Current Gastroenterology Reports (2019) 21: 10
https://doi.org/10.1007/s11894-019-0679-4

LARGE INTESTINE (B CASH AND R CHOKSHI, SECTION EDITORS)

Inflammation and Neoplasia of the Pouch in Inflammatory Bowel Disease

Freeha Khan[1] · Bo Shen[1]

Published online: 28 February 2019

Abstract

Purpose of Review Ileal pouch-anal anastomosis (IPAA) is the standard restorative procedure after proctocolectomy in patients with inflammatory bowel disease who require colectomy. The ileal pouch is susceptible to a variety of adverse outcomes including mechanical insult, ischemia, and infectious agents. There is also a risk for developing low-grade dysplasia (LGD), high-grade dysplasia (HGD), or even adenocarcinoma in the pouch. The purpose of this review is to highlight risk factors, clinical presentation, surveillance, and treatment of pouch neoplasia.

Recent Findings Patients with pre-colectomy colitis-associated neoplasia are at high risk for developing pouch neoplasia. Other purported risk factors include the presence of family history of colorectal cancer, the presence of concurrent primary sclerosing cholangitis, chronic pouchitis, cuffitis, or Crohn's disease of the pouch. Pouch adenocarcinoma tends to have a poor prognosis.

Summary It is recommended to have a combined clinical, endoscopic, and histologic approach in diagnosis and management. Surveillance and management algorithms of pouch neoplasia are proposed, based on the risk stratification.

Keywords Dysplasia · Histopathology · Ileal pouch · Inflammatory bowel disease · Neoplasia · Pouchoscopy · Surveillance

Abbreviations

ATZ	Anal transitional zone
CAN	Colitis-associated neoplasia
CD	Crohn's disease
CRC	Colorectal cancer
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
FAP	Familial adenomatous polyposis
HGD	High-grade dysplasia
IBD	Inflammatory bowel disease
IND	Indefinite for dysplasia
IPAA	Ileal pouch-anal anastomosis
LGD	Low-grade dysplasia
PSC	Primary sclerosing cholangitis
UC	Ulcerative colitis

This article is part of the Topical Collection on *Large Intestine*

✉ Bo Shen
shenb@ccf.org

[1] Department of Gastroenterology/Hepatology/Nutrition, Cleveland Clinic, Cleveland, OH, USA

Introduction

Ileal pouch-anal anastomosis (IPAA) is the standard surgical procedure after proctocolectomy in patients with ulcerative colitis (UC) or familial adenomatous polyposis (FAP) who require colectomy. Surgical intervention is a common therapy for UC patients with medically refractory disease, poor tolerance of medicines, and colitis-associated neoplasia (CAN). The goal of surgical therapy with IPAA is to remove the diseased colon with as little alteration of normal physiological functions and lifestyle as possible. Long-term follow-up studies have shown promising functional outcomes of IPAA [1–3]. However, removal of diseased colon does not completely eliminate the risk for neoplasia of the pouch. Pouch neoplasia includes a spectrum of neoplastic changes ranging from dysplasia to adenocarcinoma. Pouch neoplasia is defined as the presence of histologic evidence of low-grade dysplasia (LGD), high-grade dysplasia (HGD), or colorectal cancer (CRC) at the anal transitional zone (ATZ) or cuff, or less often in the pouch body or afferent limb. It is recommended to have a combined clinical, endoscopic, and histologic approach in diagnosis and management for pouch neoplasia as well as other pouch disorders. High-risk patients such as those with preoperative CAN should undergo routine surveillance pouchoscopy.

Incidence of Pouch Dysplasia

There are two large studies in the incidence of pouch neoplasia. A institution database study showed that the cumulative incidence of pouch neoplasia after IPAA was reported to be 1.3% and 4.2% at 10 and 20 years, respectively [5••]. A separate study from the Netherlands documented a cumulative incidence of 2.0 and 6.9% at 10 and 20 years, respectively [4••]. In a study of Dutch Pathology Registry, 1200 patients were identified with inflammatory bowel disease (IBD) who had undergone IPAA. In a median follow-up of 6.5 years, 25 (1.83%) developed pouch neoplasia, with 16 adenocarcinomas. Furthermore, subanalysis showed that the cumulative incidences at 5, 10, 15, and 20 years for overall pouch dysplasia were 0.3%, 0.5%, 1.6%, and 3.7%, respectively. The cumulative incidences at 5, 10, 15, and 20 years for pouch carcinoma were 0.6%, 1.4%, 2.1%, and 3.3% [4••]. According to the Cleveland Clinic study of 3202 patients, the cumulative incidences for pouch neoplasia at 5, 10, 15, and 20 years were 0.9%, 1.3%, 1.9%, and 4.2% [5••]. Our data showed that only 11 (0.36%) patients developed adenocarcinoma of the ATZ or pouch [5••].

Risk Factors

The exact pathogenesis of pouch-associated neoplasia is unknown. History of colorectal dysplasia or CRC prior to IPAA is a known independent risk factor for pouch neoplasia [6]. Other reported risk factors for pouch neoplasia are a preoperative diagnosis of UC-associated dysplasia or the presence of CAN before or at the time of colectomy [5••, 7]. According to the Dutch study referenced above, the reported hazard ratios were 3.76 (95% confidence interval, 1.39–10.19) for prior dysplasia and 24.69 (95% confidence interval, 9.61–63.42) for prior carcinoma [4••]. Based on our recent results, both prior colorectal dysplasia and carcinoma were risk factors for pouch-associated neoplasia, with respective hazard ratios of 3.76 (95% confidence interval, 1.39–10.19; $P = .009$) and 24.69 (95% confidence interval, 9.61–63.42; $P < .001$), respectively [5••].

The presence of CRC or precolectomy colon dysplasia is associated with an estimated 25- and 4-fold increase in risk, respectively, of developing pouch neoplasia [4••]. The presence of type C mucosa (persistent atrophy with severe inflammation) of the pouch, concurrent primary sclerosing cholangitis (PSC), a family history of CRC, and a long duration of underlying UC constitute other reported risk factors [8]. Chronic pouch inflammatory conditions, such as Crohn's disease (CD) of the pouch, chronic pouchitis, or chronic refractory cuffitis, may also increase the risk for the development of neoplasia (Table 1).

Clinical Presentation of Pouch Neoplasia

There are no specific symptoms associated with pouch neoplasia. Patients often present with symptoms of diarrhea and abdominal cramps from concurrent pouchitis, CD of the pouch, or cuffitis [9]. Systemic presentations, such as fever, anemia, and weight loss may occur from the inflammatory conditions of the pouch. However, patients with pouch neoplasia can be totally asymptomatic.

Endoscopic Features of Pouch Neoplasia

Pouchoscopy with biopsy is the gold standard for the early detection and diagnosis of pouch neoplasia. Image-enhanced endoscopy such as narrow banding imaging and chromoendoscopy can be used in conjunction with conventional white-light endoscopy (Fig. 1). Commonly seen endoscopic features are polypoid lesions, ulcerated lesions, or flat dysplasia in cuff (Fig. 2) [10]. Large, such as more than 1 cm, polypoid lesions of the pouch or ATZ should be removed to rule out neoplasia (Fig. 3). Literature review shows that 8.7% (2 of 23) of those polyps were found to be neoplastic. Endoscopic visible lesion may not be seen in some cases. This is particularly the case in those with mucosectomy and handsewn anastomosis for precolectomy CAN.

It is advisable to take six to nine pieces of biopsies from the ATZ or cuff, pouch body, and afferent for surveillance purpose. In patients with a preoperative diagnosis of CAN, it is recommended to take deep or tunnel biopsy of ATZ or cuff. Furthermore, polyps, strictures, and deep ulcers, or any abnormal or suspicious areas, should also be biopsied (Fig. 4).

The accuracy of surveillance endoscopy may be improved with image-enhanced pouchoscopy, such as chromoendoscopy and narrow band imaging (Fig. 1).

Histologic Features of Pouch Neoplasia

Histologic features of pouch neoplasia range from no dysplasia, indefinite for dysplasia (IND), LGD, HGD, to cancer [10]. The diagnosis of pouch dysplasia is based on the presence of a combination of microscopic features, including architectural alterations resulting from repair in chronic pouchitis and cytological abnormalities, after eliminating the possibility of regenerative and inflammatory changes that may affect the mucosa in chronic pouchitis [11]. Pathology specimen of LGD shows crypts lined by epithelium with enlarged and hyperchromatic nuclei. Pouch biopsy with HGD usually

Table 1 Risk factors for pouch neoplasia

	Risk factors
Established risk factors	Precolectomy colorectal cancer
	Precolectomy colorectal dysplasia
Purported risk factors	Long-standing ulcerative colitis
	Primary sclerosing cholangitis
	Chronic pouch inflammation (pouchitis, Crohn's disease, and cuffitis)
	Family history of colon cancer
	Type "C" pouch mucosa

depicts glands with marked pleomorphisms, high nuclear to cytoplasmic ratio, and abnormal mitotic figure [11]. Deep or tunnel biopsy may show adenocarcinoma underneath squamous layer. Pouch adenocarcinoma often seems to be mucinous and poorly differentiated type features on histopathology. Pouch and peri-pouch adenocarcinoma has morphologic similarities to UC-associated colonic adenocarcinoma with a reported frequency of tumor-infiltrating lymphocytes (66.7%), the lack of dirty necrosis (91.6%), mucin differentiation (58.3%), signet ring cell differentiation (25%), heterogeneity (20%), well differentiation (25%), and poor differentiation (41.6%) [11]. Fifty percent of pouch and peri-pouch adenocarcinomas have Crohn-like appearance [11].

It is strongly recommended to obtain adequate number of biopsy samples and to treat underlying mucosal inflammation in order to increase diagnostic accuracy. The pathology evaluation for pouch surveillance biopsy should clearly report the presence or absence of dysplasia. It would be ideal to have the diagnosis of pouch neoplasia verified by at least two expert gastrointestinal pathologists with a focus in IBD.

Natural History of Pouch Neoplasia

The natural history of pouch neoplasia has not been fully examined. Cuff or ATZ is the most common site of development of pouch neoplasia [4••]. LGD is the most frequently reported form of pouch neoplasia. Clinical course, natural history, and management of LGD are yet to be defined. LGD tend to relapse; however, if all LGD had advanced into HGD or cancer, the risk for developing pouch cancer may be higher [4••, 12].

The overall prognosis of pouch adenocarcinoma seems to be poor. Our previous study investigated 44 patients with LGD, HGD, or adenocarcinoma in IPAA. Of the 22 patients with an initial diagnosis of pouch LGD, 6 had persistence or progression after a median follow-up of 9.5 years. Of the 12 patients with pouch HGD, 5 had a history of synchronous pouch LGD. Pouch HGD either persisted or progressed in 3 patients after the initial management, in a median time interval of 5.4 years. Of the 14 patients with pouch adenocarcinoma, 12 had a history of or synchronous dysplasia. After a median follow-up of 2.1 years, 6 patients with pouch cancer died [8].

Indefinite for dysplasia is a histopathological term that has been used to describe a range of atypical dysplastic features with concurrent inflammatory changes [13]. A large number of patients with IND were noted to have concurrent mucosal inflammation on endoscopy and histology. The natural history of IND seems to be benign and progression to dysplasia or cancer is rare. However, the progression of IND or even chronic inflammation to neoplasia in UC patients is not uncommon. It does not reach the threshold for a confirmed diagnosis of true dysplasia by pathologists, and interobserver consensus in classifying IND and LGD among GI pathologists has been poor.

Literature review indicated that 5-year progression rates to advanced neoplasia in patients with flat LGD and IND were 37% and 5%, respectively [14]. There are no clear guidelines

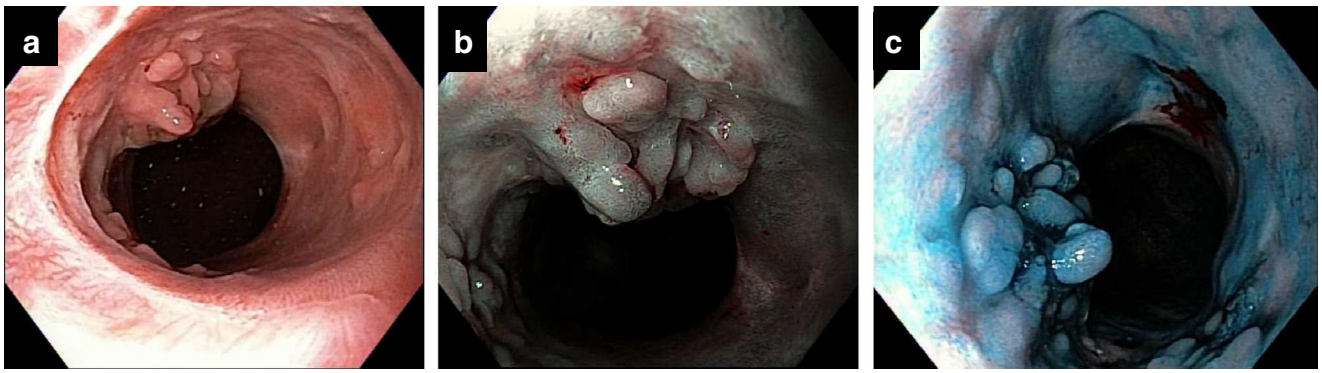

Fig. 1 Hyperplastic lesions in the cuff, on white light (**a**), narrow band imaging (**b**), and chromoendoscopy (**c**)

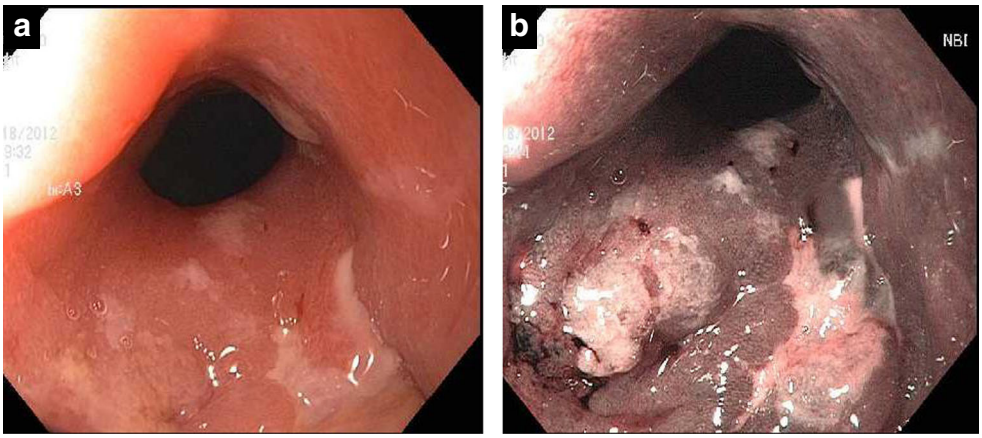

Fig. 2 Low-grade dysplasia in the cuff on white light (**a**) and narrow band imaging (**b**)

on the management of IND. It is advisable to have a repeat pouchoscopy and image-enhanced endoscopy with extensive biopsy, along with satisfactory control of concurrent inflammation.

Endoscopy Surveillance for Pouch Neoplasia

Postoperative surveillance enables clinicians to detect dysplasia or cancer at an early stage. Currently, there is no consensus or published guidelines for endoscopy surveillance for pouch neoplasia between professional societies. In some institutions, patients undergo surveillance endoscopy every 1–3 years at the discretion of the IBD specialist or colorectal surgeon.

The British Society of Gastroenterology advocates an annual pouch endoscopy for high-risk patients. Patients with previous rectal dysplasia, dysplasia, or cancer at the time of pouch surgery, persistent atrophy, PSC, or type C mucosa of pouch, and severe inflammation fall under high-risk group and require closer monitoring [15]. Patients, who are not at high risk, may undergo surveillance every 5 years.

Our recent study analyzed survey filled out by 52 eligible participants from 32 tertiary institutions. Forty-one physicians (79%) felt that surveillance pouchoscopy was mandatory and 36 (69%) believed that pouchoscopy with biopsy was effective for the detection of pouch neoplasia. Therefore, more than half of the physicians (55%) preferred that pouchoscopy should be performed every 2–3 years solely for the surveillance of pouch neoplasia. Twenty-three percent of the physicians agreed that surveillance pouchoscopy should be performed on annual basis, while 18% chose an individualized plan. Only 2% of the physicians preferred a 5-year surveillance protocol [16••]

It is strongly recommended to have a more aggressive approach, since the natural history of pouch neoplasia is poorly defined and the prognosis of pouch cancer is dismal. It is important to consider a standard surveillance protocol, taking into account the individual risk factors instead.

We have composed a surveillance algorithm for pouch neoplasia (Fig. 5 and Fig. 6). We suggest that surveillance pouchoscopy and biopsy should be performed every 1–3 years, beginning 10 years after the initial diagnosis of UC in patients without risk factors. In high-risk patients, such as those with UC diagnosis for more than 10 years, chronic pouchitis or cuffitis, type C mucosa, marked inflammation in the lamina propria along with villous atrophy, family history of CRC in a first-degree relative, or PSC, pouchoscopy and biopsy should be done every 1 to 2 years. In patients with preoperative neoplasia of the colon and/or rectum, pouchoscopy and biopsy should be performed annually, with focus on the cuff or ATZ [9, 17, 18]. It may be

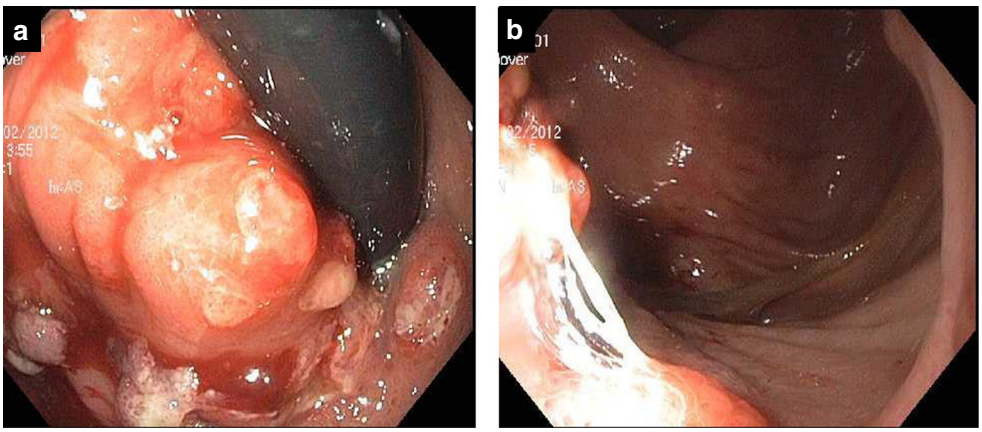

Fig. 3 Endoscopic polypectomy in a patient with distal pouch polyp (**a**, **b**)

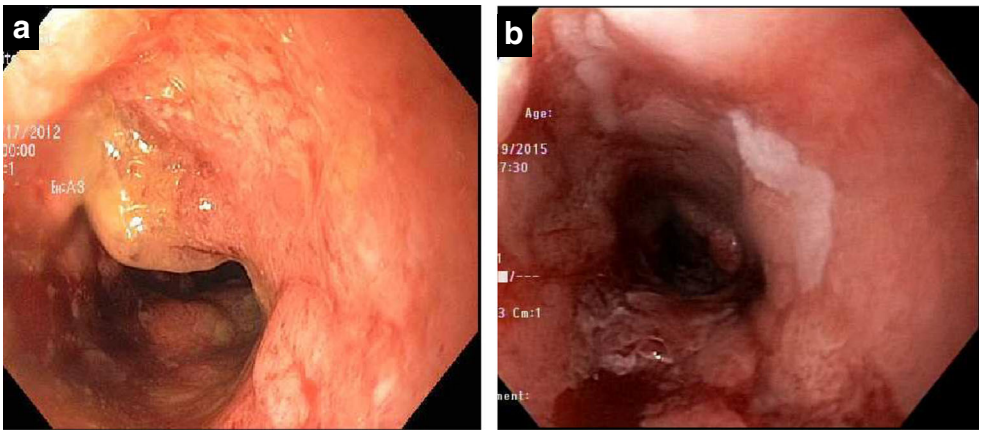

Fig. 4 Pouch cancer from chronic cuffitis. Chronic mild cuffitis (**a**). Deep biopsy showing cancer 3 years later (**b**)

prudent to biopsy patients with LGD at intervals of 3 to 6 months, even after the lesion has been endoscopically removed. Furthermore, more aggressive surveillance protocol may be necessary in large referral centers where the likelihood of detecting pouch neoplasia is higher.

It is possible to miss dysplasia or even cancer on endoscopy surveillance. Some patients may not exhibit endoscopically visible lesions even at advanced stages of pouch cancer. New techniques such as imaging-enhanced endoscopy or fecal DNA testing, which are more capable of detecting neoplasia, may be considered in the surveillance plan for high-risk patients with ileal pouches [9, 19].

Treatment of Pouch Neoplasia

There is limited literature available on the management of pouch neoplasia. Isolated polypoid LGD can be safely treated with polypectomy or endoscopic mucosal resection (EMR) with close endoscopic surveillance. EMR or endoscopic submucosal dissection (ESD) may be attempted for well-defined, small (< 1–2 cm) endoscopically liftable, unifocal LGD. Preferably, the lesion should be excised en bloc. In addition, adjacent mucosa should be extensively biopsied. Patients with unifocal slightly raised LGD should have pouchoscopy with biopsy performed, with or without prior endoscopic ablation, every 2–3 months × 2, then every year if dysplasia is not detected in the subsequent biopsies [9].

Patients with pouch cancer, HGD, persistent, multifocal LGD, or flat LGD, or HGD typically require surgical intervention [10]. Some authors proposed surgical mucosectomy and pouch advancement procedure while others advocated pouch excision for pouch-associated HGD [4••, 20, 21]. Surgical interventions, such as complete proctectomy, may be necessary, particularly for patients with risk factors for neoplastic progression or recurrence, such as preoperative diagnosis of CAN or family history of CRC [4••]. If pouch HGD persists, it should be appropriately treated with pouch excision [4••]. Since pouch neoplasia appears to have a poor prognosis, early detection of dysplasia with surveillance pouchoscopy surveillance may salvage the pouch [10] (Fig. 6).

The reported benefits or risks of administration of preoperative and/or postoperative chemotherapy or radiation therapy for the treatment of colitis-associated colorectal caner remains controversial. It is reported that adjuvant chemotherapy is safe in those patients with non-diverted pouches [22]. However, pelvic radiation therapy for the treatment of pouch cancer can compromise pouch [9].

Whether pouch cancer in patients with a prior history of handsewn anastomosis or stapled anastomosis should

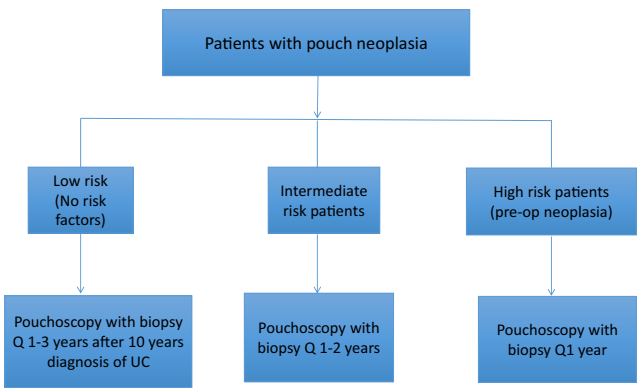

Fig. 5 Surveillance algorithm for pouch neoplasia

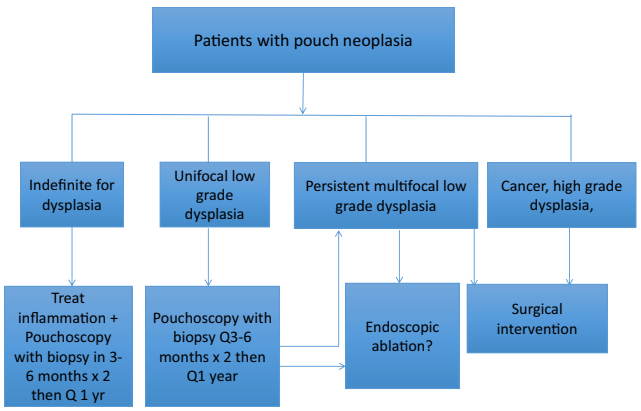

Fig. 6 Management algorithm for pouch neoplasia

be treated differently is not known. A recent study compared incidence of pouch neoplasia after stapled IPAA versus handsewn IPAA. They established that handsewn IPAA with mucosectomy should be performed in patients with dysplasia or cancer, which may account for the decreased risk of postoperative neoplasia [23••]. Buried cancer or lateral spreading phenotype of pouch cancer is common. Therefore, aggressive surgical treatment of pouch cancer is recommended.

Summary

Ileal pouch-anal anastomosis is the standard restorative procedure after proctocolectomy in patients with IBD who require colectomy. The ileal pouch is prone to some infrequent, but potentially detrimental adverse sequalae, such as pouch neoplasia. A combined clinical, endoscopic, and histologic examination plays an essential role in diagnosis and management. Proper follow-up is recommended to develop an optimal surveillance strategy in patients with suspected at risk for pouch neoplasia. Algorithm for surveillance and management is proposed (Figs. 5 and 6).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Delaney CP, Fazio VW, Remzi FH, Hammel J, Church JM, Hull TL, et al. Prospective, age-related analysis of surgical results, functional outcome, and quality of life after ileal pouch-anal anastomosis. Ann Surg. 2003;238:221–8.
2. Fazio VW, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, Kirat HT, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg. 2013;257:679–85.
3. Delaney CP, Remzi FH, Gramlich T, Dadvand B, Fazio VW. Equivalent function, quality of life and pouch survival rates after ileal pouch-anal anastomosis for indeterminate and ulcerative colitis. Ann Surg. 2002;236:43–8.
4.•• Derikx LA, Kievit W, Drenth JP, et al. Prior colorectal neoplasia is associated with increased risk of ileoanal pouch neoplasia in patients with inflammatory bowel disease. Gastroenterologia. 2014;146:119–28. **This registry-based study provides helpful information on association between prior dysplasia or colon cancer and risk of developing pouch neoplasia.**
5.•• 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. Gastroenterologia. 2010;139:806–12. **This is the first controlled study in pouch neoplasia based on a large institutional database**.
6. Althumairi AA, Lazarev MG, Gearhart SL. Inflammatory bowel disease associated neoplasia: a surgeon's perspective. World J Gastroenterol. 2016;22:961–73.
7. Remzi FH, Fazio VW, Delaney CP, Preen M, Ormsby A, Bast J, et al. Dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of prospective evaluation after a minimum of ten years. Dis Colon Rectum. 2003;46:6–13.
8. Wu XR, Remzi FH, Liu XL, Lian L, Stocchi L, Ashburn J, et al. Disease course and management strategy of pouch neoplasia in patients with underlying inflammatory bowel diseases. Inflamm Bowel Dis. 2014;20:2073–82.
9. Liu ZX, Kiran RP, Bennett AE, Ni RZ, Shen B. Diagnosis and management of dysplasia and cancer of the ileal pouch in patients with underlying inflammatory bowel disease. Cancer. 2011;117:3081–92.
10. Schaus BJ, Fazio VW, Remzi FH, Bennett AE, Lashner BA, Shen B. Clinical features of ileal pouch polyps in patients with underlying ulcerative colitis. Dis Colon Rectum. 2007;50:832–8.
11. Gonzalo DH, Collinsworth AL, Liu X. Common inflammatory disorders and neoplasia of the ileal pouch: a review of histopathology. Gastroenterology Res. 2016;9:29–38.
12. Ziv Y, Fazio VW, Sirimarco MT, Lavery IC, Goldblum JR, Petras RE. Incidence, risk factors, and treatment of dysplasia in the anal transitional zone after ileal pouch-anal anastomosis. Dis Colon Rectum. 1994;37:1281–5.
13. Liu ZX, Liu XL, Patil DT, Lian L, Kiran RP, Remzi FH, et al. Clinical significance of indefinite for dysplasia on pouch biopsy in patients with underlying inflammatory bowel disease. J Gastrointest Surg. 2012;16:562–71.
14. Van Schaik FD, Ten Kate FJ, Offerhaus GJ, et al. Misclassification of dysplasia in patients with inflammatory bowel disease: consequences for progression rates to advanced neoplasia. Inflamm Bowel Dis. 2011;17:1108–16.
15. Eaden JA, Mayberry JF. British Society for Gastroenterology, Association of Coloproctology for Great Britain and Ireland. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut. 2002;5:10.
16.•• Gu J, Remzi FH, Lian L, et al. Practice pattern of ileal pouch surveillance in academic medical centers in the United States. Gastroenterol Rep. 2016;4:119–24. **Authors provided information on performing pouchoscopy and biopsy for surveillance of ileal pouch neoplasia from fifty-two eligible participants from 32 tertiary institutions.**
17. Gadacz TR, McFadden DW, Gabrielson EW, Ullah A, Berman JJ. Adenocarcinoma of the ileostomy: the latent risk of cancer after colectomy for ulcerative colitis and familial polyposis. Surgery. 1990;107:698–703.
18. Smart PJ, Sastry S, Wells S. Primary mucinous adenocarcinoma developing in an ileostomy stoma. Gut. 1988;29:1607–12.
19. Elkowitz D, Daum F, Markowitz J, Proccaccino J, Boas E, Cuomo J, et al. Risk factors for carcinoma of the pelvic ileal pouch/anal canal in ulcerative colitis. Ann Clin Lab Sci. 2004;34:143–9.
20. Coull DB, Lee FD, Henderson AP, Anderson JH, McKee RF, Finlay IG. Risk of dysplasia in the columnar cuff after stapled restorative proctocolectomy. Br J Surg. 2003;90:72–5.

21. Heuschen UA, Heuschen G, Autschbach F, Allemeyer EH, Herfarth C. Adenocarcinoma in the ileal pouch: late risk of cancer after restorative proctocolectomy. Int J Color Dis. 2001;16:126–30.
22. Zmora O, Spector D, Dotan I, Klausner JM, Rabau M, Tulchinsky H. Is stapled ileal pouch anal anastomosis a safe option in ulcerative colitis patients with dysplasia or cancer? Int J Color Dis. 2009;24:1181–6.
23.•• Ishii H, Hata K, Kishikawa J, et al. Incidence of neoplasias and effectiveness of postoperative surveillance endoscopy for patients with ulcerative colitis: comparison of ileorectal anastomosis and ileal pouch-anal anastomosis. World J Surg Oncol. 2016;14:75. **The study compared the incidence of pouch neoplasia after stapled IPAA versus hand- sewn IPAA.**