

Responses to Reviewers' Comments

We are thankful to the reviewers for their thorough evaluation of our manuscript, and valuable comments. We are also thankful for the guidance provided by the Science Editor with regards to our pictures and legends. We have revised the manuscript according to the suggestions and have provided point-by-point responses to their comments, as follows below.

Science Editor

1. **"The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor."**

We have now provided the original figure documents, prepared and arranged using PowerPoint.

2. **"Uniform presentation should be used for figures showing the same or similar contents (using lettered panels); for example: "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...".**

We have now re-organised the figure captions as requested.

Reviewer #1

1. **"In the first paragraph of the introduction section, second line- "only 7% of cancers in the region"- better to say 7% of peri-ampullary tumours."**

The authors have changed the terminology as suggested.

2. **“Morbidity following endoscopic papillectomy (EP) occurred in 18.9%, including haemorrhage, papillary stenosis and others. what was the most common complication?”**

The authors have changed the sentence to: *“Adverse events occurred in 18.9%, most commonly haemorrhage (11.3%); other complications included papillary stenosis, acute pancreatitis, and duodenal perforation.”*

3. **“EP as a suggested treatment for carefully selected early ampullary cancer was controversial by some authors which advocates PD for all ampullary cancers- what is the reason for such advocacy? is it due to lymph node involvement?”**

The reviewer is correct to suspect potential lymphatic involvement as the main reason for many authors preferring pancreatoduodenectomy over local excision. The authors have amended the sentence to: *“EP has also been suggested as a suitable treatment for carefully selected early ampullary cancers, although this has been controversial and some authors have advocated PD for all ampullary cancers in patients who are adequately fit due to the risk of lymphatic involvement.”*

4. **“Endoscopy using a side-viewing endoscope is a technique used for visualization of the ampulla and for taking biopsies- what is the sensitivity and specificity for such technique in regard to ampullary lesion?”**

Endoscopy using either forward-viewing or side-viewing endoscopes is used for diagnosing ampullary lesions based upon their gross endoscopic appearances, and also to facilitate biopsies. Therefore, there are two diagnostic modalities to consider: histology of biopsies, and gross

appearances on endoscopy. The authors have already presented the overall diagnostic performance of endoscopic biopsies in “Pre-operative evaluation”, paragraph 2, including sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy. To address the reviewer’s interest in the diagnostic performance of biopsies obtained using the side-viewing duodenoscope, we have added another reference [32] and modified the paragraph as follows: *“Diagnostic accuracy has been reported from 45 – 100%. The type of endoscope used has been found to affect the diagnostic accuracy of biopsies: those obtained using side-viewing duodenoscopes have outperformed samples taken using forward-viewing endoscopes (85.7% versus 45%, $p = 0.004$).”* The study cited did not report sensitivity and specificity separately for forward-viewing and side-viewing endoscopes, but we believe the differences in diagnostic accuracy will be useful information for the reader.

To provide more information on the diagnostic performance of endoscopic appearances, we have modified “Pre-operative evaluation”, paragraph 5. Due to the lack of data regarding differences in performance between forward-viewing and side-viewing endoscopes, we have reworded the start of the paragraph to include both. We have also added sensitivity and specificity data for diagnosis of ampullary adenocarcinoma based on endoscopic appearances (rather than biopsies), with the caveat that the study had a small sample size and thus must be interpreted with caution. The start of the paragraph now reads: *“Endoscopy using either a forward-viewing endoscope or side-viewing duodenoscope allows visualisation of the ampullary lesion, to evaluate malignant potential and endoscopic resectability. In general, tumours which are firm,*

immobile, friable, ulcerated or have an indistinct margin are likely to be malignant. A small study in 2015 found a sensitivity of 94.7% and a specificity of 89.5% for AAC diagnosed using the following endoscopic criteria: "enlarged papilla with uneven granular or nodular appearance of overlying mucosa, associated with spontaneous bleeding, ulceration, and friable or indurated surface". However, there has not been a robust evaluation of specific criteria for distinguishing ampullary adenomas from early AAC based on endoscopic appearances."

5. "In the indication section, paragraph about FAP- "patents"- "patients"."

The authors have corrected the typing mistake as suggested.

6. "Please provide the classification table developed by Spigelman."

Spigelman's classification was originally described as text rather than a table.

The authors have therefore constructed a table (Table 2), based on

Spigelman's original textual description of his classification. A cross-reference to Table 2 has been added to the text: *"A classification of duodenal polyposis was developed by Spigelman et al., based on the number, size and histology of polyps, as shown in Table 2."*

7. "What were the advantages and disadvantages of the suggested surgical techniques."

The reviewer has asked an important question which the authors had researched whilst reviewing the literature. The techniques and variations described in the "Surgical technique" section include brief explanations of the purpose of each step. However, as reports of technique have been mostly descriptive rather than comparative, it has not been possible to provide evidence-based commentary regarding their relative advantages and

disadvantages. For example, regarding the excision and reconstruction techniques described in paragraph 2 of “Surgical technique”: it is not clear what the relative advantages and disadvantages of the two methods are. Whilst there are numerous articles reporting these techniques, their authors have generally taken descriptive approaches, without detailing justifications of their techniques. The “suturing as you go” approach described by Mathiel *et al.* was claimed to prevent the problem of retraction of the ducts. However, reports of the more common method of excision followed by reconstruction have not specified duct retraction as being problematic; several authors prevented duct retraction by simply placing a stay suture on the ducts prior to transection. To clarify this, the authors have added the following sentence to the end of the paragraph: “*There has not been a comparative evaluation of excision and reconstruction techniques.*” Similarly, whilst minimal access surgical ampullectomy appears feasible, there have been few reports, and the proposed advantages have been of a very speculative nature. It has therefore been difficult to establish the technical advantages and disadvantages of minimal access relative to open surgical ampullectomy: we have added the sentence “*Similarly, there has been a lack of comparative evaluations of minimal access versus open surgical techniques for SA*” to the first paragraph of the “Clinical outcomes” section. The “Surgical technique” section has been written in a mostly descriptive style to match the literature upon which is based.

Reviewer #2

1. **"My only suggestion to the authors is if they would consider tabulating some of the data in the section on Indications and Clinical Outcomes as currently it makes for heavy reading. The tables will help the reader appreciate the differences in the study and also reduce the amount that needs to be written in the manuscript."**

The authors have made every effort to summarise the complexities of the topic in a narrative form: for example, statistical information such as confidence intervals and p-values have been kept to a minimum.

Nevertheless, they acknowledge that the detail presented in the "Indications" and "Clinical outcomes" sections can still make for heavy reading, and the reviewer's suggestion to tabulate some of the information is welcomed. The authors have created Table 1 to present an accessible summary of generally accepted indications, contra-indications, and controversies. A cross-reference to the table has been added in the text: *"A summary of generally accepted indications, contra-indications, and controversies is presented in Table 1."* The authors have also created Table 3 to present a summary of clinical outcomes, and added a cross-reference to the table within the text: *"A summary of clinical outcomes of SA is presented in Table 3."*

However, the authors do not feel it is possible to reduce the text relating to Table 1 and Table 3, as they believe an understanding of the nuances of the topic is important: there is a risk that removing the discussions of conflicting information may present a false sense of certainty to the reader. The authors are aware that their article could have some influence on the clinical decisions

of practising surgeons, and therefore it is essential that clinicians understand the weaknesses in the evidence base.