Peer Review File

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Reviewer A

Simple, but excellent work. Important for parents, pediatrici, ans, and pediatric and adult urologist.

Reply: Thank you! We are very excited about this work and to see it in publication. Looking forward to producing the next steps in our research on the subject.

Changes in text: None indicated.

Reviewer B

This is a very interesting study, as pediatric urothelial carcinomas are an atypical group of malignancies - in the adult population, urothelial carcinomas of the bladder are usually related to prolonged environmental exposures to aromatic hydrocarbons, most predominantly cigarette smoking. How these tumours arise in children without an extended duration of direct exposure still remains uncertain.

Reply: We completely agree. While we have seen a share of cases at our institution the data remains sparce in this realm. We are very interested in long term outcomes and screening in pediatric populations which is likely very different than the adult populations given differences in exposures as delineated in your comment.

Changes in text: None indicated.

Regarding results:

Diagnostic and staging results: Histologic grade was reported her as well/moderately/intermediate/poorly differentiated - in adult urothelial carcinomas (UC) the histologic grade is commonly denoted either "low-grade" or "high-grade" - is there any mention of this for it to be more relatable to the wider audience managing urothelial carcinoma?

Reply: That is a great point. Unfortunately, the data in the NCDB is does not make the low versus high grade distinction. We suspect that given the data input fields, this was not available to those logging in their patient data. We presume that poorly differentiated disease portends worse prognosis as it may in adults but unfortunately, we are unable to ascertain further how these patients were followed

and treated.
Changes in text: We have added a sentence in our discussion at the end of the fourth paragraph to clarify.

Would also be useful to state the T-stage (e.g., non-invasive UC as Ta, or invasive as T1) as this is the most commonly understood terminology for UC.
Reply: All of the available details about staging has been included in the last paragraph of the "Diagnostics and staging results" section of the paper. Unfortunately, we do not have specifically Ta vs T1 details regarding these patients.
Changes in text: None indicated.

Tumour characteristics:
Actually, papillary urothelial carcinoma (UC) is the same as transitional cell carcinoma (TCC) - there was a change in terminology by the World Health Organisation in 2016 from the conventional TCC to UC.
PUNLMP on the other hand is a separate entity from urothelial carcinoma, as it is widely understood as a non-malignant lesion, unlike the latter.
Consider classifying UC and TCC as one entity, and PUNLMP as another.
Reply: This review looks at the database up to 2016 so unfortunately, the distinction in entering data by those categories following the change in terminology by the WHO is not captured.
Changes in text: None.

Intervention data:
It is a bit odd that no staging was performed when a malignancy was diagnosed - was there no evaluation for metastasis?
For UC, the biopsy of the tumour is essentially the same procedure as the surgical procedure - a Transurethral Resection of Bladder Tumour (TURBT) as performed as an endoscopic procedure, for resection of the tumour for histological diagnosis. Would be useful to make this section a little clearer - specify how many patients underwent TURBT, how many had open surgery, and how many had missing data.
Reply: Regarding the staging, this category simply refers specifically to the initial work up of the bladder tumor. Based on the coding for data entry, there are no specific distinctions exist for TURBT or whether biopsy falls under their "initial staging". Whether the procedure was characterized as biopsy versus TURBT both of which may fall under endoscopic intervention is a distinction made by the clinicians when inputting their data into the database. To the best detail we are able to provide based on how the information was recorded we have noted in the section that "In 95.7% (N= 134) of the patients, surgery of the primary site was

performed. Of the available data (6 missing), 87.3% (N=117) of patients underwent a surgical procedure at time of initial diagnosis and 81.3% (N=109) of patients underwent "definitive surgery" at the primary site at the time of initial diagnosis; an additional 25 (18.7%) underwent definitive surgery of the primary site at a later date. Primary surgical technique is unknown or missing in 63 patients. Of the remaining 77 patients, most - 81.8% - underwent endoscopic intervention. Surprisingly, 9.1% of these patients reportedly did not undergo surgery of the primary site, and 9.1% of these patients underwent open surgery or an unspecified surgical approach"
Changes in text: None indicated

Mortality outcomes:
Was there any data on recurrence? Urothelial carcinoma is notorious for being a tumour that recurs easily - in the adult population patients are placed on a surveillance regimen with regular cystoscopic evaluations.
Data on recurrence would be invaluable in determining how patients with pediatric bladder UCs should be monitored after the initial tumour was removed - should they undergo regular bladder ultrasound?
Reply: We wholeheartedly agree with this sentiment. One of the greatest shortcomings with this database is that information on recurrence is not available nor is information regarding follow up after these patients were input into the NCDB. We do our best to address this in our discussion section – see below. Additionally, we had attempted to suggest previously in our discussion regarding bladder ultrasound surveillance but given the lack of long-term data available in the NCDB this was removed per comments from other reviewers. (As an aside we have an ongoing systematic review to further look at long term data and hopefully be able to more definitively recommend standardized bladder surveillance as is often our practice).
"NCDB lacks information on important clinical parameters including cause of death, disease recurrence greater than 90 days from initial treatment, adjuvant intravesical/systemic therapies or subsequent invasive or non-invasive interventions related to pediatric bladder cancer. This includes information regarding disease progression or recurrence which precludes us from determining event free survival or overall survival beyond 90-day time point. NCDB does provide pathologic and staging data, which allows for a more in depth look at short term outcomes compared to other cancer databases."
Changes in text: None indicated.

Reviewer C

This article is the first clinical research report to show pediatric urothelial cancer information in a national database. It is really meaningful and important topics for pediatric urological field. However, there are some questions and comments.

Reply: Thank you for your comments. We are very much excited about this work and agree that this topic is a very important one for which there is incredibly limited data to guide physician practice.

Changes in text: None indicated.

1) Results, p7, Patient characteristics

Urothelial cancer often develops as part of familiar hereditary syndrome including Lynch syndrome, hereditary retinoblastoma, Costello syndrome, Apert syndrome, with early-onset in young generation. Therefore, the authors should show data about that.

Reply: Thank you for your comment, we agree that this is important to keep in mind. However, this data is not reported as part of the NCDB.

Changes in text: We have included a sentence in our discussion to highlight this.

The bladder is an organ that comes in constant contact with the environment and is therefore sensitive to environmental carcinogens and inflammation including heavy pollution.

Therefore, the authors should show data about that.

Reply: This certainly holds true. Per our research, there is a paucity of literature connecting these environmental carcinogens to pediatric urothelial bladder neoplasms. We have included this in our discussion to highlight the paucity of data and ensure this information is interpreted in the larger context of bladder tumor risk factors.

Changes in text: We have added more on the topic in our discussion.

2) Results, p7-8, Diagnostic and staging results

The authors should show data of urine cytology before definitive surgery, and metastatic site in stage IV patient in detail.

Reply: We agree this information would be very beneficial to know. Unfortunately, this data in not available via the NCDB. All available data and details regarding the patients for this cross-sectional analysis has been delineated in the results section.

Changes in text: None.

3) Results, p8-9, Intervention data

The authors should show surgical treatment in patients with advanced disease, including radical cystectomy and reconstructive surgery.
The authors also should show chemotherapy and radiotherapy in patients with advanced disease in detail.
Reply: We agree this information would be very beneficial to know. Unfortunately, this data in not available in the NCDB. All available data and details regarding the patients for this cross-sectional analysis has been delineated in the results section. We have noted on the scarcity of the data in our discussion section. The NCDB does not offer details on each patient separated by treatment type further than the described.
Changes in text: None.

4) Discussion, p10-13
Rezaee ME et al. already reported a systematic review and data analysis of the world literature (reference 2). They analyzed 243 patients (< 18 years), and also reported tumor recurrence and its risk factors in detail. Therefore, the authors should discuss pediatric urothelial cancer compared with this article.
Reply: We agree that this cross-sectional analysis must be interpreted in light of the existing literature reported above. We have also previously noted in the discussion the unfortunately limited detail regarding comorbid conditions reported in the NCDB outside the Charlson-Deyo mapping table.
Changes in text: We have added a clarification in our discussion.