Reviewer A

The authors of this study highlight in their conclusions the beneficial effects of adjuvant chemo-radiotherapy in the treatment of gallbladder carcinoma, compared to the absence of adjuvant treatment or adjuvant therapy based solely on chemotherapy. The results show that patients who receive chemotherapy and radiotherapy after surgery obtain a very high median survival (54.4 months). This result is spectacular. However, it could be explained by a selection of patients since a comparison of the variables with prognostic value is not made between the 3 study groups. Therefore, the methodology used seems to invalidate the conclusions.

On the other hand, there are numerous weaknesses in the study that should be reviewed:

-The title of the study does not correspond to the objective stated at the end of the introduction.

-In the introduction, the authors state that …Most commonly patients are asymptomatic. This may be the case with incidental tumors, but is not usual in the case of non-incidental tumors. However, the article does not mention the inclusion of incidental tumors or the percentage thereof.

The title is modified precisely to reflect the end of introduction

-It is not specified which edition of TNM staging has been used.

The American Joint Committee on Cancer (AJCC),2017, eighth edition, TNM staging for gallbladder cancer system was used.

-There seems to be an error in the statement of lines 113-115…The OS in stage 3-4 patients with surgery alone vs surgery & CT was 5.5 versus 28.7 months respectively (p = 0.0052; Figure 6). The PFS for the same group was 17.5 vs 4.6 months (p=0.0052; Figure 7). The results for PFS are the opposite of those for OS.

This is now corrected. 4.6 vs 17.5 months

-The results repeat data included in the Tables.

The description is now precise.

"In the evaluation of 93 patients diagnosed with gallbladder cancer: The median age was 66 years, with a majority of the patients (67%) being females. The majority of the patients were Caucasians (68%), followed by African Americans (30%).

The most common type of tumor was adenocarcinoma. According to the AJCC (American Joint Committee on Cancer) 2017 staging, 30% of the patients were diagnosed at an early stage (Stage I & II). The median time to start chemotherapy after surgery was 1.5 months. The treatment details were as follows: 10.8% of the patients received adjuvant chemotherapy (chemotherapy given after surgery to kill any remaining cancer cells and reduce the risk of recurrence). 14% received both adjuvant

-The mean number of nodes included in lymphadenectomy is very low, and there are many missing data in relation to pathology reports. This aspect suggests that the staging of patients is deficient.

I have addressed this question with our hepatobiliary surgeons. There was no standardized guidelines on the number of lymphnodes to be removed operatively. Besides, the staging is slightly variable from 2010 to 2017. This is one of the drawbacks with the single center retrospective study. I now added in the discussion section.

"This variability is likely attributable to the lack of standardized guidelines concerning the number of lymph nodes to be removed during surgery. Additionally, discrepancies in staging could stem from changes in staging criteria between 2010 and 2017."

-Line 109 reports a 5-year median OS of 23.7%. This concept seems wrong, because it is a percentage and not a median that is expressed in months.

Should be reported as 5 year survival rate. Adjusted accordingly.

-Line 104-105 indicates that only 21.5% of the patients presented recurrence, but nevertheless 71% of the patients had died. These data should be clarified, since they seem to indicate that the majority of patients did not die from a tumor.

The recurrence data is missing on majority of the patients as several of them returned to community oncologist. The cancer center followed up on survival data only. Removed this variable.

-It should be clarified whether in group 1 of Tables 3, 6 and 7, the adjuvant treatment concept includes only chemotherapy or also chemo-radiotherapy.

Adjuvant includes any modality (chemo or chemoxrt). Modified verbatim to further clarify in results section

-The discussion is basically a review of the literature and includes few comments in relation to the own results.

The discussion is now modified to incorporate newly published data and added relevant information related to the study.

Reviewer B

The authors investigated factors affecting outcomes in gallbladder cancer. In particular,

they refer to the usefulness of adjuvant chemoradiation. Unfortunately, this study utilized retrospective data collection and the information is insufficiently detailed to connect to their opinions.

There some additional concerns:

Major
1. Methods section:
(1) In this study, the descriptions for the methods and statistical analysis are insufficient and need further detail.

Survival outcomes were compared between patients who received different treatments. We conducted all statistical analyses using SAS software version 8.2 , and generated survival curves with Prism 8. Patient survival rates were evaluated using the Kaplan-Meier method, and survival rate comparisons across two or more groups were analyzed using the log-rank test. During the development of the Cox regression model, we first performed univariate analysis to identify statistically significant variables suggesting predictors of overall survival. Taking into account data integrity, we included some variables as continuous variables in the regression model. Variables that proved significant in univariate analysis were then incorporated into the Cox regression model (using a backward method) for multivariate analysis, helping us to evaluate for any independent factors that influenced patient prognosis. Overall survival (OS) was defined as the time between surgery and death or censored at the last follow-up date. Progression-free survival (PFS) was defined as the time to recurrence or death. All tests were two-sided, and we deemed a P-value of less than .05 as statistically significant

(2) Was the Cox proportional hazard model univariate or multivariate? This needs to be clearly stated.
Cox proportional hazard model. It is now mentioned as above.

2. Results section
(1) Table 1
In the staging of gallbladder carcinoma, patients were usually divided into Stage 0, 1, 2, 3a, 3b, 4a, 4b. In Table 1, does Stage 4 include stage 4b? Patients in stage 4b have distant metastasis and cannot receive surgery.
Stage 4b is not included as the patients were not surgical candidates. To avoid futher confution, the table is now modified to include stage 1 through 4 per AJCC, 2017

This study is on the patients who underwent definitive surgery.

In the treatment modality, who had surgery? Unknown (20 patients) and none (16 patients).

Who was included in the analysis?

What is the reason for selecting each therapy (none, Chemotherapy, Chemoradiation)

What kinds of chemotherapy did the authors use?

What radiation doses were given?

The analysis primarily included those patients who underwent definitive surgery. One third of these patients underwent adjuvant therapy with chemo or chemo xrt. Chemo was gemcitabine and radiation sensitizer was fluoropyramidine. The radiation doses were not available for majoriy of the patients due to lack of standardized documentations prior to EMR.. This information is now added in the manuscript

(2) Table 2

Is this analysis univariate? Or multivariate?

If multivariate, the authors should show the reasons for selecting these items.

(3) In Figures 4, 5, 6, 7

The authors should show patient characteristics, compare the two groups, and then perform Kaplan-Miere analysis. The authors should also perform multivariate analysis (Cox proportional hazard model).

Minor

1. The English requires extensive editing and proofreading.

Used grammarly to proofread.

2. Some terms are inappropriate.

addressed them

3. In the introduction and discussion section, there are many unnecessary sentences.

The introduction and discussion sections were modified extensively

4. Several items include the following:

① In the abstract

・overall survival (OS) -> overall survival time

・Progression free survival (PFS) -> progression survival time

・(Table) -> delete

・adjuvant therapy (CT or CRT) critically important. -> Adjuvant

② In the results

・3 in 77/20 -> 3 in 3.2%?

・CA19-9 was 950. -> add unit (U/mL)

③ Figures and Tables

・Several figure do not have a legend.

・The tables lack a listing of abbreviations

・Table 1. CA19 -> CA19-9

・Table 2

Neutrophil to lymphocyte ratio -> delete
P-> P value

All the above has been addressed