Dear Editor

First of all I would like to thank the Reviewers of the paper entitled «Towards curative therapy in gastric cancer: faraway, so close!» for their positive comments which I believe have contributed to increase the quality of paper.

I will now address each of the queries raised by the Reviewers and the changes performed in the manuscript which are written in red in the revised Manuscript:

RISK FACTORS: As NSAIDs are preferentially used by patients without gastric disorders, one could hypothesize that the protective effect of NSAIDs against gastric cancer onset is simply attributable to a "healthy drug user effect", similar to the "healthy worker effect" or to the "healthy smoker effect". Indeed the Authors acknowledge that randomized controlled studies, which could elucidate this point, are still lacking. The Authors should comment this point.

A new sentence was added on page 2.

PATHOGENETIC MECHANISMS: I would have expected the Authors to take into account also the new molecular characterization of gastric adenocarcinoma [The Cancer Genome Atlas Research Network 2014]. This paper cannot be ignored.

The following paragraph was added on page 3 with the suggested reference: Further knowledge about gastric cancer heterogeneity has been enlightened by The Cancer Genome Atlas Research Network. Through the molecular characterization of 295 gastric adenocarcinomas, 4 gastric cancer subtypes have been proposed: microssatellite unstable tumours; genomically stable tumours; tumours displaying chromosomal instability and Epstein-Barr positive tumours[18]. Hopefully this subtype analysis will allow a tailored therapeutic strategy for selected patients.

THERAPEUTIC STRATEGIES

When discussing neoadjuvant and adjuvant chemotherapy/chemoradiotherapy, the Authors should acknowledge that compliance to neoadjuvant treatment is much higher than compliance to adjuvant treatment.

We agree with the Reviewer and the following sentences and references were added on pages 5, 6 and 7 respectively: One proposed advantage is the usually the better compliance to chemotherapy in the neoadjuvant setting.
And (page 6)
The ongoing TOPGEAR trial address the question, whether neoadjuvant CRT is superior to CT in a phase II/III setting[40].

And (page 7) Regarding to compliance to treatment MAGIC[27] and FCCNLC[49] trials reported that postoperative treatment was performed in only 42 to 50% percent of the patients demonstrating the importance of preoperative chemotherapy and questioning the use of postoperative treatment in perioperative setting.

Also the S-1 treatment used in Eastern Asia [Sakuramoto 2007] should be mentioned. We western researchers must keep in mind that survival in gastric cancer patients is higher in the East, especially in advanced stages.

In this respect we added a statement regarding adjuvant therapy was modified and ref 48 which refers to S-1 treatment was added.

When adjuvant therapy is used, the optimal regimen is not established. Results with adjuvant capecitabine plus oxaliplatin (CAPOX, XELOX), as was used in the CLASSIC trial[47]; or XP, as was used in the ARTIST trial[41], are not as mature as those of perioperative ECF (as was used in the MAGIC trial) or S-1[48].

I would have appreciated to learn also something about optimal timing of adjuvant treatment.

On the same page the following sentence was added:

The optimal time between surgery and postoperative treatment varies widely. In MAGIC trial[27] it was to be initiated 6 to 12 weeks after surgery, in Intergroup trial (INT0116)[31] between 4 to 7 weeks and in ACTS-GC[48] patients would start within 6 weeks after surgery.

OPTIMAL TYPE OF GASTRECTOMY

References n.45 and n.46 refer to the same trial, not to two separate trials.

We apologize for this mistake which was corrected

LYMPHADENECTOMY

The issue of lymphadenectomy is poorly addressed.

In the 2nd paragraph the Authors first report that "the accepted procedure in the West is a R0 resection with adequate margins with a D1, or ideally, with modified D2 lymphadenectomy". However in the last paragraph they report that "the current consensus is that for medically fit patients D2 lymphadenectomy should be the standard procedure".

Then the Authors lump together all the clinical trials dealing with extension of lymphadenectomy. "This study did not show significant differences in operative mortality, morbidity and duration of postoperative hospital stay and rates of morbid mortality were comparable to those reported for Eastern series (Table 4) [Bonenkamp 1999; Cuschieri 1999; Degiuli 2010; Dent 1988; Bonenkamp 1995; Cuschieri 1996; Wu 2004; Wu 2006; Sasako 2008; Degiuli 2014]". As shown in the following table, only a Taiwanese study [Wu 2006] found a significant survival advantage of D2 with respect to D1, while the British [Cuschieri 1999], Dutch [Bonenkamp 1999] and Italian [Degiuli 2014] trials did not find any significant difference in long-term survival after

the two procedures. The Japanese trial [Sasako 2008] did not find any survival advantage of prophylactic para-aortic nodal dissection (PAND).

Author	*Country*	*lymphadenectomy*	*Median retrieved nodes*	*5-yr survival*	*post-oper mortality*
Cuschieri 1999	*England*	*D1*	*13*	*35*	*6,77*
		D2	*17*	*33*	*13.54*
Bonenkamp 99	*The Netherlands*	*D1*	*17*	*45*	*3.95*
		D2	*30*	*47*	*9.67*
Wu 2006	*Taiwan*	*D1*	*19.4*	*53.6*	*0*
		D2	*37.3*	*59.5*	*0*
Degiuli 2014	*Italy (Piedmont)*	*D1*	*25*	*66.5*	*3*
		D2	*33*	*64.2*	*2.2*
Sasako 2008	*Japan*	*D2*	*54*	*69.2*	*0.8*
		D2+PAND	*74*	*70.3*	*0.8*

The reasons why several trials did not find a survival advantage has been extensively discussed [Verlato 2014; de Manzoni 2015]. In addition to the "elevated morbidity and mortality associated with D2 procedure", another reason was the low (D2, British trial) or high (D1, Italian trial) number of retrieved nodes and the high percentage of adjacent organ removals. Indeed number of retrieved nodes and percentages of splenectomy/splenopancreatectomy have been included among the indexes of surgical quality [Verlato et al, 2009]. Also the Authors of the above-mentioned trials are trying to explain why there trials failed to find a survival advantage after D2 with respect to D1. In the 11th IGCC held in Sao Paulo from the 3rd to the 6th of June 2015, Degiuli reported that stage was significantly more advanced in the D2 group, while the Dutch group reported a significant survival advantage after D2 in a per-protocol analysis.

In Figure 4 5-yr overall survival after D2 in Wu (2006) is 59.5% and not 50.5%, and survival after D1 in Sasako (2008) is 69.2% and not 60.2%.

The Authors should also describe the process of centralization of gastric cancer surgery carried out in Northern Europena countries, and how this process has largely improved short-term results [Jensen 2010; de Steur 2013; Dikken 2013].

The Authors cite Siewert et al [ref. 58] to support the feasibility of D2 lymphadenectomy in the West. Another appropriate reference would be the paper by Roviello et al [2002], showing that D2 dissection was performed with acceptable mortality and morbidity (2% and 17% respectively) in GIRCG [Gruppo Italiano Ricerca Cancro Gastrico = Italian Group for Gastric Cancer Research] centres.

We really appreciate the helpful comments about surgical treatment of gastric cancer. The whole paragraph/ chapter was re-written and new references added according to the Reviewer suggestions. Table 4 was corrected as well.

TREATING GASTRIC CANCER ON THE 21st CENTURY

I disagree with the sentence "Short and long term results now approach Eastern series, with comparable morbidity and mortality". Long-term survival in advance stages is still higher in the East than in the West.

This sentence was modified accordingly: Short and long term results improved substantially in the Western, as long as carried out in specialized, high-volume centers with appropriate surgical expertise and postoperative care.

MINOR PROBLEMS

"case and control studies [4,5]" should become "case-control studies [4,5]". Modified

Figure 1: "third vertebra region". The third lumbar vertebra, I suppose. Modified

Figure 3. The reference of Baracos et al is missing.

This is now reference 88 it is actually Martin et al

Thank you again to Reviewers and Editor for the effort made because we think that the paper improved significantly. If you have any additional questions please let us know

Sincerely yours

Marilia Cravo, MD, PhD