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A Novel Classification of Small Bowel Adenocarcinoma Based on the Hidden Genome Classifier: A Multi-Institutional Study.

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INTRODUCTION: Small bowel adenocarcinoma (SBA) is a rare malignancy with poor prognosis. Data describing the clinical and pathologic characteristics of this disease are sparse, and few studies examine the genetic footprint of SBAs within the continuum of the gastrointestinal tract. METHODS: All patients with small bowel adenocarcinoma for whom primary tumor tissue was available from 1993 to 2021 at six institutions were included. A hidden genome classifier (HGC) was developed based on genomic features from 286 gastroesophageal cancers (foregut) and 286 colorectal cancers (hindgut) using targeted tumor sequencing. The SBA samples were run through the HGC to obtain the predicted probability of either foregut or hindgut lineage. For patients submitted to curative intent resection, overall survival (OS) was calculated from 90 days post resection until date of last follow up. Cox regression was used to examine factors associated with OS and to construct the multivariable model. RESULTS: Of a total of 243 patients with SBA, 60% were male. The most common anatomic locations were duodenum (53%), jejunum (28%), and ileum (12%). HGC prediction of foregut lineage was higher for duodenal (55%) and intestinal-type periampullary (64%) tumors, while prediction of hindgut lineage was higher for ileal (68%) and jejunal (54%) tumors. Patients were then divided into three HGC prediction groups based on the lowest-, highest-, and inter-quartile ranges: foregut (n=61), characterized by gene amplification of CDK12, CD3, EGFR, and KRAS and cytoband segmentation of chromosomes 8-p21.1 and 15-q26.3; hindgut (n=61), characterized by APC and KRAS mutations; and mixed-type (n=121) with elements of both. Among those undergoing curative-intent surgery (n=160), median OS was 73 months. On multivariable analysis, HGC prediction group (hindgut vs mixed-type, HR 3.22, 95%CI 1.54-6.73), age (HR 1.03, 95%CI 1.01-1.05) and positive lymph node status (HR 1.96, 95%CI 1.02-3.76) were associated with decreased survival (Table). Neither anatomic site nor the presence of other driver mutations was associated with survival. CONCLUSIONS: Small bowel adenocarcinomas display genomic heterogeneity. A novel hidden genome classifier that stratifies SBAs based on homology to foregut or hindgut genomic alterations may be superior to anatomic location for characterizing disease biology. Additional studies are needed to validate and further explore these findings.

Table. Multivariable Cox Regression Model for Overall Survival in Small Bowel Adenocarcinoma

Characteristic	Hazard Ratio (95% CI)	p-value
Prediction Group		
Mixed-Type	--	
Foregut	1.87 (0.97 – 3.60)	0.064
Hindgut	3.22 (1.54 – 6.73)	0.002
Age at Diagnosis (years)	1.03 (1.01 – 1.05)	0.031
Lymph Node Positive	1.96 (1.02 – 3.76)	0.042
Lymphovascular Invasion Positive	1.43 (0.77 – 2.68)	0.26

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Predicting Endoscopic Response Among Rectal Cancer Patients Considered for Watch and Wait: Validating a Highly Accurate Convolutional Neural Network Against Surgeon Performance.

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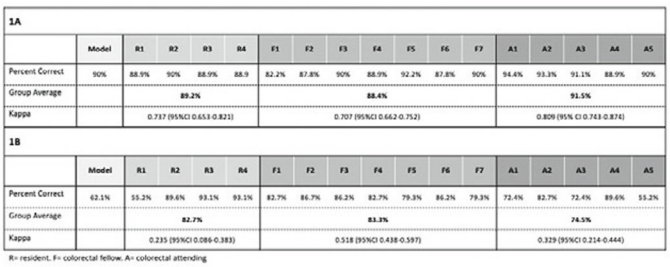
INTRODUCTION: The safety of a watch and wait (WW) approach for rectal cancer requires that surgeons correctly identify residual disease in post-treatment tumors and in the subtle mucosal changes that characterize local regrowth. Applying convolutional neural networks (CNNs) to endoscopic images may help providers interpret endoluminal response. To date, CNNs have shown only moderate accuracy in detecting residual tumor. We developed a highly accurate CNN model and validated its performance against surgeons at multiple stages of training. METHODS: Patients with stage II/III rectal cancer treated with total neoadjuvant therapy (TNT) from 2012-2020 were retrospectively reviewed and their endoscopic images collected before, during and after treatment. A CNN model was built to predict presence of tumor using ResNet-50 architecture. The model's diagnostic performance was analyzed during training and for two independent test sets. The main test set included images from patients with a) residual tumor after TNT or b) a sustained clinical complete response (cCR) for ≥2 years on WW. The second test set contained images from patients with a) local regrowth or b) a sustained cCR. Surgeons and surgical trainees at our institution completed an online survey of 119 deidentified images, with participants asked to determine whether each image contained tumor. Group averages and Fleiss' kappa were calculated by respondent experience level, with results compared to the CNN model's performance. RESULTS: A total of 2717 images from 288 patients were included, with 785 (28.9%) and 147 (5.4%) used in the main and local regrowth test sets. The CNN identified tumor with an accuracy of 95%, 91% and 78% for the training, main test and local regrowth test sets, respectively. Sixteen participants (4 residents, 7 colorectal fellows, 5 colorectal attendings) completed the survey. The model performed on par with respondents of all experience levels for the main test set (Table 1A). Interobserver agreement was good (k=0.707-0.809). All groups outperformed the model in identifying tumor from images of local regrowth, with interobserver agreement ranging from fair to moderate (k=0.235-0.518) (Table 1B). CONCLUSIONS: A highly accurate CNN matched the performance of experienced colorectal surgeons in identifying tumor from images of rectal cancers treated with TNT. Participants outperformed the model in detecting local regrowth, suggesting that improved performance requires larger image databases and incorporation of a time component into the analysis.

Table 1. CNN model performance compared to surgeons for Main (1A) and Local Regrowth (1B) test sets



1A

	Model	R1	R2	R3	R4	F1	F2	F3	F4	F5	F6	F7	A1	A2	A3	A4	A5
Percent Correct	90%	88.9%	90%	88.9%	88.9	82.2%	87.8%	90%	88.9%	92.2%	87.8%	90%	94.4%	93.3%	91.1%	88.9%	90%
Group Average		89.2%				88.4%							91.5%				
Kappa		0.737 (95%CI 0.653-0.821)				0.707 (95%CI 0.662-0.752)							0.809 (95% CI 0.743-0.874)				

1B

	Model	R1	R2	R3	R4	F1	F2	F3	F4	F5	F6	F7	A1	A2	A3	A4	A5
Percent Correct	62.1%	55.2%	89.6%	93.1%	93.1%	82.7%	86.7%	86.2%	82.7%	79.3%	86.2%	79.3%	72.4%	82.7%	72.4%	89.6%	55.2%
Group Average		82.7%				83.3%							74.5%				
Kappa		0.235 (95%CI 0.086-0.383)				0.518 (95%CI 0.438-0.597)							0.329 (95%CI 0.214-0.444)				

R= resident, F= colorectal fellow, A= colorectal attending

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Resistance to Chemo Radiation in Rectal Cancer Can Potentially be Predicted by Proteomic Analyses.

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INTRODUCTION: Chemoradiation prior to surgery in locally advanced rectal cancer results in reduced local recurrence rates and increased rates of