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OPEN PEER REVIEW

Clinico-Pathological Characteristics and Long-Term Outcomes of Incidental Appendiceal Carcinoid Tumors in Children

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

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1 Original submission

2 comments · 25 Sep 2023 – 6 Oct 2023

Referee 1 Reviewer

ACCEPT 25 Sep 2023

The manuscript is interesting.

Fatemeh Elham Mahjoub Reviewer

MINOR REVISION 6 Oct 2023

Dear Editor
Although there is no novelty in the subject of this article, due to the sample size, good follow-up, and relative rarity of the condition in children, I agree with publishing this article in IJP with minor revisions:
1- keyword: carcinoid instead of carsinoid
2- Background: " The second and third decades of life are the most common periods of carcinoid tumor; however, it can also be observed in pediatric population.5" ---- Change to: The second and third decades of life are the most common periods for carcinoid tumors.5
(Because the second decade also covers the pediatric age group).
3- Please write the depth of invasion for the three tumors that were 1-2 centimeters in size.
4- Result: " Acute appendicitis was accompanied to carcinoid tumor in eight (80%) cases." ---- Change to: Histologic evidence of acute appendicitis was seen in eight of our cases (80%).
5- Result: "Hematoxylin and eosin-stained sections showed small narrow islets of cytoplasm and cord-like structures around the nucleus "
Please rewrite the histologic description of the tumor. I cannot understand this description well.
6- Result: "In the immunohistochemical study, neuroendocrine cell components such as chromogranin A, synaptophysin (Figure 2), and neuron-specific enolase (NSE) were detected."
--- Change to: Immunohistochemistry revealed the tumoral cells to be positive for neuroendocrine cell components such as chromogranin A, synaptophysin (Figure 2), and neuron-specific enolase (NSE).
7- Page 4: months is correct ("ranging 12-84 monthts").
8- Discussion: "Although NETs are usually sporadic, some familial syndromes including multiple endocrine neoplasia I and II, von Hippel Lindau syndrome, and neurofibromatosis type I can rarely accompanie these tumors."
Correct accompanie to accompany.
9- Discussion: " PET/CT imaging technique developed with radiolabeled somatostatin analogues is used as the new gold standard" --- Change to: The PET/CT imaging technique developed with radiolabeled somatostatin analogues (68Ga-DOTATATE PET/CT) is used as the
new gold standard.
10- Discussion: " It was also determinated as a reliable method for optimizing treatment regimens for pediatric patients." --- Change to:
It was also determined to be a reliable method for optimizing treatment regimens for pediatric patients.
11- Conclusion: "For this reason, histopathology results should be carefully follow-up and advanced surgical and medical treatment options should be considered by performing further examinations when necessary."--
Change to: For this reason, after the release of the histopathological diagnosis of this tumor, careful follow-up and advanced surgical and medical treatment options should be considered by performing further examinations when necessary.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reply to Reviewers

Reviewer 1:

The manuscript is interesting

Reviewer 2:

Dear Editor

Although there is no novelty in the subject of this article but due to sample size and good follow up and also rather rarity of condition in children I agree with publishing this artilce in IJP with minor revisions:

1-Q: [keyword: carcinoid instead of carsinoid]

R: [Changed]

2- Q: [Background: " The second and third decades of life are the most common periods of carcinoid tumor; however, it can also be observed in pediatric population.5" ---- Change to: The second and third decades of life are the most common periods of carcinoid tumor .5]

(Because second decade also covers the pediatric age group).

R: [Changed]

3- Q: [Please write the depth of invasion for three tumors that were 1-2 centimer in size.]

R: [Revised]

4- Q: [Result: " Acute appendicitis was accompanied to carcinoid tumor in eight (80%) cases." ---- change to: Histologic evidence of acute appendicitis was seen in eight of our cases (80%).]

R: [Changed]

5- Q: [Result: "Hematoxylin and eosin-stained sections showed small narrow islets of cytoplasm and cord-like structures around the nucleus "

Please re write the histologic description of tumor. I can not understand this description well.]

R: [Re writed]

6- Q: [Result: "In the immunohistochemical study, neuroendocrine cell components such as chromogranin A, synaptophysin (Figure 2), and neuron-specific enolase (NSE) were detected."

--- change to: Immunohistochemistry revealed the tumoral cells to be positive for neuroendocrine cell components such as chromogranin A, synaptophysin (Figure 2), and neuron-specific enolase (NSE).]

Q: [Changed]

7- Q: [Page 4: months is correct (ranging 12-84 monthts).]

R: [Corrected]

8- Q: [Discussion: "Although NETs are usually sporadic, some familial syndromes including multiple endocrine neoplasia I and II, von Hippel Lindau syndrome, and neurofibromatosis type I can rarely accompanie these tumors.

Correct accompanie to accompany.]

R: [Corrected]

9- Q: [Discussion: " PET/CT imaging technique developed with radiolabeled somatostatin analogues is used as the new gold standard" --- Change to: PET/CT imaging technique developed with radiolabeled somatostatin analogues (68Ga-DOTATATE PET/CT) is used as the

new gold standard.]

R: [Changed]

10- Q: [Discussion: " It was also determinated as a reliable method for optimizing treatment regimens for pediatric patients." --- Change to:

It was also determined as a reliable method for optimizing treatment regimens for pediatric patients.]

R: [Changed]

11- Q: [Conclusion: "For this reason, histopathology results should be carefully follow-up and advanced surgical and medical treatment options should be considered by performing further examinations when necessary."-- Change to: For this reason, after release of histopathological diagnosis of this tumor, careful follow-up and advanced surgical and medical treatment options should be considered by performing further examinations when necessary.]

R: [Changed]

Reviewer 3:

Thank you for considering me as a reviewer for this manuscript. Overall, this manuscript provides useful information on appendiceal carcinoid tumors in the pediatric population. I would recommend minor revisions to improve clarity prior to publication. Here are some recommendations for improving this report on appendiceal carcinoid tumors in children:

Q: [Methods

- The retrospective design has limitations such as reliance on documentation in medical records. Potential issues like missing data or loss to follow-up are mitigated by the authors through reviewing available records and contacting patients for follow-up.]

R: [reviewed by us.]

Q: [Results

- The follow-up period ranged widely from 12-84 months. Longer uniform follow-up for all patients could provide more meaningful data on long-term outcomes.

- Details are lacking on how many patients were lost to follow-up or had incomplete records. This could introduce bias if there were systematic differences in those patients.

- The survival/recurrence data is reported narratively. Including figures like a Kaplan-Meier curve for recurrence-free survival could enhance the presentation.

- The study is unable to provide definitive guidance on optimal surgical management, appropriate follow-up protocols, or prognostic factors.]

R: [The Result section was reviewed and necessary corrections were made.]

Q: [Discussion

- Provide more context when comparing the current findings to prior studies. Point out where results align with or differ from previous literature and discuss possible reasons for inconsistencies.

- Discuss any insights from the data on prognostic factors or predictors of recurrence and metastases. Even if statistical analysis was not possible, the authors could still comment on clinical significance.

- Compare the current pathology practices described to consensus guidelines on classification, staging, and immunohistochemistry of neuroendocrine tumors.]

R: [The Discussion section was reviewed and necessary corrections were made.]

Q: [References:

- The authors could consider adding 1-2 very recent references if available to ensure comprehensive coverage.]

R: [A current article added.]

2 Revision 1

0 comments

No public comments in this round.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

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Reply to Reviewers

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1-Q: The manuscript is interesting

R: The article has been reviewed by us. We thank you.

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(Because second decade also covers the pediatric age group).

R: [Changed]

3- Q: [Please write the depth of invasion for three tumors that were 1-2 centimer in size.]

R: [Revised]

4- Q: [Result: " Acute appendicitis was accompanied to carcinoid tumor in eight (80%) cases." ---- change to: Histologic evidence of acute appendicitis was seen in eight of our cases (80%).]

R: [Changed]

5- Q: [Result: "Hematoxylin and eosin-stained sections showed small narrow islets of cytoplasm and cord-like structures around the nucleus "

Please re write the histologic description of tumor. I can not understand this description well.]

R: [Re writed]

6- Q: [Result: "In the immunohistochemical study, neuroendocrine cell components such as chromogranin A, synaptophysin (Figure 2), and neuron-specific enolase (NSE) were detected."

--- change to: Immunohistochemistry revealed the tumoral cells to be positive for neuroendocrine cell components such as chromogranin A, synaptophysin (Figure 2), and neuron-specific enolase (NSE).]

Q: [Changed]

7- Q: [Page 4: months is correct (ranging 12-84 monthts).]

R: [Corrected]

8- Q: [Discussion: "Although NETs are usually sporadic, some familial syndromes including multiple endocrine neoplasia I and II, von Hippel Lindau syndrome, and neurofibromatosis type I can rarely accompanie these tumors.

Correct accompanie to accompany.]

R: [Corrected]

9- Q: [Discussion: " PET/CT imaging technique developed with radiolabeled somatostatin analogues is used as the new gold standard" --- Change to: PET/CT imaging technique developed with radiolabeled somatostatin analogues (68Ga-DOTATATE PET/CT) is used as the

new gold standard.]

R: [Changed]

10- Q: [Discussion: " It was also determinated as a reliable method for optimizing treatment regimens for pediatric patients." --- Change to:

It was also determined as a reliable method for optimizing treatment regimens for pediatric patients.]

R: [Changed]

11- Q: [Conclusion: "For this reason, histopathology results should be carefully follow-up and advanced surgical and medical treatment options should be considered by performing further examinations when necessary."-- Change to: For this reason, after release of histopathological diagnosis of this tumor, careful follow-up and advanced surgical and medical treatment options should be considered by performing further examinations when necessary.]

R: [Changed]

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R: [reviewed by us.]

Q: [Results

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- Details are lacking on how many patients were lost to follow-up or had incomplete records. This could introduce bias if there were systematic differences in those patients.

- The survival/recurrence data is reported narratively. Including figures like a Kaplan-Meier curve for recurrence-free survival could enhance the presentation.

- The study is unable to provide definitive guidance on optimal surgical management, appropriate follow-up protocols, or prognostic factors.]

R: [The Result section was reviewed and necessary corrections were made.]

Q: [Discussion

- Provide more context when comparing the current findings to prior studies. Point out where results align with or differ from previous literature and discuss possible reasons for inconsistencies.

- Discuss any insights from the data on prognostic factors or predictors of recurrence and metastases. Even if statistical analysis was not possible, the authors could still comment on clinical significance.

- Compare the current pathology practices described to consensus guidelines on classification, staging, and immunohistochemistry of neuroendocrine tumors.]

R: [The Discussion section was reviewed and necessary corrections were made.]

Q: [References:

- The authors could consider adding 1-2 very recent references if available to ensure comprehensive coverage.]

R: [A current article added.]

3 Revision 2

0 comments

No public comments in this round.

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reply to Reviewers

Reviewer 1:

1-Q: The manuscript is interesting

R: The article has been reviewed by us. We thank you.

Reviewer 2:

Dear Editor

Although there is no novelty in the subject of this article but due to sample size and good follow up and also rather rarity of condition in children I agree with publishing this artilce in IJP with minor revisions:

1-Q: [keyword: carcinoid instead of carsinoid]

R: [Line number: 24]

2- Q: [Background: " The second and third decades of life are the most common periods of carcinoid tumor; however, it can also be observed in pediatric population.5" ---- Change to: The second and third decades of life are the most common periods of carcinoid tumor .5]

(Because second decade also covers the pediatric age group).

R: [Lines number: 33-34]

3- Q: [Please write the depth of invasion for three tumors that were 1-2 centimer in size.]

R: [Lines number: 71-73]

4- Q: [Result: " Acute appendicitis was accompanied to carcinoid tumor in eight (80%) cases." ---- change to: Histologic evidence of acute appendicitis was seen in eight of our cases (80%).]

R: [Line number: 76]

5- Q: [Result: "Hematoxylin and eosin-stained sections showed small narrow islets of cytoplasm and cord-like structures around the nucleus "

Please re write the histologic description of tumor. I can not understand this description well.]

R: [Lines number: 78-79]

6- Q: [Result: "In the immunohistochemical study, neuroendocrine cell components such as chromogranin A, synaptophysin (Figure 2), and neuron-specific enolase (NSE) were detected."

--- change to: Immunohistochemistry revealed the tumoral cells to be positive for neuroendocrine cell components such as chromogranin A, synaptophysin (Figure 2), and neuron-specific enolase (NSE).]

Q: [Lines number: 79-81]

7- Q: [Page 4: months is correct (ranging 12-84 monthts).]

R: [Line number: 90]

8- Q: [Discussion: "Although NETs are usually sporadic, some familial syndromes including multiple endocrine neoplasia I and II, von Hippel Lindau syndrome, and neurofibromatosis type I can rarely accompanie these tumors.

Correct accompanie to accompany.]

R: [Lines number: 134-136]

9- Q: [Discussion: " PET/CT imaging technique developed with radiolabeled somatostatin analogues is used as the new gold standard" --- Change to: PET/CT imaging technique developed with radiolabeled somatostatin analogues (68Ga-DOTATATE PET/CT) is used as the

new gold standard.]

R: [Lines number:141-142]

10- Q: [Discussion: " It was also determinated as a reliable method for optimizing treatment regimens for pediatric patients." --- Change to:

It was also determined as a reliable method for optimizing treatment regimens for pediatric patients.]

R: [Lines number: 145-146]

11- Q: [Conclusion: "For this reason, histopathology results should be carefully follow-up and advanced surgical and medical treatment options should be considered by performing further examinations when necessary."-- Change to: For this reason, after release of histopathological diagnosis of this tumor, careful follow-up and advanced surgical and medical treatment options should be considered by performing further examinations when necessary.]

R: [Lines number: 163-165]

Reviewer 3:

Thank you for considering me as a reviewer for this manuscript. Overall, this manuscript provides useful information on appendiceal carcinoid tumors in the pediatric population. I would recommend minor revisions to improve clarity prior to publication. Here are some recommendations for improving this report on appendiceal carcinoid tumors in children:

Q: [Methods

- The retrospective design has limitations such as reliance on documentation in medical records. Potential issues like missing data or loss to follow-up are mitigated by the authors through reviewing available records and contacting patients for follow-up.]

R: [Lines number: 49-52]

Q: [Results

- The follow-up period ranged widely from 12-84 months. Longer uniform follow-up for all patients could provide more meaningful data on long-term outcomes.

- Details are lacking on how many patients were lost to follow-up or had incomplete records. This could introduce bias if there were systematic differences in those patients.

- The survival/recurrence data is reported narratively. Including figures like a Kaplan-Meier curve for recurrence-free survival could enhance the presentation.

- The study is unable to provide definitive guidance on optimal surgical management, appropriate follow-up protocols, or prognostic factors.]

R: [Lines number: 65-93]

Q: [Discussion

- Provide more context when comparing the current findings to prior studies. Point out where results align with or differ from previous literature and discuss possible reasons for inconsistencies.

- Discuss any insights from the data on prognostic factors or predictors of recurrence and metastases. Even if statistical analysis was not possible, the authors could still comment on clinical significance.

- Compare the current pathology practices described to consensus guidelines on classification, staging, and immunohistochemistry of neuroendocrine tumors.]

R: [Lines number: 95-157]

Q: [References:

- The authors could consider adding 1-2 very recent references if available to ensure comprehensive coverage.]

R: [Lines number: 208-210]

4 Revision 3

0 comments

No public comments in this round.