Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-21-471

Comment 1 (Reviewer A): It would be interesting to have information on the genetic profiles of the two groups beyond BRAF and MSI status. While the authors note that the absence of archived tissue prevents an RNA based classification, since BRAF mutation status is often checked as part of a broader NGS panel, can the authors comment on whether other gene alterations differentially segregate between the groups to explain the vast difference in survival?

Reply 1: We analyzed the two populations (LS and SS) for co-occurrence of APC, TP53, PIK3CA, and SMAD4 mutations. No difference in mutation frequency was observed for any of these genes between the two groups. We have clarified this by adding a sentence to the end of paragraph 3 in the Results section.

Changes in the text: We have added data to page 8, line 129.

Comment 2 (Reviewer B): Selection of LS group : mentioned as >50 months OS. Is there a reason for this? What was the definition of SS group ?

Reply 2: Patients in the LS group and the SS group were categorized among the 187 total patients with *BRAF*^{V600E} mutated metastatic colorectal cancer in our series as being the 25 patients with the longest survival (LS) and shortest survival (SS). As mentioned by the reviewer, all patients in the LS group experienced overall survival exceeding 48 months, which is well beyond median overall survival for the *BRAF*^{V600E} mutated metastatic colorectal cancer populations reported in both retrospective series (~12 months) and in prospective randomized controlled trials (~9 months). Therefore, we believe that this LS group encompasses patients with survival well beyond median expectations as defined by the literature. In order to keep the sample sizes equal between the LS and SS groups, we selected the SS group as those 25 patients with the shortest survival. Importantly, median survival for this group was 8.6 months, which is shorter than that reported for encorafenib + cetuximab. Therefore, we believe that our SS group is reflective of patients with especially poor prognoses.

Changes in the text: We added "LS" on page 6, line 76 amid our discussion in that paragraph of the Methods section for how we defined the LS and SS groups.

Comment 3 (Reviewer B): I suggest hypothesis should be characterization of good and bad prognostic group, rather than comparing two groups. This is well reflected in the title. Perhaps update this in the introduction (line 51) and methods (line 55).

Reply 3: The suggestion from the reviewer for a clarification in the hypothesis and objective are well-taken, and we have revised the sentences accordingly. Because the final sentence of the final paragraph of the Introduction section details the objective of the retrospective work here, we deleted the first sentence (and very next sentence) of the Methods section in order to eliminate redundancy.

Changes in the text: We have modified the text as suggested by the reviewer (see page 5, lines 53-60).

Comment 4 (Reviewer B): Line 65 : did authors analyze PIK3CA, SMAD4 etc in this paper ? It's not mentioned in the results or conclusion. If not performed , suggest remove this.

Reply 4: We did analyze co-occurrence in other commonly mutated genes for colorectal

cancer beyond *BRAF*. We added a sentence to the end of paragraph 3 of the Results section desrpibing the frequency of co-occurring *APC*, *TP53*, *PIK3CA*, and *SMAD4* mutations. Here, we also confirmed that there were no differences in rates of mutations of these genes between the LS and the SS groups. Because *KRAS* and *NRAS* mutations are well described to occur mutually exclusively to $BRAF^{V600E}$ mutations in CRC, and because $BRAF^{V600E}$ mutated colorectal cancers are wild-type for the *KRAS* and *NRAS* oncogenes, we did not feel that reporting of their status was relevant to this manuscript and therefore removed this from the Methods section.
Changes in the text: We deleted "KRAS" and "NRAS" from the Methods section (page 5, line 70). We added a sentence to the Results (page 8, lines 129-131) describing the data for rates of co-occurrence of the other 4 aforementioned genes.

Comment 5 (Reviewer B): Two crucial findings in this paper were association of smoking and metastasectomy with OS. Suggest include smoking in the abstract and highlight metastasectomy in conclusion section of abstract. And perhaps the importance of metastasectomy can be highlighted and emphasized more in the discussion.
Reply 5: The abstract has been updated to include odds ratio with the association between tobacco use and the LS group, and we clarified this further in paragraph 2 of the Results section. We have also clarified the Conclusions section of the manuscript abstract by changing the phrase "locoregional" to "surgical metastectomy" to clarify that several patients with $BRAF^{V600E}$ mutated metastatic colorectal cancer did achieve excellent survival outcomes because of surgical resection.

We agree with the reviewer that a (if not the) most striking message that we are seeking to convey to the readership is that there are patients who do benefit from surgical resection despite a diagnosis of $BRAF^{V600E}$ mutated metastatic colorectal cancer. To that end, we focused our paragraph 5 in the Discussion section on the role of metastectomy in patients carefully selected by a multidisciplinary team. In order to reinforce this point further in our discussion, at the suggestion of the reviewer, we have restructured the first sentence of the final paragraph to remind readers that multiple patients experienced recurrence-free survival exceeding 4 years. We included this in the final paragraph as a take-home point for the reader that in carefully selected patients with $BRAF^{V600E}$ mutated metastatic colorectal cancer, metastectomy can offer very favorable survival in this otherwise prognostically unfavorable subpopulation of patients with metastatic colorectal cancer.
Changes in the text: In the abstract, we added the odds ratio for the association between tobacco use and the LS group (page 2, line 20). In the Results (page 7, lines 107-108), we added a sentence describing this association as well. On page 3, lines 25-26, in the Abstract we clarified "metastectomy" at the suggestion of the reviewer. On page 8, lines 262-266, we added further language at the suggestion of the reviewer about the importance of metastectomy with a multidisciplinary team in offering some patients excellent long-term survival.

Comment 6 (Reviewer B): Tables : improve consistency with terminology : Longest survival (as defined in the text) rather than best survival
Reply 6: We acknowledge this oversight, and relabeled the headings in Tables 1,2, and 3 for the Longest Survival (LS) and Shortest Survival (SS) columns in order to maintain consistency with the text of the manuscript.
Changes in the text: The headings of columns of Tables 1, 2, and 3 have been changed

at the suggestion of the reviewer.

Comment 7 (Reviewer B): Table 4 : PFS: perhaps range may be more suitable given the small numbers.
Reply 2: In Table, 4, a new column labeled "PFS range (months)" has been substituted for the column previously titled "median PFS (months)".
Changes in the text: New data in Table 4 has been added at the recommendation of the reviewer.

Comment 8 (Reviewer C): Some values have inconsistent rounding (whole number vs tenths for the Odds ratios in the abstract, or on page 8 ".5-18"). Most sections follow usual rules of significant figures but I'd suggest going to the same measure of precision (tenths).
Reply 8: Significant digits for odds ratios have been changed throughout the body of the text to the nearest tenth of a point at the suggestion of the reviewer.
Changes in the text: Significant digits for odds ratios have been changed throughout the body of the text to the nearest tenth of a point at the suggestion of the reviewer.

Comment 9 (Reviewer C): Can you provide the proportion of patients with liver and peritoneal metastases in each group with a p value comparing the 2x2 table rather than combining the rates of involvement between groups?
Reply 9: We have added in Table 1 additional rows which describe the frequency for liver, peritoneal, and lung metastases with the p-values linked to the tested associations.
Changes in the text: Additional data has been added to Table 1.

Comment 10 (Reviewer C): I often do not consider locoregional therapy when a BRAF V600E mutation is noted. Can you include in the manuscript when those patients who underwent locoregional therapy had the intervention? Was it prior to initial systemic therapy, 3 months into systemic therapy, or some other time point? A brief narrative of 2-3 sentences would provide insight into this important population.
Reply 10: All patients in the LS group who underwent metastectomy received neoadjuvant chemotherapy and had interval improvement radiographically prior to the decision to proceed with surgery. We have clarified this point raised by the reviewer in the final paragraph of the Results section with further quantitative details.
Changes in the text: Three additional sentences have been added based upon this suggestions from the reviewer (see page 9, lines 146-149).

Comment 11 (Reviewer C): On line 159 page 10, change "because" to "became"
Reply 11: The text has been modified.
Changes in the text: See page 10, lines 173-174.

Comment 12 (Reviewer C): Line 189 on page 11 needs to be rephrased for clarity.
Reply 12:We have rewritten the first sentence of this paragraph at the requested by the reviewer for further clarity of message.
Changes in the text: The change to the text can be seen on pages 11-12, lines 202-206.

Comment 13 (Reviewer C): Tobacco use is first noted in the discussion and not included in the results section. Please add to results.
Reply 13: The association between tobacco exposure and the LS group has been added

to the second sentence of paragraph 2 of the Results section.
Changes in the text: Data has been added per the suggestion of the reviewer to page 7, lines 107-108.

Comment 14 (Reviewer C): In Figure 1 it looks like the line is a different size for the bone subgroup. Please double check line size and spelling in the figure caption.
Reply 14: The range for the bone subgroup has been corrected to maintain consistency with the other sites of organ involvement.
Changes in the text: An updated Figure 1 has been included with the change suggested by the reviewer.

Comment 15 (Reviewer D): I agree focusing on 25 patients of LS, but limiting to 25 patients of SS is a bit questionable. If authors increase the number of SS patients to 50, for example, Is will be the currently listed results significantly different?
Reply 15: If we increased the sample size analyzed to N=50 for the SS group, median survival would exceed the median survival reported for entire cohorts of patients with *BRAF*^{V600E} mutated metastatic colorectal cancer in larger series. Because our objective here was to characterize a population of patients with exceptionally poor survival in this subset of patients with metastatic colorectal cancer, our concern is that increasing the sample size to N=50 may not be representative of our specified population of interest.
Changes in the text: N/A

Comment 15 (Reviewer D): In the Method, authors mentioned NGS-based test was performed in this population. However, no results of mutational status of APC, TP53,....in Result section. Researchers are interested in the differece between SS and LS.
Reply 16: We did analyze co-occurrence in other commonly mutated genes for colorectal cancer beyond *BRAF*. We added a sentence to the end of paragraph 3 of the Results section desrpibing the frequency of co-occurring *APC*, *TP53*, *PIK3CA*, and *SMAD4* mutations. Here, we also confirmed that there were no differences in rates of mutations of these genes between the LS and the SS groups. Because *KRAS* and *NRAS* mutations are well described to occur mutually exclusively to *BRAF*^{V600E} mutations in CRC, and because *BRAF*^{V600E} mutated colorectal cancers are wild-type for the *KRAS* and *NRAS* oncogenes, we did not feel that reporting of their status was relevant to this manuscript and therefore removed this from the Methods section.
Changes in the text: We deleted “KRAS” and “NRAS” from the Methods section (page 5, line 70). We added a sentence to the Results (page 8, lines 129-131) describing the data for rates of co-occurrence of the other 4 aforementioned genes.

Comment 17 (Reviewer D): Minor points: In page 9, the section title of "Conclusions" is strange. "Discussions" is better.
Reply 17: The final section has been relabeled as “Discussion” at the suggestion of the reviewer.
Changes in the text: The edit to the text is on page 10, line 161.

Comment 18 (Reviewer D): In Table 1-3, authors use "Best survival" and "Worst survival". I recommend to change "Longest survival" and "Shortest survival"
Reply 18: We acknowledge this oversight, and relabeled the headings in Tables 1,2, and

3 for the Longest Survival (LS) and Shortest Survival (SS) columns in order to maintain consistency with the text of the manuscript.
Changes in the text: The headings of columns of Tables 1, 2, and 3 have been changed at the suggestion of the reviewer.

Comment 19 (Reviewer E): Authors focused on extreme short-term survivors (SS) and long-term survivors (LS) among a series of patients with BRAFV600E mutant metastatic colorectal cancer. However, each group is very heterogeneous in terms of patients' status at the time of diagnosis and such study design considerably hinders meaningful comparisons. Some patients were eligible for loco-regional treatment and such patients were markedly enriched in the LS group. This observation is just what is expected according to the accumulated literatures. It would have been better if all patients in both groups were initially stage IV. In addition, the ECOG performance status at the time of diagnosis is also worth being considered.
Reply 19: We agree with the reviewers about the relevance regarding ECOG PS. Unfortunately, because this was a retrospective review and many patients did not have this reported/documented in their clinic notes, we did not have enough data available regarding baseline ECOG PS for reporting here.
Changes in the text: N/A

Comment 20 (Reviewer E): According to the manuscript, the favorable clinical outcome was associated with MSI-H status, mucinous histology, and surgical resection including metastasectomy. This observation has also been well known. The impacts of molecularly targeted therapies or immunotherapies seem to be difficult to determine due to sample size limitations. Readers may want to know something new besides those well known pieces of information.
Reply 20: We acknowledge the concerns raised by the reviewer. We have noticed in our clinical practice as a major referral center that providers at other academic centers and in the community setting continue to remain unwilling to consider surgical resection in some patients with metastatic colorectal cancer due to the *BRAF*^{V600E} status. Our intention here was to share our experiences with the readership that there are few patients with *BRAF*^{V600E} mutated metastatic colorectal cancer who can benefit from curative-intent procedures despite being in an exceptionally poor prognostic subgroup of patients with metastatic colorectal cancer. We do hope that this important point was conveyed in our discussion.
Changes in the text: N/A

Comment 21 (Reviewer E): Un-natural abbreviation: please use "patients" and do not use "pts"
Reply 21: We have made these substitutions at the suggestion of the reviewer.
Changes in the text: "pts' has been replaced with "patients" throughout the abstract (pages 2-3, lines 23-28).

Comment 22 (Reviewer E): The 2 BRAFV600E mCRC -> the two BRAFV600E mutant mCRC (in the 1st line of Results section of the Abstract). Also, there are many "BRAFV600E mCRC"s throughout the manuscript. "BRAFV600E mutant mCRC" is a clearer term.
Reply 22: This substitution has been made at the suggestion of the reviewer.
Changes in the text: In the entire manuscript (all sections, including abstract), we have

added the word “mutated” after *BRAF*^{V600E} at the suggestion of the reviewer.

Comment 23 (Reviewer E): Page 7, Paragraph 2, Line 7: Consistent with this increased propensity for intact primary tumors -> Consistent with this association between unresectable primary tumors and PSS group.
Reply 23: This substitution has been made at the suggestion of the reviewer.
Changes in the text: This edit is seen on page 7, lines 113-114.

Comment 24 (Reviewer E): Page 8, Paragraph 2, Line 2: Notable, -> Notably,
Reply 24: This substitution has been made at the suggestion of the reviewer.
Changes in the text: This edit is seen on page 8, line 133.