

Point-by-point responses

Manuscript Number: 75649

Title: Cumulative incidence and risk factors for pouch adenomas associated with familial adenomatous polyposis following restorative proctocolectomy

Ryu *et al.* Incidence and risk factors for pouch adenoma

Dear Editor-in-Chief Andrzej S Tarnawski

We resubmit the revised manuscript, "Cumulative incidence and risk factors for pouch adenomas associated with familial adenomatous polyposis following restorative proctocolectomy," to be considered for publication in *World Journal of Gastroenterology*. Corrections and other changes in the revised manuscript are indicated with red text. This letter contains point-by-point responses with corrections and additions.

Reviewer #1:

Q1. English needs revision in the whole manuscript.

A1. As per your suggestion, the whole manuscript has been edited by a professional language editor.

Q2. Please make a better sentence expressing the association of duodenal adenomas and pouch adenomas in the following sentence: "In addition, patients with duodenal adenomas developed pouch adenomas more frequently (66.7% vs 42.3%, $p=0.039$)". Assess if you tried to state that the presence of duodenal adenomas was associated with pouch adenomatosis?

A2. Thank you. We have rephrased the flagged passage. (Page 9, Line 9-11)

Original: patients with duodenal adenomas developed pouch adenomas more frequently (66.7% vs 42.3%, $p=0.039$).

Revised: patients with pouch adenomas (relative to those without pouch adenomas) were more likely to have duodenal adenomas (66.7% vs 42.3%, $P = 0.039$).

In patients with pouch adenomas, duodenal adenomas were more likely to be present. However, multivariate analysis showed no association between pouch adenoma and duodenal adenoma development. We have described this in the Discussion section. (Page 11, Line 13-16)

Reviewer #2:

Q1. Results. Paragraph: Clinical characteristics of the study patients with and without pouch adenomas. Line 9. In patients without pouch adenoma, the use of NSAIDs was not significantly more used for the treatment of desmoid tumors, according to the statistical criteria stated by the authors in the methods section of the manuscript, though the frequency is undoubtedly higher and near the statistical significance.

A1. Thank you for the comment. The sentence was incorrect, and we have corrected the description. (Page 9, Line 10-13)

Original: In patients without pouch adenomas, nonsteroidal anti-inflammatory drugs (NSAIDs) including celecoxib and meloxicam was significantly more used as a treatment for desmoid tumors (4.2% vs 19.7%, $p=0.07$).

Revised: Nonsteroidal anti-inflammatory drug (NSAID) treatment for desmoid tumors—including with celecoxib and meloxicam—was more common among patients without pouch adenomas, but this difference was not statistically significant (4.2% vs 19.7%, $P = 0.07$).

Q2. Fig. 1. The number of patients at risk is not well aligned with time after IPAA. This should be corrected.

A2. The number of patients is correct. We think that you are referring to the alignment of the box of excluded patients before IPAA, and we have edited Figure 1 accordingly. If our understanding is incorrect, please let us know, and we will make further modifications, as necessary.

Q3. Table2. I do not understand what is the difference between: number of colorectal polyps, and colorectal polyps < or > 1000. According to the table in the group of patients without pouch adenoma the upper limit of the range is 500, whereas, below, 7 such patients had 1000 or more adenomas at the time of surgery. The authors should explain this discrepancy, or better define the two parameters.

A3. The number of colorectal polyps is expressed as an interquartile range (1st quartile-3rd quartile). Since 500 is the number corresponding to the 3rd quartile, not the upper limit, there were seven patients with more than 1000 polyps in the group of patients without pouch adenomas. The number of polyps was a variable that indicated the overall distribution. Also,

we considered that 1000 or more colorectal polyps at the time of surgery was clinically significant. Therefore, it was included in the analysis as a dichotomous (≥ 1000 and < 1000) independent variable .

Q4. English polishing and corrections are needed all along the manuscript.

A4. As per your suggestion, the entire manuscript has been edited by a professional language editor.

Reviewer #3:

Q1. What was the indication for RPC/IPAA for FAP? was it for adenoma prophylaxis, cancer finding or presence of > 100 polyps or both. Can the authors clarify that?

A1. The indication for RPC/IPAA was a diagnosis of FAP with or without malignancy. As we mention in the Method sections, the FAP patients were identified by presence of more than 100 colorectal polyps (Page 5, Lines 10-11). Some of them had cancer. The indication for RPC-IPAA has been added to the Methods section (Page 5, Lines 11-12).

Q2. The presented data should be integrated in Cox multivariate analysis and the multivariate analysis reported in Table 3 is the appropriate to be used. • Why duodenal adenoma was entered in the multivariate (despite a $p = 0.54$ in the univariate). Why?

A2. As per your suggestion, we have included more information regarding which variables were analyzed in the multivariable model. Variables reported to be associated with pouch adenoma development in previous reports and demographic variables were adjusted in the multivariable analysis. If we considered variables to be of theoretical importance, we entered them into the model despite a lack of statistical insignificance. After backward elimination, colorectal polyps more than 1000 and duodenal adenoma remained. We have included this information in the Methods section.

Q3. A comment is needed regarding presence of small bowel polyps at videocapsule endoscopy correlated with severity of Spiegelman classification, this agrees with the finding in Table 2 about duodenal adenomas.

A3. Thank you for important comment. Unfortunately, video capsule endoscopy is not a routine procedure at our institution. Most patients were not assessed for small bowel polyps with video capsule endoscopy; therefore, it would be inappropriate for us to comment on this matter.

Q4. Clinical characteristics of the study patients according to presence of pouch adenomas, the statistics and figures need to be carefully revisited prior to publishing this paper.

A4. We have reviewed this information.

Q5. Minor language/grammatical issues.

A5. As per your suggestion, this manuscript has been edited by a professional language editor.

Reviewer #4:

Q1. A radical linguistic revision by an English native speaker is necessary.

A1. As per your suggestion, the entire manuscript has been edited by a professional language editor.

Q2. In the "study population" paragraph of Methods section, Authors have reported the process of patients selection. However, this is a result and it should be moved in the appropriate section. In the above mentioned paragraph, Authors must only report inclusion and exclusion criteria.

A2. Thank you. As per your suggestion, the patient selection process has been moved to the Results section.

Q3. Please report which was the indication to proctocolectomy: prophylaxis, cancer finding or presence of >100 polyps. This variable should be integrated in Cox multivariate analysis as well.

A3. The indication for RPC/IPAA was a diagnosis of FAP with or without malignancy. As we mention in the Method sections, the FAP patients were identified by presence of more than 100 colorectal polyps (Page 5, Lines 10-11). Some of them had cancer. The indication for RPC-IPAA has been added to the Methods section (Page 5, Lines 11-12).

As per your recommendation, the multivariate analysis was performed again and included the presence of malignancy. Malignancy was excluded from step 5 during backward elimination, and the final result of the analysis did not change. Although progression to malignancy may be associated with pouch adenoma development, previous publications do not report malignancy as a risk factor for pouch adenoma, and we did not modify the table because there was no change in results.

		B	표준오차	Wald	자유도	TPL 유의확률	Exp(B)	95.0% Exp(B)의 CI	
								하한	상한
단계 1	Colorectal polyps>1000	.739	.499	2.192	1	.139	2.095	.787	5.575
	Age	-.008	.020	.168	1	.682	.992	.953	1.032
	Sex	-.082	.471	.030	1	.862	.921	.366	2.317
	Desmoid tumor	-.362	.577	.395	1	.530	.696	.225	2.155
	Gastric polyps	.223	.545	.168	1	.682	1.250	.429	3.639
	Duodenal adenomas	.744	.451	2.729	1	.099	2.105	.870	5.092
	F/U_mo	-.004	.005	.882	1	.348	.996	.987	1.005
	Colorectal cancer	-.403	.467	.745	1	.388	.668	.267	1.669
단계 2	Colorectal polyps>1000	.754	.493	2.338	1	.126	2.126	.809	5.587
	Age	-.009	.020	.179	1	.672	.992	.953	1.031
	Desmoid tumor	-.382	.565	.458	1	.499	.682	.225	2.065
	Gastric polyps	.210	.540	.151	1	.697	1.234	.428	3.556
	Duodenal adenomas	.759	.443	2.943	1	.086	2.137	.897	5.089
	F/U_mo	-.004	.005	.956	1	.328	.996	.987	1.004
	Colorectal cancer	-.390	.460	.717	1	.397	.677	.275	1.670
단계 3	Colorectal polyps>1000	.791	.485	2.662	1	.103	2.207	.853	5.710
	Age	-.010	.020	.236	1	.627	.990	.953	1.030
	Desmoid tumor	-.371	.564	.432	1	.511	.690	.228	2.085
	Duodenal adenomas	.772	.442	3.047	1	.081	2.165	.909	5.152
	F/U_mo	-.005	.005	1.044	1	.307	.995	.987	1.004
	Colorectal cancer	-.363	.456	.635	1	.426	.696	.285	1.699
단계 4	Colorectal polyps>1000	.888	.445	3.973	1	.046	2.429	1.015	5.815
	Desmoid tumor	-.353	.564	.391	1	.532	.703	.233	2.121
	Duodenal adenomas	.795	.439	3.276	1	.070	2.215	.936	5.241
	F/U_mo	-.005	.004	1.082	1	.298	.995	.987	1.004
단계 5	Colorectal polyps>1000	-.398	.450	.781	1	.377	.672	.278	1.623
	Colorectal polyps>1000	.907	.445	4.153	1	.042	2.476	1.035	5.922
	Duodenal adenomas	.766	.438	3.068	1	.080	2.152	.913	5.073
	F/U_mo	-.004	.004	.957	1	.328	.996	.987	1.004
단계 6	Colorectal polyps>1000	-.379	.450	.708	1	.400	.685	.283	1.655
	Colorectal polyps>1000	.940	.445	4.466	1	.035	2.559	1.071	6.119
	Duodenal adenomas	.759	.438	2.996	1	.083	2.136	.905	5.043
단계 7	F/U_mo	-.005	.004	1.419	1	.233	.995	.986	1.003
	Colorectal polyps>1000	.912	.446	4.192	1	.041	2.490	1.040	5.963
	Duodenal adenomas	.733	.440	2.779	1	.096	2.081	.879	4.926

Q4. I do not understand why, in the multivariate analysis reported in Table 3, duodenal adenoma was entered in the multivariate despite a p = 0.54 in the univariate. Authors should

enter multivariate analysis parameters significant or close to statistical significance at univariate, or variables with a relationship plausibility such as NSAID use.

A4. As per your suggestion, we have included more information regarding which variables were analyzed in the multivariable model. Variables reported to be associated with pouch adenoma development in previous reports and demographic variables were adjusted in the multivariable analysis. If we considered variables to be of theoretical importance, we entered them into the model despite a lack of statistical insignificance. After backward elimination, colorectal polyps more than 1000 and duodenal adenoma remained. We have included this information in the Methods section.

Q5. Considering that presence of small bowel polyps at videocapsule endoscopy correlated with severity of Spiegelman classification, this agrees with the finding in table 2 about duodenal adenomas. Please comment.

A5. Thank you for important comment. Unfortunately, video capsule endoscopy is not a routine procedure at our institution. Most patients were not assessed for small bowel polyps with video capsule endoscopy; therefore, it would be inappropriate for us to comment on this matter.