A Novel Prognostic Assessment for Identifying Oral Pre-Malignant Lesions at High Risk for Progression to Cancer

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Background

Oral pre-malignant lesions (OPLs) are quite common, frequently asymptomatic, and generally detected during routine oral exams. While the transformation rate of pre-cancerous to cancerous lesions is less than 5% per year, most early stage cancers and OPLs are also asymptomatic, making identification more difficult. Most OPLs do not require aggressive treatment, however, preventing the transformation to malignancy is key to impacting oral cancer morbidity and mortality. Furthermore, the high mortality rate associated with oral cancer and the low transformation rate of OPLs creates a strong need for reliable assessments that more accurately identify lesions at high-risk of transformation, separating these lesions from those at lesser transformation risk. The standard of care for OPL risk assessment, dysplasia grading by histopathology, is impacted by intra- and inter-observer variation as well as significant overlap between grades, affecting its usefulness as a prognostic tool. The Straticyte™ oral prognostic assessment has been developed to meet these needs.

Methods

OPL biopsy samples from 150 cases with a follow-up history of up to 12 years were used. Immunohistochemistry for the biomarker S100A7 on tissue biopsy slides and tissue microarrays was performed at Mount Sinai Hospital in Toronto, Ontario, Canada. The slides were then digitally scanned on a Hamamatsu Nanozoomer-XR slide scanner and images were visualized and analyzed using Visiopharm VIS (version 5; Horsholm, Denmark). This project was approved by the Mount Sinai Hospital Research Ethics Board.

All statistical analyses and model building were conducted using the R package (version 3). Stepwise Cox Regression was used to select the parameters. A multivariate Cox Regression model was fitted to selected parameters and the C-index was used to assess the model. Estimated Log Relative-Hazards from the Cox model were referred to as risk scores and used in the cut-off selection stage to classify all cases into three risk groups: low, medium, and high. The Nelson-Aalen-Breslow estimate, used to calculate the baseline cancer-free survival curve, is combined with the calculated risk score to produce the expected cancer-free survival probability for each case. The Aalen-Link-Tsiatis estimate, used to estimate the variance of expected cancer-free survival probability, provided the 95% confidence interval (CI) of the cancer-free survival curve.

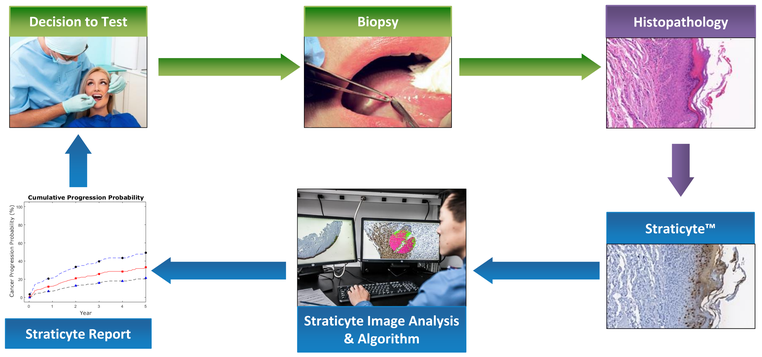

Figure 1. Straticyte can be easily incorporated into clinical practice as no additional tissue collection is needed.

Results

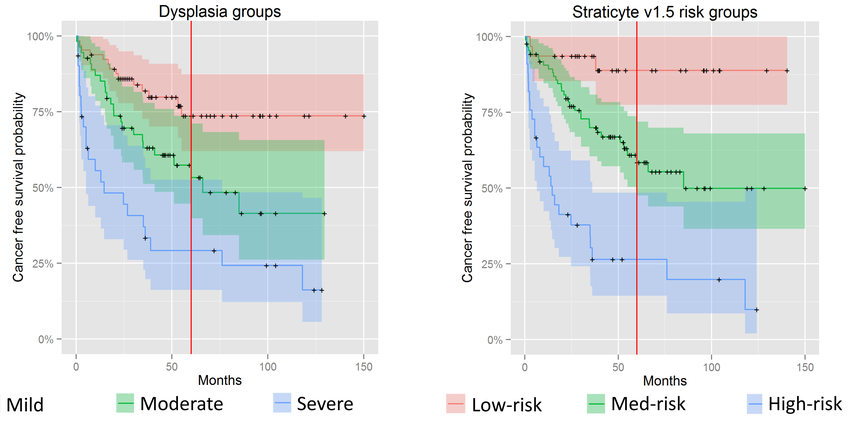

Figure 2. Dysplasia grading vs Straticyte. Straticyte better defines patient's risk for developing oral cancer by separating the lesions into risk categories with very little overlap.

		Total	Dysplasia Grading		
			Mild	Moderate	Severe
n		150	65	54	31
Cancer (% of cases with cancer)		60 (40%)	14 (22%)	24 (44%)	22 (71%)
Gender	Male	76	32	27	17
	Female	74	33	27	14
Site	Tongue	99	46	39	14
	Others	51	19	15	17
Age (year)	Mean	59	59	60	60
	Median	60	60	62	58
	Range	[32, 88]	[33, 88]	[37, 88]	[32, 83]
S100A7 Positivity Score	Mean	47	40	48	57
	Median	50	42	48	66
	Range	[1, 93]	[1, 87]	[1, 92]	[2, 93]

Table I. Patient characteristics.

Predictor	C-index	AUC
Dysplasia grading (mild, moderate, severe)	0.67	0.67
Straticyte (low, medium, high)	0.70	0.68

Dysplasia	Sensitivity	Specificity	PPV	NPV
Severe vs Moderate + Mild	37%	83%	76%	48%
Mild vs Moderate + Severe	75%	53%	69%	59%

Straticyte	Sensitivity	Specificity	PPV	NPV
High-risk vs Medium- + Low-risk	40%	85%	79%	50%
Low-risk vs Medium- + High-risk	96%	27%	65%	80%

Table II. Clinical Performance.

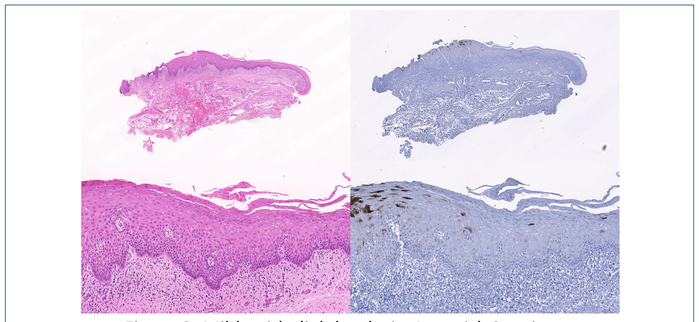

Figure 3. Mild epithelial dysplasia, Low-risk Straticyte.

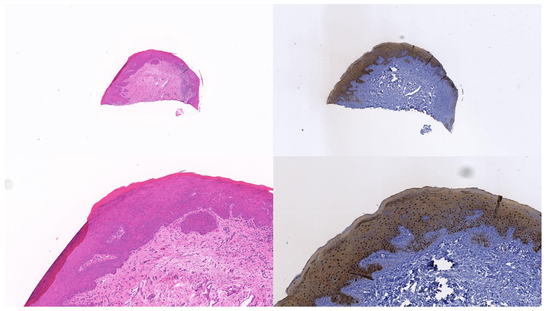

Figure 4. Mild epithelial dysplasia, Medium-risk Straticyte.

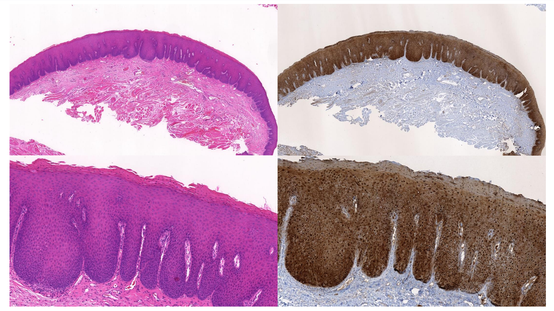

Figure 5. Mild epithelial dysplasia, High-risk Straticyte.

Conclusions

- Straticyte improves risk prediction beyond the current histopathologic grading and allows better prognostic assessment of oral dysplastic lesions
- Straticyte provides confidence to clinicians in monitoring the low-risk oral lesions over long intervals, while high-risk oral lesions can be surgically excised with greater confidence
- Straticyte should be regarded as a complement to conventional histopathology and can be easily incorporated into clinical practice