ROUND 1

Appendix: Detailed responses to the editor's and reviewers' comments

We are delighted to receive the notification on manuscript revision (World Journal of Gastrointestinal Oncology Manuscript NO: 76270). Here we will submit our revised original article entitled "Ewing sarcoma of the ileum with wide multiorgan metastases: a case report and literature review" to the BPG Editorial Office. We thank you for editor giving us a chance to submit our revised article and the reviewers' comments to help us improve our article. We have revised the article point by point according to the reviewer's and Editorial Office's comments.

Response to the Reviewer #1 comments

Comment 1: 'Ewing sarcoma (ES) is a rare aggressive variant of small round cell tumors and is an uncommon malignancy that usually occurs in childhood.' The above opening statement is widely incorrect. Reframe as 'Ewing sarcoma (ES) is an aggressive small round cell neoplasm reported in younger children and young adults. Its occurrence in elderly is rare.' It is reported to be 2% of all cancers reported between age of 15-19. [Statistics adapted from American Cancer Society's (ACS) publication, Cancer Facts & Figures 2021, and the websites of ACS and St. Jude Children's Research Hospital. Additional source was Seigel R, et al.: Cancer Statistics 2021. CA: A Cancer Journal for Clinicians. 2021 Jan; 71(1):7–33. doi/full/10.3322/caac.21654 (sources accessed January 2021).]

Response: As suggested, we rewrote the sentences in the Abstract section, as following:

Ewing sarcoma (ES) is an aggressive small round cell tumor that usually occurs in younger children and young adults but rarely in older patients. Its occurrence in elderly individuals is rare.

Comment 2: The authors must clarify that ES is difficult with widespread mets is difficult to distinguish radiologically or clinically whichever they wish to emphasize. 'ES of the ileum with wide multiorgan metastases is rarely reported and difficult to distinguish from other gastrointestinal tract tumors.' Add word radiologically in the above statement.

Response: As suggested, we add word radiologically in the above statement as following:

ES of the ileum with wide multiorgan metastases is rarely reported and difficult to distinguish radiologically from other gastrointestinal tract tumors..

Comment 3: Typographical error 'periileum.' Must be peritoneum I believe.

Response: Thank you for the kind suggestion. We have corrected the word in the Discussion section.

Comment 4: As histomorphology and IHC was diagnostic in the present case the authors must include an image collage including at least 2 positive and 1 negative marker.

Response: As suggested, we have added the positive immunoreactivity for NKX2.2, FLI-1, Syn and the negative immunoreactivity for CK, CgA.

Comment 5: The discussion is well written but the authors in their title emphasize 'review of literature'. The above is lacking. A small paragraph accompanied by a table which tells about the exact site of gastrointestinal EOES, age of presentation, reporting author and year of report will add to the discussion and make it more interesting.

Response: Thank you very much for the kind suggestion. We have added a table about the small intestinal ES accompanied by the age, gender, follow-up and reporting author and year of report in the section of discussion.

Response to the Reviewer #2 comments

Comment 1: This paper describes an interesting case of ewing's sarcoma of the ileum with metastasis. It is an interesting subject for understanding ileum tumors. Nevertheless, it presents some limitations. It needs more info in the possible differentials - radiological data and pathological information.

Response: Thank you for the kind reminder. We have added more information differential diagnosis in pathological and radiological in the discussion:

The diagnosis of Ewing sarcoma can be challenging, and a wide variety of small round cell tumors are included in the differential diagnosis. Molecular detection of specific fusion genes is currently accepted as the gold standard method for diagnosing Ewing sarcoma[20]. However, this patient did not do this due to a small tissue sample size. NKX2.2 has been identified as an important target of EWS-FLI-1, and it was shown to be a valuable immunohistochemical marker for Ewing sarcoma in the differential diagnosis of small round cell tumors[21, 22]. NKX2.2 expression in small cell carcinomas was focal in most cases, in contrast to diffuse reactivity in Ewing sarcoma[22]. A small number of non-Ewing tumors can be positive for NKX2.2, such as synovial sarcomas, mesenchymal chondrosarcomas, and malignant melanomas. Nuclear spindling and TLE1 immunoreactivity favor synovial sarcomas[23]. NKX2.2-positive synovial sarcoma exhibited weak focal staining compared to diffuse labeling of Ewing sarcoma. Mesenchymal chondrosarcomas could be excluded based on histology and immunohistochemical data[24]. Malignant melanomas could be excluded because the tumor did not express specific melanoma markers (e.g., HMB45 and Melan A)[25]. According to the exclusive diagnosis, the present case was ultimately diagnosed as synchronous ES.

Small intestinal neuroendocrine neoplasms may have mural transgression with the invasion of the serosa and mesentery and may conglomerate into spiculated masses with frequent calcification and surrounding lymphadenopathy.

Comment 2: The literature review is superficial, and should discuss the metastic forms of the disease, and other similiar reported cases.

Response: Thank you for the kind reminder. We have added the following text in the discussion: The form of distant metastasis included seeding, blood and lymphatic vessel metastasis. And other similar reported cases were listed in the table.

Response to the Reviewer #3 comments

Comment 1: - the data, treatment and follow up are not sufficient.

Response: Thank you very much for the kind reminder. We added the data of laboratory examinations as follows:

After admission, laboratory investigations showed slightly increased levels of monocytes (0.987 10 9/L; normal range: 0.10–0.60 10 9/L), decreased eosinophil rate (0.1%; normal range: 0.4–8%), decreased hemoglobin levels (119 g/L; normal range: 130–175 g/L), and prealbumin levels (14.9 mg/dL; normal range: 16–45 mg/dL), and increased platelet count (418 10 9/L; normal range: 85-303 10 9/L). All serum tumor marker levels were normal.

We also added the section of treatment and follow up as follows:

After fluid rehydration, nutritional support, and symptomatic treatment for pain relief, the patient's abdominal pain was relieved. Multidisciplinary consultation recommended adjuvant chemotherapy for the patients. However, the patient refused treatment and chose to be discharged.

One month later, the patient could not eat and received symptomatic nutritional support and analgesic treatment due to severe pain. Despite the medical advice,

the patient refused to receive any systemic treatment. Unfortunately, the patient died of multiple organ failure caused by widespread multiorgan metastases 2 months later.

Response to the Reviewer #4 comments

Comment 1: It can be seen from this paper that the diagnosis of cases mainly relies on pathological diagnosis, but this paper does not provide detailed basis for differential diagnosis in pathological aspects, so pathological analysis considering other diseases should be added.

Response: Thank you for the kind reminder. We have added the following text in the discussion:

NKX2.2 has been identified as an important target of EWS-FLI-1, and it was shown to be a valuable immunohistochemical marker for Ewing sarcoma in the differential diagnosis of small round cell tumors[21, 22]. NKX2.2 expression in small cell carcinomas was focal in most cases, in contrast to diffuse reactivity in Ewing sarcoma[22]. A small number of non-Ewing tumors can be positive for NKX2.2, such as synovial sarcomas, mesenchymal chondrosarcomas, and malignant melanomas. Nuclear spindling and TLE1 immunoreactivity favor synovial sarcomas[23]. NKX2.2-positive synovial sarcoma exhibited weak focal staining compared to diffuse labeling of Ewing sarcoma. Mesenchymal chondrosarcomas could be excluded based on histology and immunohistochemical data[24]. Malignant melanomas could be excluded because the tumor did not express specific melanoma markers (e.g., HMB45 and Melan A)[25]. According to the exclusive diagnosis, the present case was ultimately diagnosed as synchronous ES.

Comment 2: In addition, the literature review is not well reflected in this paper, so it is suggested to delete the description of the literature review in the title or

add relevant literature review content in the text (for example, add the review of the metastasis rate of other organs with multiple metastasis of ewing's sarcoma extraosseous with multiple metastasis, and present it in table form.

Response: Thank you for the kind reminder. We also added a table form. We also have added relevant literature review content in the text as follows:

We have summarized all previous publications of small intestinal ES/PNET in Table 1[10-18]. The patient gender ratio (female/male) was 13/14. The ages ranged from 9 to 69 years, and 60% of patients with small intestinal ES were younger than 30 years. The most common sites in patients with metastatic disease are the liver and peritoneum. Adrenal metastases have rarely been described[6]. Seven patients had metastases to the liver and peritoneum solitarily. Only one patient had metastases to the adrenal gland and peritoneum at the time of diagnosis. Patients of more than 40 years of age or with metastatic spread at the time of diagnosis have shorter survival than younger patients. **Comment 3:** Finally, the follow-up of patients' treatment is not perfect enough, and patients should be actively followed up during their survival after discharge to supplement relevant palliative care. I believe that the manuscript will be better after the relevant descriptions are enriched and enriched.

Response: Thank you for pointing this out. We rewrote the sentence as following:

One month later, the patient could not eat and received symptomatic nutritional support and analgesic treatment due to severe pain. Despite the medical advice, the patient refused to receive any systemic treatment. Unfortunately, the patient died of multiple organ failure caused by widespread multiorgan metastases 2 months later.

Response to the Reviewer #5 comments

Comment 1: - This case report has the objective to emphasize the rare presentation of Ewing sarcoma in the small intestine and the importance of the differential diagnosis of adult intraabdominal tumors. The text of the manuscript is concise, but is very simplistic. The addition of the photos of the resected surgical specimen would be valuable.

Response: Thank you for pointing this out. Unfortunately, the patient refused the operation after being confirmed by puncture, and we did not get the resected surgical specimen.

Comment 2: - and the in discussion session should be enriched with the recent references regarding extraskeletal Ewing sarcoma.

Response: As suggested, we have added some recent references regarding extraskeletal Ewing sarcoma, as follows:

18 Paricio JJ, Juan RM, Esther SD. Primary Ewing's sarcoma of the small intestine [J]. *Rev Esp Enferm Dig* 2021; **113**:680. [PMID:33486963 doi: 10.17235/reed.2021.7735/2020]

20 Li T, Zhang F, Cao Y, Ning S, Bi Y, Xue W, Ren L. Primary Ewing's sarcoma/primitive neuroectodermal tumor of the ileum: case report of a 16-year-old Chinese female and literature review [J]. *Diagn Pathol* 2017; **12**:37 [PMID: 28472972 doi: 10.1186/s13000-017-0626-3]

Response to the science editor's comments

Comment 1: - The follow-up of patients' treatment is not enough.

Response:. Thank you for pointing this out. We rewrote the sentence as following:

One month later, the patient could not eat and received symptomatic nutritional support and analgesic treatment due to severe pain. Despite the medical advice,

the patient refused to receive any systemic treatment. Unfortunately, the patient died of multiple organ failure caused by widespread multiorgan metastases 2 months later.

Comment 2: - Literature review is superficial in the manuscript, so it is better to delete the description of literature review in the title.

Response: Thank you for the kind reminder. We have added literature review in the discussion and a table about the small intestinal ES accompanied by the age, gender, follow-up and reporting author and year of report. So we decided to keep that the description of literature review in the title.

Comment 3: - The related ethics and relevant documents are needed.

Response: As required, we have submited related ethics and relevant documents.

Response to the Company editor-in-chief's comments

Comment 1: - I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright

information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: As required, we have changed the pictures according to the format requirements.

ROUND 2

Appendix: Detailed responses to the editor's and reviewers' comments

We are delighted to receive the second-round review report (World Journal of Gastrointestinal Oncology Manuscript NO: 76270). Here we will submit our revised article entitled "Ewing sarcoma of the ileum with wide multiorgan metastases: a case report and literature review" to the BPG Editorial Office. We have revised the article point by point according to the reviewer's and Editorial Office's comments.

Response to the Reviewer #1 comments

Comment 1: Please describe more about EOES. The prevalence on ileum. How many cases in the world had reported. Please state about prognosis, pathophysiology and management.

Response: As suggested, we rewrote the sentences in the introduction section, as following:

Ewing sarcoma (ES) of the bone represents the second most common primary malignant tumor of bone in children and adolescents, exceeded in prevalence only by osteosarcoma[1]. Osseous ES, together with extraosseous Ewing's sarcoma (EOES), primitive neuroectodermal tumor, and Askin's tumor are members of the Ewing sarcoma family of tumors [1-2]. The treatment of EOES patients includes chemotherapy, radiation therapy, and surgery. To date, the 5-year survival rate of EOES is relatively high (65-75%) [3]. The outcome for metastatic patients is usually poor (<30%), despite the use of surgery, chemo- and/or radiotherapy. EOES is rarer than ES of the bone. The prevalence of EOES is generally accepted to be between 15% and 20% of that of ES of the bone[2]. The most common sites of EOES are the paravertebral region, lower extremities, chest wall and retroperitoneum[4]. To our knowledge, EOES originating in the ileum is not common, with only nearly 30 cases reported worldwide. However, there

were few reports regarding EOES of the ileum with multiorgan metastases at the time of diagnosis [5-7]. In this paper, we present a case with an initial diagnosis of gastrointestinal stromal tumor (GIST), but histopathology indicated EOES with widespread multiorgan metastases.

Comment 2: Please be more specific for the organ, since we also have right lower quadrant of the breast.

Response: As suggested, we specify the organ "right lower quadrant abdominal pain "in the above statement as following:

A 53-year-old man suffered from right lower quadrant abdominal pain for 2 weeks. (***Chief complaints***)

The patient experienced right lower quadrant abdominal pain for 2 weeks, accompanied by acid reflux, belching, and emesis (an oral discharge without digested food and hematemesis), but denied having fevers, night sweats, unintentional weight loss, and blood in the stool. (***History of present illness***)

On physical examination, his abdomen was soft with tenderness on the right side abdominal without rebound tenderness or muscle guarding, and normal bowel sounds were present. ***(Physical examination)***

Comment 3: Please describe more the quality and quantity as well as the papatient complain, is it only acid or digested food?

Response: As suggested, we rewrote the sentences in the ***History of present illness*** section, as following:

The patient experienced right lower quadrant abdominal pain for 2 weeks, accompanied by acid reflux, belching, and emesis (an oral discharge without digested food and hematemesis), but denied having fevers, night sweats, unintentional weight loss, and blood in the stool.

Comment 4: please describe more. What kind of family history do you mean? Gastritis? Tumor? Or other diseases?

Response: As suggested, we rewrote the sentences in the ***Personal and family history*** section, as following:
The patient denied that the family had any genetic diseases. There was no similar disease in the family.

Comment 5: Please specify the location by region of abdomen. Describe the palpation of tumor. Describe why tumor 8cm in diameter cannot be palpated?

Response: As suggested, we rewrote the sentences in the ***Physical examination*** section, as following:
On physical examination, his abdomen was soft with tenderness on the right side abdominal without rebound tenderness or muscle guarding, and normal bowel sounds were present. In palpation, a mass with unclear boundary was identified in the right lower abdomen, measuring 4 × 6 cm approximately, and the mass can be mobile.

Comment 6: Please specify the location.

Response: As suggested, we rewrote the sentences in the ***Imaging examinations*** section, as following:

Contrast-enhanced CT of the abdomen showed an 8.1 × 4.0 cm mass in the right iliac fossa area, which interacted with the small intestinal lumen.

Comment 7: What kind biopsy did you performed? Open biopsy, laparascopic or core or other technique please describe more. Local anesthesia or general. Please more specific.

Response: As suggested, we rewrote the sentences in the FINAL DIAGNOSIS section, as following:

To make the diagnosis, transabdominal ultrasound guided needle biopsy was performed with the consent of the patient. The biopsy was performed as an outpatient procedure under local anesthesia.

Comment8: Please specify more the treatment, the fluid and nutritional support.

Response: As suggested, we rewrote the sentences in the TREATMENT and OUTCOME AND FOLLOW-UP sections, as following:

After multidisciplinary consultation, the physicians recommended 5 cycles of neoadjuvant chemotherapy with vincristine, ifosfamide, and doxorubicin for the patient, which could reduce the size of the primary tumor and metastases. However, the patient refused this treatment strategy. The patient was given fluid rehydration (0.9% sodium chloride solution, 5% glucose sodium chloride injection), nutritional support (Compound amino acid injection, 20% medium and long chain fat emulsion injection and ω-3 fish oil fat emulsion injection) and intravenous injection of parecoxib sodium 40 mg to relieve the pain.

One month later, the patient could not eat and received symptomatic nutritional support (Compound amino acid injection, 20% medium and long chain fat emulsion injection and ω-3 fish oil fat emulsion injection) and analgesic treatment (intravenous injection of parecoxib sodium 40 mg). Despite the medical advice, the patient refused to receive any systemic treatment. The patient chose to be transferred to hospice care ward and died of multiple organ failure caused by widespread multiorgan metastases 2-months later.