

Dear Sir,

We enclose a revised version of the manuscript entitled "Treatment of colorectal cancer in the elderly" (19156-R) and hope that it can be considered for publication in the World Journal of Gastroenterology.

The following comments by the reviewers have been addressed:

1. The authors should describe the differences of biological features of colorectal cancer including cancer biology and biomarkers between elderly patients and younger patients summarizing previous reports. The differences must have an impact to the treatment for colorectal cancer.

We have included the following text in the manuscript:

BIOLOGICAL FEATURES OF COLORECTAL CANCER IN THE ELDERLY

Colorectal cancer is related to age, but there are few available data on the genetic differences and alterations in the carcinogenesis process between younger and older patients.

In many studies, younger patients are more likely to have mucinous, poorly differentiated and signet ring tumors, but there are mixed results in terms of prognosis. Several studies have suggested that younger age was a poor prognostic factor [110-112], but others suggested the opposite when adjusting for confounding variables such as tumour, treatment and patient factors. [113-118]

The most frequently observed somatic mutations in colorectal cancer were found in the APC, TP53, KRAS and PIK3CA genes

A model has been proposed for the carcinogenic process in sporadic colorectal cancer, in which normal colonic mucosa would transform into invasive carcinoma. This model, named chromosomal instability pathway (CIN), implicates somatic mutations in a multi-step process with alterations in different genes in chronological order (APC, KRAS, Smad2 / 4 and TP53). In a minority of cases of sporadic colorectal cancer, approximately 15%, the pathway responsible for the transformation of the colon epithelium is through an inappropriate mismatch repair system (MMR). The system can not repair the mismatches, resulting in a length variability of DNA microsatellites, called microsatellite instability (MSI). Another proposed pathway responsible for the carcinogenic process is DNA hypermethylation (CpG island methylator phenotype (CIMP)) [120].

Patients with the same stage of disease have a different natural history and a different prognosis, as a result of the heterogeneity of the process. Some conditions give a more favorable prognosis (MSI, BRAF not mutated) or a worse prognosis (hypermethylation and not MSI). Currently, the only marker applicable to clinical practice is the RAS mutation.

In an analysis of 181 patients with colorectal cancer, patients were divided into different groups: those under 50 years of age, from 51 to 70, and over 70. In the group of patients over 70 years of age, the MSI and BRAF mutations were correlated, but there was no correlation in the group

under 50. Mutations in the KRAS and BRAF genes were more common with age, but no PIK3CA mutations were found, and TP53 mutations were more common in older patients. There were no differences in frequency of PTEN gene mutations. The conclusions were that older patients had a greater index of genetic mutations and the incidence of BRAF mutations was higher. CIMP tumors are more common in the older population, who also have a higher rate of KRAS and BRAF mutations. These mutations have treatment implications [120]. TP53 mutation is associated with more advanced stages and vascular and lymphatic involvement [121]. KAS gene mutation is a predictor of resistance to treatment with monoclonal antibody receptor endothelial growth factor (EGFR) [122-124]. BRAF V600E mutation confers worse prognosis [125,126]. A deficiency of the MMR system appears to be a favorable prognostic factor associated with adjuvant treatment in stage II colorectal cancer [127-128].

In an attempt to identify the subgroup of patients with stage II colorectal cancer who may benefit from adjuvant therapy, there have been efforts to find prognostic biomarkers. The deficiency of the MMR system or microsatellite instability (MSI) seems a promising marker. Several studies have found an association between high microsatellite instability (MSI-H) and better prognosis, but resistance to treatment with fluorouracil [141].

It seems reasonable to analyze the MMR deficiency in patients with T3 stage II to select those who could benefit from treatment with 5FU. Its application has not been validated in clinical practice, and therefore clinical decisions to administer chemotherapy should not be based on this analysis. It is not a common occurrence in the metastatic context, and does not seem to play a role in the prognostic stratification.

2. The authors summarized the problems of chemotherapy for elderly patients. However, the molecular- targeted therapy was not mentioned in this manuscript. The molecular-targeted therapy seems to be hopeful and effective treatment for elderly patients due to its less-toxicity. The authors should describe about that.

We have included the following text in the manuscript:

Therapy with targeted agents is not indicated in adjuvant treatment because of lack of benefit [144].

The data on the anti-epidermal growth factor receptors (EGFR) cetuximab and panitumumab in the elderly population is limited. They have been investigated in several trials either in combination or monotherapy in metastatic colorectal cancer, with a manageable toxicity profile. Patients with mutations in codon 12 or 13 of the KRAS gene should not be treated with anti-EGFR antibody due to lack of benefit. The main adverse effect of these drugs is skin toxicity. The correlation between development and severity of rash with treatment response is unclear. An analysis of EGFR polymorphisms observed that carriers of D994D polymorphism have lower dermatological toxicity than other genotypes, with no difference in PFS or OS and age [165-

^{169]}. Mutations in RAS, BRAF and PIK3CA have also been shown to be associated with resistance to anti EGFR ^[170].

The latest drug approved for the treatment of mCRC, regorafenib, a multikinase inhibitor, adds a modest increase in PFS without increasing OS. Median overall survival was 6.4 months with regorafenib versus 5.0 months with placebo (hazard ratio 0.77; 95% CI 0.64–0.94; one-sided $p=0.0052$). Adverse events due to treatment occurred in 465 (93%) patients with regorafenib and in 154 (61%) of those assigned to placebo. The most common adverse events of grade 3 or higher related to regorafenib were hand-foot skin reaction (17%), fatigue (10%), diarrhoea (7%), hypertension (7%), and rash or desquamation (6%). There were no differences in toxicity between patients older or younger than 65 years of age in the subgroup analysed, but there are no available data on efficacy or toxicity in the elderly or frail population.^[168] Ramucirumab is a human IgG-1 monoclonal antibody that targets the extracellular domain of VEGF receptor 2. Ramucirumab in combination with FOLFIRI has recently been approved in second line treatment, after progression with bevacizumab, oxaliplatin, and a fluoropyrimidine. Median overall survival was 13.3 months for patients in the ramucirumab group versus 11.7 months for the placebo with FOLFIRI group (hazard ratio 0.844, $p=0.0219$). The most frequently observed adverse effects grade 3 or worse were neutropenia (38% vs 23%), hypertension (11% vs 3%), diarrhoea (11% vs 10%), and fatigue (12% vs 8%). The median patient age was 62, and therefore there is still not enough data in the elderly or frail population. One of the latest drugs, pending FDA approval, for the treatment of colorectal cancer is TAS 102. TAS-102 is an antitumor agent composed of a combination of trifluorothymidine (FTD), a nucleoside that incorporates into DNA and inhibits a variety of genetic functions required for the proliferation of cancer cells, and tipiracil hydrochloride (TPI), an inhibitor of thymidine phosphorylase (which degrades FTD) that maintains an effective blood concentration of FTD. Tipiracil protects trifluridine from being broken down when taken orally.

In a Phase 3 study, 800 patients with advanced colorectal cancer in refractory to oxaliplatin, irinotecan, fluorouracil, bevacizumab, regorafenib and anti EGFR (RAS wild type) were randomized to TAS 102 versus placebo. An increase of median overall survival was observed, from 5.3 months with placebo to 7.1 months with 102 (HR of death 0.68, $P < 0.001$). The main grade 3 or higher toxicity was neutropenia (38%) and patients in the TAS-102 group were also more likely than those in the placebo group to have nausea of grade 3 or higher (2% vs. 1%), vomiting (2% vs. <1%), and diarrhea (3% vs. <1%). The median patient age was 63. The benefit was seen in patients younger than and older than 65, but data is lacking in elderly or frail patients ^[171].

3. The authors summarized previous reports showing that emergency surgery was associated with higher morbidity and mortality. However, the reason why the emergency surgery had adverse effect to the result was unclear. The authors should summarize the reasons.

We have included the following text in the manuscript:

The presence of obstruction or perforation increases the perioperative mortality rate in older patients.

Patients over 70 years of age after emergency surgery have been shown to have a higher rate of postoperative myocardial infarction, and this complication is associated with a 6 times higher rate of mortality in the postoperative period^[62]. Other common complications are pulmonary failure, acute renal failure, and sepsis; anastomotic leakage also occurred more frequently in elderly patients after emergency colorectal surgery, and presented a significant association with postoperative mortality ^[63].

Thank you for the opportunity of reviewing our manuscript.