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Review comments-reviewer A

Reviewer comment 1:

First, the title needs to indicate the clinical research design, i.e., a retrospective cohort study, and the outcomes of this study, OS and CSS.

Reply 1: We appreciate your valuable advice on the manuscript title and we rewrite the title with clear implication for the study design and outcomes.

Changes in the text:

Page 1 line 2-5

Title: Neoadjuvant and adjuvant chemotherapy share equivalent efficacy in improving overall survival and cancer-specific survival among muscle invasive bladder cancer patients who undergo radical cystectomy: a retrospective cohort study based on SEER database.

Reviewer comment 2:

Second, the abstract needs some revisions since it is not adequate. The background did not explain the clinical needs to compare AC and NAC and what has been known on the efficacy and prognosis of NAC for MIBC. The methods did not describe the inclusion of subjects, the assessment of baseline clinical factors including AC vs. NAC, follow up procedures, and measurements of prognosis outcomes. The results need to describe the clinical characteristics of the NAC and AC groups, and indicate the comparability of the two groups. Please report the adjusted HR values. The conclusion needs to be tone down because this is not a RCT.

Reply 2:

We are grateful for your suggestion on our deficiency in summarizing the article.

- 1. According to the comments, we briefly describe the efficacy and prognosis of NAC and illustrate the clinical significance of comparing these two strategies in the background part of the abstract section**

Changes in the text:

Page 2 line 38-46 Abstract: Background

Previous level 1 evidences have reported an approximately 6% absolute improvement in 5-year overall survival brought by neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC) which has been established as the standard treatment for muscle invasive bladder cancer (MIBC). However, criticism still exists considering that the delay of surgery may confer a risk for progression and the lack of accurate pathological evidence may lead to imprecise clinical staging and unnecessary treatment. Multiple trials have instead focused on adjuvant chemotherapy but encountered with many difficulties and there has been no randomized trial directly compared the treatment efficacy of these 2 strategies.

2. We had briefly described the inclusion criteria in the original method part. (“4,169 patients diagnosed with T2-4N0-3M0 transitional cell carcinoma from 2006 to 2019 who received RC combined with perioperative chemotherapy”) Meanwhile, the specific follow-up procedures are not available in SEER. The measurements of prognosis outcomes (OS and CSS) were calculated according to term “Survival months”, “SEER cause-specific death classification”, “SEER other cause of death classification”. We think it would be verbose to elaborate this part in the abstract. As for the assessment of baseline clinical factors, we add corresponding description as following.

Changes in the text:

Page 2 line 52- 55 Abstract: Method

The baseline clinical characteristics of the NAC and AC groups before and after weighting were compared using standardized mean differences (SMD) approach and kernel density plot to guarantee comparable groups.

3. We briefly summarized the clinical characteristics of the NAC and AC groups and add statement indicating the comparability of the two groups. All HR reported in the original result were adjusted.

Changes in the text:

Page 2 line 58-62 Abstract: Result

The majority of the study population were white (88%), male (76%) patients older than 65

years (58%), and had lymph node-negative (N0, 66%) diseases. After adjusted for propensity score, SMD for all characteristics were less than 10% which indicated that NAC and AC groups were comparable in baseline.

4. We revise the conclusion to appear more rigorous and less absolute.

Changes in the text:

Page 3 line 76-77 Abstract: Conclusion

Our population-based study suggests that NAC and AC might be interchangeable in MIBC management, especially in patients with Stage III-IV (T3-T4 and/or N+) diseases. However, this conclusion needs further validation from powerful, robust randomized trials.

Reviewer comment 3:

Third, in the introduction of the main text, an extensive review on the efficacy and safety of NAC AC for MIBC should be performed, including their strengths and limitations. The authors did not explain the clinical needs for comparing the two treatments and why the SEER data are useful for answering this question.

Reply 3:

1. In the original manuscript, we had discussed the pros and cons of NAC and AC in the Discussion section (paragraph 4), but we did not mention it in the Introduction section (except for the efficacy) which hindered us from clearly explaining the significance of the present study. So, we add the comparison of NAC and AC regarding safety, strengths, limitations and further explain the clinical needs for comparing the two strategies.

Changes in the text:

Page 4 line 99-112

Meanwhile, comparing with adjuvant chemotherapy (AC), NAC was proven to be more tolerable with higher completion rate for assigned treatment cycle (33). For advanced MIBC,

Primary chemotherapy might shrink the tumor therefore improving the tumor resectability. However, arguments exist that the delay of surgery may confer a risk for progression brought by micrometastasis especially among those who are chemoresistance. In addition, adjuvant chemotherapy could be more precise and personalized under the guidance of accurate tumor staging as well as pathological result. Theoretically, minimizing tumor burden through surgical resection before systemic treatment might improve the efficacy of chemotherapy. Even though NAC and AC have their own strengths and limitations, the central concerning regarding the selection between NAC and AC is the comparison of their treatment efficacy.

2. We also discussed the advantages of analyzing SEER data in the Discussion (paragraph 4) Currently, there is no RCT directly compared NAC with AC which could be hard to perform considering RCTs focusing on AC have encountered with many difficulties. Study on population-based data like SEER could provide suggestive but feasible reference regarding the selection between NAC and AC to fill in the blanks left by RCT. In addition, study in a real-world setting have better extensibility than RCT. However, we only partially describe these reasons in Introduction. As is advised, we add relevant description as following:

Changes in the text:

Page 5 line 124-135

However, to the best of our knowledge, a direct comparison of NAC and AC among MIBC patients who undergo definitive surgery has never been fully evaluated by convincing RCTs which might be difficult to perform considering multiple setbacks encountered with the AC arm.

Based on the above considerations, in the present cohort study, we compared the treatment efficacy between NAC and AC among patients diagnosed with locally advanced urothelial carcinoma of the bladder (T2-4N0-3M0) who were also treated with RC using the latest updated SEER database, one of the largest cancer incidence database, aiming to fill in the blanks left by RCTs and provide complementary references regarding the treatment selection among different stages of MIBC in a real-world setting.

Reviewer comment 4:

Fourth, in the methodology of the main text, the authors need to describe the clinical research design, follow up details, and the sampling frame of SEER data. In statistics, the primary analysis should be based on the whole sample because PSM can result in the selection bias. I suggest to use the PSM sample analysis as a sensitivity analysis of the primary analysis. Please describe the assessment baseline comparability of the two groups and multiple Cox regression analysis for the adjustment of covariates. Please describe P value for statistical significance. Another potential methodology issue is whether the NAC and AC groups are concurrent. Please describe the distributions of cases of the two groups according to chronological years. Please also describe how the two treatments were selected for an individual patient in the real-world clinical practice.

Reply 4:

We are very glad that the reviewers had carefully reviewed the Method section of this manuscript and provided valuable and professional advice.

1. As is advised, we add description to illustrate the research design, the sampling frame used to extract data from SEER and the follow up details available in SEER.

Changes in the text:

Page 5-6 line 148-157

Method: Study design and population

This retrospective cohort study aimed to compare NAC with AC in their impact on OS and CSS among RC-managed MIBC patients extracted from SEER database.

The sampling criteria from SEER were as following: 1) Derived AJCC Stage Group, 6th ed (2004-2015)/ 7th edition Derived SEER Cmb Stg Grp (2016-2017) / 8th edition Derived EOD 2018 Stage Group (2018+) = II-IV; 2) Diagnostic Confirmation = Microscopically confirmed; 3) Site recode ICD-0-3/WHO 2008 = Urinary Bladder; 4) Behavior cod ICD-0-3 =

Malignant.

Changes in the text:

Page 6 line 178-181

Method: Covariates and endpoints

Follow up information for each individual was extracted from SEER database according to relevant claims including Survival months, SEER cause-specific death classification and SEER other cause of death classification.

2. We are happy that the reviewers have noticed the shortcoming of PSM which is the reduced sample size causing selection bias. We have considered this problem during the statistic analysis therefore replace PSM with IPTW. IPTW is also a propensity score-based method which calculate a weight for each individual based on propensity score to account for imbalanced baseline. In this case, IPTW can avoid sample lost brought by matching process which enable us to perform full sample analysis. However, IPTW have its own problem. A small group of Individuals located in both ends of the propensity score distribution (Fig.3 B and C) will be assigned a large weight causing bias. To address this problem, we calculated the stabilized weights instead (reference 33). The specific details have been illustrated in Statistical analyses section line 188-201.
3. In sensitivity analysis section, we have originally considered using IPTW and perform multivariate Cox analysis during primary survival analysis. However, IPTW can give fully control for measured bias but unable to reduce the bias causing by unmeasured covariates. Therefore, we utilized a method developed by Lin DY et al. instead (Reference 26) to test the robustness of our result by introducing an unmeasured covariate. This method has been adopted by many well-accepted retrospective studies.
4. In the original Method section, we have described the method we utilized to compare the difference in baseline between NAC and AC group - Standardized mean differences approach (SMD). (Page 7 line 201-203) SMD is the first choice to evaluate balance between

groups when using IPTW and SMD less than 10% means adequate balance achieved. In Table 1, We describe the SMD for all covariates both before and after weighting. Figure 2 A further illustrated the baseline comparability of the two groups. Methodologically, IPTW adjusted for baseline in combination with IPTW adjusted univariate Cox regression have similar performance with multivariate Cox regression in survival analysis. We think it will be unconcise to adopt two overlapped method.

Therefore, we suggest displaying the results of multivariate Cox regression in the supplement data.

As is advised, the results of multivariate Cox regression targeting OS and CSS have been summarized in Supplementary Table 1. We also add the corresponding description in the section Method and Result.

Changes in the text:

Page 7 line 208-209

Method: Statistical analyses

Furthermore, univariate IPTW-adjusted as well as unadjusted univariate Cox proportional hazards regression model was fitted to compute the corresponding hazard ratios (HRs) and explore the potential heterogeneity of treatment effects with tests of interaction and subgroup analyses according to all covariates.

Page 9 line 271-274

Results: Survival analysis

The unadjusted multivariate Cox Analysis also revealed that NAC and AC have no significant difference in OS (HR 1.06, 95% CI: 0.95-1.17, P=0.288) and CSS (HR 1.06, 95% CI: 0.94-1.19, P=0.375).

5. As for chorological changes of enrolled patients, we have already considered the potential bias caused by different times when patients were diagnosed or treated. SEER only provides the specific year of diagnosis which we have controled for using IPTW (Table 1, Figure 2 A).

As is advised, we also add a histogram to display the distribution of diagnosis year for NAC and AC in Supplementary Figure 1.

6. As for comment: “Please also describe how the two treatments were selected for an individual patient in the real-world clinical practice”, we have already described the selection criteria between NAC and AC recommended by clinical practice guideline in Introduction line 116-119.

Reviewer comment 5:

Finally, please consider to cite the below related papers to enrich the background and discussion: 1. Zhu J, Ye X, Zhou L, He Z, Jin J, Yu W. Treatment decisions of bladder cancer in patients older than 85 years: a SEER-based analysis 2011–2015. *Transl Cancer Res* 2022;11(10):3584-3592. doi: 10.21037/tcr-22-944. 2. Eriksson V, Holmlund J, Wiberg E, Johansson M, Hüge Y, Alamdari F, Svensson J, Aljabery F, Sherif A. Adverse events during neoadjuvant chemotherapy for muscle invasive bladder cancer—a Swedish retrospective multicentre study of a clinical database. *Transl Androl Urol* 2022;11(8):1105-1115. doi: 10.21037/tau-22-78. 3. König F, Pradere B, Grossmann NC, Quhal F, Rajwa P, Laukhtina E, Mori K, Katayama S, Yanagisawa T, Mostafai H, Motlagh RS, Aydh A, Dahlem R, Shariat SF, Rink M. Quality indicators for the management of muscle-invasive bladder cancer in the perioperative setting of radical cystectomy: a narrative review. *Transl Cancer Res* 2022;11(4):908-917. doi: 10.21037/tcr-21-1116.

Reply 5:

We are grateful for the three references provided which are profound and enlightening. There are very helpful in illustrating our topic and we have cited these papers in the background and discussion.

Review comments-reviewer B

1. Abstract

a) The abstract should within 200-350 words. 350 words is maximum, please revise.

Reply 2a: We have revised the Abstract according to the words limit.

b) Please check the full term of NAC, it should be unified.

42 **Background:** Previous level 1 evidences have reported an approximately 6% absolute
43 improvement in 5-year overall survival brought by neoadjuvant cisplatin-based
44 chemotherapy (NAC) followed by radical cystectomy (RC) which has been established

61 **Results:** In total, 1,620 (38.9%) of all eligible patients received neoadjuvant
62 chemotherapy (NAC) and 2,549 (61.1%) received AC. The majority of the study

Reply 2b: We have unified the full term of NAC in page 2 line 38

2. The Declaration of Helsinki

The statement should move to the “##Study design and population” section, please revise.

265 (R Foundation for Statistical Computing, Vienna, Austria). The study was conducted in
266 accordance with the Declaration of Helsinki (as revised in 2013).

Reply 3: We have revised accordingly.

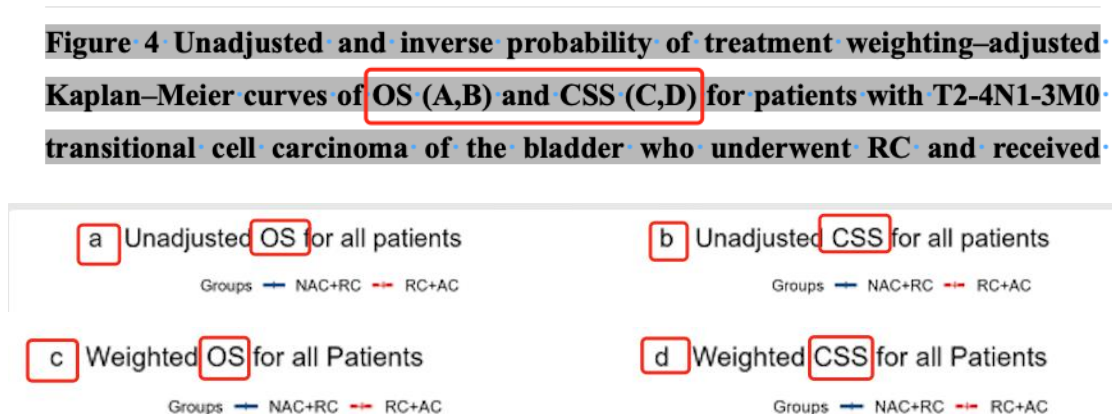
3. Figure 1

Please defined SEER in the legend.

Reply 4: We have added the definition of SEER in the legend of Figure1.

4. Figure 4

The figure is different with the legend, please unified them.



5. Figures' citations

Figure 5A should be cited after figure 4D (between 4D and 5B), please revise.

326 **Figure 4C**), respectively. In the IPTW-adjusted univariate Cox model, receiving NAC
 327 or AC was not associated with a significant difference in OS (HR 1.09, 95% CI: 0.99–
 328 1.20, P=0.1, **Figure 5A**).

329 A comparison of CSS between the 2 groups yielded similar results. The 5-year
 330 adjusted CSS was 59% (95% CI: 0.56–0.53) in the NAC group versus 57% (95% CI:
 331 0.55–0.60) in the AC group (P=0.329). The median CSS was not reached (95% CI:
 332 121–not reached) for NAC, and it was 125 months (95% CI: 89–not reached) for AC
 333 (P=0.146, **Figure 4D**). This difference was also not significant in the IPTW-adjusted
 334 Cox model (HR 1.09, 95% CI: 0.97–1.22, P=0.166, **Figure 5B**).

Reply 6: We have revised the order of figures' citations in page 9 line 276-279.

6. Table 2

Please double check if this column is necessary, if not, please remove it.

Characteristics	Univariate				Multivariate		
	OR	95% CI	P value		OR	95% CI	P value
Race							
Others	Ref				Ref		
White	0.82	0.68–1	0.050		0.84	0.68–1	0.088
Year of diagnosis	0.88	0.87–0.9	<0.001		0.9	0.89–0.92	<0.001
Grade							
Low grade	Ref						

Reply 6: We have removed the empty column.