Reviewer 1.

All the yellow text has been correctly referenced. In addition, MGMT and MLH1 methylation have been linked to good prognosis, in major part due to the absence of BRAF mutation, which is the worst prognostic marker. Regarding green text, there are no phenotypical differences between CIMP-L and KRAS tumors. p16INK4a and IGFBP7 are tumor suppressor proteins that prevent polyp growth and that drive these proliferative cells to form small senescent lesions. The exactly role of CIMP status in metastatic stage has not been elucidated. It's possible that the worst prognosis of those tumors could be due to the presence of BRAS mutations as well. Further studies regarding this issue are needed.

In red color: the term upregulation is correctly written. It refers to appearance of proteins on cells' surface. It is also no clear the speaking between BRAF and other methylated genes. Perhaps, the hypermethylation of certain genes avoided the proliferative effect of BRAF mutations, and that's why some studies found CIMP as a marker of good prognosis. On the same way, the recent introduction of subgroups of CRC implies that there are no data comparing MSI and CIMP status head to head. Available data are referred to subanalysis of different studies. patients with CIMP tumors seemed to benefit more after the tumors were stratified according to MSI status. It could be due to the better prognosis associated to unstable tumors, but further explanations regarding this are needed.

Reviewer 2.

CpG islands term is well defined in aberrant hypermethylation subsection. I consider that perhaps the definition in the introduction is too precipitate.

The MAP kinase pathway is a via of intercellular signaling transmission. Mutations in their constituent proteins mainly involve the Raf and RAS families.

In the QUASAR study, the standard CT was based on 5-Fluoruracil (5-FU) and folinic-acid.

I've introduced at the end a summary titled future directions.

Reviewer 3.

The review made by Haque has been revised and its reference has been added.

Reviewer 4.

The summarize, as I said above, has been introduced.

Reviewer 5.

No comments

Reviewer 6.

We tried to write a title that encompass all our work, and it was very difficult. We wanted to explain different aspects regarding serrated cancers (biology, prognosis, response to CT…), but we never thought that all CRCs with alteration at each of four levels (BRAF, KRAS, MSI and CIMP), had necessarily serrated morphology. There are polyps and also cancers following the chromosomal instability pathway with alterations in some of these points (i.e. subgroup 3). When we tried to explain the prognosis and response to adjuvant CT we did not find any study that reflected these 5 subgroups and that compare them because this newer classification was published on January 2015, and there was no data regarding this. Because that, in these two sections (prognosis and response to CT), we just expose the data available regarding subanalysis of different markers, but nowadays there are no studies that compare directly the response to CT among the 5 subgroups of cancers. These are the main reasons for no change the title. Moreover, the natural course from serrated polyps to advanced cancers can bee followed in this figure 5.

Best regards