Original Article

Survival in metastatic microsatellite-stable colorectal cancer correlated with tumor mutation burden and mutations identified by next-generation sequencing

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Background: Next-generation sequencing (NGS) identifies mutations and molecular abnormalities within tumors, including tumor mutation burden (TMB). If a solid tumor has high TMB, immune checkpoint inhibitors (ICIs) are approved as an option for treatment. Studies have been inconclusive regarding how effective ICI are in treating patients with colorectal cancer (CRC), and it is unclear if high TMB is a good prognostic marker for CRC. We collected data from NGS of CRC and correlated survival to both TMB and mutations of interest, as well as investigated the efficacy of ICI.

Methods: This was a retrospective cohort analysis at a single institution, collecting NGS data from January 2018 to December 2020 in patients with CRC who were microsatellite-stable (MSS), n=161. Demographics, clinical data, and results from NGS were collected, and a survival analysis looking at TMB and selected mutations of interest was performed. Patients who were treated with ICI were assessed in a descriptive subset analysis.

Results: Patients with CRC who were MSS and had high TMB trended towards worse survival [hazard ratio (HR) =1.38] though the result was not significant (P=0.28). Survival was significantly worse in patients with a *KRAS* mutation (HR =1.71, P=0.04) and/or a *CDKN2A* mutation (HR =4.45, P<0.001). In this study population, 12 patients with high TMB had treatment with ICI, with nine of these patients having shorter progression-free survival (PFS) between 0.7 and 4.1 months, and three patients having longer PFS of 26.3, 24.7, and 13.2 months.

Conclusions: High TMB in MSS CRC did not show statistical difference in outcome. Mutations in *KRAS* and/or *CDKN2A* correlated with worse prognosis. Some patients with MSS CRC and high TMB responded to ICI, though there is a need to identify a better biomarker to predict which patients will have a good response to ICI therapy.

Keywords: Colorectal cancer (CRC); immunotherapy; next-generation sequencing (NGS); tumor mutation burden (TMB)

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Introduction

Colorectal cancer (CRC) has a high incidence in the United States, with estimated 151,030 cases in 2022 (1). It causes the second highest number of cancer-related deaths in U.S., with 52,580 deaths per year (1). Despite widespread adoption of effective screening and therapy advancements, 21% of patients diagnosed with CRC are still found with distant metastasis at time of diagnosis and patients with metastatic disease have a 5-year survival rate of only 14% (1-4).

Within CRC there is significant molecular variability across patients, and alterations in *HER2*, *KRAS*, *NRAS*, and *BRAF* have ramifications in regard to treatment options. Next-generation sequencing (NGS) can readily identify actionable molecular abnormalities. One such tumor characteristic is microsatellite-instability (MSI), which reflects the presence of uncorrected short repetitive sequences in the DNA of tumors with deficient mismatch repair mechanisms (5). Such tumors may be identified by NGS [MSI high (MSI-H)] or by immunohistochemistry showing the loss of one or more proteins involved in DNA mismatch repair (dMMR). MSI-H tumors have a large burden of mutations, some of which affect coding regions, leading to higher numbers of immunostimulatory neoantigens (6). Central to treatment of these tumors is the use of immune checkpoint inhibitors (ICIs), which have shown clinical efficacy in treatment of patients with MSI-H or dMMR metastatic CRC, thereby earning Food and Drug Administration (FDA) approval for first-line treatment of metastatic CRC in 2020 (7). Beyond generalized markers for mutations, NGS has allowed for research regarding specific mutations, and previous studies have investigated the frequency of several common and uncommon genetic mutations (8,9).

Another promising biomarker in solid tumors is tumor mutation burden (TMB), which is the number of nonsynonymous mutations in cancer cells, resulting from DNA damage, mismatch repair deficiencies, or other carcinogenesis pathways. Similar to MSI-H, the increased number of neoantigens is thought to lead to increased activation of one's immune system. Treatment of high TMB solid tumors with an ICI was approved after the phase 2 trial KEYNOTE-158, which showed a higher objective response to treatment to ICI monotherapy in high TMB compared to non-high TMB solid tumor patients, though notably there were no patients with CRC included in this trial (10). Some studies suggest that TMB could be a valuable prognostic marker in CRC and could predict response to ICI therapy (11), though other studies have suggested that identifying specific mutations is more important than measuring the quantity of mutations (12), and a recent study looking at microsatellite-stable (MSS) CRC did not find a significant survival difference between patients with high or low TMB (13).

Patients with MSI-H CRC have been shown to have better outcomes and to respond to immunotherapy. Though there are data suggesting patients with high TMB have better outcomes, more research is needed, and there is often overlap between patients with MSI-H and high TMB tumors. At our institution, we have 4 years of data from patients who underwent NGS of their tumors. We conducted this study to explore the correlation of tumors

Highlight box

Key findings

- High tumor mutation burden (TMB) did not correlate with improved survival in patients with metastatic microsatellite-stable (MSS) colorectal cancer (CRC).
- CRC with mutations in *KRAS* and/or *CDKN2A* correlated with worse outcome.
- Treatment with immune checkpoint inhibitors (ICIs) was effective in some patients, though there is a need to identify a better biomarker to predict response.

What is known and what is new?

- High TMB has been previously described as a potentially positive prognostic marker, and is commonly used when determining eligibility of ICI therapy.
- To investigate this further, this study correlated survival to level of TMB and mutations identified by next-generation sequencing, and performed a descriptive subset analysis of patients with metastatic MSS CRC treated with ICIs to assess response to immunotherapy.

What is the implication, and what should change now?

- When determining the next line of therapy in patients with CRC, oncologists should take note of the potential poor response to ICIs in patients with metastatic CRC with high TMB without other unique molecular signatures.

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with high TMB to survival outcomes among patients with MSS CRC. Additionally, we aimed to correlate other validated mutations in the colorectal carcinogenesis pathway to survival outcome. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-809/rc).

Methods

We conducted a retrospective cohort analysis of patients at Oregon Health and Science University (OHSU). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the OHSU Institutional Review Board (No. STUDY00023541). Informed consent was not determined to be necessary by the IRB and was waived as this was a retrospective cohort study of clinical data. For this analysis, records of patients between 18 and 89 years old with CRC who underwent NGS at OHSU between January 2018 and December 2020 were identified from Knight Diagnostic Laboratories and the Department of Pathology. Corresponding electronic medical records (EMRs) were then reviewed by at least two reviewers (N.T., R.T., L.S.). Diagnosis of CRC and treatment at OHSU were also verified in EMRs, and any duplicates were removed from analysis. Patients who were identified as MSI-H were excluded from the analysis, and patients who did not have metastatic disease at the time of NGS were excluded from the analysis.

All tumors were sequenced at the Knight Diagnostic Laboratories using the GeneTrails® Comprehensive Solid Tumor Panel (0.61 megabases), which detects mutations and copy number alterations across 225 cancer-related genes. Included in this panel are 227 short tandem repeat sequences; the number of repeats with length alterations is used to assign MSI status. TMB is determined based on the number of coding region alterations judged to be somatic based on variant allele fraction and published germline frequency in the general population.

For each patient, sociodemographic factors, location of primary tumor, cancer staging at original diagnosis and at time of NGS, treatment details, and tumor characteristics were recorded from the EMR. Additionally, dates of cancer diagnosis, NGS results, disease progression, and death were all recorded. Data from the NGS including the comprehensive list of mutations and molecular abnormalities, their clinical relevance in CRC, and level of TMB were collected. The prevalence of each mutation was recorded. Genomic alterations were selected for statistical analysis if they were of interest prior to data collection, or if their prevalence was greater than 5%. The genes selected based on these parameters were *APC*, *KRAS*, *SMAD4*, *PIK3CA*, *MYC*, *FBXW7*, *ARID1A*, *PIK3R1*, *AMER1*, *DDX11*, *BRAF*, *CKDN2A*, *PTEN*, *ATM*, *NRAS*, *RB1*, *HER2*, *STK11*, *POLE*, *CD274* (*PD-L1*), *KEAP1*, *BRCA1*, *BRCA2*. The endpoint of this data was survival time and was defined as the date of metastasis up until the date of death or until the final data collection cut-off date (December 1st, 2021).

Statistical analysis

The Kaplan-Meier method was used to calculate survival estimates and the log-rank test was used to compare the survival curves. The univariate Cox proportional hazards regression was applied to study the association between the selected tumor markers (TMB and mutations) and the risk of death. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were reported for each fitted model. All the statistical analyses were conducted using R version 4.1.1 (R Foundation). Tests of statistical significance were determined using two-tailed tests, and a $P \leq 0.05$ was considered statistically significant. Patients who had immunotherapy treatment from this group had a subset descriptive analysis assessing treatment duration, treatment regimen, and outcome of treatment.

Results

A total of 312 patient records were obtained initially, and after the designated exclusion criteria were applied, including exclusion of 8 patients who were MSI-H, a total of 161 patients were included in the final analysis (*Figure 1*). Among the 161 patients, the mean age was 57.8 years old, the majority were Caucasian, and 38.5% were female (*Table 1*). The most common tumor location was left colon (65, 40.9%), followed by rectum (45, 28.3%) and right colon (38, 23.9%). Most patients were stage IV at initial diagnosis (72.0%) while others developed metachronous metastasis, as all patients were metastatic at the time of NGS in the final dataset. The most common mutations were *TP53* mutations (132, 82.0%), *APC* mutations (129, 80.1%), and *KRAS* mutations (70, 43.5%), as noted in *Table 2*. *BRAF* mutations were represented in 9 (5.6%), *HER2* in 7 (4.3%), *POLE* in 3 (1.9%), and *CD274* (*PD-L1*) in 2 (1.2%). Among these patients, all of whom were MSS, there were 35 patients (21.7%) with a TMB high score (10 or higher), and 126 patients (78.3%) with a TMB less

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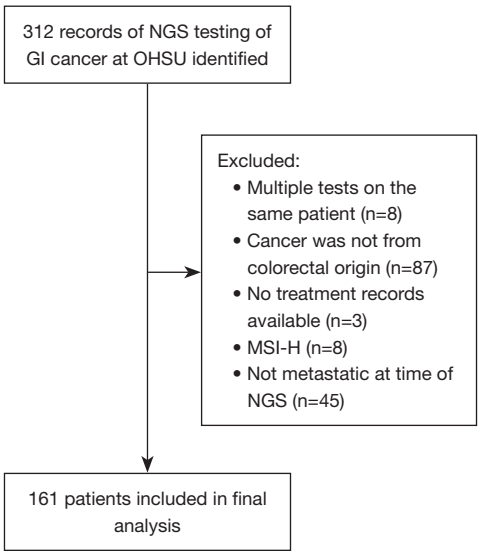

Figure 1 CONSORT diagram of patients included in the study analysis. If multiple tests were performed on the same patient, the test closest in date to the diagnosis of metastatic disease was selected. NGS, next-generation sequencing; GI, gastrointestinal; OHSU, Oregon Health & Science University; MSI-H, microsatellite-instability high.

Table 1 Patient demographics and tumor characteristics

Characteristics	Value (n=161)
Age (years), mean	57.8
Sex, n (%)	
Male	99 (61.5)
Female	62 (38.5)
Race, n/N (%) or n	
White	127/141 (90.1)
American Indian/Alaska Native	2/141 (1.4)
Asian	6/141 (4.3)
Black	4/141 (2.8)
Pacific Islander	2/141 (1.4)
Not known	20
Location of tumor, n/N (%) or n	
Right colon	38/159 (23.9)
Transverse colon	11/159 (6.9)
Left colon	65/159 (40.9)
Rectum	45/159 (28.3)
Unknown	2
Stage at diagnosis, n/N (%) or n	
Stage I	6/150 (4.0)
Stage II	11/150 (7.3)
Stage III	25/150 (16.7)
Stage IV	108/150 (72.0)
Unknown	11
TMB status, n (%)	
TMB 10 or higher (TMB high)	35 (21.7)
TMB <10	126 (78.3)
Immunotherapy, n/N (%) or n	
Treated with immunotherapy	12/147 (8.2)
No immunotherapy treatment	135/147 (91.8)
Unknown	14

TMB, tumor mutation burden.

than 10. Median overall survival of the entire cohort was 43.3 months [95% CI: 36.1–not reported (NR)].

In examining overall survival, patients with high TMB were found to trend towards worse survival, with a median of 28.5 months (95% CI: 22.2–NR) compared to 45.2 months (95% CI: 36.1–NR) in those without high TMB (HR =1.38, P=0.286) (*Figure 2*). Similar correlation analysis demonstrated worse survival in patients with *KRAS* and/or *CDKN2A* mutant tumors (*Table 2*). Similar survival was observed in patients with and without *TP53*, *APC*, *BRAF*, *HER2*, or *POLE* mutations (*Table 2*). Specifically, patients with *KRAS* mutation were found to have statistically worse survival with median 36.1 months (95% CI: 24.0–NR) compared to NR (95% CI: 38.1–NR) months in those without the mutation (HR =1.71, P=0.04) (*Figure 3*). Likewise, presence of a *CDKN2A* mutation was associated with a statistically worse survival with median 12.3 (95% CI: 8.4–NR) months compared to 45.2 (95% CI: 36.1–NR) months (HR =4.45, P<0.001) (*Figure 4*).

A total of 12 patients, all with MSS tumors, underwent treatment with ICIs, with ten being TMB-high (*Figure 5*). All of these patients had liver metastases, and none of the patients had tumors with mutations in *BRAF* or *POLE*. Eight of the 12 patients had *KRAS* mutations. Eight of 12 patients progressed on immunotherapy, with seven patients receiving treatment for fewer than 3 months. Three patients had responses longer than 1 year, including

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Table 2 HRs of selected mutations

Mutation	N (%)	HR	95% CI	P value
TMB high	35 (21.7)	1.38	0.77–2.48	0.28
TP53	132 (82.0)	0.67	0.35–1.27	0.22
APC	129 (80.1)	0.81	0.44–1.51	0.51
KRAS	70 (43.5)	1.71	1.02–2.85	0.04
SMAD4	30 (18.6)	1.79	0.99–3.23	0.05
PIK3CA	26 (16.1)	0.81	0.38–1.73	0.59
MYC	18 (11.2)	1.17	0.55–2.46	0.68
FBXW7	16 (9.9)	0.42	0.13–1.34	0.14
ARID1A	15 (9.3)	1.51	0.65–3.53	0.34
PIK3R1	13 (8.1)	1.24	0.53–2.90	0.61
AMER1	11 (6.8)	1.29	0.46–3.59	0.63
DDX11	11 (6.8)	0.67	0.21–2.14	0.50
BRAF	9 (5.6)	1.38	0.50–3.86	0.53
CDKN2A	9 (5.6)	4.45	1.97–10.04	<0.001
PTEN	9 (5.6)	0.80	0.19–3.30	0.75
ATM	8 (5.0)	0.94	0.30–3.02	0.92
NRAS	7 (4.3)	0.38	0.05–2.76	0.34
RB1	7 (4.3)	2.53	0.91–7.05	0.07
HER2	7 (4.3)	0.70	0.17–2.86	0.61
STK11	5 (3.1)	1.98	0.62–6.34	0.25

HR, hazard ratio; CI, confidence interval; TMB, tumor mutation burden.

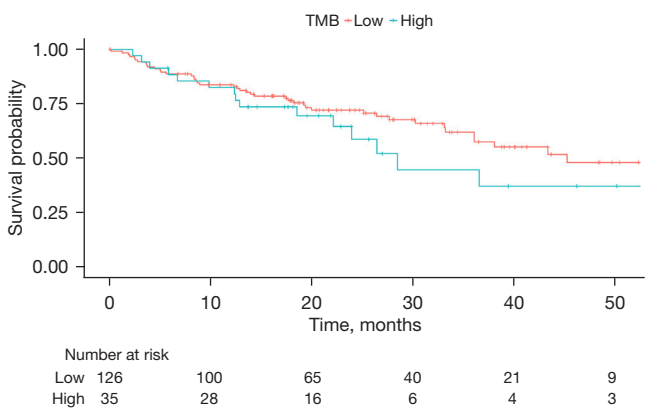

Figure 2 High TMB trended towards worse outcomes with overall survival of 28.5 (95% CI: 22.2–NR) months, compared to 45.2 (95% CI: 36.1–NR) months, with a HR of 1.38, though this was not statistically significant (P=0.28). TMB, tumor mutation burden; CI, confidence interval; NR, not reported; HR, hazard ratio.

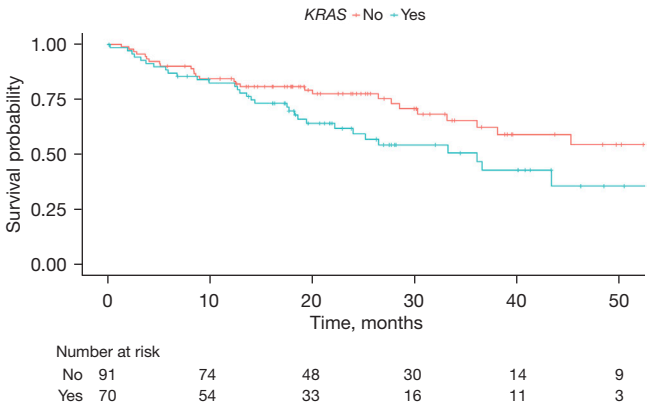

Figure 3 *KRAS* mutations had worse outcomes with median survival of 36.1 (95% CI: 24.0–NR) months compared to NR (95% CI: 38.1–NR) months, with a HR of 1.71 and P=0.04. CI, confidence interval; NR, not reported; HR, hazard ratio.

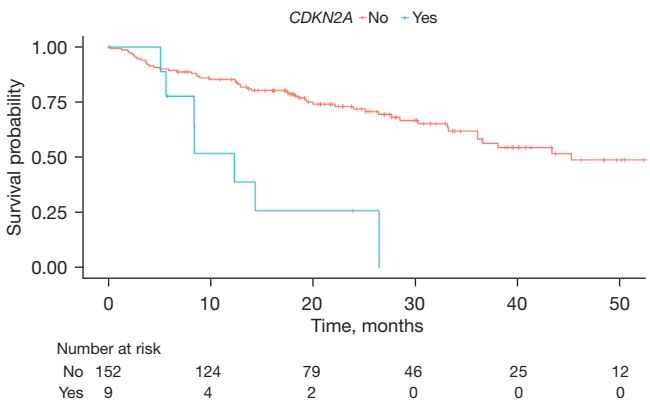

Figure 4 *CDKN2A* mutations had worse outcomes with median survival of 12.3 (95% CI: 8.4–NR) months compared to 45.2 (95% CI: 36.1–NR) months, HR of 4.45, P<0.001. CI, confidence interval; NR, not reported; HR, hazard ratio.

two who were not TMB-high but participated in a clinical trial that utilized chemo-immunotherapy rather than immunotherapy alone. The third patient, who was TMB-high, used immunotherapy monotherapy as a third-line therapy and had a response that continued for 13.1 months before progression of disease. With respect to adverse events, there was one patient who had hyper-progression on immunotherapy, and another patient who had both organizing pneumonia and thyroiditis. There were no other significant immune-related adverse events, and progression of disease was the most common reason for stopping immunotherapy.

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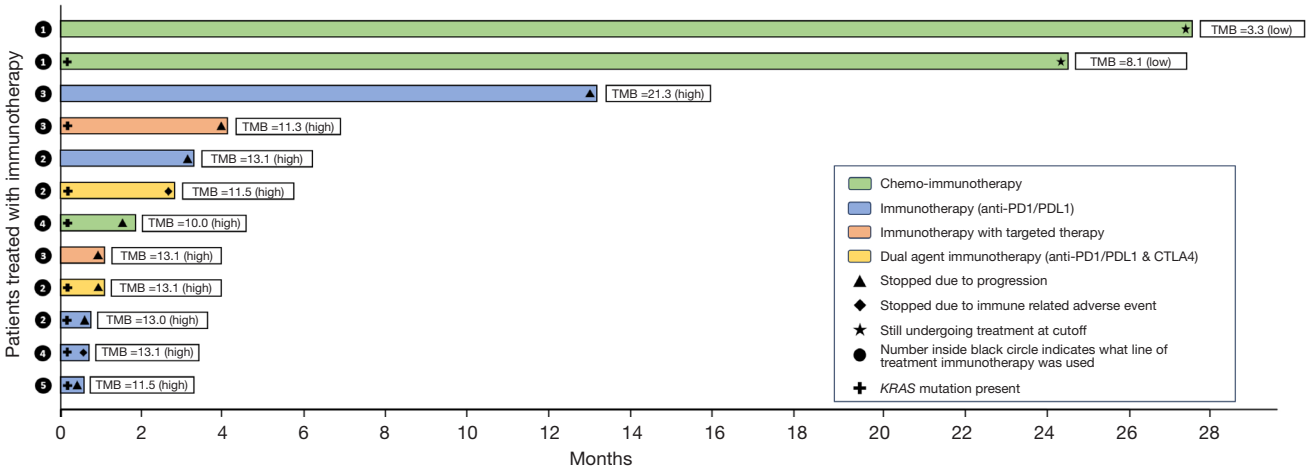

Figure 5 Swimmer plot describing the twelve patients with MSS CRC who underwent treatment with immunotherapy. The TMB, defined as mutations per megabase, is listed for each patient. TMB, tumor mutation burden; MSS, microsatellite-stable; CRC, colorectal cancer.

Discussion

This retrospective cohort study was conducted primarily to investigate correlation of TMB in patients who were MSS to CRC patient outcomes. From our dataset those who had high TMB trended towards a worse outcome, although there was no statistically significant difference. Prior studies identified MSI-H in metastatic CRC confers a poor prognosis (14), but that high TMB is associated with better prognosis in advanced stage II or stage III CRC (15). High TMB was found to have a positive prognostic role in another study assessing untreated MSS metastatic CRC (16). Our data differs from these studies as the patients in our cohort all had metastatic disease at time of analysis compared to stage II or stage III patients in the study by Lee *et al.* (15), and many in our cohort had already undergone one or more lines of treatment compared to analysis of first-line treatment in the study by Innocenti *et al.* (16). We found that those with high TMB were more likely to have received immunotherapy, and potentially this could represent that our current immunotherapy combination may not be optimized or effective for high TMB CRC. High TMB may not be a good predictive marker for patients with metastatic CRC and previous lines of treatment.

The secondary objective of this study was to assess the frequency of the genetic mutations collected from the NGS and correlate these to prognosis in reference to TMB. The prevalence of all mutations is included in Table S1 and is notable for a high percentage of tumors having *TP53* and *APC* mutations, at 82.0% and 80.1% respectively, followed by *KRAS* mutations at 43.5%. This is consistent with the current paradigm of the most common mutations in the progression of CRC (17). There was significantly worse survival in patients who had a *KRAS* and/or *CDKN2A* mutation. *KRAS* mutation has previously been described as a poor prognostic marker (18), and this study looking at *CDKN2A* mutations found a statistically significant association with worse survival (19). Typically, *BRAF* is a marker of poor prognosis in MSS tumors, but it was not noted to be so in our cohort. Given that TMB is a general marker of mutational burden it is likely that there is some overlap of TMB and these mutations, but as suggested in recent literature specific mutations may be better prognostic markers (12).

The immunotherapy subset was a small sample size (n=12), in part because many of the patients in this study were diagnosed with their disease before KEYNOTE-158, and ICI therapy in CRC was not very common during the period reflected by these data. Notably of these twelve patients, there were three patients who responded for longer than 1 year, two of which responded for longer than 2 years (and at time of cut-off were still undergoing treatment). The two longest responders had low TMB, although their treatment regimen consisted of immunotherapy in combination with chemotherapy which confounds any conclusions. The third patient was TMB high and was on immunotherapy monotherapy until progression at 13.1 months. This patient's favorable response to monotherapy indicates there is a subset of patients who are MSS who benefit from this therapy. It could also be the case that the immunotherapy regimen or combination is not optimized for

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CRC. In two of these 12 patients there were severe adverse events from immunotherapy (hyper-progression in one patient and organizing pneumonia and thyroiditis in another), a reminder that these medications have significant risks associated with use, especially if the benefit may be infrequent.

The prevalence of high TMB in the patient population was measured at 21.7%. Similar patient populations such as those reported by Voutsadakis reported prevalence of high TMB in metastatic CRC to be lower at 9.8% (13). The GeneTrails® NGS which provided the data for our report has been internally validated for accuracy (20), though there are likely to be variations between different assays.

There are several limitations to this study. It was conducted at a single institution, and the patient demographics were a higher proportion male (61.5%) which may not fully represent the greater population. Other limitations to the study include the follow-up time, as data could be more complete with more longitudinal analysis. Another possible limitation is the patients who were included in the study. Every patient with metastatic CRC undergoing treatment at this institution had NGS, however this study would not capture the patients who did not elect for treatment, had NGS previously done at different institutions, or went elsewhere for treatment. This potentially could select for patients with better performance status. As this is a cohort study there is also risk of bias due to differential loss. Another limitation as discussed above is that the FDA approved immunotherapy in 2020, and some patients were diagnosed prior to this which could have impacted treatment decisions.

Conclusions

Immunotherapy treatment for CRC patients with high TMB CRC was approved based on a study without CRC in its patient population, and while some previous publications have suggested that TMB is a favorable prognostic factor, our cohort analysis of MSS patients finds that TMB-high is not correlated with better survival. It is possible that TMB in CRC, in contrast to MSI-H, may not be as predictive of immunotherapy response as previously thought, and more research needs to be done to clarify this further. In clinical practice, oncologists should discuss the potential poor response in this clinical context and weigh the risk-benefit against other therapeutic options such as regorafenib, trifluridine/tipiracil, or referral for clinical trials. Unique genetic mutations identified from NGS may further be correlated with high TMB and prognosis in future studies with larger sample sizes. Such a tool could help clinicians better estimate survival and guide goals of care discussions. In summary, high TMB without MSI-H or other unique molecular signatures should not be misrepresented by clinicians. There is a need to identify other factors which predict response to immunotherapy treatment and to optimize the treatment regimens for CRC patients undergoing immunotherapy.

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Footnote

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Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-809/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-809/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Oregon Health & Science University Institutional Review Board (No. STUDY00023541). Individual consent for this retrospective analysis was waived as this was a retrospective cohort study of clinical data.

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References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
2. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin 2020;70:145-64.
3. Lin JS, Perdue LA, Henrikson NB, et al. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2021;325:1978-98.
4. Dekker E, Tanis PJ, Vleugels JLA, et al. Colorectal cancer. Lancet 2019;394:1467-80.
5. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010;138:2073-2087.e3.
6. Ganesh K, Stadler ZK, Cercek A, et al. Immunotherapy in colorectal cancer: rationale, challenges and potential. Nat Rev Gastroenterol Hepatol 2019;16:361-75.
7. André T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med 2020;383:2207-18.
8. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330-7.
9. Malapelle U, Pisapia P, Sgariglia R, et al. Less frequently mutated genes in colorectal cancer: evidences from next-generation sequencing of 653 routine cases. J Clin Pathol 2016;69:767-71.
10. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353-65.
11. Li Y, Ma Y, Wu Z, et al. Tumor Mutational Burden Predicting the Efficacy of Immune Checkpoint Inhibitors in Colorectal Cancer: A Systematic Review and Meta-Analysis. Front Immunol 2021;12:751407.
12. Wang J, Xiu J, Farrell A, et al. Mutational analysis of microsatellite-stable gastrointestinal cancer with high tumour mutational burden: a retrospective cohort study. Lancet Oncol 2023;24:151-61.
13. Voutsadakis IA. High tumor mutation burden (TMB) in microsatellite stable (MSS) colorectal cancers: Diverse molecular associations point to variable pathophysiology. Cancer Treat Res Commun 2023;36:100746.
14. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res 2014;20:5322-30.
15. Lee DW, Han SW, Bae JM, et al. Tumor Mutation Burden and Prognosis in Patients with Colorectal Cancer Treated with Adjuvant Fluoropyrimidine and Oxaliplatin. Clin Cancer Res 2019;25:6141-7.
16. Innocenti F, Ou FS, Qu X, et al. Mutational Analysis of Patients With Colorectal Cancer in CALGB/SWOG 80405 Identifies New Roles of Microsatellite Instability and Tumor Mutational Burden for Patient Outcome. J Clin Oncol 2019;37:1217-27.
17. Leslie A, Carey FA, Pratt NR, et al. The colorectal adenoma-carcinoma sequence. Br J Surg 2002;89:845-60.
18. Meng M, Zhong K, Jiang T, et al. The current understanding on the impact of KRAS on colorectal cancer. Biomed Pharmacother 2021;140:111717.
19. Xing X, Cai W, Shi H, et al. The prognostic value of CDKN2A hypermethylation in colorectal cancer: a meta-analysis. Br J Cancer 2013;108:2542-8.
20. Mitri ZI, Parmar S, Johnson B, et al. Implementing a comprehensive translational oncology platform: from molecular testing to actionability. J Transl Med 2018;16:358.

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