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Machine learning to predict occult nodal metastasis in early oral squamous cell carcinoma

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ABSTRACT

Objectives: To develop and validate an algorithm to predict occult nodal metastasis in clinically node negative oral cavity squamous cell carcinoma (OCSCC) using machine learning. To compare algorithm performance to a model based on tumor depth of invasion (DOI).

Materials and methods: Patients who underwent primary tumor extirpation and elective neck dissection from 2007 to 2013 for clinical T1-2N0 OCSCC were identified from the National Cancer Database (NCDB). Multiple machine learning algorithms were developed to predict pathologic nodal metastasis using clinicopathologic data from 782 patients. The algorithm was internally validated using test data from 654 patients in NCDB and was then externally validated using data from 71 patients treated at a single academic institution. Performance was measured using area under the receiver operating characteristic (ROC) curve (AUC). Machine learning and DOI model performance were compared using Delong's test for two correlated ROC curves.

Results: The best classification performance was achieved with a decision forest algorithm (AUC = 0.840). When applied to the single-institution data, the predictive performance of machine learning exceeded that of the DOI model (AUC = 0.657, p = 0.007). Compared to the DOI model, machine learning reduced the number of neck dissections recommended while simultaneously improving sensitivity and specificity.

Conclusion: Machine learning improves prediction of pathologic nodal metastasis in patients with clinical T1-2N0 OCSCC compared to methods based on DOI. Improved predictive algorithms are needed to ensure that patients with occult nodal disease are adequately treated while avoiding the cost and morbidity of neck dissection in patients without pathologic nodal disease.

Introduction

Lymph node metastasis has long been recognized as an important prognostic factor in oral cavity squamous cell carcinoma (OCSCC) and is associated with tumor recurrence and decreased survival [1,2]. Neck dissection in combination with primary tumor extirpation is indicated in all cases where nodal disease is clinically evident [3]. However, controversy has long existed surrounding the role of elective neck dissection (END) for small oral cancers without clinically evident nodal metastases. END offers potential advantages of improved disease control and survival, yet carries morbidity and may worsen health related quality of life [4–9]. How to best select patients that will benefit from END has been a subject of debate for decades.

The decision to perform END in early OCSCC may be informed by several factors. Depth of invasion (DOI) of the primary tumor is the most commonly used histopathologic variable to predict which patients are at high risk of occult nodal metastasis [10]. DOI ranging from two to five millimeters have been advocated as thresholds for END [11–13]. Additional clinicopathologic factors have been examined to determine their association with occult nodal disease, including gender, tumor location, histologic grade, pattern of invasion, perineural and lymphovascular invasion [14–17]. Combinations of these factors have been used to create multivariable regression models and nomograms to predict occult nodal metastasis [15,18,19]. However, these techniques have not been widely adopted because they are cumbersome to use and lack predictive accuracy. Using current methods to predict occult nodal

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metastasis, approximately 70% of patients with clinically node negative oral cancers who undergo END are found to be pathologically node negative [2]. Improved methods are needed to ensure that patients with occult nodal disease are adequately treated, while avoiding the cost and morbidity of neck dissection in patients without nodal disease.

Machine learning is a subset of artificial intelligence (AI) that enables computers to learn from historical data, gather insights and make predictions about new data using the information learned [20]. Machine learning has been shown to have high degrees of accuracy and precision that exceeds the abilities of standard statistical techniques and human judgement to make predictions about outcomes in medicine [21,22]. Statistics is primarily focused on inference and describes how a system of components relate to one another. For example, in one study, tumor depth of invasion > 4 mm was associated with an odds ratio of 8.3 of nodal metastasis [12]. On the other hand, machine learning focuses on making predictions about an unknown variable based on past experiences using large sets of patient data. Machine learning has not previously been used to predict nodal metastasis in clinically node-negative oral cavity squamous cell carcinoma. We hypothesize that machine learning algorithms will improve prediction of pathologic nodal status in patients with early OCSCC, allowing for more accurate identification of those patients that will benefit from END and sparing END for those that are unlikely to benefit. The objective of this study was to develop and validate machine learning algorithms to predict pathologic nodal metastasis in patients with cT1-2N0 OCSCC and to compare them to a predictive model based on tumor DOI.

Methods

This study was approved by the Institutional Review Board of the University of Kansas Medical Center. Patients were identified from two sources: the national cancer database (NCDB) and a single tertiary care academic medical center.

National cancer database

Study data was obtained from the NCDB participant user file on December 4, 2018 and included patients with oral squamous cell carcinoma diagnosed between 2007 and 2014. Established in 1989 as a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, the NCDB is a nationwide, facility-based, comprehensive oncology data set that uses the third edition of the International Classification of Diseases for Oncology (ICD-O-3) for topography (primary site) and morphology (histology) definitions and stages according to the American Joint Committee on Cancer (AJCC) manual for staging of cancer. NCDB and the hospitals participating in the NCDB are the source of the de-identified data used herein.

Single institution data

Patients treated with primary surgery for OCSCC between 2010 and 2018 at the University of Kansas Medical Center were identified using the Healthcare Enterprise Repository for Ontological Narration (HERON) research data repository. Clinical and pathologic data was extracted from the electronic health record and entered into a REDCap data collection form [23].

With the incorporation of DOI into the 8th edition AJCC staging manual, pathologists at our institution recently began measuring tumor DOI as the “plumb line” dropped from the horizon established by the basement membrane of the closest intact squamous mucosa [24]. However, prior to 2019, no standardized method of measuring or reporting tumor DOI was used at our institution. For the purpose of this study, we elected to use DOI and thickness interchangeably in order to remain consistent with how tumor depth is measured and reported in NCDB [25].

Inclusion/exclusion criteria

Inclusion and exclusion criteria were the same for NCDB and single institution patients. Patients included for study were at least 18 years of age with biopsy-proven OCSCC. Patients were included if they were clinically staged as T1 or T2 and were clinically and radiologically node negative based on physical examination and/or imaging. Patients were excluded if they were treated non-surgically or did not undergo END. Patients were also excluded if they had clinical evidence of regional nodal or distant metastatic disease. Clinical and pathologic variables included for analysis were age, sex, race, ethnicity, primary tumor site, histology, grade and DOI. Race was categorized as white, black, and other. Primary sites included mucosal subsites of the oral cavity and AJCC staging was applied to describe the extent of disease. For patients identified from the NCDB, histology was limited to squamous cell carcinoma using ICD-O-3 histology codes. The primary outcome of interest was presence or absence of nodal metastasis based on histopathologic evaluation of cervical lymph nodes after END.

Data preprocessing

For patient data extracted from NCDB, missing data for continuous variables was handled using median imputation. Missing categorical data was assigned a value of “Unknown”. The NCDB dataset was split using an 80:20 distribution whereby the machine learning algorithm was trained using 80% of the available cases and tested using the remaining 20%. The training data was then randomly down-sampled to ensure an equal frequency of pathologically node-negative (pN−) and node-positive cases (pN+) to avoid model bias.

Model training

First, a predictive model based on tumor depth alone was developed such that tumors with depth $\geq d_t$ in mm were predicted to be pN+ and tumors with depth $< d_t$ were predicted to be pN−, where d_t represents the depth threshold to recommend END. Next, recursive feature elimination was used to identify the most important variables to optimize machine learning classification performance. To ensure model stability and reduce bias, 5-fold cross validation was performed during training of all machine learning algorithms. The NCDB training dataset was then used to train multiple classification algorithms to predict pathologic nodal metastasis. Classification algorithms were developed to predict pathologic lymph node metastasis using logistic regression, decision forest, kernel support vector machines and gradient boosting machine learning architectures. Hyperparameters were tuned to maximize area under the receiver operating characteristic curve (AUC).

Validation

Classification performance of the machine learning algorithms and tumor depth model was then evaluated on the NCDB test data by comparing AUC (internal validation). All predictive models were then externally validated using single institution patient data. This data was then input into each classification model and AUC was calculated. Patient characteristics were compared using Student’s *t*-test for continuous variables and X^2 test or Fisher’s Exact test. Model performance was compared using Delong’s test for two correlated ROC curves. All machine learning and data analysis was performed with R Studio version 1.1.463 (R Studio, Boston, Massachusetts).

Results

A total of 1961 cases from NCDB and 71 cases from our institution met inclusion and exclusion criteria. A comparison of patient and tumor characteristics between NCDB and single institution cases is provided in Table 1. Single institution patients were significantly younger and more

Table 1
Patient characteristics from national cancer database and single institution cohorts of clinically T1-2N0 squamous cell carcinoma of the oral cavity undergoing primary surgical extirpation and elective neck dissection.

Variable	NCDB	Single institution	p-value
Patients (N)	1961	71	–
Age (mean(SD))	61.9 (13.7)	58.1 (12.6)	0.013
Tumor site			0.008
Buccal	125 (6.4%)	2 (2.8%)	
Floor of mouth	279 (14.2%)	5 (7.0%)	
Hard palate	21 (1.1%)	2 (2.8%)	
Lip	99 (5.0%)	1 (1.4%)	
Tongue	1254 (63.9%)	60 (84.5%)	
Alveolar ridge	149 (7.6%)	0	
Other	34 (1.7%)	1 (1.4%)	
Clinical T classification			0.010
T1	1260 (64.3%)	35 (49.3%)	
T2	701 (35.7%)	36 (50.7%)	
Histologic grade			0.010
I: Well differentiated	529 (27.0%)	31 (43.7%)	
II: Moderately differentiated	1131 (57.7%)	37 (52.1%)	
III: Poorly differentiated	208 (10.6%)	3 (4.2%)	
IV: Undifferentiated	5 (0.3%)	0	
Unknown	88 (4.5%)	0	
Tumor size, mm (mean(SD))	17.5 (6.3)	18.0 (9.4)	0.483
Tumor depth of invasion, mm (mean (SD)	5.4 (2.9)	5.5 (3.9)	0.702
Pathologic nodal status			0.570
Negative	1677 (85.5%)	59 (83.1%)	
Positive	284 (14.5%)	12 (16.9%)	

likely to have primary tumors of the oral tongue. Also, single institution patients were more likely to have tumors clinically staged as T2 and tumors that were well-differentiated. There were no significant differences in tumor size, DOI or pathologic nodal status. The NCDB dataset was then divided into training and testing datasets consisting of 1570 and 391 patients, respectively. After random down-sampling, 456 patients remained in the training dataset with equal numbers of pN+ and pN− patients. Recursive feature elimination identified five variables to be most important in developing machine learning classification models: pathologic tumor size, clinical T stage, histologic grade, DOI and primary tumor site.

Comparison of baseline patient demographics collected from the NCDB database and KU Department of Otolaryngology is shown in Table 1. The best classification performance was achieved using a decision forest architecture and had an AUC of 0.712 on the NCDB test data. Hyperparameter values selected to optimize model performance were: number of variables per split = 2, splitting rule = "gini", minimal node size = 1. Relative importance of the variables used to develop the decision forest classification model is shown in Table 2. The tumor depth model had an AUC of 0.527, significantly lower than all machine learning algorithms ($p < 0.001$).

To externally validate the machine learning algorithms, their performance was then evaluated using single institution test data. When applied to 71 patients from our institution, the tumor depth model had AUC of 0.657, sensitivity of 0.750 and specificity of 0.458. The decision forest algorithm had AUC of 0.840, sensitivity of 0.917, and specificity of 0.576 (see Fig. 1). The decision forest algorithm ($p = 0.007$) and gradient boosting ($p = 0.045$) were significantly better at predicting occult nodal metastasis than that of the tumor DOI model, as measured by AUC.

Table 2
Comparison of performance of models to predict occult nodal metastasis in T1-T2 oral squamous cell carcinoma on national cancer database test data and single institution patient data. Each model is compared to the tumor depth model using Delong's test for two correlated ROC curves. AUC: area under the curve; SVM: support vector machines; DOI: depth of invasion.

Classifier	Sensitivity	Specificity	AUC	p-value
Internal validation – National cancer database				
DOI ($d_t = 4$ mm)	0.866	0.250	0.527	–
Kernel SVM	0.649	0.636	0.698	< 0.001
Logistic regression	0.732	0.522	0.705	< 0.001
Gradient boosting	0.773	0.492	0.704	< 0.001
Decision forest	0.753	0.492	0.712	< 0.001
External validation – Single institution data				
DOI ($d_t = 4$ mm)	0.750	0.458	0.657	–
Kernel SVM	0.833	0.559	0.776	0.249
Gradient boosting	0.917	0.525	0.798	0.045
Logistic regression	0.917	0.627	0.821	0.064
Decision forest	0.917	0.576	0.840	0.007

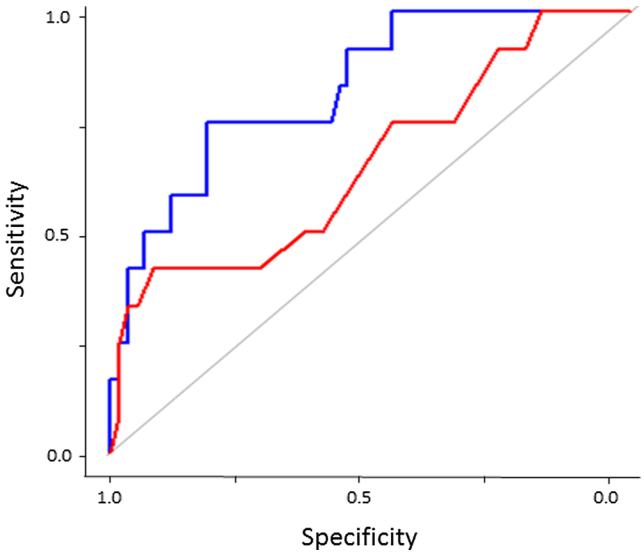

Fig. 1. Receiver Operating Characteristic (ROC) curves comparing depth of invasion (red) and decision forest algorithm (blue) in predicting pathologic nodal status of 71 patients treated at a single academic medical center. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Discussion

Machine learning holds great promise to enable clinicians to make actionable decisions based on the vast quantities of digitized health information in the "big data" era. Prior studies have applied machine learning techniques to large patient datasets to predict delirium in hospitalized patients [26] and to forecast Medicaid expenditures for high-cost patients [27]. Our group used machine learning to predict delays in initiation of adjuvant radiation therapy in patients with head and neck cancers using NCDB [28]. In this study, we evaluated the potential of machine learning to predict occult nodal metastasis in early oral squamous cell carcinoma. There is currently no universally accepted method for identifying patients that should undergo END. However, with mounting evidence of the benefits of END on disease control and survival, observation of the neck in patients known to be at high risk of occult nodal metastasis is no longer a reasonable option [2]. Numerous publications have advocated using DOI of the primary tumor to identify patients at high risk of nodal metastasis who should undergo END [11,29]. Depending on the DOI threshold, this approach can provide a sensitive method for determining whether END should be

performed in any given case. However, as with all predictive models, the price of increased sensitivity is a decrease in the specificity of the model. In this case, decreased specificity leads many patients to undergo END for pathologically N0 disease.

We found that machine learning algorithms, developed using population-based patient data from NCDB, can accurately predict pathologic nodal metastasis not only for patients in the database, but for patients treated at our own institution as well. Irrespective of the source of patient data, machine learning outperformed DOI in predicting pathologic nodal metastasis according to all performance metrics. This is significant for several reasons. First, a more sensitive predictive model will be less likely to recommend observation for a patient who has occult nodal metastasis. This is by far the most important requirement of the predictive model because the consequences of disease progression and missed opportunity for cure far outweigh the morbidity of END. Secondly, a more specific model will allow for greater numbers of patients to be safely observed. This has the advantages of reducing health care utilization and cost and improving quality of life for those patients who can avoid neck dissection.

Machine learning has several advantages over existing methods for selecting patients that should undergo END. First, it is an adaptive technology and can learn from new data. As machine learning algorithms acquire data from new patients, they can incorporate this data into their decision making to improve their predictive performance [30]. Machine learning technologies can also help provide clinicians with new insights to allow for more personalized patient care. By analyzing how similar patients have responded to treatment in the past, machine learning can provide helpful information based on the experiences of many more patients that any individual physician could incorporate into his/her medical decision making. What would have been the impact of the DOI and machine learning models in the determination to undergo END in our patient cohort? As illustrated in Fig. 2, if the DOI model had been used with a depth threshold of 4 mm, of the 71 patients treated at our institution, END would have been recommended in 41 and only nine (22%) of these would have been found to have pathologic nodal metastasis. Of the 30 patients that would have been observed, three (10.0%) would have harbored occult nodal metastasis. The result is that END would have been recommended for more than half of patients, with nearly 80% not benefiting oncologically from this surgery. Additionally, a false negative rate of 10% is unacceptably high, given the known benefits of early neck dissection in patients with occult nodal metastasis. By comparison, the decision forest algorithm would have recommended END for 36 patients and 11 (30.6%) would have been found to have pathologic nodal metastasis. Of the 35 patients in whom observation of the neck would have been recommended, only one (2.9%) would have been incorrectly predicted to be node negative.

There are several limitations to this study. First, the likelihood of selection bias is significant. Only patients who underwent END were included, which was necessary to know the outcome of pathologic nodal metastasis. It is impossible to know the criteria that led these patients to undergo END and why other similar patients may not have undergone END. Furthermore, it is unknown how these models would perform on patients who were excluded from this study because the cervical lymphatics were observed and thus pN is unknown. Secondly, the quality of data in NCDB is a significant concern. NCDB does not capture all the variables known to be associated with occult nodal metastasis in oral cancer, such as perineural invasion. Additionally, NCDB coding instructions are ambiguous and do not differentiate between tumor DOI and thickness. Although many authors use these terms synonymously, they are not the same [31]. It is therefore impossible to discern how thickness/DOI is measured in any given case in NCDB. To remain consistent with how data is collected in NCDB, we treated DOI and thickness interchangeably in our single institution data. This approach increases the variance and error of DOI used to develop and validate classifiers, which would be expected to decrease predictive performance. Future studies will aim to develop machine learning algorithms using higher quality data in which DOI is measured consistently and according to accepted standards, which will improve classifier performance [32].

Although NCDB uses rigorous quality-assurance measures, there

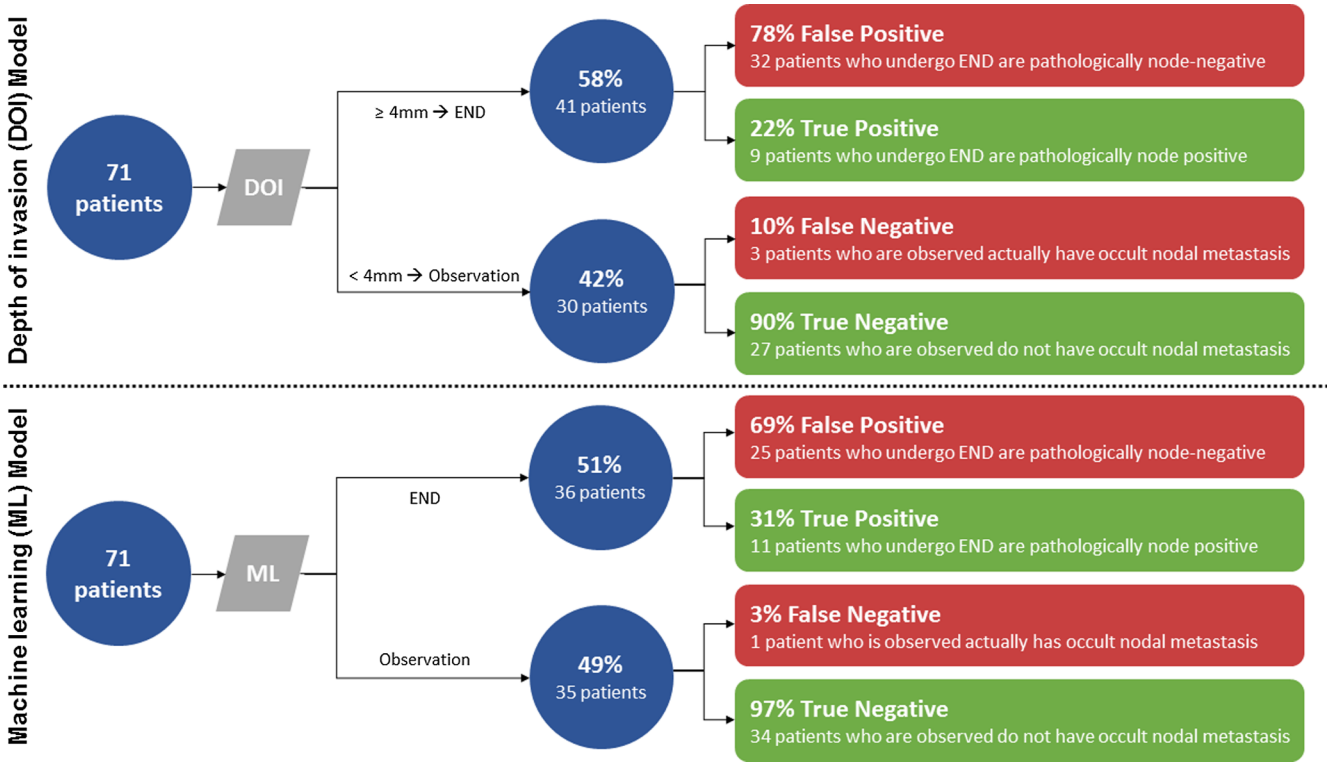

Fig. 2. Comparison of performance of depth of invasion and machine learning algorithms to predict pathologic lymph node metastasis in early oral squamous cell carcinoma using 71 patients treated at a single academic medical center.

remain inconsistencies within the data that preclude its use for developing highly accurate predictive algorithms. While NCDB is a valuable resource for clinical outcomes research and quality improvement efforts, it has never been validated for machine learning applications [33]. Finally, our institution is one of more than 1500 CoC-accredited cancer programs and our cases are included in the NCDB. It is likely that some of the 71 cases from our institution are also in NCDB. Therefore, our single institution data may not be strictly independent of the NCDB data used to train the models, though the effect of this is likely small because patients from our institution represent only a small fraction overall of patients in NCDB. This is one possible explanation for why machine learning models performed somewhat better on the single institution data (external validation) than on NCDB data (internal validation). However, the DOI model, which was not developed using NCDB data, also had better performance on the single institutional data than on the NCDB test data. Another explanation is that the variance of the single institution data may be less than that of the NCDB test data due to more consistent data abstraction and less variation in practice patterns. With fewer outlying data points, the machine learning models may be better able to predict pathologic nodal metastasis for the single institution test data. One of the major limitations of machine learning is that it is effectively a "black box." We can see the input data and the ultimate decision made by the algorithm, but how it makes decisions may be impossible to interpret [34]. Machine learning algorithms use complex non-linear calculations to maximize predictive performance and unlike statistics, machine learning does not generate measures of the effect size of individual variables. There are many ongoing efforts to better understand the inner workings of machine learning algorithms, but their lack of transparency remains a limitation [35].

The potential of machine learning to improve selection of those patients with clinically node negative OCSCC who should undergo END is clear. Improved training data is needed which includes the presence or absence of perineural invasion and consistent and accurate measurement of tumor DOI. With better training data, the performance of machine learning algorithms is likely to improve, which may allow greater numbers of patients to be safely observed. Additionally, to be clinically useful, further development of machine learning to predict pathologic nodal metastasis in early oral cancer should seek to make predictions based on data that is available prior to surgical extirpation of the primary tumor. This way, patients can undergo concurrent primary tumor extirpation and END, instead of requiring patients to undergo multiple surgeries.

Novel learning methods that can be applied to different types of data may be useful in expanding predictive algorithms for patients with early oral cancers. Machine learning is a rapidly evolving field and novel methods are always on the horizon to allow data scientists to gain new insights about complex data. Artificial neural networks are a class of machine learning algorithm that are loosely based on how biological nervous systems process information. They consist of multiple layers of interconnected nodes, with each node performing calculations based on its inputs and signaling output nodes in the subsequent layer. Complex artificial neural networks that consist of many layers are known as deep neural networks and are capable of solving the most complex problems in machine learning, including image recognition [20]. In head and neck oncology, deep neural networks have been used to identify nodal metastasis and to predict extranodal extension on pretreatment radiographic imaging [36]. Novel machine learning methods have also been applied to identify blood-based methylation profiles to differentiate patients with head and neck squamous cell carcinoma from healthy controls [37]. These sophisticated methods could, in the future, be applied to predicting the presence of occult nodal metastasis in early oral cancers using complex image or genomic data.

There are several obstacles to implementing machine learning to predict occult nodal metastasis in patients with early oral cancer. First, the algorithm must be easy and convenient for clinicians to use. This has been a major barrier to widespread adoption of other methods, including nomograms, that require multivariable input. The optimal way to interface with machine learning algorithms is directly through the electronic health record (EHR). However, existing EHRs are designed primarily for documentation and billing purposes, and while they contain enormous amounts of patient data, the majority of this data is unstructured and not directly usable by machine learning algorithms. Additionally, regulatory barriers and EHR lifecycles are such that it could take years for machine learning to be integrated into EHRs. Furthermore, EHR developers tend to incorporate new features that are driven by federally mandated requirements, and a clear return on investment would be needed to support deployment of new AI. Unfortunately, current fee-for-service payment models may actually deter health systems from adopting AI. Under fee-for-service, hospitals bill for each clinical activity and, in the case of an incorrect diagnosis, may perform and bill for follow up tests and care. Effectively, this means that AI that reduces incorrect diagnoses may actually reduce the revenue of the health systems expected to adopt it.

Finally, there are ethical questions about the clinical implementation of artificial intelligence that remain unanswered. First, development and clinical implementation of machine learning requires large amounts of patient data. How should the privacy of patient information be weighed against the need to leverage this data for medical innovation? Second, bias in the data used to train machine learning algorithms produces bias in the decisions of the algorithms themselves. How can we ensure that AI is generalizable and safe for all patients? Lastly, if medical decision-making shifts from physicians to intelligent machines, how will the relationship between otolaryngologists and their patients change? Along these same lines, who is responsible when patient harm is caused by an AI system?

Conclusion

We have developed and validated machine learning algorithms to predict pathologic lymph node metastasis in patients with clinically node-negative oral cancer. These algorithms used five clinical and pathologic variables to predict the presence of occult lymph node metastasis and were trained using 782 patients from NCDB. Machine learning consistently outperformed predictive models based on tumor DOI. Further development of machine learning using high quality multi-institutional data is needed to build algorithms that can be used clinically to ensure that patients with occult nodal disease are adequately treated while avoiding the cost and morbidity of neck dissection in patients without pathologic nodal disease.

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Conflict of interest statement

None declared.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.03.011.

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