Received: 14 July 2020 | Accepted: 17 July 2020

DOI: 10.1111/jop.13089

Journal of Oral Pathology & Medicine WILEY

ORIGINAL ARTICLE

Machine learning and treatment outcome prediction for oral cancer

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Abstract

Background: The natural history of oral squamous cell carcinoma (OSCC) is complicated by progressive disease including loco-regional tumour recurrence and development of distant metastases. Accurate prediction of tumour behaviour is crucial in delivering individualized treatment plans and developing optimal patient follow-up and surveillance strategies. Machine learning algorithms may be employed in oncology research to improve clinical outcome prediction.

Methods: Retrospective review of 467 OSCC patients treated over a 19-year period facilitated construction of a detailed clinicopathological database. 34 prognostic features from the database were used to populate 4 machine learning algorithms, linear regression (LR), decision tree (DT), support vector machine (SVM) and k-nearest neighbours (KNN) models, to attempt progressive disease outcome prediction. Principal component analysis (PCA) and bivariate analysis were used to reduce data dimensionality and highlight correlated variables. Models were validated for accuracy, sensitivity and specificity, with predictive ability assessed by receiver operating characteristic (ROC) and area under the curve (AUC) calculation.

Results: Out of 408 fully characterized OSCC patients, 151 (37%) had died and 131 (32%) exhibited progressive disease at the time of data retrieval. The DT model with 34 prognostic features was most successful in identifying "true positive" progressive disease, achieving 70.59% accuracy (AUC 0.67), 41.98% sensitivity and a high specificity of 84.12%.

Conclusion: Machine learning models assist clinicians in accessing digitized health information and appear promising in predicting progressive disease outcomes. The future will see increasing emphasis on the use of artificial intelligence to enhance understanding of aggressive tumour behaviour, recurrence and disease progression.

KEYWORDS

oral cancer, oral mucosa

1 | INTRODUCTION

Oral cancer, principally squamous cell carcinoma arising from the oral mucosal lining (OSCC), accounts for half the annual global mortality attributed to head and neck malignancy, with cancer-related deaths associated with aggressive primary tumours and advanced stage disease at clinical presentation.[1] Post-diagnosis, the natural history in any given patient, may be complicated by progressive disease in terms of loco-regional recurrence of the primary tumour and/or development of distant blood-borne metastases. Accurate classification of risk and prediction of tumour behaviour at the time of initial diagnosis and intervention is therefore crucial in delivering individualized treatment plans and developing optimal patient follow-up and surveillance strategies.[2,3]

In recent years, demographic, clinicopathological, therapeutic and bio-molecular data have all been used to populate clinical decision-making tools, including statistical regression models and prognostic nomograms, in an attempt to predict poor clinical outcome post-OSCC treatment. Unfortunately, such methods have gained limited acceptance in contemporary clinical practice due to data validity concerns and little demonstrable predictive accuracy.[3-12]

Within the last decade, machine learning algorithms that automate analytical model building have been employed in oncology research to improve prediction and attempt more reliable forecasts of clinical outcome. Their popularity is based upon a presumed ability to sequentially detect patterns, garner information and undergo automated training based on data input, especially complex non-homogenous data, ultimately making clinical predictions with minimal human intervention.[13,14] Whilst a degree of predictive accuracy for algorithms has been reported, in particular the use of support vector machines, boosted decision trees, decision forest and artificial neural networks, there is a need to validate the predictive power of machine learning by analysing disease progression within well-defined OSCC patient cohorts prior to widespread translation to clinical practice.[15-19]

In a recent publication, we reported upon post-treatment outcomes for a 467 OSCC patient cohort in Hong Kong and observed that histopathological features of invasive tumour behaviour such as perineural invasion (PNI), bone invasion (BNI), lymphovascular invasion (LVI) and extra-nodal extension (ENE), especially in combination, showed potential application as prognostic markers of rapid disease progression and poor clinical outcome.[20] The aim of this study, therefore, was to revisit this well-characterized patient cohort to evaluate the ability of supervised machine learning models to predict disease outcome.

2 | METHODS

2.1 | Study population and clinicopathological data

A retrospective review of OSCC patients treated over a 19-year period, between 1st October 2000 and 1st October 2019, at the Queen Mary Hospital in Hong Kong was performed using records from the Hospital Authority Clinical Management System (HA CMS).[20] Consecutively treated adult patients with clinical subtypes corresponding to ICD-10 C00-C06, C09 and C10 were retrieved from the database. Patient demographic information included age, sex, date of diagnosis, status at time of data retrieval (alive or dead), previous cancer history, and smoking, alcohol, human papillomavirus (HPV) and Epstein-Barr virus (EBV) status. Clinicopathological data recorded tumour site, grading, histopathological characteristics of tumour invasiveness, resection margin status, pTNM classification, disease staging and, where appropriate, use of cervical lymph node dissection and/or adjuvant chemo-radiotherapy regimes. Outcome was recorded as either disease-free or progressive disease, defined by loco-regional tumour recurrence and/or development of distant metastases. Overall survival was determined from the date of primary diagnosis until death or most recent clinic follow-up.

2.2 | Prognostic features

A series of 34 demographic, clinicopathological and lifestyle factors, extracted from the database in view of their association with progressive disease risk, were selected as prognostic features to populate the prediction models.[21] These are listed in Table 1, which also summarizes the manner in which each feature was classified in the model.

2.3 | Prediction models

MATLAB R2020a (MathWorks, Inc.), a mathematical programming platform facilitating data plotting and analysis, was employed to build linear regression (LR), decision tree (DT), support vector machine (SVM) and k-nearest neighbours (KNN) models, 4 frequently used models for outcome prediction.[22,23] The 34 prognostic features (predictors) and the presence of progressive disease (outcome) were used to develop the models, which were evaluated by 15-fold cross-validation to avoid overfitting (a model with too many variables which may just be "noise"). Two methods were used before building the models to investigate whether data reduction could enhance performance: principal component analysis (PCA) to reduce data dimensionality and highlight correlated variables, and bivariate analysis (IBM SPSS for Windows 10 version 25) to identify prognostic features positively correlated with outcome ($P < .05$). Models were validated for accuracy, sensitivity (true positive) and specificity (true negative), with diagnostic ability assessed via receiver operating characteristic (ROC) and area under the curve (AUC) calculation. For each of the models, predictive performance using all 34 prognostic features was compared with those derived from PCA and bivariate analysis.

2.4 | Ethical approval

Approval to conduct this retrospective study was granted by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number UW-19-704). All clinical data were anonymized by the researchers, and all potential patient identifiers were removed prior to data analysis.

TABLE 1 Individual prognostic features and variable classification used in machine learning

	Prognostic features	Variable classification
1	Sex	Binary (male/female)
2	Age	Numerical
3	Smoking history	Categorical (unknown/non-/past/current smoker)
4	Alcohol drinking	Categorical (unknown/non-/past/current drinker)
5	HPV status	Categorical (unknown/negative/positive)
6	EBV status	Categorical (unknown/negative/positive)
7	Past cancer history	Categorical (unknown/no/yes)
8	Anterior tongue	Binary (not involved/involved)
9	Posterior tongue	Binary (not involved/involved)
10	Buccal mucosa	Binary (not involved/involved)
11	Lips	Binary (not involved/involved)
12	Hard palate	Binary (not involved/involved)
13	Soft palate/oropharynx	Binary (not involved/involved)
14	Maxillary gingiva	Binary (not involved/involved)
15	Mandibular gingiva	Binary (not involved/involved)
16	Tonsil	Binary (not involved/involved)
17	Floor of mouth	Binary (not involved/involved)
18	Retromolar region	Binary (not involved/involved)
19	Neck dissection	Binary (no/yes)
20	Second primary tumour[a]	Binary (no/yes)
21	T classification	Binary (smaller than 4 cm/equal and larger than 4 cm)
22	N classification	Categorical (no lymph nodes/smaller than 6 cm/equal or larger than 6 cm)
23	Disease staging	Categorical (stage I/II/III/IV)
24	Frozen section results	Categorical (no assessment/margin negative/dysplasia or in-situ tumour/margin positive)
25	Resection margin status	Categorical (unknown/negative/positive)
26	Tumour grading	Categorical (unknown/well/moderately/poorly differentiated)
27	Cervical lymph node metastasis	Categorical (unknown/no/yes)
28	DOI	Categorical (unknown/less than 1 cm/equal or deeper than 1 cm)
29	BNI	Categorical (unknown/negative/positive)
30	LVI	Categorical (unknown/negative/positive)
31	PNI	Categorical (unknown/negative/positive)
32	ENE	Categorical (unknown/negative/positive)
33	Radiotherapy	Categorical (no/neo-adjuvant/adjuvant)
34	Chemo-radiotherapy	Categorical (no/neo-adjuvant/adjuvant)

Abbreviations: BNI, bone invasion; DOI, depth of invasion; EBV, Epstein-Barr virus; ENE, extra-nodal extension; HPV, human papillomavirus; LVI, lymphovascular invasion; PNI, perineural invasion.

[a]Second primary tumour was defined as the presence of two malignant tumours, at least 2 cm apart or detected 6 mo or more after primary tumour diagnosis.

3 | RESULTS

3.1 | Patients, outcome and predictions

In total, 467 OSCC patients were identified from the HA CMS database and their full demographic and clinicopathological data are summarized in Table 2. Ultimately, 59 patients were excluded from study analysis due to unavailability of clinicopathological data (43) or because patients documented as alive failed to return for their most recent clinic assessments (16). Data from 408 OSCC patients (244 males and 164 females) were thus used to populate the machine learning models; at the time of data retrieval, 151 (37%) had died, and 131 (32%) exhibited progressive disease.

Bivariate analysis identified 13 prognostic features positively predictive of progressive disease development, and these are listed in Table 3, whilst PCA utilized between 16 and 34 components dependent upon the model, as summarized in Table 4. By listing predicted and actual progressive and non-progressive disease

TABLE 2 Patient demographics and clinicopathological tumour data

Variable	All (n = 467)	Male (n = 275)	Female (n = 192)
Age in years at diagnosis, mean (SD)	61.4 (14.1)	61.2 (13.4)	61.8 (15.1)
Current status (n)			
Alive	282	159	123
Dead	181	113	68
Missing	3	2	1
Age at death in years, mean (SD)	68.3 (13.6)	68.9 (12.0)	67.3 (16.0)
History of non-head & neck cancer (n)			
Yes	85	56	29
No	381	218	163
Missing	1	1	
Tobacco smoking (at time of diagnosis) (n)			
Non-smoker	262	94	168
Past smoker	89	84	5
Current smoker	86	79	7
Unknown	30	18	12
Alcohol drinking (at time of diagnosis) (n)			
Non-drinker	248	98	150
Past drinker	36	34	2
Current drinker	109	99	10
Unknown	74	44	30
HPV status (n)			
Positive	24	20	4
Negative	50	36	14
Unknown	393	219	174
EBV status (n)			
Positive	9	7	2
Negative	18	15	3
Unknown	440	253	187
Tumour site, number (%)			
Tongue (anterior)	201 (43.0)	111 (40.3)	90 (46.8)
Tongue (base/posterior)	28 (6.0)	23 (8.4)	5 (2.6)
Buccal mucosa	69 (14.8)	32 (11.6)	37 (19.3)
Floor of mouth	26 (5.6)	23 (8.4)	3 (1.6)
Lips	3 (0.6)	3 (1.1)	0 (0.0)
Gingiva (mandibular)	57 (12.2)	30 (10.9)	27 (14.1)
Gingiva (maxillary)	18 (3.9)	8 (2.9)	10 (5.2)
Soft palate/oropharynx	6 (1.3)	5 (1.9)	1 (0.5)
Retromolar region	12 (2.6)	5 (1.8)	7 (3.6)
Hard palate	11 (2.4)	4 (1.5)	7 (3.6)
Tonsil	36 (7.7)	31 (11.3)	5 (2.6)
pTNM classification, number (%)			
pT			
T1	146 (31.3)	85 (30.9)	61 (31.8)
T2	130 (27.8)	70 (25.5)	60 (31.3)

(Continues)

TABLE 2 (Continued)

Variable	All (n = 467)	Male (n = 275)	Female (n = 192)
T3	39 (8.4)	26 (9.5)	13 (6.8)
T4a	122 (26.1)	74 (26.9)	48 (1.6)
T4b	5 (1.1)	5 (1.8)	0 (0.0)
Missing	25 (5.4)	15 (5.5)	10 (5.2)
pN			
Nx	18 (3.9)	5 (1.8)	13 (6.8)
N0	249 (53.3)	149 (54.2)	100 (52.1)
N1	56 (12.0)	30 (10.9)	26 (13.5)
N2a	11 (2.4)	6 (2.2)	5 (2.6)
N2b	66 (14.1)	40 (14.5)	26 (13.5)
N2c	29 (6.2)	20 (7.3)	9 (4.7)
N3	13 (2.8)	10 (3.6)	3 (1.6)
Missing	25 (5.4)	15 (5.5)	10 (5.2)
pM			
M0	440 (94.32)	260 (94.5)	180 (93.8)
M1	2 (0.4)	0 (0.0)	2 (1.0)
Missing	25 (5.4)	15 (5.5)	10 (5.2)
Disease staging			
Stage 1	118 (25.3)	66 (24.0)	52 (27.1)
Stage 2	75 (16.1)	43 (15.6)	32 (16.7)
Stage 3	56 (12.0)	30 (10.9)	26 (13.5)
Stage 4A	176 (37.7)	109 (39.6)	67 (34.9)
Stage 4B	15 (3.2)	12 (4.4)	3 (1.6)
Stage 4C	2 (0.4)	0 (0.0)	2 (1.0)
Missing	25 (5.4)	15 (5.5)	10 (5.2)
Neck dissection			
No	63 (13.5)	33 (12.0)	30 (15.6)
Yes	393 (84.2)	235 (85.5)	158 (82.3)
Unknown	11 (2.4)	7 (2.5)	4 (2.1)
Tumour grading			
Well differentiated	132 (28.2)	73 (26.6)	59 (30.8)
Moderately differentiated	248 (53.1)	145 (52.7)	103 (53.6)
Poorly differentiated	54 (11.6)	37 (13.5)	17 (8.9)
Missing	33 (7.1)	20 (7.3)	13 (5.2)
Use of adjuvant chemo-radiotherapy			
Combination chemo-radiotherapy	107 (22.9)	73 (26.5)	34 (17.7)
Radiotherapy	113 (24.2)	62 (22.5)	51 (26.6)
None	246 (52.7)	140 (50.9)	106 (55.2)
Missing	1 (0.2)	0 (0.0)	1 (0.5)
Frozen section margins			
Negative	314 (67.2)	185 (67.3)	129 (67.2)
Positive	52 (11.1)	33 (12.0)	19 (10.0)
Missing	101 (21.6)	57 (20.7)	44 (22.9)
Tumour resection margin status			

(Continues)

TABLE 2 (Continued)

Variable	All (n = 467)	Male (n = 275)	Female (n = 192)
Negative	406 (86.9)	234 (85.1)	172 (89.6)
Positive	36 (7.7)	25 (9.1)	11 (5.7)
Missing	25 (5.4)	16 (5.8)	9 (4.7)
Tumour invasiveness, number (%) positive			
Bony invasion	81 (17.3)	46 (16.7)	35 (18.2)
Perineural invasion	93 (20.0)	55 (20.0)	38 (19.8)
Lymphovascular invasion	91 (19.5)	65 (23.6)	26 (13.5)
Extra-nodal extension	79 (16.9)	51 (18.5)	28 (14.6)
Depth of invasion (cm)			
<1 cm	96 (20.6)	61 (22.2)	35 (18.2)
≥1 cm	67 (14.3)	44 (16.0)	23 (12.0)
Missing	304 (65.1)	170 (61.8)	134 (69.8)

Abbreviations: EBV, Epstein-Barr virus; HPV, human papillomavirus.

outcomes, Table 4 provides a performance comparison of LR, DT, SVM and KNN models with PCA and bivariate analyses.

3.2 | Linear regression

Compared to using all 34 predictive features or 13 selected by bivariate analysis, the LR model reduced to 18 components by PCA achieved the highest accuracy of 70.83% (AUC 0.68). PCA also performed best in terms of specificity (88.81%), although sensitivity was higher in the 34 feature model (35.11%).

3.3 | Decision tree

The DT model with 34 features attained 70.59% accuracy (AUC 0.67), with a sensitivity of 41.98% and specificity 84.12%, superior to both bivariate analysis and 19-component PCA.

3.4 | Support vector machine

The SVM model with 34 features shared identical accuracy with 34-component PCA (69.85%, AUC 0.68). Whilst sensitivity at 24.43% increased to 25.95% after PCA application, specificity fell by 0.73%. Bivariate analysis reduced accuracy and sensitivity, to 68.63% and 15.27% respectively, although specificity reached 93.86%. In general, all 3 SMV models performed well in terms of specificity (greater than 90%).

3.5 | K-nearest neighbour

Using bivariate analysis, the KNN model achieved 69.36% accuracy (AUC 0.71), with 35.11% sensitivity and 85.56% specificity. PCA (16 components) performed better than the 34 feature model for both accuracy (68.38% vs 66.42%) and specificity (88.45% vs 85.56%), although sensitivity was identical at 25.95%.

TABLE 3 Features positively predictive of progressive disease (bivariate analysis)

Selected features	Chi-square value	*P*-value
HPV	13.44	.001
Anterior tongue	5.90	.015
Buccal mucosa	8.22	.004
Tonsil	3.93	.047
T stage	13.04	.0003
Overall stage	9.88	.02
Neck dissection	11.84	.001
Frozen section positivity	16.02	.001
Resection margin positivity	10.08	.006
Presence of metastatic nodules	23.20	.000009
DOI	16.85	.0002
PNI	16.39	.0003
ENE	10.42	.005

3.6 | Comparison of model performance

Overall, the DT model using 34 prognostic features appeared most successful in identifying "true positive" progressive disease, achieving 70.59% accuracy, 41.98% sensitivity and a high specificity of 84.12%. In general, specificity was much higher (ranging from 79.42% to 93.86%) than sensitivity (15.27% to 41.98%) in all models.

TABLE 4 Comparative performance of machine learning models in identifying progressive disease

	Progressive (actual)	Non-progressive (actual)	Accuracy%	AUC	Sensitivity%	Specificity%
Linear regression models						
34 features						
Progressive (predicted)	46	46	67.89	0.68	35.11	83.39
Non-progressive (predicted)	85	231				
PCA-18 components						
Progressive (predicted)	43	31	70.83	0.68	32.82	88.81
Non-progressive (predicted)	88	246				
Bivariate analysis-13 selected features						
Progressive (predicted)	36	39	67.16	0.7	27.48	85.92
Non-progressive (predicted)	95	238				
DT models						
34 features						
Progressive (predicted)	55	44	70.59	0.67	41.98	84.12
Non-progressive (predicted)	76	233				
PCA-19 components						
Progressive (predicted)	47	57	65.44	0.6	35.88	79.42
Non-progressive (predicted)	84	220				
Bivariate analysis-13 selected features						
Progressive (predicted)	52	50	68.38	0.66	39.69	81.95
Non-progressive (predicted)	79	227				
Support vector machine models						
34 features						
Progressive (predicted)	32	24	69.85	0.68	24.43	91.34
Non-progressive (predicted)	99	253				
PCA-34 components						
Progressive (predicted)	34	26	69.85	0.68	25.95	90.61
Non-progressive (predicted)	97	251				
Bivariate analysis-13 selected features						
Progressive (predicted)	20	17	68.63	0.62	15.27	93.86
Non-progressive (predicted)	111	260				
K-nearest neighbours models						
34 features						
Progressive (predicted)	34	40	66.42	0.69	25.95	85.56
Non-progressive (predicted)	97	237				
PCA-16 components						
Progressive (predicted)	34	32	68.38	0.67	25.95	88.45

(Continues)

TABLE 4 (Continued)

	Progressive (actual)	Non-progressive (actual)	Accuracy%	AUC	Sensitivity%	Specificity%
Non-progressive (predicted)	97	245				
Bivariate analysis-13 selected features						
Progressive (predicted)	46	40	69.36	0.71	35.11	85.56
Non-progressive (predicted)	85	237				

4 | DISCUSSION

4.1 | Machine learning models

Machine learning is an increasingly popular application of artificial intelligence using computers to acquire and analyse complex data sets, identify patterns and develop predictive, decision-making algorithms that improve automatically with experience. Models are built from large, representative sets of "training data" and progress to additional data processing to facilitate prediction. For this study, 4 models were populated with clinicopathological data from a cohort of previously treated OSCC patients: LR to estimate relationships between dependent variables and their associated features, DT based upon individual observations (branches) and their perceived value (leaves), SVM with non-probabilistic, binary linear classification to predict categorization, and KNN non-parametric classification and regression. Machine learning differs from conventional statistics which, requiring prior knowledge of methods necessary to meet study objectives, test specific hypotheses and draw inference from study samples.[24]

4.2 | Predicting OSCC outcome

It is frustrating that our ability to predict clinical outcome for OSCC patients in contemporary clinical practice remains limited. As a general observation, the incidence of progressive disease increases with length of patient follow-up. Whilst it is possible to attempt characterization of "high-risk" patients using clinicopathological features, there is inevitable cohort bias. It seems reasonable, therefore, to utilize artificial intelligence to improve accuracy of predictive diagnoses and facilitate targeted treatment intervention.[2,20,25] All 12 models in this study performed reasonably, although DT using 34 prognostic features was best at predicting OSCC progression, achieving 71% accuracy but only 42% sensitivity. There are few comparable data in the literature, although a recent systematic review reported SVM accuracy between 56.7 and 99.4%.[26] In a study of 311 early-stage tongue SCCs, an artificial neural network (ANN) was used to characterize invasive histopathology and achieved 88% accuracy and 71% sensitivity for loco-regional recurrence prediction,[16] whilst a decision forest algorithm to predict occult nodal metastasis in 71 T1/T2 OSCC patients reported an AUC of 0.84, with 91.7% sensitivity and 57.6% specificity.[17] Predictive ability of these models may have been improved by the measurement of specific disease outcomes in better defined patient cohorts with same stage disease.

4.3 | Study limitations

This was a retrospective study of clinicopathological data retrieved from pre-existent HA CMS records. Consecutive OSCC patients were recruited from a number of HA facilities and exhibited heterogeneity of presenting disease. Machine learning algorithms are dependent upon the quality and precision of inputted data. It may be that conventional medical record information, which currently lacks genetic profiling, biomarker analyses and advanced histopathological imaging, is ultimately inadequate for predictive analyses. Deep neural networks, which facilitate multiple layer extraction of increasingly complex data and mimic human decision-making, may be better applied in the future to study the inherently complex nature of tumour biology.

5 | CONCLUSIONS

Machine learning models in this study have shown promise in predicting progressive OSCC disease outcomes. The future will see increasing emphasis on artificial intelligence to assist clinicians in utilizing digitized health information to predict outcome, inform personalized treatment decisions and rationalize intervention. It is hoped this will enhance understanding of biological mechanisms driving aggressive tumour behaviour and identify progressive disease at the earliest possible stage.

AUTHOR CONTRIBUTIONS

Sunshine Chu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing-original draft. Nikki Lee: Data curation; Formal analysis; Investigation; Methodology; Writing-original draft. John Adeoye: Conceptualization; Data curation; Investigation; Methodology; Writing-original draft. Peter James Thomson: Conceptualization; Methodology; Project administration; Supervision; Writing-original draft; Writing-review & editing. Sui-Wai Choi: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Writing-original draft.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1111/jop.13089.

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How to cite this article: Chu CS, Lee NP, Adeoye J, Thomson P, Choi S-W. Machine learning and treatment outcome prediction for oral cancer. *J Oral Pathol Med*. 2020;00:1–9. https://doi.org/10.1111/jop.13089