Response to reviewer 1

Manuscript # 24070 – Young patients with colorectal cancer; many questions, few answers.

Authors – Deen K.I. et al

Manuscript revision for "Topic Highlight" – WJGO.

1. Statement - Clarify and expand family history
   Response – This has been done and highlighted in the section "Family History''.

2. Statement - Explain " Heritable syndromes in 2 to 5% but hereditary component is estimated up to 30%"
   Response – Historic reports quote a 2 to 5% aetiology. We now know that these figures are low estimates and that the heritable component is likely to be higher based on such papers from Mork et al, Armaghany et al and Stoffel (References 30, 43 and 46 respectively).

3. Statement - Consider describing other familial syndromes that may contribute to young CRC
   Response – We have mentioned other heritable syndromes that may contribute to young CRC, but not undertaken a detailed description, to stay with the aim and focus of the review. (Section on Genetics –Page 8)

4. Statement - Clearly outline the genetics of CRC as mentioned in the core-tip

   Response – We have expanded the section on genetics of CRC (Page 8)

5. Statement – Change first sentence "Whether CRC is sporadic or part of an inherited…."

   Response – The sentence has been deleted.

6. Statement- Basis for comment "the origin of CRC may be attributed to the presence of common and rare variants…" is based on a 2010 study.
   Response – Thank you for your critique. We have included updated data and alluded the reader to NGS technology (Page 8- Frampton et al; Ref 47- Genetics)

7. Statement – "Even in the remainder, when CRC occurs in its sporadic form, acquired somatic mutations are known to play a central role in its genesis", is unclear.

   Response - To improve this paper, the aforementioned statement was deleted and we have discussed the role of germline mutations, somatic mutation, and that these may both occur in young CRC patients, and the likely future discovery of more genetic aberrations
   (Page 8-section- Genetics)

8. Statement – The CIMP and MSI pathways are not mutually exclusive. Clarify.

   Response - We have stated so in the section on genetics (page 10)

9. Statement - The authors should comment on how the CIMP pathway is involved in early CRC (page 10- Genetics section)

   Response – The role of the CIMP pathway and BRAF proteins in young CRC has been discussed (page 10- Genetics)

10. Statement - The screening section in the conclusion seems more nuanced than in the screening section.
    Response – The conclusion has been amended accordingly (pages 13,14)

Response to reviewer 2

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1 Statement – "Definition of early onset CRC is unclear…"

Response – Although most studies in young CRC mention a cut-off at 40years, we understand the lack of clarity that may result from such statement of a cut off age for young CRC patients. Hence, statement of a defining age has been deleted in the revised manuscript. Instead, where we have described the work of other authors, we have stated the age of young patients in the selected relevant study.

2. Statement – Expand the section on genetics

Response – As suggested by this reviewer, we have expanded the section on genetics and referenced the work of Maureen Mork et al and the Foundation Medicine project (pages 8,9,10)

3. Statement -Explain that there are differences between germline mutations and spontaneous somatic mutations that may arise early in life.

Response – This difference has been alluded to (pages 8 and 9).

4. Statement - Clarify the role of CIN, MSI and CIMP.

Response – The revised paper includes a description of the process of preserving genetic fidelity in the intestinal stem cell within the crypt, briefly describes creation of genetic instability, clarifies the aforementioned pathways, and loss of control of apoptosis that favours preservation of mutagenic cells. (pages 9 and10)

5. Statement –Define Lynch syndrome and HNPCC more clearly.

Response – Briefly, we have defined the syndromes including use of Amsterdam and Bethesda criteria (pages 5 and 6).

6, 7. Statements - Alarmist use of statistics "124% rise in rectal cancer by 2030" and call for global action.

Response – We beg to differ with this reviewer. We believe this statistic tells a story – one that clinicians and scientist in the developing world have encountered for a number of years – that of a high prevalence, in proportion, of young patients, which cannot be explained by environmental influences alone. Hence the call for global thought and action, now that large databases from the West are beginning to focus on young CRC. Young CRC is not rare in a colorectal practice in the developing world.

Response to reviewer 3

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1. Statement – Genetics section needs to highlight differences between CRC in the young vs. the older patient.
   Response – We have incorporated differences between young and older patients in the section on Genetics (Pages 8,9,10)

2. Statement – Risk factors; young vs. old.
   Response – Such risk factors are truly unknown in the young patient, but we have speculatively discussed environmental and hereditary factors that may influence CRC in the young and discussed the pathologic tumour-related risk factors (section on Pathology – Page7- line 1to6 and line 17 to 25; Genetics – page 8; section on Risk Factors – page 10 and 11).

3. Statement – Advanced stage of disease in young vs. older patients. Could this be reflective of presentation of young patients at a later stage?

   Response - The evidence is mixed. We have discussed possible delays in diagnosis in young patients who might otherwise be suspected of harbouring benign pathology. We have discussed aggressive tumour biology in younger patients (poor differentiation, mucinous and signet ring pathology) and lead time bias (section on Presentation – page 6 and 7; Pathology – page 7 and Conclusion – page 14).