Format for ANSWERING REVIEWERS

January 16, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15174-review.doc).

Title: Efficacy of Cap-assisted Colonoscopy According to Endoscopist Training Level and Lesion Location

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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

Reviewer 03002168's comment
(1) 'third-eye' retroscopy is not a standard term and may be proprietary; 'retrograde-viewing device' would be more appropriate.

(Answer)
Thank you for your kind review. We modified the term "third-eye retroscopy" to "retrograde-viewing device".

(2) The ADR in this population is significantly higher than what has been reported by others, such as Corley http://www.ncbi.nlm.nih.gov/pubmed/24693890. How do you account for the high rate of lesions detected in this population?

(Answer)
Thank you for your kind review. In our study, the PDR and ADR could be higher than that in other studies, because the minimal withdrawal time of most procedures was at least 7 min, all endoscopists were aware of self-recording of withdrawal time, all procedures were performed with HD colonoscopies and NBI, and optimal or fair bowel preparation, and quality improvement program of colonoscopy was performed every month.

(After revision)

We added the following sentences in the discussion:

Rex DK et al. suggested that ADR must be at least 25% for male and at least 15% for female[1], and ADR is known to vary widely among providers in both academic and community settings[2]. Our study reported higher PDR (40.7%) and high ADR (28.3%) in SC group than previous studies. However, recent studies reported the high PDR and ADR with long withdrawal times, self-recording of withdrawal time, HD colonoscope, fair bowel preparation and an academic setting of improving ADR[3-7]. In our study, the minimal withdrawal time of most procedures was at least 7 min, all endoscopists were aware of self-recording of withdrawal time and all procedures were performed with HD colonoscopies and NBI, and optimal or fair bowel preparation. Furthermore, quality improvement program of colonoscopy was performed at PNUYH every month. These are the reason that our PDR and ADR in SC group were higher than those of previous studies.

(References)

1 Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO, Pike IM, Endoscopy AAToQi. Quality indicators for colonoscopy. *The American journal of gastroenterology* 2006; **101**(4): 873-885 [PMID: 16635231 DOI: 10.1111/j.1572-0241.2006.00673.x]

2 Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP. Adenoma detection rate and risk of colorectal cancer and death. *The New England journal of medicine* 2014; **370**(14): 1298-1306 [PMID: 24693890 PMCID: 4036494 DOI: 10.1056/NEJMoa1309086]

3 Barclay RL, Vicari JJ, Greenlaw RL. Effect of a time-dependent colonoscopic withdrawal protocol on adenoma detection during screening colonoscopy. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2008; **6**(10): 1091-1098 [PMID: 18639495 DOI: 10.1016/j.cgh.2008.04.018]

4 Taber A, Romagnuolo J. Effect of simply recording colonoscopy withdrawal time on polyp and adenoma detection rates. *Gastrointestinal endoscopy* 2010; **71**(4): 782-786 [PMID: 20363418 DOI: 10.1016/j.gie.2009.12.008]

5 Subramanian V, Mannath J, Hawkey CJ, Ragunath K. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. *Endoscopy* 2011; **43**(6): 499-505 [PMID: 21360420 DOI: 10.1055/s-0030-1256207]

6 Anderson JC, Butterly LF, Robinson CM, Goodrich M, Weiss JE. Impact of fair bowel preparation quality on adenoma and serrated polyp detection: data from the New Hampshire Colonoscopy Registry by using a standardized preparation-quality rating. *Gastrointestinal endoscopy* 2014; **80**(3): 463-470 [PMID: 24818550 PMCID: 4134990 DOI: 10.1016/j.gie.2014.03.021]

7 Ussui V, Coe S, Rizk C, Crook JE, Diehl NN, Wallace MB. Stability of Increased Adenoma Detection at Colonoscopy. Follow-Up of an Endoscopic Quality Improvement Program-EQUIP-II. *The American journal of gastroenterology* 2014 [PMID: 25267326 DOI: 10.1038/ajg.2014.314]

(3) Table 1: was there a difference in ADR and/or PDR based on age (20-50, 50-65, 65-75, 75+) AND gender in terms of lesions detected in the right, transverse, and descending colon?

(Answer)

Thank you for your review. Your inquiry is very interesting. In our definition, the right-side colon included the cecum, ascending colon, hepatic flexure and transverse colon. We analyzed the PDR, ADR, and the number of polyps and adenomas based on age and gender.

(After revision)

We added the following sentences;

PDR, ADR, and the number of polyps and adenomas per patient based on age

We evaluated the PDR, ADR, and the number of polyps and adenomas per patient of whole colon (Table 5) and right-side colon (Table 6) based on age (20-49, 50-65, 66-75, 76+). In summary, the number of polyps and adenomas per patient of right-side colon in the CAC group was significantly higher than that in the SC group, on all ages except ≥75. On the age ≥75, none of PDR, ADR and the number of polyps and adenomas per patient in the CAC group was significantly higher than those in the SC group, perhaps because the sample size of the age ≥75 was too small. When we analyzed the number of polyps and adenomas per patient based on each colon segment, which of ascending colon in the CAC group was significantly higher than that in the SC group on the all ages except ≥75. The number of polyps and adenomas per patient of transverse and descending colon in the CAC was not significantly different than that in the SC group on the all ages.

Table 5. PDR, ADR, and the number of polyps and adenomas of whole colon based on age

Whole colon				
Age	Total	CAC	SC	p value
20-49, n	308	147	161	
polyps per patient	0.51±1.07	0.63±1.32	0.41±0.77	0.078
PDR, n (%)	94 (30.5%)	51 (34.7%)	43 (26.7%)	0.128
adenomas per patient	0.26±0.77	0.37±1.02	0.16±0.41	**0.013**
ADR, n (%)	57 (18.5%)	35 (23.8%)	22 (13.7%)	**0.022**
50-65, n	544	293	251	
polyps per patient	1.01±1.47	1.09±1.57	0.92±1.34	0.194
PDR, n (%)	260 (47.8%)	146 (49.8%)	114 (45.4%)	0.305
adenomas per patient	0.67±1.22	0.76±1.34	0.57±1.04	0.068
ADR, n (%)	190 (34.9%)	107 (36.5%)	83 (33.1%)	0.400
66-75, n	154	68	86	
polyps per patient	1.55±1.84	1.93±1.91	1.26±1.74	**0.024**
PDR, n (%)	91 (59.1%)	47 (69.1%)	44 (51.2%)	**0.024**
adenomas per patient	1.04±1.53	1.28±1.62	0.85±1.43	0.084
ADR, n (%)	71 (46.1%)	38 (55.9%)	33 (38.4%)	**0.030**

≥76, n	17	7	10	
polyps per patient	1.24±1.20	1.14±0.90	1.30±1.41	0.959
PDR, n (%)	12 (70.6%)	6 (85.7%)	6 (60.0%)	0.338
adenomas per patient	1.00±1.11	0.71±0.75	1.20±1.31	0.502
ADR, n (%)	10 (58.8%)	4 (57.1%)	6 (60.0%)	1.000

Table 6. PDR, ADR, and the number of polyps and adenomas of right-side colon based on age

Right-side colon				
Age	Total	CAC	SC	p value
20-49, n	308	147	161	
polyps per patient	0.25±0.82	0.35±1.09	0.15±0.45	**0.030**
PDR, n (%)	49 (15.9%)	30 (20.4%)	19 (11.8%)	**0.039**
adenomas per patient	0.13±0.61	0.20±0.83	0.06±0.25	**0.033**
ADR, n (%)	28 (9.1%)	20 (13.6%)	8 (5.0%)	**0.008**
50-65, n	544	293	251	
polyps per patient	0.59±1.00	0.68±1.13	0.49±0.82	**0.025**
PDR, n (%)	194 (35.7%)	110 (37.5%)	84 (33.5%)	0.322
adenomas per patient	0.41±0.86	0.50±1.00	0.31±0.66	**0.009**
ADR, n (%)	138 (25.4%)	82 (28.0%)	56 (22.3%)	0.129
66-75, n	154	68	86	
polyps per patient	0.91±1.31	1.21±1.38	0.67±1.21	**0.012**
PDR, n (%)	86 (55.8%)	38 (55.9%)	30 (34.9%)	**0.009**
adenomas per patient	0.62±1.04	0.81±0.99	0.47±1.07	**0.043**
ADR, n (%)	54 (35.1%)	34 (50.0%)	20 (23.3%)	**0.001**
≥76, n	17	7	10	
polyps per patient	0.59±1.00	0.86±1.06	0.40±0.96	0.167
PDR, n (%)	6 (35.3%)	4 (57.1%)	2 (20.0%)	0.162
adenomas per patient	0.41±0.71	0.57±0.78	0.30±0.67	0.362
ADR, n (%)	5 (29.4%)	3 (42.9%)	2 (20.0%)	0.593

PDR, ADR, and the number of polyps and adenomas per patient based on gender

We evaluated the PDR, ADR, and the number of polyps and adenomas per patient of whole colon and right-side colon based on gender (Table 7). The number of adenomas per patient and ADR of right-side colon in the CAC group were significantly higher than those in the SC group, based on the both genders. When we analyzed the number of polyps and adenomas per patient based on each colon segment, which of ascending colon in the CAC group was significantly higher than that in the SC group on the both genders. The number of polyps and adenomas per patient of transverse and descending colon in the CAC was not significantly different than that in the SC group on both genders.

Table 7. PDR, ADR, and the number of polyps and adenomas based on gender

	Whole colon			
Gender	Total	CAC	SC	p value
Male, n	549	280	269	
Polyps per patient	1.25±1.67	1.37±1.84	1.12±1.47	0.082
PDR, n (%)	300 (54.6%)	158 (56.4%)	142 (52.8%)	0.392
Adenomas per patient	0.81±1.38	0.90±1.53	0.71±1.20	0.109
ADR, n (%)	219 (39.9%)	114 (40.7%)	105 (39.0%)	0.688
Female, n	474	235	239	
Polyps per patient	0.60±1.08	0.71±1.14	0.49±1.00	**0.029**
PDR, n (%)	157 (33.1%)	92 (39.1%)	65 (27.2%)	**0.006**
Adenomas per patient	0.38±0.84	0.50±0.98	0.26±0.67	**0.002**
ADR, n (%)	109 (23.0%)	70 (29.8%)	39 (16.3%)	**<0.001**
	Right-side colon			
Male, n	549	280	269	
Polyps per patient	0.70±1.20	0.87±1.39	0.52±0.94	**0.001**
PDR, n (%)	205 (37.3%)	118 (42.1%)	87 (32.3%)	**0.018**
Adenomas per patient	0.49±1.00	0.60±1.14	0.37±0.82	**0.007**
ADR, n (%)	153 (27.9%)	90 (32.1%)	63 (23.4%)	**0.023**
Female, n	474	235	239	
Polyps per patient	0.35±0.73	0.41±0.78	0.28±0.67	0.066
PDR, n (%)	112 (23.6%)	64 (27.2%)	48 (20.1%)	0.067

Adenomas per patient	0.21±0.56	0.29±0.67	0.13±0.42	**0.002**
ADR, n (%)	72 (15.2%)	49 (20.9%)	23 (9.6%)	**0.001**

(4) What % of patients had a lesion detected in the ascending AND another segment of the colon using CAP vs. SC?

(Answer)
Thank you for your review. The number of patients who had lesions detected in the ascending colon (AC) and another segments in the CAC group was significantly higher than that in the SC group (65 (12.6%) vs 40 (7.9%), P=0.012).

	Total (N=1023)	**CAC (N=515)**	**SC (N=508)**	**P value**
patients with lesions in the AC and another segments	105 (10.3%)	65 (12.6%)	40 (7.9%)	**0.012**

(5) What % of patients had a significant (>=5mm) lesion detected in the ascending AND another segment of the colon using CAP vs. SC?

(Answer)
The number of patients who had a significant lesion in the AC and another segments in the CAC group was not significantly higher than that in the SC group (15 (2.9%) vs 8 (1.6%), P=0.149).

	Total (N=1023)	**CAC (N=515)**	**SC (N=508)**	**P value**
patients with significant lesions in the AC and another segments	23 (2.2%)	15 (2.9%)	8 (1.6%)	0.149

(6) What was the average # of lesions detected per patient?

(Answer)
Thank you for your review. The number of polyps and adenomas per patient was 0.95±1.46 and 0.61±1.18 (mead ± Standard deviation). The number of polyps per patient was significantly higher in the CAC than that in the SC (1.07±1.59 vs 0.82±1.31, *P*=0.008). The number of adenomas per patient was significantly higher in the CAC than that in the SC (0.72±1.32 vs 0.50±1.01, *P*=0.003).

(After revision)
We modified the Table 2 and Table 3 with the number of polyps and adenomas per patient.

Table 2. Polyp detection with CAC versus SC on the all ages and both genders.

Whole colon	**Total (N=1023)**	**CAC (N=515)**	**SC (N=508)**	**P value**
Total polyps	967	549	418	**0.008**
Polyps per patient	0.95±1.46	1.07±1.59	0.82±1.31	**0.008**
PDR, n (%)	457 (44.7%)	250 (48.5%)	207 (40.7%)	**0.012**
Right-side colon	**Total (N=1023)**	**CAC (N=515)**	**SC (N=508)**	**P value**
Total polyps	547	339	208	**<0.001**
Polyps per patient	0.53±1.03	0.66±1.18	0.41±0.83	**<0.001**
PDR, n (%)	317 (31.0%)	182 (35.3%)	135 (26.6%)	**0.002**
Polyps of segment	**Total (N=1023)**	**CAC (N=515)**	**SC (N=508)**	**P value**
Cecum	85	42	43	0.888
Ascending colon	266	179	87	**<0.001**
Hepatic flexure	80	56	24	**0.001**
Transverse colon	116	62	54	0.560
Splenic flexure	30	24	6	**0.001**
Descending colon	65	31	34	0.683
Sigmoid colon	223	105	118	0.406
Rectum	102	50	52	0.804

Table 3. Adenoma detection with CAC versus SC on the all ages and both genders.

Whole colon	**Total (N=1023)**	**CAC (N=515)**	**SC (N=508)**	**P value**
Total adenomas	623	370	253	**0.003**
Adenomas per patient	0.61±1.18	0.72±1.32	0.50±1.01	**0.003**
ADR, n (%)	328 (32.1%)	184 (35.7%)	144 (28.3%)	**0.011**
Right-side colon	**Total (N=1023)**	**CAC (N=515)**	**SC (N=508)**	**P value**
Total adenomas	365	236	129	**<0.001**
Adenomas per patient	0.36±0.84	0.46±0.97	0.25±0.67	**<0.001**
ADR, n (%)	225 (22.0%)	139 (27.0%)	86 (16.9%)	**<0.001**

Adenomas of segment	Total (N=1023)	CAC (N=515)	SC (N=508)	P value
Cecum	45	20	25	0.490
Ascending colon	179	129	50	**<0.001**
Hepatic flexure	62	44	18	**0.002**
Transverse colon	79	43	36	0.529
Splenic flexure	28	22	6	**0.003**
Descending colon	46	23	23	0.966
Sigmoid colon	130	61	69	0.490
Rectum	54	28	26	0.829

Reviewer 03003148's comment

1. In the "Introduction", lanes 8 and 9, it would be better if the authors use "flat lesions" instead of "flat polyps" and "missed lesions" instead of "missed polyps", respectively.

(Answer)
Thank you for your kind review. We modified the term "flat polyps" to "flat lesions" and "missed polyps" to "missed lesions".

2. In the "Methods" the authors claim to have used Paris classification for morphology classification of lesions. However, all lesions were classified as "polyps" in the results. All lesions were 0-Is or 0-Isp or 0-Isp? There were no flat lesions detected in the study population? Please clarify in the "Methods" and include in the "Results" and "Discussion" if necessary.

(Answer)
At first, we tried to classify all lesions using the Paris classification. However, because the height of nearly all diminutive lesions was below 2.5 mm (the thickness of biopsy forcep), nearly all diminutive lesions were considered as flat lesions. In addition, we could evaluate easily the size of the significant lesions (≥ 5mm) by the width of opened forceps. However, because it was difficult to measure the height of the lesions by the thickness of closed forceps, we couldn't classify the lesion exactly, Is or IIa. Therefore, we didn't classify the lesion morphology using the Paris classification. However, because the number of diminutive lesions was higher than that of significant lesions, most lesions of our study were thought to be the flat lesions.

(After revision)
(Patients and Methods - Polyps) We removed the following sentence; and their morphology was classified using the Paris classification.

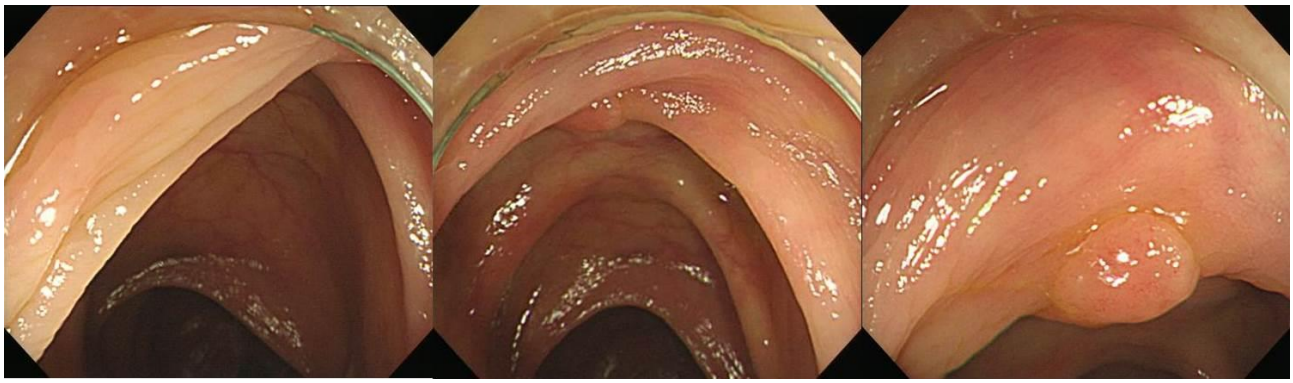
3. Could authors provide representative figures of endoscopic images?

(Answer)

Thank you for your review. We will provide figures of endoscopic images.

Figure 2. The images of cap-assisted colonoscopy.

A lesion was located in the proximal aspect of a haustral fold. The lesion was not observed before CAC depressed the haustral fold. When a cap depressed the haustral fold, the lesion was able to be observed.



4. In the discussion the authors described that the reason for having longer withdrawal time in CAC group was the higher number of polyps detected and removal in this group compared to in SC group. However, it is known that withdrawal time is associated with increase in ADR. Could the withdrawal time be responsible for increasing of ADR in CAC group? Please explain this.

(Answer)

Thank you for your review. We analyzed a withdrawal time of non therapeutic (no biopsy or polypectomy) colonoscopies between the CAC and SC group. Although the combined withdrawal time of both therapeutic and non therapeutic colonoscopies in the CAC group was significantly longer than that in the SC group, the withdrawal time of only non therapeutic colonoscopies was not significantly different between the CAC group and SC group. Therefore, we consider that the withdrawal time of CAC was longer than that of SC because more lesions were detected in CAC than SC, and more procedure time, such as cold forcep biopsy or hot snare polypectomy, was needed in CAC than SC. We also consider that the inspection time of CAC was not significantly longer than that of SC. We concluded that the higher ADR of CAC was not associated with the longer withdrawal time of CAC.

(After revision)

(Results)

We added the following results; the withdrawal time of only non therapeutic colonoscopies in the CAC was not significantly different than that in the SC (10.68 ± 3.09 min vs 10.33 ± 4.24 min, P=0.272).

(Discussion)

The part of the discussion section we modified is as follows;

This study has several limitations. First, it was a single-center, retrospective, case-controlled study. Second, four of the trainees performed the SC from May 2011 to December 2011, and the other four trainees performed CAC from May 2012 to December 2012. Thus, there is a potential for selection bias, and the sample performed by experts was relatively small. Third, the combined withdrawal time of both therapeutic and non therapeutic (no biopsy or polypectomy) colonoscopies in the CAC group was significantly longer than that in the SC group, indicating that the withdrawal time is associated with increase in PDR and ADR. However, although the combined withdrawal time of both colonoscopies in the CAC group was significantly longer than that in the SC group, the withdrawal time of only non therapeutic colonoscopies was not significantly different between the CAC group and SC group. Moreover, more polyps and adenomas were detected in CAC than SC. Therefore, we concluded that the withdrawal time of CAC was longer than that of SC because more lesions were detected in CAC than SC, and more lesion removal time, such as cold forcep biopsy or hot snare polypectomy, was needed in CAC than SC. We believe that the inspection time of CAC was not longer than that of SC, and the higher ADR of CAC was not associated with the longer withdrawal time of CAC.

3. References and typesetting were corrected

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

Sincerely yours,

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