Reviewer's report

Title: Allelotyping identification of genomic alterations in rectal chromosomally unstable tumors without preoperative treatment

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Reviewer: Andrea Tannapfel

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This manuscript attempted to study the chromosomal allelic imbalances and correlate their frequency with tumour progression and subsequently identify potential molecular markers of progression in rectal chromosomally unstable tumours without pre-operative treatment. The authors demonstrate that tumours without pre-operative treatment displayed higher allelic imbalance frequency in contrast to tumours with pre-operative treatment. In addition, their survival analysis identified D1S197, D5S430 and D14S65 as three potential prognostic molecular survival markers. Although it is being increasingly recognized that colon and rectal tumours are distinct entities and several attempts have been made to identify novel panels of molecular and biochemical markers that can be used to more precisely define their prognosis, there is a constant need for new prognostic survival markers. Hence, this study by Romain et al directly addresses this need for further potential prognostic molecular survival markers and represents an important area to focus in colorectal carcinoma research.

Our review comments on the manuscript titled “Allelotyping identification of genomic alterations in rectal chromosomally unstable tumours without preoperative treatment” are enumerated below:

1. Allelotyping identifies chromosome loci rather than specific genes and does not specify whether the alteration corresponds to a deletion or a gain of locus. However considering the non-randomn accumulation of instability and that rectal tumours are often irradiated before surgery, this study evaluating the status of 33 microsatellites in patients with and without pre-operative treatment in chromosomal regions previously described to be frequently altered, is well conceived.

2. Investigation of apoptosis and cell proliferation as measured by immunohistochemical detection of p53, Bax, bcl-2 or cleaved caspase 3 and Ki-67 expression and mutational analysis of p53 in patient samples included for this study is strongly recommended. Radiochemotherapy has been associated with an increase in bax expression and apoptotic cell death in p53-negative tumors in rectal cancer as the p53 background of these samples will provide additional useful prognostic information.

3. Since the data of the authors involves cluster analysis, they must substantiate in their materials and methods- if bootstrapping to assess the stability of the
clusters was employed or not?.

4. It is conceivable that tumour free mucosa could have a different prognostic impact in colon and rectal cancers, recent studies increasingly propose to exploit “field effect” of colo-rectal carcinogenesis to obtain a global overview of prognosis by evaluating distal normal sites. The present manuscript should treat this emerging concept in their discussion section while discussing the prognostic relevance of these three molecular survival markers.

We appreciate the potential and relevance of this well conceived study that identified genomic alterations in rectal chromosomally unstable tumours without preoperative treatment. However the manuscript in its present form presents lacunae that need to be addressed as suggested in the above recommendations before being accepted for publication in this journal. We therefore recommend that this manuscript is suitable for publication in this journal conditional to the fulfillment of the above enumerated recommendations.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests