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Review Article

Exploring the Intersection of Artificial Intelligence and Oral Cancer: Diagnostic Advances, Genetic Insights, and Precision Medicine

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Abstract

Background: Oral cancer poses a serious global health challenge due to its high morbidity and mortality rates, largely stemming from late-stage diagnosis and limited treatment success. Recent technological advances, particularly in artificial intelligence (AI), have opened new avenues for early detection and personalized treatment approaches.

Objectives: This review aims to explore the role of AI, including machine learning (ML) and deep learning (DL), in the diagnosis, prognosis, and management of oral cancer. It also examines the systemic effects of oral cancer, underlying genetic and hormonal influences, and the impact of oxidative stress and chronic inflammation on disease progression.

Methodology: A systematic literature review was conducted covering publications from 1997 to 2024, using PubMed, Scopus, and the Cochrane Library. Studies involving AI, ML, and DL in oral cancer detection and treatment were selected based on predefined inclusion and exclusion criteria. Bibliometric and trend analyses were also performed to assess global research output and collaborative networks.

Results: AI techniques such as convolutional neural networks and support vector machines have demonstrated significant utility in early detection, histopathological analysis, and survival prediction. The review also highlights key genetic mutations (e.g., TP53, CDKN2A) and hormonal imbalances (e.g., estrogen, androgen receptors) linked to oral cancer pathogenesis. Furthermore, systemic involvement of organs like the liver, brain, and bone is discussed. Bibliometric data indicate increasing global collaboration and the emergence of AI as a dominant research focus in oral oncology.

Conclusion: AI-based diagnostic tools and predictive models offer promising pathways for early detection and personalized treatment in oral cancer. Understanding the molecular, systemic, and epidemiological dimensions of the disease, alongside leveraging computational advancements, can significantly enhance patient outcomes and support the development of precision medicine in oral oncology.

Keywords:

Oral Cancer
Artificial Intelligence
Machine Learning
Deep Learning
Convolutional Neural Networks
Personalized Medicine

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1. INTRODUCTION

Despite recent advancements in therapeutic strategies, oral cancer remains one of the malignancies with a persistently low survival rate worldwide. According to GLOBOCAN 2020, there were 377,713 newly diagnosed cases of lip and oral cancer (264,211 in males and 113,502 in females), resulting in 177,757 deaths (125,022 in males and 52,735 in females). The majority of oral and oropharyngeal carcinomas are diagnosed at advanced stages, leading to a higher disease burden, increased treatment-related morbidities, and preventable deaths [1, 2].

Early detection is a critical factor in improving treatment outcomes, as diagnosing malignancies at an early stage significantly enhances therapeutic efficacy. The stage at diagnosis is closely linked to survival rates, treatment-related complications, and healthcare costs, with advanced-stage tumors—especially those in anatomically complex regions—being associated with poorer prognoses and increased treatment burdens [3-5].

Globally, oral cancer accounts for approximately 2% of all newly diagnosed cancers. Notably, an unexpected rise in oral tongue cancer has been observed in young females without traditional risk factors such as tobacco and alcohol use. This emerging epidemiological pattern underscores the need for further research to explore potential underlying mechanisms, including genetic predisposition, viral oncogenesis, and environmental influences [6-9].

Table 1 provides a summary of the various types of oral cancers, their defining features, key clinical characteristics, and the role of artificial intelligence (AI) in their detection, diagnosis, and management. It also highlights the potential of AI-driven methodologies to improve early detection, classification, and personalized treatment strategies.

2. METHODOLOGY

A comprehensive and methodologically rigorous literature review was conducted to examine the latest advancements in oral cancer detection and treatment using AI, Machine Learning (ML), Deep Learning (DL). A systematic search was performed on the Web of Science (WoS), Scopus, and Google Scholar, employing Boolean queries to refine the search and emphasize the intersection of oral cancer research with computational methodologies. A thorough screening process, based on inclusion and exclusion criteria, ensured the selection of highly relevant studies while minimizing less applicable or lower-quality research. This approach allowed for the extraction of a diverse body of work, capturing emerging trends and perspectives on AI, ML, and DL in the diagnosis, pathology, and treatment of oral cancer.

2.1. Search Strategy

A literature review of the study was performed between June 1, 1997, and July 31, 2024. The following Boolean queries were used in the search strategy: (TS = (Oral Cancer)) AND TS = (Detection) and one with terms such as TS= (Oral Cancer) AND TS= treatment; TS= (Oral Cancer) AND TS= Deep Learning; TS= (Oral Cancer)) AND TS = Artificial Intelligence; TS= (Oral Cancer)) AND TS Machine Learning.

2.2. Database

This literature review utilized multiple leading databases to ensure comprehensive coverage of significant studies. WoS was selected for its extensive biomedical and clinical literature coverage, Scopus for its broad interdisciplinary scope, and Google Scholar for its ability to retrieve diverse academic papers. These databases were chosen for their strong track record in curating peer-reviewed research and supporting complex search queries. An automated search, tailored to predefined criteria, was conducted using integrated tools for reviewing, extracting, and summarizing studies. This systematic approach enabled a structured analysis of research on oral cancer detection, treatment options, and the application of AI, ML, and DL methodologies.

2.3. Inclusion and Exclusion Criteria

Research focusing on oral cancer detection or treatment was considered, with an emphasis on AI, ML, or DL algorithms for oral cancer. Priority was given to studies that significantly advanced the resolution or application of oral cancer technologies. Studies that did not align with the specified topics or methodologies, were published outside the designated timeframe, or were non-peer-reviewed, were excluded. Research with inadequate methods or unrelated to the focus was also omitted.

2.4. Data Analysis

Two primary bibliometric indicators were used: publication productivity (NP) and impact/quality measured by total citations (TC). The H-index, a key metric for evaluating the scientific productivity of individuals, regions, countries, or institutions, was also applied. Data were analyzed to identify relationships or trends, using VOSviewer for graphical organization (e.g., reference networks) and R for analysis.

Table 1. Artificial Intelligence Applications in Oral Cancer Diagnosis and Classification

Types of Oral Cancer	Characteristics	Key Features	AI Application	References
Oral Squamous Cell Carcinoma (OSCC)	The type of oral cancer that accounts for as high as 90 percent occurs in the squamous cells lining the mouth.	Higher incidence in men, often found among smokers and heavy alcohol users; often associated with HPV infection among the youth.	Histopathological images of OSCC and CT scans can be used for early detection and classification using automated AI models such as convolution neural networks. The method can also use AI to determine the probability of HPV-positive vs. HPV-negative tumors.	[10]
Verrucous Carcinoma	A slow-growing exophytic cancer with a verrucous appearance is frequently seen in the buccal mucosa or gingiva.	More locally invasive with low metastatic potential; often related to tobacco chewing or snuff use.	AI-based techniques assist in recognizing unique imaging surface characteristics of verrucous carcinoma to enhance diagnostic accuracy and minimize misinterpretation.	[11]
Adenoid Cystic Carcinoma	Salivary gland cancer, low grade; unusual because it spreads along nerves.	Slow-growing but very malignant; common recurrence and frequent distant metastases.	Imaging analysis using AI models can identify perineural invasion and assess surgical margins, assisting in developing a personalized treatment for ACC.	[12]
Mucoepidermoid Carcinoma	From the salivary gland, mucus-producing and squamous cells.	Can be either aggressive (high grade) or slow-growing (low grade) depending on histological grade.	By integrating histological and imaging data, AI systems may be able to distinguish between low- versus high-grade forms of the disease and therefore help guide treatment choices according to an individual tumor's degree of aggression.	[13]
Sarcomatoid Carcinoma	A very rare subtype but with both sarcoma-like and carcinoma features.	Highly aggressive with a propensity for local invasion and distant metastasis; Poor prognosis.	Introducing such AI tools may help recognize the unusual histopathological features of sarcomatoid carcinoma, assisting pathologists in diagnosing and taking necessary therapeutic approaches.	[14]

3. UNDERSTANDING OF ORAL CANCER BASED ON MEDICAL PROSPECTIVE

Oral cancer is a systemic disease, with consequences that extend beyond the oral cavity, affecting multiple organ systems through metastatic spread, systemic responses, and immune defenses. As the disease progresses, it may impact vital organs such as the brain, heart, blood vessels, bones, and liver, leading to a complex clinical course and poorer prognosis. These effects are primarily caused by tumor invasion, metastatic spread, oxidative stress, inflammation, genetic alterations, and hormonal changes, which will be further discussed.

3.1. Effect of Oral Cancer on Human Organs

This section examines the impact of oral cancer on various organs and their systems, focusing on metastasis and associated systemic complications:

3.1.1. Brain: Brain metastasis from oral cancer is uncommon but can occur in advanced stages. When it does spread, it can lead to neurological issues such as meningoencephalitis, resulting in symptoms like headaches, seizures, and dizziness. Patients with brain metastasis often require palliative care, including radiation to manage symptoms, which can significantly affect both prognosis and quality of life [15].

3.1.2. Heart: While rare, oral cancer can directly invade the heart. More commonly, treatments for oral cancer, such as chemotherapy and radiation, can adversely affect heart function. These therapies may weaken the heart muscle, leading to heart failure and an increased risk of arrhythmias, both at rest and during physical exertion. Additionally, these treatments can contribute to coronary artery disease [16].

3.1.3. *Bone:* Bone metastasis from oral cancer is less frequent than in other cancers, but when it occurs, it can cause bone pain, fractures, and hypercalcemia. These complications can significantly impair mobility and quality of life, and they often do not respond well to pain management. Treatment typically involves bisphosphonates or radiation therapy [17].

3.1.4. *Liver:* In advanced stages, oral cancer may metastasize to the liver, resulting in hepatic insufficiency. Symptoms of liver metastasis include jaundice, fatigue, weight loss, and abdominal pain. Liver involvement complicates cancer treatment and worsens prognosis, as the liver is essential for detoxification and protein production [18].

3.1.5. *Adrenal Glands:* Metastasis to the adrenal glands can lead to adrenal insufficiency, reducing the production of critical hormones like cortisol and aldosterone. Symptoms of adrenal insufficiency include fatigue, weight loss, muscle weakness, and low blood pressure, which further weaken the patient's condition [19].

3.1.6. *Kidneys:* While oral cancer rarely metastasizes directly to the kidneys, treatments such as chemotherapy and radiation can harm kidney function. Nephrotoxicity may result in fluid retention, electrolyte imbalances, and decreased renal clearance, leading to various systemic complications [20].

3.1.7. *Spinal Cord:* Oral cancer can cause spinal cord compression through vertebral metastasis. This condition can be extremely painful and may result in paralysis or bladder/bowel incontinence. Timely treatment, such as radiation or surgical decompression, is crucial to prevent irreversible nerve damage [21].

3.1.8. *Lymphatic System:* Similar to throat cancer, oral cancer can spread to the lymphatic system, causing the enlargement of lymph nodes in the neck and other distant areas. Lymph node involvement is a concerning sign, indicating systemic spread of the disease and complicating treatment. Patients typically receive a combination of surgery, radiation, and chemotherapy [22].

3.1.9. *Digestive System:* Metastasis of oral cancer to the gastrointestinal tract is rare unless caused by treatment-induced complications like nausea, vomiting, and obstruction. Additionally, treatments can damage the mucosal lining of the esophagus, leading to conditions such as gastritis or mucositis [23].

3.2. Generical and Hormonal Changes in Oral Cancer

Carcinoma of the oral cavity often involves genetic mutations that affect cell growth, differentiation, and apoptosis. These mutations typically include the activation of oncogenes and the inactivation of tumor suppressor genes, leading to uncontrolled malignant cell proliferation.

3.2.1. *TP53 Mutations:* One of the most frequently mutated genes in oral cancers is TP53, a well-known tumor suppressor gene. Mutations in TP53 result in a loss of function, impairing cell cycle arrest and apoptosis mechanisms. This loss allows cancer cells to proliferate uncontrollably [24].

3.2.2. *CDKN2A/P16 Inactivation:* The CDKN2A gene encodes a cell cycle protein that regulates p34cdc2. CyclinA inhibition prevents the phosphorylation of specific substrates of p34cdc2 cyclin-dependent kinase. In oral squamous cell carcinoma (OSCC), changes in CDKN2A lead to unregulated progression of the cell cycle [25].

3.2.3. *Epidermal growth factor receptor (EGFR) Amplification:* EGFR is commonly overexpressed in oral cancers. As a key target in OSCC therapy, EGFR signaling promotes cell proliferation and survival [26].

3.2.4. *PI3K/AKT/mTOR Pathway:* The PI3K/AKT/mTOR pathway is a crucial signaling cascade that supports cancer cell growth and survival. Mutations in various genes within this pathway activate it, leading to uncontrolled cell proliferation [27].

Hormones play a significant role in the development of oral cancer, particularly with regard to sex hormones and their impact on carcinogenesis. The imbalance of estrogen and testosterone levels contributes to the development of oral cancer through genomic DNA methylation.

3.2.5. *Estrogen Receptors (ER) Expression:* Estrogen receptors are expressed in several oral cancers, and studies highlight the impact of estrogen on tumor progression. It is suggested that estrogen, particularly in women, acts as a tumor promoter by increasing cell proliferation and reducing apoptosis [28].

3.2.6. *Androgen Receptors Expression:* The androgen receptor is also overexpressed in some oral

cancers. While the exact relationship between testosterone and cancer growth is not fully understood, there is an ongoing hypothesis that androgen signaling plays a role in carcinogenesis [29].

3.2.7. *Role of Cortisol:* Managing chronic stress and controlling cortisol levels may help prevent and treat oral cancer. Elevated cortisol levels can suppress immune mechanisms, allowing cancer cells to evade normal immune surveillance and grow [30].

3.2.8. *Insulin-like growth Factor (IGF) Pathway:* The IGF signaling pathway is known to play a significant role in oral cancer progression. High levels of IGF-1 stimulate cell proliferation and impair apoptosis, influencing cancer advancement. Hormonal control of IGF-1 levels is crucial in regulating cancer progression [31].

Together, these genetic and hormonal alterations shed light on the complex mechanisms driving oral cancer development. They have important implications for targeted therapies, allowing for treatment tailored to individual patient needs.

3.3. Association of Oxidative Stress and Inflammation in Oral Cancer

The growth of oral cancer cells is primarily driven by oxidative stress and inflammation, both of which promote tumor formation, survival, and metastasis.

3.3.1. *Oxidative stress in Oral Cancer:* Oxidative stress occurs when reactive oxygen species (ROS) are produced in excess, overwhelming the body's antioxidant defense mechanisms. It plays a key role in the development of oral cancer, particularly through the genetic mutations induced by factors like alcohol, tobacco use, and human papillomavirus (HPV) infection. Elevated ROS levels cause oxidative damage to essential biomolecules such as proteins, lipids, and DNA. These genetic alterations affect oncogenes and tumor suppressor genes, promoting tumor growth. Additionally, oxidative stress activates critical survival and proliferation signaling pathways, regulated by NF-κB and MAPK. It also induces epithelial-to-mesenchymal transition, which enhances the invasiveness and metastatic potential of oral cancer cells [32].

3.3.2. *Inflammation and Oral Cancer:* Chronic inflammation is a well-established factor contributing to the development of oral cancer. Prolonged exposure to irritants like alcohol, betel quid, and tobacco causes persistent inflammation in the oral mucosa. Immune cells produce pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, creating a tumor-supportive microenvironment. This inflammation promotes cancer growth by facilitating angiogenesis, cellular dysregulation, and DNA damage. Chronic conditions like oral lichen planus and periodontitis, which maintain an inflammatory microenvironment, are associated with a higher risk of developing oral cancer [33].

3.3.3. *Interplay Between Oxidative stress and Inflammation:* Oxidative stress and inflammation interact to further exacerbate OSCC progression. Increased ROS production activates pro-inflammatory pathways, particularly the NF-κB pathway, leading to gene activation that drives inflammation. This, in turn, promotes more oxidative damage as immune cells generate additional ROS. This feedback loop makes it more challenging for the body to control cancerous growth. Breaking this cycle of oxidative stress and inflammation offers a promising approach to halting tumor progression and metastasis [34].

3.3.4. *Therapeutic Implications:* Understanding the role of oxidative stress and inflammation in oral cancer provides new opportunities for treatment. Antioxidant therapies aimed at reducing ROS levels have been suggested to prevent oxidative damage. Additionally, anti-inflammatory treatments, such as COX-2 inhibitors or IL-6 blockers, could target tumor-promoting inflammation. Targeted therapies that inhibit NF-κB and STAT3 signaling pathways are being explored to disrupt oral cancer progression. When combined with chemotherapy and immunotherapy, these approaches offer promising prospects for improving patient outcomes in oral cancer treatment [35].

3.4. Oral Cancer Based on Epidemiological Prospective

This section aims to provide a comprehensive overview of oral cancer, with particular reference to differences in incidence, mortality, and survival worldwide. Oral cancer, a disease of great public health significance, is associated with different risk factors such as tobacco and alcohol use, HPV infection, and social disparities. In this review, using recent epidemiologic statistics, we analyze the worldwide

prevalence of oral cancer and investigate how preventive measures and advances in leading efforts to detect it as early as possible and treat patients have resulted in better patient outcomes.

3.4.1. Incidence: Oral cancer shows wide area variations in incidence and prevalence, with South Asia, Eastern Europe, and Latin America having higher incidences—these geographic variations in considering the betel quid chewing or access to healthcare and culture-based habits. Oral cancer is a common malignant tumor and the sixth most common malignancy globally, with significant regional differences in incidence [36]. As one of the consequences, Southeast Asia, particularly India and Sri Lanka, has high oral cancer rates because of the regular use of betel quid, a habitual practice in these countries [37]. Oral cancers arising from HPV have increased in the United States and other developed nations, where oral cancers associated with tobacco use have declined [38].

3.4.2. Mortality and Survival: The stage at diagnosis determines the survival rate of oral cancer. While early cancers have a good prognosis, late cancer stages have dismal survival. Mortality is well over 20% in those parts of the world with few health services. In areas with reduced access to healthcare services, the death rate is extremely high. Identification of cancer early boosts the chances of survival to 5 years or more, depending on the type of cancer: for example, 90% for breast and skin cancers but lower for lung disease (13%) and pancreatic disease (3%). Oral cancer is now being diagnosed late, and there are some states where mortality due to oral cancer has started increasing due to the lack of availability of qualitative health care. One of the reasons for the increasing mortality rate from oral cancer in some geographical locations is the late diagnosis and unavailability of quality healthcare [39].

4. BIBLIOMETRIC PERFORMANCE ANALYSIS ON CLASSIFICATION AND DETECTION FOR ORAL CANCER

In bibliometric studies, scientists assess the contributions of academics to a specific research field and how these contributions have advanced that field. This study also conducted a bibliometric performance analysis, which evaluates the use of data to assess performance metrics linked to key performance indicators in oral cancer research between 2000 and 2024. The analysis covered key metrics, including the number of oral cancer publications, citation trends, key authors' contributions, and the leading institutions and countries involved. The goal was to provide a comprehensive understanding of the state of oral cancer research, highlighting key players, trends, and the field's impact during this period.

4.1. Leading Countries, Authors, Affiliations, and Sources by Publication Volume

This section examines the countries, authors, organizations, and sources that have made the most significant contributions to oral cancer research based on publication volume.

4.1.1. Most Relevant Countries

A WoS-based bibliometric analysis of oral cancer publications reveals significant national differences in research productivity, influenced by collaboration types: Multiple Country Publications (MCP) versus Single Country Publications (SCP) as shown in **Figure 1**.

The United States ranks first with over 500 publications, primarily SCPs, reflecting a strong focus on domestic research. China follows in second place, with a notable number of SCPs, signaling continued investment in national research. India ranks third, emphasizing self-reliance in research with a substantial share of SCPs. Japan and Germany generate a higher volume of SCPs than MCPs, indicating a preference for national research with limited international collaboration. Italy and the United Kingdom show moderate productivity levels, with a more balanced output but still SCP-dominant, reflecting some degree of international cooperation.

In contrast, Brazil, the Netherlands, and France produce fewer publications overall, with international publications making up less than half of their output, indicating limited cross-border collaboration. Overall, the data reveals a strong preference for domestic research in developing countries, with SCPs dominating over multinational studies.

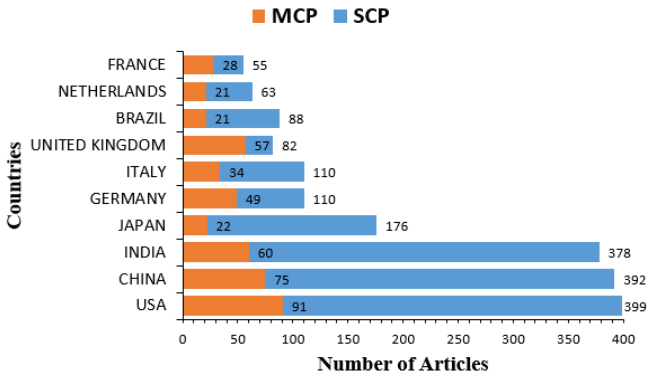

Figure 1. Most relevant countries.

4.1.2. Most Relevant Affiliations

Figure 2 presents the most prolific affiliations in oral cancer research. UCLA leads with the highest number of publications (97), highlighting its prominent role in the field. The University of Malaya follows in second place with 87 publications, demonstrating its active involvement in oral cancer research. Sichuan University ranks third with 79 publications, underscoring its significant contribution to the area. Chang Gung University and the University of Helsinki both contribute 69 articles, reflecting their collaborative efforts in the field. King's College London ranks fifth with 62 publications.

Other notable contributors include the University of Groningen (56 articles), the University of Illinois (51 articles), the University of Queensland (50 articles), and Chang Gung Memorial Hospital (49 articles). Together, these institutions form a global network of expertise, showcasing the widespread geographical distribution of impactful oral cancer research.

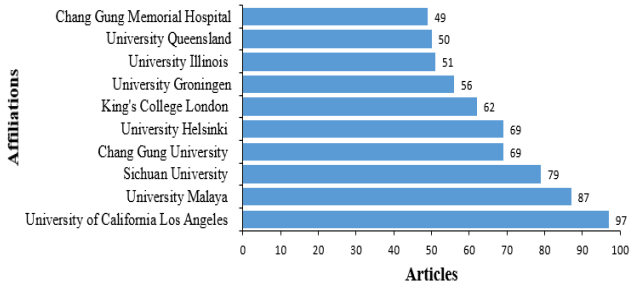

Figure 2. Most relevant Affiliations.

4.1.3. Most Relevant Journals

Figure 3 highlights the top journals contributing to oral cancer research, including both specialized and broader journals that play a significant role in disseminating academic knowledge. Oral Oncology stands out as the leading journal, with 177 published articles, making it the dominant publication in this field. The Journal of Oral Pathology & Medicine ranks second, with 68 publications, emphasizing its key role in oral pathology studies.

The journals *Cancers* and *Head and Neck Journal for the Sciences and Specialties* both contributed 53 articles each, reflecting their importance in interdisciplinary research on head and neck malignancies. *Journal of Biomedical Optics* (49 articles) and *Oral Diseases* (44 articles) are also significant, indicating strong interest in biomedical techniques and oral health issues.

Other important publications include the *International Journal of Cancer* (33 articles), the *International Journal of Oral and Maxillofacial Surgery* (30 articles), and the *Journal of Cancer Research and Therapeutics* (30 articles). These journals, along with the others mentioned, offer a comprehensive range of research covering oncological and maxillofacial topics. Finally, the *Journal of Chromatography B-Analytical Technologies* completes the list with 29 articles, highlighting its focus on analytical methodologies relevant to cancer research. Together, these journals provide a critical platform for the circulation and discussion of oral cancer research findings.

Figure 3. Most relevant journals.

4.1.4. Most Relevant Authors

Figure 4 presents the most prolific authors in oral cancer research based on the number of published documents. Warnakulasuriya S leads with the highest number of publications (24), marking a significant impact on the field. Farah CS follows closely with 22 articles, reflecting a strong research focus in oral cancer. De Bree R ranks third with 21 publications, demonstrating consistent scholarly engagement.

Patil S (20 publications) and Zain RB (18 publications) also make substantial contributions to oral cancer research. Other notable contributors include Kumar S, Wilder-Smith P, Kowalski LP, and Leemans CR, each with 15–16 publications. U and Liu Y each have 14 publications, further enriching the literature. Collectively, these authors form a critical group whose extensive work has significantly advanced oral cancer research.

Figure 4. Most relevant authors.

4.2. Trend Analysis

Trend analysis in academic research involves tracking changes in a specific topic over time, helping researchers understand shifts in variables, concepts, or components. It provides valuable insights into the relationships and influences between different factors within a study area, helping to identify emerging research themes or new areas of focus. Trend analysis also reveals how research methodologies, technology, and themes evolve, offering a glimpse into the future direction of the field. By predicting upcoming developments, it informs decisions on where to invest resources, what research to prioritize, and how to foster collaboration. It also strengthens understanding of the processes and advancements in scholarly research, laying the foundation for evidence-based decisions and structured research planning.

4.3. Keyword Word Cloud

Figure 5 presents a word cloud that reflects the diverse themes and areas in oral cancer research, highlighting its complexity. The most dominant terms, such as "oral cancer," "head and neck cancer," and "squamous cell carcinoma," indicate the primary focus of research in these critical areas. Other important keywords, including "human papillomavirus," "biomarkers," "prognosis," and "saliva," emphasize ongoing efforts to identify diagnostic and predictive tools for early detection and disease monitoring.
Emerging technologies, such as "artificial intelligence," "machine learning," and "deep learning," underline the growing use of computational techniques for screening and predictive analytics. Terms like "early detection," "screening," and "diagnosis" highlight a focus on preventive strategies, while "leukoplakia," "dysplasia," and "metastasis" point to research on both early and late stages of the disease. Additionally, terms like "immunohistochemistry," "liquid biopsy," and "pharmacokinetics" reflect the use of advanced molecular techniques and drug assessments.
Overall, the word cloud captures the broad spectrum of oral cancer research, from foundational pathophysiology to cutting-edge diagnostic and therapeutic approaches.

Figure 5. Author keywords word cloud.

4.4. Top Author's Keywords Growth

Figure 6 illustrates the cumulative development of significant author keywords related to oral cancer from 2000 to 2022, revealing shifts in research focus over time. The term "oral cancer" shows the most significant growth, with 600 cumulative occurrences by 2022, indicating its central role in the ongoing research focus. Keywords like "oral squamous cell carcinoma" and "squamous cell carcinoma" also appear prominently, reflecting their importance in studies related to mouth tumors. The term "head and neck cancer" has also seen increasing mentions, emphasizing its relevance to oral cancers more broadly. The generic term "cancer" shows a moderate but consistent rise, indicating its fundamental role in the overall research landscape. Together, these trends highlight a concentration on specific types of oral cancer, diagnostic methods, treatment approaches, and the integration of broader oncological research. The growth of these keywords signals a growing interest and an expanding understanding of oral cancer over the past two decades.

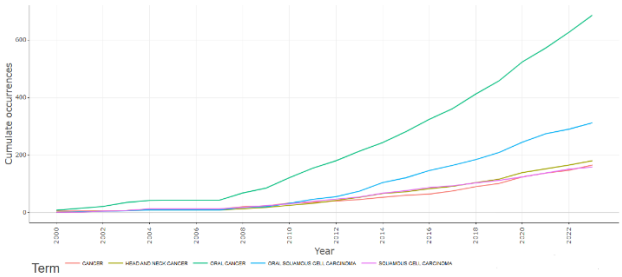

Figure 6. Author keywords growth.

4.5. Trending Topics

Figure 7 highlights emerging and trending topics in oral cancer research based on term frequency and usage over time. The term "oral cancer" remains the leading keyword, maintaining its prominence and underscoring the subject's continued importance. Other high-performing terms include "oral squamous cell carcinoma," "squamous cell carcinoma," and "head and neck cancer," further emphasizing the focus on major cancer types and their associated pathologies.
A notable shift in recent years is the growing interest in new technologies. Terms like "artificial intelligence" and "machine learning" have gained traction, reflecting their increasing application in diagnosis, treatment planning, and predictive modeling within oral cancer research. The term "saliva" is also gaining attention, particularly in its use as a non-invasive diagnostic tool alongside plasma, such as liquid biopsy, for early disease detection and monitoring.

Additionally, "human papillomavirus" has emerged as a high-priority research area, given its established role as a risk factor for oral cancers. While these new trends point to innovations, the analysis also reveals that core topics continue to evolve, indicating a dynamic shift in the research landscape. These developments integrate cutting-edge technologies and methodologies into dentistry, aimed at addressing the ongoing challenges in oral cancer prevention, diagnosis, and treatment.

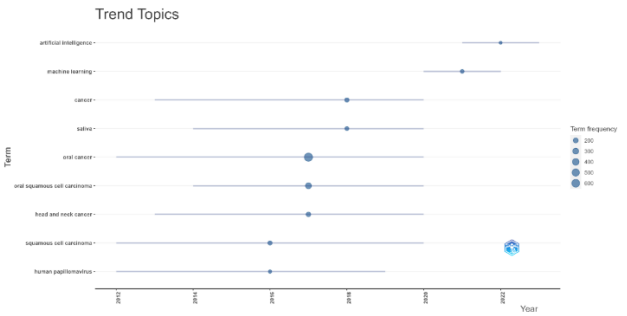

Figure 7. Trending topics for oral cancer.

4.6. Citation Analysis

Bibliometrics is a field of science focused on citation analysis, using metrics like citation count, citation location, authorship, and context to assess the value and impact of academic research. This analysis helps determine the influence of specific authors and their work, as well as the quality and relevance of research findings on a particular topic.

4.6.1. Most Cited Authors

Figure 8 highlights the most cited authors in oral cancer research, showcasing their academic influence and contributions to the field. Notably, Kerr AR and Warnakulasuriya S have the highest number of local citations, each with 223, indicating their significant impact on oral cancer research. Zain RB follows closely with 213 citations, and Farah CS ranks fourth with 209 citations, underscoring their pivotal roles in raising awareness about oral cancer.

Other notable contributors include Lingen MW (194 citations), Almengush A (181 citations), Wilder-Smith P. and Speight PM (176 citations), all of whom are recognized for their substantial influence in the field. Epstein JB (71 citations) and Cheong SC (18 citations) have also made significant contributions, particularly in their specialized areas of research. Together, these authors form the foundation of modern oral cancer research, with their work frequently cited across the literature.

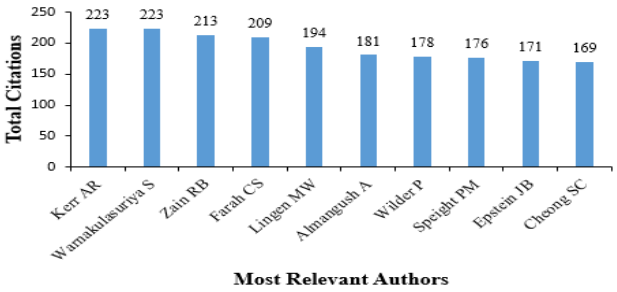

Figure 8. Most cited authors.

4.6.2. Most Cited Countries

Figure 9 illustrates the most cited countries in oral cancer research, highlighting the global academic influence in this field. The United States leads with 24,726 citations, accounting for 54% of the total, solidifying its dominant role in oral cancer research and its substantial output in this area. China follows in second place with 14,975 citations, reflecting its growing strength and significant contribution to oral cancer research.

India ranks third with 9,591 citations, demonstrating its active involvement in this research domain. The United Kingdom (7,635 citations) and Japan (5,831 citations) hold the fourth and fifth positions, respectively, showcasing their continued engagement in global research efforts. Other key contributors include Germany (4,283 citations), Italy (3,782 citations), the Netherlands (3,171 citations), France (2,765 citations), and Brazil (1,957 citations).

These citation patterns reveal that oral cancer research is represented by a diverse mix of both developed and emerging economies, forming a globally distributed network of influential contributions that shape progress in the field.

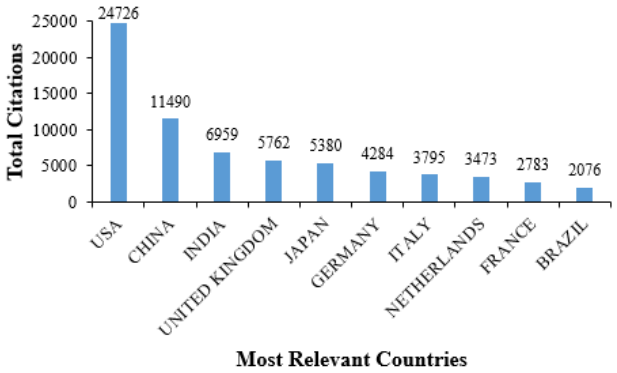

Figure 9. Most cited countries.

4.6.3. Most Cited Journals

Figure 10 highlights the most locally indexed journals in oral cancer research based on citation frequency. Oral

Oncology leads with 5,317 local citations, making it the primary reference in the field. The International Journal of Cancer follows with 2,532 citations, emphasizing its strong interdisciplinary presence in cancer research.

The Head and Neck Journal for the Sciences and Specialties and Cancer Research rank third and fourth, with 2,321 and 2,253 citations, respectively, underscoring their significant role in advancing knowledge on head, neck, and oral cancers. Clinical Cancer Research (1,919 citations) and Journal of Oral Pathology & Medicine (1,093 citations) also rank highly, reflecting their relevance in diagnostics and treatment studies.

Other prominent journals include the Journal of Clinical Oncology (967 citations), PLOS ONE (817 citations), The New England Journal of Medicine (481 citations), and Cancer - A Journal of the American Cancer Society (462 citations). These journals, through their high-impact publications and significant contributions, form a crucial foundation for the academic literature in oral cancer research.

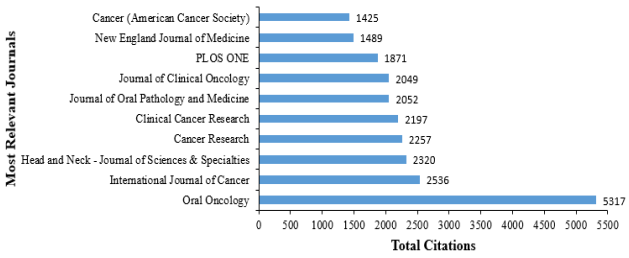

Figure 10. Most cited journals.

4.7. Science Mapping

A method akin to science mapping is applied here to visualize and identify the relationships between different scientific concepts and research areas. This approach typically produces a network diagram, illustrating the connections between various authors, institutions, and their works. These links can be generated through co-citation patterns, collaboration between institutes, or citation links, which help display the intertwined nature of research within a specific domain.

4.8. Network Analysis

Network analysis is a technique used to explore the relationships among publications, organizations, and countries. Academic tools like co-citation networks, journal networks, and institutional collaboration networks are frequently employed in the analysis of academic articles. The main advantage of network analysis lies in its ability to help researchers identify opportunities for collaborative learning or partnerships with other scholars working on similar topics.

4.8.1. Network of Authors for Collaboration

Figure 11 presents a network visualization that illustrates the collaborative relationships between key authors in oral cancer research, organized into distinct clusters based on co-authorship patterns. The blue cluster includes key authors like Almangush, Alhadi, Mäkitie, Antti A., Elmsurati, and Mohammed, demonstrating their close collaborations and a focus on diagnosis and prognosis.

The green cluster, comprising authors such as Kowalski, Luiz P., Leivo, Ilmo, and De Bree, Remco, represents a network of clinical and surgical work related to oral cancer. Authors in the yellow cluster, including Coletta, Ricardo D. and Salo, Tuula, are associated with partnerships centered on molecular and cellular pathology. Finally, the red cluster, led by Warnakulasuriya, Saman, and including authors like Dos Santos, Harim Tavares, Fonseca, and Felipe Paiva, is indicative of research focused on epidemiology and the risk factors associated with oral cancer.

This network analysis reveals that oral cancer research is global in nature, with distinct, yet interconnected, research clusters spanning multiple disciplines. The visualization emphasizes the diverse and collaborative nature of the field.

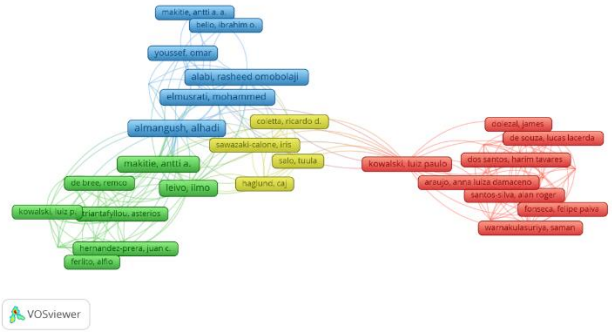

Figure 11. Authors collaboration network.

4.8.2. Network of Countries for Collaboration

Figure 12 illustrates a network visualization of co-authorship relationships between countries in oral cancer research, organized into clusters based on the strength of their co-authorship ties. The purple cluster, which includes the USA, Canada, and Japan, stands out as a key feature of the plot. It highlights the close research collaboration between these nations, particularly in the areas of advanced clinical studies and technological innovation. The blue

cluster consists of Italy, Spain, and Germany, reflecting the strong cooperation among European countries, with a focus on epidemiology and public health concerning oral cancer. The green cluster represents collaboration between England, Australia, Sri Lanka, and Switzerland, emphasizing interdisciplinary research and global outreach in oral cancer studies. The red cluster centers around India, with strong connections to Saudi Arabia, Malaysia, and Thailand, illustrating the regional focus on oral cancer research and its connections within the broader Asian research network. Finally, the yellow cluster includes Brazil, Sweden, and Finland, indicating collaborative efforts at both regional and intercontinental levels, particularly in molecular biology and diagnostic research. Overall, the visualization underscores the international and collaborative nature of oral cancer research. It also highlights the interconnected networks of countries, working together to exchange knowledge and innovations aimed at addressing common challenges in the field.

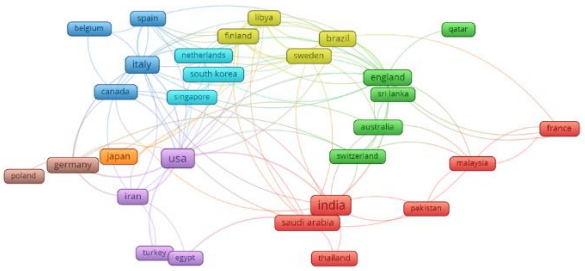

Figure 12. Countries collaboration network.

4.8.3. Network of Institutions for Collaboration

Figure 13 presents a network visualization illustrating the collaborative relationships between institutional affiliations in oral cancer research, classifying them according to their contributions and interconnections over time. The network highlights leading institutions such as Helsinki University Hospital, Sichuan University, and Wuhan University, which play a central role in oral cancer research. Other active institutions like Jazan University, Islamic Azad University, and the University of Chicago also contribute significantly and connect to research networks worldwide. Emerging institutions such as Qatar University and University of Peradeniya demonstrate the increasing participation of developing regions in collaborative oral cancer research, particularly in addressing healthcare issues specific to their regions. The network also showcases interdisciplinary and cross-border collaborations led by institutions like Thammasat University and Tokyo Medical & Dental University, which engage in diverse research approaches. Region-specific research efforts are exemplified by institutions like Altamash Institute of Dental Medicine and China Medical University, which focus on local oral cancer challenges. Several other key institutions, including Aichi Gakuin University, IRCCS San Raffaele Hospital, and All India Institute of Medical Sciences, also contribute extensively to clinical and translational research in oral cancer. This visualization highlights the diversity of institutional partnerships in oral cancer research and emphasizes the evolving structure of these collaborations over time.

Figure 13. Affiliations collaboration network.

4.8.4. Co-Citation Network of Journals

Figure 14 presents a co-citation network visualization, which displays the interrelationships between journals that are frequently cited together, highlighting the major clusters of journals within the field of oral cancer research. One key observation is the central role of Oral Oncology, which serves as a significant node in the network, indicating its influence both in the field of oral cancer and in terms of citation across various areas of research. Scientific Reports (UK), PLOS ONE, and Journal of Oral Pathology & Medicine are also top journals with strong interlinkages, reinforcing their importance in oral cancer research. The green cluster includes journals such as Head Neck - Journal for the Sciences and Specialties, Clinical Cancer Research, and JAMA Otolaryngology, reflecting a focus on head and neck oncology, clinical science, and therapeutic interventions related to oral cancer. The red cluster includes journals like Journal of Cranio-Maxillofacial Surgery, IEEE Access, and Oral Radiology, which are known for their impact on imaging, diagnostics, and computational methods in oral cancer research. In the blue cluster, we find some of the highest-impact journals, including the Nature Journal publishing group, Cancer Research, and the New England Journal of Medicine, which underpin most citation relationships through foundational and translational

research. Another noteworthy aspect is the yellow cluster, which highlights journals like Journal of Biomedical Optics and Biomedical Optics Express, focusing on innovative optical technologies that address diagnostic and therapeutic needs in oral cancer. This co-citation network underscores the multidisciplinary nature of oral cancer research, showcasing contributions from clinical, technological, and basic sciences. It also suggests which central journals play a pivotal role in shaping knowledge dissemination and development within this field.

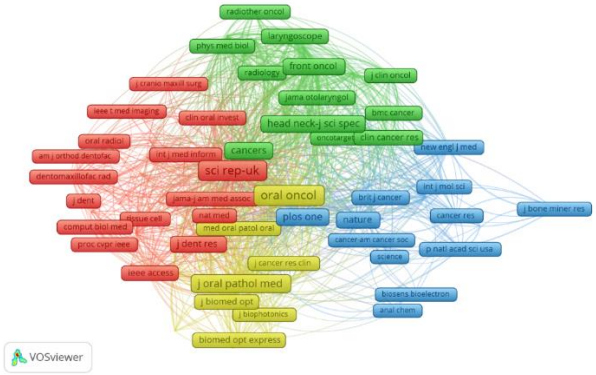

Figure 14. Journals co-citation.

4.9. Overview of the performance analysis

4.9.1. Thematic Evolution

Figure 15 presents the thematic evolution of oral cancer research from 2000 to 2024, illustrating how the focus of research has shifted over three distinct periods:

- Early Phase (2000–2008):

The predominant themes during this period were pharmacokinetics, squamous cell carcinoma, and OSCC. Research in this era was heavily focused on understanding fundamental cancer biology and drug metabolism, laying the groundwork for subsequent studies on the biological processes that drive oral cancers. The focus was largely on the biochemical and cellular mechanisms behind the development of oral cancer, with significant attention given to drug interactions and therapeutic modalities.

- Interim Phase (2009–2016):

During this phase, the scope of oral cancer research expanded to include a broader range of topics such as oral cancer and head and neck cancer. This shift reflected an evolving understanding of the links between oral cancers and broader neoplasms of the head and neck. Although oral squamous cell carcinoma remained a key theme, there was a continued interest in pharmacokinetics, particularly in the context of therapeutics. This period marked a transition toward a more comprehensive view of cancer in the head and neck region, incorporating both local and systemic factors influencing the disease.

- Recent Period (2017–2024):

The most recent period is characterized by specialization and diversification. A major theme emerging from this phase is the role of HPV as a significant contributor to oral cancer risk. HPV research marks a pivotal shift toward understanding viral contributions to oral cancer development, which reflects a broader trend in cancer research focusing on viral oncogenesis. Other themes such as oral squamous cell carcinoma and pharmacokinetics continue to be relevant, particularly in the context of clinical and translational research. This shift highlights a growing awareness of HPV-related oral cancers and further specialization in understanding their pathophysiology, incidence, risk factors, and potential preventive strategies.

The thematic evolution of oral cancer research shows a nonlinear trajectory, with early foundational studies in cancer biology giving way to broader interdisciplinary research that includes viral factors like HPV. The ongoing relevance of pharmacokinetics underscores the continued importance of drug development and therapeutic management. The evolution also highlights the increasing importance of diagnostic technologies and therapeutic innovations, particularly in relation to clinical practice. This progression reflects the dynamic nature of oral cancer research, where new insights into cancer risk factors, clinical management, and diagnostic tools are increasingly integrated into a broader understanding of the disease.

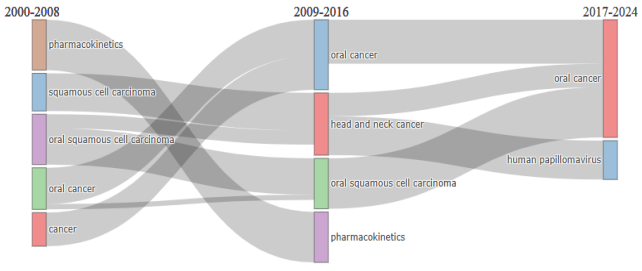

Figure 15. Thematic evolution for oral cancer.

4.9.2. Three Field Plot

The three-field plot in **Figure 16** shows the relationship among countries (AU_CO), authors (AU), and disciplinary themes (DE) in oral cancer, which confirms that this field has a broad global and interdisciplinary nature. India, the USA, and the United Kingdom play important roles in

leading as contributing countries, as well as countries with many connections to many authors and a number of research areas. Prominent authors, including but not limited to Warnakulasuriya S, Kowalski LP, and Patil S, serve as important intermediaries, linking the research activity of their nations with particular thematic foci. The remaining principal connection themes, such as ORAL CANCER, ORAL SQUAMOUS CELL CARCINOMA and SQUAMOUS CELL CARCINOMA, demonstrate their relevance to the field and being at the heart of the subject area. Up-and-coming themes like machine learning show how new technologies are melding into oral cancer study, especially with diagnostics and predictive modelling. Other cancer sites, such as head and neck cancer, saliva, and cancer, indicate that the discipline prioritizes related cancers, biomarkers, and oncology as a whole. This visualization highlights the collaborative networks powering oral cancer research, connecting countries with thriving research ecosystems, key authors, and emerging thematic focus. It illustrates the interconnectivity of global regions, individual contributors, and specific topics at a glance — a snapshot of the multidimensional efforts addressing oral cancer on a worldwide scale.

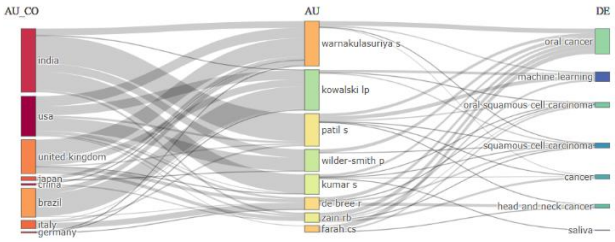

Figure 16. Three fields plot.

5. AI FOR ORAL CANCER

5.1. DL in Oral Cancer Research

Various architectures of deep learning have been used in the field of oral cancer examination for early diagnosis and prognosis assessment. Few studies have investigated the variations for medical image classification and analysis. For example, a convolutional neural network (CNN) that aided the classification of oral cavity medical images for early detection of oral cancer achieved 154 total citations (normalized citation score 1.5) in a 2018 study published in the Journal of Cancer Research and Clinical Oncology. In the same line of work, a study in Oral Surgery, Oral Medicine, and Oral Radiology (106 citations, normalized impact = 1.03) applied the AlexNet architecture to detect the presence and the extent of cervical lymph node metastasis in patients with oral cancer using presurgical contrast-enhanced CT images. Moreover, a study in IEEE Access that used ResNet-101 for automatic detection and categorization of oral lesions for early diagnosis was impactful, with 94 citations and the highest normalized citation count of 2.34. Importantly, CNN-based classification of cancerous tissue in laser endomicroscopy images reported in Scientific Reports received 156 citations and a normalized citation score of 1.94. This finding is complemented by the significant impact of a deep learning-based survival prediction model, also published in Scientific Reports using DeepSurv, which had 213 citations and a normalized score of 2.07. These studies demonstrate the significant adaptive nature and positionality of deep learning and big data analytics techniques towards healthcare and oral cancer diagnostic accuracy and predictive analytics, driving better clinical decision-making.

5.2. ML in Oral Cancer

In oral cancer prognosis and detection, several types of algorithms have been applied to improve the predictive accuracy from machine learning using data up to October 2023. The hybrid approach comprising Adaptive Neuro-Fuzzy Inference System (ANFIS), Artificial Neural Networks (ANN), Support Vector Machines (SVM) and Logistic Regression (LR) were proposed for oral cancer prognosis prediction, resulting in a total of 97 citations with a normalized citation score of 1.75 [40]. An analysis of 83 studies showed four out of three achieving the highest number of citations, including one in Oral Oncology that applied multiple machine learning techniques, such as employing LR, decision forests, kernel SVM and gradient boosting algorithms to predict occult nodal metastasis in early OSCC, that got 89 citations and the highest TC per year (12.71). A systematic review in Artificial Intelligence in Medicine discussed the current challenges, future directions and trends in machine learning applications for OSCC, and it exhibited a strong normalized citation impact of 3.28. Two studies compared different supervised learning approaches in the International Journal of Medical Informatics. A study on the prediction of locoregional recurrences in early oral tongue cancer using SVM, Naïve Bayes, Boosted Decision Trees, Decision Forest, and Permutation Feature Importance was cited 73 times with a normalized score of 2.24. Another study compared survival prediction based on nomograms versus machine learning models, including logistic regression, SVM, Naive Bayes, neural networks, and random decision trees, applying a total of 43 citations, resulting in a normalized score of 1.83. These studies highlight the increasing contributive role of machine learning in enhancing oral cancer diagnostics, risk stratification, and treatment planning as shown in **Table 2**.

Table 2. Highly Cited Studies on Machine Learning Applications in Oral Cancer: Models, Methods, and Impact Metrics.

Title	Ref	Journal	Method	TC	TC per Year	Normalized TC
Computer-assisted medical image classification for early diagnosis of oral cancer employing deep learning algorithm	[40] [40]	Journal of Cancer Research and Clinical Oncology	CNN	154	22	1.5
Contrast-enhanced CT image assessment of cervical lymph node metastasis in oral cancer patients using a deep learning system of artificial intelligence	[41] [41]	Oral Surgery, Oral Medicine, Oral Radiology	AlexNet architecture	106	15.14	1.03
Automated Detection and Classification of Oral Lesions Using Deep Learning for Early Detection of Oral Cancer	[42] [42]	IEEE Access	ResNet-101	94	15.67	2.34
Automatic Classifcation of Cancerous Tissue in Laser endomicroscopy Images of the Oral Cavity using Deep Learning	[43] [43]	Scientific Reports	CNN	156	17.33	1.94
Deep learning-based survival prediction of oral cancer patients	[44] [44]	Scientific Reports	DeepSurv	213	30.43	2.07

5.3. AI in Oral Cancer Research

In the early detection and diagnosis of oral cancer, AI, ML, and DL techniques have shown great promise. A systematic review of papers relating to artificial intelligence in dentistry, which is published in BioMed Research International, reported 75 citations (TC) and annual citation rates of 15, with a normalized TC of 2.69, showing the increasing impact. Different architectures of neural networks were explored by the Journal of Dental Research, which included the CNNs, recurrent neural networks (RNN), multiscale CNNs (M-CNN) and the multi-instance learning CNNs (MIL-CNN), and achieved TC of 72 and annual citation of 12, asserting the efficacy of deep learning models for oral cancer imaging. Likewise, "AI's Role in Diagnosing Precancerous and Cancerous Lesions: A Systematic Review", published in Oral Oncology, demonstrated a TC of 71 and an annual citation of 11.83, which is another evidence demonstrating the trustworthiness of AI-assisted diagnostics. In another study, in Cancers, a scoping review was performed on different ML and DL techniques for early oral cancer detection, with TC, annual citation rate, and normalized TC of 41, 8.2, and 1.47, respectively, indicating AI's potential for improving early diagnosis. Finally, Diagnostics published the use cases and hurdles of AI in oral disease diagnosis, generating 39 TC and a yearly citation rate of 9.75, with the highest normalized TC being 3.07, identifying it as most relevant in the area. Together, these studies demonstrate the transformational impact of artificial intelligence on enhancing the precision and speed of oral cancer detection and set the stage for future AI-based diagnostic solutions for oral oncologists.

6. DISCUSSION

6.1. Detection and Prognostication Oral Cancer Using AI

6.1.1. Histopathologic and Imaging Analysis

AI-enabled algorithms have drastically improved the diagnostic accuracy of histopathology images as well as imaging techniques like CT and MRI. Analysis of microscopic tissue structures enables the early detection of OSCC, verrucous carcinoma, and adenoid cystic carcinoma using deep learning techniques such as CNNs. Combining imaging with AI provides the ability to differentiate between HPV-positive and HPV-negative tumors, which translates to treatment decisions.

6.1.2. AI Applications Based on Molecules and Biomarkers

TP53 inactivation or EGFR amplification is a vital genetic mutation in oral cancer, and machine learning-based models have been built to analyze such mutations. AI-powered genomic profiling alongside predictive analytics can characterize tumor aggressiveness and resistance to treatment, which helps physicians identify targeted therapies. Furthermore, AI-enabled liquid biopsy methods

exploit circulating tumor DNA for non-invasive early disease detection and progression monitoring.

6.2. Systemic Consequences of Oral Cancer

6.2.1. Metastatic Spread, Organ Involvement

Oral cancer metastases to distant organs like the brain, liver, and bones, greatly reducing prognosis. Although rare, brain metastasis results in drastic neurological sequelae, including seizures and alteration of cognition. Whereas liver metastasis leads to hepatic failure, bone metastasis can cause skeletal weakness and hypercalcemia. In addition, systemic inflammation and oxidative stress seriously aggravate cardiovascular and renal dysfunction in oral cancer patients.

6.2.2. Genetic Factors and Hormonal Influence

Major oncogenic signaling pathways leading to oral cancer development include the PI3K/AKT/mTOR pathway and the NF-κB pathway, which promote tumor cell proliferation and immune evasion. Tumor growth and therapy response are influenced by hormonal factors, especially the expression of estrogen and androgen receptors. Chronic stress causes changes in hormones, particularly cortisol, which can affect the way tumors develop — for example, the synthesis of cortisol suppresses immune surveillance mechanisms, enabling cancer progression.

6.3. Bibliometric and Epidemiological Information

6.3.1. Trends in global research and collaborative networks

The three countries contributing most to oral cancer research are the United States, China, and India, per the bibliometric analysis. Prominent institutions like UCLA and Sichuan University have contributed extensively to the literature on AI applications in oncology. Emergent Trends in AI-based Oral Cancer Studies: Towards Precision Diagnostics and Personalized Medicine Co-citation and collaboration networks reveal cross-disciplinary collaboration between pathologists, oncologists, and data scientists to develop advanced machine learning-based models.

6.3.2. Epidemiology, Mortality, and Risk Factors

The global prevalence of oral cancer is quite different in the world; e.g., South Asian countries have a higher prevalence due to the consumption of betel quid, whereas HPV-associated diseases are increasing in Western countries. In late-stage diagnosis, the five-year survival rate is still low, which highlights the importance of early detection strategies. Even tobacco use, alcohol consumption, and genetic predisposition take the cake as a risk factor for the emergence of diseases.

7. CONCLUSION

This study emphasizes the beneficial impact of AI in the detection, prognostication, and treatment of oral carcinoma. Deep learning and machine learning algorithms enhance detection accuracy, improving treatment selection and facilitating personalized therapeutic approaches. The wide-ranging and indirect impact of oral cancer on whole-body physiology, such as organ function and metabolism, must also be appreciated to inform patient management. Additionally, bibliometric data highlight the increasing international collaboration in AI-oncology research. We recommend future studies integrate AI-based multi-omics analysis, create real-time monitoring devices, and improve early screening programs to lower mortality rates of oral cancer.

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Conflict of interest

The authors declare no conflict of interest.

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