

## Peer Review File

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### Reviewer A

**Comment 1:** The authors should include the article by Kufukihara et al. (DOI: 10.1245/s10434-021-09750-0) in the introduction and discussion. The previous article reported that a history of non-urothelial malignancy may lead to worse clinical outcomes in patients with NMIBC, particularly in smokers, and is therefore relevant to the current manuscript.

**Reply 1:** Thank you for the recommendation. We have included the article by Kufukihara et al. in both the introduction and discussion sections as suggested.

**Changes in the text:** Added on Page 2, Line 56 and Page 7, Line 302.

**Comment 2:** The authors should verify whether reference number 9 (Kim et al.) is accurate.

**Reply 2:** We have replaced reference number 9 with the correct citation: "Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008."

**Changes in the Text:** Updated on Page 9, Line 355.

**Comment 3:** The authors mention in the introduction that: "Bladder cancer patients with a history of prior tumors typically present with a more complex clinical profile and prognosis."; please provide a reference to support this statement.

**Reply 3:** We have added a reference to support this statement and modified the content to "Therefore, the clinical presentation and prognosis of bladder cancer patients with a history of prior tumors may be more complicated[13]."

**Changes in the Text:** Modified on Page 2, Line 54-56.

**Comment 4:** Do the authors have information regarding the type of prior tumor? It would be informative to see whether there is a high rate of a certain type of tumor and whether specific characteristics of the previous non-urothelial tumor could predict a worse outcome.

**Reply 4:** We appreciate this valuable input. We have described the types of prior tumors in Table 2 under the "Primary Site" category, highlighting that the Overlapping lesion of bladder has the highest risk ratio.

**Changes in the Text:** Updated on Page 13, Line 427.

**Comment 5:** The authors should consider omitting the variables OS and CSS from Table 1 as these are time-dependent variables and should not be compared using the Chi-squared test.

**Reply 5:** We have removed OS and CSS from Table 1.

**Comment 6 :** When evaluating the outcomes of OS and CSS, both of which are time-

dependent variables, multivariable Cox regression models should be used rather than logistic regression models. Therefore, the use of logistic regression for these outcomes is less suitable (section 3.4 of the manuscript).

**Reply 6:** We appreciate the reviewers' insightful suggestion regarding our statistical analysis approach. After careful consideration, we have decided to remove the logistic regression models from our analysis. We concur that the multivariable Cox regression models are more appropriate for evaluating time-dependent variables, particularly in the context of survival outcomes.

**Changes in the Text:** Page 4-5, Line 172-199.

**Comment 7:** How did the authors decide which variables to include in the multivariable Cox regression model? Please comment on this in the material and methods section.

**Reply 7:** Variables with  $P < 0.1$  in the univariate analysis were included in the multivariate regression analysis, followed by the application of a stepwise bidirectional regression method.

**Changes in the Text:** Clarified on Page 3, Line 100-102.

**Comment 8:** In the discussion – lines 260 – 274 repeat information that appears in the introduction. The authors should consider shortening or omitting this paragraph.

**Reply 8:** We have shortened the content in question to avoid repetition.

**Changes in the Text:** Reduced on Page 5-6, Line 215-219.

**Comment 9:** Please verify reference number 16 which appears in line 292 of the discussion is the correct reference. The reference is aimed at esophageal cancer while the text within the manuscript refers to bladder cancer.

**Reply 9:** Thank you for highlighting this. We have removed the original reference 16, which was incorrectly aimed at esophageal cancer, and replaced it with references more relevant to bladder cancer. The revised text now states: "This study found that bladder cancer patients with prior tumors had shorter overall survival, likely due to shared risk factors such as smoking and occupational exposures, which can exacerbate tumor severity and progression [13, 21]. Additionally, treatments for previous tumors may have affected the overall health status of the patients [22]. It is speculated that these factors may have intensified the malignancy and progression speed of the tumor, thereby affecting the treatment response and prognosis of bladder cancer."

**Changes in the text:** Amended on Page 6, Line 232-238.

**Comment 10:** Please mention possible limitations of the study in the discussion.

**Reply 10:** Thank you for your suggestion. We have added a discussion on the study's limitations as follows: "Despite offering valuable insights, our study has limitations. First, SEER data, mostly from the U.S., may not fully represent global patient populations. Second, SEER lacks details on treatment specifics (e.g., radiation, chemotherapy), genetic information, and lifestyle factors (e.g., smoking, occupational exposure), which are significant bladder cancer risk factors [6, 7]. The absence of this data may have hindered our ability to comprehensively understand the multifaceted

risks associated with bladder cancer. For instance, previous studies have highlighted the negative impact of a history of prior non-urothelial malignancies on clinical outcomes of Non-Muscle Invasive Bladder Cancer (NMIBC) patients who are current smokers, revealing that smoking and prior tumor history may co-affect tumor recurrence and progression [13]. This is something our research has not fully explored. Additionally, the nomogram survival model developed here was validated internally but lacks external validation, limiting its generalizability. Future studies will gather large clinical datasets to further validate the nomogram and explore additional prognostic factors."

**Changes in the text:** Added on Page 2, Line293-306.

### Reviewer B

#### 1. Abstract:

Please report the exact P value.

$\pm 39.96$  months, significantly lower than the  $70.28 \pm 39.36$  months for patients without a prior tumor history ( $P < 0.05$ ). Significant differences were observed between

Response: The exact P value has been reported as requested.

#### 2. Main text

- 1) Please provide the full name of CI in the main text.
- 2) Please provide website link/URL for SEER database.

Response:

1) The full name of CI (Confidence Interval) is specified the first time it appears in the "3.2 Hazard Ratio (HR) analysis" section.

2) The website link/URL for the SEER database, "<https://seer.cancer.gov/>", has been incorporated into the "2.1 Patient Selection" section as requested.

#### 3. Figures

- 1) Please define all abbreviations in all figure legends.
- 2) Figure 2A and B: the words are too close and not clear. Please check and revise.
- 3) Figure 2A and B: the word is incomplete. Please check and revise.



- 4) Figure 4B: please provide C-index in the figure.

Response:

- 1) All abbreviations in the legends have been defined.
- 2) The images have been re-edited to ensure that the text in Figure 2A and B is no longer too close together and is now clear and legible.
- 3) Any incomplete words have been corrected to maintain the integrity and readability of the figure.
- 4) The C-index has been included in Figure 4B.

#### 4. Tables

- 1) Table 1: Please add unit for survival time.

Survival, Mean ± SD 66.45 ± 40.02 70.28 ± 39.36

- 2) Table 1: you have removed the variables of OS and CSS. Please also remove these two in the text.

195 tumor grade, surgical intervention, radiotherapy, chemotherapy, OS, and CSS. The

- 3) Table 2: the citation of Table 2 is missing in the text. Please check and revise.  
 4) Table 2: please check the following information.

265 demonstrated an elevated risk of mortality. Compared to Black patients, those of other  
 266 races (HR = 0.73, 95% CI: 0.61-0.88, P = 0.001) and White patients (HR = 0.79, 95%  
 267 CI: 0.68-0.91, P < 0.001) exhibited a lower risk of death. Patients who were single (HR

Race				
Black				1.00 (Reference)
Others	-0.32	0.09	-3.33	<0.001
White	-0.24	0.07	-3.25	0.001

- 5) Table S1: please provide the full name of OS and CSS in the table footnote.

Response:

- Units for survival time have been added to Table 1.
- Variables of OS and CSS have been removed from Table 1 and the text as requested.
- The citation for Table 2 has been incorporated into the text, specifically within the "3.4.1 Multifactorial Cox Regression Analysis" section.
- The text that corresponds to Table 2 has been revised to ensure alignment and consistency between the table and the narrative in the manuscript.
- The full names of OS and CSS have been provided in the table footnote for Table S1.

5. Please unify the following age in the text/figures/tables. Should it be "≥80years" or ">80years"? please check through and revise.

Age, n(%)				$\chi^2=557.34 < .001$
<60years	1851 (15.10)	1642 (18.33)	209 (6.33)	
60-69years	3242 (26.44)	2572 (28.71)	670 (20.30)	
70-79years	3696 (30.15)	2626 (29.31)	1070 (32.41)	
≥80years	3471 (28.31)	2119 (23.65)	1352 (40.96)	

  

Age, n(%)			
<60years	1851 (15.10)	577 (15.69)	1274 (14.85)
>80years	3471 (28.31)	1043 (28.36)	2428 (28.29)
60-69years	3242 (26.44)	954 (25.94)	2288 (26.66)
70-79years	3696 (30.15)	1104 (30.02)	2592 (30.20)

Response: The age expression has been uniformly updated to "≥80 years" throughout the text, figures, and tables where applicable.