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## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 23251

**Title:** Ampullary neuroendocrine tumour diagnosed by endoscopic papillectomy in previously confirmed ampullary adenoma

**Reviewer's code:** 02683307

**Reviewer's country:** South Korea

**Science editor:** Jing Yu

**Date sent for review:** 2015-11-04 15:01

**Date reviewed:** 2015-11-11 07:39

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

### COMMENTS TO AUTHORS

This case report is worthy to publicate because of the rarity of the NET in ampulla of Vater accompanied by tubular adenoma treated with endoscopic papillectomy.

**Answer:** Thank you for kind review.

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 23251

**Title:** Ampullary neuroendocrine tumour diagnosed by endoscopic papillectomy in previously confirmed ampullary adenoma

**Reviewer's code:** 02793333

**Reviewer's country:** Switzerland

**Science editor:** Jing Yu

**Date sent for review:** 2015-11-04 15:01

**Date reviewed:** 2015-11-12 16:17

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

### COMMENTS TO AUTHORS

The report "Ampullary neuroendocrine tumour diagnosed by endoscopic papillectomy in previously confirmed ampullary adenoma" review an very interesting topic that is i current debate. It is written in a clear line of thought. Obviously, it is an important case. Minor items: 1. I would appreciate a clearer description of histology: - First papillektomy: what where the microscopic findings. Was there any tumour tisoe (e. g., adenoma or NET) and if yes, was it resected incompletely ?. - Second intervention: what where the microscopic findings.Was there any tumour tisoe (e. g., adenoma or NET) and if yes, was it resected incompletely ?.

**Answer:** Thank you for valuable comments. Presented pathologic figures resulted from figure 2D. First papillectomy tissue was mucosal layer of inner whitish mass like lesion. There was no definite pathologic lesions. Second papillectomy tissue was composed of NET and adenoma as we shown in figure 3. There was no remnant tissue. It was completely resected. As we described in case, there was also no recurrence during 2 years. So that, for more clear description, we revised the figure 3 legend as follows. Thank you.

“Figure 3. The protruding whitish mass lesion (second papillectomy tissue, figure 2D) was composed of two lesions that differed in their histological characteristics: tubular adenoma (closed arrow) and neuroendocrine tumor (open arrow, H&E stain, ×4; A). The tubular adenoma lesion exhibited round-to-oval enlarged glands with stratified epithelial cells. (H&E stain, ×100; B). The neuroendocrine tumor showed cord-like arrangement of monotonous tumor cells (H&E stain, ×100; C). Immunohistochemistry showed that the tumor cells were positive for synaptophysin (×100; D).”

2. Histology revealed a Ki67 of < 3%. Thus, besides synaptophysin it would be helpful to know the expression of the somatostatin receptor phenotype (at least the sstr2-subtype). Knowing the expression of sstr it would be possible to use radioactive somatostatin agonists for follow up imaging (SPECT/CT, PET/CT) and therapy. Did the authors perform immunohistochemistry of SSTR? and, if not, why.

Answer: Thank you for valuable comment. As your recommendation, the immunohistochemical staining for sstr subtypes would be helpful for making a decision for usage of radioactive somatostatin agonists for imaging study and therapy. However, our case was a localized disease and the tumor was NET, WHO grade 1 that could be completely resectable by endoscopic papillectomy. Further treatment did not be needed. Furthermore, in our pathologic department, the immunohistochemistry for sstr did not be set up in routine inhouse test. So, immunohistochemistry for sstr does not routinely performed, especially in localized, completely resectable and low grade NETs. Thank you.

3. p5: ...Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis was not occurred.... --> Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis did not occur.

Answer: Thank you for comments. We revised the sentence as your comment. Thank you.



ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 23251

Title: Ampullary neuroendocrine tumour diagnosed by endoscopic papillectomy in previously confirmed ampullary adenoma

Reviewer's code: 03261281

Reviewer's country: Japan

Science editor: Jing Yu

Date sent for review: 2015-11-04 15:01

Date reviewed: 2015-11-18 18:28

Table with 4 columns: CLASSIFICATION, LANGUAGE EVALUATION, SCIENTIFIC MISCONDUCT, CONCLUSION. It contains checkboxes for various criteria like 'Grade A: Excellent', 'Priority publishing', 'Google Search', 'Accept', etc.

COMMENTS TO AUTHORS

This case report describe a rare case of ampullary neuroendocrine tumor (NET) combined with adenoma. The authors successfully resected the ampullary NET accompanied by adenoma in the ampulla of Vater using endoscopic papillectomy without any evidence of local or distant metastasis during the 24 months of follow-up, although a deep resection margin for the tumor was not clear pathologically. This report is well written overall and provides useful information on NETs located in the ampulla of Vater. However, several points need to be elucidated. 1. The endoscopic findings of the ampullary tumor presented here showed a non-exposed and protruded-type of ampullary tumor. In general, papillary tumors are often pathologically heterogeneous, and it is possible that the lesion may have harbored malignant components deeper within the ampulla of Vater, even though the endoscopic biopsy from the superficial layer revealed adenoma. In addition, the possibility of intraductal extension could not be excluded. Therefore, careful judgement is required in the performance of endoscopic papillectomy in cases of non-exposed type tumors. Please describe the reason why endoscopic retrograde cholangiopancreatography and biopsy from deeper sites within

the ampulla of Vater were not performed prior to endoscopic papillectomy.

Answer: Thank you for valuable comment. Given the CT findings, there are no abnormal dilated pancreatic or biliary duct, ductal invasion, or enlarged lymph nodes. Also, EUS at the major ampulla revealed slightly hypoechoic round ampullary mass confined to the submucosa without a definite wall disruption or adjacent invasion. So, we judged that further evaluation is unnecessary and tried papillectomy to treatment and formal diagnosis. Thank you.

2. The pathological distribution of the adenoma is unclear. Please describe the pathological findings of the papillary roof from the first resection and elucidate the site of the adenoma component exposed in the orifice of the duodenal papilla.

Answer: Thank you for comment. We revised the sentence like this, reflecting your comment.

Page 5, line 9~11 The protruding lesion ~ neuroendocrine tumor (open arrow, H&E stain x 4) => "There was no evidence of NET and tubular adenoma in the first primary papillectomy specimen. But, the second resection specimen showed a collision tumor composed of tubular adenoma (closed arrow) and NET (open arrow, H&E stain, x 4) and it measured about 1.0 cm. The tubular adenoma component was mainly found in intra-ampullary portion of the ampulla of Vater. And we also added a new sentence "The NET component was also found in the second resection specimen, abutting the tubular adenoma" in page 5, in front of the sentence "The NET showed cord-like arrangement of monotonous tumor cells (H&E stain, ×100)".

3. Please describe the size of the NET in the resected specimen.

Answer: Thank you for comment. The size of NET in the resected specimen is about 1cm. We described about it in text. Thank you.

4. The first endoscopic resection of the major papilla did not include the main NET, while the second resection was successful in this regard. Submucosal injection of diluted epinephrine was performed before endoscopic papillectomy in this case. Was the cause of the failed primary endoscopic resection due to over-injection, which may obscure the ampulla of Vater among the duodenal mucosa?

Answer: We also think it could be like that. A diluted epinephrine injection may obscure the ampulla of Vater resulting in incomplete resection. However, given reported studies did not show these difference. More comparative studies comparing injection with non-injection method are needed. Thank you.



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**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 23251

**Title:** Ampullary neuroendocrine tumour diagnosed by endoscopic papillectomy in previously confirmed ampullary adenoma

**Reviewer's code:** 03317261

**Reviewer's country:** China

**Science editor:** Jing Yu

**Date sent for review:** 2015-11-04 15:01

**Date reviewed:** 2015-11-19 20:51

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

### COMMENTS TO AUTHORS

The authors report an interesting rare case of ampullary neuroendocrine tumor (NET) combined with adenoma. I suggest the case report be published.

**Answer:** Thank you for kind review.