

## ANSWERS TO REVIEWERS

First of all thanks to the reviewers for their timely comments.

Reviewer # 1:

- We modified the abstract conclusion: “Serous infiltration and lymph node involvement of the primary cancer indicate an unfavorable prognosis, while the presence of single metastasis or < 3 metastases associated with a size of < 5 cm may be considered data that do not contraindicate liver resection”
- We corrected reference n. [10] changing it with references [8,10-14].
- We deciphered the meaning of “H2-H3” according to Japanese Gastric Cancer Association: “This would present future therapeutic opportunities even in H2–H3 patients. This is in accordance with the 1998 Japanese Gastric Cancer Association proposal of H2 for a few lesions scattered in both lobes of the liver, and H3 for multiple diffusely distributed metastases in both hepatic lobes<sup>[60]</sup>.”
- We have included in the “discussion” the influence that the morphological structure of the primary tumor has on the survival: “As mentioned earlier, a factor to keep in high consideration is the histological classification of the tumor; according to the Lauren classification, gastric adenocarcinoma can be divided into two major histological types: diffuse and intestinal<sup>[67]</sup>. Lauren types have several distinct molecular and clinical characteristics, including etiology, carcinogenesis, epidemiology, and progression. The expression of human epidermal growth factor receptor 2 (HER2) is more common in intestinal-type cancer, and such patients have better outcome than patients with diffuse-type cancer<sup>[68-70]</sup>. Some studies<sup>[71,72]</sup> have shown that the diffuse type has more angiogenic factors and microvessel density than the intestinal type; this explains the worse prognosis of such patients and their tendency to develop metachronous metastases. Although not present in all the studies analyzed, histological differentiation was reported as a statistically significant factor of survival (Table 3); the data must be taken in account in the hypothesis of directing the metastatic patient to surgical treatment”

Reviewer #2:

- We I have inserted and expanded into the “discussion” the differences of incidence, localization, histology and risk factors that gastric cancer has in East and West countries: “Gastric cancer survival is substantially different in Asian and Western countries. The better survival in Asian countries is due to the introduction of screening programs, based on the high incidence of this type of cancer in the region<sup>[61,62]</sup>. This is shown in a higher rate of early diagnosis, with the cancer being detected at the early stages. In addition the different location, histology and risk factors explain some of the differences in Asian and Western patients with gastric cancer<sup>[63]</sup>. Distal localization with structural intestinal morphology differentiation is more frequent in Asian countries than the predominance of proximal localization with diffuse histology in the Western countries<sup>[64,65]</sup>. This is reflected in better survival in Asian countries. A high dietary salt intake in the Japanese is a significant risk factor for gastric cancer, and its association might be stronger in the presence of *Helicobacter pylori* infection<sup>[66]</sup>. These data must be taken into account based on the fact that the heterogeneity of the patient groups examined in the present review are from both Asian and Western countries”

- We expanded the role of neoadjuvant chemotherapy in the “discussion”, although the data are difficult to extrapolate from the analyzed papers, in which the difference of chemotherapy schemes used and the lack of clear data in many cases on chemotherapy treatment, do not make it possible to draw precise conclusions. “Although both neoadjuvant and adjuvant chemotherapy is a fundamental step in treating patients with metastatic gastric cancer, in the studies analyzed, the heterogeneous treatments administered to patients in the last 20 years do not allow concrete conclusions to be drawn. Preoperative chemotherapy was administered less frequently than adjuvant chemotherapy in the cohorts analyzed in the present study, and the response to neoadjuvant chemotherapy should be considered an unfavorable prognostic index, thus avoiding futile surgery<sup>[73,74]</sup>. In accordance with Viganò<sup>[37]</sup>, who reported that although patients with and without neoadjuvant chemotherapy had similar 5-year survival rates (36.5% vs. 27%), stratifying patients according to their response to chemotherapy tended to improve survival, which became significant. Today, the key cytotoxic drugs of chemotherapy for gastric cancer include fluoropyrimidine, platinum, taxanes, and irinotecan, as well as molecular target agents, e.g., the anti-HER2 antibody trastuzumab for HER2-positive gastric cancer, and the anti-angiogenesis agent ramucirumab combined with paclitaxel, which have been proven to improve the survival of patients with gastric cancer <sup>[75,76]</sup>”