Additional Validation of a Deep Learning Algorithm to Quantify Histologic Features in Colorectal Carcinoma

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INTRODUCTION

- Several histologic features, such as grade, tumor budding, and stroma type, are well characterized as having prognostic impact in colorectal cancer (CRC)[1-2]
- Routine reporting of many of these features is challenging in practice owing to varying experience and limited reproducibility between pathologists
- We recently described[3] the development of a novel deep learning algorithm to quantify and evaluate several histologic features in colorectal cancer, which showed strong associations with adverse features derived from pathologist-based assessment

OBJECTIVES

- Apply this algorithm to a larger cohort of CRCs to further evaluate the association between algorithm-based assessment and expert pathologist assessment
- Evaluate the relationship between algorithm derived features, molecular alterations, and CD8 immunohistochemistry.

METHODS

- 6468 unique CRCs from 6 different cohorts were included in this study
- Pathologic data for each case was obtained from the final surgical pathology report, with a subset additionally having undergone expert pathologist review for the assessment of TB, PDC, and venous invasion
- For each case, a single representative tumour slide was digitized and evaluated by the algorithm (Figure 1)
- The associations between algorithm outputs and expert pathologist assessment, molecular alterations, and CD8 T-cell density were evaluated

RESULTS

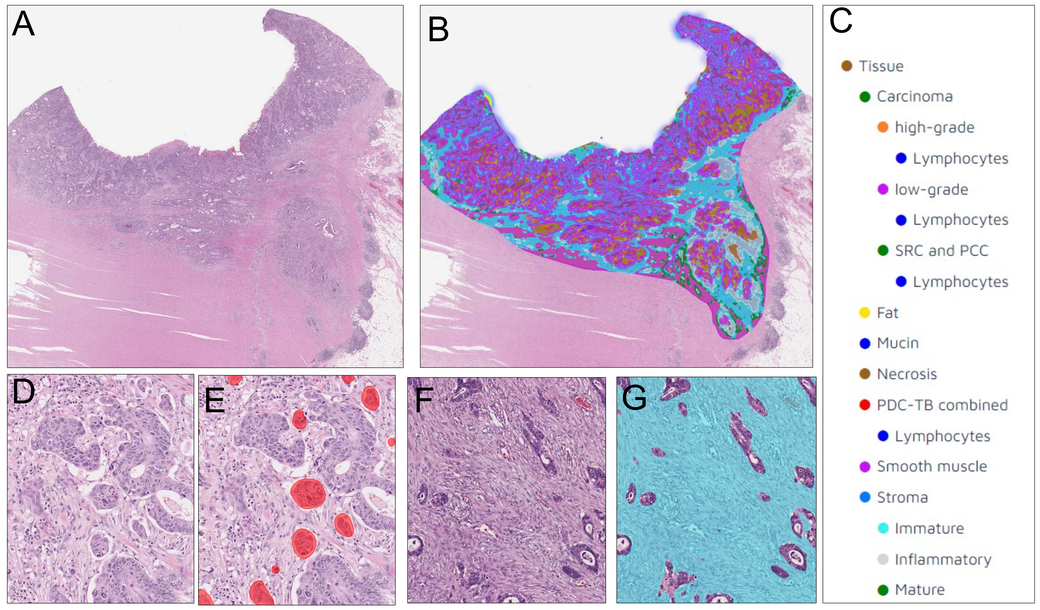

Figure 1. A,B. The algorithm evaluates the whole slide image and segments the carcinoma into 14 unique features and 1 object (outlined in panel C). Algorithm-based detection of TB/PDC (D,E) and immature stroma (F,G) was highly concordant with expert pathologist-based assessment.

Characteristic	Median Tumor: Stroma ratio (IQR)	Median %TB/PDC within tumor (IQR)	Median %High-grade (IQR)	Median %Immature stroma within tumor bed (IQR)	Median %Inflammatory stroma within tumor bed (IQR)	Median TILs per mm² of tumor (IQR)
Lymphatic invasion						
Absent (N=1070)	1.3 (1.0)	0.7 (1.3)	9.3 (16.3)	33.0 (17.6)	3.8 (6.4)	39.5 (62.6)
Present (N=762)	0.9 (0.9)	1.4 (2.9)	13.5 (23.2)	35.6 (19.1)	3.0 (5.1)	32.6 (39.9)
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Venous invasion						
Absent (N=4131)	1.2 (1.0)	0.9 (1.7)	11.5 (19.6)	37.4 (18.4)	2.8 (5.2)	32.4 (51.4)
Present (N=1136)	0.8 (0.8)	2.0 (3.7)	16.1 (26.8)	42.9 (21.4)	2.1 (3.6)	27.4 (34.2)
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Perineural invasion						
Absent (N=1196)	1.3 (1.0)	0.8 (1.4)	9.9 (17.8)	32.0 (17.7)	4.0 (6.4)	37.8 (57.1)
Present (N=330)	0.8 (0.7)	2.3 (3.9)	14.9 (22.4)	40.2 (20.7)	2.3 (3.9)	30.1 (33.7)
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 1. Association between algorithm derived features and adverse histologic features (as assessed by expert pathologist review)

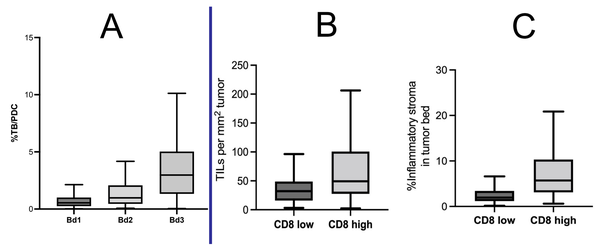

Figure 2. Algorithm-based assessment of TB/PDC (as a proportion of the total tumor area) was significantly associated with pathologist-based TB grade assessment (A). Algorithm-based assessment of TIL count (B) and area of inflammatory stroma (C; as a proportion of total tumour bed) were significantly associated with CD8 expression as assessed by immunohistochemistry

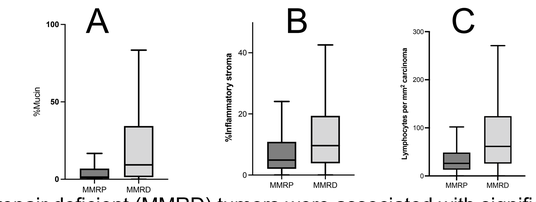

Figure 3. Mismatch repair deficient (MMRD) tumors were associated with significantly greater proportions of mucin (A) and inflammatory stroma (B), as well as higher numbers of tumor infiltrating lymphocytes (C), compared with mismatch repair proficient (MMRP) tumors

Characteristic	Median Tumor: Stroma ratio (IQR)	Median %TB/PDC within tumor (IQR)	Median %Mucin within tumor (IQR)	Median %High-grade (IQR)	Median %Necrosis (IQR)	Median %Immature stroma within tumor bed (IQR)	Median %Inflammatory stroma within tumor bed (IQR)	Median %Mature stroma within tumor bed (IQR)	Median TILs per mm² of tumor (IQR)
Mismatch repair status									
MMRP (N=4923)	1.0 (0.9)	1.2 (2.2)	1.4 (6.5)	11.3 (18.2)	4.2 (5.3)	39.7 (19.3)	2.3 (4.0)	2.4 (4.1)	26.8 (35.9)
MMRD (N=1375)	1.3 (1.1)	1.0 (1.7)	9.1 (33.4)	18.5 (38.9)	5.2 (8.25)	34.5 (18.4)	4.0 (6.6)	2.0 (3.3)	64.0 (104.0)
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
MMRP RAS/RAF mutation status									
KRAS/BRAF WT (N=2018)	1.1 (0.8)	1.1 (2.0)	1.1 (3.5)	11.3 (18.0)	4.5 (5.6)	39.5 (18.5)	2.2 (3.9)	2.3 (4.0)	24.5 (33.2)
KRAS Mutation (N=1312)	1.1 (0.9)	1.2 (2.4)	2.3 (12.6)	10.9 (17.0)	4.1 (5.1)	41.1 (18.8)	1.8 (3.3)	2.3 (3.8)	22.9 (34.2)
BRAF Mutation (N=223)	1.1 (0.9)	2.2 (4.5)	5.1 (25.6)	18.0 (31.6)	3.6 (6.3)	43.6 (20.2)	2.1 (4.2)	2.7 (3.6)	27.0 (43.3)
P-value	0.06	<0.001	<0.001	<0.001	0.01	<0.001	0.001	0.04	0.07
MMRD RAS/RAF mutation status									
KRAS/BRAF WT (N=411)	1.2 (1.0)	1.0 (1.6)	5.5 (27.8)	17.7 (36.8)	5.4 (8.4)	36.5 (17.1)	4.1 (6.5)	1.9 (3.4)	50.4 (92.9)
KRAS Mutation (N=220)	1.5 (1.1)	0.8 (1.3)	11.6 (32.0)	13.2 (27.0)	5.2 (9.3)	33.9 (18.8)	3.2 (5.5)	1.8 (2.2)	64.4 (91.7)
BRAF Mutation (N=350)	1.4 (1.2)	1.0 (2.2)	15.0 (35.6)	26.1 (43.0)	4.7 (8.3)	33.1 (19.3)	3.8 (5.9)	2.1 (4.1)	73.7 (122.4)
P-value	<0.001	0.06	<0.001	<0.001	0.4	0.003	0.01	0.02	0.005
MMRP CpG island methylation									
CIMP-Negative (N=1982)	1.1 (0.9)	1.2 (2.1)	1.7 (5.3)	11.8 (18.5)	4.1 (5.3)	40.9 (18.4)	1.8 (3.4)	2.0 (3.3)	23.0 (33.8)
CIMP-Positive (N=157)	1.0 (0.9)	2.2 (4.8)	6.3 (28.1)	18.0 (26.1)	3.4 (5.1)	45.4 (19.1)	2.1 (3.1)	2.6 (2.8)	24.8 (42.0)
P-value	0.2	<0.001	<0.001	<0.001	0.06	<0.001	0.9	0.003	0.09
MMRD CpG Island methylation									
CIMP-Negative (N=260)	1.3 (1.2)	1.0 (1.5)	6.9 (29.2)	15.6 (35.6)	5.2 (2.5)	35.6 (16.6)	3.7 (5.7)	1.7 (2.4)	58.8 (107.0)
CIMP-Positive (N=204)	1.3 (1.2)	1.5 (2.5)	10.6 (30.7)	28.8 (49.1)	4.9 (8.8)	36.0 (17.0)	3.3 (6.2)	1.5 (1.8)	78.6 (150.7)
P-value	0.6	<0.001	0.3	<0.001	0.7	0.9	0.4	0.3	0.006

Table 2. Association between algorithm derived features and underlying molecular alteration

CONCLUSIONS

- There was a strong association between algorithm-derived measures of adverse risk factors (TB/PDC, immature stroma) and pathologist-based assessment of histologic risk factors, as well as algorithm-based assessment of TILs and assessment based on quantitative CD8 immunohistochemistry
- Significant differences in algorithm-derived features were seen when the cohort was stratified by underlying molecular alteration (mismatch repair (MMR) status, BRAF mut, KRAS mut, and CpG island methylation)
- The findings further validate this quantitative segmentation algorithm, suggesting that it may prove a useful ancillary tool in the histologic and molecular assessment of CRC

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