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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6175-review.doc).



Title: Prognostic factors in patients with middle and distal bile duct cancers

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6175

I would like to express my gratitude for the valuable comments from the reviewer on our manuscript. Based on the reviewer's comment, we have revised the manuscript to reflect the opinion. The revised parts were highlighted by using red colored text.

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 reviewers

Reviewer 1

The manuscript entitled "Prognostic factors in patients with middle and distal bile duct cancers " is a large retrospective study on those patients who underwent different types of surgery based on different limitations and anatomical location of tumors. The ultimate results were determined by the 5-year survival. The interim analysis was based on the percentage of patient who achieved R0 and R1 resection.

Comments 1. Hypothetically, PD is a more extensive surgery than BDR. Therefore the result of PD should be better than that of BDR. However, those who underwent BDR with R0 result should also had a good survival.

Since there were 4 patients in BDR group had positive lower margin and could not receive PD. In my opinion, these patients should be excluded for a fair comparison between PD and BDR groups in term of survival.

Comments 2. I would rather call all these patients as "Non-hilar cholangiocarcinoma" than middle and distal bile duct cancers. The other option to say as "it is a distal cholangiocarcinoma" is still fair.

Comments 3. The definition to split patients by using a cystic duct as a landmark is uncertain since a patient with low-lying cystic duct may be mistakenly classified as as hilar cholangiocarcinoma since its nature is closer to the non-hilar one.

Reply to Reviewer 1

(about Comments 1)

We agree with the comment that PD hypothetically results in better survival because PD can achieve higher R0 rate. Our data also showed that the PD group had a higher rate of R0 resection than the BDR group (90.0%, 89/90 vs. 48.8%, 21/43 p<0.0001).

The 5-year survival rates of all patients with PD (R0, R1, R2) and BDR (R0, R1, R2) were 46.6% and 30.0% (p=0.105), respectively; this difference, although not statistically significant, can be attributed to a

higher rate of positive resection margins in patients with bile duct resection. For fair comparison of PD with BDR, we compared only R0 cases of both group. The result showed 5-year survival rates after R0 bile duct resection was similar to R0 PD (46.5% vs. 49.4%; $p=0.762$) (Fig. 3).

(about Comments 2)

Currently, there is no clear consensus regarding the terminology of extrahepatic bile duct cancer. As the reviewer commented non-hilar bile duct cancer included middle and distal bile duct cancer. Thus, non-hilar bile duct or distal bile duct cancer can be alternatively used. The reason we chose the term 'middle and distal bile duct cancer' is that this term can describe the location of the tumor more precisely.

(about Comments 3)

We agree with the comments so we corrected the definition of middle and distal bile duct cancers as tumors with the main lesions located at middle and distal third of extrahepatic bile duct. We described as "Middle and distal bile duct cancer was defined by imaging studies and by the operative findings of tumors with the main lesions located at middle and distal third of extrahepatic bile duct." In page 6

Reviewer 2

The authors present the results of a retrospective study of middle and distal bile duct cancer. They identified the influence of the surgery type (PD or BDR) and prognostic factor.

Questions / Comments

1. Many studies have been published on this topic. How dose this paper add anything new to the literature?
2. They focus on the clinicopathological factors and survival. But, at the same time, they also focus on the two types of surgery. Please mention whether BDRs were less postoperative morbidity or mortality, early recover from surgery, or early initiation of adjuvant chemotherapy.
3. Many factors as well as clinicopathological factors may affect patient survival. Why did they analyze only clinicopathological factors? Because the background of study subjects is unclear, they should show a descriptive figure of all the subjects including performance status, presence of jaundice, preoperative biliary drainage, adjuvant therapy, tumor marker, postoperative complication etc.
4. Did you look at first recurrent site? It would be interesting add this information and disease free survival curves. R0 and R1 did not differ in survival because distant metastases occurred and limit the patient life? PD caused less local recurrence comparing to BRD?
5. Fig 4 b,c,d,e,f are unnecessary. Those makes us confuse and unclear. Why did they stratify N-/ + or T factor? Multivariate analyses resulted LVI and Stage. So, they should show LVI and Stage curves or their combination.
6. It is unclear: Page 8, "Lymphovascular invasion was present in 41.4% and 19.5%, respectively."
7. It is unclear: Page 9, "The five-year survival rates of patients at TNM stage 0 or 1 were higher than those of patients with TNM stage 2 or 4 (64.5%, 30.1%, and 0%; $p=0.006$)."

8. Please provide 95% confidence interval in table 2.

Reply to Reviewer 2

(*about* 1) Our study found that the presence of lymphovascular invasion is independent prognostic factors. Although this finding is not the first finding, only few reports have been published regarding the significance of LVI in middle and distal bile duct cancers. Our data once more showed that the presence of lymphovascular invasion was an independent prognostic factor.

(*about* 2 and 3)

In this study we aimed to identify the clinico-pathological prognostic factors rather than to find out the surgical outcomes such as morbidity and mortality related with each type of surgery. We described that the mortality cases were excluded from this study in the part of statistical analysis of the patients and methods section.

Our unpublished data showed that there were no mortality cases among bile duct resection group and the mortality rate was not different between two types of surgery.

Regarding the chemotherapy, we added the description regarding as “None of the patients received chemotherapy before or after surgery”

The univariate analysis of preoperative CA19-9 showed no statistical significance for survival and the data was added newly to table 1.

We routinely select the patients with ECOG grade from 0 to 2 for surgery. Although performance status and preoperative biliary drainage are important before surgery, these factors usually does not affect the long term postoperative survival. Thus we did not analyzed these factors for survival analysis.

(*about* 4) As the reviewer suggested, we describe the recurrent site and compared disease free survival between R0 PD and R0 BDR. We also showed the disease free survival curve of R0 PD and R0 BDR was not different. We described as following sentences. “Recurrence after surgery occurred in 58.8% (60/102) of the patients with R0 resection during the period of follow up. The most common site of first recurrence was abdominal lymph nodes only (38.3%, periportal, around Superior mesenteric artery, paraaortic) followed by liver only (35%), anastomosis site (8.3%), and lung (1.7%). The abdominal lymph node metastasis was present in combination with local recurrence and liver metastasis at the time of first recurrence in 5% and 1.7% respectively. Lymph node metastases were found in 55.0% of the patients with first recurrence in the pattern of lymph node metastasis only (38.3%) or combination with other organ metastases (16.7%). The long term disease free survival of R0 PD was similar to R0 BDR (Fig. 3 b).”

(*about* 5) We removed the Fig 4 and added newly Fig 3b, which illustrates the comparison of the long term disease free survival between R0 PD and R0 BDR

(*about* 6) We corrected the sentence as “Lymphovascular invasion was present in 25 of 128 (19.5%) (page 9).”

(*about* 7) We corrected the sentence as “The five-year survival rates of the patients at TNM stage 0 and 1 were higher than those of patients with TNM stage 2 and 4 respectively (64.5% vs 30.1%, and 0%; $p=0.006$) (page 9).”

(*about* 8) We added the 95% confidence interval in table 2 (page 21).

Reviewer 3

This is a well-designed retrospective study with a quite big sample size. The conclusions are reasonable and credible. Here I have only one Minor point of concern: The references cited in this article are not quite updated, since that nearly half of the references are published before the year 2000, and only 2 of them are within 5 years. The authors should review the up-to-date literatures and update the corresponding data cited in the manuscript.

Reply to Reviewer 2

According to the reviewer's comment we changed reference Number 1 and 7.

References and typesetting were corrected

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

Sincerely yours,

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