Comparison of supervised machine learning classification 1 techniques in prediction of locoregional recurrences in early oral 2 tongue cancer 3 4 Rasheed Omobolaji Alabi M.Sc^a, Mohammed Elmusrati D.Sc^a, Iris Sawazaki-Calone DDS, PhD^b, Luiz Paulo Kowalski MD, PhD^c, Caj Haglund MD, PhD^d, Ricardo D. 5 Coletta DDS, PhD^e, Antti A. Mäkitie MD, PhD^f, Tuula Salo DDS, PhD^g, Alhadi 6 Almangush DDS, PhD^{h*,}, Ilmo Leivo MD, PhD^{i*,} 7 8 ^a Department of Industrial Digitalization, School of Technology and Innovations, University of Vaasa, 9 Vaasa, Finland. 10 11 ^bOral Pathology and Oral Medicine, Dentistry School, Western Parana State University, Cascavel, PR, 12 Brazil. 13 14 ^c Department of Head and Neck Surgery and Otorhinolaryngology, A.C. Camargo Cancer Center, São 15 Paulo-SP, Brazil. 16 17 ^d Research Programs Unit, Translational Cancer Biology, University of Helsinki, Helsinki, Finland, 18 Department of Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. 19 20 ^e Department of Oral Diagnosis, School of Dentistry, State University of Campinas, Piracicaba, São 21 Paulo, Brazil. 22 23 ^f Department of Otorhinolaryngology – Head and Neck Surgery, University of Helsinki and Helsinki 24 University Hospital, Helsinki, Finland. 25 Research Program in Systems Oncology, Faculty of Medicine, University of Helsinki, Helsinki, 26 Finland. 27 Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and 28 Technology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden. 29 30 ^g Department of Pathology, University of Helsinki, Helsinki, Finland. 31 Department of Oral and Maxillofacial Diseases, University of Helsinki, Helsinki, Finland. 32 Cancer and Translational Medicine Research Unit, Medical Research Center Oulu, University of 33 Oulu and Oulu University Hospital, Oulu, Finland. 34 35 ^hDepartment of Pathology, University of Helsinki, Helsinki, Finland. 36 Institute of Biomedicine, Pathology, University of Turku, Turku, Finland 37 Faculty of Dentistry, University of Misurata, Misurata, Libya. 38 39 ⁱUniversity of Turku, Institute of Biomedicine, Pathology, Turku, Finland. 40 41 *The last two authors have equal contributions. 42 43 Corresponding Author: Rasheed Omobolaji Alabi 44 Department of Industrial Digitalization, School of Technology and Innovations, University of Vaasa, 45 Vaasa, Finland. 46 E-mail address: rasheed.alabi@student.uwasa.fi (or rasheed.alabii@yahoo.com), +358442056910 **Disclosure:** The authors declare no conflicts of interest. 47

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1 Abstract

Background: The proper estimate of the risk of recurrences in early-stage oral tongue squamous cell
carcinoma (OTSCC) is mandatory for individual treatment-decision making. However, this remains a
challenge even for experienced multidisciplinary centers.

5 Objectives: We compared the performance of four machine learning (ML) algorithms for predicting
6 the risk of locoregional recurrences in patients with OTSCC. These algorithms were Support Vector
7 Machine (SVM), Naive Bayes (NB), Boosted Decision Tree (BDT), and Decision Forest (DF).

8 Materials and methods: The study cohort comprised 311 cases from the five University Hospitals in 9 Finland and A.C. Camargo Cancer Center, São Paulo, Brazil. For comparison of the algorithms, we 10 used the harmonic mean of precision and recall called F1 score, specificity, and accuracy values. These 11 algorithms and their corresponding permutation feature importance (PFI) with the input parameters 12 were externally tested on 59 new cases. Furthermore, we compared the performance of the algorithm 13 that showed the highest prediction accuracy with the prognostic significance of depth of invasion (DOI). 14 **Results:** The results showed that the average specificity of all the algorithms was 71%. The SVM 15 showed an accuracy of 68% and F1 score of 0.63, NB an accuracy of 70% and F1 score of 0.64, BDT 16 an accuracy of 81% and F1 score of 0.78, and DF an accuracy of 78% and F1 score of 0.70. Additionally, 17 these algorithms outperformed the DOI-based approach, which gave an accuracy of 63%. With PFI-18 analysis, there was no significant difference in the overall accuracies of three of the algorithms; PFI-19 BDT accuracy increased to 83.1%, PFI-DF increased to 80%, PFI-SVM decreased to 64.4%, while PFI-20 NB accuracy increased significantly to 81.4%. Conclusions: Our findings show that the best 21 classification accuracy was achieved with the boosted decision tree algorithm. Additionally, these 22 algorithms outperformed the DOI-based approach. Furthermore, with few parameters identified in the 23 PFI analysis, ML technique still showed the ability to predict locoregional recurrence. The application 24 of boosted decision tree machine learning algorithm can stratify OTSCC patients and thus aid in their 25 individual treatment planning.

26 **KEYWORDS**: Artificial Intelligence; Oral tongue cancer; Machine Learning; Prediction

1 **1. Introduction**

2 Oral tongue squamous cell carcinoma (OTSCC) refers to squamous cell carcinoma that arises 3 from the anterior two thirds of the tongue (also known as mobile tongue). It is usually reported 4 as part of oral squamous cell carcinoma (OSCC), which includes all anatomical subsites of the 5 oral cavity. A recent international study including 22 registries reported 89,212 incident cases 6 of OTSCC and an increasing annual incidence [1], which has been confirmed by others [2]. 7 The primary treatment of choice for OTSCC is surgical excision. However, even early-stage 8 tumors may express a pattern of aggressive behavior [3,4]. Thus, OTSCC with aggressive 9 behavior and those with advanced stage require multimodality treatment including neck 10 dissection and adjuvant (chemo)radiotherapy. Therefore, it is important to precisely estimate 11 the clinical behavior and outcome of OTSCC. Predicting the risk of recurrences is one of the 12 important assessments for the clinician during treatment planning. More importantly, early diagnosis and predicting the risk of recurrences form a milestone in the management of OTSCC 13 14 as the recent analysis of Finnish cases reported that about 67% of OTSCC cases were diagnosed 15 at an early stage (I-II) [5]. With accurate and timely recurrence prediction, high-risk cases of OTSCC can be identified and multimodality treatment applied accordingly. In a large cohort 16 17 of early OTSCC, about one fourth of cases (27.8%) developed a recurrence, and all of them 18 might have benefitted from early prediction and corresponding treatment planning [6].

Many recent studies have examined the use of machine learning (ML) techniques for prognostication of different cancers [7,8]. Interestingly, predicting patient outcome by ML techniques has shown better accuracy than Cox regression [9]. This is why the use of ML has been in active research focus during recent years. For instance, ML techniques have been used to predict the outcome of various cancer types [10–12] and a web-based tool based on artificial neural network to predict outcome in cancer has been reported [13].

1 In this study, we examined four different ML algorithms, namely, support vector 2 machine (SVM), naive Bayes (NB), boosted decision tree (BDT), and decision forest (DF) in 3 terms of their performances to predict locoregional recurrence in OTSCC patients. Also, the 4 predictive performance of a permutation feature importance (PFI) of these algorithms was 5 evaluated. Many researchers have used this approach for comparing ML techniques for survival 6 prediction in different malignancies like breast and lung cancers [14–17]. Tapak et al. examined 7 six ML algorithms and two traditional methods for the prediction of breast cancer survival and 8 metastasis [15]. In our study, we aimed to identify the best algorithm that would effectively 9 classify patients as either low-risk or high-risk OTSCC recurrence. The algorithm with the 10 overall best classification performance was further compared to a recently reported risk model 11 based on the depth of invasion (DOI) [18]. This comparison was a result of the fact that DOI 12 of 4mm or deeper has been considered to be a factor that accurately predicts locoregional 13 recurrence [6]. Moreover, the recent American Joint Committee on Cancer (AJCC) 8th edition 14 incorporated depth of invasion (DOI) into T-stage [19]. Similarly, the study by Almangush et al. suggested that DOI is one of the strongest pathological predictors for locoregional 15 16 recurrence [6]. This suggestion is in agreement with reports by others [20,21].

We hypothesize that the application of the above-mentioned supervised learning
classifiers may be used in the prediction of OTSCC locoregional recurrences and will thereby
add value for the management of OTSCC.

20

21 **2. Material and Methods**

Patients: We used data from a study cohort comprising patients treated at the five Finnish University Hospitals of Helsinki, Oulu, Turku, Tampere, and Kuopio and at the A.C. Camargo Cancer Center, Sao Paulo, Brazil. This is a multicenter study from six institutions and data were provided for many cases as locoregional recurrences without specification. The

1 clinicopathologic characteristics of this cohort have been previously reported and summarized 2 [22]. The primary treatment for all cases was surgical excision. In addition, some cases received 3 neck dissection and/or adjuvant radiotherapy. The parameters included were age, gender, Tstage, WHO grade, tumor budding, depth of invasion, worst pattern of invasion (WPOI), 4 5 lymphocytic host response (LHR), and perineural invasion (PNI) as shown in Table 1. Several 6 studies have confirmed the prognostic importance of these variables [6,13,22–25]. Neck 7 dissection and adjuvant radiotherapy were also included in the machine learning algorithms 8 due to the impact of variation in the treatment modality that might influence the risk of 9 recurrence. The use of patient samples and data inquiry were approved by the Hospital 10 Research Ethics Committees of all individual hospitals, by the Finnish National Supervisory 11 Authority for Welfare and Health (VALVIRA) and by the Brazilian Human Research Ethics 12 Committee. 13 14 2.1. The classification algorithms examined 15 The algorithms considered in this study are basic and have been commonly used in other cancer 16 studies [14-18]. 17 18 2.1.1. Support vector machine (SVM) is an elegant and powerful ML technique extensively 19 used for both classification and regression problems [26]. This is due to its ability to classify 20 non-linearly separable patterns by projecting the original features into a higher dimensional 21 space (hyperplane) [27]. 22 23 2.1.2. Naive Bayes (NB) is known as Bayes point machine in the Azure ML studio and it is 24 based on the generally-known Bayes theorem [26,27]. The algorithm operates by learning and 25 estimating the prior probability of belonging to each class using the training data. [27,28].

2.1.3. Boosted Decision Tree (BDT) with gradient boosting machine was the subtype of BDT
 used in this study. It is an ensemble learning method where the second tree corrects the errors
 of the first tree, the third tree corrects the errors in the second trees, the fourth tree corrects the
 errors in the third trees, etc. Predictions are based on the entire ensemble of trees [27,28].

2.1.4. Decision Forest (DF) relies on the combination of multiple related models to get better
results and a more generalized model. Therefore, it works by using a bootstrapped sample of
data to build each tree where only a proportion of the variable set is considered for each tree.
Each tree in the decision forest outputs a frequency histogram of labels that is non-normalized.
These frequency histograms were aggregated in the process that sums these histograms and
then normalizes the results to get the probabilities for each label [27].

12

2.1.5. Permutation Feature Importance (PFI) is a model-agnostic ranker feature ranker that
computes the scores for each of the variables contained in a dataset. It basically examines the
contribution of each feature to the overall predictive performance of the algorithm [27].

16

17 **2.2.** Evaluation of the performance of the algorithms

18 The performance metrics were aimed to evaluate how the algorithms performed [29–31]. Most 19 of these metrics have been previously used in other studies [15,32]. However, in addition to 20 accuracy, only two (F1 score and specificity) of these statistical measures that are medically 21 more relevant in the clinic, were discussed in the current study.

22

3. The training-validation phase for the algorithms in Microsoft Azure for prediction of recurrence

Microsoft Azure Machine Learning Studio (Azure ML 2019) was used in this study [27]. The
input parameters were age, gender, stage, grade, tumor budding, depth of invasion (DOI), worst

1 pattern of invasion (WPOI), lymphocytic host response (LHR), perineural invasion (PNI) and 2 treatment given, while the target output was locoregional recurrence. Disease-free survival 3 (DFS) time of the cases ranged from 1 to 267 months. Specifically, the DFS in cases with 4 recurrence varied between 1 and 120 months. Firstly, a potential class imbalance with respect 5 to the number of patients who experienced a tumor recurrence in the target class (locoregional 6 recurrence) was handled by up-sampling in order to balance the classes used in the training. 7 Synthetic minority oversampling technique (SMOTE) [33] offers a better way to handle 8 imbalance than simply duplicating existing cases. The dataset and the corresponding samples 9 are therefore more general [33]. The dataset was divided into two sets of training and 10 validation. Due to the relatively limited amount of data, a 5-fold cross validation was used with 11 50% training and 50% validation {50:50} percentage splitting sets [15]. Each of the algorithms of interest was then configured as shown in Figure 1 [27,28]. After training, the algorithms 12 13 were evaluated for the various quality metrics (Table 3).

14 Furthermore, these algorithms were further tested with new cases (Section 3.1). The 15 result obtained from this approach was considered as the gold standard in this study as it gives 16 an account of how the algorithm is expected to predict in reality. Also, it addresses any concerns 17 about the generalizability of the trained models. In addition, the contribution of each of the 18 input variables on the predictive ability of each model was examined using permutation feature 19 importance (PFI) analysis. Their contributions were given in the form of PFI-performance 20 scores. To avoid bias in the algorithm, disease-free survival and treatment were removed from 21 the PFI analysis that was aimed to examine the predictive ability of each variables. The input 22 features with positive scores were selected. Also, only one of the inputs was selected when two 23 or more inputs give the same negative score. The variables with least scores were not selected. 24 These selected variables were used to train the algorithms. The given accuracies in the PFI 25 analysis were compared with the accuracies obtained without PFI. Similarly, the PFI-based algorithms were tested with new cases. 26

2	3.1 Testing performance of the model with new cases: In this phase, the trained algorithms
3	were tested with 59 new cohort cases that were not included in the training or in the validation
4	sets (Figure 1). These new independent data were obtained from a cancer center in Brazil. The
5	results are presented in Table 4. The PFI-based models were also tested with these new cases
6	as presented in Table 5.
7	3.2 Comparison with the depth of invasion (DOI): The algorithm that showed the highest
8	overall accuracy when tested with these new external cases (section 3.1) was also compared
9	with the depth of invasion (DOI) based model as shown in Figure 3.
10	
11	4. Results
12	4.1 Data Description
13	The study cohort included 311 patients with cT1-T2cN0M0 OTSCC; 165 men and 146 women,
14	resulting in a male-to-female range of 1.1:1. Out of these 311 cases, 57 cases had missing
11	
15	details about any postoperative treatment information. Therefore, these cases were excluded
15 16	details about any postoperative treatment information. Therefore, these cases were excluded and the machine learning training was performed with 254 cases. These cases included 141
15 16 17	details about any postoperative treatment information. Therefore, these cases were excluded and the machine learning training was performed with 254 cases. These cases included 141 men and 113 women with the mean age at diagnosis was 61.51 (SD \pm 14.81: range 10-95) and
15 16 17 18	details about any postoperative treatment information. Therefore, these cases were excluded and the machine learning training was performed with 254 cases. These cases included 141 men and 113 women with the mean age at diagnosis was 61.51 (SD \pm 14.81: range 10-95) and the median age was 62.0 years. The distribution according to tumor diameter showed that 100
15 16 17 18 19	details about any postoperative treatment information. Therefore, these cases were excluded and the machine learning training was performed with 254 cases. These cases included 141 men and 113 women with the mean age at diagnosis was 61.51 (SD \pm 14.81: range 10-95) and the median age was 62.0 years. The distribution according to tumor diameter showed that 100 patients had stage T1 and 154 stage T2. The histopathologic parameters are briefly summarized
15 16 17 18 19 20	details about any postoperative treatment information. Therefore, these cases were excluded and the machine learning training was performed with 254 cases. These cases included 141 men and 113 women with the mean age at diagnosis was 61.51 (SD \pm 14.81: range 10-95) and the median age was 62.0 years. The distribution according to tumor diameter showed that 100 patients had stage T1 and 154 stage T2. The histopathologic parameters are briefly summarized in Table 2. In terms of the treatment, 157 patients had surgery alone while 97 had adjuvant
15 16 17 18 19 20 21	details about any postoperative treatment information. Therefore, these cases were excluded and the machine learning training was performed with 254 cases. These cases included 141 men and 113 women with the mean age at diagnosis was 61.51 (SD \pm 14.81: range 10-95) and the median age was 62.0 years. The distribution according to tumor diameter showed that 100 patients had stage T1 and 154 stage T2. The histopathologic parameters are briefly summarized in Table 2. In terms of the treatment, 157 patients had surgery alone while 97 had adjuvant (chemo)radiotherapy (92 radiotherapy and 5 chemoradiotherapy). Similarly, 185 had neck
15 16 17 18 19 20 21 22	details about any postoperative treatment information. Therefore, these cases were excluded and the machine learning training was performed with 254 cases. These cases included 141 men and 113 women with the mean age at diagnosis was 61.51 (SD \pm 14.81: range 10-95) and the median age was 62.0 years. The distribution according to tumor diameter showed that 100 patients had stage T1 and 154 stage T2. The histopathologic parameters are briefly summarized in Table 2. In terms of the treatment, 157 patients had surgery alone while 97 had adjuvant (chemo)radiotherapy (92 radiotherapy and 5 chemoradiotherapy). Similarly, 185 had neck dissection while 69 had no neck dissection performed. Thus, from the 185 patients who had
15 16 17 18 19 20 21 22 23	details about any postoperative treatment information. Therefore, these cases were excluded and the machine learning training was performed with 254 cases. These cases included 141 men and 113 women with the mean age at diagnosis was 61.51 (SD \pm 14.81: range 10-95) and the median age was 62.0 years. The distribution according to tumor diameter showed that 100 patients had stage T1 and 154 stage T2. The histopathologic parameters are briefly summarized in Table 2. In terms of the treatment, 157 patients had surgery alone while 97 had adjuvant (chemo)radiotherapy (92 radiotherapy and 5 chemoradiotherapy) . Similarly, 185 had neck dissection while 69 had no neck dissection performed. Thus, from the 185 patients who had neck dissection, 43% were exposed to adjuvant radiotherapy while 57% had only surgery as
 15 16 17 18 19 20 21 22 23 24 	details about any postoperative treatment information. Therefore, these cases were excluded and the machine learning training was performed with 254 cases. These cases included 141 men and 113 women with the mean age at diagnosis was 61.51 (SD \pm 14.81: range 10-95) and the median age was 62.0 years. The distribution according to tumor diameter showed that 100 patients had stage T1 and 154 stage T2. The histopathologic parameters are briefly summarized in Table 2. In terms of the treatment, 157 patients had surgery alone while 97 had adjuvant (chemo)radiotherapy (92 radiotherapy and 5 chemoradiotherapy). Similarly, 185 had neck dissection while 69 had no neck dissection performed. Thus, from the 185 patients who had neck dissection, 43% were exposed to adjuvant radiotherapy while 57% had only surgery as single-modality treatment. Similarly, out of the 69 cases who had no dissection performed,

1 The number of patients with disease recurrences was 68 (26.8%). While the disease-2 free survival (DFS) time ranged from 1 to 267 months, the DFS time for cases with a 3 locoregional recurrence was between 1 to 120 months. Overall, 89.6% of the recurrences 4 occurred in the first 2 years, while 10.45% recurrence was recorded after 2 years. The mean 5 follow-up time was 75 months (SD \pm 64.6; range 1 - 258 months) and the median was 60 6 months. Similarly, for the 59 new OSCC cases used for external testing, DFS time varied 7 between 1 to 146 months. Also, 74% had a recurrence in the first year, 16% after the first and 8 before end of second year, and 10% of the patients recurred after the second year. The mean 9 age in this external validation cohort was 56.2 years (range, 31-84 years). All these new cases 10 had neck dissection, where 34 cases had surgery alone while 25 had adjuvant 11 (chemo)radiotherapy (22 radiotherapy and 3 chemoradiotherapy). The DOI model performance 12 in terms of accuracy in the training set was 47.2% and the overall accuracy in the new cohorts 13 used for external validation was 63%.

14

15 Performance metrics for the algorithms

16 The distribution of true and false positives, true and false negatives, and other performance 17 metrics for the algorithms in the training phase are given in Figure 2a and Table 3, respectively. 18 During the training phase, decision forest showed the highest accuracy while naive Bayes and 19 decision forest showed the best area under receiving operating characteristic (AUC of ROC). 20 When these algorithms were tested on the 59 new external cases from the cancer center in 21 Brazil, the average specificity of all the algorithms was 71%. The tested algorithms i.e. support 22 vector machine, naive Bayes, decision forest, and boosted decision tree gave an overall 23 accuracy of 68%, 70%, 78% and 81%, respectively. The details of the performance of parameters with this new cohorts are given in Table 4. Considering the harmonic mean of 24 25 precision and recall, that is, F1 score, the support vector machine, naive Bayes, decision forest, 26 and boosted decision tree gave 0.63, 0.64, 0.70 and 0.78, respectively. Therefore, the best

1 overall classification performance to predict recurrence was achieved with the boosted decision 2 tree algorithm. Comparison of the boosted decision tree algorithm and the DOI model is shown 3 in Figure 3; the DOI model showed an accuracy of 63% where 54.1% of the patients would be 4 observed, thereby not subjected to adjuvant therapy or elective neck dissection (END). The 5 boosted decision tree on the other hand showed 81% overall accuracy where 21.1% of the 6 patients would have been observed and not subjected to END. Similarly, about half (49.5%) of 7 the patients were correctly identified as having OTSCC recurrence using the DOI model. 8 Boosted decision tree machine learning technique correctly identified 78.9% as having OTSCC 9 recurrence as shown in Figure 3. Thus, each of these algorithms performed significantly better 10 than the DOI-based model.

11 The results of the permutation feature importance (PFI) analyses are given in Table 5. 12 The PFI scores were calculated for each feature independently. A zero score is returned when 13 there is no difference in the performance metrics before and after PFI of that feature. Similarly, 14 a negative score is returned when a random PFI of that feature produced a higher accuracy and 15 lower error (better performance metrics) compared to the performance before PFI was applied. 16 Moreover, a higher importance score (positive) gives an indication of the contribution of that 17 feature to the predictive ability of the model. The PFI of boosted decision tree (PFI-BDT) 18 showed the highest accuracy (83.1%). Also, it was observed that the accuracy of BDT increased 19 from 81.0% to 83.1% and DF increased from 78% to 80%, while SVM showed a reduction in 20 accuracy from 68% to 64.4% in the PFI analysis. Interestingly, the accuracy of NB increased 21 significantly from 70.0% to 81.4% in the permutation feature importance fitting. The ranking 22 of the scores of the features is as shown in Table 5.

23 **5. Discussion**

The present study compared the performance of ML algorithms to stratify patients with OTSCC
into low or high-recurrence risk group. In this regard, four ML algorithms, namely, boosted
decision tree, naive Bayes, support vector machine, and decision forest were examined. We

1 found that the performance of these techniques was higher than that of depth of invasion (DOI) 2 based approach. Our multicenter cohort of cases is one of the largest published series. Majority 3 of the previous publications including hundreds of cases have mixed early-stage cases with 4 those with advanced stage, and/or have mixed different subsites of the oral cavity (e.g. oral 5 tongue with floor of mouth and retromolar region). Therefore, heterogeneity of such series 6 makes it difficult to identify robust prognostic markers. The advantage of our homogenous 7 cohort (only early stage and only oral tongue) allows for reaching definitive conclusions that 8 can be considered to be applied in daily practice.

9 Although significant progress has been made in early diagnostics, treatment strategies 10 and prevention of OTSCC in recent years, the prognosis of OTSCC is poor due to aggressive 11 local invasion and metastasis, leading to recurrence. The mortality rates in cases with 12 recurrence has been reported to be very high [34]. When recurrence is diagnosed earlier, the 13 mortality rates have been reported to decrease [35,36]. The reported rates of recurrence in oral 14 squamous cell carcinoma range from 6.9 % to 37.4% of patients [37,38]. This is in accordance 15 with the 26.8% locoregional recurrence rate within the dataset used in this study. Improved 16 prediction of locoregional recurrences in early-stage OTSCC can lead to an adjusted, patient-17 oriented follow-up program. For example, based on prediction of the patient as a high-risk case 18 a customized surveillance could be organized instead of the general follow-up program.

Abundant studies exist that have considered DOI as a strong histologic feature that correlates with locoregional recurrence. The machine learning algorithms examined in this study, however, outperformed the power of prediction of locoregional recurrence based on DOI. However, it will offer a better approach with significant accuracy in stratifying the patients as carrying a high- or low-risk for recurrence. Therefore, it seems obvious, that the described challenge in the treatment-decision making would be successfully addressed by the machine learning model due to increased specificity, F1 score and overall accuracies of the ML

algorithms. Thus, this study has potentially high impact to clinicians in the management of
 early OTSCC.

3 With regards to the performance metrics examined, F1 score used as the benchmark to 4 choose the best algorithm as it finds the optimal blend between two other performance metrics 5 (precision and recall). As shown in Table 4, the F1 score for the boosted decision tree algorithm 6 showed to be very good at stratifying the patients as having either low-risk or high-risk of 7 recurrence of OTSCC. This justifies why boosted decision tree was compared to the DOI as 8 shown in Figure 3 [18]. It is important to note that the support vector machine showed 9 promising evaluation performance metrics in the training phase. This is due to the fact that it 10 is an empirical risk minimizer algorithm. Hence, it is not usually prone to overfitting related 11 issue as it avoids the danger of getting trapped into local minima [39]. However, the ensemble 12 algorithms performed better than the support vector machine because they were able to create 13 a fleet of algorithms with relatively similar bias and subsequently combining their outputs to 14 reduce variance.

15 Furthermore, a major challenge in the treatment of patients with early OTSCC is in 16 finding the right parameters that predict prognosis and help to properly identify patients at high 17 risk of locoregional recurrences. This would carry the potential to minimize the incidence 18 treatment failure of patients with OTSCC [35]. With the PFI-analyses, the exact contribution 19 of each parameter to the predictive ability of the machine learning algorithms was known. 20 Interestingly, there was no significant difference in the overall accuracies achieved in the 21 ensemble methods (decision forest and boosted decision tree) with reduced parameters 22 identified in the PFI analyses compared to the algorithms without PFI. Therefore, the cost and 23 resources associated with getting numerous parameters can be properly managed. Also, the 24 time taken to properly prepare an individualized treatment plan for the patients can be 25 improved. This is because a few but important features that are needed for the ML algorithms were identified in the PFI analysis while producing the same range of prediction accuracies. 26

Thus, predicting recurrence with such accuracy as shown in this study would be crucial to the
 clinicians in terms of management decisions.

3 Numerous studies have compared the performance of various machine learning 4 classifiers to predict an outcome of interest in cancer. Tapak et al. compared various machine 5 learning classifiers in series of 550 breast cancer patients, and found that the support vector 6 machine predicted survival better than other classifiers [15]. Similarly, the study by Tseng et 7 al. compared decision tree ML technique with a traditional statistical model such as logistic 8 regression in series of 673 oral cancer patients and the decision tree was found to perform better 9 [40]. De Melo et al. used decision tree to evaluate the quality of life among patients with head 10 and neck cancer [41]. Similarly, Sumbaly et al. used the decision tree in the diagnosis of breast 11 cancer [42]. The decision forest also produced the highest prognostic performance when 12 compared with other machine algorithms by Zhang et al. for the radiomics-based prediction of 13 failure in advanced nasopharyngeal carcinoma [43].

14 In conclusion, this study investigated four different ML algorithms and found that the 15 boosted decision tree algorithm showed the best overall performance accuracy. Due to the 16 sensitive nature of the application of machine learning in medicine, it is important for these 17 algorithms to produce very high accuracies. In this study, the ensemble algorithms such as the 18 boosted decision tree and the decision forest algorithms performed better than non-ensemble 19 algorithms such as support vector machine, naive Bayes and a method based on depth of 20 invasion. Therefore, the ensemble machine algorithms should be considered in medical 21 applications. Presently, it is challenging for clinicians to assess the outcomes of clinical early-22 stage oral cancer. For the clinicians, knowledge of potential locoregional prediction to stratify 23 the patients into low-risk or high-risk groups using machine learning applications can help to 24 guide clinical practice. Patients can be counseled accordingly with realistic expectations and 25 clinicians can be guided in making informed decisions. Furthermore, this contributes to the individual data regarding patient and tumor-related factors and thereby helps the clinician in 26

1 planning the optimal patient-specific treatment and follow-up (post-operative adjuvant 2 treatment). For instance, high-risk patients might benefit from adjuvant oncological therapy 3 after surgery. Future research should consider including other prognostic parameters as inputs 4 for the selected algorithms. In terms of the limitation of this study, we are limited by the number 5 of available cases as this was a retrospective study of five teaching hospitals in Finland and 6 one in Brazil. Also, the external data used to test the performance of the algorithms were 7 relatively limited. Therefore, with larger external data, the performance of the algorithms could 8 be improved.

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10 Authors Contribution

11 Institutional Coordinators: Salo T, Coletta RD, Kowalski LP, Leivo I, Mäkitie AA, Haglund 12 C. Study concepts and study design: Alabi RO, Elmusrati M, Almangush A, Coletta RD, 13 Salo T, Leivo I. Data acquisition and quality control of data: Sawazaki-Calone I, Kowalski 14 LP, Leivo I. Data analysis and interpretation: Alabi RO, Elmusrati M, Almangush A, 15 Sawazaki-Calone I, Mäkitie AA, Salo T, Leivo I. Manuscript preparation: Alabi RO, Elmusrati M, Almangush A, Mäkitie AA, Coletta RD. Manuscript review: Mäkitie AA, Leivo 16 17 I, Salo T, Kowalski LP, Sawazaki-Calone I. Manuscript editing: Salo T, Leivo I, Mäkitie AA, 18 Haglund C. All authors approved the final manuscript for submission.

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22	a	• 4
23	Summarv	points
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24 What was already known on the topic:

25 • There are few published studies on the comparison of machine learning techniques to
 26 predict locoregional recurrence of oral tongue squamous cell carcinoma (OTSCC).

Accuracy value is the most considered performance metrics to choosing the machine
 learning technique for prediction.

3 What knowledge this study adds:

- To the best of our knowledge, this is the first study that analyzed more than three
 machine learning techniques to predict risk of locoregional recurrence in oral tongue
 squamous cell carcinoma (OTSCC) as low-risk or high-risk.
- It is important to consider other performance metrics such as specificity and F1 score
 (weighted average of precision and recall) in medical applications.
- 9 The permutation importance feature (PFI) algorithm to extract important features does
- not correspond to better overall prediction and does not necessarily perform better than
 the ensemble algorithms.
- The application of these supervised learning techniques to stratify the patients as having
 low-risk or high-risk for the recurrence of OTSCC may be useful for effective cancer
 management.
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23 Figure Legend

24 **Figure 1.** The training process in azure machine learning studio.

25 Figure 2. The classification results of the four basic parameters for each algorithm in the

training and also for PFI analysis.

- 1 (TP: True Positive, TN: True Negative, FP: False Positive, FN: False Negative, BDT: Boosted Decision Tree, SVM: Support
- 2 Vector Machine, NB: Naive Bayes, and DF: Decision Forest).
- 3 **Figure 3**. The comparison of the boosted decision tree algorithm to the depth of Invasion model

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Number Parameters		Description	Туре		
1	Age	Age at the time of diagnosis	Discrete		
2	Gender	The sexual orientation of the patient	Categorical 1 = Male; 2 = Female		
3	T-stage	T stage describing tumor size	Categorical $1 = T1; 2 = T2.$		
4	WHO Grade	Histopathologic grading according to World Health Organization (WHO) criteria	Categorical 1 = Grade I; 2 = Grade II; 3 = Grade III		
5	Tumor budding	Tumor budding is defined as the presence of single cells or small clusters of cancer cells detached from the main tumor mass	Categorical 0 = No budding; 1 < 5 buds; $2 \text{ for } \ge 5 \text{ buds}.$		
6	Tumor depth	This is the measure of tumor depth of invasion. It was measured in millimetres (mm)	Categorical 1 for < 4 mm, 2 for ≥ 4 mm		
7	WPOI	Worst pattern of invasion	Categorical Value of 0 for WPOI type 1 to 3; Value of 1 for WPOI type 4; Value of 3 for WPOI type 5.		
8	LHR	Lymphocytic host response	Categorical Value of 0 for LHR type 1; Value of 1 for LHR type 2; Value of 3 for LHR type 3.		
9	PNI	Perineural invasion	Categorical 0 = Absent; 1 = Present		
10	Treatment	This indicates the type of treatment offered for the patient. It could either be surgery alone or adjuvant (chemo)radiotherapy in addition to the surgery	Categorical 0 = Surgery alone 1 = Surgery + Adjuvant (chemo)radiotherapy		
11	Neck treatment	This variable indicates whether neck dissection was performed or not	Categorical 0 = No neck dissection 1 = Neck dissection performed.		
12	Recurrence*	The occurrence of disease after treatment	Categorical 0 = Low-Risk: 1 = High-Risk		

Table 1. The parameters contained in the dataset and their respective descriptors.

* Recurrence was considered as the output/target label. The disease-survival (DFS) ranges from 1 to 267 months while DFS for locoregional recurrence patient ranges from 1 to 120 months.

Table 2: Summary of histopathologic parameters included for the machine learning training.

Variable	Category (Definition)	Number
WHO grade		
	Grade I (Well-differentiated tumor)	78
	Grade II (Moderately-differentiated tumor)	103
	Grade III (Poorly-differentiated tumor)	73
Tumor budding		
	None (There is no tumor budding)	93
	Low (Tumor has less than five buds)	85
	High (Tumor has five buds or more at the invasive front)	76
Depth of invasion		
	Superficial (Tumor < 4 mm in depth)	96
	Deep (Tumor \geq 4 mm in depth)	158
Worst pattern of invasion (WPOI)		
	Type 1 (Pushing border)	64
	Type 2 (Finger-like growth)	
	Type 3 (Large tumor islands)	
	Type 4(Small tumor islands of ≤ 15 cancer cells)	158
	Type 5 (Tumor satellites)	32
Lymphocytic host response (LHR)		
	Type 1 (Strong)	36
	Type 2 (Intermediate)	88
	Type 3 (Weak)	130
Perineural invasion (PNI)		
	Absent (PNI was not observed)	223
	Present (PNI was observed)	31

50% Training and 50% Testing Cross Validation Scheme									
Algorithm	Sensitivity	Specificity	Precision	NPV	LR ⁺	LR ⁻	F1 Score	AUC	Accuracy %
NB	0.67	0.81	0.77	0.92	3.53	0.41	0.66	0.89	80.0
SVM	0.94	0.79	0.59	0.97	4.48	0.08	0.73	0.88	82.7
DF	0.77	0.86	0.65	0.92	5.50	0.27	0.71	0.89	84.0
BDT	0.68	0.87	0.62	0.89	5.23	0.37	0.65	0.82	82.0
PFI-NB	0.77	0.83	0.59	0.92	4.53	0.28	0.67	0.89	81.0
PFI-SVM	0.87	0.72	0.50	0.95	3.11	0.18	0.64	0.87	76.0
PFI-DF	0.77	0.83	0.60	0.92	4.53	0.28	0.68	0.85	82.0
PFI-BDT	0.65	0.85	0.59	0.88	4.33	0.41	0.62	0.84	80.0

Table 3. The overall performance metrics of the classifiers in the training phase

BDT = Boosted Decision Tree, SVM = Support Vector Machine, BPM = Bayes Point Machine, DF = Decision Forest, Precision (PPV = Predictive positive value), NPV = Negative predictive value, LR⁺ = Positive likelihood ratio and LR⁻ = Negative likelihood ratio, Sensitivity (recall), Area under receiving operating characteristics curve (AUC), and CDE = Custom Designed Ensemble.

Table 4. The performance of the algorithms with external cases.

Parameter	SVM	NB	BDT	DF
True Positive (TP)	16	16	15	15
False Positive (FP)	16	15	07	09
True Negative (TN)	24	25	33	31
False Negative (FN)	03	03	04	04
Sensitivity	0.84	0.84	0.79	0.79
Specificity	0.60	0.63	0.83	0.78
Precision (PPV)	0.50	0.52	0.76	0.63
NPV	0.89	0.89	0.89	0.89
LR⁺	2.10	2.27	4.65	3.59
LR ⁻	0.27	0.25	0.25	0.27
F1 Score	0.63	0.64	0.78	0.70
Accuracy	68%	70%	81%	78%

PFI-DF		PFI-BDT		PFI-SVM		PFI-NB	
Features	Scores	Features	Scores	Features	Scores	Features	Scores
PNI	0.0078	Age	0.0315	Gender	0.0079	Age	0.0079
Depth	0.0000	Depth	0.0236	Stage	0.0079	Gender	0.0079
Tumor Budding	0.0158*	WPOI	0.0236	Tumor Budding	0.0079	Stage	0.0079
Stage	0.0315*	PNI	0.0079	Depth	0.0079	Depth	0.0079
LHR	0.0315*	Tumor Budding	0.0000	LHR	0.0079	Grade	0.0000
Gender	0.0394*	LHR	0.0079*	PNI	0.0079	Tumor Budding	0.0079*
Grade	0.0394*	Stage	0.0158*	Age	0.0000	LHR	0.0079*
WPOI	0.0472*	Grade	0.0158*	Grade	0.0000	PNI	0.0079*
Age	0.0551*	Gender	0.0236*	WPOI	0.0000	WPOI	0.0236*
Accuracy (External	80.0%	Accuracy (External	83.1%	Accuracy (External	64.4%	Accuracy (External Testing)	81.4%
Testing)		Testing)		Testing)			

 Table 5. Permutation Feature Importance (PFI) of the algorithms.

* Negative score. DF : Decision Forest, BDT: Boosted Decision Forest, SVM: Support Vector Machine, NB: Naive Bayes. WPOI: Worst Pattern of Invasion, PNI: Perineural Invasion, LHR: Lymphocytic host response.

Figures



Figure 1





Figure 2



Figure 3