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Peer Review File

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Reviewer A

1. The purpose of the article was not clear in the introduction.

Reply We have included this.

Comment Changes in the text line 52-54 .*The purpose of this article is to present a review of the literature evaluating the evolving role of MIS in the management of paediatric renal tumours and details regarding some of the technical aspects*

2. In the discussion, authors mentioned about 3 critical questions regarding MIS in paediatric renal tumours. However, they didn't show the answers about these questions.

Reply *The entire discussion is based on those three questions as subheadings.*

The conclusion has been reworked to show the answer more succinctly.

3. Authors didn't show the patients background of 30 papers (age, Size of tumor et al) I would like to know the patients background to judge the effectiveness of MIS.

Reply *The appendix table was expanded as per the reviewers suggestion and incorporated into the text as a results table line 142.*

Comment *The appendix table is difficult to expand because there is no standardised way of reporting the data and that is why the mention of Abdelhafeez in the discussion (line 157) is so important as he proposes guidelines to standardise this.*

Tumour volume is not measured the same way in each paper. Some will incorrectly report the volume calculated as a sphere and some will correctly report the volume as a prolate ellipsoid as per SIOP and COG guidance. Often there is no comment made about whether the measurements are pre chemo or pre surgery. The complications are not reported in a standardised fashion and should at least be divided into surgical and oncological as well as early and late.

Survival is also not standardised – EFS vs OS and no standard time frames.

Reviewer B

This manuscript concerns the position of MIS in the surgical treatment of renal tumours. It is intended as an overview of the literature, however not as a critical review but as a narrative review.

I agree with the authors that there is a role for MIS in the management of pediatric renal tumours. However I do have some comments

1. The narrative style of the review bothers me a little. There is no critical view at all and articles are presented as equal. The appendix should be integrated in the manuscript and should be more extensive.

Reply *The appendix table was expanded as per the reviewers suggestion.*

Comment The appendix table is difficult to expand because there is no standardised way of reporting the data and that is why the mention of Abdelhafeez in the discussion (line157) is so important as he proposes guidelines to standardise this.

Tumor volume is not measured the same way in all papers. Some incorrectly use the volume of a sphere, whereas others correctly employ the volume of a prolate ellipsoid. Additionally, some papers will only employ the maximum diameter of the tumour as a measurement. Additionally there is often no comment about whether the measurements are pre chemo or pre surgery. The complications are not reported in a standardised fashion and should at least be divided into surgical and oncological as well as early and late.

Survival is also not standardised – EFS vs OS and no standard time frames.

2. I do feel the case reports about 1 or 2 patients should not be included. If we want MIS and the (beneficial) outcome thereof taken seriously we should at least limit the overview to case series. In the appendix 30 articles/studies are mentioned. However the references are only 28 articles. Apparently not all articles are included in the text. This is confusing.

Reply The authors agree with this comment

Comment Case reports were removed and the results table amended.

3. The table should be expanded a bit more with inclusion of important parameters mentioned in the text that need to be taken into account when deciding on MIS: Size of the tumour/median age of the child/neoadjuvant chemo/experience of the surgeons. And perhaps even complications.

Reply - This was done but the same comment applies that was noted under 1.

4. In the text follow up is mentioned and it is stated that survival is comparable for MIS and open, however information concerning the length of follow up and information of exact comparison is missing

Reply The authors have referenced papers with follow up and survival data

Comment Line 305-306 now reads Overall survival between the two approaches has been comparable in most articles reported in the literature (24) (28) (7) (6) (8) (15)

The results table has also been expanded to include this data where available.

5. The fact that MIS is possible in smaller tumours may have an influence on outcome. This is not mentioned in the manuscript.

Reply see line 359-364

We acknowledge that there is a bias towards MIS been applied to smaller more favourable tumours, but argue that these are exactly the type of tumours that are suitable for a newly evolving technique and as experience expands and outcomes remain favourable this bias will self-correct. Open and MIS surgery both have a role in the management of paediatric renal tumours and should not be viewed as competing entities but rather complimentary techniques that should be applied to the correct patient population for optimal benefit.

6. The description of the laparoscopic technique: is this based on several articles or is this a description of the current protocol from the authors. That should be stated in the article.

Reply *Many thanks for this comment. The procedure is based on the current protocol at the senior authors unit and is referenced in the literature. Add refs (Gavens et al Surg Onc and Pachi/Arul JPES)*

7. The discussion is rather extensive. I think the manuscript would benefit from a different layout. The questions that are raised in the discussion are better as separate sections and the conclusion more of a discussion.

Reply *The discussion was focused more under the three subheadings – which were also the 3 key questions posed in the beginning and the conclusion was reworked to be more succinct.*

8. The tone of the manuscript is quite optimistic and large claims are made about the benefit of MIS, however direct comparisons concerning hospital stay start adjuvant treatment, duration of post-operative ileus, use of pain medication etc are not made. So I would suggest to state these claims a little more carefully.

Reply *Many thanks for this helpful comment. There is much literature comparing MIS and open surgery in adult and paediatric practice. We did not think that including this level of information made a vast difference to the paper. We would be happy to do this if it was thought worthwhile, although I would hope most surgeons would be cognisant of these advantages. We have edited the manuscript in line with these comments*

Comment Line 145-147 now reads *Minimally invasive surgical techniques have expanded rapidly over the last 20 years and have been incorporated into various areas of paediatric surgery including the definitive treatment of paediatric renal tumours in **carefully selected cases***

Line 226-231 *There are many variables that influences the feasibility of MIS including size of the patient, intra-abdominal space achieved by a pneumoperitoneum, degree of bowel dilatation, favourable position of the hilum for vascular control, position of the tumour and surgical experience. Case selection should take into account the size of the tumour but ultimately case selection will rely on a fine interplay between all of these patient, tumour and surgeon factors.*

Line 348 *In carefully selected cases of paediatric renal tumours, MIS is the best surgical option*

9. Furthermore I miss any critical note concerning the risk of expanding indications while having little experience, concerning the fact that probably only good results have been published, concerning the number of MIS per surgeon/hospital per year in the reported series etc.

Reply *Many thanks for this comment which is entirely accurate and the text has been edited in the manuscript.*

Comment See line 151 -156 *We acknowledge that one of the limitations of any narrative review is the likely publication bias towards positive results as authors and journals are often hesitant to publish results negative results.*

*However, surgeons should be encouraged to continue publishing their experience with MIS in a **standardised** way because it is only through this collaborative effort that we will be able gather enough evidence to offer patients the best treatment options.*

Line 199-200 now reads *Caution should be exercised when considering cases that fall outside the current proposed criteria and surgeon experience and strict audit and follow-up is mandatory.*

Reviewer C

I understood this paper to be a Review of minimally invasive surgery for paediatric renal tumors

Please see the following comments

1. There is no description of the results in the abstract

Reply

This is a narrative review and there were no clear results to describe in the abstract. As per the article 'Writing narrative literature reviews for peer-reviewed Journals: secrets of the trade' the format suggested is given and the authors have followed these criteria as directed by the editors

Abstract

Background and Objective

Methods

Key content and findings

Conclusion

2. The patient flow, including the total number of patients and the inclusion and exclusion criteria is unclear.

Reply *Inclusion criteria and exclusion criteria is listed in line 92-96*

This was clarified further and the exclusion criteria reflecting the exclusion of case studies were updated. The total number of patients were added.

Comment the text now reads line 92-102

Only full text articles in English corresponding to the relevant search terms were included. All renal tumours were included.

Exclusion criteria included articles referring to the adult population, articles exclusively related to robotic surgery or nephron sparing surgery(NSS). All case reports with only 1 or 2 patients were excluded.

The articles identified were screened based on abstracts and relevant articles were selected. The selected articles were reviewed and their reference lists screened for further relevant literature outside the initial search time line.

A total of 256 cases of MIS nephrectomies were identified 246 laparoscopic and 10 robotic.

<i>Laparoscopic nephrectomies</i>	<i>246</i>
<i>Laparoscopic converted to open</i>	<i>16</i>
<i>Robotic nephrectomies</i>	<i>10</i>
<i>Total completed with MIS</i>	<i>256</i>

Table 1 Breakdown of minimally invasive nephrectomy cases identified in the literature search

3. There is a description of the surgical procedure but at which institution? Reference to the criteria and differences between the facilities are necessary.
Reply *This has been added*
4. The surgeon is listed as an expert but the criteria are unclear.
Many thanks for this comment. The definition of an expert is a little unclear and very subjective. We did not think that adding all the details of cases done and the senior authors CV would add to the paper but literature from the unit is present within the manuscript. Additionally, the senior authors credentials are freely available on ORCID
5. Your results do not give us a clear vision. Please clarify what you communicated
Reply *Many thanks for the comments, the article was commissioned as a review of paediatric MIS tumour nephrectomy. We hope that it contains all the relevant data and information to enable surgeons to make their own decision about how to proceed with their patients. It is not meant to be pre or proscriptive. We hope that the edits that have been done convey this better.*
6. Since this is a review please discuss the bias between the papers.
Reply
Comment line 151-153 We acknowledge that one of the limitations of any narrative review is the likely publication bias towards positive results as authors and journals are often hesitant to publish results negative results.

Line 56-62 now reads

Clinical trials are lacking and there is a significant bias in the literature which can potentially be explained by the difference in approach between Children's Oncology Group (COG) and the International society of paediatric oncology (SIOP) Although outcomes between the two groups are similar, COG favours upfront resection, whereas SIOP protocols utilise neoadjuvant chemotherapy in most cases. One of the key aspects when considering MIS in paediatric renal tumours is whether the patient has had neoadjuvant chemotherapy (tumour shrinkage and fibrosis of the capsule potentially reducing intra-operative tumour rupture).

Reviewer D

Major comments

1. The introduction needs more work. The objectives are not well defined and the authors should clearly tell the readers why there is a need for a review of MIS in paediatric renal tumours and why a focus on its technical aspects.

Reply – *this has been done*

Comment Line 56-66 now reads Clinical trials are lacking and there is a significant bias in the literature which can potentially be explained by the difference in approach between Children’s Oncology Group (COG) and the International society of paediatric oncology (SIOP) Although outcomes between the two groups are similar, COG favours upfront resection, whereas SIOP protocols utilise neoadjuvant chemotherapy in most cases. One of the key aspects when considering MIS in paediatric renal tumours is whether the patient has had neoadjuvant chemotherapy (tumour shrinkage and fibrosis of the capsule potentially reducing intra-operative tumour rupture).

Some interesting details regarding technical aspects such as how to improve lymphnode sampling with modification of the surgical technique and new technology such as indocyanide green is also highlighted.

2. To the best of my knowledge, MIS is not always the recommended approach, even in selected cases that biopsy is required in renal tumour. And there is clear expert consensus against laparoscopic tumour nephrectomy . (PMID: 31704809). Please also describe disadvantages associated with MIS and criteria that guides how to choose between MIS and open surgery. This would make the discussion more objective and comprehensive.

Reply We are grateful for the comments. The authors agree absolutely that MIS is not always the recommended approach and in our unit we undertake less than 50% of our Wilms tumour nephrectomies by this method. The clear expert consensus which the reviewer references is an APSA paper and COG is particularly against MIS given that most nephrectomies are performed upfront where MIS may pose a problem with rupture. The provision of paediatric oncology surgery within North America is also radically different to that in Europe. SIOP guidelines give pre-operative chemotherapy which reduces the rupture risk along with evidence showing that it can downgrade tumour histology and shrink tumours. In common with COG, the SIOP-RTSG is also unlikely to recommend MIS for upfront tumour nephrectomy in all tumours although it will definitely have a place in the right hands.

Comment 1 Disadvantages of MIS

Line 338-345 now reads ‘Disadvantages of MIS include that smaller body size of children leading to restricted working space. Visceral injury during port placement can happen during MIS. The surgeon may still need a fairly large incision to remove the tumour which may negate some of the benefit of MIS. There is limited haptic feedback and thus limited tactile sense which can be a drawback in tumour surgery. The lack of surgeon experience and a steep learning curve are disadvantages that should certainly be taken into careful consideration. Anaesthetic difficulties including higher airway pressures and hypercarbia should be taken into account. Tumour spillage and incomplete resection as well as inadequate lymph node sampling is a risk during both open and MIS. ‘

Comment 2 *Criteria that guide how to choose between MIS and open surgery* Reference 5

See text line 175-191 *SIOP Renal Tumour Study Group RTSG 2016 Umbrella guidelines details the indications and contra indications for laparoscopic surgery in Wilms tumour*

Indications for MIS in the surgical treatment of Wilms Tumour

1. *Resection must adhere to oncological principles and include lymph node sampling.*
2. *MIS is appropriate for small, central tumours with rim of “normal” renal tissue.*
3. *Extraction of the specimen in a bag without morcellation through an adequate abdominal wall incision is mandatory, not only to control the risk of dissemination but also to ensure adequate histopathological staging.*
4. *If feasible, NSS should be preferred over MIS, even if an open approach is needed.*

Contra-indications for MIS in the surgical treatment of Wilms Tumour:

1. *Tumour infiltrating extra renal structures or extended beyond the ipsilateral border of spinal column.*
2. *Thrombus in the renal vein or vena cava.*
3. *Peripheral location if NSS is not deemed feasible.*
4. *Tumour without any response to chemotherapy (risk of tumour rupture).*
5. *Little or no experience in laparoscopic nephrectomy.*

Minor comments

1. I suggest the authors reconsider phrasing “Technical aspects in the title. Since seldom technical information were given compared to the literature review. Or for the authors reference please consider using “Minimally Invasive surgery (MIS) for paediatric renal tumours: a narrative review of the technical aspects”

Reply The authors have changed the title as suggested by the reviewer.

Comment Title line 2 and 3 “Minimally Invasive surgery (MIS) for paediatric renal tumours: a narrative review of the technical aspects”

2. Abbreviations should be explained in the abstract, such as MIS.

Reply This has been done

Comment Line 6 to 8 To present a review of the literature evaluating the evolving role of minimally invasive surgery (MIS) in the management of paediatric renal tumours and present a section detailing the technical aspects.

3. Line 43 ‘with at least 300 cases of laparoscopic nephrectomies reported in the literature’ but I only found 281 cases. Please check and make sure all the comments were reported. And why did the authors include pre-chemotherapy robotic assisted radical nephrectomy for adolescent with Wilms tumour?

Reply *As per the reviewers suggestion the single or 2 patient cases were excluded.*

The appendix table and article content was updated. The review now includes 256 cases in the literature between 2012 and 2022

Line 34-36 now reads With 246 cases of laparoscopic nephrectomies(and an additional 10 robotic procedures) reported in the literature between 2012 and 2022 (see results table1) it is clear that there is a role for MIS in the management of paediatric renal tumours

4. Line 62 'Craft and Pearson' Add reference

Reply This has been done Ref 6 added

Comment Line 78 -81 now reads Craft and Pearson (6) are credited with the coining of the phrase 'cure at any cost to cure at least cost' referring to their article about the improvements in chemotherapy for childhood cancers in 1989 and this certainly holds true for the surgical interventions utilised today

5. Line 72 SCOPUS Should be Scopus. PUBMED should be PubMed Cochran should be Cochrane.

Reply This has been done

Comment Line 88 Scopus, PubMed and Cochrane databases were searched

6. Line 133 the authors said 2012 to 2022 in the methods so why 2009 here
Comment line 88 Scopus, PubMed and Cochrane databases were searched. The search was limited to the last ten years including articles from January 2012 to January 2022.

A total of 272 cases were identified. A breakdown of the cases are given in the table below

<i>Laparoscopic nephrectomies</i>	<i>246</i>
<i>Laparoscopic converted to open</i>	<i>16</i>
<i>Robotic nephrectomies</i>	<i>10</i>
<i>Total completed with MIS</i>	<i>256</i>

Table 1 Breakdown of minimally invasive nephrectomy cases identified in the literature search.

7. Line 134 no need to define NSS here again

Reply This has been done

Comment Nephron sparing surgery was removed in the text

8. Line 136 please remove reference to other solid organ malignancies as this manuscript focusses on renal tumours
 Reply *This has been done*
 Comment Line 162 now reads *Critical questions regarding MIS in paediatric renal tumours include:*
9. Line 141 the third critical question regarding MIS was ‘How does MIS impact on overall survival event free survival and the incidence of recurrence?’ Therefore we suggest the authors change the subheading ‘Outcomes must be comparable to open surgery on page 8 line 263 to it.
 Reply *This has been done*
 Comment: line 294 in the text now reads ‘How does MIS impact on overall survival event free survival and the incidence of recurrence?’ as the subheading
10. Line 147 please define COG SIOP and GPOH
 Reply The authors changed the introduction defined COG and SIOP in line 62-68
 GPOH was defined in line
 Comment line 56-58 *Clinical trials are lacking and there is a significant bias in the literature which can potentially be explained by the difference in approach between Children’s Oncology Group (COG) and the International society of paediatric oncology (SIOP)*
 Comment Line 172 to 175 in the text now reads: *Collaborative and multi-modal treatment advances in childhood cancer has largely been accomplished through the guidance of steering committees such as COG, SIOP, German paediatric oncology society(GPOH) and the Japanese Paediatric Liver Tumour Study Group (JPLT)*
11. Line 304 the advantages of MIS was already given on line 296
 Reply The authors have shortened the conclusion to be more succinct as per the reviewers suggestions.
 Comment Line 351 -358 *MIS has shown comparable oncological outcomes and an improved post operative course. ~~profile in terms of survival and recurrence as well as the advantage of decreased post-operative complications, improved cosmesis, shorter hospital stay and earlier administration of adjuvant chemotherapy.~~ MIS can successfully be performed adhering to oncological principles and there is no outcome differences regarding tumour rupture or positive margins.* Lymph node sampling remains problematic in both the open and MIS surgery groups, but indocyanine green fluorescent guidance during laparoscopic surgery may offer a further advantage to MIS when it comes to lymph node sampling.
12. The chapters frequently composed of single sentence paragraphs. The authors should try to combine sentences into proper paragraphs.
 Reply *This has been done where appropriate*

13. Usually citations are not necessary in the conclusion part. Now it has. Maybe it is because the structure of this conclusion is a bit long. May the authors consider using the first paragraph of the present conclusion 'In selected cases of paediatric renal tumours ... when it comes to lymph node sampling ' as the whole conclusion section.
Reply *The conclusion has been abridged*