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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: Case Western Reserve University
Cleveland, OH

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6. AUTHOR(S)

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13. SUPPLEMENTARY NOTES

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 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.

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:

Specific Aim 1: Developing novel computational pathology markers for risk stratification of p16 positive oropharyngeal cancers	**Timeline (Months)**	**% Completion**
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	80%
Subtask 2: Generate a de-identified dataset using clinical features (pathologic grade, treatment, and clinical outcomes) of each sample.	1-2	80%
Subtask 3: Quality check of the digitized images.	3	80%
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	60%
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	80%
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	80%
Subtask 2: Evaluation of stability of features and selection of top features (with their respective coefficients).	7	80%
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	70%
Subtask 2: Applying different machine learning classification approaches to build a definitive model for prediction of patient outcome.	9	70%
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	80%
Subtask 2: Employing the DigiTIL trained model for predicting outcome in the validation cohorts.	12-14	50%

B. Significant results:

In this project, we have employed image processing and machine learning to develop a biomarker that captures the spatial interplay between tumor-infiltrating lymphocytes (TILs) and surrounding cells across H&E images for risk stratification in p16-positive OPSCC (OP-TIL). Association between OP-TIL and overall (OS) and disease-free survival (DFS) has been explored on whole slide images from 985 patients across six independent institutional cohorts. Cohort D1 (n=94) has been used to identify the most prognostic features and train a Cox proportional hazards regression model to predict risk of recurrence and death. The model performance has been evaluated in the remaining cohorts, D2-D6 (n=891). OP-TIL was also evaluated individually in low-risk patients (age ≤55 years, non-smokers, or low T/N stages) and within separate overall stage groups I, II, and III (AJCC 8th ed.)

The trained models for OS and DFS identified the most prognostic features to be those related to spatial arrangement/co-localization features of TILs and non-TILs, to the grouping factor of TILs, and to the density of non-TILs. Low-risk patients tended to have more TILs intermixed with non-TILs, more heterogeneous TIL grouping factors, and less dense non-TIL populations compared to high-risk patients.

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-D5 combined. For univariable analysis, T/N/overall stages and age were dichotomized, while for multivariable they were used continuously. OP-TIL was prognostic for OS and DFS. T/N stages were also prognostic ($p<0.05$). Although age has been reported to be prognostic, in this experiment, it was statistically significant for both OS and DFS in multivariable analysis but not in univariable analysis, suggesting dependency on the choice of cutoff. Smoking has also been reported as prognostic, but, as captured in this study as “ever’ versus “never”, it was prognostic for OS only in univariable analysis, not for OS or for DFS in multivariable analysis.

Table 1. Univariable and multivariable survival analysis for OS and DFS in the testing sets (D2-D6). Two-sided p-values in bold are considered as statistically significant (≤0.05). When analyzing OP-TIL using three risk groups, two hazard ratios were generated: Low vs. High (top) and Low vs. Intermediate (bottom). Abbreviations: HR, Hazard Ratio; CI, 95% confidence interval.

Univariable analysis				
Variable	**Overall Survival**		**Disease-free Survival**	
	p-value	**HR (CI)**	**p-value**	**HR (CI)**
Age > 55 vs ≤ 55	0.0753	1.40 (0.98-1.99)	0.0773	1.31 (0.98-1.74)
Race Caucasian vs Non-Caucasian	0.8711	0.94 (0.45-1.97)	0.8786	1.05 (0.58-1.90)
Sex Male vs Female	0.9396	0.98 (0.55-1.75)	0.7286	1.09 (0.68-1.74)
Smoking Ever vs Never	**0.0078**	1.72 (1.20-2.48)	0.0834	1.32 (0.98-1.77)
Overall stage (AJCC 8th ed.) III/IV vs I/II	**<0.0001**	2.43 (1.56-3.78)	**<0.0001**	2.17 (1.51-3.12)
T-stage T4 vs T1/T2/T3	**<0.0001**	2.74 (1.68-4.48)	**<0.0001**	2.33 (1.56-3.47)
N-stage N3 vs N0/N1/N2	**0.0447**	1.82 (1.01-3.31)	**0.0029**	2.03 (1.07-3.85)
OP-TIL High vs Low risk	**<0.0001**	2.13 (1.48-3.06)	**<0.0001**	2.15 (1.62-2.85)
Multivariable analysis				
Variable	**Overall Survival**		**Disease-free Survival**	
	p-value	**HR (CI)**	**p-value**	**HR (CI)**
Age	**<0.0001**	1.05 (1.03-1.07)	**0.0001**	1.03 (1.02-1.05)
Race Caucasian vs Non-Caucasian	0.6301	0.85 (0.44-1.65)	0.4303	0.79 (0.45-1.41)
Sex Male vs Female	0.6143	0.86 (0.48-1.54)	0.9751	0.99 (0.61-1.62)
Smoking Ever vs Never	0.0941	1.43 (0.94-2.17)	0.5087	1.11 (0.81-1.53)
Overall stage (AJCC 8th ed.)	0.4712	0.84 (0.53-1.34)	0.2018	0.78 (0.53-1.14)
T-stage	**0.0067**	1.57 (1.13-2.18)	**0.0008**	1.58 (1.21-2.06)
N-stage	**0.0165**	1.45 (1.07-1.97)	**0.0030**	1.48 (1.14-1.91)
OP-TIL High risk vs Low risk	**0.0022**	1.82 (1.24-2.67)	**<0.0001**	1.86 (1.38-2.51)

Additionally, the prognostic ability of OP-TIL was tested on patients at low risk (≤55 years, non-smokers, and low N/T stages), which may require further stratification. For OS, OP-TIL was able to separate patients at low N/T stages (p=0.01) but was not able to separate younger (age≤55 years) and non-smoker patients (Figure 1). For DFS, OP-TIL was prognostic for all low risk patients (p<0.01) (Figure 2).

OP-TIL was also tested on patients at AJCC 8th edition overall stages I, II, and III. For OS, using two risk groups, OP-TIL was only prognostic for Stage I (p<0.01), and for DFS, OP-TIL was prognostic for Stages I and III (p<0.05) (Figure 3).

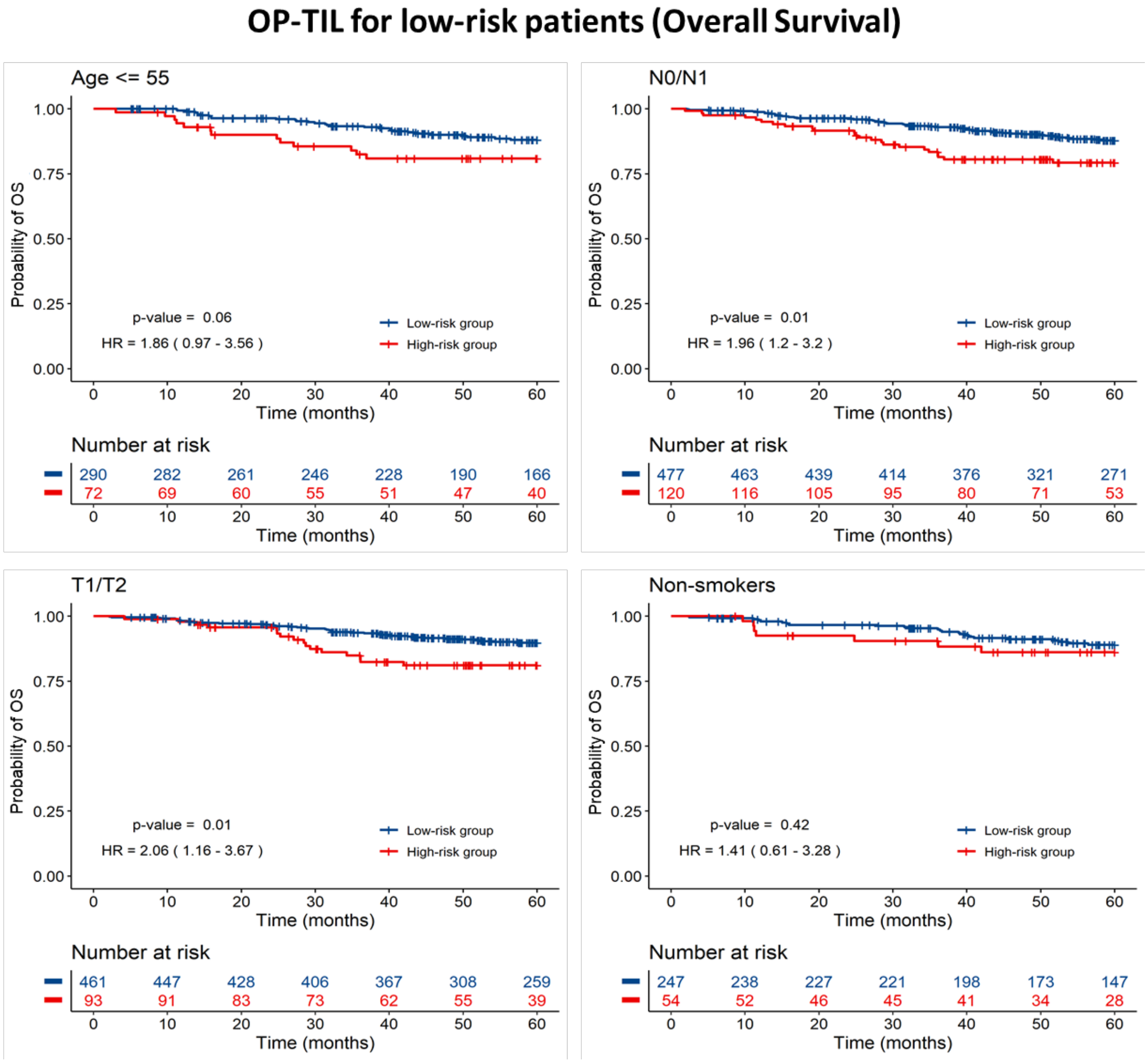

Figure 1. Kaplan–Meier plots for the OP-TIL model using OS as endpoint for patients younger than 55 years, at an early-stage of disease (N0/N1 and T1/T2), and for patients who were non-smokers.

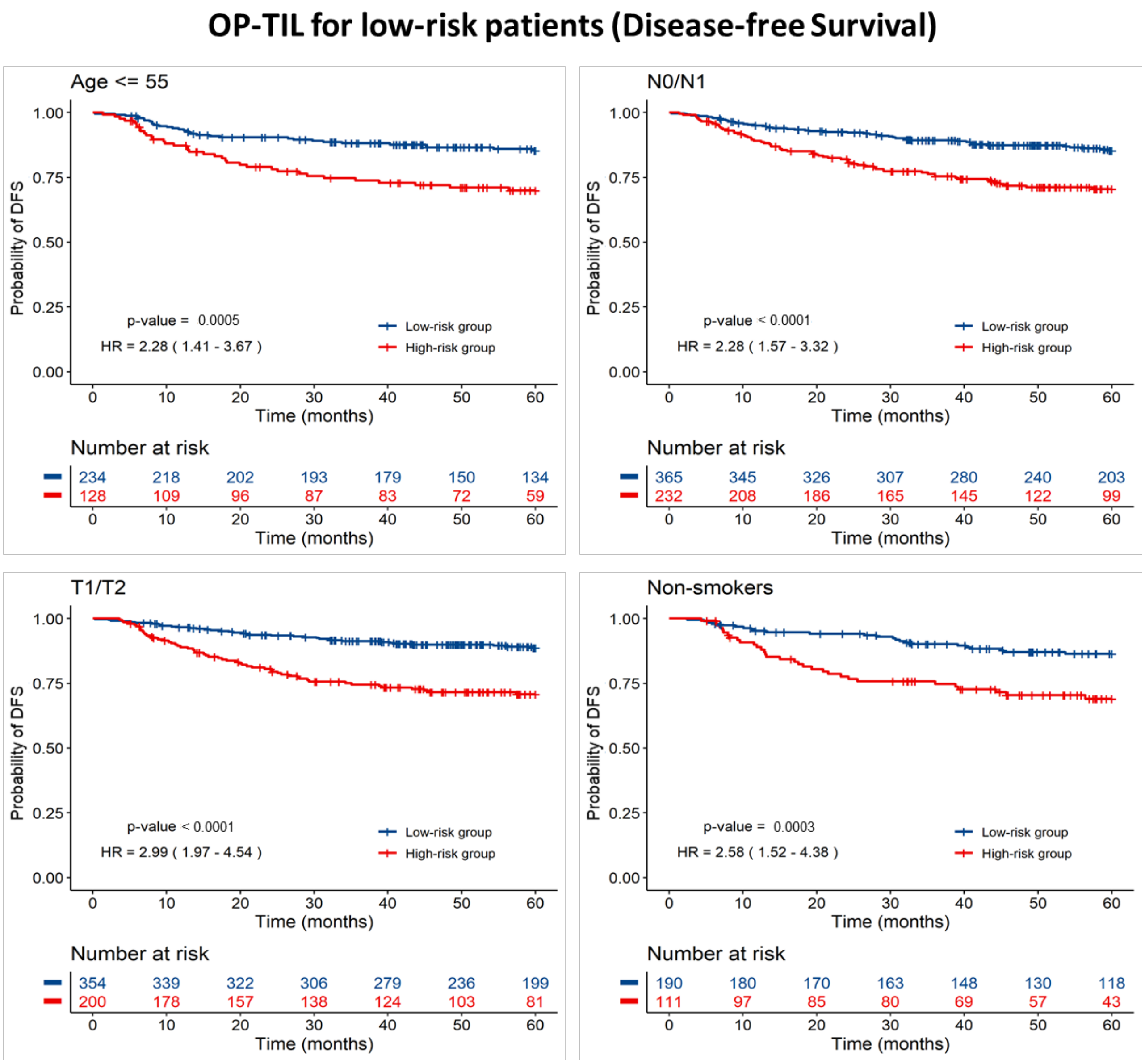

Figure 2. Kaplan–Meier plots for the OP-TIL model using DFS as endpoint for patients younger than 55 years, at an early-stage of disease (N0/N1 and T1/T2), and for patients who were non-smokers.

OP-TIL applied to patients by Overall Stage (AJCC 8th ed.)

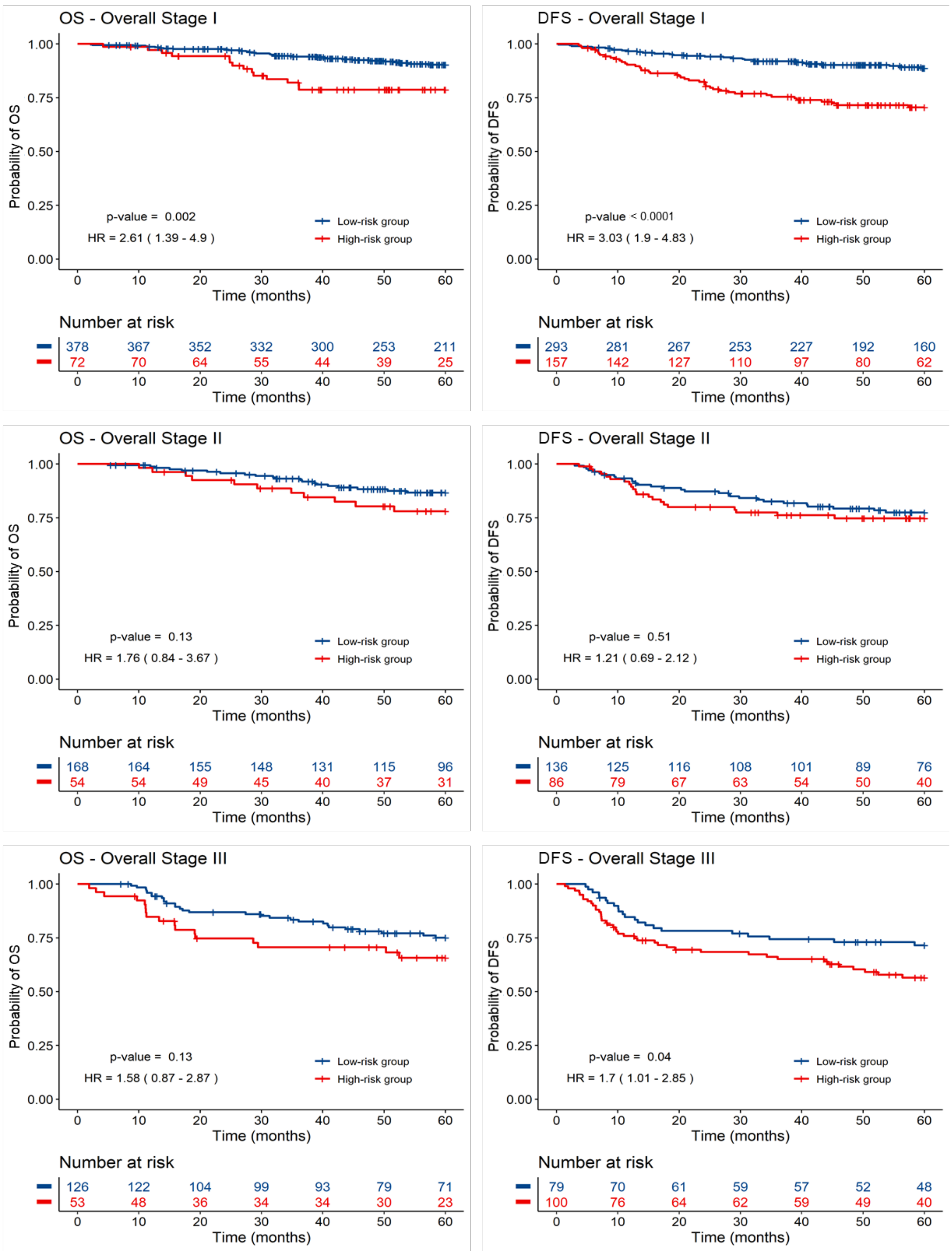

Figure 3. Kaplan–Meier plots for the OP-TIL models using OS and DFS as endpoints for patients at overall stages I, II, and III (AJCC 8th ed.), individually.

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 & 2022, USCAP 2021 & 2022, SITC 2021, SPIE 2022, and AADOCR 2022, 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. 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?

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

Due to delays in receiving IRB and HRPO approval, we experienced some delay at the beginning of the grant period, which impacted our ability to spend grant funds. However, during this process, we focused on the algorithmic part of the project that involves the use of computer vision and machine learning techniques for automatic identification of structures in tissue images and risk prediction.

As the IRB was finally approved, we were able to begin the analysis of a large set of images. We still expect to obtain some additional images (and respective clinical data) from our collaborators and from the clinical trials RTOG-0522 and 0129. Additionally, we are in the process of identifying a graduate student that will assist with achieving the established aims of project.

Finally, in the summer of 2022, I will be moving to Emory University in Atlanta GA, and will be submitting a request to transfer this grant to the new institution. We have been in contact with the team at Emory, so we expect a smooth transition without any major delays.

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:

- S Arabyarmohammadi, P Leo, VS Viswanathan, A Janowczyk, **G Corredor**, P Fu, H Meyerson,L Metheny, A Madabhushi. “Machine Learning to Predict Risk of Relapse Using Cytologic Image Markers in Patients With Acute Myeloid Leukemia Posthematopoietic Cell Transplantation”. JCO Clinical Cancer Informatics 6 (2022).

- S Azarianpour, **G Corredor**, K Bera, P Leo, P Fu, P Toro, A Joehlin-Price, M Mokhtari, H Mahdi, A Madabhushi. “Computational Image Features of Immune Architecture Is Associated with Clinical Benefit and Survival in Gynecological Cancers Across Treatment Modalities”. Journal for ImmunoTherapy for Cancer 10.3 (2022).

- **G Corredor**, R Ding, P Prasanna, C Barrera, P Zens, C Lu, P Velu, P Leo, N Beig, H Li, P Toro, S Berezowska, V Baxi, D Balli, M Belete, DL Rimm, V Velcheti, K Schalper, A Madabhushi “Image Analysis Reveals Molecularly Distinct Patterns of Tumor Infiltrating Lymphocytes in Non-Small Cell Lung Cancer associated with Clinical Outcome and Treatment Response”. Accepted for publication - npj Precision Oncology (2022).

- M Lopez de Rodas, V Nagineni, A Ravi, IJ Datar, M Mino-Kenudson, **G Corredor**, C Barrera, L Behlman, DL Rimm, R Herbst, A Madabhushi, J Riess, V Velcheti, M Hellmann, JF Gainor, KA Schalper. “Role of Tumor Infiltrating Lymphocytes and Spatial Immune Heterogeneity in sensitivity to PD-1 axis blockers in Non-small cell Lung Cancer”. Accepted for publication - Journal for ImmunoTherapy of Cancer (2022).

- D Wilde, P Castro, K Bera, S Lai, A Madabhushi, **G Corredor**, C Koyuncu, H Skinner, J Lewis, C Lu, M Frederick, A Frederick, A Haugen, J Zevallos, E Sturgis, J Shi, A Huang, D Hernandez, J Kemnade, W Yu, A Sikora, V Sandulache, “Oropharyngeal cancer outcomes correlate with p16 status, multinucleation and immune infiltration”. Modern Pathology (2022).

- **G Corredor**, P Toro, K Bera, D Rasmussen, V Viswanathan, C Buzzy, P Fu, LM Barton, E Stroberg, E Duval, HL Gilmore, S Mukhopadhyay, A Madabhushi. “Computational pathology reveals unique spatial patterns of immune response in H&E images from COVID-19 autopsies: preliminary findings”. Journal of Medical Imaging 8.S1 (2021).

- **G Corredor**, P Toro, C Koyuncu, C Lu, C Buzzy, K Bera, P Fu, M Mehrad, KA Ely, M Mokhtari, K Yang, D Chute, DJ Adelstein, LDR Thompson, JA Bishop, F Faraji, W Thorstad, P Castro, V Sandulache, SA Koyfman, JS Lewis, A Madabhushi. An Imaging Biomarker of Tumor-Infiltrating Lymphocytes to Risk-Stratify Patients With HPV-Associated Oropharyngeal Cancer. Journal of the National Cancer Institute (2021).

- CF Koyuncu, C Lu, K Bera, Z Zhang, J Xu, P Toro, **G Corredor**, D Chute, P Fu, WL Thorstad, F Faraji, JA Bishop, M Mehrad, PD Castro, AG Sikora, LDR Thompson, RD Chernock, KA Lang Kuhs, J Luo, V Sandulache, DJ Adelstein, S Koyfman, JS Lewis, A Madabhushi. "Computerized tumor multinucleation index (MuNI) is prognostic in p16+ oropharyngeal carcinoma".
  The Journal of Clinical Investigation 131.8 (2021).

Books or other non-periodical, one-time publications:

Nothing to report

Other publications, conference papers and presentations:

- A Aqeel, **G Corredor**, VS Viswanathan, C Chen, P Fu, Joseph Willis, A Madabhushi. "Computer extracted features related to tumor-infiltrating lymphocytes (TILs) are prognostic of progression-free survival in stage III colorectal cancer". SPIE Medical Imaging 2022 (San Diego - CA, USA), 2022

- **G Corredor**, R Ding, P Prasanna, C Barrera, P Toro, VS Viswanathan, P Zens, S Berezowska, V Baxi, D Balli, M Belete, V Velcheti, K Schalper, A Madabhushi. "Density patterns of tumor-infiltrating lymphocytes and association with objective response to nivolumab in patients with lung adenocarcinoma from CheckMate 057". American Society of Clinical Oncology Annual Meeting 2022 (Chicago – IL, USA)

- R Nag, H Li, **G Corredor**, P Toro, VS Viswanathan, P Fu, J Lewis, J Wasman, TN Teknos, M Patel, Q Pan, A Madabhushi. "Imaging biomarkers of collagen architecture on baseline biopsies are associated with response in head and neck squamous cell carcinoma patients treated with immunotherapy". American Society of Clinical Oncology Annual Meeting 2022 (Chicago – IL, USA)

- J Salguero, P Prasanna, **G Corredor**, A Cruz-Roa, D Becerra, E Romero. "Selecting Training Samples for Ovarian Cancer Classification via a Semi-supervised Clustering Approach". SPIE Medical Imaging 2022 (San Diego - CA, USA)

- R Nag, **G Corredor**, VS Viswanathan, P Fu, J Lewis, J Wasman, T Teknos, M Patel, Q Pan, A Madabhushi. "Spatial arrangement and density of tumor-infiltrating lymphocytes (TILs) predicts response to immunotherapy in head and neck squamous cell carcinoma patients". The Society for Immunotherapy of Cancer Annual Meeting 2021 (Washington D.C., USA)

- **G Corredor**, P Toro, C Lu, P Fu, S Vinayak, M Castillo-Garcia, LA Bernabe, C Castaneda, AJ Montero, A Harbhajanka, H Gilmore, A Madabhushi. "Computational features of tumor-infiltrating lymphocyte architecture of residual disease after chemotherapy on H&E images as prognostic of overall and disease-free survival for triple-negative breast cancer". American Society of Clinical Oncology Annual Meeting 2021 (Virtual meeting)

- C Koyuncu, **G Corredor**, C Lu, P Toro, P Fu, S Koyfman, DJ Chute, D Adelstein, W Thorstad, JA Bishop, F Faraji, JS Lewis, A Madabhushi. "Combination of Computerized Patterns of Tumor Multinucleation and Tumor-Infiltrating Lym-phocytes 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". United States and Canadian Academy of Pathology annual meeting 2021 (Virtual meeting)

- P Toro, **G Corredor**, K Bera, D Rasmussen, E Stroberg, L Barton, E Duval, H Gilmore, S Mukhopadhyay, A Madabhushi. "Characterizing Spatial Patterns of Immune Response in H&E Images from COVID-19 and H1N1 Autopsies Using Digital Pathology". United States and Canadian Academy of Pathology annual meeting 2021 (Virtual meeting)

- Y Chen, H Li, AR Janowczyk, C Koyuncu, P Toro, **G Corredor**, J Whitney, C Lu, S Ganesan, MD Feldman, P Fu, H Gilmore, A Harbhajanka, HN Sechrist, S Desai, V Parmar, A Madabhushi. "Computerized measurements of Nuclear Morphology Features, Mitosis Rate, and Tubule Formation from H&E Images Predicts Recurrence-Free Survival in ER+ & LN- Invasive Breast Cancer: A Multi-Institutional Study". United States and Canadian Academy of Pathology annual meeting 2021 (Virtual meeting)

- **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*

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?

Nothing to report

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: