February 1st , 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7149-review.doc).

**Title: McGill Brisbane Symptom Score for patients with resectable pancreatic head adenocarcinoma**

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**Name of Journal:** *World Journal of Gastroenterology*

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We thank the reviewers very much for helping to significantly improve the quality of our paper and the clarity of its message.

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

**1 Format has been updated**

**2 These are our answers to the reviewer:**

Major problems:

1) After a detailed report of the pathological procedure, the AJCC tumor staging and grading, the number of lymph nodes retrieved and the number of eventually positive lymph nodes is not reported. The positive lymph node ratio is also lacking.

We inserted the status of lymph nodes in table 2

2) Rows 78-84: The reported R0 resection rate is quite high (67%). With a R2 resection rate of 6% the R1 resection rate is only 27%. This is probably due to considering an R1 resection only if tumor cells were present at the inked margin. A negative 0.5 or 1 mm tumor cells free resection margin may increase the number of R1 resections.

We used the guidelines of the Royal College of Pathologists and the Leeds Pathology Protocol. Thus, large slices were obtained, allowing a precise study of each inked margin in increments of 0.5 mm from 0 mm to 2.0 mm. Margin involvement (R1) was defined for the 0-mm margin if tumour cells were present at the inked margin; R1 was also defined for each margin width if tumour cells were present within the margin, independently of the mode of tumour spread. The resection was considered as curative (R0) if no tumour cells were identified in the peripancreatic fat or at any of the resection margins (bile duct, pancreatic neck and uncinate resection margins).

Yes, if we *had* defined an R1 resection as a negative 1mm from the resection margin, then that theoretically may have increased our R1 rate.

3) In the previous paper (Jamal MH, et al. HPB (Oxford) 2010; 12:561-6) the definition of symptoms that independently predict survival was based on the Odds Ratios calculated on the original cohort and verified in the validation cohort. Why the same procedure was not repeated in the present study on patients undergoing pancreaticoduodenectomy for pancreatic head adenocarcinoma. It is possible that, in an earlier phase of the disease, the weight of the different parameters will be different.

We did not use odds ratios at all in the previous paper. What has been labeled “odds ratios” in Table 3 of that paper are actually the coefficients from a Cox regression and were re-labeled in the proofs which we missed. The legend interprets the HR as an odds of the event occurring first but this refers to the interpretation of the HR and not to an odds ratio. An erratum is being sent to change “odds ratios” in Table 3 of that paper to “regression coefficient”.

4) The Authors state that the proposed MBSS is better than radiological staging, Ca 19-9, and the nomogram published by Brennan et al in 2004 in predicting patient survival. Apart the great value of postoperative normalization of CA 19-9 in predicting survival, they omit also the predictive value of an high SUV (Standardized Uptake Value) on 18FDG PET or PET/TC (Wang Z, Chen JQ, Liu JL, Qin XG, Huang Y. FDG-PET in diagnosis, staging and prognosis of pancreatic carcinoma: a meta-analysis. World J Gastroenterol. 2013; 19 :4808-4817.

We did not look at the correlation of SUV with survival. As this is a retrospective review, we did not perform PET scans routinely in all patients, and availability in Quebec for this group of patients is limited. It was therefore not possible to look at this variable. In future prospective studies we will look at it. In this study we did not compare the MBSS to Dr.Brennan’s nomogram, therefore we cannot state how it compares in terms of survival prediction (including test characteristics profile). However the MBSS is more useful clinically as all it factors are present at the time of diagnosis prior to any intervention as opposed to the MSK nomogram.

5) Patient’s follow-up was completed until February 2011 (Row 48). Why the Authors didn’t try to obtain more recent data? Furthermore, how many patients were still alive in the low and high MBSS group at the time of writing?

Obtaining further data would require further funding to access the provincial government of Quebec database. The purpose of the study was served we thought by clearly showing a

discrimination between the low and high MBSS groups in survival. We do not have data on how many patients were alive at the time of writing as this would require re-accessing the provincial government of Quebec database and further funding. This would not alter the fact that the MBSS discriminate survival in pancreatic adenocarcinoma patients.

6) Row 70 "…pancreaticoduodenectomy was performed with gastric transaction …". Specify the extent of lymphadenectomy.

We perform a standard pancreaticoduodenectomy therefore the following lymph node groups are removed:
Lymph nodes of the right side of the hepatoduodenalligament (stations 12b1, 12b2, and 12~) Anterior (stations 17a and 17b) and posterior (stations13a and 13 b) pancreaticoduodenal nodes to the right side of the superior mesenteric artery (stations 14a and 14b). Removal of the lymph nodes of the anterior region of the common hepatic artery (station 8a)

7) Row 71: "Some patients had a pancreaticojejunal anastomosis, while others had a pancreaticogastrotomy according to surgeon preference." It should be better to include the exact number.

25 patients had a pancreatogastrostomy (30%).

8) Row 90-93 "The postoperative treatment includes adjuvant therapy as per protocol in the form of gemcitabine for 6 months for the study period." How many patients in each MBSS group had adjuvant chemotherapy and how many completed the 6 months scheduled therapy?

Fifty three patients in total received adjuvant chemotherapy. Twenty seven in the high MBSS group and 26 in the low MBSS group. Seven patients in the high MBSS group could not continue their 6 months of adjuvant chemotherapy, while 3 patients in the low MBSS could not continue their adjuvant chemotherapy.

Minor problems:

1) Row 29, reference 11: it may be include also a reference on KRAS, CDKN2A/p16, TP53, and SMAD4/DPC4 (Oshima M, Okano K, Muraki S, Haba R, Maeba T, Suzuki Y, Yachida S. Immunohistochemically detected expression of 3 major genes (CDKN2A/p16, TP53, and SMAD4/DPC4) strongly predicts survival in patients with resectablepancreatic cancer. Ann Surg. 2013; 258: 336-346).

2) Row 151 “pre-op stent.” Incomplete statement.

Removed

3) R0 resection is different at row 137 “A majority (80%) of patients had R0 resections” and within the Table 3: 56 patients (67%).

Corrected

4) Row 142: “Median overall survival was 23 months, and 5-year survival was 29.4% (95% CI 19.2-40.3%).” Row 175: “: the overall median survival was 25 months, and 5-year survival was 28%. “ Which is correct?

The values in the results section (23 months and 29.4%) are correct and this has been rectified in the paper

**3 References and typesetting were corrected**

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

Sincerely yours,

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