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Review

Machine-Learning Applications in Oral Cancer: A Systematic Review

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Abstract: Over the years, several machine-learning applications have been suggested to assist in various clinical scenarios relevant to oral cancer. We offer a systematic review to identify, assess, and summarize the evidence for reported uses in the areas of oral cancer detection and prevention, prognosis, pre-cancer, treatment, and quality of life. The main algorithms applied in the context of oral cancer applications corresponded to SVM, ANN, and LR, comprising 87.71% of the total published articles in the field. Genomic, histopathological, image, medical/clinical, spectral, and speech data were used most often to predict the four areas of application found in this review. In conclusion, our study has shown that machine-learning applications are useful for prognosis, diagnosis, and prevention of potentially malignant oral lesions (pre-cancer) and therapy. Nevertheless, we strongly recommended the application of these methods in daily clinical practice.

Keywords: oral cancer; OSCC; machine learning; applications

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1. Introduction

Oral cancer has emerged as a serious public health issue across the world. According to the literature, the global incidence, mortality, and disability-adjusted life years of this disease increased by nearly 1.0-fold between 1990 and 2017 [1]. Based on the GLOBOCAN estimates of incidence and mortality, 377,713 new cases and 177,757 deaths for lip and oral cavity cancer were reported for the year 2020 [2]. Most oral cancers are squamous cell carcinomas, which is an aggressive disease with a high tendency to metastasize locally and to distant sites. It has a considerable impact on a patient's life and on society as a whole. Oral cancer has a 5-year overall survival rate of just approximately 51.7 percent due to frequently late diagnosis [3].

The methods used for oral cancer diagnosis include the traditional anamnesis and clinical examination, complemented with image and hematoxylin–eosin histopathological analysis, the latter being the most common method [4,5]. Immunohistochemistry is routinely used to distinguish the disease in more complex instances and to aid in disease staging. For its examination, molecular approaches have been devised with the goal of finding biomarkers that can anticipate early alterations. In situ hybridization, gel electrophoresis and blotting, flow cytometry, mass spectrometry, polymerase chain reaction, microarrays, Sanger sequencing, and next-generation sequencing are common techniques employed in molecular diagnostics of oral squamous cell carcinomas [6].

In the practice of clinical medicine and in all health-related tasks, the diagnostic process is critical. A correct diagnostic evaluation is essential for the effectiveness of disease therapy. This diagnostic process is based on the interpretation of information supplied by the patient in the anamnesis, as well as the clinician's clinical examination, in addition to the information provided by the complementary tests. In short, an accurate diagnosis is obtained after analyzing the data of the disease.

Artificial intelligence (AI) is commonly employed among diverse areas of medicine [7,8]. Radiology and sophisticated imaging technologies, pathology, ophthalmology, and dermatology are the disciplines to which it has made significant contributions [7,8]. In each case, a number of impediments must be assessed [8]. Three factors are commonly used to apply the regulations: the danger to patient safety, the presence of a predictive algorithm, and the amount of human involvement [8].

Mathematical models have been used to analyze specific aspects related to oral cancer. Multistage clonal expansion models have been used to analyze the incidence of human papillomavirus (HPV)-related and unrelated oral squamous cell carcinoma, concluding that this model can be useful to identify temporal trends in cancer mechanisms [9]. Additionally, mathematical modeling combined with vitro experimentation has been used to analyze the nanoparticle uptake of oral cancer cells, concluding that the number of receptors per cell was the dominant mechanism in the process [10].

Machine learning (ML) has also been used in oral cancer studies to explore the discrimination between well-differentiated (WD) oral squamous cell carcinoma (OSCC) and moderately or poorly differentiated OSCC [11], to evaluate its ability to predict disease outcome [12], to predict the occurrence of lymph node metastasis of early-stage oral tongue squamous cell carcinoma [13], among other topics of this disease.

ML applications can be classified based on the clinical context of the disease, including diagnosis and prevention, prognosis, potentially malignant oral lesions (pre-cancer), and therapy and quality of life.

According to the NCI Dictionary of Cancer Terms (https://www.cancer.gov/publications/dictionaries/cancer-terms, accessed on 1 March 2022), diagnosis corresponds to the process of identifying a disease, condition, or injury from its signs and symptoms. Cancer prevention includes avoiding risk factors and increasing protective factors. Prognosis is the likely outcome or course of a disease, i.e., the chance of recovery or recurrence. Potentially malignant oral lesions are states of the oral mucosa that are at an increased risk of malignant transformation compared to healthy mucosa [14]. Therapy and quality of life represent the clinical approach to cancer and how it affects an individual's sense of well-being and ability to carry out activities of daily living.

Considering the current characteristics of oral cancer in terms of the increase in its incidence, the need to strengthen the diagnostic tools, and the existence of abundant literature on the use of machine learning in the study of this disease, a comprehensive study was carried out with the goal of analyzing the potential uses of machine learning in oral cancer.

2. Materials and Methods

This systematic review was conducted according to guidelines reported in the indications of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [15].

This study aimed to answer the question: "Which are the machine-learning applications used in oral cancer?". For this, a systematic literature search based on keywords was performed. The search was carried out considering the following databases: Web of Science, PubMed, ScienceDirect, and IEEE.

2.1. Search Strategy

The literature search was carried out through four journal databases (Web of Science, PubMed, ScienceDirect, and IEEE) and ran up to 22 May 2020. The search strategy used both medical subject headings (MeSH) and free-text terms. The search with MeSH terms was run through PubMed, and the terms corresponded to: "machine learning" AND "mouth neoplasms", and "artificial intelligence" AND "mouth neoplasms". With regard to the free-text terms, they corresponded to: (machine learning AND oral cancer) OR (artificial intelligence AND oral cancer) OR (machine learning AND OSCC) OR (artificial intelligence AND OSCC).

2.2. Inclusion Criteria and Study Selection Process

The studies considered were only studies that dealt with machine-learning applications in the field of oral cancer. Specifically, we sought studies evaluating the different uses of the machine-learning field in oral cancer disease.

For inclusion within this review, studies were selected according to the following inclusion and exclusion criteria:

- Articles reporting data related to the machine-learning applications in oral cancer disease.
- Only original articles in English language were considered.
- Case reports, lectures, data in brief, reviews, in vitro studies (on animals and on human cell lines) and non-original data were excluded from this study.
- Articles that did not involve a concrete machine-learning application in oral cancer disease were excluded.

2.3. Data Collection and Extraction

In an unblinded but separate approach, two researchers (X.A.L.C. and F.M.) assessed the titles of the papers found by the search method across the four online databases. Articles that were duplicated were removed. The abstracts were then screened by two researchers who worked separately (X.A.L.C. and F.M.). Any article that appeared to fit the inclusion criteria was subjected to a full-text review. Disagreements between the four writers throughout the abstract screening stage and full-text eligibility were settled by consensus.

For data extraction, three researchers (X.A.L.C., C.R., and B.V.) performed a training phase in order to discuss the data extraction (items to consider) from the selected final articles. Finally, two authors were in charge of independently extracting these items (X.A.L.C. and F.M.). This process was cross-checked. All performances were considered when a study reported several classification experiments. In the case when a study compared several feature combinations, the performance of the best combination was considered. Performance analysis was conducted according to the following statistic metrics: accuracy (ACC), sensitivity (SE), specificity (SP), and area under the ROC curve (AUC).

Cohen's kappa statistic was used to calculate the agreement between the reviewers. In addition, the risk of bias (ROB) in the studies was calculated by using the Prediction model Risk of Bias Assessment Tool (PROBAST) [16]. PROBAST contains a set of 20 signaling questions from four domains, which involve aspects such as participants, predictors, results, and analysis to allow the evaluation of the risk of bias in predictive model studies.

3. Results

The PRISMA flow diagram followed is depicted in Figure 1. In detail, 478 articles were identified in the four databases. After eliminating the duplicate articles and applying the inclusion and exclusion criteria, 63 articles were obtained. From these, six articles were excluded for different reasons, including: out of goal (one article), unavailability online (two articles), and lack of ML techniques (three articles). Finally, 57 articles were included (Figure 1).

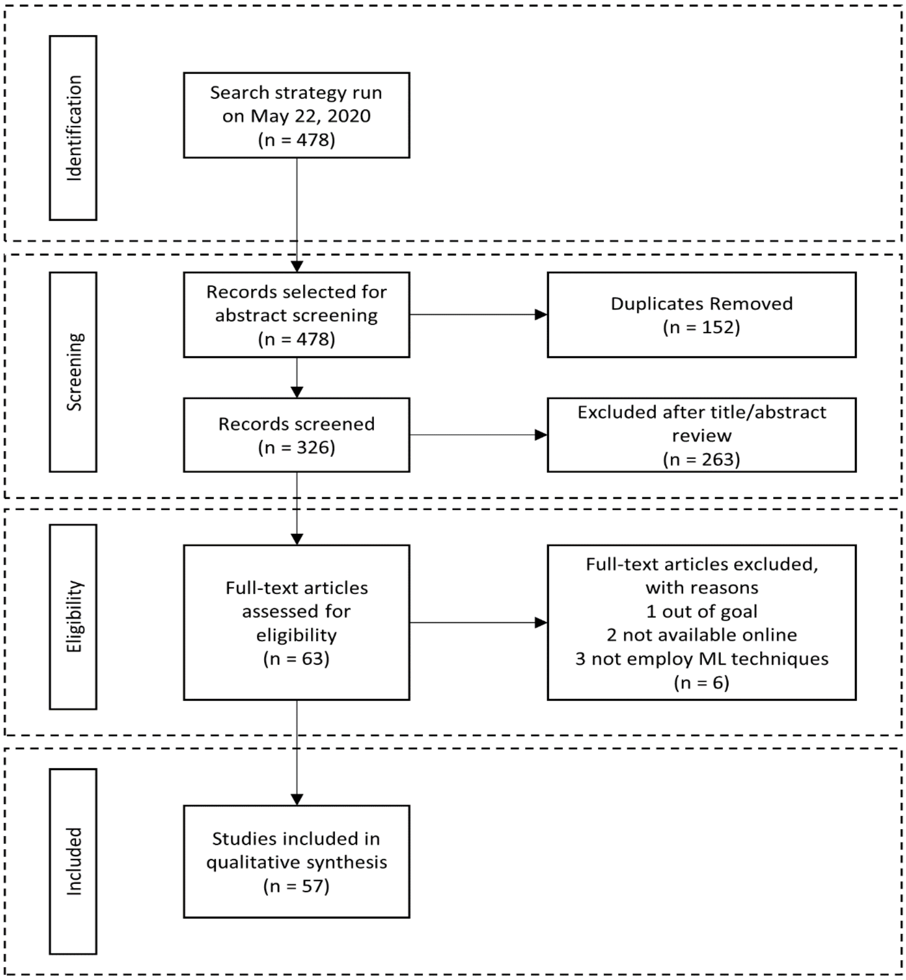

Figure 1. Flow diagram of literature search and selection criteria.

The selected studies (57 in total) were screened; the inputs of model, number of samples, outcomes, ML techniques employed, and risk of bias were recorded. These parameters are summarized in Table 1. The first study dates from 1996. Most studies included in this systematic review were published in the years 2018 and 2020.

The included studies were conducted in Brazil, Israel, Taiwan, Japan, Malaysia, Netherlands, and others. The number of samples ranged from 20 to 33,065 (mean 1192). The result of the kappa agreement was 0.85, which classifies as almost perfect. Differences were resolved by consensus of reviewers. Regarding the oral pathologist–oral cancer context, the selected studies were grouped according to different ML applications in the field. These applications correspond to the following clinical contexts: (i) diagnosis and prevention, (ii) prognosis, (iii) potentially malignant oral lesions (pre-cancer), and (iv) therapy and quality of life (Figure 2).

Table 1. Original research studies that applied machine-learning methods to oral cancer pathology.

Ref.	Year	Clinical Context	Applied Algorithm	Input Features	*n* Samples	ROB	Concluding Remarks
[17]	2019	Prognosis	XGBOOST	Expression profiles and clinical data	291	+	A three-mRNA signature (CLEC3B, C6, and CLCN1) successfully predicted the survival of OSCC patients
[18]	2016	Prognosis	GP, SVM, LR	Personal details, medical history, p53, p63	31	+	Genetic programing (GP) an ideal prediction model for cancer clinical and genomic data
[19]	2018	Diagnosis and Prevention	SVM	miRNA expression	122	+	Using the platform with an ML algorithm, it discovers miRNA expression patterns capable of separating healthy subjects from OSCC patients
[20]	2005	Potentially malignant oral lesions (pre-cancer)	WNN	TEM images of collagen fibers from oral subepithelial region	145	+	The trained network was able to classify normal and oral pre-cancer stages
[21]	2019	Potentially malignant oral lesions (pre-cancer)	SVM, RF, LR, LDA, KNN	Cytology images	60	+	Applicability of tele-cytology for accurate, remote diagnosis and use of automated ANN-based analysis in improving its efficacy
[22]	2015	Therapy and quality of life	CTREE, RF, BA, SVM	Gene expression data	486	+	Analyzed the dysregulated gene pairs between control and tumor samples and then implemented an ensemble-based feature selection approach to prioritize targets in oral squamous cell carcinoma (OSCC) for therapeutic exploration
[23]	2018	Prognosis	KSTAR, IBK, RFC, RT	Personal details, medical history, smoking, betel nut chewing, and drinking	1428	+	Evidence-based diagnostic model using machine-learning techniques for the prediction of risk factors of recurrent oral cancer
[24]	2010	Diagnosis and Prevention	LDA	Spectral data	57	+	Presents an approach to adaptively adjust spectral window sizes for feature extraction from optical spectra
[25]	1998	Diagnosis and Prevention	ANN	Personal details, dental attendance, and smoking and drinking habits	2027	+	Sensitivity analysis using a decision model to simulate opportunistic screening for oral cancer and pre-cancer
[26]	2017	Prognosis	LDA, QDA, RF, SVM	Images of H&E-stained tissue sections	115	+	Investigates computer-extracted image features of nuclear shape and texture on digitized images of H&E-stained tissue sections for risk stratification of oral cavity squamous cell carcinoma patients compared with standard clinical and pathologic parameters
[27]	2011	Therapy and quality of life	ANN	Speech recording	51	-	Applicability of neural network feature analysis of nasalance in speech to assess hypernasality in speech of patients treated for oral or oropharyngeal cancer
[28]	2009	Potentially malignant oral lesions (pre-cancer)	SVM	Images of SECT (sub-epithelial connective tissue) of NOM and OS	20	+	Automated classification method using SVM for understanding the deviation of normal structural profile of oral mucosa during precancerous changes
[29]	2020	Diagnosis and Prevention	CNN	Histopathological images	8321	+	CNN-based multi-class grading method of OSCC could be used for diagnosis of patients with OSCC
[30]	2011	Potentially malignant oral lesions (pre-cancer)	SVM	Images of surface epithelium from oral mucosa	158	+	Classification based on textural features for the development of a computer-assisted screening of oral sub-mucous fibrosis (OSF)
[31]	2020	Diagnosis and Prevention	DTREE, SVM, KNN, LDA, LR	Histopathological images	720	+	SVM and linear discriminant classifier gave the best result for texture and color features, respectively, from the histopathological images
[32]	2017	Diagnosis and Prevention	CNN	Images of confocal laser endomicroscopy (CLE)	7894	+	Novel automatic approach for OSCC diagnosis using deep-learning technologies on CLE images

Table 1. *Cont.*

Ref.	Year	Clinical Context	Applied Algorithm	Input Features	*n* Samples	ROB	Concluding Remarks
[33]	2018	Diagnosis and Prevention	CNN, RF	Microscopic images of the oral mucosa	100	+	CNN approach is proposed for segmentation of different constituent layers from oral mucosa histology images
[34]	2000	Potentially malignant oral lesions (pre-cancer)	ANN	Spectral data	28	-	Neural networks provide a very good discrimination between autofluorescence spectra of leukoplakia and normal tissue
[35]	2019	Diagnosis and Prevention	CTA	Medical/dental experience, psychosocial factors, demographics	2401	+	Classification tree analysis (CTA) to identify population subgroups that are less likely to have an oral cancer examination (OCE)
[36]	2004	Diagnosis and Prevention	ANN, KLLC, PCA	Spectral data	134	+	Classification and detection of invisible tissue alterations through autofluorescence spectroscopy applying PCA and ANN methods
[37]	2003	Prognosis	LR, DTREE	Tumor size, mode of invasion, and keratinization	118	+	Three statistical methods for the prediction of lymph node metastasis in carcinoma of the tongue are compared
[38]	2017	Diagnosis and Prevention	RF	Histopathological images of OSCC	150	+	Automated technique for accomplishing the task of mitotic cell count from related histopathological images
[39]	2019	Diagnosis and Prevention	CNN	Hyperspectral images	100	+	Proposed regression-based partitioned CNN learning algorithm for a complex medical image of oral cancer diagnosis
[40]	2019	Diagnosis and Prevention	CNN	Computed tomography scan images	441	+	Deep-learning image classification system for the diagnosis of lymph node metastasis on CT images
[41]	2019	Diagnosis and Prevention	CNN, SVM, LDA	Spectral data	1440	+	Classification method that discriminates tongue squamous cell carcinoma (TSCC) from non-tumorous tissue
[42]	2018	Diagnosis and Prevention	SVM	Infrared (IR) thermal imaging	90	+	Automatic analysis by an entropy gradient support vector machine (EGSVM) using a digital infrared thermal imaging system
[43]	2019	Prognosis	RF, DJU, LR, ANN	Personal details, tumor, and treatment characteristics	33,065	+	Describes a model using machine learning to help predict 5-year overall survival among patients with oral squamous cell carcinoma (OSCC)
[44]	2015	Potentially malignant oral lesions (pre-cancer)	RVM, SVM, MLC	Images of lip border	150	+	Using robust macro-morphological descriptors of the vermillion border from non-standardized digital photographs with a probabilistic model (RVM) for solar cheilosis recognition
[45]	2015	Diagnosis and Prevention	SVM	Spectral data	47	+	Classification of two oral lesions, namely oral leukoplakia (OLK) and oral squamous cell carcinoma (OSCC), was performed with SVM using different combinations of spectral features
[46]	2019	Diagnosis and Prevention	LDA, SVM	Spectral data	34	?	Showed the specific IR spectral signature for OC salivary exosomes, which was accurately differentiated from HI exosomes based on detecting subtle changes in the conformations of proteins, lipids, and nucleic acids using optimized ANN
[47]	2019	Diagnosis and Prevention	LR	Tissue microarray chips	105	+	The effectiveness of Aurora kinase A and Ninein interacting protein (AUNIP) in diagnosing OSCC was evaluated by machine learning
[48]	2015	Prognosis	SVM	Protein intensity	30	+	Proteomeof whole saliva and salivary extracellular vesicles (EVs) from patients with OSCC and healthy individuals were analyzed. The proteomics data could classify OSCC with 90% accuracy
[49]	2019	Diagnosis and Prevention	SVM	Putrescine, glycyl-leucine, and phenylalanine	31	+	With three-marker panel, consisting of putrescine, glycyl-leucine, and phenylalanine using a support vector machine (SVM) model that can discriminate paired cancerous (T) from adjacent noncancerous (AN) tissues

Table 1. *Cont.*

Ref.	Year	Clinical Context	Applied Algorithm	Input Features	n Samples	ROB	Concluding Remarks
[50]	2015	Prognosis	LR	Gene expression profiles	486	+	The proposed network-driven integrative analytical approach can identify multiple genes significantly related to an OSCC stage
[51]	2019	Prognosis	SVM, GB, LR, DTREE	Clinicopathologic data	782	+	Machine learning improves prediction of pathologic nodal metastasis in patients with clinical T1-2N0 OCSCC compared to methods based on DOI
[52]	2020	Prognosis	PLS-DA, OPLS-DA	Spectral data	180	+	Spectral data on 180 tissues comprising tumor, margin, and bed from 43 OSCC patients were used to perform machine-learning models to identify malignancy status
[53]	2018	Therapy and quality of life	DFG	Family, gene, compound, bile mutation, GWAS phenotype, OMIM phenotype, kidney mutation, and oral mutation	400	+	Algorithm Medusa in parallel with binary classification was used in order to find potential compounds to inhibit oral cancer
[54]	2013	Prognosis	ANFIS, ANN, SVM, LR	Clinicopathologic and genomic data	31	+	The results revealed that the prognosis is superior with the presence of both clinicopathologic and genomic markers
[55]	2006	Potentially malignant oral lesions (pre-cancer)	WNN	TEM images of collagen fibers from oral subepithelial region	145	+	The trained network could classify normal fibers from less advanced and advanced stages of OSF successfully
[56]	1996	Diagnosis and Prevention	ANN	Intra-oral smears	348	+	A neural network differentiated between normal/non-dysplastic mucosa and dysplastic/malignant mucosa
[57]	2011	Prognosis	LR, ANN	Medical history	211	?	Suggests the importance of routinely investigating PTI in OSCCs as useful marker of tumoral behavior and prognosis
[58]	2003	Diagnosis and Prevention	PLS, ANN	Spectral data	97	+	The PLS-ANN classification algorithm based on autofluorescence spectroscopy at 330 nm excitation is useful for in vivo diagnosis of OSF, as well as oral pre-malignant and malignant lesions
[59]	2020	Potentially malignant oral lesions (pre-cancer)	KNN	Demographics, lesion characteristics, and cell phenotypes	999	+	Cytopathology tools represent a practical solution for rapid PMOL assessment, with the potential to facilitate screening and longitudinal monitoring in primary, secondary, and tertiary clinical care settings
[60]	2018	Potentially malignant oral lesions (pre-cancer)	CNN	Images oral cavity	170	+	CNN was implemented in the cloud and used for automatic image analysis and classification of pairs of images into "suspicious" and "non-suspect"
[61]	2017	Potentially malignant oral lesions (pre-cancer)	SVM	DIC images of oral exfoliative cells	119	+	The selected morphological and textural features of epithelial cells are compared with the non-smoker (-ve control group) group and clinically diagnosed pre-cancer patients (+ve control group) using SVM classifier
[62]	2020	Prognosis	DTREE, ANN, NB, KNN	Contrast-enhanced CT images	40	+	A radiomic ML approach applied to PTLs is able to predict TG and NS in patients with OC and OP SCC
[63]	2006	Diagnosis and Prevention	ANN, PCA	Spectral data	143	+	Spectral analyses were used to classify and discriminate among normal, pre-malignant, and malignant conditions on oral tissue. Sensitivity and specificity gave results of > 92% in PCA and ANN
[64]	2017	Potentially malignant oral lesions (pre-cancer)	RF, SVM, KNN	Exfoliative cytology, histopathology, and clinical follow-up data	364	?	Developed an exfoliative cytology-based method for quantitative prediction of cancer risk in patients with oral leukoplakia

Table 1. *Cont.*

Ref.	Year	Clinical Context	Applied Algorithm	Input Features	*n* Samples	ROB	Concluding Remarks
[65]	2005	Diagnosis and Prevention	SVM, RVM	Spectral data	325	+	The Bayesian framework of RVM formulation makes it possible to predict the posterior probability of class membership in discriminating early SCC from the normal squamous tissue sites of the oral cavity in contrast to dichotomous classification provided by the non-Bayesian SVM
[66]	2012	Potentially malignant oral lesions (pre-cancer)	BC, SVM	Images of normal and OSF oral mucosa	119	+	Bayesian classification and support vector machines (SVM) to classify normal and OSF
[67]	2020	Diagnosis and Prevention	SVM, DTREE, NCA, LDA	H&E-stained microscopic images of squamous epithelial layer	676	+	ML-based automatic OSCC classifier named as stratified squamous epithelial biopsy image classifier (SSE-BIC) to categorize H&E-stained microscopic images of squamous epithelial layer in four different classes: normal, well-differentiated, moderately differentiated, and poorly differentiated
[68]	2015	Prognosis	DTREE, LR, ANN	Medical history	673	-	Determines the differences between the symptoms shown in past cases where patients died or survived oral cancer
[69]	2018	Diagnosis and Prevention	SVM	Spectral data	186	+	Diffuse reflectance spectra were used to discriminate tumor from healthy tissue, and SVM models were used to classify them
[70]	2015	Diagnosis and Prevention	LIR, DTREE, RF, TREEB, ANN, CCNN, PNN/GRNN	Medical history	1025	-	Data-mining model using probabilistic neural network and general regression neural network (PNN/GRNN) for early detection and prevention of oral malignancy
[71]	2005	Diagnosis and Prevention	FNN	Age, gender, smoking, alcohol, bcl-2, PCNA, surviving	21	?	FNN were effectively used to analyze the relationship between oral leukoplakia and HPV infection
[72]	2018	Prognosis	RF, DTREE, NB, LR, SVM, ANN	Peptides and proteins	40	+	Proteomics analysis of proteins in saliva in combination with machine-learning methods were applied to study prognosis classification
[73]	2005	Prognosis	FNN	Age, gender, smoking, alcohol, bcl-2, PCNA, surviving	21	?	FNNs were used to build up a predictive model to study the relationship between HPV infection and different variables in the OSCC

"+" indicates low risk of bias, "-" indicates high risk of bias, and "?" indicates unclear risk of bias, CNN = Convolutional neural network, ANN = Artificial neural network, SVM = Support vector machine, RF = Random forest, DTREE = Decision tree, LR = Regression logistic, BC = Bayesian classifier, ANFIS = Adaptive neuro-fuzzy inference system, WNN = Wavelet neural network, CTREE = Conditional inference trees, BA = Bagging, LDA/QDA = Linear/quadratic discriminant analysis, RVM = Relevance vector machine, MLC = Mahalanobis classifier, LIR = Linear regression, TREEB = Tree boost, CCNN = Cascade correlation neural network, GB = Gradient boosting, NCA = Neighborhood component analysis, DJU = Decision jungle, CTA = Classification tree analysis, PLS-DA = Partial least square discriminant analysis, OPLS-DA = Orthogonal partial least square discriminant analysis, DFG = Data fusion graph, RFC = Randomizable filtered classifier, RT = Random tree, PCA = Principal component analysis, PLS = Partial least squares, NB = Naïve Bayes, KNN = K nearest neighbors, GP = Genetic programing, RT = Random tree, KLLC = Karhunen–Loeve linear classifier, XGBOOST = Extreme gradient boosting, PNN/GRNN = Probabilistic neural network /general regression neural network, FNN = Fuzzy neural network, KSTAR = Instance-based learner using an entropic distance measure, ROB = Risk of bias.

In concordance with the four application areas found, the diagnosis and prevention [19,24,25,29,31–33,35,36,38–42,45–47,49,56,58,63,65,67,69–71] register the largest number of articles with 45.61%, followed by prognosis [17,18,23,26,37,43,48,50–52,54,57,62,68,72,73] with 28.07%, and potentially malignant oral lesions (pre-cancer) [20,21,26,30,34,44,55,59–61,64,66] with 21.05%, as shown in Figure 2. On the other hand, 5.26% of the articles focus on therapy and quality of life [22,27,53]. Furthermore, from 2018, a sustained increase in the number of publications that address the prognosis and diagnosis of oral cancer pathology can be observed.

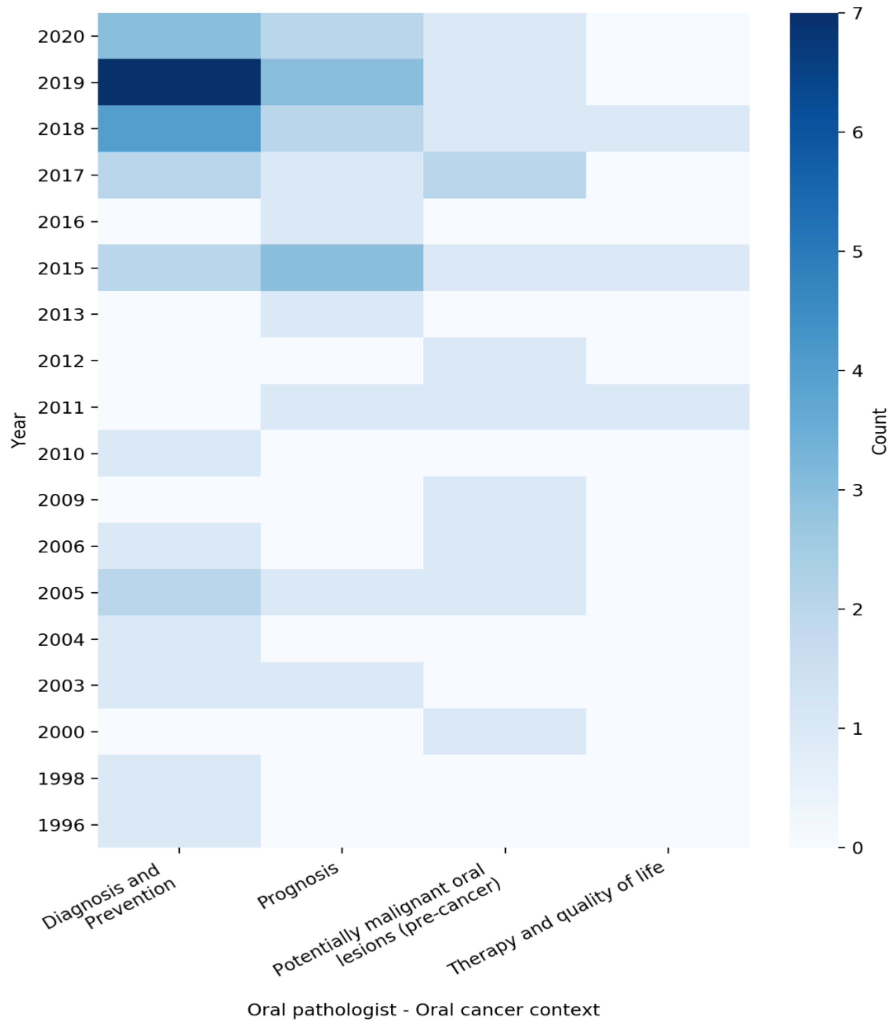

Figure 2. Year-wise distribution of the number of publications on oral cancer context.

Various machine-learning algorithms were used in the investigations. The first study was conducted in 1996, using the performance of a computer-generated neural network trained to identify normal, premalignant, and malignant oral smears using an artificial neural network [56]. Among the most frequently applied algorithms in oral cancer pathology (Figure 3) is the support vector machine (SVM) with 42.10%, the artificial neural network (ANN) with 24.56%, and the logistic regression (LR) with 21.05%. On the other hand, in the deep-learning subarea, the application of the convolutional neural network (CNN) was 12.28%.

Studies of machine-learning applications in oral cancer analyzed different types of data (Table 1), for example: genomic data [17,19,22,47,48,50,53,54,72], histopathological data [49,56,64], image data [20,21,26,28–33,38–40,42,44,55,60–62,66,67], medical history/clinical data [18,23,25,35,37,43,51,57,59,68,70,71,73], spectral data [24,34,36,41,45,46,52,58,63,65,69], and speech data [27].

3.1. Risk of Bias

In a systematic review, the ROB is a necessary stage. The findings of the ROB assessment were assessed in this fashion using PROBAST, as indicated in Table 1. A ROB judgment was applied to each investigated category in order to determine if the prediction model's predictive performance/accuracy was likely biased.

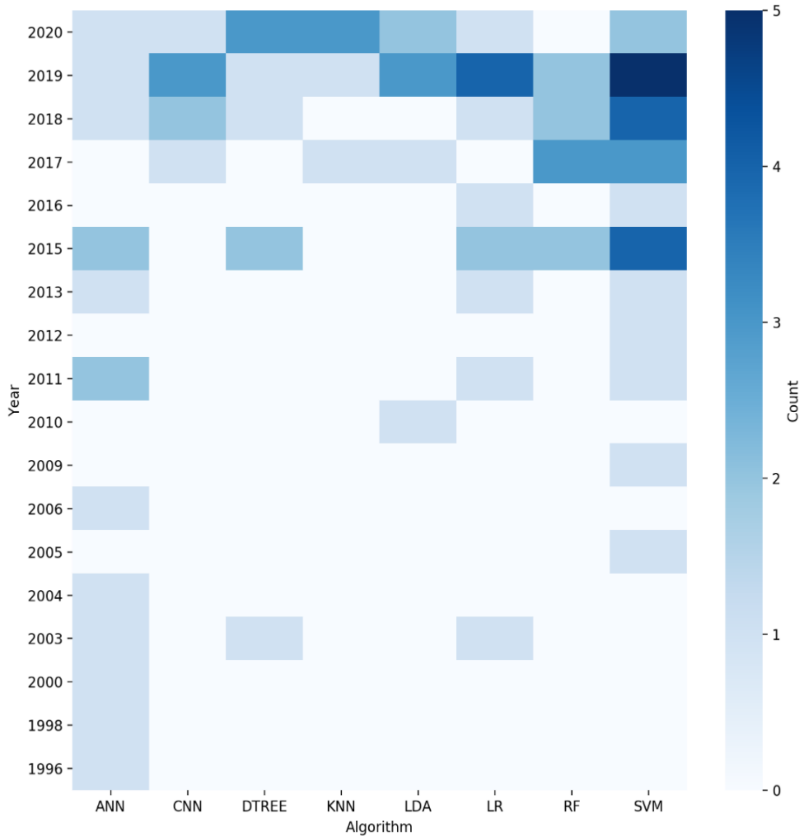

Figure 3. Distribution of publications per year according to different algorithms employed. In this graphic are plotted those algorithms that are most usually used.

Of the total studies analyzed, 84.21% of the studies presented a low ROB, 7.01% presented a high ROB, and 8.77% presented an unclear ROB (Table 1).

3.2. *Predictive Model Evaluation*

The performance of the methods was reported by the authors in terms of the accuracy, area under the ROC curve, sensitivity, and/or specificity. However, not all of these metrics were reported all the time. In total, 57.89% of the studies reported sensitivity, 63.15% of the studies reported accuracy, 59.64% of the studies reported specificity, and 38.59% of the studies reported AUC. For instance, the metrics of ACC, AUC, SE, and SP, for the most part, used algorithms among the studies (Figure 3) and are shown in Table 2. Specifically, SVM gave an ACC of 85.83%, AUC of 0.83, SE of 86.45%, and SP of 88.20%. ANN gave an ACC of 75.72%, AUC of 0.69, SE of 76.90%, and SP of 84.59%. In the case of LR, the media for ACC, AUC, SE, and SP was 75.47%, 0.7 76.53%, and 77.51%, respectively. In addition, ANOVA analysis was performed (Table 2). Statistical significance was obtained for metrics of ACC, SE, and SP (p-value < 0.05).

According to the studies included in the analysis, 94.73% present some method of validation of the model, as shown in Table 3. Only four studies did not use a validation method (Table 3). Specifically, the "hold out" validation was used in 31.57 % of the studies. The hold out validation consists of a method that divides the dataset into training and test set. The other most used method corresponds to the "cross validation" (CV), with 50.87% of the studies. This validation method considers the division of the set-in k-folds, where it uses one of the subsets as test data and the rest (K-1) as training data. Finally, the most used validations among the different studies were 5 and 10-fold CV (Table 3).

Table 2. Statistical comparisons of reported performance metrics for support vector machine, neural network, and logistic regression algorithms. Metrics are shown according to the clinical contexts (diagnosis and prevention, prognosis, pre-cancer, and therapy and quality of life).

	Performance Metricas Mean (SD; *n*)			
	Accuracy %	**Sensitivity %**	**Specificity %**	**AUC**
SVM	85.83 (10.01; 19)	86.45 (8.06; 17)	88.20 (10.72; 15)	0.83 (0.15; 9)
ANN	75.72 (13.08; 8)	76.90 (13.65; 9)	84.59 (13.44; 8)	0.69 (0.14; 5)
LR	75.47 (12.67; 9)	76.53 (13.68; 6)	77.51 (10.78; 4)	0.7 (0.14; 4)
ANOVA	*p*-value = 0.037	*p*-value = 0.058	*p*-value = 0.270	*p*-value = 0.213
	Diagnosis and Prevention			
SVM	90.22 (5.79; 8)	87.19 (4.69; 7)	89.99 (7.80;7)	0.95 (0.04; 3)
ANN	84.03 (20.18; 2)	84.51 (7.97; 5)	83.28 (15.48; 5)	0.6 (0.18; 2)
LR	93.50 (9.19; 2)	87.00 (0; 1)	—-	—
ANOVA	*p*-value = 0.570	*p*-value = 0.761	*p*-value = 0.343	*p*-value = 0.039
	Prognosis			
SVM	74.72 (13.19; 5)	78.90 (11.95; 4)	74.00 (26.87; 2)	0.75 (0.16; 5)
ANN	71.55 (11.69; 5)	61.17 (7.80; 3)	80.15 (4.44; 2)	0.76 (0.09; 3)
LR	68.21 (5.97; 6)	73.05 (15.98; 4)	74.35 (10.69; 3)	0.7 (0.14; 4)
ANOVA	*p*-value = 0.600	*p*-value = 0.249	*p*-value = 0.903	*p*-value = 0.861
	Potentially malignant oral lesions (pre-cancer)			
SVM	89.69 (2.65; 5)	90.61 (5.38; 6)	90.86 (3.34; 6)	—
ANN	—	86.00 (0; 1)	100 (0; 1)	—
LR	83.00 (0; 1)	80.00 (0; 1)	87.00 (0; 1)	—
ANOVA	p-value = 0.082	p-value = 0.255	p-value = 0.083	—
	Therapy and quality of life			
SVM	87.00 (0; 1)	—	—	0.89 (0; 1)
ANN	80.00 (0; 1)	—	—	—
LR	—	—	—	—
ANOVA	—	—	—	—

—: Data not reported by authors of those articles.

Table 3. Total number of studies according to the type of validation method implemented.

Method	**Count**
Hold out	18
5-fold CV	11
10-fold CV	10
LOOCV	7
3-fold CV	3
7-fold CV	2
4-fold CV	2
9-fold CV	1
Without validation (not mentioned)	3
Total	57

The performance of the top three most frequently applied algorithms (SVM, ANN, and LR) was compared statistically with each other. Algorithms were compared according to ACC, SE, SP, and AUC (Table 2). With respect to ACC performance, the algorithms differed significantly ($p < 0.05$). The SE performance of SVM, ANN, and LR did not differ significantly ($p = 0.058$). Regarding SP, the three algorithms did not differ significantly ($p = 0.270$). Finally, the AUC performance of SVM, ANN, and LR did not differ significantly ($p = 0.213$) (Table 2).

4. Discussion

In this study, we systematically reviewed the literature and described the state-of-the-art, as well as current, applications of machine learning in oral cancer. In this systematic review, we quantified the chosen studies and classified them according to four areas of application: diagnosis and prevention, prognosis, potentially malignant oral lesions (pre-cancer), and therapy and quality of life. To our knowledge, this is the first systematic review of ML applications in oral cancer.

In recent years, many studies have been published by using genomic, histopathological, image, medical/clinical, spectral, and speech data in combination with machine-learning techniques with the aim of applying this knowledge to the four previously mentioned application areas [17–73].

The most cited machine-learning algorithms in the context of oral cancer applications corresponded to SVM, ANN, and LR, comprising 87.71% of the total published articles in the field. In the area of ANN, it is important to mention the growth of the deep-learning subarea since 2017. This growth can be explained due to the greater availability of data, as well as the greater computing power through architectures that are dedicated to machine learning, and the use of graphic processing units (GPUs) that considerably reduce the processing time of the data [74].

Most of the machine-learning applications were concentrated in the analysis of medical history/clinical data, spectral data, genomic data, and image analysis. With respect to the different clinical contexts analyzed, for diagnosis and prevention, most of the applied algorithms were SVM, ANN, and LR. The best one was SVM due to its AUC value in comparison to ANN and LR. In addition, the ANOVA p-value was 0.039, showing statistical difference between SVM, ANN, and LR (Table 2). In the case of prognosis, most of the applied algorithms were SVM, ANN, and LR. The best one was ANN due to its AUC value (0.76) in comparison to the other algorithms (Table 2). Nevertheless, SVM is also a good predictor due to its homogenous values among the different metrics of ACC, SE, SP, and AUC (0.75). In this way, it is possible to say that SVM and ANN are the most adequate algorithms in the clinical context of prognosis. According to potentially malignant oral lesions (pre-cancer), most of the applied algorithms were also SVM, ANN, and LR. The best one was SVM; the metrics of ACC, SE, and SP were equal to or greater than 89.69% (Table 2). Finally, for therapy and quality of life, most of the applied algorithms were SVM and ANN. The best one was SVM, with and AUC value of 0.89 (Table 2).

The most common machine-learning applications were focused on diagnosis and prevention, followed by prognosis and potentially malignant oral lesions. However, oral cancer is not a particularly difficult malignancy to diagnose. The mouth is a part of the body that is readily accessible for early detection [75]. A great clinical challenge is to establish which lesions will progress to oral cancer. Early diagnosis of oral pre-cancerous lesions is particularly challenging because it requires dentists to be familiar with the range of clinical presentations of potentially malignant oral lesions, many of which may resemble less serious lesions [76]. Here, algorithms have many opportunities to have a clinical impact, for example, in supporting the histopathological evaluation of dysplastic lesions. In this aspect, the applications in potentially malignant oral lesions comprise the 21.05% of the total studies analyzed. Recent studies in this area performed image analysis [21,60,61]. Otherwise, despite the promising results, none of the studies demonstrated an improvement in detecting potentially malignant oral lesions.

According to the most frequent types of data per area of application, we found: (i) spectral data with 40.90% in the diagnosis and prevention area, (ii) medical/clinical data with 50.00% in prognosis, (iii) image data with 72.72% in potentially malignant oral lesions (pre-cancer), and (iv) genomic data representing 66.66% in the therapy and quality of life application area.

As mentioned before, deep-learning has been applied in diverse areas (Table 1). In specific, it was used for the analysis of image and spectral data (Table 1) [20,21,24,26,28–34,36,38–42,44–46,52,55,58,60–63,65–67,69].

The main areas of application of deep-learning were in diagnosis and prevention, and potentially malignant oral lesions (pre-cancer). In both areas, the images were the most used type of data, representing 83.33% and 100% of the total studies for diagnosis and prevention, and potentially malignant oral lesions (pre-cancer), respectively. The use of new technologies in high-quality image acquisition devices has made it possible to develop and enhance deep-learning approaches by employing convolutional neural networks.

SVM is among the most used algorithms in ML by area of application. SVM is the focus of the largest number of studies, representing 45.45% and 63.63% of the total studies for diagnosis and prevention, and potentially malignant oral lesions (precancer), respectively. Furthermore, for prognosis, LR was the most frequently used algorithm, with 43.75%, while in therapy and quality of life, the algorithms CTREE, RF, BA, SVM, ANN, and DFG represented 100%. On the other hand, in the deep-learning subarea, the CNN stood out in diagnosis and prevention, and in potentially malignant oral lesions (precancer) with 100%.

Studies varied according to the algorithm applied, the input and output variables, and the methods for assessing predictive model performance. SVM, ANN, and LR were the most commonly applied algorithms. Genomic, histopathological, image, medical/clinical, spectral, and speech data were the most often used to predict the four areas of application found in this review.

ML, with algorithms such as SVM, ANN, LR, CNN, represents a powerful method, capable of effectively predicting outcomes in order to support diagnosis and prevention, prognosis, potentially malignant oral lesions (pre-cancer), and therapy and quality of life.

It is important to note that not all these algorithms are intuitive. For example, ANN and SVM are nonlinear and inscrutable in the way they generate their outputs. In this sense, clinicians tend to lack trust in the outputs of a clinical decision support system when it is not clear how the algorithm gives the classification result, unlike decision trees, which identify the set of rules that there are behind the classification. In this aspect, it is very important to promote the transparency of these methods, which can be useful to facilitate their implementation in the field. This transparency can be achieved by reporting, in the case of SVM, the values of sigma (available only in some kernel types), C parameter, and type of kernel, whereas for ANN, it is important to report the number of layers and the corresponding number of nodes or neurons.

Of the total included articles, most of the studies showed a low risk of bias. In addition, most of the studies used some type of validation. The most commonly applied validation method corresponded to a 5-fold CV and a 10-fold CV. In this aspect, avoiding the overfitting was a task considered in most of the studies included. Nevertheless, not all of the performance metrics were reported in all of the studies. Future studies would do well to report at least AUC, ACC, SE, and SP due to their importance in the analysis of the machine-learning method in order to enable the comparison between studies and facilitate performance evaluation.

Additionally, not all the metrics were reported all the time; 63.15% of the studies reported accuracy, 29.82% of the studies did not report sensitivity, 38.59% of the studies did not report specificity, and 59.64 % of the studies did not report AUC.

Today, there are no tumor biomarkers routinely used in the clinical setting to predict high-risk oral dysplastic lesions [77]. The recognition of histological patterns that may go unnoticed by the pathologist could provide an opportunity for early therapeutic interventions, which would improve the prognosis. It is known that early diagnosis of oral cancer is associated with high survival rates. Therefore, if carcinogenesis is seen like an arrow from left to right, being placed leftmost of the passage of a susceptibility state to a canzerisable field is even better [78]. Unfortunately, our results show that the frequency of studies in this field is still low.

One of the findings in this systematic review is that diagnosis and prevention is the main field approached in the articles analyzed. This is coincident with what we find in the clinical practice of oral pathology and medicine. Most oral cancer diagnoses are made in advanced stages of the disease, i.e., in the III and IV TNM stages. The result is the existence of poor survival rates, plus a severe morbidity in survivors due to strong sequelae associated with surgery and radiotherapy. It is interesting to note that, in spite of the great advances in oncology research, which has brought considerable improvements in oncotherapy, the diagnostic problem continues to be unsolved. Great advances have also been made in early diagnosis, mainly based on general practitioners training, but the problem persists in most countries. Two approaches that look for solutions can be considered: prevention strategies for patients and new additional methods to assist the diagnostic process. According to this systematic review, machine learning could be among these new methods.

In addition to the diagnostics issue, the prognostic approach is also a problem that must be analyzed. When a clinician finds a white lesion in the oral mucosa, they have to decide about its possible cancerization. Leukoplakias vary in their percentages of transformation to malignant states. Biopsy will help that decision, but the clinician and the pathologist also frequently need additional information. Neural networks have been proved a useful method for discrimination between leukoplakia and normal tissue by using tissue autofluorescence spectra properties. Although it must be considered as a complementary tool after clinical examination, it helps determine the intrinsic abnormalities of oral mucosa that can lead to a malignant disease.

From a therapeutic point of view, usually, the surgical team has to decide if neck dissection needs to be performed or not, following primary tumor excision. Depth of invasion (DOI) has been shown to be useful to predict nodal metastasis, but it is still frequent to find N0 patients with neck recurrences after surgery without neck dissection, and, on the other hand, neck dissections with no nodal metastasis are found when microscopic examination is conducted. This systematic review found that machine-learning algorithms can be useful when this decision has to be made.

5. Conclusions

To conclude, our study showed that machine-learning applications can be useful in different areas of the oral cancer disease. These areas include prognosis, diagnosis and prevention, potentially malignant oral lesions (pre-cancer), and therapy.

Regarding the most suitable algorithms by area of application in oral cancer, we can say that the SVM is more appropriate for the diagnosis and prevention clinical context, and the ANN and SVM are the most suitable for the prognosis clinical context in terms of the performance of the algorithms. For potentially malignant oral lesions (pre-cancer) and therapy and quality of life, the data do not allow us to determine which is the most appropriate algorithm due to the smaller number of studies. Nevertheless, despite the few data reported, we can suggest that SVM and ANN are potentially appropriate algorithms to apply in the clinical context of pre-cancer and therapy.

We strongly suggest continuing exploring the application of these new methods in daily clinical practice.

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