OPEN PEER REVIEW

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# Peer Review Report for "Comparison of the Imaging and Pathological Features of Telangiectatic Osteosarcoma and Aneurysmal Bone Cyst of Long Tubular Bones"

**Author(s):** Yun-Heng Shi, Shu-Man Han, Tao Sun, Bao-Hai Yu, Hui-Zhao Wu, Wen-Juan Wu, Bu-Lang Gao

## Review Timeline:

Submit Date: 30 May 2019
Revised Date: 7 Mar 2020
Accepted Date: 18 Mar 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

**REFEREE**: Reviewer | **Revision** (0) 12 Jun 2019

Dear AE,
Although it is clear that the researchers made a great effort to design and conduct a high-quality study, unfortunately, there are a number of major problems:
1. The study was not properly designed and it was better to use a case-control design.
2. The principles and structure of the scientific writing of articles were not met and, for example, some results were presented in the method section.
3. Statistical analysis of the study data was not performed properly, and, moreover, it is necessary that statistical analysis be performed based on important factors that affect the outcome values such as age, sex, and so on.
4. Conclusions are also beyond the results of the study.
Thanks.

**REFEREE**: Reviewer | **Revision** (0) 24 Jun 2019

Dear AE,

There are some comments which should be addressed by the author:
1- Please add background and objective parts for the abstract according to journal format. In addition, please add objective part to paper before method section.
2- Please add the numerical profile to result of abstract.
3- Most parts of the method are in fact results material. Please write the paper appropriately.
4- It is unknown what is the imaging method of findings in table 1? For example, lytic features in this table are seen in plain X-Ray or CT or MRI? Please mention the data in the table?
5- Did the authors determine compatibility of different imaging methods regarding certain findings? For example, if 13 TOS were lytic, did they showed lytic feature both in plain X Ray and CT? was any mismatch between findings in different imaging methods? please add the data.
6- What were the data of TOS staging? Did the findings were associated with the tumor stage?
7- What is the meaning of: ".... for recognizing proper patients with these diseases."?
8- Did the authors enrolled all patients with TOS and ABC in the study time period?
Thanks.

**REFEREE**: Reviewer | **Revision** (0) 31 Jul 2019

Dear AE,
The manuscript is a descriptive study and the method of analysis is not clear .there are some English errors, so after major revision, the article could be reevaluated.
Regards

**REFEREE**: Associate Editor | **Revision** (0) 31 Jul 2019

Dear EIC,
Although it is clear that the researchers made a great effort to design and conduct a high-quality study, unfortunately, there are a number of major problems for the authors:
1- Please add background and objective parts for the abstract according to the journal format. In addition, please add the objective part to the paper before the method section.
2- Please add the numerical profile to the result of the abstract.
3- Most parts of the method are in fact results material. Please write the paper appropriately.
4- It is unknown what is the imaging method of findings in table 1? For example, lytic features in this table are seen in plain X-Ray or CT or MRI? Please mention the data in a table?
5- Did the authors determine the compatibility of different imaging methods regarding certain findings? For example, if 13 TOS were lytic, did they showed lytic feature both in plain X Ray and CT? was any mismatch between findings in different imaging methods? please add the data.
6- What were the data of TOS staging? Did the findings were associated with tumor stage?
7- What is the meaning of: ".... for recognizing proper patients with these diseases."?
8- Did the authors enrolled all patients with TOS and ABC in the study time period?
9- The study was not properly designed and it was better to use a case-control design.

10- The principles and structure of the scientific writing of articles were not met and, for example, some results were presented in the method section
11- Statistical analysis of the study data was not performed properly, and, moreover, it is necessary that statistical analysis be performed based on important factors that affect the outcome values such as age, sex, and so on.
12- Conclusions are also beyond the results of the study.
so the manuscript needs major revision
Regards

**REFEREE**: EIC | **Revision (0)** 3 Aug 2019

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
Thanks.

OPEN PEER REVIEW

Revision (1)

## Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

**Reviewers' Comments:**

*Reviewer 1:*
*Hi Dear Authors*
*Although it is clear that the researchers made a great effort to design and conduct a high-quality study, unfortunately, there are a number of major problems:*
*1. The study was not properly designed and it was better to use case-control design.*
*Response: Thank you very much for your professional comments. We have used the case-control design based on your suggestions.*

*2. The principles and structure of the scientific writing of articles were not met and, for example, some results were presented in the method section.*
*Response: Thank you very much for your professional comments. We have put the data from the method section into the results section.*

*3. Statistical analysis of the study data was not performed properly, and, moreover, it is necessary that statistical analysis be performed based on important factors that effect on the outcome values such as age, sex, and so on.*
*Response: Thank you very much for your professional comments. We have revised the statistical analysis as follows:* Categorical data were tested with fisher's exact test. We have done some statistical analysis and found and added the following information in the results section: No significant (P>0.05) difference existed in the age of disease onset between the two groups. However, the duration of symptom persistence was significantly (P=0.01) shorter in the TOS group than in the ABC before correct diagnosis.
Moreover, some items have their statistical significance changed after re-calculation of the statistics using the new method as shown in the table.

*4. Conclusions are also beyond the results of the study.*
*Response: Thank you very much for your professional comments. We have revised the conclusion as follows:* The clinical, imaging and pathological characteristics should be combined to make a correct differential diagnosis between telangiectatic osteosarcoma and aneurysmal bone cyst.

*Reviewer 2:*
*1-please add background and objective parts for abstract according to journal format. In addition, please add objective part to paper before method section.*
*Response: Thank you very much for your comments. We have done this accordingly.*

*2-please add the numerical profile to result of abstract.*
*Response: Thank you very much for your comments. We have added the numerical profile to the results of abstract.*

*3-most parts of method are in fact results material. Please write the paper appropriately.*

*Response: Thank you very much for pointing out our mistakes. We have put the data from the method section into the results section.*

*4-it is unknown what is the imaging method of findings in table 1? For example, lytic feature in this table are seen in plain X-Ray or CT or MRI? Please mention the data in table?*

*Response: The imaging signs in Table 1 are obtained with plainX-ray, CT, and MRI. CT is better than plain films to show the bone destruction, soft masses and lesion edges. MRI is better to show the lesion range and fluid-fluid levels. Among these signs, bone destruction, transitional band, periosteal reaction and soft tissue masses are assessed using plain films and CT. Soft tissue masses and fluid-fluid levels are evaluated with CT and MRI.*

*We have added the following information in the not below the table as follows:* The imaging signs here are obtained with plain X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). Bone destruction, transitional band, periosteal reaction and soft tissue masses are assessed using plain films and CT, whereas soft tissue masses and fluid-fluid levels are evaluated with CT and MRI.

*5-did the authors determine compatibility of different imaging methods regarding certain findings? For example, if 13 TOS were lytic, did they showed lytic feature both in plain X Ray and CT? was any mismatch between findings in different imaging methods? please add the data.*

*Response:* The long tubular bones in limbs are not overlapped with each other, and plain films and CT have the same diagnostic effect in evaluating bone destruction, edges of destruction and periosteal reaction in long tubular bones. However, CT can better show details of bone destruction, soft tissue masses and lesion edges. MRI is better to show lesion range and fluid-fluid levels. The combination of the three imaging modalities helps making a correct diagnosis. *We have added the above information in the discussion section.*

*6-what were the data of TOS staging? Did the findings were associated with tumor stage?*

*Response: TOS staging principles are the same as in other malignant tumors of bone. This study did not perform tumor staging, and all the patients were diagnosed on the first visit to the hospital with no metastasis to other organs or locations.*

*7-what is the meaning of: ".... for recognizing proper patients with these diseases."?*

*Response: Thank you very much for your comments. It is to select patients with TOS or ABC for comparison. So, we have revised the sentence to the following one:* The clinical data were reviewed at our hospital between 1990 and 2010 for patients with TOS or ABC for comparison.

*8-did the authors enrolled all patients with TOS and ABC in the study time period?*

*Response: Thank you for your question. We enrolled all patients with TOS and ABC in this study period.*

*Reviewer 3:*
*Dear associate editor*
*the manuscript is a descriptive study and the method of analysis is not clear .there are some English errors,so after major revision the article could be reevaluated.*
*Response: Thank you very much for your comments. We have revised the language and corrected the mistakes.*

*Regards*
*M.Malek*

**Associate Editor's Comments:**

*Associate Editor 1:*
*Dear editor in chief*
*Although it is clear that the researchers made a great effort to design and conduct a high-quality study, unfortunately, there are a number of major problems:*
*1-please add background and objective parts for abstract according to journal format. In addition, please add objective part to paper before method section.*
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*Response: Thank you very much for your comments. We have added the numerical profile to the results of abstract.*

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*Response: TOS staging principles are the same as in other malignant tumors of bone. This study did not perform tumor staging, and all the patients were diagnosed on the first visit to the hospital with no metastasis to other organs or locations.*
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*Response: Thank you very much for your comments. It is to select patients with TOS or ABC for comparison. So, we have revised the sentence to the following one:* The clinical data were reviewed at our hospital between 1990 and 2010 for patients with TOS or ABC for comparison.

*8-did the authors enrolled all patients with TOS and ABC in the study time period?*
*Response: Thank you for your question. We enrolled all patients with TOS and ABC in this study period.*

*9- The study was not properly designed and it was better to use case-control design.*
*Response: Thank you very much for your professional comments. We have used the case-control design based on your suggestions.*

*10- The principles and structure of the scientific writing of articles were not met and, for example, some results were presented in the method section*
*Response: Thank you very much for your professional comments. We have put the data from the method section into the results section.*

*11- . Statistical analysis of the study data was not performed properly, and, moreover, it is necessary that statistical analysis be performed based on important factors that effect on the outcome values such as age, sex, and so on.*
*Response: Thank you very much for your professional comments. We have revised the statistical analysis as follows:* Categorical data were tested with fisher's exact test. We have done some statistical analysis and found and added the following information in

the results section: No significant (P>0.05) difference existed in the age of disease onset between the two groups. However, the duration of symptom persistence was significantly (P=0.01) shorter in the TOS group than in the ABC before correct diagnosis.
Moreover, some items have their statistical significance changed after re-calculation of the statistics using the new method as shown in the table.

*12- Conclusions are also beyond the results of the study.*
*Response: Thank you very much for your professional comments. We have revised the conclusion as follows:* The clinical, imaging and pathological characteristics should be combined to make a correct differential diagnosis between telangiectatic osteosarcoma and aneurysmal bone cyst.

*so the manuscript needs major revision*
Response: Thank you very much. We have revised the manuscript based on your suggestions.

**OPEN PEER REVIEW**

**Revision (1)**

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

**REFEREE**: Reviewer | **Revision** (1) 28 Aug 2019

Dear AE,
Although, the purpose of this article is to help discriminate between two diseases, which can be valuable, but the article needs a lot of modifications that are briefly outlined below and detailed in the manuscript file.
1. The main goal of study was differential diagnosis of TOS and ABC; therefore, must be presented these finding along with p-value in results. Currently, all results that presented are descriptive.
2. Must be mentioned, what is your study design name?
3. Must be described what is your mean from treatment?
4. Must be specified clinical data related to when time (before or after any treatment)?
5. Clearly, must be written about inclusion and exclusion criteria of two groups (source population).
6. Results presented in method part and must be transferred to the later section.
7. Selection of paired t-test is not accurate; because, two groups are independent and must be applied t-independent or Mann Whitney test according to Kolmogorov Smirnov Test results.
8. In this study, did not collect information on many demographic variables such as age, education, weight, and other diseases such as diabetes, hypertension, and so on. As a result, in comparison between these two groups cannot rule out their roles in making a difference between clinical and pathological features (the probability of confounding is strong).
9. All descriptive results must be presented in a table.
10. Detailed comments annexed in the draft file.
Thanks.

**REFEREE**: Reviewer | **Revision** (1) 2 Sep 2019

Dear AE,
The study is reviewed carefully. According to comments and revisions by the author, this manuscript is accepted.
Thanks

**Leila Aghaghazvini**: Reviewer | **Revision** (1) 15 Nov 2019

Dear AE,
The article was reviewed and it seems that many errors have been relatively solved and if there is no statistical error, the article could be accepted.
With best regards

**Mahrooz Malek**: Associate Editor | **Revision (1)** 5 Dec 2019

Dear EIC,
The revised version is acceptable.
Regards
M.Malek

**Kavous Firouznia**: EIC | **Revision (1)** 14 Dec 2019

Dear authors,
Your article needs Major Revision, especially in the statistical and scientific writing.
Regards

OPEN PEER REVIEW

Revision (2)

## Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

**Reviewers' Comments and responses:**

*Reviewer 1:*
*Hi Dear Authors*
*Although, the purpose of this article is to help discriminate between two diseases, which can be valuable, but the article needs a lot of modifications that are briefly outlined below and detailed in the manuscript file.*
*1. The main goal of study was differential diagnosis of TOS and ABC; therefore, must be presented these finding along with p-value in results. Currently, all results that presented are descriptive.*

*Response: The P value has been added in Table 3 AND also in the text like in the result section indicated by significantly different or not.*

*2.Must be mentioned, what is your study design name?*

*Response: This study is* a case-controlled retrospective study which has been stated in the text.
*3.Must be described what is your mean from treatment?*

*Response: This study was a retrospective study with imaging of diseases before treatment after hospitalization. We have indicated this in the text.*

*4.Must be specified clinical data related to when time (before or after any treatment)?*

*Response: All the imaging in this study is before the treatment.* The imaging signs were obtained with plain X-ray, CT, and MRI before treatment.

*5.Clearly, must be written about inclusion and exclusion criteria of two groups (source population).*

*Response: The inclusion and exclusion criteria have been added in the text as follows:*
The inclusion criteria were primary TOS or ABC confirmed by histopathology, presentation for the first time to the hospital without any treatment, and imaging examination of plain radiography, computed tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria were patients with TOS or ABC who had been treated and patients who had co-existence of other tumors.

*6.Results presented in method part and must be transferred to the later section.*

*Response: Thank you very much. We have transferred the data to the results as follows:* Seventeen patients with TOS in the long tubular bones confirmed by histopathology were retrieved including 10 males and 7 females with an age range of 1-60 years (mean 25.4±8.7) (Table). Seventeen patients with ABC were also retrieved for comparison including seven males and ten females with an age range of 3-43 years (mean 20.1±8.7) (Table). All patients had plain radiography, twelve TOS and eleven ABC cases had both CT and MRI.

*7.Selection of paired t-test is not accurate; because, two groups are independent and must be applied t-independent or Mann Whitney test according to Kolmogorov Smirnov Test results.*

*Response:* We have used the recommended test for the statistical analysis in this study as follows: and the differences between groups were tested with the Mann-Whitney U test.

*8.In this study, did not collect information on many demographic variables such as age, education, weight, and other diseases such as diabetes, hypertension, and so on. As a result, in comparison between these two groups cannot rule out their roles in making a difference between clinical and pathological features (the probability of confounding is strong).*

*Response:* The general information regarding these patients was presented in Table 1.

Table 1： General information regarding TOS and ABC

| | TOS(n=17) | ABC(n=17) |
|---|---|---|
| Sex(M/F) | 10/7 | 7/10 |
| Onset age (y) | 25.4±8.7 (1-60 y) | 20.1±8.7 (3-43 y) |
| Profession | Student (11)and farmer (6) | Student (7), farmer (8), and freelancer (2) |
| Past history | Healthy (15), hypertension (1), smoking(1)and alcohol abuse (1) | Healthy (15), hypertension(2) |
| Lesion location | Femur (11), humerus (2), tibia (2) and ulna (2) | Femur (7), tibia (6), humerus (1), radius (1), ulna (1) and fibula (1) |
| Symptoms | Local swelling (14) and pathological fracture (3) lasting 3.0±1.5 months (range 1-5) | Local pain or swelling (17) and pathological fracture (3) lasting |

| | | |
|---|---|---|
| | | 9.8±10.1months (2 m – 3 y) |
| Signs | Soft tissue mass (9), high skin temperature (2) and venous engorgement (2) | Hard apophysis (3) |
| Laboratory | Rise in serum alkaline phosphatase (3) | Rise in serum alkaline phosphatase (1) |
| Treatment | Local resection + artificial joint replacement (4) and local resection + chemotherapy (13) | Curettage + bone grafting + internal fixation (6), curettage + bone cement filling + internal fixation (5), curettage + inactivation + bone grafting (3), curettage + inactivation (1), curettage + grafting (1) and cephalectomy of ulna (1) |

Note: TOS, telangiectatic osteosarcoma; ABC, aneurysmal bone cysts.

*9.All descriptive results must be presented in a table.*

*Response: Thank you. We have done so as suggested in Tables (Table 1-2).*

Table 2. Imaging presentations of telangiectatic osteosarcoma and aneurysmal bone cyst

| | | telangiectatic osteosarcoma (17) | aneurysmal bone cyst (17) |
|---|---|---|---|
| Plain radiography | Soft tissue mass | 14 | 3 |
| | Bone destruction | Lytic (13) | Lytic (17) and eccentric destruction (10) |
| | Expansive | Marked (5) and slight (3) | Marked (11) and slight (5) |
| | Calcification | 2 | 1 |
| | Bone ridge | 0 | 8 |
| | Boundary | Unclear with a transition band (12) | Unclear (15) and thin sclerotic rim (12) |
| | Periosteal reaction | 8 and Codman triangle (5) | 2 |
| | Pathological fracture | 3 | 3 |
| CT | Bone destruction | 10 | 11 |
| | Fluid level | 3 | 4 |

| | | | |
|---|---|---|---|
| | Boundary | Unclear with a transition band (12) | Unclear and irregular(9) |
| | Bone cortex | Discontinued (10) with mesh-like destruction (2) | Discontinued (3) |
| | Periosteal reaction | 5 | 2 |
| | Expansive | Marked (3) and slight (3) | Marked (6) and slight (5) |
| | Soft tissue mass | 11 | 3 |
| MRI | Signal | Uneven low signal (12) in T1WI, mixed (9) and high signal (3) in T2WI, and strip separation (5) | Uneven low signal in T1WI and mixed signal in T2WI (11) and strip separation (3) |
| | Cyst change and fluid level | Multiple cysts and fluid levels (5) | Multiple cysts and fluid levels (8) |
| | Soft tissue mass | 11 | 3 |

Note: CT, computed tomography; MRI, magnetic resonance imaging.

*10. Detailed comments annexed in the draft file.*

*Reviewer 2:*
*a*
*Reviewer 3:*
*Dear associated editor*

*The article was reviewed and it seems that many errors have been relatively solved and if there is no statistical error, the article could be accepted .*
*With best regards*

**OPEN PEER REVIEW**

**Revision (2)**

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

**REFEREE**: Reviewer | **Revision** (2) — 29 Dec 2019

Dear AE,
Thanks to authors for implementation of requested comments and corrections. At present, it can be said that according to the methodology point of view, the manuscript is appropriate and can be accepted for publication.
Thanks.

**Mahrooz Malek**: Associate Editor | **Revision** (2) — 7 Jan 2020

Dear EIC,
The revised version is acceptable.
Regards

**Mehranoosh Dolatshahi**: Associate Editor | **Revision** (2) — 17 Feb 2020

Dear EIC,
Please the authors respond to the following comment. Then, highlight any changes they make in the manuscript.
There are mismatches between data in the tables and data in the manuscript. You mentioned two cases of calcification in the table and one case in the manuscript. The same has happened with the lytic and expansile lesions. Please check the tables and data in the manuscript and make sure there are no discrepancies between them.
- Do they mean expansile lytic lesions? Please clarify.
Thank you.

**REFEREE**: EIC | **Revision** (2) — 18 Feb 2020

Dear authors,
Your article needs Minor Revision.
Regards

OPEN PEER REVIEW

Revision (3)

## Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Review comments and response:

**Reviewers' Comments:**

*Reviewer 1:*
*Hi*
*Thanks to authors for implementation of requested comments and corrections. At present, it can be said that according to the methodology point of view, the manuscript is appropriate and can be accepted for publication.*

*Response: Thank you very much for your positive comments. We really appreciated it.*

**Associate Editor's Comments:**

*Associate Editor 1:*
*Dear editor in chief*
*The revised version is acceptable*
*Regards*

*Response: Thank you very much for your positive comments. We really appreciated it.*

*Associate Editor 2:*
*Dear author,*
*Please respond to the following comment. Then, highlight any changes you make in the manuscript. Please do not make any changes in the manuscript other than responding to the comments, because they will not be considered.*

*There are mismatches between data in the tables and data in the manuscript. You mentioned two cases of calcification in the table and one case in the manuscript. The same has happened with the lytic and expansile lesions. Please check the tables and data in the manuscript and make sure there are no discrepancies between them.*

*Response: Thank you very much for pointing our mistakes. The calcification was in one and we have revised it to one in the table. Also, in the text, we have revised the text more clearly to be consistent with the information in the table: as follows:*

Three cases had slight expansion of the tumor, and five had marked expansile osteolytic changes. In 17 cases with ABC, an ill-defined border was found in fifteen cases, lytic bone destruction in 17, marked expansile bone destruction in eleven, slightly expansile destruction in five----

*Do you mean expansile lytic lesions? Please clarify.*

*Response: Thank you very much for your careful evaluation. Lytic bone destruction and expansile bone destruction are both bone destruction, and we classified the bone destruction into lytic and expansile. We have made it clear in the text as follows:* Bone destruction was classified into lytic and expansile destruction.

OPEN PEER REVIEW

Revision (3)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

**Mehranoosh Dolatshahi**: Associate Editor | **Revision** (3) 18 Mar 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

**Kavous Firouznia**: EIC | **Revision** (3) 18 Mar 2020

Dear authors,
Your article is acceptable for the publication.
Regards