Author’s response to reviews

Title: Impact of KRAS, BRAF and PI3KCA mutations in rectal carcinomas treated with neoadjuvant radiochemotherapy and surgery

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Author’s response to reviews: see over
Reviewer 1
Abstract and introduction are too long and needs to be shortened References are more than required.
Done
Results are negative as non expected and the number of patients could explain partially that.
Authors must stress on tumor volume and histologic characteristics to find any Correlation.
Done
Reviewer2
Discretionary revisions:
Specific Comments:

1. Page 2, Introduction, 5th Line from the bottom of page: Replace “despite of a low local recurrence rates” with “despite low local recurrence rates”
   Done
2. Page 2, Introduction, 4th Line from the bottom of page: Replace “continue to die” with continue to have high mortality
   Done
3. Page 2, Introduction, 4th Line from the bottom of page: Rephrase “at the opposite”
   Done

   Done

5. Page 3, Introduction, Lines 8-10: This sentence is confusing. Reword.
   Done

   Done
7. Page 3, Introduction, Line 18: Replace “only” with “alone”

Done


Done

9. Page 5, Results, Patient’s characteristics: Capitalize Table 1 in last line

Done

10. Page 6, Results, Survival:

It was a little unclear if you did the analyses comparing results for patients with each mutation versus those who did not have the mutation, or comparing results for those who had at least one of the 3 mutations versus those who had no mutations. If you did not do the latter analysis, this might be an interesting analysis, especially given limited sample size and patient events. Also, a table of the results (maybe as a supplemental table) would be nice for clarity of which comparisons you made, even if they are mostly null.

Survival analyses compared results for patients with each mutation versus those who did not have the mutation, and also compared results for those who had at least one of the 3 mutations versus those who had no mutations.

Table 2 and 3 were added.

11. Page 6, Discussion, Line 3: Replace “disease’s” with disease

Done

12. Page 6, Discussion, Line 5: Replace “are known as local recurrence’s risk factors as depth” with “are associated with local recurrence, including depth”

Done

13. Page 6, Discussion, Lines 8-9: Reword sentence to say “These factors
may be used in therapeutic decisions regarding administration of...”

14. Page 6, Discussion, Line 13: Replace “spares” with spare

15. Page 6, Discussion, Line 15: Clarify which signaling pathway you are referring to.

16. Page 6, Discussion, 5th line from the bottom: Remove the word “Then”; start paragraph with “The mutation frequency...”

17. Page 7, Discussion, Line 2: Replace “seems” with is.

18. Page 7, Discussion, Line 12: Replace “who undergone” with “who had undergone”.

19. Page 7, Discussion, Line 20-21: Is this sentence referring to the same study referenced in the previous sentence. If so, make this clear, if not, insert appropriate reference.

20. Page 7, Discussion, Line 24: Replace “investigate” with investigated

21. Page 7, Discussion, Last paragraph: Replace “Michelassi et al found that KRAS wild type tumors were trended to tumor downstaging (Michelassi et al., 1988) as well as Grana et al who reported that KRAS mutations potentially...” with “Michelassi et al found that KRAS wild type tumors
trended toward tumor downstaging (Michelassi et al., 1988) and Grana et al reported that KRAS mutations potentially...

22. Page 8, Discussion, Line 4: Add “reported” or “described” after “previously”  

23. Page 8, Discussion, Last paragraph, Second sentence: I don’t know that you can draw any strong conclusions from this study given that the study had limited overall numbers and limited number of events. Reword. Sentence was suppressed.

24. Page 8, Discussion, Last paragraph, last sentence: Reword to say “Finally, the follow-up period was probably too short to draw definitive conclusions.” done

Minor Essential Revisions:

General Comments:

1. Throughout the paper italicize names when referring to genes or RNA. done

2. Even though most of your associations with different outcomes are null, it would be useful to provide some kind of table, even if it is supplemental Table 2 and 3 were added

Specific Comments:

3. Page 1, Abstract, Results, Lines 6-7: KRAS is mentioned twice with different percentages and PI3KCA is not mentioned. Should the second KRAS in this sentence be PI3KCA? Yes. Modification was done.

4. Page 1, Abstract, Results, Line 9: The phrase “no longer” with overall survival is confusing. Was it previously associated? If not remove those two words. done

5. Page 2, Introduction, Line 1: “Since last decades” is an unusual phrase, do you mean to say “over the last decade” or “in the last decade”? We mean: over the last decade.

6. Page 2, Introduction, 8th Line from the bottom of page: Replace “prognostic” with prognosis Done
7. Page 2, Introduction, 6th Line from the bottom of page: Reword “tumor response can’t be exactly anticipated”

The tumor response can be evaluated only after the pathological examination

8. Page 6, Results, Survival:

1) The phrase “no longer with survival” is confusing. I would remove “no longer”. Done

2) P<0.01 implies that there was a significant association; did you mean to say p>0.01? Yes. P<0.01 was removed.

9. Page 6, Discussion, Line 1: Replace “progresses” with progress: Done

Major Compulsory Revisions:

1. General Comments: There should be a strengths and limitations paragraph in the Discussion section.

Done