Peer Review File

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Comment 1: Because the clinical TNM stages are different, isn't it difficult to say that nCRT/OLT is more effective than other treatments?
Reply 1: Thank you for this comment. We acknowledge that patients in the nCRT/OLT group are highly selected and must have early-stage disease to qualify. However, treatment pathway was a significant independent factor on MVA. We modified the text in the Discussion section to make this limitation clearer (See page 15, lines 303-307).
Changes in the text: Page 15, lines 305-309: "It is acknowledged that patients eligible for nCRT/OLT are a highly selected group with potentially more favorable risk factors than patients treated with surgery and aCRT. However, treatment strategy was identified as an independent prognostic factor on multivariable analysis. This finding is also consistent with prior data from a Mayo Clinic."

Comment 2: If the therapeutic outcome is to be compared according to various treatment methods, it would be desirable to select the same TNM stage and proceed with case-control comparison.
Reply 2: Thank you for this comment. We agree this would be a desirable analysis. However, our patient numbers were too small to allow for case matching.
Changes in the text: No changes.

Comment 3: Because comparative results in same clinical stage were not presented in your study, the rationale for why neoadjuvant + OLT is recommended instead of conventional resection should be added. In addition, there should be a detailed description of the actual indications for OLT other than surgery (ex. drainage, preoperative tissue confirmation, jaundice, and liver function evaluation) at your institute.
Reply 3: Thank you for this follow-up comment. Criteria for liver transplantation in the setting of cholangiocarcinoma is the standard criteria that has been adopted by the transplant community. A description of OLT selection criteria and key references are included in Methods. With respect to whether OLT or surgery is the selected treatment option, anatomic location of the tumor is typically the primary determinant. Liver transplantation is indicated for hilar cholangiocarcinoma, and we never pursued liver transplantation for distal cholangiocarcinoma that is isolated to the biliary tree below the cystic duct insertion. Distal cholangiocarcinoma is managed with surgical resection only. OLT is favored for eligible patients based on previously reported superior results as discussed in the text, especially if the patient had an underlying liver disease such as PSC. We have provided further clarification of treatment selection in the text (page 9, 152-156).
Changes in the text: Page 9, 152-156: "Patients were selected for each treatment based on anatomic factors, staging, and medical comorbid conditions. Patients were always considered first for transplant or surgery. Patients with hilar cholangiocarcinoma were screened for eligibility for nCRT and OLT as the preferred treatment. Patients with distal cholangiocarcinoma were evaluated for primary surgery."

Comment 4: - Why have the authors chosen to name/divide the groups based on neoadjuvant/adjuvant/definitive CRT? Is it hypothesized that the type of CRT or liver transplant/resection/no surgical treatment defines the groups and determines prognosis?
Reply 4: Thank you for this comment. We are grateful for the opportunity to clarify this point. Our purpose was to evaluate our experience using CRT in our 3 major treatment paradigms. We therefore defined the groups via nomenclature using timing and purpose of CRT. We acknowledge that different patient groups are eligible for different treatments. We hypothesized that patients treated with neoadjuvant CRT followed by liver transplant have better outcomes than patients who undergo resection followed by adjuvant CRT or definitive

CRT, which are likely the result of both selection bias and treatment pathway. On MVA, nCRT/OLT treatment pathway was an independent predictor of better OS. Additional text was added to the Abstract and Introduction to clarify (page 5, line 66; page 8, lines 121-122; page 8, lines 136-138)
Changes in the text: Page 5, line 66: "We report our experience with 3 strategies for treating hilar and extrahepatic cholangiocarcinoma including chemoradiotherapy."
Page 8, lines 121-122: "Various regimens including radiation therapy combined with concurrent chemotherapy have been used to treat CCA."
Page 8, lines 136-138: "The purpose of this investigation was to evaluate outcomes of patients with hilar and distal cholangiocarcinoma in which chemoradiation was included as part of the treatment strategy."

Comment 5: - What data supports the statement that chemotherapy combined with EBRT is a curative treatment for CC?
Reply 5: Thank you for this question. We acknowledge that our data confirm that CRT with traditional radiation doses and techniques does not provide a realistic chance at cure. Jethwa et al. included 48 patients in a retrospective analysis who received chemoRT for extrahepatic cholangiocarcinoma and gall bladder cancer. Forty-one of those patients had extrahepatic cholangiocarcinoma. The 2-, 3-, and 5-year OS was 33%, 20%, and 7%. On univariate analysis, >59.5 Gy10 was associated with improved OS and PFS. Therefore, it may be possible to achieve cure in a small proportion of patients treated with dCRT with modern radiotherapy and dose escalation. We have edited the text to incorporate these points (page 16, lines 326-330).
Changes in the text: Page 16, lines 326-330: "It would be reasonable to conclude that dCRT with traditional radiotherapy dose techniques and fluorouracil-based chemosensitization is not truly curative but instead only palliative. However, studies have demonstrated more promising outcomes when radiation dose escalation can be achieved safely (25)."

Comment 6: - Both patients with distal and hilar cholangiocarcinoma were included in this study, however in methods is stated that patients with extrahepatic disease were excluded in the OLT group. Is distal cholangiocarcinoma not defined as extrahepatic cholangiocarcinoma?
Reply 6: Thank you for this comment and the opportunity to clarify the text. Distal cholangiocarcinoma should be included as extrahepatic cholangiocarcinoma. The reference to exclusion criteria for OLT should be "metastatic" and not "extrahepatic." The text has been modified (Page 9, line 162)
Changes in the text: (Page 9, Line 162): "extrahepatic" was changed to "metastatic."

Comment 7: Why are all patient with CCA subjected to pancreaticoduodenectomy? What was the reason for the 5 patient with pCCA to extent partial liver resection with external bile duct resection to a pancreaticoduodenectomy?
Reply 7: Thank you for this comment. Hilar CCA would only involve pancreaticoduodenectomy in cases with there was distal common duct involvement. We do our best assessment to make sure that patients with hilar CCA are without extension of the disease below the cystic duct. Our current diagnostic modalities can miss certain cases of dysplasia or tumor that are identified only at surgery and that will result in pursuing the Whipple procedure. The text was modified for additional clarity (Page 10, lines 171-176).
Changes in the text: Page 10, line 171-176: "In the aCRT group, radical resection for hilar or distal CCA was performed, which included resection of the extrahepatic biliary tree with or without hepatic resection (partial or total) or Whipple, depending on the anatomic extension of disease in the biliary tree. Patients who were not eligible for OLT or radical surgery for anatomic or medical reasons but did not have distant metastatic disease on staging received dCRT."

Comment 8: And visa versa, were all patients with dCCA undergoing liver resection?
Reply 8: Thank you for your question. The dCCA patients did not undergo liver resection. Consideration of liver resection depends on location of the tumor, and it is routine to check the bile duct margin for presence of tumor to determine extent of the final resection. In evaluating further the types of location of disease in patients in the aCRT group, we identified that 1 patient was mislabeled as perihilar and technically had a dCCA. This patient underwent a Whipple procedure like other patients with dCCA. The text was modified to provide additional information and clarity (page 11, lines 206-209).
Changes in the text: Page 11 Line 206-209: "Of patients undergoing radical resection in the aCRT group, 4 patients with perihilar disease underwent bile duct resection, partial hepatectomy, and Roux-en-Y hepaticojejunostomy; and 12 patients with distal bile duct disease underwent the Whipple procedure (pancreaticoduodenectomy, cholecystectomy, common bile duct resection)."
Page 21, Table 1: "In aCRT column: Perihilar: 5 changed to 4. Distal: 11 changed to 12."

Comment 9: In methods it is stated that patients with tumors >3 cm are excluded from OLT, however Table 1 shows that 1 patient in this group had a tumor size >3 cm. Please specify why?
Reply 9: Thank you for this comment and the opportunity to clarify. This was a mistake in our reporting of the data. The criteria for OLT eligibility was preoperative imaging. All 20 patients in the OLT group had a clinical tumor size of <3 cm. One patient was found to have a tumor size difficult to assess after nCRT, but 5.5 cm of fibrotic tissue was noted at time of pathologic review. Final staging at pathology was still ypT1. Table 1 was amended to clearly reflect clinical staging characteristics, and the text in the Methods section was modified for additional clarity (page 9, line 163).
Changes in the text: Table 1 was changed to state "Clinical tumor size" and all 20 patients had clinical tumor size ≤3 cm." Page 9, line 163. "…tumor size greater than 3 cm on pre-operative imaging,…"

Comment 10: - What percentage in the aCRT group had a radical resection at pathological assessment? And how was this defined?
Reply 10: Thank you for the questions addressing extent of surgery. All patients in the aCRT group underwent a radical resection, and the text in the Methods section was modified as described above for clarity (page 10, lines 176-181).
Changes in the text: Page 10, line 171-176: "In the aCRT group, radical resection for hilar or distal CCA was performed, which included resection of the extrahepatic biliary tree with or without hepatic resection (partial or total) or Whipple, depending on the anatomic extension of disease in the biliary tree. Patients who were not eligible for OLT or radical surgery for anatomic or medical reasons but did not have distant metastatic disease on staging received dCRT.

Comment 11: - As treatment strategy was the variable of interest in this study, why was this variable added in the uni/multivariate analysis?
Reply 11: Thank you for your comment. Treatment strategy was not included in the univariate analysis to determine which other clinical risk factors were possible predictors of our events (OS, DFS, etc). Since treatment strategy was our variable of interest and was a significant

factor, it was included in all multivariate models.
Changes in the text: No changes

Comment 12: - - How many patients treated in the aCRT group would retrospectively qualified for the nCRT/OLT group?
Reply 12: Thank you for this interesting question. Treatments are necessarily defined preoperatively. As stated above, anatomic tumor location is a major determinant of the decision between nCRT/OLT and radical surgery. This factor would not be expected to be altered after postsurgical retrospective review. However, this might be an interesting analysis in a subgroup of patients. Although a retrospective analysis of operative and pathologic factors relative to eligibility for OLT was beyond the scope of this current manuscript, this could be interesting to look at in the future.
Changes in the text: No changes.

Comment 13: Why did the authors chose to compare survival of three groups, as patients included in dCRT (and probably some aCRT) did not qualify for the nCRT group?
Reply 13: Thank you for the question. Our purpose was to evaluate the outcomes of the 3 major groups of patients with chemoradiation included in their course of potentially curative treatment. As discussed in the text, we acknowledge that these groups have quite different initial prognostic factors that led to inherent bias in the selection of treatment and numerous factors that could be influencing outcomes. As rightly stated, the nCRT/OLT group was more favorable, which could be a factor in more favorable outcomes. Nevertheless, treatment pathway was a significant variable on multivariable analysis for survival.
Changes in the text: NA

*****: Tables 1, 2, 3 were updated after data was updated after further review. The numbers that were changed are highlighted.**
