CLINICAL SCIENCE

Histopathological evaluation and risk factors related to the development of pouchitis in patients with ileal pouches for ulcerative colitis

Roberta Thiery de Godoy Arashiro,[I] Magaly Gemio Teixeira,[I] Viviane Rawet,[II] Alina Guimarães Quintanilha,[I] Henrique Moura de Paula,[I] Adriano Zanon Silva,[I] Sérgio Carlos Nahas,[I] Ivan Cecconello[I]

[I] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Departamento de Gastroenterologia, Serviço de Cirurgia do Cólon e Reto, São Paulo/SP, Brazil. [II] Rawet Patologia Especializada Ltda, São Paulo/SP, Brazil.

OBJECTIVE: Many changes in mucosal morphology are observed following ileal pouch construction, including colonic metaplasia and dysplasia. Additionally, one rare but potential complication is the development of adenocarcinoma of the reservoir. The aim of this study was to evaluate the most frequently observed histopathological changes in ileal pouches and to correlate these changes with potential risk factors for complications.

METHODS: A total of 41 patients were enrolled in the study and divided into the following three groups: a non-pouchitis group (group 1) (n = 20; 8 males; mean age: 47.5 years) demonstrating optimal outcome; a pouchitis without antibiotics group (group 2) (n = 14; 4 males; mean age: 47 years), containing individuals with pouchitis who did not receive treatment with antibiotics; and a pouchitis plus antibiotics group (group 3) (n = 7; 3 males; mean age: 41 years), containing those patients with pouchitis who were administered antibiotics. Ileal pouch endoscopy was performed, and tissue biopsy samples were collected for histopathological analysis.

RESULTS: Colonic metaplasia was found in 15 (36.6%) of the 41 patients evaluated; of these, five (25%) were from group 1, eight (57.1%) were from group 2, and two (28.6%) were from group 3. However, no correlation was established between the presence of metaplasia and pouchitis ($p = 0.17$). and no differences in mucosal atrophy or the degree of chronic or acute inflammation were observed between groups 1, 2, and 3 ($p > 0.45$). Moreover, no dysplasia or neoplastic changes were detected. However, the degree of mucosal atrophy correlated well with the time of postoperative follow-up ($p = 0.05$).

CONCLUSIONS: The degree of mucosal atrophy, the presence of colonic metaplasia, and the degree of acute or chronic inflammation do not appear to constitute risk factors for the development of pouchitis. Moreover, we observed that longer postoperative follow-up times were associated with greater degrees of mucosal atrophy.

KEYWORDS: Colonic metaplasia; Atrophy; Ileal Pouch; Pouchitis; Proctocolectomy.

INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become the gold standard procedure for the treatment of familial adenomatous polyposis (FAP), as well as ulcerative colitis (UC) that is refractory to clinical treatment. This procedure reduces the inconvenience of the diarrhea associated with direct ileoanal anastomosis while preserving sphincter function. In the case of the UC, this technique has become the most widely used elective surgical procedure (1).

However, IPAA is not free of complications; nonspecific inflammation of the ileal pouch, or pouchitis, is the most common long-term complication, with an incidence ranging from 14 to 59% (2-12).

Although the physiopathology of pouchitis remains controversial, there is strong evidence that this condition represents a reactivation of UC. In particular, pouchitis occurs almost exclusively in patients who underwent IPAA for UC, rather than for FAP (7,12,13), which suggests an autoimmune etiology for this condition in genetically predisposed individuals. Other factors in support of this theory include the existence of extra-intestinal events associated with an increased risk of developing pouchitis (3,9,14) and the endoscopic and histopathological similarities observed between patients with pouchitis and those with UC (15,16).

There is also an increased risk for the development of pouchitis in female patients (6) and in those with extensive or severe UC (7), extra-intestinal manifestations (3,9,14), early disease onset (3), the use of non-steroidal anti-inflammatory drugs (10), gene polymorphisms in the interleukin-1 receptor and TNF-1 antagonists (11) and the presence of perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) (17). Additionally, colonic metaplasia is a common histopathological finding for the ileal pouch and is observed in approximately 50% of patients with pouchitis and approximately 18% of patients undergoing IPAA without pouchitis (18).

In addition, it was observed that the occurrence of pouchitis, particularly in its chronic course, appears to increase the risk of the development of adenocarcinoma of the ileal pouch according to the sequence of atrophy-dysplasia-carcinoma (19-21). Furthermore, it was found that up to 71% of ileal pouches with severe atrophy develop dysplasia, which is in contrast to cases of discrete atrophy that generally do not develop dysplastic changes (22).

This study sought to characterize the most frequent histopathological changes of ileal pouches and to correlate these changes with potential risk factors for the development of pouchitis.

PATIENTS AND METHODS

Patients

This study included 41 patients who underwent IPAA for UC between 1985 and 2006 at the Hospital of the Faculty of Medicine at the University of São Paulo (HC-FMUSP) in the Division of Colon and Rectal Surgery. The ileal J-pouch technique was used according to the description provided by Utsunomiya et al. (23).

A total of 15 men and 26 women with a mean age of 46.2 (range: 23 to 66) years were included in the study. The mean time-course of the disease was 190 (range: 15 to 312) months, and the mean duration of the postoperative follow-up period was 141.7 (range: 24 to 276) months. A total of 33 patients retained a temporary ileostomy for an average period of 22.3 (range: 1 to 168) months, whereas eight patients underwent a single surgery with primary anastomosis.

The pouchitis disease activity index (PDAI), which was previously used by Sandborn et al. (24), was adopted to define the presence or absence of pouchitis in patients based on clinical, endoscopic, and histopathological criteria.

Thus, the patients were divided into the following three groups: the non-pouchitis group (NP), containing individuals without pouchitis at the time of evaluation (n = 20); the pouchitis/no antibiotics group (PNA), containing individuals with pouchitis who were not administered antibiotics (n = 14); and the pouchitis plus antibiotics group (PA), including patients who had pouchitis and were administered antibiotics (n = 7).

The research project was approved by the CAPPESQ (Commission for Ethics Review of Research Projects) of the HCFMUSP under protocol number 1162/07. All included patients signed an informed consent form prior to participation.

METHODS

Endoscopic evaluation of the ileal pouch

All patients underwent an endoscopic evaluation of the ileal pouch (using a sterile rigid rectoscope for children) with no prior bowel preparation. The endoscopic assessment of the ileal pouch was performed and analyzed according to the PDAI (24).

Histopathological assessment

After the luminal contents were aspirated, two biopsies were taken from areas of major inflammation, if present, and care was taken to avoid suture lines and stapling. The fragments were then sent for histopathological assessment. Three pathologists participated in the study, and in addition to the criteria of the PDAI previously cited (24), these individuals described the histological patterns observed in accordance with the following criteria: the degree of acute inflammation, the degree of chronic inflammation, the degree of activity, the presence of colonic metaplasia, the degree of atrophy of the mucosa and the degree of malignancy. These data are shown in Table 1.

Statistics analysis

An un-paired T-test was used for the histopathological analysis of the three groups. Furthermore, the Shapiro-Wilk normality test was applied to the NP, PNA, and PA groups to evaluate both the duration of the disease ($p = 0.661, 0.589$, and 0.442, respectively) and the postoperative follow-up period ($p = 0.389, 0.051$, and 0.218, respectively). Next, an ANOVA was performed on the same groups, which led us to conclude that these three groups were homogeneous in terms of both the duration of the disease ($p = 0.222$) and the postoperative follow-up period ($p = 0.139$). Additionally, $p < 0.05$ was defined as the threshold of significance.

RESULTS

Histopathological evaluation of biopsies

According to the histopathological biopsy results, we observed that longer post-operative follow-up times were associated with a greater degree of mucosal atrophy ($p = 0.055$). However, there was no correlation between this

Table 1 - Graduation and criteria adopted for the histopathological characterization of ileal pouches.

Histopathological Change	Graduation
Degree of chronic inflammation (eosinophilic and lymphoplasmacytic)	Mild (0)
	Moderate (1)
	Intense (2)
Degree of acute inflammation (polymorphonuclear granulocytes)	Absent (0)
	Mild (1)
	Moderate (2)
	Intense (3)
Degree of activity	Absent (0)
	Acute cryptitis (1)
	Crypt microabscesses (2)
	Erosion or ulceration (3)
Presence of colonic metaplasia	Absent (0)
	Present (1)
Degree of mucosal atrophy	Absent (0)
	Distortion of crypts (1)
	Atrophy of crypts (2)
Degree of malignancy (cytoarchitectural atypia)	Mild (0)
	Low grade (1)
	High degree (2)
	Intramucosal Carcinoma (3)
	Invasive Carcinoma (4)

Table 2 - Correlation between elapsed times of disease and post-operative follow-up with the degree of mucosal atrophy.

Degree of mucosal atrophy	Elapsed time of disease			Elapsed time of post-operative follow-up		
	Average	Standard error	*p*-value	Average	Standard error	*p*-value
0	184.6154	13.28076	0.5632	126.0000	12.75617	**0.0552**
1	199.6875	22.04535		162.0000	12.96148	

histopathological change and the elapsed disease time ($p = 0.5632$). These data are presented in Table 2.

The histopathological pattern observed in healthy ileal pouches is shown below in Figure 1, whereas atrophy of the mucosa is illustrated in Figure 2.

Colonic metaplasia was observed in 15 (36.6%) of the 41 patients evaluated; of these, five (25%) were from the NP group, eight (57.1%) were from the PNA group, and two (28.6%) were from the PA group. No dysplasias or neoplastic changes were observed.

In addition, there were no statistically significant differences between the three groups with regard to the degree of mucosal atrophy ($p = 0.5203$) (Figure 2); the presence of colonic metaplasia ($p = 0.1697$) (Figure 3); the degree of acute inflammation ($p = 0.4434$) (Figure 4); and the degree of chronic inflammation ($p = 0.9999$).

There were also no significant correlations between colonic metaplasia and elapsed disease time ($p = 0.4670$) or elapsed post-operative follow-up time ($p = 0.2041$) and between the degree of chronic inflammation and the degree of mucosal atrophy ($p = 0.2396$), the presence of colonic metaplasia ($p = 0.8275$), elapsed disease time ($p = 0.2031$) or elapsed post-operative follow-up time ($p = 0.4980$).

DISCUSSION

Since its first description in 1978 by Parks and Nicholls (25), the ileal pouch technique has been widely used to achieve sphincter preservation and a reduction in the number of bowel movements in patients undergoing total proctocolectomy. Apart from its contraindications (acute complicated diseases, sphincter dysfunction, malnutrition or coexistence of cancer of the middle or distal portion of the rectum or anus), this technique has become the most widely used elective surgical procedure for patients with UC (1).

Prior to the introduction of the ileal pouch, patients underwent either the permanent ileostomy of Brooke (26) or ileoanal anastomosis and experienced a consequently high number of daily bowel movements. The first pouch technique, described by Parks and Nicholls, uses three folds of small intestine that are formed into an "S" shape. Subsequently, other ileal pouch techniques have been described, such as the isoperistaltic loop technique of Fonkalsrud and Ament (27), which uses four loops shaped into a "W", that described by Lubowski and Nicholls (28), and the "J" pouch described by Utsunomiya (23), which was the technique employed in the current study.

Clinically, pouchitis is characterized by watery diarrhea, an increased number of bowel movements, abdominal pain, fecal urgency, incontinence, fever, malaise, and in certain cases, intestinal bleeding. This disorder can also be accompanied by extra-intestinal manifestations of UC. Acute or chronic forms can be observed, although the acute forms are more common (29). Additionally, recurrent episodes are reported at variable rates, ranging from 24.6 (7) to 66% (12).

We used the PDAI criteria in our study because we believed that appropriate diagnostic tests for pouchitis should be performed, including endoscopic examination, biopsy, and histopathological analysis. It has previously been shown that the diagnoses of as many as 25% of patients with the typical symptoms of pouchitis are not confirmed endoscopically or histopathologically (8). Differential diagnoses are
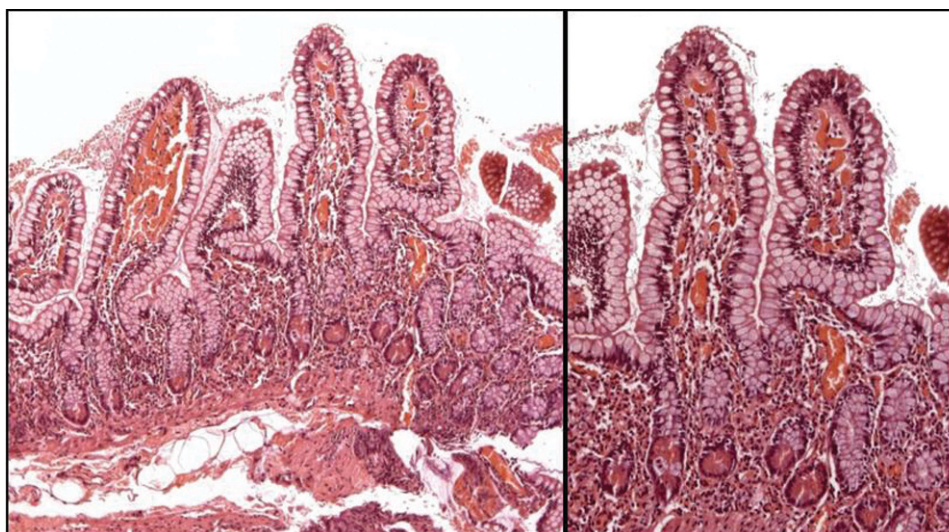

Figure 1 - Healthy ileal pouch mucosa, where villous: crypt ratio is 3 : 1. Presence of Paneth cells, "brush border" and less amount of goblet cells compared to colon.
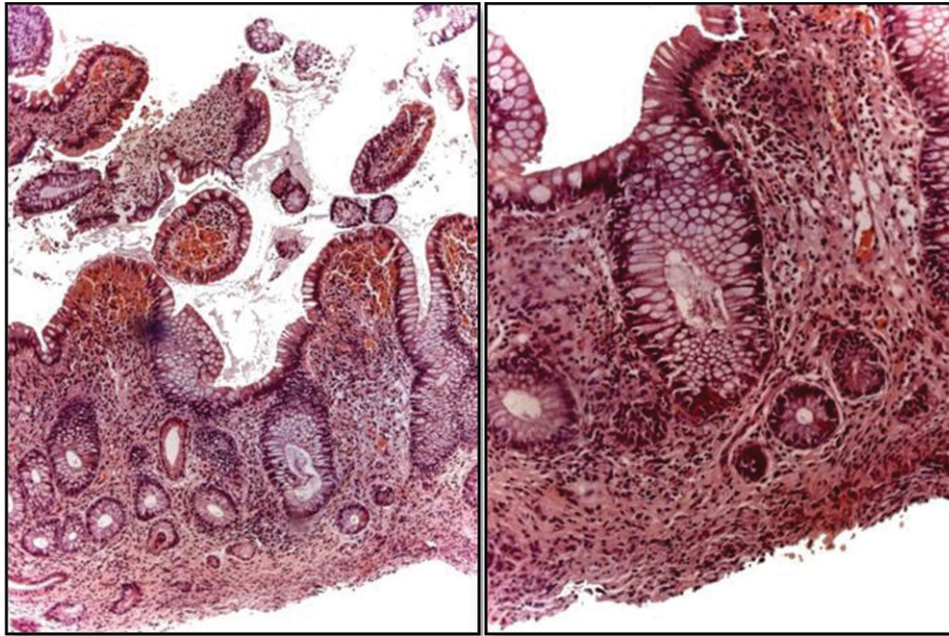
Figure 2 - Mucosal atrophy, where villous: crypt ratio is 1:1. Enlargement of the villi, Lymphocytic predominance and *lamina propria's* fibroplasia.

important to rule out other inflammatory (e.g., cuffitis, Crohn's disease, certain infections of the pouch) and non-inflammatory conditions (e.g., decreased complacency, irritable pouch syndrome, stenosis, a long efferent loop, decreased emptying, pelvic floor dysfunction or adhesions) (10,30).

A previous study correlated the presence of colonic metaplasia with inflammation of the ileal pouch and suggested that villous atrophy and crypt hyperplasia predominantly represent a reparative response to the construction of the ileal pouch. In addition, the absence of metaplasia in pouches constructed by FAP would suggest that such a transformation of the mucosa is attributable to

both the basic disease, as well as to adaptive responses to anatomical conformation (31).

However, our study did not confirm an association between colonic metaplasia and the presence of pouchitis. However, we did observe a correlation between mucosal atrophy and the duration of post-operative follow-up, regardless of the presence of pouchitis, and this finding is contrary to that of Apel et al., which suggested that the presence of villous atrophy does not increase with elapsed disease time (32). Thus, additional factors besides fecal stasis and bacterial proliferation are likely involved in the adaptive process of the ileal pouch mucosa, as preliminary studies have suggested (33).
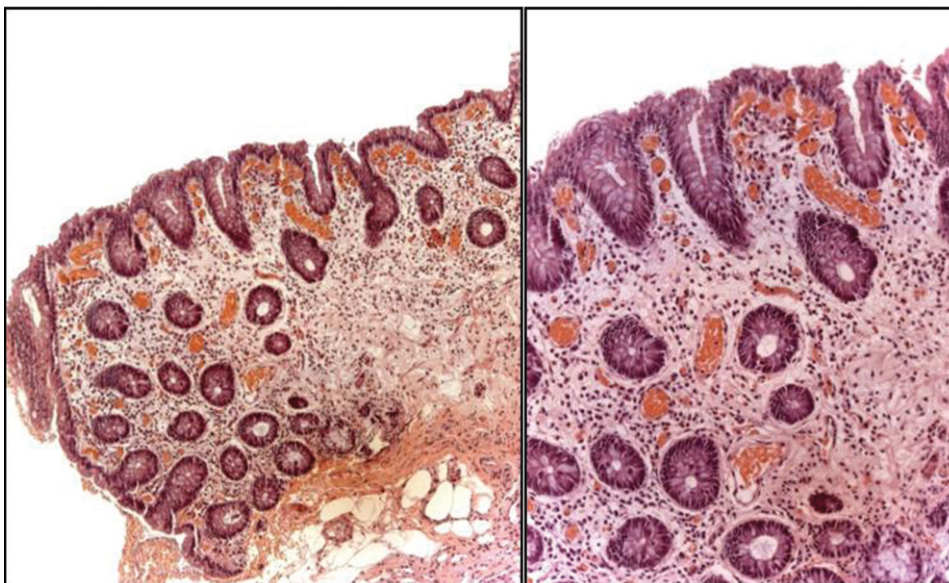

Figure 3 - Colonic Metaplasia. Only crypts are observed. Absence of Paneth cells or villi.
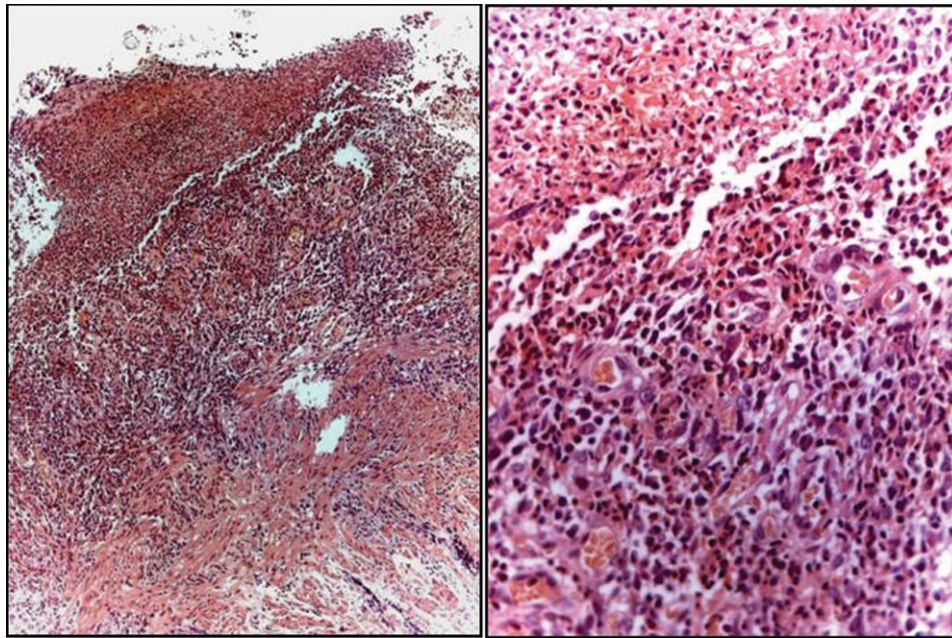
Figure 4 - Acute inflammation with erosions. There are erosions in the muscular layer of the mucosa, a fibrin-leukocyte buffer and adjacent granulation tissue.

Trovato et al. (34) assessed ileal pouches using either confocal laser endomicroscopy in vivo or conventional histopathological analysis and found incidences of colonic metaplasia of 67.7% and 83.3%, respectively, as well as an incidence of villous atrophy of 83.3% using both techniques. In our study, both colonic metaplasia and villous atrophy were observed in 36.6% of patients, and no dysplasia was detected in either study.

Although the neoplastic transformation process was not the focus of our study, we considered the complete histopathological characterization of the ileal pouch to be relevant, including the detection of pre-neoplastic changes. Although rare, adenocarcinoma of the reservoir has been described and is thought to be a consequence of atrophic chronic pouchitis. It has also been assumed that persistent inflammation of the pouch may result in malignant degeneration to resemble what occurs in the inflamed colon. Additionally, there are reports of the development of adenocarcinomas in the ileal pouch mucosa that exhibit intense chronic inflammation and atrophy without a prior history of neoplasms or other risk factors (19,35,36).

No dysplasia or ileal pouch neoplasia was detected in our patients, which is consistent with the results of most previous studies (37-41). The study by Kariv et al. (42) evaluated 3,203 patients with ileal pouches and found dysplasia and adenocarcinoma incidences of 0.72% and 0.36%, respectively. However, the only parameters that these authors considered to represent risk factors for ileal pouch neoplasia were a preoperative diagnosis of dysplasias or adenocarcinomas of the colon or rectum.

The study by MKoma et al. (43) reviewed 12 studies from retrospective case series and 15 case reports and observed the following risk factors for the neoplastic transformation of ileal pouches: pouchitis, preoperative dysplasia or cancer, an interval greater than 10 years from the onset of UC, type C mucosal changes of the pouch mucosa, extra-intestinal manifestations and prior treatment with the stapled anastomotic technique. Pouch-related cancer did not occur in any of these patients within 10 years of the diagnosis of UC.

Thus, early postoperative endoscopic surveillance is generally not justified for these patients. However, for pouch patients with longer postoperative times, it would be interesting to perform routine endoscopic examinations, even in asymptomatic patients, to pursue mucosal atrophy due to the typical sequence of atrophic pouchitis - dysplasia – adenocarcinoma (19-21).

The degree of mucosal atrophy, the presence of colonic metaplasia and the degree of acute or chronic inflammation do not appear to constitute risk factors for the development of pouchitis. Moreover, we found that longer postoperative follow-up times were associated with greater degrees of mucosal atrophy.

AUTHOR CONTRIBUTIONS

REFERENCES

1. Habr-Gama A, Teixeira MG. Tratamento cirúrgico da Retocolite Ulcerativa / Proctocolectomia restauradora com bolsa ileal. In: Habr-Gama A (ed). Doença Inflamatória Intestinal, Clínica Brasileira de Cirurgia, Ano III, Volume III. Atheneu, Brasil, 1997.
2. Rauh SM, Schoetz DJ Jr, Roberts PL, Murray JJ, Coller JA, Veidenheimer MC. Pouchitis – is it a wastebasket diagnosis? Dis Colon Rectum. 1991;34(8):685-9, http://dx.doi.org/10.1007/BF02050351.
3. Stahlberg D, Gullberg K, Liljeqvist L, Hellers G, Löfberg R. Pouchitis following pelvic pouch operation for ulcerative colitis – Incidence, cumulative risk and risk factors. Dis Colon Rectum. 1996;39(9):1012-8, http://dx.doi.org/10.1007/BF02054692.
4. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup DM, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. Ann Surg. 1990;211(5):622-9.
5. Svaninger G, Nordgren S, Öresland T, Hultén L. Incidence and characteristics of pouchitis in the Koch continent ileostomy and the

pelvic pouch. Scand J Gastroenterol. 1993;28(8):695-700, http://dx.doi.org/10.3109/00365529309098275.

6. Simchuk EJ, Thirlby RC. Risk factors and true incidence of pouchitis in patients after ileal pouch-anal anastomosis. World J Surg. 2000;24(7):851-6, http://dx.doi.org/10.1007/s002680010136.

7. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milson JW, et al. Ileal pouch-anal anastomosis complications and function in 1005 patients. Ann Surg. 1995;222(2):120-7, http://dx.doi.org/10.1097/00000658-199508000-00003.

8. Shen B, Achkar JP, Lashner BA, Ormsby AH, Remzi FH, Bevins CL, et al. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. Gastroenterology. 2001;121(2):261-7, http://dx.doi.org/10.1053/gast.2001.26290.

9. Hata K, Watanabe M, Shinozaki M, Nagawa H. Patients with extraintestinal manifestations have a higher risk of developing pouchitis in ulcerative colitis: multivariate analysis. Scand J Gastroenterol. 2003;10:1055-8, http://dx.doi.org/10.1080/00365520310005938.

10. Shen B, Fazio VW, Remzi FH, Delaney CP, Bennett AE, Achkar JP, et al. Comprehensive evaluation of inflammatory and noninflammatory sequelae of ileal pouch-anal anastomoses. Am J Gastroenterol. 2005;100(1):93-101, http://dx.doi.org/10.1111/j.1572-0241.2005.40778.x.

11. Aisenberg J, Legnani PE, Nilubol N, Cobrin GM, Ellozy SH, Hegazi RAF, et al. Are pANCA, ASCA or cytokine gene polymorphisms associated with pouchitis? Long-term follow-up in 102 ulcerative colitis patients. Am J Gastroenterol. 2004;99(3):432-41.

12. Hurst RD, Molinari M, Chung P, Rubin M, Michelassi F. Prospective study of the incidence, timing, and treatment of pouchitis in 104 consecutive patients after restorative proctocolectomy. Arch Surg. 1996;131(5):497-500, http://dx.doi.org/10.1001/archsurg.1996.01430170043007.

13. Dozois RR, Kelly KA, Welling DR, Gordon H, Beart RW, Wolff BG, et al. Ileal pouch-anal anastomosis: comparison of results in familial adenomatous polyposis and chronic ulcerative colitis. Ann Surg. 1989;210(3):268-71, http://dx.doi.org/10.1097/00000658-198909000-00002.

14. Teixeira WGJ, Silva JH, Teixeira MG, Almeida MG, Calache JE, Habr-Gama A. Pouchitis: extracolonic manifestation of ulcerative colitis? Rev Hosp Clin Fac Med S Paulo. 1999;54(5):155-8.

15. Stallmach A, Moser C, Hero-Gross R, Muller-Molaian I, Ecker KW, Feifel G, et al. Pattern of mucosal adaptation in acute and chronic pouchitis. Dis Colon Rectum. 1999;42(10):1311-7, http://dx.doi.org/10.1007/BF02234221.

16. Kmiot WA, Youngs D, Tudor R, Thompson H, Keighley MRB. Mucosal morphology, cell proliferation and faecal bacteriology in acute pouchitis. Br J Surg. 1993;80(11):1445-9, http://dx.doi.org/10.1002/bjs.1800801132.

17. Sandborn WJ, Landers CJ, Tremaine WJ, Targan SR. Antineutrophil cytoplasmic antibody correlates with chronic pouchitis after ileal pouch-anal anastomosis. Am J Gastroenterol. 1995;90(5):740-7.

18. Kuisma J, Mentula S, Luukkonen P, Jarvinen H, Kahri A, Farkkila M. Factors associated with ileal mucosal morphology and inflammation in patients with ileal pouch-anal anastomosis for ulcerative colitis. Dis Colon Rectum. 2003;46(11):1476-83, http://dx.doi.org/10.1007/s10350-004-6796-6.

19. Knupper N, Straub E, Terpe HJ, Vestweber KH. Adenocarcinoma of the ileoanal pouch for ulcerative colitis–a complication of severe chronic atrophic pouchitis? Int J Colorectal Dis. 2006;21(5):478-82, http://dx.doi.org/10.1007/s00384-005-0063-8.

20. Stein RB, Lichtenstein GR. Complications after ileal pouch-anal anastomosis. Semin Gastrointest Dis. 2000;11(1):2-9.

21. Gullberg K, Lindforss U, Zetterquist H, Stålberg D, Reinholt FP, Veress B, et al. Cancer risk assessment in long-standing pouchitis. DNA aberrations are rare in transformed neoplastic pelvic pouch mucosa. Int J Colorectal Dis. 2002;17(2):92-7.

22. Gullberg K, Ståhlberg D, Liljeqvist L, Tribukait B, Reinholt FP, Veress B, et al. Neoplastic transformation of the pelvic pouch mucosa in patients with ulcerative colitis. Gastroenterology. 1997;112(5):1487-92, http://dx.doi.org/10.1016/S0016-5085(97)70029-5.

23. Utsunomiya J, Iwana I, Imajo M, Matsuo S, Sawai S, Yaegashi K, et al. Total colectomy mucosal proctectomy and ileoanal anastomosis. Dis Colon Rectum. 1980;23(7):459-66, http://dx.doi.org/10.1007/BF02987076.

24. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips S. Pouchitis after ileal pouch-anal anastomosis: a pouchitis disease activity index. Mayo Clin Proc. 1994;69(5):409-15.

25. Parks AG, Nicholls RJ. Proctocolectomy without Ileostomy for Ulcerative-Colitis. Brit Med J. 1978;2(6130):85-8, http://dx.doi.org/10.1136/bmj.2.6130.85.

26. Brooke BN. The outcome of surgery for ulcerative colitis. Lancet. 1956;271(6942):532-6, http://dx.doi.org/10.1016/S0140-6736(56)92021-9.

27. Fonkalsrud EW, Ament ME. Endorectal mucosal resection without proctocolectomy as an adjunct to abdominoperineal resection for non malignant conditions: clinical experience with five patients. Ann Surg. 1978;188(2):245-8, http://dx.doi.org/10.1097/00000658-197808000-00019.

28. Nicholls RJ, Lubowski DZ. Restorative proctocolectomy: the four loop W reservoir. Br J Surg. 1987;74(7):564-6, http://dx.doi.org/10.1002/bjs.1800740705.

29. Teixeira MG, Ponte ACA, Sousa M, Almeida MG, Silva Filho E, Calache JE, et al. Short- and long-term outcomes of ileal pouch-anal anastomosis for ulcerative colitis. Rev Hosp Clin Fac Med S Paulo. 2003;58(4):193-8.

30. Pardi DS, Sandborn WJ. Systematic review: the management of pouchitis. Aliment Pharmacol Ther. 2006;23(8):1087-96, http://dx.doi.org/10.1111/j.1365-2036.2006.02884.x.

31. Fruin AB, El-Zammer O, Stucchi AF, OBrien M, Becker JM. Colonic metaplasia in the ileal pouch is associated with inflammation and is not the result of long-term adaptation. J Gastrointest Surg. 2003;7(2):246-54, http://dx.doi.org/10.1016/S1091-255X(02)00191-9.

32. Apel R, Choen Z, Andrews CW Jr, McLeod R, Steinhart H, Odze R. Prospective evaluation of early morphological changes in pelvic ileal pouches. Gastroenterology. 1994;107(2):435-43.

33. De Silva HJ, Millard PR, Kettlewell M, Mortensen NJ, Prince C, Jewell DP. Mucosal characteristics of pelvic ileal pouches. Gut. 1991;32(1):61-5, http://dx.doi.org/10.1136/gut.32.1.61.

34. Trovato C, Sonzogni A, Fiori G, Ravizza D, Tamayo D, Botti F, et al. Confocal laser endomicroscopy for the detection of mucosal changes in ileal pouch after restorative proctocolectomy. Dig Liver Dis. 2009;41(8):578-85, http://dx.doi.org/10.1016/j.dld.2008.09.019.

35. Heuschen UA, Heuschen G, Autschbach F, Allemeyer EH, Herfarth C. Adenocarcinoma in the ileal pouch: late risk of cancer after restorative proctocolectomy. Int J Colorectal Dis. 2001;16(2):126-30, http://dx.doi.org/10.1007/s003840000276.

36. Hassan C, Zullo A, Speziale G, Stella F, Lorenzetti R, Morini S. Adenocarcinoma of the ileoanal pouch anastomosis: an emerging complication? Int J Colorectal Dis. 2003;18(3):276-8.

37. Nilubol N, Scherl E, Bub DS, Gorfine SR, Marion J, Harris MT, et al. Mucosal dysplasia in ileal pelvic pouches after restorative proctocolectomy. Dis Colon Rectum. 2007;50(6):825-31, http://dx.doi.org/10.1007/s10350-007-0217-6.

38. Herline AJ, Meisinger LL, Rusin LC, Roberts PL, Murray JJ, Coller JA, et al. Is routine pouch surveillance for dysplasia indicated for ileoanal pouches? Dis Colon Rectum. 2003;46(2):156-9, http://dx.doi.org/10.1007/s10350-004-6517-1.

39. Hultén L, Willén R, Nilsson O, Safarani N, Haboubi N. Mucosal assessment for dysplasia and câncer in the ileal pouch mucosa in patients operated on for ulcerative colitis- a 30-year follow-up study. Dis Colon Rectum. 2002;45(4):448-52, http://dx.doi.org/10.1007/s10350-004-6218-9.

40. Thompson-Fawcett MW, Marcus V, Redston M, Cohen Z, McLeod RS. Risk of dysplasia in long-term ileal pouches and pouches with chronic pouchitis. Gastroenterology. 2001;121(2):275-81, http://dx.doi.org/10.1053/gast.2001.26442.

41. Ettore GM, Pescatori M, Panis Y, Nemeth J, Crescenzi A, Valleur P. Mucosal changes in ileal pouches after restorative proctocolectomy for ulcerative and Crohns colitis. Dis Colon Rectum. 2000;43(12):1743-8, http://dx.doi.org/10.1007/BF02236861.

42. Kariv R, Remzi FH, Lian L, Bennett AE, Kiran RP, Kariv Y, et al. Preoperative colorectal neoplasia increases risk for pouch neoplasia in patients with restorative proctocolectomy. Gastroenterology. 2010;139(3):806-12, http://dx.doi.org/10.1053/j.gastro.2010.05.085.

43. MKoma AE, Moses HL, Adunyah SE. Inflammatory bowel disease-associated colorectal cancer: proctocolectomy and mucosectomy do not necessarily eliminate pouch-related cancer incidences. Int J Colorectal Dis. 2011;26(5):533-52, http://dx.doi.org/10.1007/s00384-011-1137-4.