

Reviewer #1

1. Minor typos should be corrected: We have checked the text and typography again, and this article has been edited by a professional linguistic reviewer.
2. Full form of the abbreviations should be provided when used for the first time: We checked the abbreviations of this text, and marked the full names when used for the first time.
3. Some limitations for chemotherapy like systemic toxicity, low tumor-specific selectivity, response rate issues, and resistance should be included in the review paper: The limitations for chemotherapy are mentioned in the "current treatment for colorectal cancer" and highlighted in yellow.
4. There is no figure or table in the paper. Authors are requested to support their review with some figures and tables. It will help readers in keeping track of the relevant details. For instance, pathways for targeted therapy could be represented as a schematic diagram to the readers. Agents which target EGFR or EGFR-related pathways under clinical investigation could be given as a table: We have summarized all the clinical studies of this review in a table.
5. The side effects of targeted therapy such as asthenia, mucositis, anorexia, diarrhea, vomiting, skin rash, hand-foot syndrome, fatigue and cardiotoxicity should be discussed briefly in the manuscript: The toxic effects of targeted therapy are briefly mentioned in the "current treatment for colorectal cancer" section and highlighted in yellow.
6. Contribution of tumor microenvironment, microbiota and exosomes to resistance mechanism should be given briefly in the manuscript: This section has been added at the end of the review.

Reviewer #2

1. There is a distinction between the treatments for colon and rectal cancer. For rectal cancer, radiotherapy is included in the standard regimen. Therefore, it needs to be organized into a separate section for the summarization of regimens for rectal cancer treatment: For this part, this review is mainly about targeted therapy, drug resistance and new strategies for colorectal cancer, so, although radiotherapy is an important treatment for rectal cancer, we believe that it is not suitable to propose it in current treatment. Radiotherapy is not mentioned in similar article.
2. Immunotherapy is less effective in MMR proficient or microsatellite stable (MSS) mCRC. This is because the MMR/MSS CRC is classified as a cold tumor. As various therapies are being investigated clinically to overcome the characteristics of cold tumors, supplementing the contents is necessary: We have added the treatment of MSS CRC in the immunotherapy section.

Reviewer #3

1. Although it was reported that the English of the article was revised by "a professional linguistic reviewer", the readability of the text suffers several times due to grammar issues: We have checked the syntax again, and this article has been edited by a professional linguistic reviewer. The two typical examples mentioned by the editor

have been revised.

2. There are several abbreviations throughout the text that were never resolved: We checked the abbreviations of this text, and marked the full names when used for the first time.
3. There were several currently running RCT-s that were not cited: all currently running studies has been cited in this review.
4. Authors should further discuss that line of thought that was just mentioned in the conclusion, that no study ever investigated these molecular markers in complete for treatment selection: This part has been discussed at the beginning of the review, and it is also mentioned in the "BRAF" section.
5. The paragraph presenting the current therapeutic options is very rough: We have appropriately modified the current treatment, and added some classic and important clinical studies.
6. Although the title of the manuscript suggests a broader topic, the article deals with mCRC only: We acknowledged that most of the clinical studies focused on the metastatic colorectal cancer, so we have revised the review as requested by the editors.