Dear editor and reviewer:

Thank you very much for your decision and comments on our manuscript. Your comments are of great significance for us to improve the quality of the manuscripts. We have read your comments carefully and tried our best to improve and made some changes in the manuscript. A revised manuscript has been resubmitted. Now in this reply, we will response the reviewer's comments point by point.

Reviewer's code: 05465429

1. DISCUSSION: line 315 the term "systematic" should be obviated.

Thank you very much for your valuable advice. We read the part of Discussion carefully and found that the word was really out of place here. According to your opinion, this word has been deleted.

Reviewer's code: 05238069

1. The abstract content is complex, some of which can be described in 'introduction', and the statistical contents involved should be summarized briefly.

Thank you very much for your professional advice. We have read the abstract carefully several times. In accordance with your suggestion, its content has been summarized briefly. A lot of complicated statistical content was deleted, and only the more important description was left. In addition, we modified the format of the abstract section according to the requirements. The abstract before and after the modification is as follows:

Before:

Angiosarcoma is a highly malignant soft tissue sarcoma derived from vascular endothelial cells that mainly occurs in the skin and subcutaneous tissues. Small-intestinal angiosarcoma is rare and has a poor prognosis. We reported a primary multifocal ileal angiosarcoma case and

analyzed previously reported cases to improve the understanding of small intestinal angiosarcoma. Together with our patient, we collected 82 cases. Angiosarcoma of the small intestine is more likely to occur in men with a male-to-female ratio of 2.04:1. The patients' mean age was 63.28 years. Gastrointestinal bleeding, anemia, abdominal pain, weakness, and weight loss were the common symptoms. The diagnosis of small-intestinal angiosarcoma relies on morphological features and immunohistochemistry. CD31, CD34, VIII, ERG, Fli-1, and vWF are valuable diagnostic markers. Small-intestinal angiosarcoma most commonly occurs in the jejunum, followed by the ileum and duodenum. Angiosarcoma is prone to metastasis, and at least 56.5% of collected primary cases have definite distant metastasis. Radiation and toxicant exposure are risk factors for angiosarcoma. The average radiation dose is 48.03±14.18 Gray, and the duration from exposure to diagnosis is 16.12±10.05 years, with a range of 7-45 years. After a definite diagnosis of small-intestinal angiosarcoma, the survival time of patients ranged from 3 days to 3 years. The mean and median survival time were 8 month and 3 months, respectively. Kaplan–Meier survival analysis showed that age, infiltration depth, chemotherapy, and the number of small intestinal segments invaded by tumor lesions were prognostic factors for small intestinal angiosarcoma ($p<0.05$). Multivariate COX regression analysis showed that chemotherapy and surgery significantly improved patient prognosis. Angiosarcoma should be considered for unexplained melena and abdominal pain, especially in older men and in patients with a history of radiation exposure. Prompt treatment, including surgery and adjuvant chemotherapy, is essential for prolonging patients' survival.

After:

BACKGROUND

Angiosarcoma is a highly malignant soft-tissue sarcoma derived from vascular endothelial cells that mainly occurs in the skin and subcutaneous tissues. Small -intestinal angiosarcomas are rare, and the prognosis is poor.

CASE SUMMARY

We reported a case of primary multifocal ileal angiosarcoma and analyze previously reported cases to improve our understanding of small intestinal angiosarcoma. Small intestinal

angiosarcoma is more common in elderly and male patients. Gastrointestinal bleeding, anemia, abdominal pain, weakness, and weight loss were the common symptoms. CD31, CD34, VIII, ERG, Fli-1, and vWF are valuable immunohistochemical markers for the diagnosis of small-intestinal angiosarcoma. Small-intestinal angiosarcoma most commonly occurs in the jejunum, followed by the ileum and duodenum. Radiation and toxicant exposure are risk factors for angiosarcoma. After a definite diagnosis, the mean and median survival time were 8 mo and 3 mos, respectively. Kaplan–Meier survival analysis showed that age, infiltration depth, chemotherapy, and the number of small intestinal segments invaded by tumor lesions were prognostic factors for small intestinal angiosarcoma. Multivariate Cox regression analysis showed that chemotherapy and surgery significantly improved patient prognosis.

CONCLUSION

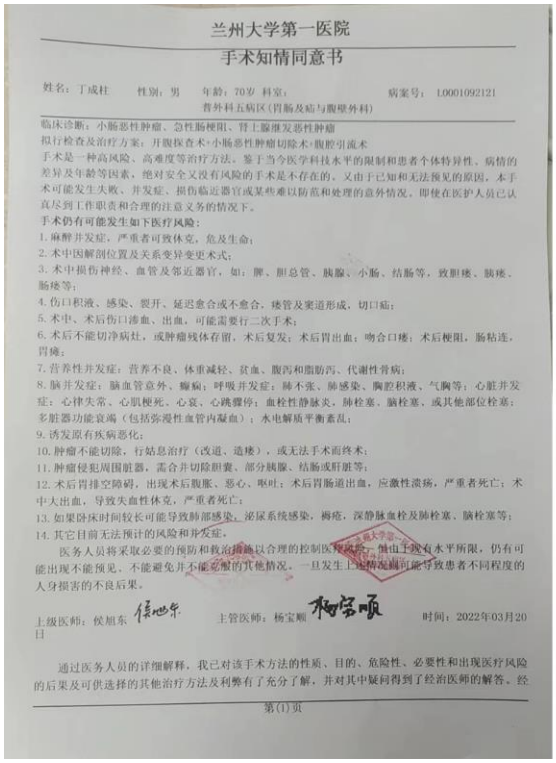
Angiosarcoma should be considered for unexplained melena and abdominal pain, especially in older men and patients with a history of radiation exposure. Prompt treatment, including surgery and adjuvant chemotherapy, is essential to prolonging patient survival.

2. The journal requests author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee.

Thanks for your kind reminder. This study has passed the ethical review of The First Affiliated Hospital of Lanzhou University and informed consent was obtained from the patient's family. We can provide the ethical review number and the informed consent signed by the patient' family at the time of hospitalization. However, because of epidemic lockdown, we were unable to provide written ethics documents at the moment. The study protected patient privacy and did not cause any harm to patient. After the epidemic is unsealed, other supporting documents can be added.

Ethical review number: LDYYLL2022-484

Written informed consent:



兰州大学第一医院

手术知情同意书

姓名：丁成柱　性别：男　年龄：70岁 科室：普外科五病区（胃肠及疝与腹壁外科）　病案号：L0001092121

临床诊断：小肠恶性肿瘤、急性肠梗阻、肾上腺继发恶性肿瘤

拟行检查及治疗方案：开腹探查术+小肠恶性肿瘤切除术+腹腔引流术

手术是一种高风险、高难度等治疗方法。鉴于当今医学科技水平的限制和患者个体特异性、病情的差异及年龄等因素，绝对安全又没有风险的手术是不存在的。又由于已知和无法预见的原因，本手术可能发生失败、并发症、损伤临近器官或某些难以防范和处理的意外情况。即使在医护人员已认真尽到工作职责和合理的注意义务的情况下。

手术仍有可能发生如下医疗风险：

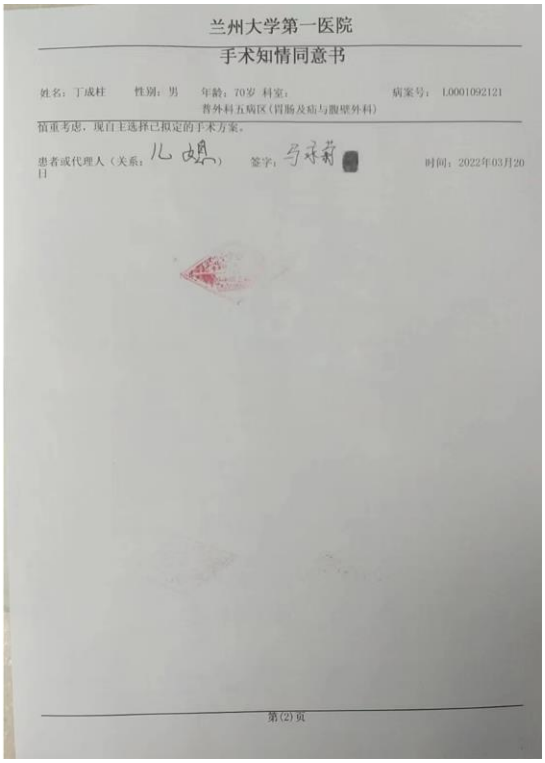
1. 麻醉并发症，严重者可致休克，危及生命；
2. 术中因解剖位置及关系变异变更术式；
3. 术中损伤神经、血管及邻近器官，如：脾、胆总管、胰腺、小肠、结肠等，致胆瘘、胰瘘、肠瘘等；
4. 伤口积液、感染、裂开、延迟愈合或不愈合，瘘管及窦道形成，切口疝；
5. 术中、术后伤口渗血、出血，可能需要行二次手术；
6. 术后不能切净病灶，或肿瘤残体存留，术后复发；术后胃出血；吻合口瘘；术后梗阻，肠粘连，胃瘫；
7. 营养性并发症：营养不良、体重减轻、贫血、腹泻和脂肪泻、代谢性骨病；
8. 脑并发症：脑血管意外、癫痫；呼吸并发症：肺不张、肺感染、胸腔积液、气胸等；心脏并发症：心律失常、心肌梗死、心衰、心跳骤停；血栓性静脉炎，肺栓塞、脑栓塞、或其他部位栓塞；多脏器功能衰竭（包括弥漫性血管内凝血）；水电解质平衡紊乱；
9. 诱发原有疾病恶化；
10. 肿瘤不能切除，行姑息治疗（改道、造瘘），或无法手术而终术；
11. 肿瘤侵犯周围脏器，需合并切除胆囊、部分胰腺、结肠或肝脏等；
12. 术后胃排空障碍，出现术后腹胀、恶心、呕吐；术后胃肠道出血，应激性溃疡，严重者死亡；术中大出血，导致失血性休克，严重者死亡；
13. 如果卧床时间较长可能导致肺部感染、泌尿系统感染，褥疮，深静脉血栓及肺栓塞、脑栓塞等；
14. 其它目前无法预计的风险和并发症。

医务人员将采取必要的预防和救治措施以合理的控制医疗风险，但由于现有水平所限，仍有可能出现不能预见、不能避免并不能克服的其他情况。一旦发生上述情况时能导致患者不同程度的人身损害的不良后果。

上级医师：侯旭东　主管医师：杨宝顺　时间：2022年03月20日

通过医务人员的详细解释，我已对该手术方法的性质、目的、危险性、必要性和出现医疗风险的后果及可供选择的其他治疗方法及利弊有了充分了解，并对其中疑问得到了经治医师的解答。经

第(1)页



兰州大学第一医院

手术知情同意书

姓名：丁成柱　性别：男　年龄：70岁 科室：普外科五病区（胃肠及疝与腹壁外科）　病案号：L0001092121

慎重考虑，现自主选择已拟定的手术方案。

患者或代理人（关系：儿媳）　签字：马玉荣　时间：2022年03月20日

第(2)页

3. In the line of 54, "month" should change with "months".

We are very sorry for our negligence and thanks for your correction. This mistake has been corrected.

4. The quantity of references is too much, which should be simplified.

Thanks for your comments. This study has two main objectives, one is to present rare case, and the other is to provide a comprehensive review and analysis of this disease. In order to make the statistical results more reliable, we included all the reported cases that we searched, including 76 references and 82 cases. Therefore, the quantity of cited references had to be large. According to your suggestion, we read these literatures carefully and tried to cite as few literatures as possible in manuscript. And we finally reduced the number of references from 90 to 81. We hope you can understand and we would appreciate it.

5. *Now, molecular findings might be proved valuable as targets of an immunotherapeutic approach, constituting a promising alternative treatment of angiosarcoma. Hence, molecular finding of the patient should be recommended.*

Thank you very much for your professional comments, which are very important to improve the quality of our manuscript. Molecular targeted therapy is indeed a key point that has to be mentioned in tumor treatment. In fact, we recommended the patient undergo genetic testing to allow for the selection of precisely targeted therapy. However, due to the patient's older age and family financial difficulties, they refused and chose to be discharged after surgery. This is indeed a major defect of this case report. In addition, the published case reports of small intestinal angiosarcoma are also lacking genetic testing. To make up for this deficiency. We reviewed the relevant literature to supplement the research progress of molecular targeted therapy in angiosarcoma. In general, most of the current studies have focused on cutaneous angiosarcoma, and there is a lack of clinical trials on small intestinal angiosarcoma. However, with the progress of research and the emphasis on gastrointestinal angiosarcoma, we believe that molecular targeted therapy will make a great contribution to the treatment of this disease. We also hope that our added description of molecular targeted therapy for angiosarcoma will make clinicians pay attention to molecular findings and targeted therapy for small intestinal angiosarcoma. The added content of molecular targeted therapy in the discussion section is shown below:

With the development and clinical application of molecular targeted drugs, molecular targeted therapy for tumors has become a research hotspot in medical oncology. Studies have shown that vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are highly expressed in angiosarcoma. VEGF and VEGFR inhibitors or multi-tyrosine kinase inhibitors, including bevacizumab and pazopanib, are potential drug targets for angiosarcoma. Malignant vascular tumors, including angiosarcoma, express high levels of adrenergic receptors. Targeting these receptors with drugs such as protamine inhibited tumor growth in mouse vascular cell lines (80). In addition, a few cases with cutaneous angiosarcoma showed significant responses to checkpoint inhibitors, including pembrolizumab, anti-PD-L1 antibody,

and anti-CTLA-4 antibody (81).

In addition, there are the following points to note.

1. We modified the format of the manuscript as requested by the journal for successful publication.

2. We note that the number of references in case reports is generally controlled at 30 to 60. However, our study has two main objectives, one is to present rare case, and the other is to provide a systematic review and analysis of this disease. In order to make the statistical results more reliable, we included all the reported cases that we searched, including 76 refernces and 82 cases. Therefore, the number of references we finally cited reached 81. We hope you can understand and we would appreciate it. In addition, 15 of the cited references were not indexed on PubMed. In accordance with the regulations, we provided the printed copy of the first page and uploaded them as Supplementary Material. The PDF files were named in accordance with the order in which the reference was cited in the manuscript.

3. Moreover, although this is a serious problem because the manuscript has been reviewed, we are wishing to add Mr. Hou as an extra author to the manuscript. Xu-Dong Hou is the patient's chief surgeon and he contributed a lot to the patient's entire treatment and follow-up process. In revison process, he did a great job for the expansion of literature review so as to provide a deeper insight into the related work. After consultation among all the authors, we decide to add Xu-Dong Hou as the ninth author. If you give us this chance, we will be grateful.

Thanks for your time and attention. The above is the main modification and improvement we have made to the manuscript. We sincerely hope you find our responses and modifications satisfactory and that this manuscript is accepted to publication.

Sincerely yours,

Qinghong Guo