

ANSWERING REVIEWERS

October 10. 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13490-review.doc).

Title: Endoscopic resection using band ligation for esophageal SMT in less than 10mm

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Thank you very much for your kind comments.

Reviewer 01202064's comment

1. In this article the Authors presented a study that aimed to evaluate the safety and the feasibility of endoscopic resection using band ligation (EMR-B) for the diagnostic and therapeutic removal of tumors located in the esophageal subepithelial region with origin from the submucosa. The manuscript and the subject matter are original, interesting and well presented. The main limitations are pointed out by the Author themselves: 1) The

retrospective nature of the study. 2) The experience of the procedure limited at a single center. I have a few comments that may complement and enrich the text: - In the Patents and Methods section can be appropriate to mention how are performed the endoscopic procedures in the patients, whether with sedation or with general anesthesia.

(Answer)

Thank you for your kind reviews. In this study, EMR-B procedure was performed under conscious sedation using midazolam and/ or meperidine.

(After revision)

(In the Patients and methods) We added the following sentence ; The procedures were performed under conscious sedation (intravenous administration of midazolam and/or meperidine) by two endoscopists (CW, Choi. and HW, Kim) with > 5 years of experience in performing therapeutic endoscopy (including endoscopic submucosal dissection). For sedation, 2.5mg of midazolam and 12.5mg of meperidine were initially administered and another dose of 2.5mg of midazolam and 12.5mg of meperidine were injected at endoscopist's discretion when required.

2. In the Results section can be useful to extend the follow-up with more details, since even the table 1 cites the outcome. No recur after many years? The study considers a time between 2009 and 2014.

(Answer)

We have regularly followed up the patients during the period of 4 year and 9 months (from May 2009 to September 2014) as it is demonstrated in Table 1.

(After revision)

Table 1. Summary of clinicopathologic features and treatment outcome in 15 patients underwent endoscopic resection using band ligation for esophageal submucosal layer tumor

N	G	Ag	Pathol	Sympt	Locatio	Pro	Co	Minor	Si	Enb	Margin	Follo	Out
---	---	----	--------	-------	---------	-----	----	-------	----	-----	--------	-------	-----

u m b e r	e n d er	e (ye ars)	ogy	oms	n	ced ure tim e (mi n)	mp lica tio n	compl icatio n	ze ,m m	loc rese ctio n	status	w-up (mont hs)	come s
1	M	54	GCP	None	Middle	10	No	chest pain	8	Yes	LM (-) / VM (+)	64	No recur
2	F	52	GCP	None	Upper	4	No	No	7	Yes	LM (-) / VM (-)	46	No recur
3	M	44	GCP	Reflux	Lower	7	No	No	8	Yes	LM (-) / VM (-)	41	No recur
4	M	52	Lipoma	None	Lower	17	No	No	7	Yes	LM (-) / VM (-)	41	No recur
5	F	31	Leiomyoma	None	Upper	7	No	Hot burn	13	Yes	LM (-) / VM (-)	25	No recur
6	M	46	GCP	Heartburn	Middle	10	No	Chest pain	7	Yes	LM (-) / VM (-)	20	No recur
7	M	57	GCP	None	Lower	8	No	Chest pain	7	Yes	LM (-) / VM (-)	17	No recur
8	F	42	GCP	Epigastric pain	Upper	8	No	No	2	Yes	LM (-) / VM (-)	17	No recur
9	F	46	GCP	None	Upper	10	No	No	9	Yes	LM (-) / VM (-)	12	No recur
10	M	58	GCP	Epigastric pain	Middle	15	No	No	4	Yes	LM (-) / VM (-)	5	No recur
11	F	48	GCP	Globus	Lower	9	No	No	12	Yes	LM (-) / VM (-)	43	No recur
12	F	44	Leiomyoma	None	Middle	5	No	No	6	Yes	LM (-) / VM (-)	43	No recur
1	F	70	Leiomyoma	None	Middle	5	No	No	7	Yes	LM (-) /	45	No

3			yoma								VM (-)		recur
1	F	46	GCP	None	Lower	12	No	No	1	Yes	LM (-) /	12	No
4											VM (-)		recur
1	F	65	Leiomyoma	None	Upper	6	No	Hot burn	6	Yes	LM (-) /	45	No
5											VM (-)		recur

GCP granular cell tumor, LM lateral margin, VM vertical margin

Reviewer 02570299's comment

1. There were no minor complications including chest pain or heart burn?

(Answer)

Thank you for your kind reviews. The minor complications of chest pain / heartburn were added after the medical chart review again on Table 1.

(After revision)

(In results) Minor complications such as chest pain (2/15,13.3%) and heartburn (3/15,20.0%) were reported but they symptoms were controlled by proton pump inhibitors, ulcermin and/or analgesics.

Table 1. Summary of clinicopathologic features and treatment outcome in 15 patients underwent endoscopic resection using band ligation for esophageal submucosal layer tumor

N	u	G	Ag	Pathol	Sympt	Locatio	Pro	Co	compl	Si	Enb	Follo	Out
m	e	e					ure	mp	icatio	ze	loc	w-up	come
b	n	(ye	ogy	oms	n	tim	lica	n		,m	rese	(mont	s
e	d	ars)				e	tio			m	ctio	hs)	
r	er					(mi	n			n			
						n)							
1	M	54	GCP	None	Middle	10	No	chest pain	8	Yes	LM (-) /	64	No
											VM (+)		recur

2	F	52	GCP	None	Upper	4	No	No	7	Yes	LM (-) / VM (-)	46	No recur
3	M	44	GCP	Reflux	Lower	7	No	No	8	Yes	LM (-) / VM (-)	41	No recur
4	M	52	Lipoma	None	Lower	17	No	No	7	Yes	LM (-) / VM (-)	41	No recur
5	F	31	Leiomyoma	None	Upper	7	No	Hot burn	13	Yes	LM (-) / VM (-)	25	No recur
6	M	46	GCP	Heartburn	Middle	10	No	Chest pain	7	Yes	LM (-) / VM (-)	20	No recur
7	M	57	GCP	None	Lower	8	No	Chest pain	7	Yes	LM (-) / VM (-)	17	No recur
8	F	42	GCP	Epigastric pain	Upper	8	No	No	2	Yes	LM (-) / VM (-)	17	No recur
9	F	46	GCP	None	Upper	10	No	No	9	Yes	LM (-) / VM (-)	12	No recur
10	M	58	GCP	Epigastric pain	Middle	15	No	No	4	Yes	LM (-) / VM (-)	5	No recur
11	F	48	GCP	Globus	Lower	9	No	No	12	Yes	LM (-) / VM (-)	43	No recur
12	F	44	Leiomyoma	None	Middle	5	No	No	6	Yes	LM (-) / VM (-)	43	No recur
13	F	70	Leiomyoma	None	Middle	5	No	No	7	Yes	LM (-) / VM (-)	45	No recur
14	F	46	GCP	None	Lower	12	No	No	1	Yes	LM (-) / VM (-)	12	No recur
15	F	65	Leiomyoma	None	Upper	6	No	Hot burn	6	Yes	LM (-) / VM (-)	45	No recur

GCP granular cell tumor, LM lateral margin, VM vertical margin

2.This study is a retrospective review. Was this approved by the institutional review board?

(Answer)

This study was reviewed and approved by the Institutional Review Board at Pusan National University Yangsan Hospital. (IRB Number: L-2014-447)

(After revision)

(In patient and methods) We added the following sentence ; This study was reviewed and approved by the Institutional Review Board at Pusan National University Yangsan Hospital .

3.Was written informed consent obtained from the patients for all procedures?

(Answer)

Of course, all patients received a treatment agreement. In addition, the method has been added to it. Written informed consent was obtained from all the patients prior to the procedure and we stipulated it by supplementing the content.

(After revision)

(In patient and methods) We added the following sentence ; Written informed consent was obtained from all the patients prior to EMR-B.

4.When the diet restarted after endoscopic resection?

(Answer)

On the following day after the procedure, routine second look endoscopy was done. When the absence of high risk ulcer stigma was confirmed by routine second look endoscopy, liquid diet was started. Soft diet was started on the second day after the procedure and normal diet after the third day.

5.Can the authors recommend the EMR-B for all esophageal subepithelial regions?

(Answer)

According to our research results, EMR-B is recommended for solid tumors with origin of the submucosa less than 10 mm in size, except for cystic or vascular lesions (described on the 4th line of the 2nd paragraph in discussion.

6. Is it possible to take a wait-and-see approach?

(Answer)

Although the majority of tumors originated from the submucosal layer are benign, tumors with malignant potential such as neuroendocrine tumors or lymphoma may be found as subepithelial tumors originated from the submucosal layer. For example, when gastrointestinal subepithelial tumors originated from the submucosal layer are suspected by EUS, endoscopic resection is recommended.

(reference)

Hwang, J. H.,Rulyak, S. D.Kimmey, M. B. Gastroenterolgy 2006;130:2217–28 14

Khashab, M. A. and Pasricha, P. J. Gastrointest Endosc 2013;77:146,8

Reviewer 02542077's comment

1.In the figure 1 there are some acronyms undefined.

(Answer)

Thank you for your kind reviews. GCP was granular cell tumor on Figure 1.

(After revision)

(Figure 1.) We added the following sentence in Figure 1.; GCP granular cell tumor

2. There are publications with the same technique that could be cited in the discussion.

(Answer)

Safe and effective resection of submucosal lesions using EMR-B has been reported. Yumi et al. reported effective and safe treatment of rectal lesion using endoscopic submucosal resection with a ligation device and Lee et al. demonstrated that complete resection of esophageal submucosal lesions < 13mm that are localized within the muscularis mucosae or submucosa without complications. The procedure is technically simple, minimally invasive, and safe for treatment of selected esophageal submucosal lesions.

(In discussion) We added the following sentence ; It is known that EMR-B is safe to remove the subepithelial tumor in the submucosal layer less than 10mm on any sites of digestive tract.

3. It is necessary to review some typing errors.

(Answer)

'ysts' is wrong spelling. We modified the spelling to 'cysts'.

4. The authors have data of minor complications, not mentioned?

(Answer)

Minor complications including chest pain and heartburn were reported. We revised Table 1.

(After revision)

Table 1. Summary of clinicopathologic features and treatment outcome in 15 patients underwent endoscopic resection using band ligation for esophageal submucosal layer tumor

N	G	Ag	Pathol	Sympt	Locatio	Pro	Co	Minor	Si	Enb	Margin	Follo	Out
u	e	e	ogy	oms	n	ced	mp	compl	ze	loc	status	w-up	come

Case no.	Sex	Age (years)	GCP	Symptoms	Location	Duration (months)	Lipoma	Leiomoma	Pain	Surgery	Histology	Follow-up (months)	Recurrence
1	M	54	GCP	None	Middle	10	No	Chest pain	8	Yes	LM (-) / VM (+)	64	No recur
2	F	52	GCP	None	Upper	4	No	No	7	Yes	LM (-) / VM (-)	46	No recur
3	M	44	GCP	Reflux	Lower	7	No	No	8	Yes	LM (-) / VM (-)	41	No recur
4	M	52	Lipoma	None	Lower	17	No	No	7	Yes	LM (-) / VM (-)	41	No recur
5	F	31	Leiomyoma	None	Upper	7	No	Hot burn	13	Yes	LM (-) / VM (-)	25	No recur
6	M	46	GCP	Heartburn	Middle	10	No	Chest pain	7	Yes	LM (-) / VM (-)	20	No recur
7	M	57	GCP	None	Lower	8	No	Chest pain	7	Yes	LM (-) / VM (-)	17	No recur
8	F	42	GCP	Epigastric pain	Upper	8	No	No	2	Yes	LM (-) / VM (-)	17	No recur
9	F	46	GCP	None	Upper	10	No	No	9	Yes	LM (-) / VM (-)	12	No recur
10	M	58	GCP	Epigastric pain	Middle	15	No	No	4	Yes	LM (-) / VM (-)	5	No recur
11	F	48	GCP	Globus	Lower	9	No	No	12	Yes	LM (-) / VM (-)	43	No recur
12	F	44	Leiomyoma	None	Middle	5	No	No	6	Yes	LM (-) / VM (-)	43	No recur
13	F	70	Leiomyoma	None	Middle	5	No	No	7	Yes	LM (-) / VM (-)	45	No recur

1	F	46	GCP	None	Lower	12	No	No	1	Yes	LM (-) /	12	No
4											VM (-)		recur
1	F	65	Leiomyoma	None	Upper	6	No	Hot burn	6	Yes	LM (-) /	45	No
5											VM (-)		recur

GCP granular cell tumor, LM lateral margin, VM vertical margin

5. The authors recommend this technique to any submucosal lesions, except vascular or cystic lesions?

(Answer)

In general, EMR-B method can be used for submucosal tumor within 1cm in sized. Endoscopic resection of cyst or vascular lesions is not recommended in many guidelines. Cysts or vascular lesions have a risk of rupture when removed by EMR-B.

(After revision)

(In patients and methods)We added the following sentence ; There is a general consensus that solid tumors in the submucosal layer (hypoechoic lesions on EUS) are to be removed. However, EMR-B is not recommended for cystic or vascular lesions because they have a tendency to rupture during band ligation.

Reviewer by 02542621's comment

Reviewer comments to author: The purpose of this retrospective study is report a case series describing a single-center experience of endoscopic resection using band ligation for the removal of esophageal subepithelial tumors. Abstract and main text is clear and well organized but there are several issues with this paper that concerns: Several issues to comment: Major comments: - Title and main text (introduction, last line; patients and methods, last line of 1st paragraph) explains that esophageal tumor is originated from the submucosa layer ('an esophageal tumor originating from the submucosa, 'esophageal subepithelial region having originating from the submucosa', 'and confined to the submucosal layer as assessed by the EUS probe').

How can be explained that there were 4 leiomyomas at the histological examination?.

(Answer)

Endoscopic resection was decided based on EUS findings not pathologic results of submucosal tumors. Interpretation of EUS findings can be subjective and endoscopist-dependent. Therefore, in some cases, the lesions were overestimated during EUS and later confirmed to be leiomyomas originated from muscularis mucosa. In general, most gastrointestinal leiomyomas are originated from proper muscle layer, but in esophagus, especially within 1 cm, most of the leiomyomas are originated from muscularis mucosa. In Pathologically confirmed lipoma in our study was looked hypoechoic and solid on the initial assessment and endoscopic resection was decided for the pathologic diagnosis.

Esophageal leiomyomas are defined as benign smooth muscle neoplasms, that are originated from the fourth layer (muscularis propria) and rarely from the second hypoechoic layer (muscularis mucosae on deep mucosa or lamina propria). But, it cannot be possible find a leiomyoma growing from the submucosa because non smooth muscle exists in the submucosal layer. - In 'patient and methods' section and figure 1 is commented that '18 hypoechoic was located submucosal layer by EUS'. How is possible to explain that there was 1 lipoma diagnosed in this cohort?. By EUS, it is well-known in the wide literature, that lipomas appear as intensely hyperechoic, homogeneous well-demarcated lesion located in the third echogenic layer, and only a non-homogeneous (as iso or hypoechoic) internal pattern can be seen if the tumor is large (and this is not the case, table 1; #4 case, lipoma, size 7mm).

- Discussion section, 3rd paragraph. 'Most of the tumors were granular cell tumors', 'no generally accepted management of the tumor has yet been established because the precise natural course of the lesion is unknown'. Granular cell tumor (or myoblastic myoma or Abrikosov tumor), by EUS are homogeneously iso or hypoechoic lesions with smooth margins, originated from the second (muscularis mucosae) or third (submucosa) layers. They are benign tumors as the leiomyomas, and very rarely can be malignant. No guidelines recommend their endoscopic resection in asymptomatic patients. For these reasons, the message that this resection is safe and effective with an study of 15 cases, it can not be accepted.

(Answer)

We agree with you. The most of GCP may be managed by treatment guidelines for benign lesions. But, the present study's focus was not to treat GCP by endoscopic resection. The aim of the present study was to examine the feasibility of endoscopic resection using band ligation for esophageal tumors originated from the submucosa measuring less than 10mm. Although the majority of tumors originated from the submucosal layer are benign, tumors with malignant potential such as neuroendocrine tumors or lymphoma may be found as a subepithelial tumor originated from submucosal layer. For example, gastrointestinal subepithelial tumors originated from the submucosal layer are identified by EUS, endoscopic resection is recommended.

(Reference)

Hwang, J. H., Rulyak, S. D., Kimmey, M. B. Gastroenterology 2006;130:2217–28 14

Khashab, M. A. and Pasricha, P. J. Gastrointest Endosc 2013;77:146,8

Minor comments: - The term 'submucosally' should be checked if it is correct (Patient and methods section, 2nd paragraph, line 4). - Figure 2, image B, EUS showed a hypoechogenic lesion in the submucosal layer. The image B showed in this document, as I can see, is isoechoic (same echogenicity that the submucosal layer, clear grey colour, non dark), non hypoechoic (as the hypoechoic muscular propia, seen below the lesion).

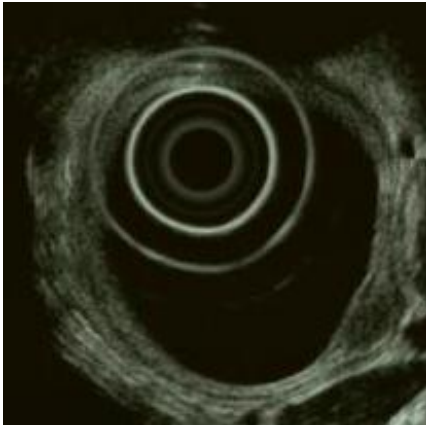
(Answer)

We modified the term 'submucosally' to 'submucosal layer'. The originally submitted image B was replaced by another photo (figure 2, image B)

(After revision)

(In patient and methods) We changed the following sentence; After the careful inspection, a solution (10% glycerin plus 5% fructose in 0.9% saline diluted 1:100,000 with epinephrine-normal saline solution and mixed with a small amount of indigo carmine) was injected into submucosal layer around the lesion to lift it off the muscle layer.

(in figure 2, image B)



Reviewer 02953378's comment

I really appreciate the effort done by done Joung et al in such interesting and nice study and the new procedure of endoscopic resection using band ligation (EMR-B) for the diagnostic and therapeutic removal of tumors originated from the submucosa and located in the esophagus that could replace surgery in certain circumstances. But I have some comments could be helpful for every one;

1.The title is attractive but it should be more specified ; The procedure is only used for lesions less than 1 cm ; should be considered in the Title

(Answer)

Thank you for your kind reviews. We appreciate your comment. We revised the title. Tumors endoscopically estimated at 10 mm in diameter, without atypical features, including ulceration or depressed areas, were considered good candidates for endoscopic resection.

(After revision)

(In title) We changed the following sentence; Endoscopic resection using band ligation for esophageal SMT in less than 10mm

2.The authors mention that (After exclusion of cystic and vascular lesions by EUS, endoscopic biopsies had been performed in these patients) and my wondering that why did not perform EUS-FNA to the suspected lesion???

(Answer)

Most of the lesion diameters were less than 10 mm in size. In our experience, endoscopic removals of such lesions were safe. In addition, although a diagnosis can be made by EUS FNA, both a diagnosis and treatment can be achieved by EMR.

3. In my opinion we cannot consider the safety of the procedure in few number of only 15 cases and further evaluation should be performed

(Answer)

We agree with your opinion. This is a limited single center, retrospective study. But, EMR-B could be safely performed if it is done by an experienced endoscopist.

(After revision)

(In conclusion) We changed the following sentence ; EMR-B might be considered safe and effective for the diagnosis and treatment of lesions measuring less than 10 mm in diameter.

Reviewer 01553211's comment

This is an interesting. The authors utilized band ligation to resect esophageal tumor. A few points need to be revised or clarified:

1. Table 1 is not informative. This could be omitted and described in the text.

(Answer)

Thank you for your kind reviews. We have revised Table 1; minor complications including chest pain and heartburn were recorded and the follow-up period was corrected as four years and nine months from May 2009 to September 2014.

(After revision)

Table 1. Summary of clinicopathologic features and treatment outcome in 15 patients underwent endoscopic resection using band ligation for esophageal submucosal layer tumor

N	Sex	Age (years)	Pathology	Symptoms	Location	Procedural time (min)		Minor complications		Endoscopic resection	Margin status	Follow-up (months)	Outcome
						ced	Completed	Si	Enb				
1	M	54	GCP	None	Middle	10	No	chest pain	8	Yes	LM (-) / VM (+)	64	No recur
2	F	52	GCP	None	Upper	4	No	No	7	Yes	LM (-) / VM (-)	46	No recur
3	M	44	GCP	Reflux	Lower	7	No	No	8	Yes	LM (-) / VM (-)	41	No recur
4	M	52	Lipoma	None	Lower	17	No	No	7	Yes	LM (-) / VM (-)	41	No recur
5	F	31	Leiomyoma	None	Upper	7	No	Hot burn	13	Yes	LM (-) / VM (-)	25	No recur
6	M	46	GCP	Heartburn	Middle	10	No	Chest pain	7	Yes	LM (-) / VM (-)	20	No recur
7	M	57	GCP	None	Lower	8	No	Chest pain	7	Yes	LM (-) / VM (-)	17	No recur
8	F	42	GCP	Epigastric pain	Upper	8	No	No	2	Yes	LM (-) / VM (-)	17	No recur
9	F	46	GCP	None	Upper	10	No	No	9	Yes	LM (-) / VM (-)	12	No recur
10	M	58	GCP	Epigastric pain	Middle	15	No	No	4	Yes	LM (-) / VM (-)	5	No recur

1	F	48	GCP	Globus	Lower	9	No	No	12	Yes	LM (-) /	43	No
1											VM (-)		recur
1	F	44	Leiom	None	Middle	5	No	No	6	Yes	LM (-) /	43	No
2			yoma								VM (-)		recur
1	F	70	Leiom	None	Middle	5	No	No	7	Yes	LM (-) /	45	No
3			yoma								VM (-)		recur
1	F	46	GCP	None	Lower	12	No	No	1	Yes	LM (-) /	12	No
4											VM (-)		recur
1	F	65	Leiom	None	Upper	6	No	Hot	6	Yes	LM (-) /	45	No
5			yoma					burn			VM (-)		recur

GCP granular cell tumor, LM lateral margin, VM vertical margin

2. Was there any incidence of fever after resection ? Was antibiotics instituted ?

(Answer)

Fever was not reported in our study and use of antibiotics was unnecessary.

3. Discussion Line 6, ysts ---. meaning ?

(Answer)

'ysts' is wrong spelling. We modified the spelling to 'cysts'.

4. A case of lipoma was noted. Was it found on biopsy ? The necessity of resection is dubious.

(Answer)

On initial assessment, it was unclear that the mass confirmed as lipoma was hypoechoic and the mass was solid. So, endoscopic resection was performed for pathologic confirmation.

5. --present Study's results--. Please revise this sentence.

(After revision)

(In discussion) We changed the following sentence in discussion; According to our research results, -.

6. Gastric Perforation after Banding ligation of gastric polyp has been ever reported. Please add this point in Discussion to warn against this potential hazard.

(Answer)

We agree with the reviewer's opinion. So it is important to implement a sufficient submucosal injection before EMR-B.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



Joung Boom Hong, MD

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