Dear Editor and reviewers, thanks for considering and reviewing our

manuscript, and thanks for your valuable comments.

This is a point to point response to your comments; we are hoping that it will

satisfy your valuable queries and comments, thanks.

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The case series described by hidden Local

recurrence of colorectal adenocarcinoma diagnosed by EUS-FNA. Although

important, the novelty is low. To preform EUS for submucosal tumor is the standard

procedure.

1. What types of ultrasonic endoscope did you use? Inserting the ultrasonic endoscope

is difficult especially for the right hemicolon.

Answer: thanks for your comment. We are using oblique view linear Pentax

Echoendoscope type EG-3870UTK connected to Hitachi Avius machine. We

added the type of the Echoendoscope in the manuscript.

All cases had ano-rectal lesions, maximum 15-20 cm from the anal verge, so easy

to be scanned by the side view scope. No right hemicolon masse were included as

it is very difficult to be approached by the side view scope.

2. What is the initial EUS imaging diagnoses for the 5 patients? If malignancy was

suspected, combined with CT/MRI/PET-CT imagings, derict surgical resection can be

performed. So why you perform EUS-FNA, if the serosal layer was broken, the risk

of tumor seeding will increase.

Answer: thanks for your comment. All patients had MRI examination before

EUS. Two cases had marked wall thickening at the anastomotic line, so their

attending surgeons asked for EUS and FNA to differentiate malignant from

dysmoplastic reaction, and other patients had a mass and the attending

physicians asked for histopathological diagnosis for possible neoadjuvant

chemotherapy before surgery.

3. The figures failed to clearly show the layers of digestive tract. The identification of

each layer would be better.

Other more clear pictures were added instead of the previous non clear ones

(Figure 2 and Figure 3). It demonstrates the invaded mascularis propria layer by

the mass while this layer is clearly intact adjacent to the malignant mass. Text

was added to the new figures pointing to the normal and invaded muscularis

propria.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This article has presented five case reports with

submucosal recurrence after CRC resection during surveillance. It has provided a

useful clinical note for some cases with difficult diagnosis due to irregular recurrence.

Because of rare proportion, LCRCs with submucosal recurrence were often difficult

to diagnose and manage. With EUS-FNA and/or EUS-FNB, LCRCs with submucosal

recurrence can be diagnosed accurately, so that, avoid late applications of treatment

strategies.

Thanks for your comments. EUS sampling could differentiate between inflammatory

and malignant recurrence, so our patients were directed towards neoadjuvant

chemotherapy and surgery

2 Editorial Office's comments

- 1) Science Editor: The five case series described by hidden Local recurrence of colorectal adenocarcinoma diagnosed by EUS-FNA. Although important, the novelty is low. Further, some issues have to be addressed:
- 1. What types of ultrasonic endoscope did you use? Inserting the ultrasonic endoscope is difficult especially for the right hemicolon.

Answer: thanks for your comment. We are using oblique view linear Pentax Echoendoscope type EG-3870UTK connected to Hitachi Avius machine. We added the type of the Echoendoscope in the manuscript.

All cases had ano-rectal lesions, maximum 15-20 cm from the anal verge, so easy to be scanned by the side view scope. No right hemicolon masse were included as it is very difficult to be approached by the side view scope.

2. What is the initial EUS imaging diagnoses for the 5 patients? If malignancy was suspected, combined with CT/MRI/PET-CT imagings, derict surgical resection can be performed. So why you perform EUS-FNA, if the serosal layer was broken, the risk of tumor seeding will increase.

Answer: thanks for your comment. All patients had MRI examination before EUS. Two cases had significant wall thickening at the anastomotic line, so their attending surgeons asked for EUS and FNA to differentiate malignant drom dysmoplastic reaction, and other patients had a mass and the attending physicians asked for histopathological diagnosis for possible neoadjuvant chemotherapy before surgery.

3. The figures failed to clearly show the layers of digestive tract. The identification of each layer would be better.

Other more clear pictures were added instead of the previous non clear ones (Figure 2 and Figure 3). It demonstrates the invaded mascularis propria layer by the mass while this layer is clearly intact adjacent to the malignant mass. Text was added to the new figures pointing to the normal and invaded muscularis propria.

4. Can the author give the indications of EUS in CRC surveillance more clearly? Because the regularity.

Answer: thanks for your comment. The indications of EUS in CRC surveillance include all of the following:

- It has a role as a method for the evaluation of precancerous polyps and subepithelial lesions found during screening of CRC. However it has a great role of follow up after resection of rectal carcinoma for early detection and tissue confirmation of locally recurrent cancer colon, also it allows the collection of specimens for histological and immuno- histochemical analysis, and overcoming some of the inherent user bias.
- it also has a great role in post-treatment surveillance for resected colon and rectal cancer as recommended in NCCN guidelines that stated that flexible sigmoidoscopy with EUS or MRI should be done every 3 to 6 months for 2 years, then every 6 months to complete 5 years for patients with rectal cancer undergoing transanal excision only. *National Comprehensive Cancer Network*. *Available at: www.nccn.org*.
- Surveillance after surgical resection For post-treatment surveillance after surgical resection for rectal cancer, rectal EUS may be more accurate than other imaging modalities for early detection of local recurrence. However, the optimal selection criteria for patients who would benefit from including rectal EUS in the surveillance strategy are uncertain. Steele SR, Chang GJ, Hendren S, et al. Practice Guideline for the Surveillance of Patients After Curative Treatment of Colon and Rectal Cancer. Dis Colon Rectum. 2015;58(8):713-725. doi:10.1097/DCR.00000000000000010
- Guidelines from the United States Multi-Society Task Force include EUS as an alternative to sigmoidoscopy in the testing strategy for patients at higher risk of recurrence. Rex DK, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 2017;112(7):1016-1030. doi:10.1038/ajg.2017.174

- The current US Multi-Society Task Force recommendation suggests EUS at 3-6 months for the first 2 years after resection as a reasonable option in patients with a curative resection for rectal cancer. Kahi CJ, Boland CR, Dominitz JA, et al. Colonoscopy Surveillance after Colorectal Cancer Resection: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 2016;111(3):337-347. doi:10.1038/ajg.2016.22
- While the National Comprehensive Cancer Network includes EUS as an alternative to flexible sigmoidoscopy for patients with rectal cancer who undergo transanal excision only. *Tombazzi CR, Loy P, Bondar V, Ruiz JI, Waters B, Tombazzi CR. Accuracy of Endoscopic Ultrasound in Staging of Early Rectal Cancer. Fed Pract.* 2019;36(Suppl 5):S26-S29.
- Unfortunately, not all recurrences are evident at the mucosal surface. In these cases, (EUS), which allows highly detailed visualization of all the bowel wall layers as well as the surrounding structures, is a useful adjunct. (Beynon J, Mortensen NJ, Foy DM, et al. The Detection and Evaluation of Locally Recurrent Rectal Cancer with Rectal Endosonography. Dis Colon Rectum 1989;32:509-517.)
- 5. Can other imaging tools like pelvic magnetic resonance imaging (MRI) can replace EUS to diagnose submucosal recurrence?

MRI is as accurate as EUS in detection of submucosal recurrence and wall thickness, however, EUS has a great advantage of obtaining tissue sampling either by FNA or FNB to differentiate tumor recurrence from inflammatory reaction, postoperative granulation tissue and post chemo-radiation proctitis.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Thanks again for your valuable comments and the meticulous revision of our manuscript.

Dear Editor and reviewers, thanks for considering and reviewing our manuscript, and thanks for your valuable comments.

This is a point to point response to your comments; we are hoping that it will satisfy your valuable queries and comments, thanks.

Reviewer #1: I had no more comment. The case report was suitable for publishing in this journal.

Reviewer #2: The case series described by hidden Local recurrence of colorectal adenocarcinoma diagnosed by EUS-FNA. Although important, the novelty is low. To preform EUS for submucosal tumor is the standrad procedure. 1. What types of ultrasonic endoscope did you use? Inserting the ultrasonic endoscope is difficult especilly for the right hemicolon. 2. What is the initial EUS imaging diagnoses for the 5 patients? If malignancy was suspected, combined with CT/MRI/PET-CT imagings, derict surgical resection can be performed. So why you perform EUS-FNA, if the serosal layer was broken, the risk of tumor seeding will increase. 3. The firures failed to clearly show the layers of digestive tract. The identification of ech laryer would be better.

Reviewer #3: This article has presented five case reports with submucosal recurrence after CRC resection during surveillance. It has provided a useful clinical note for some cases with difficult diagnosis due to irregular recurrence. Because of rare proportion, LCRCs with submucosal recurrence were often difficult to diagnose and manage. With EUS-FNA and/or EUS-FNB, LCRCs with submucosal recurrence can be diagnosed accurately, so that, avoid late applications of treatment strategies.

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The case series described by hidden Local recurrence of colorectal adenocarcinoma diagnosed by EUS-FNA. Although important, the novelty is low. To preform EUS for submucosal tumor is the standard procedure.

1. What types of ultrasonic endoscope did you use? Inserting the ultrasonic endoscope is difficult especially for the right hemicolon.

Answer: thanks for your comment. We are using oblique view linear Pentax Echoendoscope type EG-3870UTK connected to Hitachi Avius machine. We added the type of the Echoendoscope in the manuscript.

All cases had ano-rectal lesions, maximum 15-20 cm from the anal verge, so easy to be scanned by the side view scope. No right hemicolon masse were included as it is very difficult to be approached by the side view scope.

2. What is the initial EUS imaging diagnoses for the 5 patients? If malignancy was suspected, combined with CT/MRI/PET-CT imagings, derict surgical resection can be performed. So why you perform EUS-FNA, if the serosal layer was broken, the risk of tumor seeding will increase.

Answer: thanks for your comment. All patients had MRI examination before EUS. Two cases had marked wall thickening at the anastomotic line, so their attending surgeons asked for EUS and FNA to differentiate malignant from dysmoplastic reaction, and other patients had a mass and the attending physicians asked for histopathological diagnosis for possible neoadjuvant chemotherapy before surgery.

3. The figures failed to clearly show the layers of digestive tract. The identification of

each layer would be better.

Other more clear pictures were added instead of the previous non clear ones

(Figure 2 and Figure 3). It demonstrates the invaded mascularis propria layer by

the mass while this layer is clearly intact adjacent to the malignant mass. Text

was added to the new figures pointing to the normal and invaded muscularis

propria.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This article has presented five case reports with

submucosal recurrence after CRC resection during surveillance. It has provided a

useful clinical note for some cases with difficult diagnosis due to irregular recurrence.

Because of rare proportion, LCRCs with submucosal recurrence were often difficult

to diagnose and manage. With EUS-FNA and/or EUS-FNB, LCRCs with submucosal

recurrence can be diagnosed accurately, so that, avoid late applications of treatment

strategies.

Thanks for your comments. EUS sampling could differentiate between inflammatory

and malignant recurrence, so our patients were directed towards neoadjuvant

chemotherapy and surgery

2 Editorial Office's comments

1) Science Editor: The five case series described by hidden Local recurrence of

colorectal adenocarcinoma diagnosed by EUS-FNA. Although important, the novelty

is low. Further, some issues have to be addressed:

1. What types of ultrasonic endoscope did you use? Inserting the ultrasonic endoscope

is difficult especilly for the right hemicolon.

Answer: thanks for your comment. We are using oblique view linear Pentax Echoendoscope type EG-3870UTK connected to Hitachi Avius machine. We added the type of the Echoendoscope in the manuscript.

All cases had ano-rectal lesions, maximum 15-20 cm from the anal verge, so easy to be scanned by the side view scope. No right hemicolon masse were included as it is very difficult to be approached by the side view scope.

2. What is the initial EUS imaging diagnoses for the 5 patients? If malignancy was suspected, combined with CT/MRI/PET-CT imagings, derict surgical resection can be performed. So why you perform EUS-FNA, if the serosal layer was broken, the risk of tumor seeding will increase.

Answer: thanks for your comment. All patients had MRI examination before EUS. Two cases had significant wall thickening at the anastomotic line, so their attending surgeons asked for EUS and FNA to differentiate malignant drom dysmoplastic reaction, and other patients had a mass and the attending physicians asked for histopathological diagnosis for possible neoadjuvant chemotherapy before surgery.

3. The figures failed to clearly show the layers of digestive tract. The identification of each layer would be better.

Other more clear pictures were added instead of the previous non clear ones (Figure 2 and Figure 3). It demonstrates the invaded mascularis propria layer by the mass while this layer is clearly intact adjacent to the malignant mass. Text was added to the new figures pointing to the normal and invaded muscularis propria.

4. Can the author give the indications of EUS in CRC surveillance more clearly? Because the regularity.

Answer: thanks for your comment. The indications of EUS in CRC surveillance include all of the following:

- It has a role as a method for the evaluation of precancerous polyps and subepithelial lesions found during screening of CRC. However it has a great role of follow up after resection of rectal carcinoma for early detection and tissue confirmation of locally recurrent cancer colon, also it allows the collection of specimens for histological and immuno- histochemical analysis, and overcoming some of the inherent user bias.
- it also has a great role in post-treatment surveillance for resected colon and rectal cancer as recommended in NCCN guidelines that stated that flexible sigmoidoscopy with EUS or MRI should be done every 3 to 6 months for 2 years, then every 6 months to complete 5 years for patients with rectal cancer undergoing transanal excision only. *National Comprehensive Cancer Network*. *Available at: www.nccn.org*.
- Surveillance after surgical resection For post-treatment surveillance after surgical resection for rectal cancer, rectal EUS may be more accurate than other imaging modalities for early detection of local recurrence. However, the optimal selection criteria for patients who would benefit from including rectal EUS in the surveillance strategy are uncertain. Steele SR, Chang GJ, Hendren S, et al. Practice Guideline for the Surveillance of Patients After Curative Treatment of Colon and Rectal Cancer. Dis Colon Rectum. 2015;58(8):713-725. doi:10.1097/DCR.00000000000000010
- Guidelines from the United States Multi-Society Task Force include EUS as an alternative to sigmoidoscopy in the testing strategy for patients at higher risk of recurrence. Rex DK, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 2017;112(7):1016-1030. doi:10.1038/ajg.2017.174
- The current US Multi-Society Task Force recommendation suggests EUS at 3-6 months for the first 2 years after resection as a reasonable option in patients with a curative resection for rectal cancer. *Kahi CJ, Boland CR, Dominitz JA, et al.*Colonoscopy Surveillance after Colorectal Cancer Resection: Recommendations of

the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 2016;111(3):337-347. doi:10.1038/ajg.2016.22

- While the National Comprehensive Cancer Network includes EUS as an alternative to flexible sigmoidoscopy for patients with rectal cancer who undergo transanal excision only. *Tombazzi CR*, *Loy P*, *Bondar V*, *Ruiz JI*, *Waters B*, *Tombazzi CR*. *Accuracy of Endoscopic Ultrasound in Staging of Early Rectal Cancer*. *Fed Pract.* 2019;36(Suppl 5):S26-S29.

- Unfortunately, not all recurrences are evident at the mucosal surface. In these cases, (EUS), which allows highly detailed visualization of all the bowel wall layers as well as the surrounding structures, is a useful adjunct. (Beynon J, Mortensen NJ, Foy DM, et al. The Detection and Evaluation of Locally Recurrent Rectal Cancer with Rectal Endosonography. Dis Colon Rectum 1989;32:509-517.)

5. Can other imaging tools like pelvic magnetic resonance imaging (MRI) can replace EUS to diagnose submucosal recurrence?

MRI is as accurate as EUS in detection of submucosal recurrence and wall thickness, however, EUS has a great advantage of obtaining tissue sampling either by FNA or FNB to differentiate tumor recurrence from inflammatory reaction, postoperative granulation tissue and post chemo-radiation proctitis.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Thanks again for your valuable comments and the meticulous revision of our manuscript.