Dear reviews;

Your comments have been revised one by one.

Comment 1.- Treatments section: currently there are a well-known biomarkers that will guide treatment choice such as BRAF, MSI, HER2, NTRK...this fact should be mentioned (treatment choice is not only based on TNM stage).

Answer 1: We have changed the sentence into "The existing guidelines for the diagnosis and treatments of CRC were primarily based on TNM staging, biomarkers including *BRAF*, *RAS*, *HER2*, microsatellite status and etc."

2.- HIPEC section: in this section authors should clarify that this kind of surgery + HIPEC should be made after a carefully patient-by-patient decision (ECOG, previous lines, BRAF status should be considered). Moreover, the most well-design clinical trial, the PRODIGE-7 trial is a negative trial.

Answer 2: We have added a sentence. "CRS plus HIPEC should be chosen after a careful and individualized assessment including Eastern Cooperative Oncology Group (ECOG) performance-status scores, peritoneal cancer index (PCI), previous chemotherapy lines, etc."

3.- Targeted therapy: when the Wendy et al trial is mentioned, authors should highlight that currently there are strong recommendations that support the negative predictive value of RAS mutations and antiEGFR treatments.

Answer 3: We have added the negative predictive value of RAS mutations and anti-EGFR treatments. "Studies also pointed out that patients with metastatic CRC harboring a mutation in *KRAS* or *NRAS* could not have a response to anti-EGFR therapy. Therefore, activating *RAS* mutations were regarded as negative predictive biomarkers for anti-EGFR therapy[98-100]".

4.- Immunotherapy section: it's important to remark that pembrolizumab

approval was "...the first drug that did not consider tumor types..." based only in overall response rates (ORR). Moreover, will be of interested to mention that in the keynote-177, a subgroup analysis show that KRAS mutated tumors didn't achieve clinical benefit.

Answer 4: It was modified into “Therefore, pembrolizumab was the first drug that did not consider tumor types and only used biomarkers (dMMR/MSI-H) as treatment options based on overall response rates (ORR).” The subgroup analysis of the keynote-177 trial was added as follows. “However, a subgroup analysis in the KEYNOTE-177 trial indicated that patients with metastatic dMMR/MSI-H CRC with *KRAS* or *NRAS* mutations could not benefit from pembrolizumab alone[118]. Whether adding chemotherapy or anti–CTLA-4 to PD-1 blockade could overcome this apparent resistance remains unknown.”

5.- Prognosis section: stage II, MSI-h tumors have a good prognostic. However, in the metastatic scenario MSI-h tumors have worse prognostic compared with MSS.

Answer 4: Worse prognostic of metastatic scenario MSI-H tumors was mentioned as follows. “It is worth noting that in metastatic CRC, dMMR indicates a poorer prognosis compared with pMMR[123]. Immunotherapies including anti-PD-1, CTLA-4 emerged in recent years are promising to improve this situation.”

Thanks for your comments.

Best regards,

Jin Gu