November 5, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5963-review.doc).

Title: The interval to surgery after neoadjuvant treatment for rectal cancer",
Author: Nir Wasserberg
Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5963

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer:

1. Reference 1 is too out-dated. ? Reference 3 is not appropriate. ? In page 4, "pathologic tumor regression" should be (26% vs. 10.3%) not (10.3% vs. 26%). And the p value should be <0.05 not =0.05 for both factors.

1 Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60: 277-300. doi:10.3322/caac.20073

(26% vs.10.3%) than the shorter-interval group (p<0.05 for both factors). (p.5)

2. - I would only suggest to replace ref 13 (related to oesophageal cancer) by two recent references from WJG Early dynamic transcriptomic changes during preoperative radiotherapy in patients with rectal cancer: A feasibility study Stephane Supiot, Wilfried Gouraud, Lo?c Campion, Pascal Jez équel, Bruno Buecher, Josiane Charrier, Marie-Francoise Heymann, Marc-Andre Mah é, Emmanuel Rio and Michel Ch érel. World J Gastroenterol19(21):3249 -3254 . Published online 2013 June 07. doi:10.3748/wjg.v19.i21.3249. Prognostic role of sensitive-to-apoptosis gene expression in rectal cancer. Ozden SA, Ozyurt H, Ozgen Z, Kilinc O, Oncel M, Gul AE, Karadayi N, Serakinci N, Kan B, Orun O. World J Gastroenterol. 2011 Nov 28;17(44):4905-10. doi: 10.3748/wjg.v17.i44.4905. 2 - It would also be interesting to cite two recent articles of interest for the topic : Neoadjuvant vs adjuvant pelvic radiotherapy for locally advanced rectal cancer: Which is superior? Sarah Popek and Vassiliki Liana Tsikitis. World J Gastroenterol17(7):848 -854 . Published online 2011 February 21. doi:10.3748/wjg.v17.i7.848. Oncologic outcomes of primary and post-irradiated early stage rectal cancer: a retrospective cohort study. Du CZ, Chen YC, Cai Y, Xue WC, Gu J. World J Gastroenterol. 2011 Jul 21;17(27):3229-34. doi: 10.3748/wjg.v17.i27.3229. 3 - In the "prognosis section", ref 61 suggested that "an interval of more than 16 weeks between diagnosis and surgery may reduce overall survival of patients treated with preoperative RT for locally advanced rectal cancer. Surgery should be performed shortly after completion of RT for patients with no possibility of

sphincter preservation, or a minimal risk of morbidity from an abdominoperineal excision". Could you please comment ?

3 Cellini F, Valentini V. Current perspectives on preoperative integrated treatments for locally advanced rectal cancer: a review of agreement and controversies. Oncology (Williston Park) 2012; 26: 730-735, 741 PMID:22957406

4 Popek S, Tsikitis VL. Neoadjuvant vs adjuvant pelvic radiotherapy for locally advanced rectal cancer: Which is superior? World J Gastroenterol 2011; 17: 848-854. doi:10.3748/wjg.v17.i7.848 PMID:21412494

5 Du CZ, Chen YC, Cai Y, Xue WC, Gu J. Oncologic outcomes of primary and post-irradiated early stage rectal cancer: a retrospective cohort study. World J Gastroenterol 2011; 17: 3229-3234. doi:10.3748/wjg.v17.i27.3229 PMID: 21912472

6 Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev 2012; 3: CD004078 doi:10.1002/14651858.CD004078.pub2 Review PMID:22419291

16 Supiot S, Gouraud W, Campion L, Jezéquel P, Buecher B, Charrier J, Heymann MF, Mahé MA, Rio E, Chérel M. Early dynamic transcriptomic changes during preoperative radiotherapy in patients with rectal cancer: a feasibility study. World J Gastroenterol 2013; 19: 3249-3254 doi:10.3748/wjg.v19.i21.3249 PMID:23745026

17 Ozden SA, Ozyurt H, Ozgen Z, Kilinc O, Oncel M, Gul AE, Karadayi N, Serakinci N, Kan B, Orun O. Prognostic role of sensitive-to-apoptosis gene expression in rectal cancer. World J Gastroenterol 2011; 17: 4905-4910 doi:10.3748/wjg.v17.i44.4905 PMID:22171132

By contrast, a retrospective multivariate analysis of 102 patients with low rectal cancer demonstrated that delaying surgery beyond 16 weeks from rectal cancer diagnosis had a negative impact on overall and metastasis-free survival (OR = 2.59 (1.33–5.79), p = 0.005) [57]. A long interval between radiation therapy and surgery (6-8 weeks) was not recommended for patients who may not benefit from tumor

downstaging by sphincter preservation. (p.8)

3. 1. There are some typographical mistakes e.g. in page 4: significantly, & page 7, under sphincter preservation " … findings statistically significant findings", line 5 under Summary: localy advanced. 2. Page 6: what is meant by " Nevertheless was similar in the two groups."? 3. Page 9: the results are expected in 2013. The recruitment for the trial ends in October 2013, so results will not be expected in 2013.

Yet in neither this study nor others that investigated sphincter preservation rates by CRT-surgery interval were the findings statistically significant[22,28,36].(p.8)

Recent studies that sought to further improve outcome in patients with locally advanced,….(p.9)

Nevertheless, survival was similar in the two groups.(p.8)

]. In another study begun in 2009 in the UK, patients are randomized to undergo CRT and surgery after 6 or 12 weeks. The final cohort will include 218 patients at the end of recruitment[67].(p.10)

3 References and typesetting were corrected

Thank you again for considering publishing the manuscript in the *World Journal of Gastroenterology.*

Sincerely yours

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