the analysis of large-scale datasets. In recent years, various ML methodologies, including

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Address for Correspondence: Tunahan Ateş, MD, Defne State Hospital, Clinic of Urology, Hatay, Türkiye
E-mail: drtunahanates0101@gmail.com **ORCID:** orcid.org/0000-0001-9087-290X
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supervised learning, unsupervised learning, and reinforcement learning, have been increasingly applied in the diagnosis and management of PCa treatment processes (4). Deep learning (DL) and convolutional neural networks (CNN), which are a class of neural networks specialized in extracting spatial features from image data, have demonstrated considerable success, particularly in the analysis of mpMRI (5). The utilization of these techniques in cancer diagnostics (6-8), which predict the aggressiveness of the disease (9,10) and facilitate risk classification (11,12) for the development of treatment plans, is becoming increasingly prevalent.

Bibliometric analysis serves as a quantitative method for evaluating publications in a specific research area, enabling the identification of prominent authors, institutions, countries, and emerging research trends (13). This analysis facilitates the identification of prominent topics within the literature, the journals that publish the most articles, and the studies that are cited most frequently (14). In recent years, software applications such as VOSviewer and Bibliometrix have gained significant traction for visualizing scientific networks and conducting bibliometric analyses. These tools enable researchers to examine the structures of collaborative networks within the scientific literature, trace the evolution of research themes, and forecast future trends (15).

The study will examine literature published between 1997 and 2025 by utilizing the Web of Science (WoS) Core Collection (CC) database and employing bibliometric analysis methods for data visualization. The objective of this research is to construct a comprehensive scientific map that delineates the relationship between PCa and ML. The findings of this study are anticipated to provide valuable insights for future research endeavors and to contribute to the advancement of AI-supported diagnostic and treatment systems in clinical applications. Furthermore, this research may foster increased international collaboration by analyzing scientific collaboration networks in the domain of ML-based PCa research.

Materials and Methods

Search Strategy

In this study, WoS CC was utilized as the primary data source. The WoS comprises numerous articles across various disciplines and is widely acknowledged by researchers as a high-quality database (16). The database is acknowledged as the most appropriate for conducting bibliometric analysis (15). We used the following search strategy: topic search (TS) = (“prostate cancer” or “prostate neoplasm” or “Gleason score” or “prostate carcinoma” or “PSA” or “prostate-specific antigen” or “multiparametric MRI” or “mpMRI”) and TS = (“machine learning” or “supervised learning” or “unsupervised learning” or “reinforcement learning” or “reinforced learning” or “deep learning” or “transfer learning”). The timeframe for this search encompassed articles published up to the current year, with a submission deadline for queries set for 21 January 2025. The literature selected for this study was restricted to articles, review articles, and to those published in the English language. This search yielded a total of 3,277 articles. Full records and cited references were exported as plain text files for subsequent visualization and analysis. The search process is illustrated in Table 1.

Eligibility Criteria

This study employed specific criteria for the inclusion and exclusion of literature. The inclusion criteria encompassed original research articles and review articles published in relevant English language journals. Conversely, the following materials were excluded from the analysis: conference proceedings, meeting abstracts, early access publications, book chapters, editorial content, corrections, letters, retracted publications, books, and meeting reports. Additionally, duplicate articles were eliminated from consideration. The literature search was conducted independently by two reviewers to ensure comprehensive identification of all pertinent studies. In instances of discrepancies, the matter was referred to a third researcher for resolution. The process of the literature search is illustrated in Figure 1.

Data Analysis and Visualisation

Bibliometric analysis emerged in the twentieth century and was formally recognized as an independent discipline in 1969 (17). This study applies quantitative methods to analyze the existing literature in this field. This study involved the extraction of authors, keywords, journals, countries, references during the analytical process. Additionally, bibliometric analysis frequently employs the co-citation technique, which occurs when two articles are cited concurrently by one or more other articles. Co-citation analysis has been demonstrated to enhance data interpretation, thereby rendering the results more comprehensive.

Table 1. Criteria in the search process

Category	Specific standard requirements
Research database	Web of Science Core Collection
Citation indexes	SCIE, ESCI, SSCI, AHCI
Searching period	Database build to Jan 21, 2025
Language	English
Retrieval formula	**TS = (“prostate cancer’’ or ’’prostate neoplasm’’ or “gleason score’’ or “prostate carcinoma” or “PSA” or “prostate-specific antigen” or “multiparametric MRI” or “mpMRI”) and TS = (“machine learning” or “supervised learning” or “unsupervised learning” or “reinforcement learning” or “reinforced learning” or “deep learning” or “transfer learning”)**
Document types	“Articles”, “Review articles”
Data extraction	The export should include comprehensive records along with cited references in plain text format, BibTeX, and tab-delimited file formats.
Final documentation	3,277

SCIE: Science Citation Index Expanded, ESCI: Emerging Sources Citation Index, SSCI: Social Sciences Citation Index, AHCI: Arts and Humanities Citation Index, TS: Topic search, mpMRI: Multiparametric magnetic resonance imaging

The following software applications were utilized for statistical and visualization analyses: VOSviewer version 1.6.20 (14) and R version 4.4.2, which includes the Bibliometrix R package and the Biblioshiny tool, accessible at https://www.bibliometrix.org/home/. These tools are widely employed in the medical research domain. The VOSviewer software, developed by Leiden University in the Netherlands, employs a chain-based data standardization method that offers diverse visualization perspectives on keywords, collaborating institutions, co-authors, and other relevant entities. These visualizations encompass mesh, overlap, and density views, characterized by notable features such as straightforward mapping and a visually informative structure (14). Different clusters within a network diagram are denoted by distinct colors and are indicative of collaborations, co-working relationships, and connectors. The size of each circle corresponds to the number of references, publications, and keywords associated with that cluster. The Bibliometrix R package, which is available in the R environment, was utilized alongside the Biblioshiny tool for conducting bibliometric analysis and visualization. This approach assists researchers in comprehending the prevailing research trends, focal areas of inquiry, and academic impact within a specific field (13). During the data processing phase, challenges such as name disambiguation (e.g., authors with similar names), keyword unification, and institutional name variations were encountered. Additionally, some inconsistencies in metadata (e.g., missing affiliations or citation counts) required manual checking. Despite these challenges, the use of VOSviewer and Bibliometrix allowed for effective network visualizations and thematic clustering.

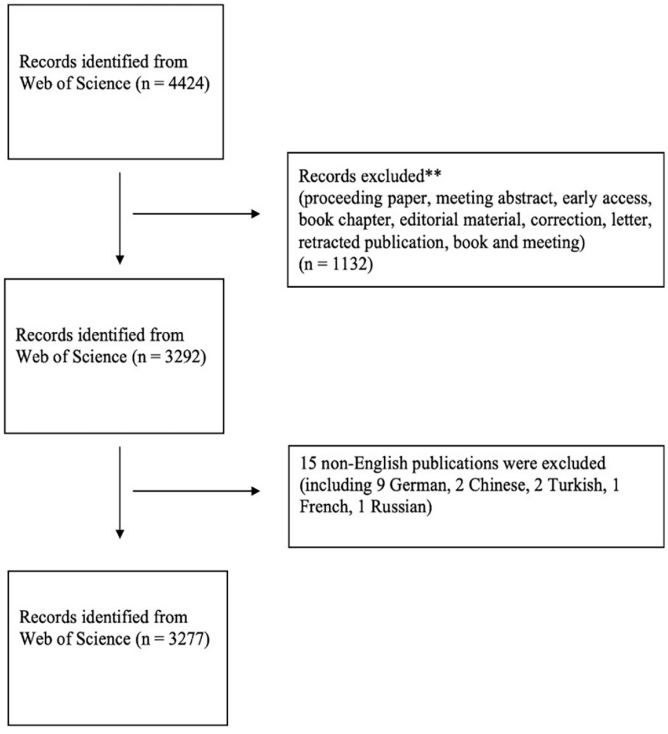

Figure 1. Flowchart of literature review

Statistical Analysis

Linear regression analysis of the number of publications by year was performed with IBM SPSS Statistics version 26.0.

Statements of Ethics

Not applicable, as this bibliometric analysis did not involve direct interaction with human participants or collection of personal data.

Results

General Informations

The initial search resulted in the identification of 4,424 articles. Following the application of selection criteria that included only original research articles, review articles, and articles published in the English language, a total of 3,277 articles were included in the final analysis. The flowchart illustrating the study's methodology is presented in Figure 1. Among the 3,277 articles, 2,911 are classified as original research articles, while 366 are categorized as review articles. Key findings from the analysis are depicted in Table 2 and Figure 2.

The inaugural article was published in 1997. Over the past five years, there has been a significant increase in the number of articles published. The increase in 2020 and beyond is reaching a significant level. The year 2024 recorded the highest output, with a total of 711 articles. Figure 2 shows that the number of publications on this topic has gradually increased over time ($R2=0.474$, $p<0.001$). Additionally, the annual average number of citations reached its zenith in 2019, during which each published article received an average of 10.74 citations. The trends in published articles and the average number of citations by year are illustrated in Figure 3.

Table 2. Main information

Main information about data	Results
Timespan	1997-2025
Sources (journals, books, etc)	927
Documents	3277
Annual growth rate %	14.38
Document average age	3.84
Average citations per doc	24.31
References	107675
Keywords plus (ID)	4909
Author's keywords (DE)	6401
Authors	18812
Authors of single-authored docs	38
Single-authored docs	40
Co-authors per doc	9.39
International co-authorships %	32,1
Article	2911
Review	366

Figure 2. Main information

Co-authorship Analysis

In the author-coauthorship analysis, Anant Madabhushi occupies the most central position (Supplementary Figure 1). He stands out as the author with the highest number of publications and citations. The authors with the highest number of publications are presented in Supplementary Table 1. Lotka's law posits that a small number of authors produce a large volume of articles, whereas a larger number of authors contribute only a few articles, with productivity following an inverse square law. The analysis conducted aligns closely with Lotka's law, achieving a near-perfect fit (Supplementary Figure 2).

In the analysis of co-authorship by country, the United States and China occupy central positions (Supplementary Figure 3). Notably, China's connections are more current. The United States leads in both the number of articles and citations, with a total of 1,216 articles and 41,635 citations, followed closely by China. The countries with the highest number of publications are detailed in Supplementary Table 2 and Supplementary Figure 4 illustrates the distribution of articles among the countries. Most countries in Africa have not published any articles.

In the analysis of co-authorship among the organizations, Case Western Reserve University and Emory University play a central role (Supplementary Figure 5). Case Western Reserve University distinguishes itself as the institution with the highest number of articles and citations, with 101 articles and 6,986 citations. The organizations with the most publications are presented in Supplementary Table 3. Notably, seven of the ten organizations with the highest publication counts are located in the United States, while only one of the top 10 organizations is based in China.

Source, Document and Keyword Analysis

The citation-source analysis shows that medical physics, and cancers journals are central (Supplementary Figure 6). Medical physics leads in both publications and citations, significantly outpacing other sources. Article and citation counts are detailed in Supplementary Table 4.

In author keyword co-occurrence analysis, the most central author keywords are ML, PCa, and DL (Supplementary Figure 7). The top three author keywords are ML, DL, and PCa. The most commonly used author keywords are presented in Supplementary Table 5. The presence of the keywords "magnetic resonance imaging" and "MRI" is among the top ten keywords,

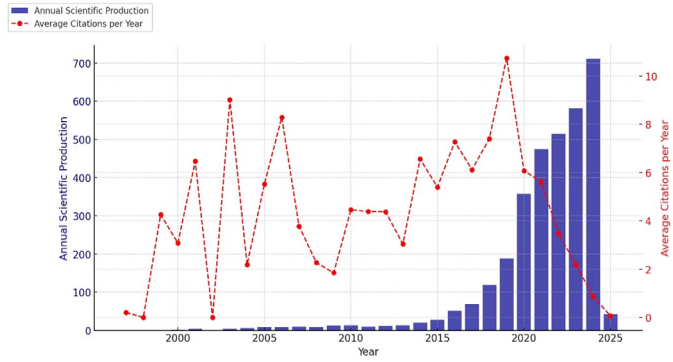

Figure 3. Annual scientific production and average citations per year

which indicates that ML is predominantly utilized in imaging techniques for PCa.

The most frequently cited articles are the studies titled "Clinical-Grade Computational Pathology Using Weakly Supervised Deep Learning on Whole Slide Images" and "Artificial Intelligence in Cancer Imaging: Clinical Challenges and Applications," both published in 2019. The prominence of these studies in the literature indicates that a significant portion of research in this field is dedicated to enhancing the accuracy and reliability of diagnoses. Furthermore, it underscores the central role of diagnostic AI applications in the management of PCa. The most cited articles are presented in Supplementary Table 6.

Thematic Map

The thematic map analysis using Bibliometrix identified three main themes in PCa research (Supplementary Figure 8). The first theme focuses on the diagnosis of PCa and ML methods, highlighting topics such as clinically relevant diagnosis, biochemical recurrence prediction, and genomic analyses. This theme includes ML-based approaches for processing clinical data, optimizing diagnostic processes, and discovering biomarkers. The second theme examines the integration of mpMRI with AI systems, covering AI algorithms for mpMRI data analysis, image segmentation, and enhancement of diagnostic accuracy. AI-based systems are increasingly used as clinical decision support tools in radiological evaluations. The third theme, the narrowest, centers on AI-supported

applications for PCa treatment, particularly in radiotherapy. This involves AI models for radiotherapy planning, dose calculation optimization, and predicting treatment outcomes. The potential of AI-enabled systems to offer more precise and personalized treatment approaches is driving research in this area. Together, these themes illustrate the expanding role of AI and ML across the diagnostic, imaging, and therapeutic dimensions of PCa management.

Thematic Evaluation

The Sankey diagram created using Bibliometrix is based on abstracts and illustrates the evolution of research themes related to AI applications in PCa from 1997 through 2025, divided into three distinct time periods (Supplementary Figure 9). In the initial period (1997-2010), classical ML methods, including artificial neural networks and support vector machines, along with the use of clinical diagnostic parameters such as MRI and the Gleason score, were predominant in PCa studies. However, during the subsequent period (2011-2020), DL techniques, particularly CNN, gained prominence in fields such as MRI analysis. In the final period (2021-2025), PCa research has shifted towards multifaceted, high-tech, and multidisciplinary themes, such as treatment planning systems, radiomics analysis, and the cancer genome atlas, with an increased emphasis on integration into clinical applications.

Discussion

This bibliometric analysis underscores the growing importance of ML in the diagnosis and treatment of PCa, as reflected by a notable surge in related scientific publications over the past decade. The upward trajectory in research output not only signals increasing academic interest but also highlights the transformative potential of ML technologies within the field of urologic oncology.

ML has become increasingly integrated into several critical aspects of PCa management. It plays a pivotal role in early disease detection, enabling more accurate identification of clinically significant cancer cases. Moreover, ML contributes to risk stratification by distinguishing between indolent and aggressive forms of the disease, and supports personalized treatment planning through predictive modeling and data-driven decision support.

Over the past 25 years, ML has become a key driver of the information technology revolution, shaping various domains. As a subfield of AI, ML enables computers to learn from data without explicit programming, a concept introduced by Samuel (18). His application of ML in checkers pioneered the use of games as experimental platforms for evaluating ML algorithms (18).

Campanella's work, which is the most frequently cited in this analysis, represents a milestone in the field of computational pathology (4). The authors developed a clinical-grade decision support system using a weakly supervised DL approach, applying multiple instance learning to 44,732 whole slide images from 15,187 patients. A ResNet34-based CNN was used for tile-level feature extraction, and the extracted features were integrated via a recurrent neural network to produce slide-level predictions. The system achieved exceptional performance with area under the curves of 0.991 for PCa, 0.989 for basal cell carcinoma, and 0.965 for breast cancer metastases. Notably, the model maintained 100% sensitivity for PCa detection while reducing the number of slides requiring pathologist review by over 75%. This demonstrates the feasibility of deploying DL systems in clinical workflows without manual pixel-level annotations, thanks to the scale and diversity of the data used.

Over the past year, a significant number of bibliometric analyses have been conducted regarding the application of ML in various medical fields, including kidney diseases (19,20), Crohn's disease (21), cardiomyopathy (22), psychiatry (23), and gynecology (24). The findings of these papers, similar to those of our study, indicate that the United States, China, and various European countries are at the forefront of research in ML.

The United States is home to some of the world's most prestigious universities, well-funded research programs, and a strong academic infrastructure. Over the past two decades, China has significantly increased its investments in science and technology, which has led to the development of numerous international collaborations. Institutions such as the National Cancer Institute (NCI) in the United States (https://www.cancer.gov), the National Science Foundation (https://www.nsf.gov), and the National Natural Science Foundation (NSFC) in China (https://www.nsfc.gov.cn/english/site_1/index.html) have supported joint projects in cancer research. In China, both the NSFC and the state Council support AI-based biomedical initiatives. The launch of China's AI strategy in 2017 (https://www.gov.cn/zhengce/content/2017-07/20/content_5211996.htm) represents an effort to bridge the gap with United States leadership in this field. Scientific collaboration between China and the United States persists despite fluctuations in political relations; for instance, the NCI and the Chinese Cancer Institute have engaged in joint projects for many years. The prominence of these two nations in scientific research can be attributed to their ongoing investments in AI and their status as economically and technologically advanced countries.

ML research in the field of PCa is predominantly led by countries such as China, the United States: the United Kingdom, Germany, Spain, and Italy. The authors with the highest number of publications and citations are primarily affiliated with institutions in these countries. Notably, the United States is prominent due to its high publication volume, leading citation metrics, and centrality in international collaborations. However, recent years have witnessed a significant increase in contributions from countries like China and India, which have rapidly emerged in the research landscape concerning PCa. This trend can be attributed to the rise in global scientific collaborations and advancements in data sharing practices. Furthermore, the substantial number of recent studies underscores the contemporary relevance of this subject. The integration of AI into various domains has been extensively investigated within the medical field, and it is reasonable to assert that AI will play an increasingly integral role in the future of medicine.

The prominence of the keywords "magnetic resonance imaging" and "MRI" among the top ten highlights that medical imaging, particularly MRI, remains the central focus of ML applications in

PCa research. This suggests a strong reliance on non-invasive diagnostic approaches and reflects the maturity of image-based datasets available for training algorithms. For future research, this trend implies a need to refine ML models for imaging tasks—such as lesion segmentation, radiomic feature extraction, and image-based risk assessment—while also encouraging the integration of imaging with other data types like genomics and clinical notes, to enable more comprehensive and personalized diagnostic tools.

The thematic mapping and keyword analyses conducted in this study reveal several underrepresented yet promising research directions in the field of ML-based PCa studies. Notably, while the majority of current research emphasizes diagnostic imaging—particularly MRI—there is considerable potential for expanding ML applications into areas such as treatment response prediction, active surveillance optimization, and long-term patient outcome modeling. Furthermore, the integration of radiomics with genomic data, often referred to as radiogenomics, represents an emerging field that remains insufficiently explored in PCa. This integration could facilitate more personalized risk stratification and treatment planning. Another crucial future direction involves enhancing the explainability and interpretability of ML models to ensure their acceptance in clinical settings. As AI systems become more complex, transparent mechanisms for decision-making and output justification will be essential for clinician trust and regulatory approval. Encouraging multidisciplinary collaborations, standardizing data formats, and establishing public repositories for high-quality annotated datasets will also be pivotal in driving innovation and clinical translation.

The analysis of the thematic map reveals that studies in urological oncology, particularly those focused on PCa detection, are increasingly influenced by AI and imaging techniques. It is crucial for urologists to identify clinically significant PCa. Numerous studies have been conducted on this topic (25,26). Additionally, there are publications that specifically examine the application of ML in this field (27,28). The clinical significance of this topic is substantial. Our thematic mapping indicates that studies pertaining to the diagnosis of PCa are encompassed by the primary themes. It is anticipated that CNN and DL will assume pivotal roles in the future diagnosis and treatment of PCa. This subject, which remains perpetually relevant, is expected to gain further prominence in the coming years.

The studies conducted in this domain are multidisciplinary, with the most commonly associated fields being radiology, nuclear medicine, and biochemistry. Bioinformatics methodologies, including ML, DL, radiomics, and gene expression analysis, are leading advancements in keyword analysis. Notably, there has been a substantial increase in both the volume of publications and citation density within this field over the past decade. Projections suggest that this trend will continue to escalate exponentially.

Here, we must also emphasize the necessity of thorough clinical validation before AI systems can be safely implemented in PCa care. Such validation processes generally include prospective studies, multi-center trials, and external validation using independent datasets that reflect clinical heterogeneity. These steps are crucial to ensure that models not only perform well on retrospective benchmarks but are also generalizable, reliable, and ethically sound for real-world use.

Although this study is bibliometric in nature and does not evaluate clinical or generative AI applications directly, the emergence of models such as ChatGPT underscores the accelerating pace and expanding scope of AI technologies across healthcare and biomedical research. While not the focus of this analysis, such developments contextualize the broader ecosystem in which ML-based PCa studies are evolving.

Recommendations for Future Research

One of the major concerns in ML-based PCa studies is the lack of comprehensive clinical validation, particularly through prospective and multicenter trials. Although many algorithms demonstrate strong performance with retrospective data, their clinical applicability remains limited without real-world validation. Additionally, our findings reveal that research collaborations are predominantly concentrated in a few countries, which restricts the global generalizability and adaptability of ML models. Beyond these structural limitations, several content-specific gaps have also been identified. For instance, ML applications in advanced stages of PCa—especially metastatic and treatment-resistant cases—are significantly underexplored. Moreover, while imaging data dominates current studies, there is a marked absence of research integrating diverse data modalities such as genomics, laboratory results, clinical narratives, and patient-reported outcomes. These data types hold the potential to enhance the predictive accuracy and clinical utility of AI-driven systems. Furthermore, limited attention has been given to developing real-time decision support tools for use during critical clinical procedures, including biopsy and radiotherapy planning. Addressing these gaps requires the development of interpretable, ethically responsible AI models that are rigorously validated and seamlessly integrated into routine clinical workflows.

Study Limitations

This study has several limitations. First, it relied solely on the WoS CC, thereby excluding studies indexed in other major databases such as PubMed and Scopus. Second, only English language articles were considered, potentially omitting high-quality research in other languages. It is noteworthy that there may be recent high-quality articles available in other languages. The citation of articles necessitates a systematic process, and the identification of quality studies will require time. Bibliometric analysis is based on publication counts and citation networks, which do not permit a direct evaluation of methodological quality. Future research should incorporate systematic reviews and meta-analyses to provide a more comprehensive evaluation of the field.

Conclusion

In conclusion, ML and AI applications present promising advancements in the management of PCa. However, further validation, use of large-scale datasets, and multidisciplinary collaborations are essential for the broader implementation of

these technologies in clinical settings. Future research should prioritize the development of models that are validated with real-world data, promote extensive international collaborations, and expedite clinical validation processes. Notably, the integration of large language models and generative AI-based solutions into clinical practice represents a significant area for future investigation. Nevertheless, it is imperative to address concerns related to ethics, reliability, and the generalizability of these models.

Ethics

Ethics Committee Approval: Not applicable, as this bibliometric analysis did not involve direct interaction with human participants or collection of personal data.

Informed Consent: Not applicable, as this bibliometric analysis did not involve direct interaction with human participants or collection of personal data.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: T.A., F.O., M.D., Concept: T.A., İ.H.Ş., Design: N.T., İ.Ö.Y., Data Collection or Processing: İ.H.Ş., V.İ., Analysis or Interpretation: V.İ., Literature Search: İ.H.Ş., İ.Ö.Y., Writing: T.A., F.O., İ.Ö.Y.

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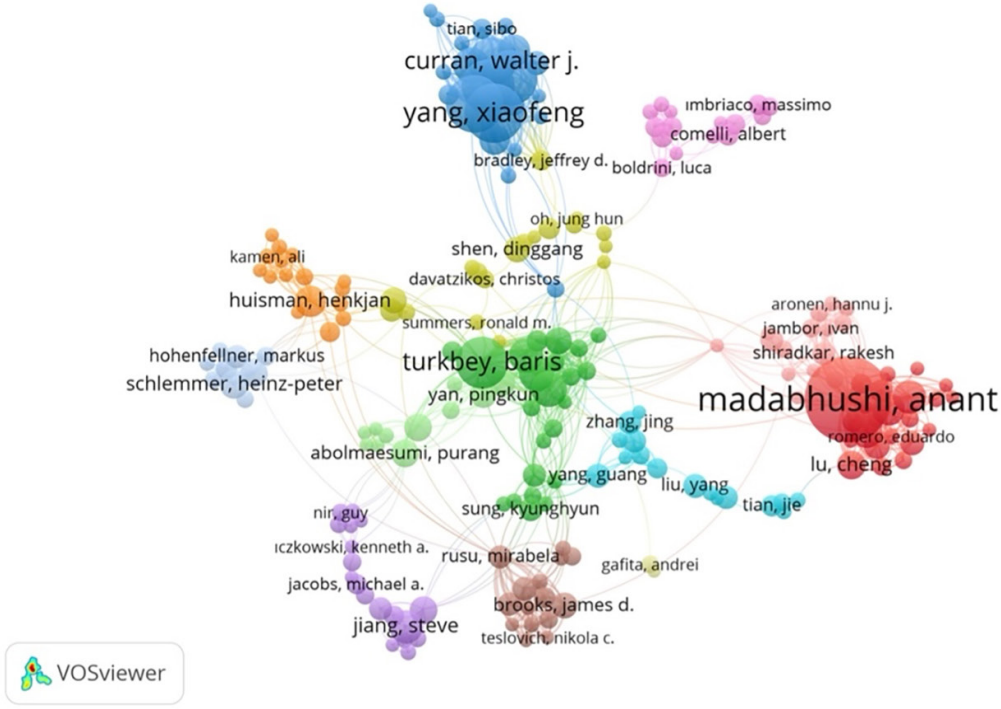
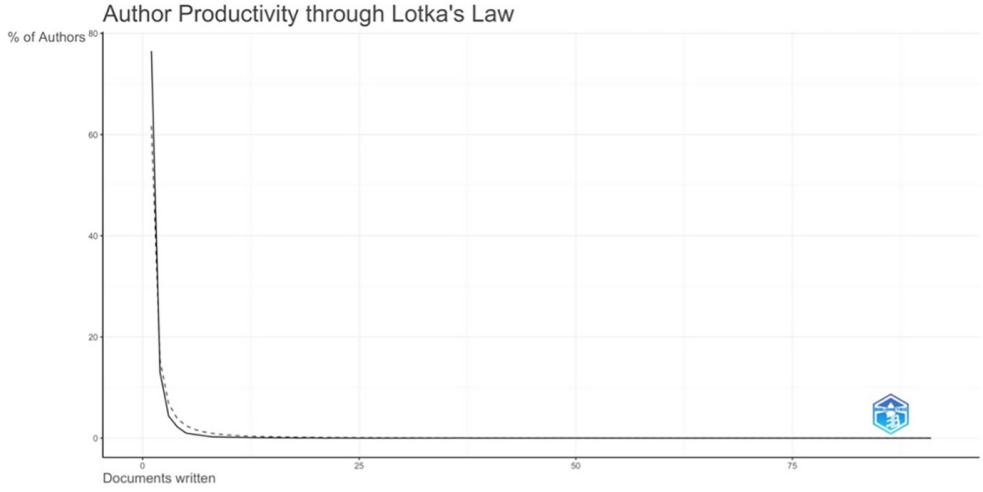
References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73:17-48.
2. Litjens G, Kooi T, Bejnordi BE, et al. A survey on deep learning in medical image analysis. Med Image Anal. 2017;42:60-88.
3. Bi WL, Hosny A, Schabath MB, et al. Artificial intelligence in cancer imaging: clinical challenges and applications. CA Cancer J Clin. 2019;69:127-157.
4. Campanella G, Hanna MG, Geneslaw L, et al. Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. Nat Med. 2019;25:1301-1309.
5. Liu Y. 3D Image Segmentation of MRI prostate based on a pytorch implementation of V-Net. J Phys Conf Ser. 2020;1549:1-6.
6. Abbasi AA, Hussain L, Awan IA, et al. Detecting prostate cancer using deep learning convolution neural network with transfer learning approach. Cogn Neurodyn. 2020;14:523-533.
7. Mylona E, Zaridis DI, Kalantzopoulos CN, et al. Optimizing radiomics for prostate cancer diagnosis: feature selection strategies, machine learning classifiers, and MRI sequences. Insights Imaging. 2024;15:265.
8. Nematollahi H, Moslehi M, Aminolroayaei F, et al. Diagnostic performance evaluation of multiparametric magnetic resonance imaging in the detection of prostate cancer with supervised machine learning methods. Diagnostics (Basel). 2023;13:806.
9. Bertelli E, Mercatelli L, Marzi C, et al. Machine and deep learning prediction of prostate cancer aggressiveness using multiparametric MRI. Front Oncol. 2021;11:802964.
10. Rodrigues A, Santinha J, Galvão B, et al. Prediction of prostate cancer disease aggressiveness using bi-parametric mri radiomics. Cancers (Basel). 2021;13:6065.
11. Cysouw MCF, Jansen BHE, van de Brug T, et al. Machine learning-based analysis of [18F]DCFPyL PET radiomics for risk stratification in primary prostate cancer. Eur J Nucl Med Mol Imaging. 2021;48:340-349.
12. T JMC, Arif M, Niessen WJ, et al. Automated classification of significant prostate cancer on MRI: a systematic review on the performance of machine learning applications. Cancers (Basel). 2020;12:1606.
13. Aria M, Cuccurullo C. Bibliometrix: an R-tool for comprehensive science mapping analysis. Journal of Informetrics. 2017;11:959-975.
14. Van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2010;84:523-538.
15. Ding X, Yang Z. Knowledge mapping of platform research: a visual analysis using VOSviewer and CiteSpace. Electron Commer Res. 2022;22:787-809.
16. Thelwall M. Bibliometrics to webometrics. J Inf Sci. 2008;34:605-621
17. Pritchard A. Statistical bibliography or bibliometrics? J Doc. 1969;25:348-349.
18. Samuel AL. Some studies in machine learning using the game of checkers. IBM J Res Dev. 1959;3:206-226
19. Rao HH, Guo F, Tian J. Improving search strategies in bibliometric studies on machine learning in renal medicine. Int Urol Nephrol. 2025;57:1987-1988.
20. Li F, Hu C, Luo X. Research hotspots and frontiers of machine learning in renal medicine: a bibliometric and visual analysis from 2013 to 2024. Int Urol Nephrol. 2025;57:907-928.
21. Zhou Z, Yu C, Liu B, et al. Landscape of surgery in Crohn's disease across twenty years: insights from machine learning. Transl Gastroenterol Hepatol. 2024;9:64.
22. Chao T, Ge Y, Sun J, Wang C. Research landscape of genetics in dilated cardiomyopathy: insight from a bibliometric analysis. Front Cardiovasc Med. 2024;11:1362551.
23. Liu Z, Zhou Z, Ma J, et al. Major depressive disease research in BRICS: a bibliometric analysis of publications from 2003 to 2022. Asian J Psychiatr. 2024;92:103900.
24. Zhao Z, Hu B, Xu K, et al. A quantitative analysis of artificial intelligence research in cervical cancer: a bibliometric approach utilizing CiteSpace and VOSviewer. Front Oncol. 2024;14:1431142.
25. Rojo Domingo M, Conlin CC, Karunamuni R, et al. Utility of quantitative measurement of T2 using restriction spectrum imaging for detection of clinically significant prostate cancer. Sci Rep. 2024;14:31318.
26. Tamada T, Takeuchi M, Watanabe H, et al. Differentiating clinically significant prostate cancer from clinically insignificant prostate cancer using qualitative and semi-quantitative indices of dynamic contrast-enhanced MRI. Discov Oncol. 2024;15:770.
27. Zhao W, Hou M, Wang J, et al. Interpretable machine learning model for predicting clinically significant prostate cancer: integrating intratumoral and peritumoral radiomics with clinical and metabolic features. BMC Med Imaging. 2024;24:353.
28. Cai JC, Nakai H, Kuanar S, et al. Fully Automated deep learning model to detect clinically significant prostate cancer at MRI. Radiology. 2024;312:e232635.



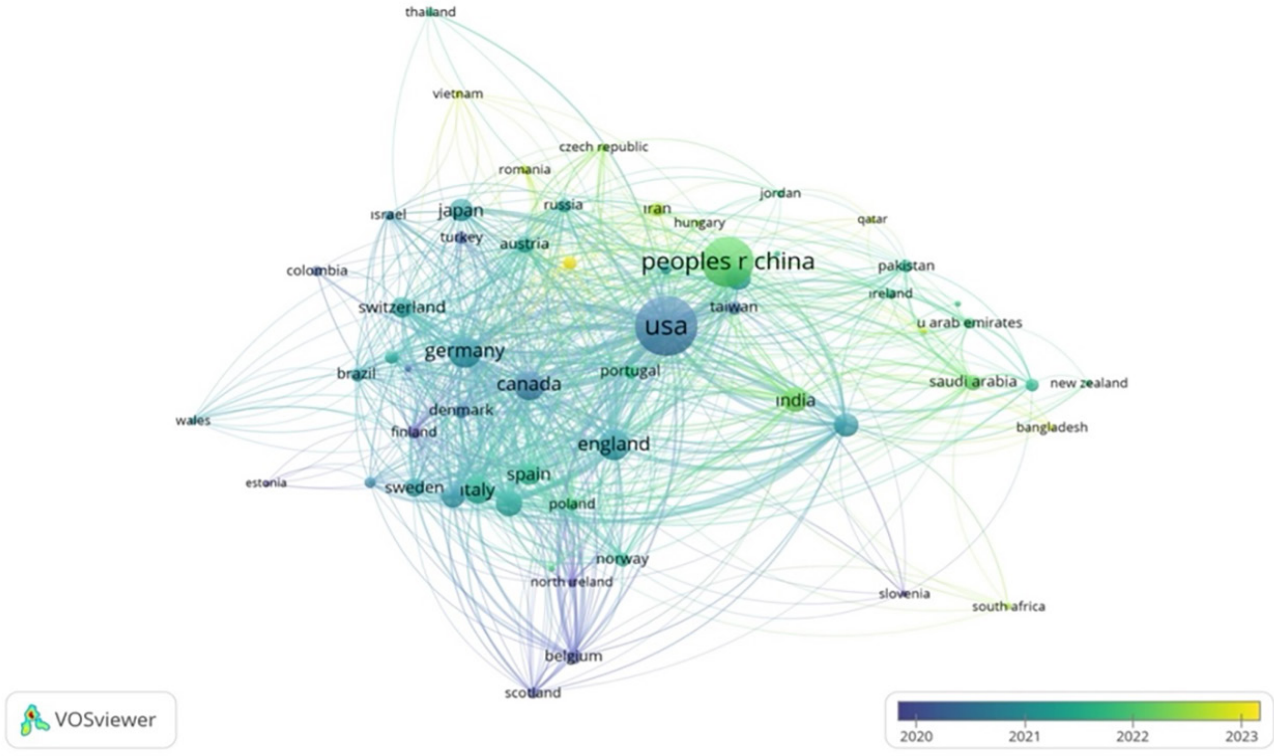
Supplementary Figure 1. Author co-authorship visualization

Articles with more than 25 authors were excluded and the complete count method was selected. The minimum number of articles and citations for an author was set at 5 and 100, respectively. These criteria were met by 259 authors. Weighting was based on the number of publications and the circle size on the map represents the number of articles



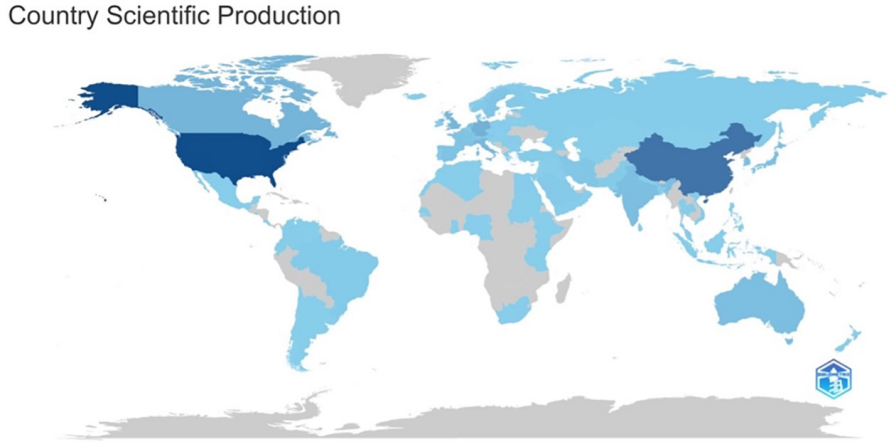
Supplementary Figure 2. Lotka's law graphics

Dashed lines indicate Lotka's law, while solid lines indicate the author productivity of the analysis



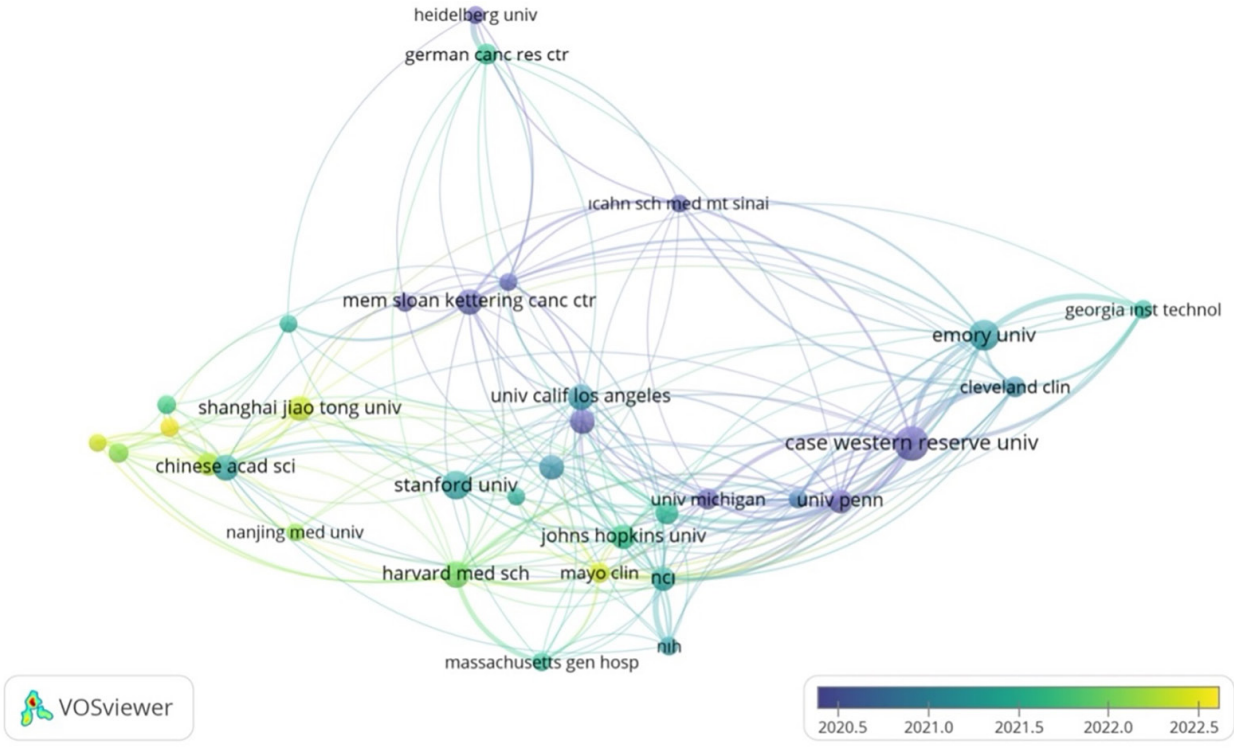
Supplementary Figure 3. Country co-authorship visualization

Articles with authors from more than 25 different countries were excluded and the full count method was selected. The minimum number of articles and citations for a country was set as 5. These criteria were met by 59 countries. The weighting was based on the number of publications and the circle size on the map represents the number of articles



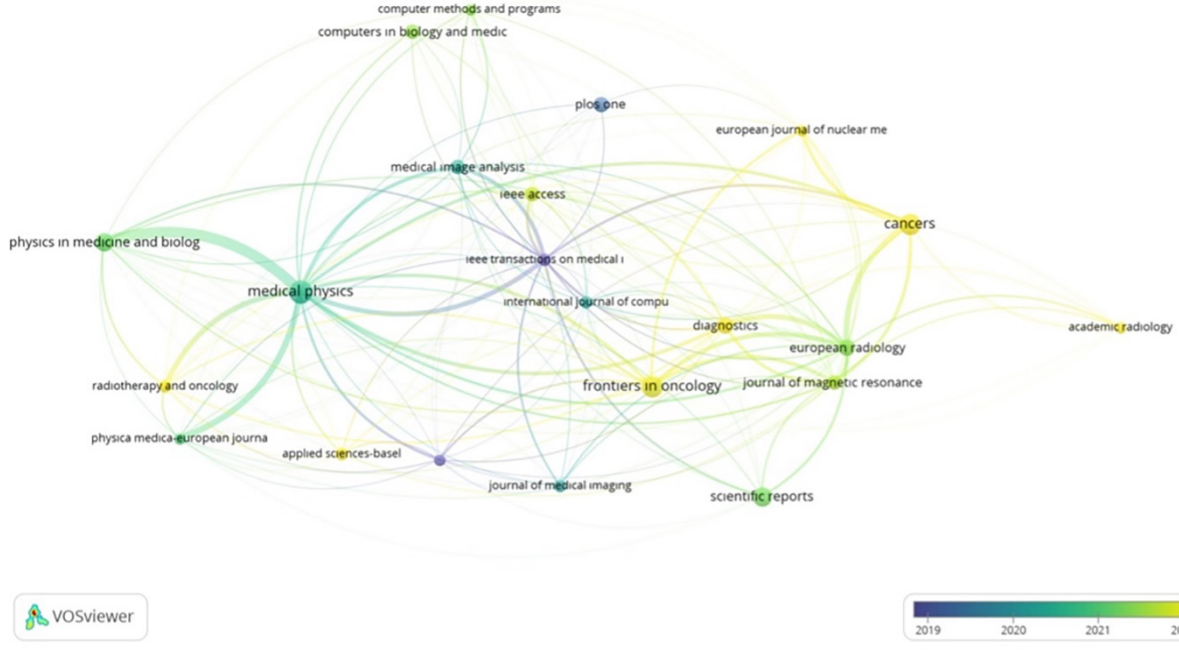
Supplementary Figure 4. Article status of countries

The countries depicted in grey do not have an associated article, while the darker shades represent those countries with the highest number of articles



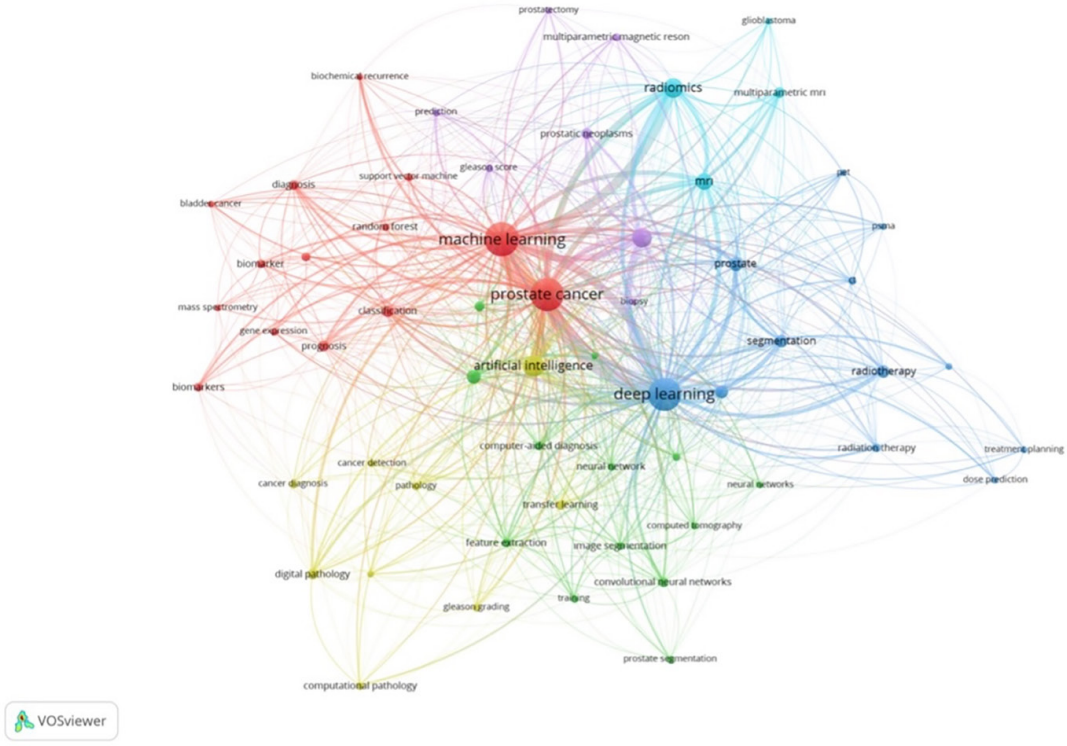
Supplementary Figure 5. Organization co-authorship visualization

Articles with authors from more than 25 different institutions were excluded and a complete count method was selected. The minimum number of articles and citations for an institution was set at 30 and 50, respectively. These criteria were met by 34 institutions. Weighting was based on the number of publications and the circle size on the map represents the number of articles



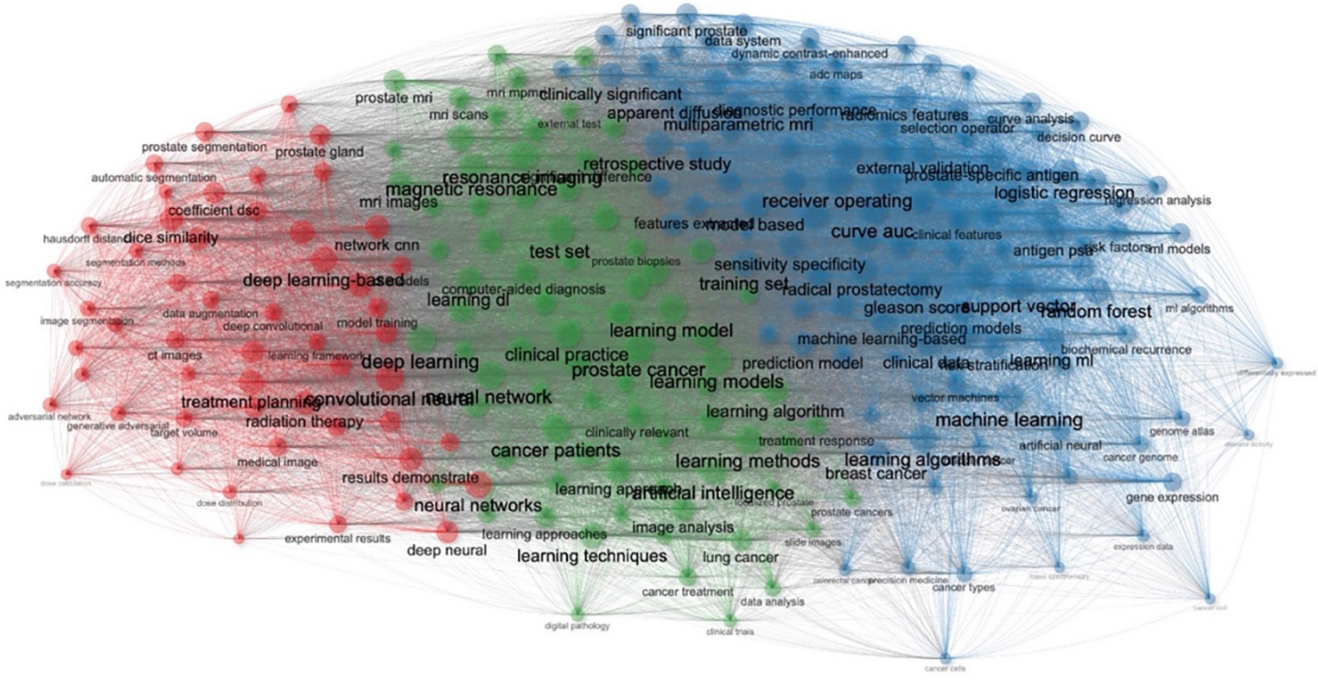
Supplementary Figure 6. Citation-source analysis visualization

The minimum number of articles and citations of a source was determined as 20 and 50, respectively. These criteria were met by 22 sources. Weighting was based on the number of publications and the circle size on the map represents the number of articles



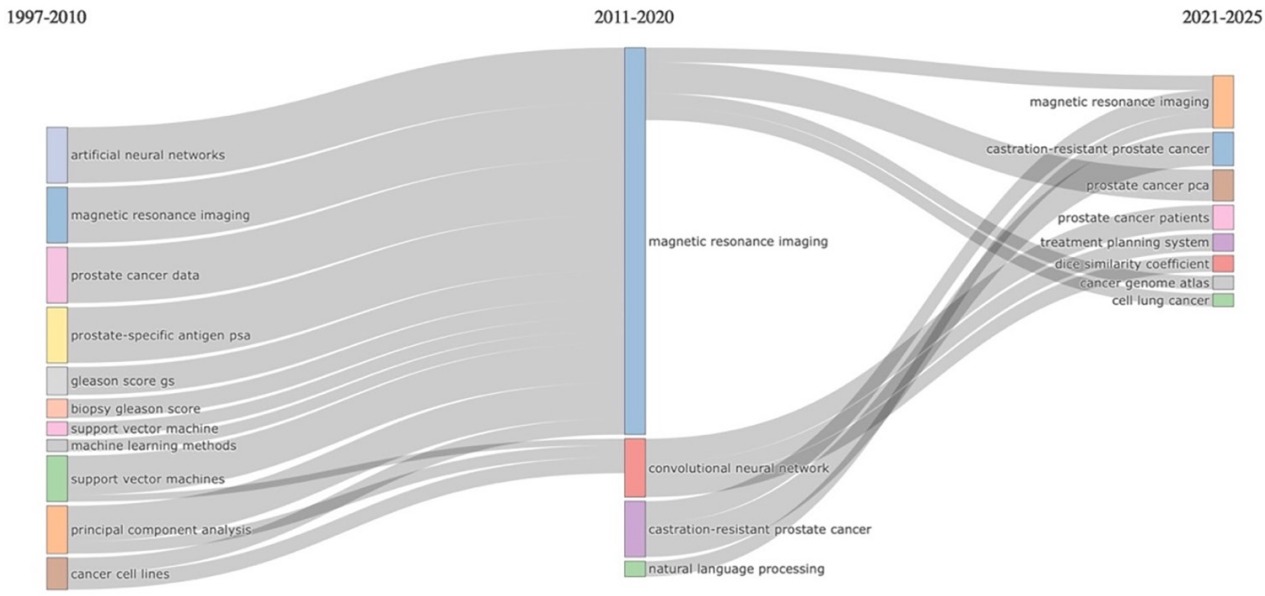
Supplementary Figure 7. Author Figure 6. keyword co-occurence visualization

The visualisation was based on the total number of occurrences and included author keywords that appeared at least 20 times. This criterion was met by 59 author keywords. Weighting was based on occurrence



Supplementary Figure 8. Thematic map

Field: Abstract, N-gram: Bigram, Word stemming: No



Supplementary Figure 9. Thematic evolution

Field: Abstract, N-gram: Trigram

Supplementary Table 1. Top ten authors with the highest number of publications

Author	Documents	Citations
Madabhushi, Anant	91	6,161
Yang, Xiaofeng	50	2,860
Liu, Tian	47	2,834
Lei, Yang	45	2,831
Wang, Tonghe	41	2,698
Turkbey, Baris	40	1,192
Curran, Walter J.	36	2,763
Patel, Pretesh	23	1,174
Choyke, Peter L.	23	499
Wood, Bradford J.	22	649

Supplementary Table 2. Top ten countries with the highest number of publications

Country	Documents	Citations
United States	1,216	41,635
China	794	14,092
Germany	262	8,339
England	245	7,529
Canada	235	8,405
Italy	192	4,256
Netherlands	163	7,347
India	147	2,138
South Korea	136	2,203
Australia	133	3,950

Supplementary Table 3. Top ten instutions with the highest number of publications

Organization	Documents	Citations	Country
Case Western Reserve University	101	6,986	USA
Emory University	79	3,904	USA
Stanford University	70	2,016	USA
Harvard Medical School	62	3,456	USA
Chinese Academy of Sciences	58	1,850	China
Memorial Sloan Kettering Cancer Center	58	3,390	USA
University of California Los Angeles	57	1,683	USA
University Toronto	55	2,356	Canada
University British Columbia	55	3,096	Canada
Johns Hopkins University	54	1,341	USA

USA: United States of America

Supplementary Table 4. Top ten sources with the highest number of publications				
Source	**WoS Index**	**WoS Quartil**	**Documents**	**Citations**
Medical Physics	SCIE	Q1	140	4,383
Cancers	SCIE	Q1	113	1,338
Frontiers in Oncology	SCIE	Q2	110	1,225
Scientific Reports	SCIE	Q1	88	2,948
Physics in Medicine and Biology	SCIE	Q1	70	2,253
Diagnostics	SCIE	Q1	57	964
European Radiology	SCIE	Q1	52	2,055
PLos One	SCIE	Q1	44	1,389
Journal of Magnetic Resonance Imaging	SCIE	Q1	42	1,211
IEEE Access	SCIE	Q2	41	518
SCIE: Science Citation Index Expanded, WoS: Web of Science, IEEE: Institute of Electrical and Electronics Engineers				

Supplementary Table 5. Top ten occurence author keywords	
Keyword	**Occurrences**
Machine learning	900
Deep learning	846
Prostate cancer	817
Artificial intelligence	298
Radiomics	242
Magnetic resonance imaging	228
MRI	147
Prostate	104
Cancer	95
Convolutional neural network	84
MRI: Magnetic resonance imaging	

Supplementary Table 6. Top ten documents with the highest number of citations		
Document	**DOI number**	**Citations**
Campanella (2019)	DOI:10.1038/s41591-019-0508-1	1295
Bi (2019)	DOI:10.3322/caac.21552	990
Bera (2019)	DOI:10.1038/s41571-019-0252-y	758
Lu (2021)	DOI:10.1038/s41551-020-00682-w	736
Cruz (2006)	N/A	718
Litjens (2016)	DOI:10.1038/srep26286	680
Mobadersany (2018)	DOI:10.1073/pnas.1717139115	616
Xu (2016)	DOI:10.1109/TMI.2015.2458702	597
Su (2001)	N/A	536
Choy (2018)	DOI:10.1148/radiol.2018171820	493
N/A: Not applicable		

Original Article

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May High Levels of Systemic Immune-inflammation Index Suggest a Further Stage in Seminomatous Testicular Germ Cell Tumors

Engin Kölükçü, Kenan Yalçın

Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Urology, Tokat, Türkiye

Abstract

Objective: This study aimed to investigate the relationship between preoperative systemic immune-inflammation index (SII) and postoperative tumor stage in patients with seminomatous testicular germ cell tumors.
Materials and Methods: A total of 33 patients who underwent radical orchiectomy and were histopathologically diagnosed with seminoma were included in the study. Patients with tumors localized to the testis were designated as group 1, while those with extratesticular spread (advanced-stage tumors) were classified as group 2. Each group was then compared based on preoperative SII levels.
Results: Group 1 consisted of 22 patients. The mean ages of groups 1 and 2 were 36.14 and 35.09 years, respectively, with no statistically significant difference between the groups ($p>0.05$). However, SII levels in group 2 were significantly higher than those in group 1, with a reported value of 924.70 ($p=0.002$). Moreover, a 10-unit increase in SII was found to increase the likelihood of advanced-stage tumors, with extratesticular spread, by approximately 6% (odds ratio =1.006).
Conclusion: This study demonstrated that high preoperative SII is significantly associated with advanced tumor stage in patients with seminoma.
Keywords: Seminom, systemic immune inflammation index, markers of inflammation, cancer, stage

Introduction

Testicular cancer accounts for 1% of all male neoplasms and 5% of all urological tumors (1). Over the past decade, the incidence of newly diagnosed testicular cancer cases has increased by an average of 0.8% per year. However, advancements in imaging techniques, the widespread adoption of cisplatin-based chemotherapy regimens, and multidisciplinary treatment approaches have significantly contributed to a decline in mortality rates (2). Radical inguinal orchiectomy and pathological assessment play a critical role in confirming the diagnosis of cancer in the evaluation of suspicious testicular masses (3). Germ cell tumors account for 90-95% of all testicular tumors (4,5). Seminomas, which account for more than half of testicular germ cell tumors, generally have a favorable prognosis (2). Although some cases exhibit elevated β-subunit of human chorionic gonadotropin (β-hCG) levels, no specific tumor marker for seminomas has been identified to date (6). In the 21st century, intensive research has continued to focus on tumor markers with different biological bases for the clinical follow-up of seminomas following radical orchiectomy.

Since Rudolf Virchow documented the presence of leukocytes in tumor tissues in the 19th century, numerous clinical and experimental studies have explored the relationship between cancer and inflammation. Today, chronic inflammation is widely recognized by oncologists as a key player in pro-tumorigenic processes, primarily by increasing the secretion of growth factors that promote rapid cell proliferation and cytokines that enhance cell motility (7,8). Consequently, the association between systemic inflammatory responses, cancer stage, and prognosis has been extensively investigated in clinical studies (1,9).

Systemic inflammatory markers can be readily assessed during the preoperative period through routine blood tests. In this context, several systemic inflammatory markers, incuding the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), have been described in previous studies (5). The systemic immune-inflammation index (SII) is another important inflammatory marker, calculated using platelet, neutrophil, and lymphocyte counts. Currently, SII is widely used in clinical studies investigating the relationship between cancer and

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Address for Correspondence: Engin Kölükçü Assoc. Prof, Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Urology, Tokat, Türkiye
E-mail: drenginkolukcu@gmail.com **ORCID:** orcid.org/0000-0003-3387-4428
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inflammation, as it combines three independent prognostic factors into a single index, making it a popular biomarker. Elevated SII levels have been documented in various studies as being associated with aggressive biological behavior of tumor cells and decreased overall survival (1,5). However, there are a limited number of studies in the English literature analyzing the relationship between SII and testicular germ cell cancer. In this retrospective study, we aimed to evaluate the association between SII and seminomatous testicular germ cell tumors.

Materials and Methods

Patients

Our study was performed in accordance with the Declaration of Helsinki Principles and with the approval of Tokat Gaziosmanpaşa University Local Ethics Committee (decision no: 25-MOBAEK-040, date: 06.02.2025). Between 2010 and 2024, the data of patients who underwent radical orchiectomy due to a preliminary diagnosis of testicular cancer at our hospital were retrospectively analyzed. A total of 33 male patients diagnosed with seminomatous testicular germ cell tumors based on the histopathological evaluation of radical orchiectomy specimens were included in the study. For all patients, the following data were recorded: age, demographic characteristics, β-hCG, lactate dehydrogenase, alpha-fetoprotein levels, complete blood cell count, tumor stage, and histopathological findings, according to the 2009 tumor, node, metastasis classification. Routine blood samples were collected within 24 hours before surgery (5). Hematological parameters were analyzed using a biochemistry analyzer that underwent regular maintenance and quality control (Mindray BC6800, China).

To assess the statistical power of the study, a post-hoc power analysis was used. An effect size of 1.5, with an α error amount of 0.05 and a subject number of n=31, determined the power of the study using an independent two-sample test, determined the power of the study as 0.97. This value shows that the statistical power of the study is relatively high.

Classification of Groups

Patients without retroperitoneal or distant metastases on computed tomography and without elevated serum tumor markers after orchiectomy (stage 1B and 1A) were categorized as localized disease and designated group 1. Patients with retroperitoneal or distant metastases or with elevated serum tumor markers after orchiectomy (stage 1S, 2, and 3), were categorized as having non-localized disease, referred to as group 2 (10).

Measurement of SII

For each patient, SII values were determined. The SII value was calculated using the formula: neutrophil × platelet / lymphocyte count (1.5). The SII values between the groups were statistically compared, aiming to analyze their predictive power in identifying advanced-stage seminomatous germ cell tumors.

Exclusion Criteria

Patients with testicular stromal tumors, non-seminomatous germ cell tumors, testicular masses suspected to be metastases from other tumors, end-stage renal disease, diabetes mellitus, cardiovascular diseases, chronic inflammatory or rheumatic diseases, receiving immunosuppressive therapy, or with infectious pathologies were excluded from the study (3,5).

Statistical Analysis

Descriptive statistics were performed to provide information about the general characteristics of the study groups. Variables were expressed as the mean ± standard deviation and the median (min-max). Differences between groups were analyzed using an independent samples t-test. P-values less than 0.05 were considered statistically significant. Receiver operating characteristic (ROC) curve analysis determined the cut-off values of the variable, according to the diagnostic group, and the area under the ROC curve (AUC) was also calculated (IBM SPSS Statistics 22, SPSS inc., an IBM Co., Somers, NY).

Results

A total of 33 patient data points were analyzed. Patients with tumors localized to the testis were classified as group 1, which consisted of 22 patients. The mean ages of groups 1 and 2 were 36.14±10.40 years and 35.09±8.65 years, respectively. There was no statistically significant difference between the groups in terms of age distribution (p>0.05). The SII value in group 2 was 924.70±298.34, which was significantly higher than in group 1 (p=0.002). Similarly, NLR and PLR values were found to be high in group 2 (p=0.003 and p<0.001, respectively) (Table 1).

Table 1. The distribution of age, and inflammatory markers by groups

	Group				p-value
	Group 1 (n=22)		Group 2 (n=11)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Age	36.14±10.40	36 (22-54)	35.09±8.65	38 (22-46)	0.776
Neutrophil	4.85±1.73	4.48 (1.90-9.90)	4.79±.83	4.51 (3.73-6.40)	0.909
Platelet	249.64±55.49	237.00 (149.0-367.0)	257.27±50.01	255.0 (192.0-360.0)	0.703
Lymphocyte	2.32±.94	2.05 (1.60-5.80)	1.43±.51	1.30 (0.80-2.60)	0.006*
NLR	2.28±1.14	2.15 (1.00-5.82)	3.65±1.20	3.5 (2.17-5.63)	**0.003***
PLR	116.33±35.24	118.50 (37.93-175.56)	193.53±56.29	176.0 (126.54-286.2)	**<0.001***
SII	536.97±203.23	504.60 (211.0-972.0)	924.70±298.34	809.8 (550.6-1288.0)	0.002*

Group 1 = Stage 1A, stage 1B, Group 2 = Stage 1S, 2, 3, Test: Independent samples t-test, *: The p-value is significant at the 0.05 level
NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SD: Standard deviation

ROC analysis was performed to evaluate the predictive ability of SII scores in staging, and the following were calculated: AUC values, accuracy, sensitivity, specificity, positive and negative predictive values, and likelihood ratio (+) values, all with 95% confidence intervals, as shown in Table 2. The ROC curve is presented in Figure 1. As a result of the ROC analysis, the SII score was found to be statistically significant between groups 1 and 2 (AUC =0.855 (0.689-0.953), p<0.001), and the discriminatory power of SII was strong. The cut-off point for the SII score was determined as 525. For this cut-off point, classification success was determined as 100.0% sensitivity and 54.55% specificity (Table 2).

Moreover, a 10-unit increase in SII was associated with a 6% increase in the likelihood of advanced-stage tumors with extratesticular spread.

Table 2. The result of ROC analysis for tumor stage

	SII
AUC	0.855 (0.689-0.953)
Level of significance p-value (area=0.5)	<0.001*
Cut-off point	>525
Sensitivity (%95 CI)	100.0 (71.5-100.0)
Specificity (%95 CI)	54.55 (32.2-75.6)

*: The p-value is significant at the 0.05 level
ROC: Receiver operating characteristic, SII: Systemic immune-inflammation index, AUC: Area under the curve, CI: Confidence interval

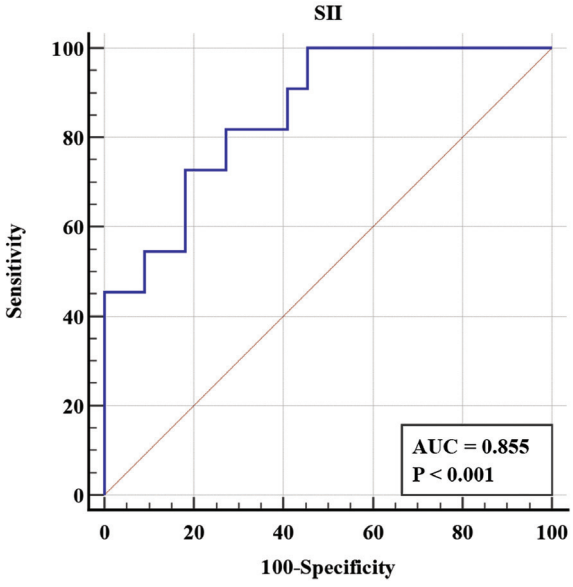

Figure 1. The result of ROC analysis for tumor stage

As a result of ROC analysis, performed according to the diagnosis group, the cut-off point for the predictor SII variable was calculated as >525. The area under the ROC curve (AUC) for this value was found to be 0.558. (0.689-0.953, 95% CI)

ROC: Receiver operating characteristic, SII: Systemic immune-inflammation index, AUC: Area under the curve, CI: Confidence interval

Discussion

In this study, we investigated the relationship between SII and tumor stage in patients with seminomatous testicular germ cell tumors. According to the data in our study, the SII value was found to be significantly higher in patients with advanced-stage tumors than in those with localized tumors. Moreover, a 10-unit increase in SII was found to increase the likelihood of advanced-stage tumors with extratesticular spread by approximately 6% (odds ratio =1.006).

Seminoma is the most common form of testicular cancer, accounting for 50% of all testicular malignancies (2). Approximately 80% of seminomas are diagnosed as stage 1 disease. These tumors are highly sensitive to both chemotherapy and radiotherapy. Unlike some specific malignancies, even in the metastatic stage, the likelihood of achieving a cure remains high. However, treatment-related morbidity should not be underestimated (6). Currently, physical examination, ultrasonography, and tumor markers are utilized by clinicians for preliminary diagnosis (4). Additionally, radiological imaging and tumor markers play a critical role in postoperative follow-up protocols (3,4). However, the sensitivity of these tumor markers is low, and they have high false-positive rates (3). Consequently, the search for an ideal biomarker for seminomas remains ongoing.

Inflammatory cells produce a vast array of cytokines that can induce tumor growth, invasion, angiogenesis, and metastasis. On the other hand, the hypothesis that the synthesis of inflammatory cytokines is triggered by the tumor microenvironment, and that this process is directly associated with changes in acute-phase reactants, has been widely accepted by many researchers (10). Neutrophils, which constitute the majority of inflammatory cells, promote tumor growth. Additionally, activated neutrophils suppress lymphocyte function and lead to a decrease in the antitumor immune response. Platelets, on the other hand, facilitate the epithelial-mesenchymal transition of tumor cells, thereby enhancing tumor invasion and metastasis. In this context, elevated SII reflects stronger pro-inflammatory activity and is thought to be associated with a greater number of circulating tumor cells and poorer tumor outcomes (4,5).

SII was first described approximately a decade ago and has been identified as a strong prognostic predictor in hepatocellular carcinoma (11). The popularity of SII has significantly increased in recent years, as it incorporates three independent inflammatory prognostic factors—platelet, neutrophil, and lymphocyte counts—which can be easily assessed using simple and routine blood tests (1,11). Additionally, SII is reported to provide a more comprehensive reflection of systemic inflammation and to have a higher predictive value compared to other inflammatory markers. In this context, SII has been extensively analyzed as a tumor marker in various types of cancer (11). A recent meta-analysis reported that SII could serve as a valuable prognostic indicator in urinary system cancers and contribute to the formulation of treatment strategies as an important inflammatory marker (12). In another meta-analysis, Li et al. (13) reported that elevated pre-treatment SII was associated with poor prognosis in urinary system cancers.

A review of previous literature indicates that studies investigating the relationship between SII and the progression of testicular cancer are limited. In their study on germ cell tumors, Chovanec et al. (14) reported that patients with low SII had significantly longer overall survival compared to those with high SII. Similarly, in the study conducted by Bumbasirevic et al. (15), it was observed that systemic inflammatory markers—including SII, NLR, PLR, LMR, and C-reactive protein—demonstrated strong performance in predicting metastatic disease in testicular germ cell tumors. In another study, Haberal et al. (16) evaluated the role of NLR, PLR, LMR, SII, and the De Ritis ratio in testicular tumors and documented that only SII was an independent prognostic factor for this malignancy. Wang et al. (4), in their study involving 112 cases (54 in the control group), reported that SII could be used as an effective tumor marker in predicting testicular germ cell tumors. Similarly, in the study conducted by Göger et al. (1), it was concluded that high SII values could serve as an important marker in the diagnosis and follow-up of testicular tumors. In the study by Imamoglu et al. (5), it was determined that SII values were significantly higher in advanced-stage seminomas compared to stage 1 seminomas. However, no significant association was observed in non-seminomas (5). In the existing literature, there are limited data on the relationship between SII and survival in testicular cancer. A recent systematic review by Salazar-Valdivia et al. (11) reported that high SII values were associated with poor overall and progression-free survival in testicular cancer (4). On the other hand, in the study by Şimsekoglu et al. (17), high SII levels were found to be associated with non-seminomatous testicular germ cell tumors; however, SII was not reported to be associated with survival outcomes. In our study, SII levels were found to be high in advanced-stage seminomatous testicular germ cell tumors. However, due to the limited study period, survival outcomes were not documented.

Study Limitations

The primary limitations of our study include its retrospective design, limited sample size, lack of survival data, and single-center nature.

Conclusion

Based on the findings of this retrospective study, elevated pre-orchiectomy SII levels were identified as a predictive marker of advanced-stage disease in seminomatous testicular germ cell tumors. In this context, it was calculated that a 10-unit increase in the SII level increased the likelihood of advanced tumors with extratesticular spread by approximately sixfold.

Ethics

Ethics Committee Approval: Our study was performed in accordance with the Declaration of Helsinki Principles and with the approval of Tokat Gaziosmanpaşa University Local Ethics Committee (decision no: 25-MOBAEK-040, date: 06.02.2025).

Informed Consent: Between 2010 and 2024, the data of patients who underwent radical orchiectomy due to a preliminary diagnosis of testicular cancer at our hospital were retrospectively analyzed.

Acknowledgements

Publication: The results of the study were not published in full or in part in form of abstracts.

Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K., K.Y., Concept: E.K., K.Y., Design: E.K., K.Y., Data Collection or Processing: E.K., K.Y., Analysis or Interpretation: E.K., K.Y., Literature Search: E.K., K.Y., Writing: E.K., K.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Göger YE, Özkent MS, Karaağaç M, et al. Prognostic value of systemic immune-inflammation index in patients with testicular cancer: a retrospective case control study. Bull Urooncol. 2021;20:252-257.
2. Gürsoy P, Çakar B, Gökmen E, et al. Epidemiological and overall survival characteristics of testicular cancers in Ege University Hospital database. Ege Journal of Medicine. 2019;58:126-132.
3. Karaslan M, Yılmaz M, Odabaş Ö. Preoperative systemic inflammation response index is associated with stage I non-seminoma testicular germ cell tumors: a retrospective pilot study. Haydarpasa Numune Med J. 2023;63:490-4.
4. Wang S, Yang X, Yu Z, et al. The values of systemic immune-inflammation index and neutrophil-lymphocyte ratio in predicting testicular germ cell tumors: a retrospective clinical study. Front Oncol. 2022;12:893877.
5. Imamoglu GI, Eren T, Baylan B, Karacın C. May high levels of systemic immune-inflammation index and hematologic inflammation markers suggest a further stage in testicular tumours? Urol Int. 2019;103:303-310.
6. Gökyer A, Küçükarda A, Köstek O. Clinical features and follow-up of pure seminoma cases: single center experience. Namik Kemal Med J. 2019;7:128-132.
7. Ravindranathan D, Master VA, Bilen MA. Inflammatory markers in cancer ımmunotherapy. Biology (Basel). 2021;10:325.
8. Hart PC, Rajab IM, Alebraheem M, Potempa LA. C-reactive protein and cancer-diagnostic and therapeutic insights. Front Immunol. 2020;11:595835.
9. Singh N, Baby D, Rajguru JP, et al. Inflammation and cancer. Ann Afr Med. 2019;18:121-126.
10. Ilktac A, Dogan B, Ersoz C, et al. The relationship of neutrophil to lymphocyte ratio with testicular cancer. Int Braz J Urol. 2020;46:101-107.
11. Salazar-Valdivia FE, Valdez-Cornejo VA, Ulloque-Badaracco JR, et al. Systemic immune-inflammation index and mortality in testicular cancer: a systematic review and meta-analysis. Diagnostics (Basel). 2023;13:843.
12. Wang Q, Zhu SR, Huang XP, et al. Prognostic value of systemic immune-inflammation index in patients with urinary system cancers: a meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25:1302-1310.
13. Li X, Gu L, Chen Y, et al. Systemic immune-inflammation index is a promising non-invasive biomarker for predicting the survival of urinary system cancers: a systematic review and meta-analysis. Ann Med. 2021;53:1827-1838.

14. Chovanec M, Cierna Z, Miskovska V, et al. Systemic immune-inflammation index in germ-cell tumours. Br J Cancer. 2018;118:831-838.
15. Bumbasirevic U, Bojanic N, Simic T, et al. Interplay between comprehensive inflammation indices and redox biomarkers in testicular germ-cell tumors. J Pers Med. 2022;12:833.
16. Haberal HB, Sarıkaya K, Sadioğlu FE, et al. The predictive role of preoperative full blood count markers and the De-Ritis ratio in the diagnosis of testicular tumor. Ege Journal of Medicine. 2022;61:145-150.
17. Şimsekoglu MF, Vural A, Macit M, et al. The clinical value of complete blood count-based immun parameter in predicting testicular cancer pathology and prognosis. Anatol Clin. 2024;29:210-216.

Original Article

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Exploring the Role of Granuloma Formation in the Prognosis of BCG-treated Bladder Carcinoma

Yasemen Adalı Ruşen[1], Uğur Mungan[2], Kutsal Yörükoğlu[3]

[1]*İzmir Democracy University Faculty of Medicine, Department of Pathology, İzmir, Türkiye*
[2]*Dokuz Eylül University Faculty of Medicine, Department of Urology, İzmir, Türkiye*
[3]*Dokuz Eylül University Faculty of Medicine, Department of Pathology, İzmir, Türkiye*

Abstract

Objective: Bacillus Calmette-Guérin (BCG) therapy continues to be a fundamental component in the treatment of non-muscle invasive bladder cancer. The objective of this study was to assess the relationship between granuloma formation resulting from BCG therapy and histopathological and clinical parameters.

Materials and Methods: This study encompassed 96 patients who underwent intravesical BCG therapy from 1990 to 2003. Post-treatment biopsy specimens were re-evaluated for the presence of granulomas. Cases demonstrating any number of granulomas were classified as positive for granulomatous response. The presence of granulomas was analyzed in relation to various factors including age, sex, pathological tumor stage, tumor grade, and the status of tumor recurrence and progression.

Results: The mean age of the cases was 64.13±10.34 years. The cases were predominantly male (85.4%, n=82) compared to those who were female (14.6%, n=14). Granuloma formation was identified in 39 cases (40.6%). Recurrence occurred in 48 cases (50%). Progression was observed in 11 patients (11.5%). The distribution of pathological stages was as follows: non-invasive tumors (pTa) in 70 cases (72.9%) and pT1 in 26 cases (27.1%). Tumor grading revealed 38 grade 1 cases (39.6%), 45 grade 2 cases (46.9%), and 13 grade 3 cases (13.5%).

Statistical analysis revealed no significant differences between cases with and without granuloma in terms of age (p=0.703), gender (p=0.052), recurrence (p=0.301), progression (p=0.761), time to recurrence (p=0.186), survival (p=0.367) or tumor grade (p=0.353). However, a significant difference was observed in the distribution of pathological stages and the frequency of granulomas was higher in cases with pT1 (p=0.011).

Conclusion: The study revealed a higher prevalence of stage pTa in patients without granulomas, suggesting that granuloma formation might be more likely in tumors that exhibit invasion. This could reflect differences in immune response elicited by BCG therapy or in biological/molecular characteristics of the tumor itself. The presence of granulomas doesn't strongly correlate with the overall prognosis. These results emphasize the need for further research to explore the mechanisms behind granuloma formation and its potential implications for treatment efficacy and patient management in more standardized case series.

Keywords: Bladder cancer, granuloma, BCG, prognosis

Introduction

Bladder cancer ranks as the ninth most common malignancy worldwide in both males and females (1). The majority of these tumors are histologically classified as urothelial carcinomas, where the extent of invasion into the bladder muscle tissue plays a crucial role in determining both the treatment strategy and prognosis. Urothelial carcinomas that do not invade the lamina propria are staged as non-invasive tumors (pTa), while those that have invaded the lamina propria are staged as pT1 (2). These tumors together are categorized as non-muscle-invasive bladder cancer (NMIBC) (3).

Intracavitary Bacillus Calmette-Guérin (BCG) instillation is a treatment modality selected based on the stage of bladder tumors and is used in addition to tumor excision (3). BCG, first introduced as an immunotherapy for NMIBC by Morales et al. (4) in 1976, is an attenuated strain of *Mycobacterium bovis* initially developed as a vaccine for *Mycobacterium tuberculosis*. A key characteristic of chronic inflammation caused by *Mycobacterium* species is granulomatous inflammation, marked by the formation of granulomas. In the context of bladder tumors, an increase in inflammatory cells within the bladder is observed following BCG instillation (5). Histopathologically, this manifests as erosion of

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Address for Correspondence: Yasemen Adalı Ruşen Assoc. Prof, İzmir Democracy University Faculty of Medicine, Department of Pathology, İzmir, Türkiye
E-mail: yasemenadali@hotmail.com **ORCID:** orcid.org/0000-0002-8004-7364
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the surface epithelium, lymphoplasmacytic cell infiltration, and granulomatous inflammation (6). These histological findings contribute to the immune response and are, in some cases, regarded as complications of BCG therapy. Among the most common local complications associated with intravesical BCG therapy, where the optimal number and frequency of applications have yet to be fully established, are cystitis and hematuria (3). BCG therapy can also lead to systemic reactions that may result in multiorgan failure, in addition to local complications such as granulomatous prostatitis and epididymoorchitis (3,7).

One of the primary objectives of administering BCG in bladder cancer, an example of field cancerization, is to prevent tumor recurrence (8). BCG functions as an immunomodulator, and its therapeutic effect is expected to be associated with granulomatous inflammation in the bladder. However, it is noteworthy that granulomas are not observed in some cases where BCG is administered, as seen in routine pathological practice. This absence of granuloma formation may be attributed to an inadequate immune response. Therefore, the aim of this study is to evaluate granuloma presence or absence, particularly focusing on recurrence and progression, with an emphasis on prognostic data.

Materials and Methods

The study was conducted following the approval of the Ethics Committee of İzmir University of Economics for Non-Interventional Research at its 52nd session (approval number: B.30.2.İEÜSB.0.05.05-20-172, date: 19.07.2022). Due to the retrospective design of the study, patient informed consent was waived. Ninety-six cases diagnosed with urothelial carcinoma between 1990 and 2003, who subsequently received intravesical BCG therapy, were included in the study. Cases diagnosed within the same time frame but lacking repeat biopsy, incomplete follow-up, or unavailable biopsy material were excluded. Hematoxylin and eosin stained sections from the repeat biopsy specimens were retrieved from the pathology archive and assessed for the presence of granulomas. Cases were considered positive for granulomas regardless of the number observed. Age and gender data were extracted from the hospital information management system, while recurrence, progression, and survival data were obtained from the records of the Department of Urology.

Statistical Analysis

Statistical analyses were conducted using the SPSS 15.0 software package (SPSS Inc., Released 2006, SPSS for Windows, Version 15.0, Chicago, SPSS Inc.). Analyses were performed using the Mann-Whitney U test and chi-square test, with a 95% confidence interval. A p-value of <0.05 was considered statistically significant.

Results

The mean age of the 96 cases included in the study was 64.1±10.3 years, with the youngest patient being 32 years old and the oldest 89 years old. Of the cases, 82 were male (85.4%) and 14 were female (14.6%), with granuloma formation observed in 39 cases (40.6%). Tumor recurrence was documented in 50% of the cases, with a mean time to recurrence of 8.0±13.8 months. Progression was noted in 11 cases (11.5%). Pathological staging revealed that 70 cases were classified as pTa (72.9%) and 26 as pT1 (27.1%). Tumor grading showed that 38 cases (39.6%) were grade 1, 45 cases (46.9%) were grade 2, and 13 cases (13.5%) were grade 3. During the follow-up period, 5 cases (5.2%) died due to causes unrelated to bladder cancer.

The mean age of the cases with granuloma was 64.5±9.6 years. Regarding the gender distribution, 30 cases (76.9%) were male, and 9 cases (23.1%) were female. Tumor recurrence was detected in 22 cases (56.4%), while progression was noted in 4 cases (10.3%). The pathological stages among these cases were classified as pTa in 23 cases (59.0%) and pT1 in 16 cases (41.0%). Tumor grading revealed that 16 cases (41.0%) were grade 1, 13 cases (33.3%) were grade 2, and 10 cases (25.6%) were grade 3.

The mean age of the cases without granuloma was 63.9±10.9 years. Among these cases, 52 (91.2%) were male and 5 (8.8%) were female. Tumor recurrence was observed in 26 cases (45.6%), while progression was noted in 7 cases (12.3%). In this group, 47 cases (82.5%) were classified as pTa, and 10 cases (17.5%) as pT1. Tumor grading showed that 22 cases (38.6%) were grade 1, 32 cases (56.1%) were grade 2, and 3 cases (5.3%) were grade 3. Clinicopathological characteristics and outcomes in cases with and without granuloma formation following BCG therapy are summarized in Table 1.

In statistical analyses using the Mann-Whitney U test, no statistically significant relationship was found between granuloma formation and age ($p=0.703$), gender ($p=0.052$), or tumor grade ($p=0.353$). Similarly, no significant association was observed between granuloma formation and progression ($p=0.761$), recurrence ($p=0.301$), time to recurrence ($p=0.186$), or survival ($p=0.367$). In gender analyses, which were found to be close to statistical significance ($p=0.052$), it was observed that male dominance was striking in cases where granuloma formation was not observed (91.2% vs. 23.1%). Statistically significant results were obtained in the analysis of granuloma formation in relation to pT stage, indicating that granuloma development is less common in pTa ($p=0.011$).

Discussion

Approximately 25% of bladder cancers are muscle-invasive or metastatic, and treatment modalities for this patient group include neoadjuvant chemotherapy, radical cystectomy, and adjuvant chemotherapy (9). In non-muscle-invasive bladder cancers, intravesical chemotherapy can be administered following tumor resection via transurethral resection of the bladder tumor, which is advantageous, as it avoids the systemic effects of chemotherapy and significantly reduces disease recurrence (3,10). Although non-muscle-invasive bladder cancers generally have a relatively favorable prognosis, with a 5-year survival rate exceeding 85%, they present challenges related to patient quality of life and impose a substantial burden on the healthcare system due to frequent recurrences (11-13).

Intracavitary BCG is utilized as the primary treatment option for non-muscle-invasive bladder cancers at high risk of recurrence (14). Intravesical BCG administration has been shown to reduce recurrence, inhibit tumor progression, and improve

Table 1. Clinicopathological characteristics and outcomes in cases with and without granuloma formation following BCG therapy			
Variable	**Total cases (n=96)**	**With granuloma (n=39)**	**Without granuloma (n=57)**
Mean age (years)	64.1±10.3	64.5±9.6	63.9±10.9
Age range (years)	32-89	-	-
Gender			
- Male	82 (85.4%)	30 (76.9%)	52 (91.2%)
- Female	14 (14.6%)	9 (23.1%)	5 (8.8%)
Granuloma formation	39 (40.6%)	-	-
Pathological stage			
- pTa	70 (72.9%)	23 (59.0%)	47 (82.5%)
- pT1	26 (27.1%)	16 (41.0%)	10 (17.5%)
Tumor grade			
- Grade 1	38 (39.6%)	16 (41.0%)	22 (38.6%)
- Grade 2	45 (46.9%)	13 (33.3%)	32 (56.1%)
- Grade 3	13 (13.5%)	10 (25.6%)	3 (5.3%)
Tumor recurrence	48 (50%)	22 (56.4%)	26 (45.6%)
Mean time to recurrence (months)	8.0±13.8	-	-
Tumor progression	11 (11.5%)	4 (10.3%)	7 (12.3%)
BCG: Bacillus Calmette-Guérin, pTa: Non-invasive tumors, pT1: Low-grade and invasive tumors			

survival rates (15-17). Since Pearl's (18) 1928 article, which noted a lower incidence of tumors in autopsies of patients with tuberculosis, numerous studies have explored the relationship between tumors and tuberculosis (19-22). Early experimental studies evaluating the effects of BCG on tumors suggested that its mechanism of action was not direct cytotoxicity but rather the host's immune response (23,24). Since then, the therapeutic efficacy of BCG has been investigated across various tumor types, including melanoma (25). A significant milestone following the development of the BCG vaccine by Albert Calmette and Camille Guérin in 1921 was the 1976 report by Morales et al. (4), which demonstrated the efficacy of intracavitary BCG in treating non-muscle-invasive bladder tumors.

Since the introduction of BCG in the treatment of bladder cancer, our understanding of its mechanism of action has been continually refined. Tissue and fluid analyses from patients undergoing BCG therapy suggest that intravesical administration induces a multifaceted and complex immune response, involving both innate and adaptive immunity (26). Following BCG administration, inflammatory cells, predominantly granulocytes, macrophages, and lymphocytes, are readily observed in the urine (27). It has been reported that CD4+ T lymphocytes are the predominant cell typewhile similar cells are observed in the tissue response (5). Indeed, some studies have indicated that BCG immunization results in an accelerated T cell response (22). Histopathological examination of tissues reveals granulomatous inflammation, with lymphoplasmacytic inflammatory cells surrounding the granulomas (6).

Following intracavitary BCG administration, cytokine and chemokine secretions from urothelial and antigen-presenting cells are believed to stimulate the cellular components of the immune system (26). Histopathological examinations have demonstrated the presence of macrophages and dendritic cells in the bladder tissues of patients receiving BCG therapy (5) with an increased pre-treatment number of these cells being associated with poor prognosis (28,29). There are relatively few prognostic studies on granulomatous inflammation, the characteristic inflammation type induced by BCG treatment. Two of the few studies available suggest that granuloma formation is not associated with prognosis (30,31). However, Jallad et al. (32), who reported a relationship between granuloma formation and prognosis, evaluated granuloma and inflammation as two separate parameters in their study involving 215 cases. In their analysis, which grouped cases according to the presence or absence of granuloma/inflammation, they found that the absence of granuloma/inflammation was associated with a higher recurrence rate. Additionally, progression-free survival was reported to be higher in the presence of granuloma/inflammation (32).

In this study, no significant relationship was observed between granuloma formation and tumor grade, progression, recurrence, or survival. However, granuloma formation was significantly more common in pT1 tumors than in pTa tumors (p=0.011). This finding suggests that immune response alterations due to tumor invasion may trigger the immune mechanisms necessary for granuloma formation. While this phenomenon may be related to the immune response elicited by BCG, it could also be associated with the expression of different antigens at various pT stages of the tumor or even an increase in tumor mutational burden (TMB). The existence of studies highlighting the central role of the CD4+ T cell response in BCG treatment; the significance of the CD8+ T cell response; and their relationship with the programmed cell death ligand response supports this hypothesis (33,34). Additionally, considering the critical role of T cells in the

antitumor response, including granuloma formation, there is a need for further investigation in homogeneous and larger case series across different pT stages, in which tumor antigen load and TMB are evaluated alongside the depth of invasion.

Study Limitations

The preimmunization status of the cases included in this study with the BCG vaccine is unknown. This limitation, which is also present in many studies in the literature (32), impacts the study's ability to measure the effect of cytokine and T cell responses that could directly develop by bypassing the antigen-presenting cell step (potentially influenced by preimmunization). We believe that future studies should consider the inclusion of distinct groups of preimmunized and non-immunized cases in the selection of case series. This approach could be a significant step toward optimizing study outcomes.

Another limitation of this study is that the tumor grading was derived from the original pathology reports. Grading based on the 1973 World Health Organization criteria was found not to influence granuloma formation. Given that pTa are typically low-grade and invasive tumors (pT1) tend to be high-grade, similar results could be obtained when considering tumor stage (5).

Conclusion

While the roles of innate and adaptive immunity are evident in the mechanism of action of BCG, the precise mechanisms that determine the response to treatment remain incompletely understood. The evaluation of granuloma formation—potentially one of these mechanisms—alongside immune system components and the biological and molecular characteristics of the tumor at different stages, could provide valuable insights for predicting treatment response. Unraveling the mechanisms involved in BCG treatment may also provide information that guides immunotherapy, which has come to the forefront in cancer treatment today.

Ethics

Ethics Committee Approval: The study was conducted following the approval of the Ethics Committee of İzmir University of Economics for Non-Interventional Research at its 52nd session (approval number: B.30.2.İEÜSB.0.05.05-20-172, date: 19.07.2022).

Informed Consent: Due to the retrospective design of the study, patient informed consent was waived.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.A.R., U.M., K.Y., Concept: Y.A.R., K.Y., Design: Y.A.R., U.M., K.Y., Data Collection or Processing: Y.A.R., K.Y., Analysis or Interpretation: Y.A.R., U.M., K.Y., Literature Search: Y.A.R., U.M., K.Y., Writing: Y.A.R., U.M., K.Y.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:359-386.
2. College of American Pathologists. Protocol for the examination of specimens from patients with urinary bladder biopsy. 2020. Available from: https://documents.cap.org/protocols/cp-urinary-bladder-biopsy-20-4020.pdf [Accessed 11 Aug 2020].
3. Babjuk M, Burger M, Compérat EM, et al. European association of urology guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) - 2019 update. Eur Urol. 2019;76:639-657.
4. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol. 1976;116:180-183.
5. Böhle A, Gerdes J, Ulmer AJ, et al. Effects of local bacillus Calmette-Guerin therapy in patients with bladder carcinoma on immunocompetent cells of the bladder wall. J Urol. 1990;144:53-58.
6. Lage JM, Bauer WC, Kelley DR, et al. Histological parameters and pitfalls in the interpretation of bladder biopsies in bacillus Calmette-Guerin treatment of superficial bladder cancer. J Urol. 1986;135:916-919.
7. Kiely B, McLaughlin AM, Lynch TH, Keane J. Intravesical bacille Calmette-Guérin-induced multiorgan failure after treatment for transitional cell carcinoma. Scand J Urol Nephrol. 2011;45:278-280.
8. Curtius K, Wright NA, Graham TA. An evolutionary perspective on field cancerization. Nat Rev Cancer. 2018;18:19-32.
9. Witjes JA, Bruins HM, Cathomas R, et al. European association of urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. Eur Urol. 2021;79:82-104.
10. Messing EM, Tangen CM, Lerner SP, et al. Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. JAMA. 2018;319:1880-1888.
11. Berdik C. Unlocking bladder cancer. Nature. 2017;551:34-35.
12. James AC, Gore JL. The costs of non-muscle invasive bladder cancer. Urol Clin North Am. 2013;40:261-269.
13. Abdollah F, Gandaglia G, Thuret R, et al. Incidence, survival and mortality rates of stage-specific bladder cancer in United States: a trend analysis. Cancer Epidemiol. 2013;37:219-225.
14. Álvarez-Maestro M, Guerrero-Ramos F, Rodríguez-Faba O, et al. Current treatments for BCG failure in non-muscle invasive bladder cancer (NMIBC). Actas Urol Esp (Engl Ed). 2021;45:93-102.
15. Malmström PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol. 2009;56:247-256.
16. Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol. 2002;168:1964-1970.
17. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol. 2000;163:1124-1129.
18. Pearl R. On the pathological relations between cancer and tuberculosis. Exp Biol Med (Maywood). 1928;26:73-75.

19. Old LJ, Clarke DA, Benacerraf B. Effect of bacillus Calmette-Guerin infection on transplanted tumours in the mouse. Nature. 1959;184(Suppl 5):291-292.
20. Davignon L, Lemonde P, St-Pierre J, Frappier A. B.C.G. vaccination and leukaemia mortality. Lancet. 1971;1:80-81.
21. Mathé G, Amiel JL, Schwarzenberg L, et al. Active immunotherapy for acute lymphoblastic leukaemia. Lancet. 1969;1:697-699.
22. Yada Y, Tanaka N, Orita K. Augmentation of anti-tumor activity by immunization with Mycobacterium tuberculosis (Tbc) and tuberculin-coupled tumor cells. Acta Med Okayama. 1985;39:131-141.
23. Rosenthal SR, Crispen RG, Thorne MG, et al. BCG vaccination and leukemia mortality. Natl Cancer Inst Monogr. 1973;39:189-192.
24. Bast RC Jr, Zbar B, Borsos T, Rapp HJ. BCG and cancer. N Engl J Med. 1974;290:1458-1469.
25. Morton DL, Eilber FR, Holmes EC, et al. BCG immunotherapy of malignant melanoma: summary of a seven-year experience. Ann Surg. 1974;180:635-643.
26. Pettenati C, Ingersoll MA. Mechanisms of BCG immunotherapy and its outlook for bladder cancer. Nat Rev Urol. 2018;15:615-625.
27. Chevalier MF, Trabanelli S, Racle J, et al. ILC2-modulated T cell-to-MDSC balance is associated with bladder cancer recurrence. J Clin Invest. 2017;127:2916-2929.
28. Takayama H, Nishimura K, Tsujimura A, et al. Increased infiltration of tumor-associated macrophages is associated with poor prognosis of bladder carcinoma in situ after intravesical bacillus Calmette-Guerin instillation. J Urol. 2009;181:1894-1900.
29. Ayari C, LaRue H, Hovington H, et al. Bladder tumor-infiltrating mature dendritic cells and macrophages as predictors of response to bacillus Calmette-Guérin immunotherapy. Eur Urol. 2009;55:1386-1395.
30. Bassi P, Milani C, Meneghini A, et al. Clinical value of pathologic changes after intravesical BCG therapy of superficial bladder cancer. Urology.1992;40:175-179.
31. Pieras-Ayala E, Palou-Redorta J, Tomero-Ruiz JI, et al. Prognostic value of cystoscopically pseudotumoral lesions (inflammation/granuloma) in primary stage T1 grade 3 bladder tumors treated with BCG. Int Urol Nephrol. 2001;33:469-472.
32. Jallad S, Goubet S, Symes A, et al. Prognostic value of inflammation or granuloma after intravesical BCG in non-muscle-invasive bladder cancer. BJU Int. 2014;113:22-27.
33. Antonelli AC, Binyamin A, Hohl TM, et al. Bacterial immunotherapy for cancer induces CD4-dependent tumor-specific immunity through tumor-intrinsic interferon-γ signaling. Proc Natl Acad Sci U S A. 2020;117: 18627-18637.
34. Kates M, Matoso A, Choi W, et al. Adaptive immune resistance to intravesical BCG in non-muscle invasive bladder cancer: implications for prospective BCG-unresponsive trials. Clin Cancer Res. 2020;26:882-891.

Original Article

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Learning Curve of Laparoscopic Radical Prostatectomy Without Mentor Guidance: A Single Surgeon's Experience Following a 2-Month Observership

Fatih Bıçaklıoğlu

Kartal Dr. Lütfi Kırdar City Hospital, Department of Urology, İstanbul, Türkiye

Abstract

Objective: To evaluate the learning curve of a single surgeon performing 72 laparoscopic radical prostatectomy (LRP) cases without mentorship, following a two-month advanced laparoscopy observership.

Materials and Methods: The urologist, without prior LRP experience, underwent observership in a high-volume center before independently performing 72 LRP procedures over three years. Cases were divided into two groups: group A (first 36 cases) and group B (subsequent 36 cases). Data on demographics, operative parameters, complications, and surgical outcomes were analyzed. Crucial parameters, including total operation time, lymphadenectomy time, and urethrovesical anastomosis time, were compared between groups.

Results: Group B showed significant improvements in total operation time ($p=0.008$), lymphadenectomy time ($p=0.001$), and urethrovesical anastomosis time ($p<0.001$). However, group B, significantly influenced by high-risk cases and a rectal injury complication, had longer hospital stays and urinary catheter durations. Despite a higher rate of high-risk cases in group B, there was no significant difference in overall complication rates or positive surgical margins. One case required conversion to open surgery due to rectal injury.

Conclusions: Significant improvements in operative times were observed; however, complication rates and positive surgical margins did not differ significantly between groups, likely influenced by the higher proportion of high-risk patients in the second group. While these findings suggest that LRP can be performed without direct mentorship, the study's single-surgeon experience and limited sample size restrict generalizability. Longer follow-up and larger studies are needed to assess oncological and functional outcomes and to further optimize the learning curve.

Keywords: Prostate cancer, laparoscopic radical prostatectomy, learning curve, advanced laparoscopy

Introduction

According to Global Cancer Observatory 2022 data, prostate cancer is the second most common cancer and the fifth leading cause of cancer-related death among men (1). Radical prostatectomy, a definitive surgical intervention for the treatment of prostate cancer, may be performed using open, laparoscopic, and robot-assisted laparoscopic techniques. The rise of robotic-assisted radical prostatectomy (RARP) is driven by its benefits, including reduced blood loss, faster recovery, improved functional outcomes, and a shorter learning curve compared to open radical prostatectomy (ORP) and laparoscopic radical prostatectomy (LRP). Due to the high costs of robotic-assisted surgery, LRP remains a cost-effective and minimally invasive alternative in some countries (2,3).

Surgeons in high-volume prostate cancer centers around the world have transitioned from LRP to RARP over the years, as observed in the study by Sivaraman et al. (4). The reduction in the number of high-volume centers and experienced surgeons performing LRP has made it increasingly difficult for trainees to gain exposure to this technique. This decline also complicates the learning curve, particularly in the early stages, where having a mentor is critical for developing proficiency (5).

The present study was designed to evaluate the LRP learning curve of a urologist naive to LRP education who started performing LRP without a mentor-initiated approach after a two-month advanced laparoscopy observership in a high-volume center.

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Address for Correspondence: Fatih Bıçaklıoğlu MD, Kartal Dr. Lütfi Kırdar City Hospital, Department of Urology, İstanbul, Türkiye
E-mail: fatihbicaklioglu@hotmail.com **ORCID:** orcid.org/0000-0001-7175-713X
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Materials and Methods

Education and LRP Training

The urologist who performed the procedures in this study completed his residency in a clinic where LRP was not performed, but ORP and RARP were commonly. During his residency, the urologist assisted in numerous ORP and RARP cases and performed a limited number of ORP cases as the primary surgeon. In terms of laparoscopic surgery, the surgeon performed renal cyst excision and nephrectomies during his residency.

In the six-year period following his residency, the urologist performed renal cyst excisions, nephrectomies, ureterolithotomies, and pyelolithotomies as laparoscopic surgeries, and a small number of ORP for prostate cancer. In the sixth year after completing residency, the urologist received a two-month advanced laparoscopy observership at a high-volume center where all radical prostatectomies were performed laparoscopically, although robotic surgery was not available. During this two-month training, the urologist did not assist in or perform LRP cases but observed them externally. In his free time, the urologist extensively reviewed video archives of past surgeries from the clinic and practiced on a personal laparoscopic training box. Specifically, he worked on "laparoscopic urethrovesical anastomosis'' using a urethrovesical anastomosis model created with a condom catheter (Figure 1).

LRP Technique and Incorporation Into Home Practice

In September 2021, the urologist began performing LRP at a center where LRP had not been previously performed, without mentorship, performing all of his radical prostatectomies laparoscopically. Between September 2021 and July 2024, a total of 72 cases were performed by the same urologist in two different centrers. Each case was performed with two urology residents and one surgical nurse, without the assistance of a senior urologist or a mentor.

All LRP procedures were performed using "The Descending Technique (Clinique Saint Augustine)'' (6). According to the European Association of Urology (EAU) risk classification system, extended pelvic lymphadenectomy (eLND) was not performed on patients classified as low-risk. Additionally, intermediate-risk patients with a less than 5% predicted risk of lymph node invasion, as calculated by Briganti nomogram, were also excluded from eLND. eLND was performed on patients classified as high-risk and intermediate-risk with a greater than or equal to 5% predicted risk of lymph node invasion. Initially, the urologist opted for an extraperitoneal approach for patients undergoing LRP and a transperitoneal approach for those with eLND. However, from the 53rd case onward, all procedures were performed using the transperitoneal approach, in accordance with the surgeon's preference. The urethrovesical anastomosis was performed using the Van Velthoven et al. (7) technique with a running 2-arm 3-0, 5/8 V-Loc suture (Medtronic, Minneapolis, USA).

Data Collection

Ethics approval was obtained from the local ethical board. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital (protocol no: 2024/010.99/10/4, date: 29.11.2024). Written informed consent was obtained from all participants included in the study. Prospectively collected retrospective demographic, operative and postoperative data of 72 patients were collected. "Total operation time" was measured from the insertion of the first trocar to the removal of the last trocar. "Lymphadenectomy time" was measured from the first peritoneotomy to the placement of the lymphadenectomy specimens into a bag. "Radical prostatectomy time" was calculated by subtracting the lymphadenectomy time from the total operation time in patients who underwent lymphadenectomy. For patients without lymphadenectomy, the total operation time was considered "radical prostatectomy time". "Urethro-vesical anastomosis time" was measured from the initial grasp with the needle holder to the final knot of the anastomosis. The presence of tumor cells at the inked margin in the prostatectomy specimen is considered evidence of a positive surgical margin. Serum prostate specific antigen (PSA) levels of 0.1 ng/mL or higher were defined as persistent PSA. Serum PSA levels of 0.2 ng/mL or higher were defined as biochemical recurrence (BCR).

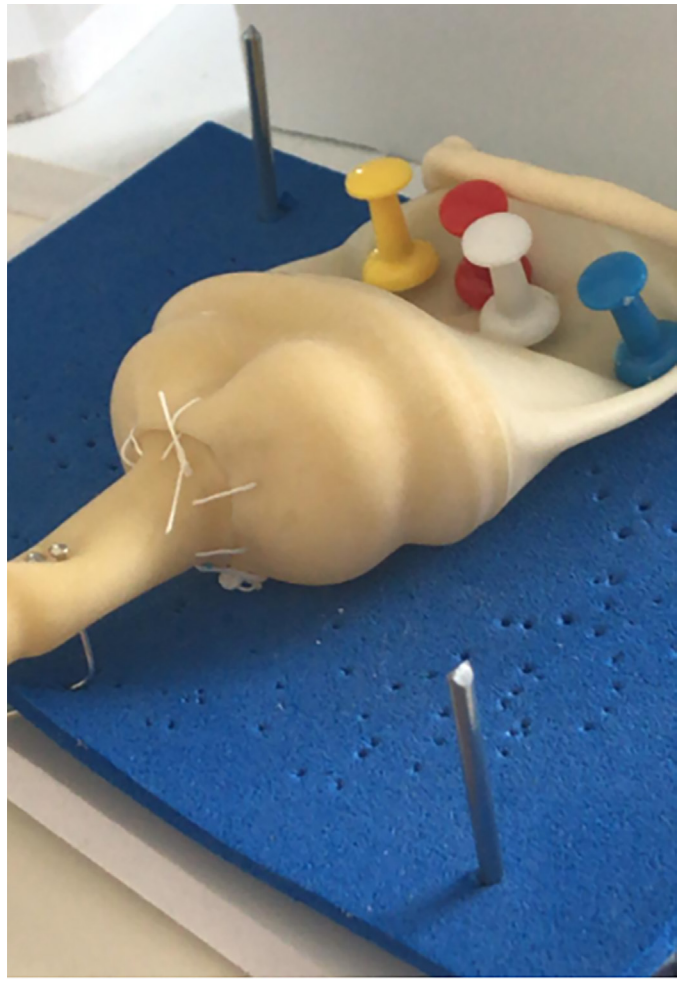

Figure 1. Urethrovesical anastomosis model created with a condom catheter

The study group of 72 patients was divided into two groups: group A comprising the first 36 patients, and group B comprising the subsequent 36 patients. The learning curve was evaluated by analyzing various parameters between these two groups, including operation time, complications, hospitalization time, and others.

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). The data were divided into 2 groups, each containing 36 patients. Normality of continuous variables was assessed using the Shapiro-Wilk test. Variables that followed a normal distribution were analyzed using the Student's t-test, while variables that did not follow a normal distribution were analyzed using the Mann-Whitney U test. Categorical variables were compared using the chi-square test. When the expected frequency in any cell was less than 5, Fisher's exact test was used to ensure the accuracy of the results. A p-value of less than 0.05 was considered statistically significant.

Results

The mean age of all patients was 63.72±6.08. The mean PSA value was 8.24±4.65. Patient characteristics, peroperative, and postoperative data are presented in Table 1. There were no significant differences among the groups in age, PSA and PSA density (p>0.05, all). Patient characteristics, and peroperative and postoperative data of the two groups are presented in Table 2 and Table 3.

There was a statistically significant difference in total operation time, lymphadenectomy time, radical prostatectomy time, and urethro-vesical anastomosis time (p-values, respectively: 0.008, 0.001, <0.001, <0.001). All of these operative times were shorter in group B.

Table 1. Patient characteristics, perioperative and postoperative data of all patients

	N	Mean	SD
Age (years)	72	63.72	6.08
PSA (prostate spesific antigen - ng/mL)	72	8.24	4.65
Prostate weight (g)	72	56.25	35.49
PSA density	72	0.219	0.233
Total operation time (min)	72	212.42	53.91
Lymphadenectomy time (min)	26	81.92	21.74
Radical prostatectomy time (min)	71*	183.31	44.24
Urethro-vesical anastomosis time (min)	71*	33.34	14.34
Hematocrit drop	72	6.54	316
Hospitalization time (day)	72	5.06	4.41
Urinary cathater time (day)	72	15.53	13.93
Removed lymph node count	26	16.62	6.89

*: One patient's surgery converted to open after rectal injury and urethro-vesical anastomosis was not performed laparoscopicaly. This patient excluded from "radical prostatectomy time" and "urethro-vesical anastomosis time"
PSA: Prostate specific antigen, SD: Standard deviation

There was a statistically significant difference in hospitalization time and urinary catheter time (p-values, respectively: 0.012 for urinary catheter time). But hospitalization time and urinary catheter time were shorter in group A. One patient in group B, who suffered a rectal injury, had an extended hospitalization time of 38 days and a urinary catheter time of 130 days due to complications, which significantly influenced the statistical analysis. Upon excluding these outliers, the median values were recalculated, and a statistically significant difference between the two groups remained (p-values: 0.029 and 0.019, respectively).

There was a statistically significant difference in prostate biopsy Gleason grades and EAU risk groups (p-values: 0.012 and 0.019, respectively). There were more low-risk patients in group A and more high-risk patients in group B. As a result, there were statistically significant differences in nerve-sparing surgery, bilateral pelvic eLND, pathological lymph node involvement, radical prostatectomy pathology, and radical prostatectomy Gleason grades (p-values, respectively: 0.009, 0.049, 0.011, 0.031, and 0.022).

Nerve-sparing status, complications, and additional intervention data of all patients are in Table 4. Nerve-sparing surgery was performed on 35 of our patients (48.6%), and non-nerve-sparing surgery was performed on 37 patients (51.4%). Only one patient required a general surgery consultation following a rectal injury, and conversion to open surgery was performed. This was based on the general surgeon's decision for rectal repair and indwelling colostomy. No other patient in the series required conversion from laparoscopy to open surgery. The overall complication rate was 26.4% (19 out of 72 patients). Among these, only 3 patients (4.1%) experienced grade 3 complications according to the Dindo et al. (8) classification. Due to early postoperative spontaneous urethral catheter removal, cystourethroscopy for urethral catheter placement over a guidewire under local anesthesia, (grade 3A) was performed in two patients. In one patient, a lymphocele required drainage under local anesthesia (grade 3A), and the same patient underwent perineal rectourethral fistula repair with a gracilis muscle flap under general anesthesia (grade 3B). The remaining complications were classified as grade 1 and grade 2.

Among 72 patients, 20 had positive surgical margins. The sites of positive surgical margins were as follows: 1 at the base, 4 at the apex, 12 at the posterolateral, 1 at both the base and the posterolateral, 1 at both the apex and the posterolateral, and 1 at both the apex and the base. Importantly, none of our patients had intraprostatic incision on pathology reports and of these 20 patients with positive margins, 6 had 1 mm Gleason grade 3 at the margin, and 3 had 1 mm Gleason grade 4 at the margin. Additionally, 4 patients had pathological lymph node involvement in this surgical margin positive group, of which 3 experienced persistent PSA and 2 developed metastatic disease as confirmed by postoperative prostate-specific membrane antigen positron emission tomography/computed tomography. With the exception of the patients exhibiting persistent PSA levels, none of the other patients has yet developed BCR. However, the follow-up periods for these patients were as follows: 6 patients with 1 year of follow-up, 2 patients with 9 months of follow-up, 4 patients with 6 months of follow-up, and 5 patients with 3 months of follow-up.

Table 2. Comparison of group A and group B's patient characteristics, perioperative and postoperative data					
	Group	**N**	**Mean**	**SD**	**p-value**
Age (years)	Group A	36	63.64	6.366	0.908**
	Group B	36	63.81	5.879	
PSA (prostate spesific antigen - ng/dL)	Group A	36	7.4225	3.31286	0.195***
	Group B	36	9.0586	5.62605	
PSA density	Group A	36	0.17647	0.116065	0.146***
	Group B	36	0.2625	0.30601	
Total operation time (min)	Group A	36	229.03	55.541	**0.008****
	Group B	36	195.81	47.362	
Lymphadenectomy time (min)	Group A	9	102.56	19.957	**0.001*****
	Group B	17	71	13.177	
Radical prostatectomy time (min)	Group A	36	203.39	45.797	**<0.001****
	Group B	35*	162.66	31.713	
Urethro-vesical anastomosis time (min)	Group A	36	38.33	13.506	**<0.001*****
	Group B	35*	28.2	13.497	
Hematocrit drop	Group A	36	6.0111	3.44448	0.157**
	Group B	36	7.0722	2.81736	
Hospitalization time (day)	Group A	36	4.22	1.791	**0.019*****
	Group B	36	5.89	5.908	**[ı]0.029*****
Urinary cathater time (day)	Group A	36	13.08	2.687	**0.012*****
	Group B	36	17.97 ([ı]14.76)	19.346	**[ı]0.019*****
Removed lymph node count	Group A	9	17.11	5.231	0.344***
	Group B	17	16.35	7.77	

*: One patient's surgery converted to open after rectal injury and urethro-vesical anastomosis was not performed laparoscopicaly. This patient excluded from "radical prostatectomy time" and "urethro-vesical anastomosis time"
**: Independent Samples t-test was used for normally distributed variables
***: Mann-Whitney U test was applied for variables that did not follow normal distribution
[ı]: One patient in group 2 had an extended hospitalization time of 38 days and a urinary cathater time of 130 days due to complications (rectal injury patient), which significantly influenced the statistical analysis. Upon excluding these outliers, the mean and the median values were recalculated, and a statistically significant difference between the two groups remained
PSA: Prostate specific antigen, SD: Standard deviation

Discussion

"The time to achieve skills necessary to satisfactorily perform a surgical procedure'' is defined as completion of the learning curve by many authors. Based on this definition, it is expected that operation time, complication rates, and oncological and functional outcomes will improve over time, and there will be a statistically significant difference between the patients operated on at the beginning of the learning curve and those operated on later as experience increases (9). In the study by Bollens et al. (10), it is evident that significant improvements in the learning curve of LRP were observed even when the early learning curve was divided into groups of ten cases. This finding demonstrates that significant progress can be made in the learning curve of LRP with relatively few cases in the early stages of the learning curve.

LRP remains a challenging procedure, especially when performing without the guidance of a mentor. In our study, we evaluated the learning curve by dividing 72 patients into two groups. In our study, we observed a statistically significant improvement in operation times (total operation, lymphadenectomy, radical prostatectomy, urethrovesical anastomosis). However, no statistically significant difference was found between the two groups regarding complications (general, intraoperative, and early) and positive surgical margins. On the other hand, contrary to expectations, we observed a statistically significant difference in hospitalization time and urinary catheter time, with longer times in group B.

In our study, we observed a statistically significant reduction in total operative time, lymphadenectomy time, radical prostatectomy time, and urethrovesical anastomosis time. In the studies by Fabrizio et al. (5) and Skrekas et al. (11), patients were divided into three groups: the first group was operated on with the mentor as primary surgeon and the trainee assisting, the second group was operated on by the trainee with the mentor assisting, and the third group was operated on by the trainee with residents assisting. In these studies, no improvement in operative time was observed between the 2nd and 3rd groups. In Fabrizio et al. (5) study, the median operative time for group 3's 20 cases (the trainee with residents assisting) was 313 minutes, whereas in our study, this value was 247 minutes for the first 20 cases. In Skrekas et al. (11) study, the mean operative time for group 3's 16 cases (the trainee with residents assisting) was 248 minutes, whereas in our study, the mean operative time

Table 3. Comparison of group A and group B's peroperative and postoperative data				
		Group A n (%)	**Group B n (%)**	**p-value**
Prostate biopsy Gleason grades	Gleason 6	25 (69.4%)	12 (33.3%)	**0.012****
	Gleason 7	9 (25.0%)	18 (50.0%)	
	≥ Gleason 8	2 (5.6%)	6 (16.7%)	
EAU risk groups	Low-risk	17 (47.2%)	9 (25%)	**0.019***
	Intermediate-risk	16 (44.4%)	15 (41.7%)	
	High-risk	3 (8.3%)	12 (33.3%)	
Transperitoneal vs extraperitoneal	Transperitoneal	9 (25.0%)	29 (80.6%)	**<0.001***
	Extraperitoneal	27 (75.0%)	7 (19.4%)	
Bilateral pelvic eLND	No	27 (75.0%)	19 (52.8%)	**0.049***
	Yes	9 (25.0%)	17 (47.2%)	
Nerve-sparing surgery (Any type of nerve-sparing)	No	13 (36.1%)	24 (66.7%)	**0.009***
	Yes	23 (63.9%)	12 (33.3%)	
General complications (Intraoperative + early, per patients)	No	29 (80.6%)	24 (66.7%)	0.181*
	Yes	7 (19.4%)	12 (33.3%)	
Intraoperative complications (Per patients)	No	34 (94.4%)	31 (86.1%)	0.233**
	Yes	2 (5.6%)	5 (13.9%)	
Early postoperative complications (per patients)	No	30 (83.3%)	28 (77.8%)	0.551*
	Yes	6 (16.7%)	8 (22.2%)	
Blood transfusion	No	35 (97.2%)	32 (88.9%)	0.164**
	Yes	1 (2.8%)	4 (11.1%)	
Additional intervention	No	35 (97.2%)	33 (91.7%)	0.614**
	Yes	1 (2.8%)	3 (8.3%)	
Seminal vesicle invasion	No	33 (91.7%)	29 (80.6%)	0.173*
	Yes	3 (8.3%)	7 (19.4%)	
Extraprostatic extension	No	26 (72.2%)	18 (50.0%)	0.053*
	Yes	10 (27.8%)	18 (50.0%)	
Surgical margin positivity	No	27 (75.0%)	25 (69.4%)	0.599*
	Yes	9 (25.0%)	11 (30.6%)	
Pathological lymph node involvement	No	36 (100.0%)	30 (83.3%)	**0.011***
	Yes	0 (0.0%)	6 (16.7%)	
Radical prostatectomy pathology	T2	26 (72.2%)	17 (47.2%)	**0.031***
	≥ T3	10 (27.8%)	19 (52.8%)	
Radical prostatectomy gleason grades	Gleason 6	13 (36.1%)	7 (19.4%)	**0.022****
	Gleason 7	22 (61.1%)	21 (58.3%)	
	≥ Gleason 8	1 (2.8%)	8 (22.3)	
Postoperative PSA (3rd month)	Nadir	36 (100%)	33 (91.7%)	**0.239****
	Persistent	0 (0.0%)	3 (8.3%)	

*: Chi-square test, **: Fisher's exact test
EAU: European Association of Urology, eLND: Extended pelvic lymphadenectomy, PSA: Prostate specific antigen

was also 248 minutes for the first 16 cases. Similar to our study, Di Gioia et al. (12) and Mitre et al. (13), in their single-surgeon series, also divided their cohorts of 165 and 240 patients into three groups and observed a statistically significant reduction in operative times as the series progressed. In Çelen et al. (14) study, which evaluated the first 80 LRP cases divided into four groups following a 2-year modular mentored training (first-hand assistant in the first 50 LRP cases and surgeon in 20 LRP

Table 4. Nerve-sparing status, complications and additional intervention data of all patients		
	Frequency	**Percent (%)**
Nerve-sparing procedure		
-Bilateral intrafascial	15	20.8
-Unilateral intrafascial	7	9.7
-Bilateral interfascial	7	9.7
-Unilateral interfascial	2	2.8
-Unilateral intrafascial, unilateral interfascial	4	5.6
-Non-nerve sparing	37	51.4
Intraoperative complications*		
-Bleeding requiring blood transfusion	5	6.9
-Rectal injury	1	1.4
- Spontaneous urethral catheter removal after anastomosis	1	1.4
Early Postoperative complications*		
-Lymphatic leakage	5	6.9
-Urinary leakage	3	4.2
-Spontaneous urethral catheter removal	2	2.8
-Fewer and an infection requiring IV antibiotics (pneumonia, urinary tract infection, epididymo-orchitis)	3	4.2
-Wound infection	1	1.4
-Lymphocele requiring drain placement	1	1.4
-Rectourethral fistula	1	1.4
Additional intervention		
-Cystourethroscopy for urethral catheter placement over a guide wire (under local anesthesia)	2	2.8
-Cystourethroscopy for urethral catheter placement over a guide wire (at the end of the procedure with same anesthesia)	1	1.4
-Perineal rectourethral fistula repair with gracilis muscle (under general anesthesia)	1	1.4
*: Some patients experienced multiple complications. For example, one of our patients had an intraoperative rectal injury, and in the early postoperative period, a rectourethral fistula, urinary tract infection requiring IV antibiotics, and lymphocele requiring drain placement developed		

cases with the assistance of an experienced LRP surgeon,) during residency, a statistically significant decrease in operative times was observed. In this study, the mean operation time in the first group of 20 patients was 177 minutes, while in the fourth group, it decreased to 126 minutes, and the mean operation time of all 80 patients was 156 minutes (14). In both Çelen et al. (14) study and the present study, the training center was the same. Compared with the 2-month observership training, it be considered that the a 2-year modular mentored training during residency had an impact on operative times from the beginning of the learning curve.

In our study, we did not observe a statistically significant difference in complications. In the studies by Di Gioia et al. (12) and Mitre et al. (13), a statistically significant reduction in complications was observed between the groups. We believe that the primary reason for not achieving a reduction in complications is that group B consisted of a higher number of high-risk patients according to the EAU risk groups, which also led to more lymphadenectomies being performed in this group. An analysis of complications related to lymphadenectomy in group B, including a rectal injury in a patient with locally advanced prostate cancer, showed no statistically significant difference in complications compared to group A. Unlike the present study, in Mitre et al. (13) study, there were fewer pathological T3 or higher prostate cancers in the second and third groups. In the present study, the transperitoneal approach was statistically significantly more common in group B; however, no cases of bowel injury or ileus occurred in any of the patients. As the learning curve for LRP progresses, many series, including Mitre et al. (13) study, have demonstrated a decrease in blood transfusion rates. However, in the present study, no statistically significant difference was detected; in fact, an increase in blood transfusion rates was observed in group B. Similarly, in Skrekas et al. (11) study, the transfusion rate was found to be higher in group 1, where the mentor acted as the primary surgeon and the trainee assisted, compared to other groups (13). In the present study, one patient experienced a rectal injury, and despite repair and colostomy, a rectourethral fistula developed. At postoperative month 4, perineal rectourethral fistula repair was performed using a gracilis flap, and the colostomy was closed in the following months. When comparing similar series, Brown and Sajadi (15) reported one case of rectal injury in a series of 32 patients, Mitre et al. (13) reported three cases in a series of 55 patients, and Jakóbczyk et al. (16) reported three cases in a

series of 30 patients. However, in Çelen et al. (14) study, which involved 80 cases following a 2-year modular mentored training during residency, no rectal injuries were observed.

In the literature, as seen in studies by Skrekas et al. (11), Fabrizio et al. (5) and Çelen et al. (14) no statistically significant changes in hospitalization time have been observed. In contrast, in the present study, hospitalization time increased statistically significantly. This is likely due to the significantly higher rate of lymphadenectomy performed in group B, resulting in longer hospital stays for these patients. Similarly, in the present study, we observed a statistically significant increase in urinary catheter time in group 2. We believe this is because, in the first 17 patients of the series, catheter removal was performed between 7-10 days after performing cystograms and there was one patient in group 2 with a urinary catheter duration of 130 days. After the first 17 cases, as we no longer had the option to routinely perform cystograms the urinary catheter was kept for 14 days based on the surgeon's preference.

As the learning curve in LRP progresses, the rate of positive surgical margins, which is an important criterion for evaluating the oncological outcomes of the surgery, begins to decrease and eventually reaches a plateau (9). In the present study, we did not observe a statistically significant difference in terms of positive surgical margins between the two groups, similar to Çelen et al. (14) study, which also did not find a statistically significant difference across four groups. In fact, the rate of positive surgical margins was 25% in group A, while it was 30.6% in group B. In fact, the expected outcome is a decrease in the rate of positive surgical margins as experience increases, similar to Mitre et al (13) study, where the rates of positive surgical margins were 29.1% in group A, 21.8% in group B, and 5.5% in group C. An even more interesting finding is that, although no statistically significant difference was detected in Skrekas et al. (11) study, the rate of positive surgical margins (43.8%) in group 1, which consisted of patients operated on by a mentor with prior experience of over 200 LRP cases, was higher than in the other groups, which were operated on by a trainee. At this point, it is important to consider also pathological stage T3 and above, which is one of the most significant factors influencing positive surgical margins. In many studies, the rate of positive surgical margins for pathological T3 and higher disease is around 50% (15,17). In the present study, group B had a significantly higher number of patients with pathological stage T3 and above.

Study Limitations

This study has several limitations that should be acknowledged. First, as the data were collected prospectively but analyzed retrospectively, potential biases may have affected the interpretation of outcomes. Additionally, the follow-up period for the patients in this study was relatively short, especially concerning long-term cancer control measures such as BCR-free survival, progression-free survival, and overall survival, which were not assessed, and long-term functional outcomes such as urinary continence and erectile function. These outcomes were not included in the analysis due to incomplete data. Another limitation is the uneven distribution of high-risk patients between two groups, which may have affected the evaluation of complications, operation times, and oncological outcomes. This study reflects the experience of a single surgeon, which may limit the generalizability of the findings to other surgeons with different training backgrounds or institutional settings. The results may not be directly applicable to surgeons with varying levels of prior laparoscopic experience. Lastly, the relatively small sample size of 72 patients, divided into two groups, limits the generalizability of the findings to larger patient populations and other surgical settings.

Conclusion

This study evaluated the learning curve of a single urologist performing 72 LRP cases, without mentor guidance after a 2-month advanced laparoscopy observership. Significant improvements were observed in operative times; however, no statistically significant difference was found in complication rates or positive surgical margins between the two groups. The higher proportion of high-risk patients in the second group may have influenced this outcome.

While these findings indicate that LRP can be performed without direct mentorship, they should be interpreted with caution due to the study's limitations, including its single-surgeon experience and relatively small sample size. The results may not be generalizable to surgeons with varying levels of laparoscopic training or to different institutional settings. Additionally, the lack of long-term follow-up prevents a comprehensive assessment of oncological and functional outcomes. Future studies with larger cohorts and standardized training protocols could provide more definitive insights into optimizing the learning curve and improving surgical outcomes.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital (protocol no: 2024/010.99/10/4, date: 29.11.2024).

Informed Consent: Written informed consent was obtained from all participants included in the study.

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Footnotes

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References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229-263.
2. Howard JM. Robotic, laparoscopic, and open radical prostatectomy-ıs the jury still out? JAMA Netw Open. 2021;4:e2120693.
3. Bandin A, Staff I, McLaughlin T, et al. Outcomes over 20 years performing robot-assisted laparoscopic prostatectomy: a single-surgeon experience. World J Urol. 2023;41:1047-1053.
4. Sivaraman A, Sanchez-Salas R, Prapotnich D, et al. Learning curve of minimally invasive radical prostatectomy: Comprehensive evaluation and cumulative summation analysis of oncological outcomes. Urol Oncol. 2017;35:149.e1-149.e6.
5. Fabrizio MD, Tuerk I, Schellhammer PF. Laparoscopic radical prostatectomy: decreasing the learning curve using a mentor initiated approach. J Urol. 2003;169:2063-2065.
6. Ramalingam M, Patel VR. Operative atlas of laparoscopic reconstructive urology. Springer London, London. 2009
7. Van Velthoven RF, Ahlering TE, Peltier A, et al. Technique for laparoscopic running urethrovesical anastomosis: the single knot method. Urology. 2003;61:699-702.
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-213.
9. Good DW, Stewart GD, Stolzenburg JU, McNeill SA. A literature-based analysis of the learning curves of laparoscopic radical prostatectomy. EMJ Urol. 2014;1:90-96.
10. Bollens R, Vanden Bossche M, Roumeguere T, et al. Extraperitoneal laparoscopic radical prostatectomy. Results after 50 cases. Eur Urol. 2001;40:65-69.
11. Skrekas T, Mochtar CA, Lagerveld BW, et al. Mentor-initiated approach in laparoscopic radical prostatectomy. J Endourol. 2006;20:831-835.
12. Di Gioia RF, Rubinstein M, Velasque L, Rubinstein I. Impact of a low-volume laparoscopic radical prostatectomy learning curve on perioperative outcomes: is it acceptable? J Laparoendosc Adv Surg Tech A. 2013;23:841-848.
13. Mitre AI, Chammas MF Jr, Rocha JE Jr, et al. Laparoscopic radical prostatectomy: the learning curve of a low volume surgeon. ScientificWorld Journal. 2013;2013:974276.
14. Çelen S, Özlülerden Y, Mete A, et al. Laparoscopic radical prostatectomy: a single surgeon's experience in 80 cases after 2 years of formal training. Afr J Urol. 2021;27:1-6.
15. Brown JA, Sajadi KP. Laparoscopic radical prostatectomy: six months of fellowship training doesn't prevent the learning curve when incorporating into a lower volume practice. Urol Oncol. 2009;27:144-148.
16. Jakóbczyk B, Wrona M, Wrona-Lis M, et al. Endoscopic extraperitoneal radical prostatectomy: an initial report following the first 30 cases. Cent European J Urol. 2017;70:48-52.
17. Martina GR, Giumelli P, Scuzzarella S, Remotti M, Caruso G, Lovisolo J. Laparoscopic extraperitoneal radical prostatectomy--learning curve of a laparoscopy-naive urologist in a community hospital. Urology. 2005 May;65(5):959-63.

Case Report

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Giant Angiomyolipoma with Epithelial Cyst (AMLEC): Case Report and Review of Literature

Ekansh Gupta, Madhumohan Prabhudessai, Prashant Lawande, Rajesh Halarnakar, Prashant Mandrekar, Mekhala Naik

Goa Medical College and Hospital, Clinic of Urology, Goa, India

Abstract

Angiomyolipoma with epithelial cyst (AMLEC) is a rare variant of angiomyolipoma (AML). Hereby, we report a unique case which is the largest size of AMLEC ever reported, the patient being the youngest one ever recorded, and the first case of AMLEC associated with tuberous sclerosis complex reported from India. The patient was a 19-year-old woman who presented with hematuria. Contrast-enhanced computed tomography (CT) and positron emission tomography-CT detected a large complex cystic lesion, which was reported to be AML with a less likely possibility of cystic renal cell carcinoma. The patient underwent radical nephrectomy. Histopathology and immuno-histochemistry identified the tumor to be AMLEC. On further evaluation, the patient was found to satisfy clinical criteria of tuberous sclerosis complex. Rare forms of renal tumor like AMLEC need to be kept in mind whenever we encounter complex cystic lesions in the kidney.

Keywords: Angiomyolipoma with epithelial cyst, angiomyolipoma, renal tumor, renal cyst, tuberous sclerosis complex

Introduction

Angiomyolipoma (AML) is a member of a tumor family known as perivascular epithelioid cell (PEC) tumors which originate from the histologically, ultra-structurally and immunohistochemically distinctive PEC (1). AML is easily picked up on ultrasound by virtue of hyperechogenicity generated by its fat content and negative Hounsfield units on unenhanced computed tomography (CT). A rare form of AML, like AML with epithelial cyst (AMLEC), often mimics more sinister pathology due to its solid-cystic nature. Moreover, AMLEC does not readily come to the mind of clinicians due to its rarity (2). It is a relatively new entity, and it is difficult to segregate it from common lesions like mixed epithelial stromal tumor (MEST), cystic nephroma (CN) and even cystic renal cell carcinoma (RCC), both clinically and histologically (2,3). We report a case of AMLEC, which is the first of its kind from multiple perspectives, and a review of relevant literature is incorporated.

Case Reports

1. Case history and clinical findings: A 19-year-old female presented with left flank pain and intermittent painless visible hematuria for 2 months. On examination, she was pale and there was a palpable left renal mass.

2. Imaging findings: Multiphasic CT showed a normal right kidney. In the left kidney, there was a well-defined fat-attenuating partly exophytic, 10x10 mm sized lesion at the lower pole, diagnosed as AML. A second lesion, 3.4 mm sized, rounded non-enhancing fat attenuating lesion in the interpolar region, was diagnosed as AML. A third fairly large, upper polar, solid cystic lesion measuring 18.4x15x9.5 cm including a cystic component of size 5.4x5.2x5.0 cm was also observed. There were multiple enhancing septa of thickness up to 3 mm in the cyst (Bosniak IV). The lesion produced a bulge on the lateral aspect of the kidney with protrusion into perirenal fat, without loss of the fat plane. There was a linear non-occlusive poorly enhancing filling defect, measuring 38x12 mm, in the hilar

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Address for Correspondence: Ekansh Gupta, Goa Medical College and Hospital, Clinic of Urology, Goa, India
E-mail: ekansh.urology@gmail.com **ORCID:** orcid.org/0009-0006-9642-1847
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region of left renal vein, and the radiologist considered it to be a possible tumor thrombus. CT considered differentials of large AML or fat-containing RCC. CT also reported a 22x21 mm sized, enhancing lesion with persistent post-contrast enhancement, hence labeled as a hemangioma in segment VIII of the liver. Further work-up of the renal mass with positron emission tomography (PET)-CT revealed a large ametabolic solid-cystic, predominantly fat containing lesion in the left kidney, and was considered to be a fat-rich AML (4).

3. Surgical findings: The patient was subjected to left radical nephrectomy. The cut section of the specimen showed an upper polar large tumor mass, measuring 19x15x10 cm, which was pale yellow, solid and homogeneous, and had a cyst in the parapelvic region (Figure 1).

4. Pathology findings: On histology, it was found to be a triphasic tumor composed of (a) myoid spindle cells without any atypia, pleomorphism or epithelioid features, (b) mature adipose tissue and (c) dysmorphic thick-walled blood-vessels without elastic lamina.

The cystic spaces were lined with cuboidal to columnar epithelium having eosinophilic cytoplasm and prominent nuclei protruding into the lumen (hobnailed appearance). There was condensation of small stromal cells (cambium-like) with congested capillaries and lymphoplasmacytic infiltrate in the subepithelial layer (Figure 2). Fascicles of smooth muscle bundles with entrapped, non-cystic native renal tubules were arranged in the external 3rd layer.

This was a characteristic picture of AMLEC as described in the literature. The renal sinus, renal artery and vein, renal capsule, ureter, and peri-renal fat were not involved by the tumor.

5. Immuno-histochemistry: Considering rarity of AMLEC, the specimen was subjected to immuno-histochemistry. The subepithelial layer was strongly positive for HMB45. Smooth muscle actin (SMA) stain produced a strong reaction in the outer muscular layer (Figure 3), and S100 was negative, thereby

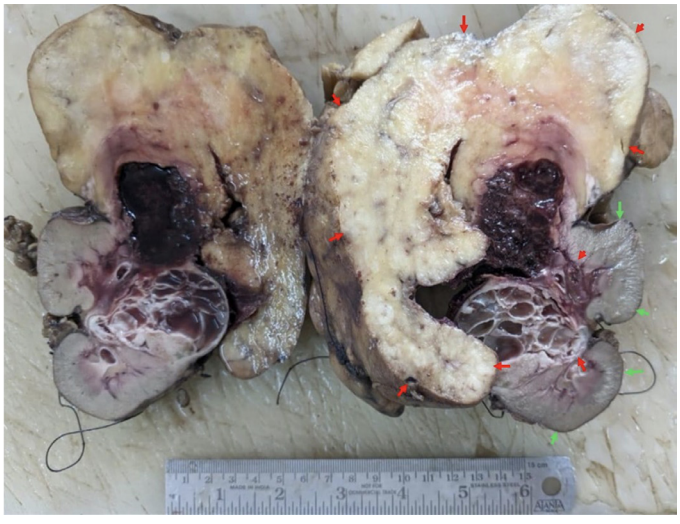

Figure 1. Cut section of nephrectomy specimen showing tumor (red arrows), left kidney (green arrows) and fluid-filled cyst in between. For estimation of dimensions, a metallic scale was placed at the bottom

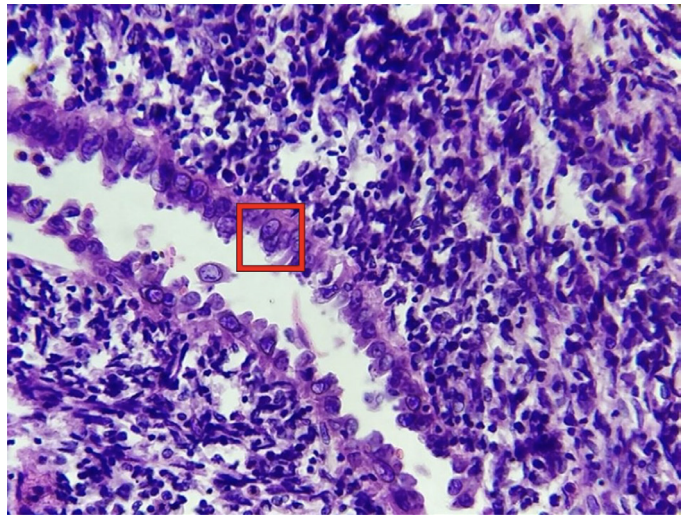

Figure 2. Microphotograph of H&E-stained slide showing cyst wall lined by hob-nailed epithelium (red rectangle); condensed "cambium-like" subepithelial stroma with multiple vessels and lymphoplasmacytic infiltrate is seen

H&E: Hematoxylin and eosin

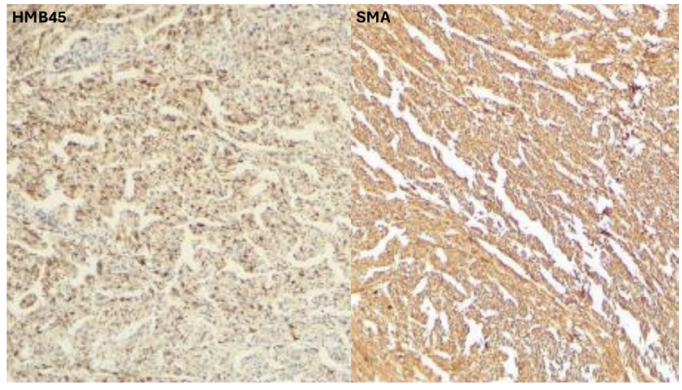

Figure 3. Strongly positive reaction with HMB45 stain (left half) and smooth muscle actin stain (right half) is seen

SMA: Smooth muscle actin

confirming the diagnosis of AMLEC. The proliferation index Ki-67 was <1%.

After reviewing the literature on AMLEC, the patient was again evaluated. She was found to be meeting one major (multiple AMLs) and two minor criteria (hepatic hamartoma and "confetti" skin lesions) of tuberous sclerosis complex (TSC).

Discussion

AMLEC as an entity was recognized in the recent past, and reports appeared in the literature in the past 2 decades. Although the description of cystic AML with HMB45 positive subepithelial stroma given by Davis et al. (5) was very close to that of AMLEC, the first accurate description of AMLEC was given by Fine et al. (6). It is believed that, in fact, some of the previously reported cases of fat-containing RCC carcinoma were AMLECs. Awareness among urologists is desired because clinically AMLEC closely mimics other complex cystic lesions, especially cystic RCC and histologically MEST (2,3).

AMLEC is a late addition to the list of cystic renal tumors, which previously included cystic RCC, CN and MEST (Table 1). It is known that entrapped renal tubules can be seen in the histological architecture of AML under a high-resolution microscope, but they never undergo gross dilatation to form cysts (2). AMLEC needs to be differentiated from cystic RCC. Histological features which segregate AMLEC from RCC are the absence of clusters of clear cells and papillary carcinoma cells, the single-layered clear cell epithelial lining of the cyst wall, necrotic debris, cholesterol clefts, and calcification. It has been suggested that the cyst of AMLEC originated from the epithelium of collecting ducts because of positive immunoreactivity for soybean agglutinin (2), in contrast to the origin of RCC from the epithelium of the proximal renal tubule. Hence, AMLEC does not stain with the RCC marker. Cuboidal or columnar epithelium with clear or eosinophilic cytoplasm and prominent nuclei projecting into the lumen of cyst (hob-nail appearance) is surrounded by mullerian-type endometrium-like highly vascular stroma infiltrated by lymphoplasmacytic infiltrate forming a layer of so-called "cambium". An outer layer of fascicles of muscular stroma with dysplastic vessels is characteristic and unmistakable in AMLEC (2,3,6). Cysts lined by cuboidal or hob-nailed epithelium are common to AMLEC, CN, and MEST. The stroma in CN is sparse and ovarian-type, unlike the thick, condensed endometrial stroma of AMLEC. Characteristic features of AMLEC, e.g., condensed sub-epithelial cambium-like stroma, thick muscular outer layer, and dysmorphic vessels are absent in CN (2,3,7). MEST can have solid-cystic components, but thick-walled blood vessels of MEST are distinctly different from dysmorphic blood vessels of AMLEC (2). Micro and macro-cystic spaces are a feature of MEST compared to the large cysts of AMLEC. SMA, desmin and ER/PR can be positive in both AMLEC and MEST, but melanocytic markers like HMB45 and Melan-A, which are features of PEC, form the line of demarcation between AMLEC and MEST. Markers of immunohistochemistry are not mono-specific, but a battery of multi-specific markers does help in recognizing the exact cell lineage of the lesion in the present case (Table 2). Since the patient is young, we need to differentiate the lesion from cystic poorly differentiated nephroblastoma (CPDN), but CPDN occurs before age 2. Typical nephroblastomatous epithelial and stromal elements along with blastema of CPDN are absent in our case (2). The present case needs to be differentiated from epithelioid AML (eAML) because of young age, its association with TSC, positivity for HMB45 and SMA, and negative reaction for S100. Typical features of eAML like epithelioid cells, nuclear atypia, and mitotic figures were absent in the present case. Secondly, proliferative index, Ki-67, which was reported to be <1%, in our case, rules out the possibility of eAML (8).

Pre-operatively, this patient had shown heterogeneous enhancement on contrast-enhanced CT although unenhanced CT had demonstrated fat. Heterogeneous enhancement can occur in fat-poor AML and non-clear cell RCC both, raising suspicion (4). Unusual size of tumor and heterogeneous

Table 1. Histological differentials of complex renal lesion

Kidney lesion	Cyst	Characteristic features	
		Epithelium	Stroma
Cystic RCC	Present	Nests of clear cells or papillary carcinoma cells; Cyst wall lined by single layered clear cell epithelium with distinct membrane	Non-descript with little inflammatory response; Haemorrhage, necrotic debris, cholesterol clefts, Calcification; Network of arborizing thin-walled blood-vessels
AMLEC	Present	Cuboidal or columnar epithelium with clear or eosinophilic cytoplasm with prominent nuclei projecting into the lumen of cyst (hob-nail appearance) is common to AMLEC, CN and MEST	Mullerian-type endometrium-like highly vascular "cambium'-like" stroma infiltrated by lymphoplasmacytic infiltrate; Outer thick muscular layer with dysmorphic blood-vessels
CN	Present		Sparse, ovarian type stroma
MEST	Present		Thick-walled blood-vessels seen in stroma
CPDN	Present	Nephroblastomatous	Nephroblastomatous stroma and Islands of undifferentiated blastema
AML	Entrapped renal tubules may be seen under high resolution but there is no gross dilatation to form cyst		

AMLEC: Angiomyolipoma with epithelial cyst, AML: Angiomyolipoma, RCC: Renal cell carcinoma, MEST: Mixed epithelial stromal tumour, CN: Cystic nephroma, CPDN: Cystic poorly differentiated nephroblastoma

Table 2. Immunostaining findings in various complex cystic lesions of kidney

Type of lesion	Immunoreactive antibody				
	Cytokeratin	S100	HMB45	Melan-A	SMA
Cystic RCC	+ve	+ve	-ve	-ve	-ve
AMLEC	-ve	-ve	+ve	+ve	+ve
MEST	+ve	-ve	-ve	-ve	+ve
CN/CPDN	+ve	-ve	-ve	-ve	+ve
AML	-ve	-ve	+ve	+ve	+ve

SMA: Smooth muscle actin, AMLEC: Angiomyolipoma with epithelial cyst, AML: Angiomyolipoma, RCC: Renal cell carcinoma, MEST: Mixed epithelial stromal tumour, CN: Cystic nephroma, CPDN: Cystic poorly differentiated nephroblastoma

enhancement are indicative for the use of magnetic resonance imaging (MRI) in differentiating fat-poor AML from a malignant lesion. Based on MRI findings, AML is classified into 3 categories, namely fat-rich, fat-poor, and fat-invisible. Fat-rich AML needs no further work-up; fat-poor AML can be differentiated from non-clear cell RCC by using MRI, but MRI findings are similar in fat-invisible AML and malignant lesions. If MRI does not help in diagnosis, percutaneous biopsy is indicated (4). In our case, we preferred to confirm AML by PET-CT, which revealed a metabolic lesion, because AML is not fluorodeoxyglucose-avid, unlike malignant lesions which show FDG uptake. The heterogeneous enhancement in the present case, was due to the tumor being fat-poor, just like any other AMLEC and unlike the majority of AMLs, which are usually fat-rich.

To date, a total of 28 cases of AMLEC have been reported in 12 publications worldwide (9). This patient is just 19 years old and is the youngest ever to have AMLEC. Before this, the youngest patient of AMLEC ever reported was 23 years old (10). If the lesion in our case is considered sporadic AML or its variant, then how could it grow to this size by the age of 19 years? This idea forced us to think about whether the patient belongs to some familial neoplastic syndrome, associated with renal tumor. This patient fulfills one major criterion (multiple AMLs) and two minor criteria (hepatic hamartoma and confetti skin lesion) of TSC (11). AML in TSC usually occurs in the 3rd or 4th decade of life (3). Secondly, this lesion is the biggest AMLEC ever noticed, far bigger than the commonly reported size in the literature. If this case is accepted as AMLEC in TSC, then this is the first case from India in that category.

As of today (2,9,12), there is no tumor marker or imaging modality that can diagnose AMLEC preoperatively. There is no standardized treatment for AMLEC because of its rarity. In the literature, partial nephrectomy is recommended if size is up to 5 cm, it beyond which it is indicated that radical nephrectomy is necessary (2). There is no role of chemotherapy or radiotherapy as of now. Inactivation of tumor suppressor gene TSC2 due to a non-sense mutation, which results in unregulated signaling of the mammalian target of rapamycin (mTOR) complex 1 pathway, has been proposed to be the causative mechanism in TSC-associated AMLEC (9). Based on this finding, mTOR inhibitor everolimus has been suggested as an adjunct in the treatment of AMLEC (9). In fact, cell-lines of all renal tumors need to be defined very precisely, to maximize the benefit from fast emerging molecular biology-based targeted therapeutic options. Clinically, the behavior of AMLEC is no different from AML, it has never been found to recur or metastasize; and it has never been blamed for mortality (2).

Ethics

Informed Consent: Treatment of this patient was in accordance with standard urological protocol. The operation was carried out after obtaining the patient's written informed consent, as is required for invasive procedures in our institution. For academic purposes, permission from the Institutional Review Board was obtained, and a waiver of consent for publication from the patient was granted, as the patient's identity was not disclosed for review of records and publication.

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Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

Design: M.P., P.L., R.H., Data Collection or Processing: P.M., Literature Search: M.N., Writing: E.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Martignoni G, Amin MB, Angiomyolipoma. In: Eble JN, Sauter G, Epstein JI, et al. eds. World Health Organization Classification of tumours. Pathology and genetics of tumours of urinary system and male genital organs. Lyon France:IARC Press; 2004. P. 65-67.
2. Wei J, Li Y, Wen Y, et al. Renal angiomyolipoma with epithelial cysts: a rare entity and review of literature. Int J Clin Exp Pathol. 2015;8:11760-11765.
3. Esheba Gel S, Esheba Nel S. Angiomyolipoma of the kidney: clinicopathological and immunohistochemical study. J Egypt Natl Canc Inst. 2013;25:125-134.
4. Park BK. Renal angiomyolipoma: radiologic classification and imaging features according to the amount of fat. AJR Am J Roentgenol. 2017;209:826-835.
5. Davis CJ, Barton JH, Sesterhenn IA. Angiomyolipoma, cystic type. Mod Pathol. 2004;17:147A.
6. Fine SW, Reuter VE, Epstein JI, et al. Angiomyolipoma with epithelial cysts (AMLEC): a distinct cystic variant of angiomyolipoma. Am J Surg Pathol. 2006;30:593-599.
7. LeRoy MA, Rao P. Angiomyolipoma with epithelial cysts. Arch Pathol Lab Med. 2016;140:594-597.
8. Kato I, Inayama Y, Yamanaka S, et al. Epithelioid angiomyolipoma of the kidney. Pathol Int. 2009;59:38-43.
9. Song H, Mao G, Jiao N, et al. TSC2 nonsense mutation in angiomyolipoma with epithelial cysts: a case report and literature review. Front Oncol. 2024;14:1274953.
10. Avadhani V, Macias A. AMLEC with Squamous epithelium lining: a distinct morphology in this unique entity. Am J Clinic Pathol. 2014;142(Suppl 1):A286.
11. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. NEJM. 2006;355:1345-1356.
12. Varshney B, Vishwajeet V, Madduri V, et al. Renal angiomyolipoma with epithelial cyst. Autops Case Rep. 2021;11:e2021308.