Comparative analysis of tumor immune microenvironment in primary tumors vs metastatic tissue in microsatellite stable metastatic colorectal cancer

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INTRODUCTION

We previously demonstrated differences in responses to checkpoint inhibitors between liver and non-liver metastases (mets) in microsatellite stable (MSS) metastatic colorectal cancer (mCRC). Here, we investigate differences in the tumor microenvironment (TME) and mutational landscape of primary and metastatic CRC sites.

METHODS

The Tempus database was utilized to analyze de-identified cases of MSS mCRC which underwent Tempus xT testing. Tempus xT is a 648-gene NGS panel that detects somatic alterations and includes RNA sequencing. Analyzed tumors were divided into 4 categories based on the tissue sequenced: primary tumor (colon), and liver, lung, and peritoneal mets.

Demographics, genomic alterations, tumor mutational burden (TMB), PD-L1 expression, and proportions of B, T (CD4+, CD8+), NK cells, and macrophages were compared between all 4 categories. Gene expression patterns of different immune cells were used to predict their relative abundance within the tumor. Chi-squared/Fisher's exact tests or Kruskal-Wallis tests were used to assess statistical significance.

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SIGNIFICANCE

- The tumor microenvironment of lung metastatic tumors have a more favorable immune composition than that of liver and peritoneal mets, including increased CD8+ T cells and B cells and decreased macrophages.
- The differences in tumor microenvironment immune profile by site of metastatic disease cannot be attributed to PD-L1 positivity rate, TMB, or tumor neoantigen burden, which vary minimally across liver, lung, and peritoneal disease. Our findings suggest that MSS mCRC to the lung may potentially be more responsive to immunotherapy.

RESULTS

Table 1. Cohort Characteristics

Characteristic	Overall, N = 5,422[1]	Colon, N = 2,044[1]	Liver, N = 2,321[1]	Lung, N = 634[1]	Peritoneum, N = 423[1]	p-value[2]
Age at Diagnosis	59 (50, 68)	60 (50, 69)	59 (51, 68)	57 (49, 66)	60 (49, 69)	0.001
Unknown	476	89	221	122	44	
Gender						0.009
Male	3,116 (58%)	1,139 (56%)	1,368 (59%)	385 (61%)	224 (53%)	
Female	2,293 (42%)	901 (44%)	947 (41%)	246 (39%)	199 (47%)	
Unknown	13	4	6	3	0	
Race						0.11
White	2,370 (76%)	865 (74%)	1,040 (76%)	282 (79%)	183 (77%)	
Black or African American	445 (14%)	169 (15%)	195 (14%)	42 (12%)	39 (16%)	
Other	179 (5.7%)	74 (6.4%)	83 (6.1%)	14 (3.9%)	8 (3.4%)	
Asian	127 (4.1%)	57 (4.9%)	45 (3.3%)	18 (5.1%)	7 (3.0%)	
Unknown	2,301	879	958	278	186	
Ethnicity						<0.001
Not Hispanic or Latino	1,581 (86%)	564 (82%)	687 (87%)	210 (90%)	120 (93%)	
Hispanic or Latino	262 (14%)	124 (18%)	105 (13%)	24 (10%)	9 (7.0%)	
Unknown	3,579	1,356	1,529	400	294	
Primary Cancer Site						<0.001
Colon	4,327 (80%)	1,854 (91%)	1,734 (75%)	366 (58%)	373 (88%)	
Rectum	864 (16%)	99 (4.8%)	488 (21%)	241 (38%)	36 (8.5%)	
Rectosigmoid junction	231 (4.3%)	91 (4.5%)	99 (4.3%)	27 (4.3%)	14 (3.3%)	

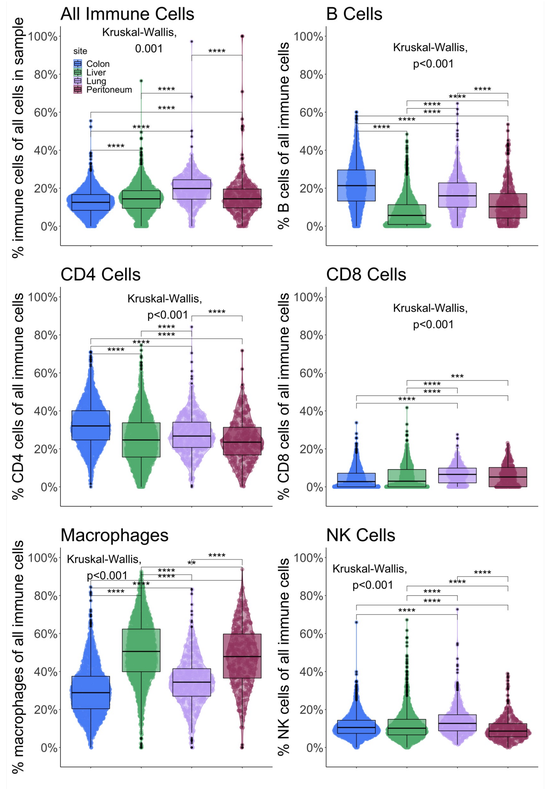

Figure 1. Lung mets exhibited a higher percentage of B cells and lower percentage of macrophages than liver and peritoneum (p< 0.001), similar to primary tumors. CD4+ T cells were highest in primary tumors, whereas CD8+ T cells were highest in lung mets (p < 0.001).

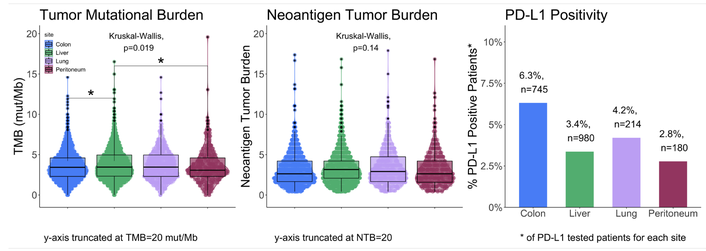

Figure 2. Median TMB and PD-L1 expressions had small differences across sites that were statistically significant

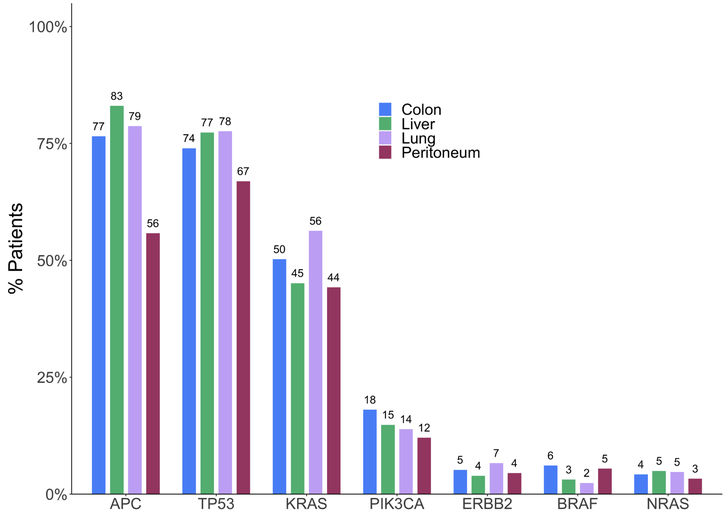

Figure 3. Genomic profiles from 4,345 unique mCRC patients were analyzed. *KRAS* mutations were more frequent in lung mets.