Peer Review File
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Title: Advances in the management of pediatric genitourinary rhabdomyosarcoma

Response to Reviewers:
We thank the Reviewers for their helpful comments and suggestions, which we have incorporated to improve this manuscript. In addition to the edits to the text, we have added Tables 1-9 to provide additional clarity as suggested by the Reviewers in order to provide additional clarity.

Reviewer #1

The manuscript "*Advances in the Management of Pediatric Genitourinary Rhabdomyosarcoma*" aims to provide an update on the management rhabdomyosarcoma of the genitourinary tract in pediatric patients. The authors review the findings of recent collaborative trials with a focus on approaches to local control and chemotherapeutic regimens. In addition, they review the changes to risk stratification of RMS with particular focus on importance molecular classification. The authors do an excellent job summarizing the most recent RMS studies on from both sides of the Atlantic, and effectively discuss the balance between minimizing toxicities while maintaining failure-free survival.

Reply: We thank the Reviewer for these positive comments, and for each of the comments and suggestions below which have improved the manuscript considerably.

Major Points:

Comment 1: It would be extremely helpful to include a Table that highlights the differences between COG and EpSSG classifications that are discussed in the section on **Advances in RMS Risk Stratification** (and other European cooperative groups). RMS classification is confusing, and it is particularly difficult to appreciate the differences discussed in this section without seeing them laid out.

Reply 1: Thank you for this helpful suggestion. We have added Tables 1-4 to summarize schema for both COG and EpSSG.

Comment 2: It would also be helpful to provide a Table (or several Tables) that summarize the outcomes that are referred to in the subsequent sections. Again, it is challenging to appreciate the differences (or lack of differences) among the different approaches when presented in narrative form as opposed to in Tables – the narrative does not need to be changed, but reference could be made to individual summary Tables for each section.

Reply 2: Thank you for this suggestion as well. We have added summary Tables 5-9 to summarize the various differences in study outcomes for the various sections.

Comment 3: The manuscript is inconsistent in its specific descriptions of failure-free and survival rates – for some of these, 5-year rates are mentioned, but for many others it is not indicated whether the rates are 3- or 5-year rates. As an example, in the third paragraph of the **Advances in RMS Risk Stratification** section, the time (3 vs. 5 vs. 10 years) of the OS rates of 88% vs. 65% and 58% vs. 19% are not indicated. The authors should carefully review each of the times that rates are mentioned and indicate the time frame.

Reply 3: Thank you for this helpful suggestion. We have added outcome time frames throughout the manuscript.

Comment 4: Because of the growing appreciation of the importance of Maintenance therapy, it would be appropriate to have a separate, titled section about Maintenance Therapy, instead of just having it be a paragraph in the **Intermediate-Risk GU RMS** section.

Reply 4: Thank you for this helpful suggestion. We have added outcome time frames throughout the manuscript.

Comment 5: In the **Intermediate-Risk GU RMS** section, there appears to be an error – it is stated (2nd paragraph) that "*ARST0531 was associated with higher failure-free rates, which was most pronounced … 5-year local failure cumulative incidence was 27.9% compared to 19.4% on D9803*" – should this say "*5-year local failure-**free** cumulative incidence*"?

Minor points Comments 6-13:

Reply 6-13: Thank you for each of these suggestions. We have updated the texts to reflect each of the edits.

Comment 6: Abstract

Line 1 – the complexities are not "unrecognized" – perhaps change to "unanticipated" or "previously unappreciated"

Line 12 – "require cautious deliberation" should be changed to "require careful consideration"

Comment 7: Introduction

Paragraph 2, line 6 – "differences exists" should be "differences exist"

Comment 8: Advances in Rhabdomyosarcoma Risk Stratification

Paragraph 3, line 15 – "fusion status are" should be "fusion status is"

Paragraph 4, line 3: "immediate-risk" should be "intermediate-risk"

Comment 9: Genitourinary RMS

Paragraph 1, line 1 – "RMS cases and represent" should be "RMS cases and includes"

Paragraph 1, line 7 – "polyploidy" should be "polypoid"

Paragraph 3, line 4 "Using historical IGSG/COG risks stratification" should be "Using a historical IGSG/COG risk stratification"

Comment 10: Advanced Approaches to Local Control for Genitourinary RMS

Paragraph 1, line 7 – "local control for bladder" should be "local control approach for bladder"

Paragraph 2, line 2 – "European trails" should be "European trials"

Comment 11: Advances in Chemotherapy for Genitourinary RMS

Paragraph 2, line 6 – "intermediate risks" should be "intermediate risk"

Comment 12: Low-Risk Genitourinary RMS

Paragraph 1, line 1 – "intermediate-risks" should be "intermediate-risk"

Please be consistent about using "intermediate risk" vs. "intermediate-risk" throughout the manuscript i.e. either include a dash/hyphen or don't – just choose one convention

Paragraph 2, line 15 – "who receive treated" should be "who receive treatment"

Comment 13: Relapsed Genitourinary RMS

Paragraph 1, line 13 – "Breakthroughs…is" should be "Breakthroughs … are"

Reviewer #2

Great article covering all aspects of RMS treatment with focus on GU primaries. Authors have done good job of covering complicated and different treatment strategies internationally, changes in risk groups categorization, and outcomes of relevant recent studies.

Reply: We thank the Reviewer for these positive comments and for each of the comments and suggestions below, which have improved the manuscript considerably.

Comment 1: However, it is easy to get bogged down in amount of information and I would recommend adding table or chart to serve as a quick reference for most current risk stratifications for the GU. Perhaps even visual way to highlight those GU groups that have changed in recent years

Reply 1: Thank you for this helpful suggestion. We have added Tables 1-4 to highlight risk stratification considerations and also Tables 5-9 to highlight differences in clinical trial outcomes for low- and intermediate-risk RMS.

Very important point about cancer predisposition syndromes. Absolutely agree testing should be done under certain circumstances- Great ASCO article about specifics. The Advantages and Challenges of Testing Children for Heritable Predisposition to

Cancer Chimene Kesserwan, MD, Lainie Friedman Ross, MD, PhD, Angela R. Bradbury, MD, and Kim E. Nichols, MD 2016 ASCO EDUCATIONAL BOOK | asco.org/edbook.

Comment 2: Please consider expanding to recommending genetic counseling referral (not just testing). Several groups are giving recs for genetic counseling for all RMS to help determine if testing indicated.

Reply 2: Thank you for this suggestion. We edited the manuscript to suggest referral for genetic counseling and also included the above useful reference.

Comment 3: In low-risk GU RMS section last sentence "the aforementioned difference in prospective" (perspective) between cooperative groups…most European groups are more willing to accept local recurrence rates…" comes across as more authors opinions as it is difficult to represent all European groups based of IRS-III.

Reply 3: Thank you for this suggestion. We edited the text to indicate some European groups rather than all.

Comment 4: Typo Most of European "trails" – in Advanced Approaches to Local Control

Reply 4: Corrected. Thank you.