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TITLE: DigiTIL, a Computational Histomorphometric Predictor of Disease Recurrence and Overall Survival for p16-Positive Oropharyngeal Squamous Cell Carcinoma

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CONTRACTING ORGANIZATION: Emory University, Atlanta, GA

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14. ABSTRACT

In this project, we propose to develop DigiTIL, a novel computational tool for risk stratification of p16-positive oropharyngeal squamous cell carcinoma (OPSCC). The tumor microenvironment on digitized H&E images will be characterized using image-extracted features and predictors will be built using machine learning approaches. DigiTIL will be independently validated on a dataset from 7 institutions across the US and two well documented Clinical Trials (RTOG-5022 and RTOG-0129). The predictions made by DigiTIL will be compared against clinical/pathological variables and human estimations. Finally, DigiTIL will be used to identify possible population specific morphologic differences in the tissue phenotype of OPSCC, e.g., between African/Caucasian Americans and Veterans/Non-Veterans.

15. SUBJECT TERMS

None listed.

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1. INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) has become increasingly prevalent over the last two decades. Transcriptional activation of Human Papilloma Virus (HPV) is the most important cause of OPSCC throughout Canada and the United States, representing approximately 80% of all cases, with an estimated prevalence of 16,000 cases annually. Although these tumors usually have favorable outcomes, there is a subset of patients exposed to traditional treatment regimens that experience disease recurrence and even death. Consequently, there is an unmet need to develop accurate, validated biomarkers to predict which patients are at the highest risk of recurrence or death. Additionally, there are also several p16-positive (HPV-associated) OPSCCs which tend to respond to treatment, and these patients could potentially experience a successful de-escalation of therapy. We hypothesize that characterization of the tumor microenvironment (e.g., morphology and spatial patterns immune cells, cancerous cells, and multinucleation) can provide a more accurate prognostic assessment of disease outcome.

This project aims to develop DigiTIL, a novel computational tool for risk stratification of p16-positive OPSCC. The tumor microenvironment on digitized hematoxylin and eosin (H&E) images will be characterized using image-extracted features and predictors will be built using machine learning approaches. DigiTIL will be independently validated on a dataset from 6 institutions across the US and two well documented Clinical Trials (RTOG-5022 and RTOG-0129). The predictions made by DigiTIL will be compared against clinical/pathological variables and human estimations. Finally, DigiTIL will be used to identify possible population specific morphologic differences in the tissue phenotype of OPSCC, e.g., between African/Caucasian Americans and Veterans/Non-Veterans.

2. KEYWORDS

Oropharyngeal squamous cell carcinoma, human papillomavirus, histopathology, machine learning, computer-aided diagnosis, risk stratification

3. ACCOMPLISHMENTS

What were the major goals of the project?

Aim 1: Develop novel computational pathology markers for risk stratification of p16 positive oropharyngeal cancers

Aim 2: Validate the risk stratification model developed in Aim 1in a multi- institutional setting

Aim 3: Using the approaches developed in Aim 1, identify potential morphologic differences in the disease phenotype between (a) African- and Caucasian-Americans and (b) Veterans and non-Veterans

What was accomplished under these goals?

A. Major activities and specific objectives:

Aims and Tasks	Timeline (Months)	% Completion
Specific Aim 1: Developing novel computational pathology markers for risk stratification of p16 positive oropharyngeal cancers		
Major Task 1: Automated Digital Slide Quality Assessment	1-3	
IRB and HRPO approval	1-3	100%
Subtask 1: Digitize existing whole tissue slides of p16 OPSCC using a high-resolution digital slide scanner.	1-2	100%
Subtask 2: Generate a de-identified dataset using clinical features (pathologic grade, treatment, and clinical outcomes) of each sample.	1-2	100%

Subtask 3: Quality check of the digitized images.	3	100%
Major Task 2: Feature extraction from multiple fields of view to describe (a) tumor, (b) stroma, (c) TILs, and (c) intratumor heterogeneity	3-6	
Subtask 1: Automatic identification/segmentation of primitives: (a) tumor, (b) stroma, (c) TILs, and (c) intratumor heterogeneity.	3-4	100%
Subtask 2: Design and extraction of metrics that describe the tumor microenvironment from the detected primitives (interplay of TILs and cancerous cells, intra-tumoral heterogeneity, multinucleation index, etc.)	5-6	100%
Major Task 3: Rigorously evaluate reproducibility of DigiTIL features to pre- analytic sources of variation	7	
Subtask 1: Application of different algorithms and techniques for identifying the most discriminating features.	7	100%
Subtask 2: Evaluation of stability of features and selection of top features (with their respective coefficients).	7	100%
Major Task 4: Combine extracted image features to construct models for risk prediction	8-9	
Subtask 1: Computing a risk score for each patient by combining image-based metrics and their corresponding coefficients.	8	100%
Subtask 2: Applying different machine learning classification approaches to build a definitive model for prediction of patient outcome.	9	100%
Specific Aim 2: Validate the risk stratification model developed in Aim 1in a multi- institutional setting		
Major task 1: Independent validation of DigiTIL	10-15	
Subtask 1: Extraction of DigiTIL features from the validation cohorts.	10-12	100%
Subtask 2: Employing the DigiTIL trained model for predicting outcome in the validation cohorts.	12-14	100%
Subtask 3: Carry out a statistical analysis to validate the DigiTIL model in terms of its ability to predict recurrence and death.	15	100%
Major task 2: Validation of DigiTIL on completed randomized clinical trial datasets	16-21	
Subtask 1: Extraction of DigiTIL features from the clinical trial datasets.	16-18	100%
Subtask 2: Employing the DigiTIL trained model for predicting outcome in the clinical trial datasets.	18-20	100%
Subtask 3: Carry out a statistical analysis to validate the DigiTIL model in terms of its ability to predict recurrence and death.	21	50%
Major task 3: Validation against comparative strategies	21-27	
Subtask 1: Building alternative automatic models for prognostic prediction in p16 OPSCC.	21-23	80%

B. Significant results:

B.1. Risk stratification of OPSCC low-risk patients (overall stage I and light smokers)

In this study, we employed image processing and machine learning to develop OP-TIL, an imaging biomarker that quantitatively characterizes the spatial patterns of tumor-infiltrating lymphocytes (TILs) and surrounding nucleated cells in digitized hematoxylin and eosin (H&E) slides of HPV-associated (p16-positive) OPSCC patients. OP-TIL was trained to distinguish between the majority of low-risk patients (overall stage I [T1-T2/N0-N1/M0, AJCC 8th ed.] and never or light smokers) who will have a favorable disease-free survival (DFS) and are potential candidates for therapy de-escalation vs those patients who will have a poor DFS and for whom de-intensification would be inappropriate. We carried out the analysis on patients with less than 10 pack-year, matching the inclusion criteria of smoking history in NRG-HN002 and also analyzed patients with less than 30 pack-year, a risk cutoff suggested by other works. Cohort D1 (n = 94) was employed for feature discovery and model training while cohorts D2 (n = 51), D3 (n = 45), D4 (n = 66), D5 (n = 123), and D6 (n = 60) were used for independently evaluating the prognostic ability of OP-TIL in low-risk patients. Computer algorithms automatically identified 2 types of nuclei (TILs & non-TILs) and built clusters for each nucleus type based on proximity. Metrics related to density, intersection, and neighborhood were computed from these clusters. The top metrics, determined by least absolute shrinkage and selection operator (LASSO), were used to train a Cox regression model that assigned a risk of recurrence to each patient.

Figure 1 illustrates the Kaplan-Meier plots for OP-TIL applied to different subgroups of patients in the validation set (D2-D6) using DFS as endpoint. A total of 88 (36.6%) patients with less than 10 pack-year smoking history was classified as OP-TIL high risk (2-year DFS = 81.8%; 5-year DFS = 72.7%) and 152 (63.3%) patients as low risk (2-year DFS = 96.1%; 5-year DFS = 90.8%). Similarly, 120 (34.7%) patients with less than 30 pack-year smoking history were classified as high risk (2-year DFS = 82.5%; 5-year DFS = 74.2%) and 225 (65.2%) as low risk (2-year DFS = 94.2%; 5-year DFS = 88.4 %). Table 1 shows the results of univariate and multivariable survival analyses for OP-TIL and other clinical and pathological variables in the testing sets D2-D6 combined (≤30 pack-year smoking history). For univariable analysis, T/N/overall stages and age were dichotomized, while for multivariable they were used continuously. Multivariable survival analysis showed that OP-TIL was prognostic independent of age, T and N stages, treatment, and smoking history (number of pack-year) for DFS.

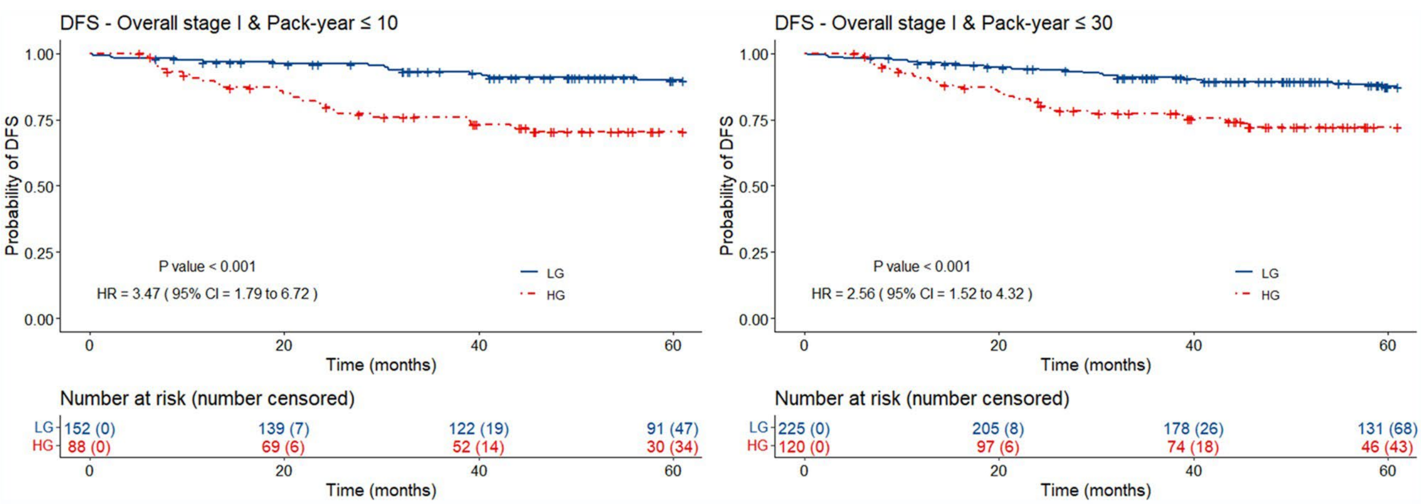

Figure 1. Kaplan-Meier plots for the DFS OP-TIL classifier applied to patients in the validation set (D2-D6) with overall stage I [AJCC 8th ed. (13)]. and with less than 30 pack-year of smoking history. Patients with less than 10- and 30 pack-year classified by OP-TIL as high risk (dashed line) are approximately 3 and 2 times, respectively, more likely to develop disease recurrence and/or die. AJCC = American Joint Committee on Cancer; CI = confidence interval; DFS = disease-free survival; HG = high-risk group; HR = hazard ratio; LG = low-risk group.

Table 1. Univariate and multivariable survival analyses for disease-free survival including all comers (≤30 pack-year smoking history) in the testing sets (D2-D6). AT = adjuvant therapy; CI = confidence interval; HR = hazard ratio.

	Univariate		**Multivariable**	
Variable	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**
Age >=55 vs. <55	0.0847	1.63 (0.96-2.75)	0.0010	1.05 (1.02-1.09)
Smoking (pack-year) >=10 vs. <10	0.5451	1.18 (0.68-2.03)	0.7564	1.00 (0.97-1.02)
T-stage T1 vs. T2	0.0012	2.52 (1.49-4.25)	0.0052	2.28 (1.27-4.27)
N-stage N0 vs. N1	0.8276	1.14 (0.38-3.41)	0.6119	1.32 (0.50-4.87)

Treatment Surgery + AT vs. others	0.8183	0.94 (0.55-1.61)	0.8133	1.07 (0.61-1.83)
OP-TIL Low- vs. high-risk	0.0002	2.56 (1.52-4.32)	0.0032	2.271.32-3.94)

B.2. Using OP-TIL for risk-stratifying patients with oral cavity squamous cell carcinoma

In this work, we evaluated the prognostic ability of OP-TIL when applied to samples of patients with oral cavity squamous cell carcinoma (OCSCC) obtained from The Cancer Genome Atlas (TCGA). Whole slide images (WSIs) from a cohort of 94 pts with HPV-associated OP-SCC were obtained from the Houston VA Medical Center (D1). Additionally, WSIs from 283 pts with OCSCC were obtained from TCGA. D1 was used to train a prognostic model while TCGA was used for independent validation. The median risk score on D1 was used as a threshold for stratifying patients on TCGA as either low or high risk. Survival analysis was then used to evaluate the performance of this approach.

Patients in TCGA defined as "low risk" (27%) based on spatial arrangement of TILs has significantly better OS than those identified as "high risk" (73%) with hazard ratio (HR)=2.02 (95% confidence interval (CI): 1.29-3.17, p<0.01) (Figure 2). Additionally, multivariable survival analysis showed that OP-TIL was prognostic independent of T/N stages, age, race, and sex (Table 2).

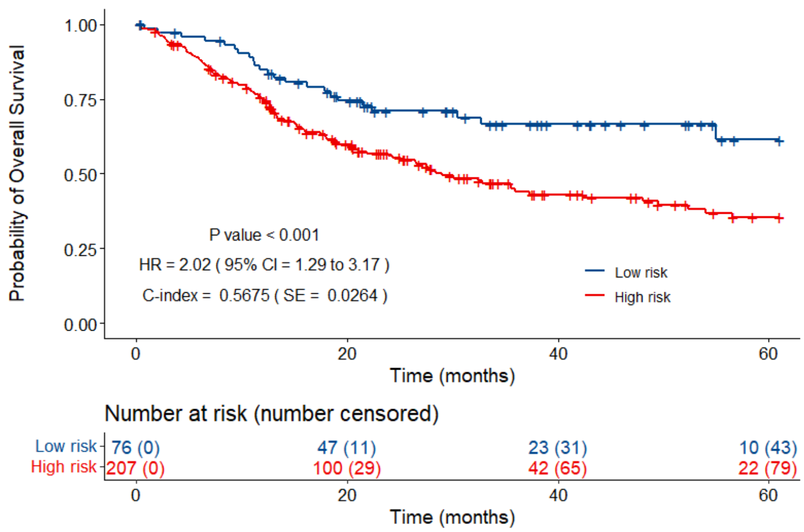

Figure 2. Kaplan-Meier plots for the DFS OP-TIL classifier applied to patients with OCSCC obtained from TCGA. CI = confidence interval; HR = hazard ratio

Table 2. Multivariable survival analysis for overall survival on TCGA. CI = confidence interval; HR = hazard ratio

Variable	HR (95% CI)	P-value
T-stage	1.32 (1.06-1.64)	0.0139
N-stage	1.54 (1.24-1.91)	0.0001
Age	1.03 (1.01-1.05)	0.0018
Sex (Male vs Female)	1.16 (0.74-1.82)	0.5141
Race (White vs Black/African American)	1.36 (0.66-2.78)	0.4059
TIL spatial arrangement (Low vs High risk)	1.75 (1.07-2.88)	0.0268

Although this method was designed and trained using HPV-associated OPSCC patients, it was able to differentiate between OCSCC patients at high and low risk of death, suggesting that this feature may be prognostic for squamous cell carcinoma in general. With more modeling and development of cutoffs specifically designed for OCSCC, this model may provide a risk classifier for use in routine clinical practice.

B.3. Combining multinucleation and TILs for risk-stratifying patients with HPV-associated OPSCC

Multinucleations as well as density of tumor-infiltrating lymphocytes (TILs) has been shown to be prognostic, but manual quantification is time-consuming and variation prone. In this study, we employed image processing and machine learning to develop a biomarker that quantifies multinucleations and the spatial arrangement of TILs in the tumor microenvironment of H&E images for risk stratification in HPV-associated OPSCC. Association between the integrated classifier (i.e., multinucletion and TILs) and (DFS) was explored on whole slide images from 968 patients across six independent institutional cohorts. Dataset S_TR (n=463) was used to identify the most prognostic features and train a survival random forest to compute risk of death. The model performance was independently evaluated in dataset S_VA (n=480). Results are shown in Figure 3.

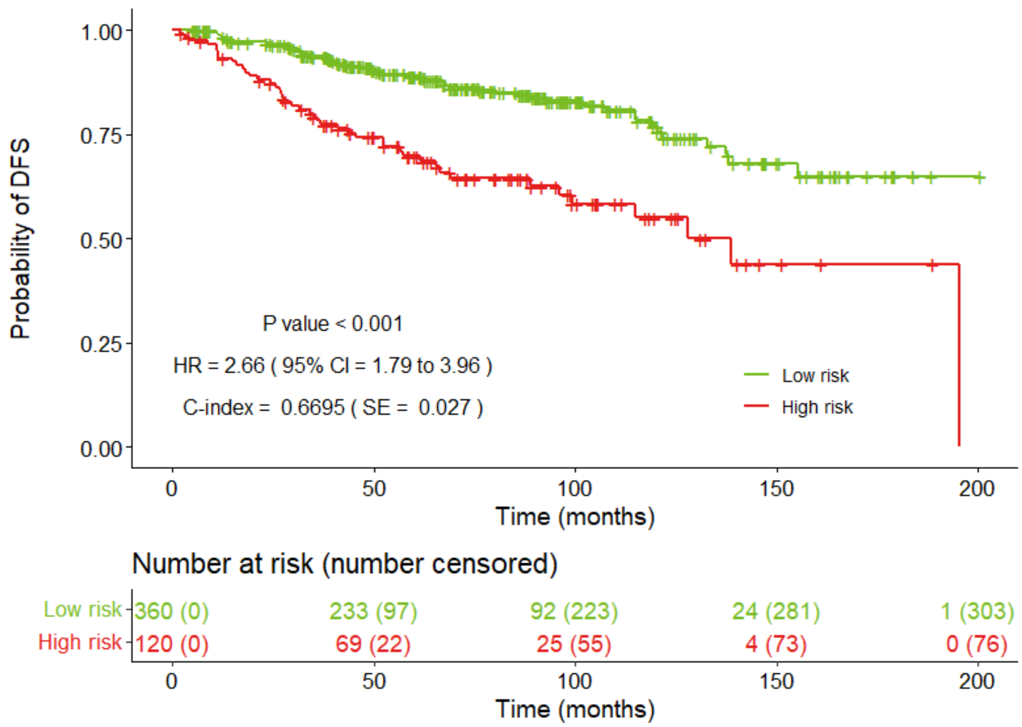

Figure 3. Kaplan-Meier plots for the DFS integrated classifier applied to patients with HPV-associated OPSCC from the validation cohort (S_VA). CI = confidence interval; HR = hazard ratio

This model will be validated in clinical trials RTOG 0129 and 0522 in a blind fashion. This means that the clinical information will be hidden from the authors and the predictions will be evaluated by external RTOG personnel. This single-shot blinded validation provides a more realistic evaluation of clinical utility than experiments in which the model can be repeatedly tuned to optimize performance on external datasets.

What opportunities for training and professional development has the project provided?

1) This project has facilitated a deeper understanding of the histomorphometric basis of head and neck cancer, and more specifically, oropharyngeal carcinoma. Leading this project has allowed me specifically to more fully engage and interact with both my mentor and co-mentor at a higher level of project direction. The collaboration has allowed me to become more independent in my research. It has also made me more thoughtful in terms of designing experimental strategies, planning for future grant opportunities, identifying publishing opportunities in higher impact journals and addressing peer-review concerns.
2) The work related to this project has been presented at different conferences, including ASCO 2021 and 2022; USCAP 2021, 2022, and 2023; SITC 2021; SPIE 2022 and 2023, which has provided a wide out-reach and discussion.

How were the results disseminated to communities of interest?

The major dissemination has been through presentation at conferences (e.g., ASCO, USCAP, SPIE). In addition, I was invited to present my research at the American Association for Dental, Oral, and Craniofacial Research Annual Meeting 2022. Also, I was invited to present at the 2nd International Conference of Smart Systems and Emerging Technologies, held in Quito, Ecuador. This research was also presented at a virtual seminar held in Bogotá, Colombia.

What do you plan to do during the next reporting period to accomplish the goals?

We have acquired the images from clinical trials RTOG 0522 and 0129. The images are being processed right now and an OP-TIL risk score is going to be computed for each patient. The evaluation of the performance of OP-TIL on these cohorts will be carried out blindly: our team does not have access to the clinical data of the patients, so the risk scores of all the patients will be sent to the RTOG team, who will run the corresponding statistical analysis.

Additionally, we are going to receive additional data from Houston VA, which is going to be used to develop population-specific models for Veterans and non-Veterans.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. Changes/Problems

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Delays were experienced because of the movement of the project from Case Western Reserve University to Emory University. However, during this process, part of the team was working the algorithmic part of the project. We anticipate remaining on track to meet the proposed milestones going forward.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS

- **Publications, conference papers, and presentations**

Journal publications:

– Wilde DC, Castro PD, Bera K, Lai S, Madabhushi A, **Corredor G**, Koyuncu C, Lewis JS, Lu C, Frederick MJ, Frederick AM, Haugen AE, Zevallos JP, Sturgis EM, Shi J, Huang AT, Hernandez DJ, Skinner HD, Kemnade JO, Yu W, Sikora AG, Sandulache VC. Oropharyngeal cancer outcomes correlate with p16 status, multinucleation and immune infiltration. Mod Pathol. 2022 Aug;35(8):1045–54.

– Wu Y, Koyuncu CF, Toro P, **Corredor G**, Feng Q, Buzzy C, Old M, Teknos T, Connelly ST, Jordan RC, Lang Kuhs KA, Lu C, Lewis JS, Madabhushi A. A machine learning model for separating epithelial and stromal regions in oral cavity squamous cell carcinomas using H&E-stained histology images: A multi-center, retrospective study. Oral Oncol. 2022 Aug;131:105942.

– **Corredor G**, Toro P, Koyuncu C, Lu C, Buzzy C, Bera K, Fu P, Mehrad M, Ely KA, Mokhtari M, Yang K, Chute D, Adelstein DJ, Thompson LDR, Bishop JA, Faraji F, Thorstad W, Castro P, Sandulache V, Koyfman SA, Lewis JS, Madabhushi A. An Imaging Biomarker of Tumor-Infiltrating Lymphocytes to Risk-Stratify Patients With HPV-Associated Oropharyngeal Cancer. JNCI J Natl Cancer Inst. 2022 Apr 11;114(4):609–17.

– Koyuncu CF, Lu C, Bera K, Zhang Z, Xu J, Toro P, **Corredor G**, Chute D, Fu P, Thorstad WL, Faraji F, Bishop JA, Mehrad M, Castro PD, Sikora AG, Thompson LDR, Chernock RD, Lang Kuhs KA, Luo J, Sandulache V, Adelstein DJ, Koyfman S, Lewis JS, Madabhushi A. Computerized tumor multinucleation index (MuNI) is prognostic in p16+ oropharyngeal carcinoma. J Clin Invest. 2021 Apr 15;131(8):e145488.

– Lu C, Koyuncu C, **Corredor G**, Prasanna P, Leo P, Wang X, Janowczyk A, Bera K, Lewis Jr. J, Velcheti V, Madabhushi A. Feature-driven local cell graph (FLocK): New computational pathology-based descriptors for prognosis of lung cancer and HPV status of oropharyngeal cancers. Med Image Anal. 2021 Feb;68:101903.

Books or other non-periodical, one-time publications:
Nothing to report

Other publications, conference papers and presentations:

– **Corredor G**, Koyuncu C, Aqeel A, Toro P, Nag R, Lu C, Yang K, Koyfman SA, Castro P, Frederick MJ, Sandulache V, Lewis Jr JS, Madabhushi A. Spatial Arrangement of Tumor-Infiltrating Lymphocytes Identifies Low-Risk Oral Cavity Squamous Cell Cancer Patients with Favorable Prognosis. In: Abstracts from USCAP 2023. New Orleans, LA, USA; 2023.

– Koyuncu C, **Corredor G**, Song B, Lu C, Nag R, Viswanathan V, Yang K, Koyfman SA, Chute DJ, Castro P, Frederick MJ, Sandulache V, Lewis Jr JS, Madabhushi A. Machine Learning Driven Index of Tumor Multinucleation on H&E Images is Prognostic for TCGA Oral Cavity Squamous Cell Carcinoma Patients and is Associated with Immune Cell Depletion. In: Abstracts from USCAP 2023. New Orleans, LA, USA; 2023.

– **Corredor G**, Koyuncu CF, Janowczyk A, Toro P, Azarianpour S, Lewis J, Madabhushi A. Spatial connectivity of tumor and associated cells (SpaCell): a novel computational pathology biomarker. In: Tomaszewski JE, Ward AD, editors. Medical Imaging 2023: Digital and Computational Pathology. San Diego, United States: SPIE; 2023. p. 32

– Koyuncu C, **Corredor G**, Lu C, Toro P, Fu P, Koyfman SA, Chute DJ, Adelstein DJ, Thorstad WL, Bishop JA, Faraji F, Lewis Jr JS, Madabhushi A. Combination of Computerized Patterns of Tumor Multinucleation and Tumor-Infiltrating Lymphocytes on H&E Images is Prognostic for Overall and Disease-Free Survival in p16 positive Oropharyngeal Squamous Cell Carcinoma Patients Including AJCC 8th Edition Stage Groups: A Multi-Site Study. In: Abstracts from USCAP 2021: Head and Neck Pathology (635-663). 2021.

- Nag R, **Corredor G**, Viswanathan V, Fu P, Lewis J, Wasman J, Teknos T, Patel M, Pan Q, Madabhushi A. 829 Spatial arrangement and density of tumor-infiltrating lymphocytes (TILs) predicts response to immunotherapy in head and neck squamous cell carcinoma patients. J Immunother Cancer. 2021 Nov;9(Suppl 2):A868–A868.

- **Website(s) or other Internet site(s)**

  Nothing to report

- **Technologies or techniques**

  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Germán Corredor*
Project Role:	*PI*
Researcher Identifier:	*0000-0003-3002-0937*
Nearest person month worked:	*9*
Contribution to Project:	*Dr. Corredor is serving as the contact PI for this project and is responsible for technical and fiscal administrative of the project. Dr. Corredor is working on the image analysis and algorithmic development in this project and is coordinating data acquisition and analysis across the multiple institutions. Working together with the other clinical collaborators on this project, he is developing a digital pathology-based companion prognostic tool for p16-positive oropharyngeal squamous cell carcinoma patients.*
Funding Support:	*W81XWH-21-1-0160, P50CA116201*

Name:	*Anant Madabhushi*
Project Role:	*Career guide*
Researcher Identifier:	*0000-0002-5741-0399*
Nearest person month worked:	*0.78*
Contribution to Project:	*Dr. Madabhushi is responsible for providing guidance in experimental approach, data interpretation, paper publication, and assist with acquiring patient samples needed for completion of the aims. Dr. Madabhushi also provides career development advice to the PI to ensure successful attainment of long-term career goals.*
Funding Support:	*R01CA249992-01A1, R01CA202752-01A1, R01CA208236-01A1, R01CA216579-01A1, R01CA220581-01A1, R01CA257612-01A1, 1U01CA239055-01,1U01CA248226-01, 1U54CA254566-01, 1R01HL15127701A1, R01HL15807101A1, 1R43EB028736-01, 1 C06 RR12463-01, IBX004121A, W81XWH-19-1-0668, W81XWH-15-1-0558, W81XWH-20-1-0851, W81XWH-18-1-0440, W81XWH-20-1-0595, W81XWH-18-1-0404, W81XWH-21-1-0345, W81XWH-21-1-0160.*

Name:	*James Lewis*
Project Role:	*Co-mentor*
Researcher Identifier:	*0000-0001-9002-1283*
Nearest person month worked:	*0.6*
Contribution to Project:	*Dr. Lewis is providing extensive expertise in the characterization of tumor cell anaplasia, multinucleation, and immune cell infiltration for prognosis in oropharyngeal squamous cell carcinoma patients, which are key features of this proposal.*
Funding Support:	*W81XWH-21-1-0160, R01CA220581-01A1, R01CA249992*

Name:	*Pingfu Fu*
Project Role:	*Biostatistician*
Researcher Identifier:	*0000-0002-2334-5218*
Nearest person month worked:	*0.6*
Contribution to Project:	*Dr. Fu has provided key biostatistical analysis support for this project. He will play a key role in the validation of the image-based predictor on datasets from clinical trials RTOG 0522 and 0129.*
Funding Support:	*W81XWH-21-1-0160, 1R01 CA220581-01A1, P50CA150964, R01 CA249992-01A1*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

During the reporting period, the PI has received additional funding from the Mayo Clinic Breast Cancer SPORE grant P50 CA116201 from the NIH for his research on breast cancer. The funding period is from November 2022 to August 2024. This additional funding will not overlap with the work proposed in this grant.

What other organizations were involved as partners?

Organization Name: Vanderbilt University Medical Center
Location of Organization: 1211 Medical Center Dr., Nashville, TN 37232
Partner's contribution to the project: Collaboration

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Non-applicable

QUAD CHARTS:

Non-applicable

9. APPENDICES: