Risks and benefits of ileal pouch–anal anastomosis for ulcerative colitis

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is the surgical treatment of choice for patients with medically refractory ulcerative colitis (UC) or UC with dysplasia, and for the majority of patients with familial adenomatous polyposis. Colectomy substantially reduces the risk for UC-associated colonic neoplasia and for the long-term need of immunosuppressive medications. The pouch procedure is a safe operation, with a low postoperative mortality rate at 0–1%, which significantly improves patients' quality of life. However, patients with IPAA are susceptible to a number of surgical/mechanical, inflammatory and functional complications, such as anastomotic leaks, pelvic sepsis, pouchitis, Crohn's disease of the pouch, cuffitis and irritable pouch syndrome. IPAA may also impact the patient's sex life and fertility. There is also a small risk for the development of neoplasia of the anal transitional zone. These complications adversely affect the outcome and compromise the improvement in the patient's quality of life gained initially from the restorative proctocolectomy. Recognition and discussion of the advantages and disadvantages of IPAA will be helpful for patients and clinicians in decision-making regarding pursuing further medical therapy versus surgical intervention when their UC becomes refractory to conventional medical therapy.

KEYWORDS: ileal pouch–anal anastomosis ▪ inflammatory bowel disease ▪ pouchitis ▪ proctocolectomy ▪ quality of life

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There have been rapid advances in medical and surgical therapy for ulcerative colitis (UC), including the widespread use of immunomodulators and biological agents, and routine application of restorative proctocolectomy. Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) has become the surgical treatment of choice for patients with medically refractory UC or colitis-associated neoplasia, and for the majority of patients with familial adenomatous polyposis [1,2]. Approximately 30% of patients with UC eventually require colectomy, and the majority of these patients elect to have an IPAA [3]. The standard surgical procedure for patients with UC before the advent of IPAA was proctocolectomy with a Brooke ileostomy or, in some cases, continent ileostomy. Since its introduction in 1978, IPAA has become increasingly popular, owing to the fact that bowel continuity is maintained. Immediately following the IPAA surgery, the initial functional outcome is affected by a high evacuation frequency with anal incontinence in some patients. However, the overall functional result gradually improves and the evacuation frequency decreases and stabilizes to four to seven evacuations/day as the pouch is becoming 'mature'. While undergoing IPAA is not necessarily a step to cure UC, the procedure does offer a way for patients to reduce the use of medicines and, therefore, medicine-associated adverse effects, avoid permanent ileostomy, decrease the risk for dysplasia, and improve health-related quality of life (QOL) [4].

On the other hand, IPAA is often accompanied by a number of complications even when performed by an experienced surgeon. Similar to most natural anatomy-altering surgical procedures, IPAA has a 'price tag'. There is significant incidence of early postoperative morbidities, including small bowel obstruction, ileus, anastomotic stricture, anastomotic leaks and pelvic abscess [4]. In the long term, patients with IPAA are susceptible to a number of inflammatory and noninflammatory complications, such as pouchitis, Crohn's disease (CD) of the pouch, cuffitis and irritable pouch syndrome (IPS), which adversely affect the outcome and compromise the patient's health-related QOL [5].

Pouchitis is the most frequent long-term complication of IPAA in patients with UC, with a cumulative prevalence of up to 50% [1,2,6]. In addition, IPAA surgery can be associated with significant adverse sequelae, and may lead to pouch excision or permanent diversion in 4–10% of cases [7–10]. A meta-analysis comprising 43 studies and 9317 patients reported

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the frequency of pouch failure to be 7% with a median follow-up period of 37 months; the frequency increased to 9% after more than 60 months [11]. Pelvic sepsis [12,13], chronic pouchitis and CD of the pouch are the leading causes of pouch failure [6,12,13]. In addition, patients are also susceptible to other problems, including infertility, particularly in women, and sexual dysfunction in both sexes [4,14].

Although some studies highlight that the QOL is substantially higher following IPAA surgery [15,16], others reported only a minimal change [17] or, in fact, a lower QOL following surgery [18]. The discrepancy may largely be explained by the disease status of the ileal pouch. Given the available data, it is crucial to balance the risks and benefits of medical and surgical therapies for clinical decision-making when the clinician is confronted with a challenging patient with refractory disease and when surgery may be contemplated.

The main goals of this article are to provide information on the advantages and disadvantages of surgical therapy for UC, and to discuss the current status in management of complications associated with IPAA.

Review criteria

In April 2010, we searched MEDLINE from 1978 to the present using the Medical Subject Heading terms pouchitis, restorative proctocolectomy, QOL and restorative proctocolectomy, benefits and restorative proctocolectomy, infertility and restorative proctocolectomy, CD and restorative proctocolectomy, pelvic sepsis and restorative proctocolectomy, pouchitis and classification, and the key term 'restorative proctocolectomy'. Full papers and abstracts without language restrictions were considered. Important developments in research, reports from centers of excellence, and our own research developments form the basis of this review article. In addition to the published literature, we have incorporated our own experience into this article, taking advantage of a large patient volume at the subspecialty Pouchitis Clinic.

Construction of IPAA & its benefits over medical therapy

Ileal pouch–anal anastomosis surgery was developed by Sir Alan Parks and John Nicholls in 1978, where the ileal pouch reservoir was anastomosed to the dentate line using a perianal suturing technique [19]. The surgery involves removal of the colon and rectum, construction of a reservoir or pouch from the distal 30–40 cm of ileum, followed by an IPAA. The anastomosis can either be constructed with staple or hand-sewing techniques. The hand-sewn technique typically combines mucosectomy, which involves stripping of the columnar mucosa above the dentate line [20]. While mucosectomy may decrease the risk for cuffitis and, theoretically, the risk for dysplasia at the anal transitional zone (ATZ), it may be associated with a higher incidence of anal leakage and soiling than those without mucosectomy [21]. This is because mucosectomy involves excision of mucosa at the ATZ, an area of cuboidal epithelium richly innervated by sensory nerve endings that mediate anal sampling reflexes [22]. Conversely, the advent of stapling instruments greatly simplified IPAA surgery. The staple technique without mucosectomy may reduce the risk for incontinence. Staple technique leaves a 1–2 cm cuff of residual rectum *in situ*, which may become inflamed (cuffitis) and may be at risk for dysplasia. In a large study involving 3109 patients with IPAA, patients who underwent a stapled IPAA had better outcomes and QOL than those undergoing a hand-sewn IPAA [23]. For the last decade, the stapled IPAA has become the preferred approach.

Ulcerative colitis is considered to be a life-long disease that requires long-term therapy. Step-up medical therapy is routinely applied, starting from 5-aminosalicylic acid (5-ASA) compounds, corticosteroids, immunomodulators and biologics. With life-long treatment, there are always concerns regarding patients' compliance to medical therapy, cost and side effects of medications, and dysplasia risk. IPAA would be beneficial and may circumvent this problem by offering an option to patients who do not want to continue life-long medications and may minimize medication use.

Pouch surgery is aimed to deliver four to seven semiformed bowel movements per day, with no nighttime evacuation and no incontinence. However, approximately half of patients have the need to evacuate at night time. Urgency is uncommon (5%), but appears to increase with time [24,25]. With regard to functional QOL in patients with IPAA, fecal leakage during the day occurs in less than 4% of patients. Seepage during the day and at night occurs in 7 and 9% of patients, rising to 11 and 18%, respectively, 25 years after IPAA. Antidiarrheal medication is required in approximately a third of patients after 10 years and in 45% of patients after 25 years [26]. Successful outcomes are built upon

sensible patient selection, clear preoperative counseling, an operative strategy appropriate to the patient and expedient management of complications.

Problems with adherence to medical therapy

Nonadherence has been observed in a significant proportion of patients with UC. Reported prevalence rates for nonadherence varied from 35 to 72% [27–30]. In a retrospective survey of inflammatory bowel disease (IBD) patients, the overall compliance rate with a maintenance dose of mesalamines was only 40%. The median dosage of medication dispensed per patients was 71% of the prescribed regimen [28]. Noncompliant patients were more likely to be male, single and to have disease limited to the left colon [28]. Nonadherence rates in pediatric IBD patients have ranged from 50 to 66% [31,32]. Nonadherence is more of a problem in children and adolescents than adults, given the complex challenges unique to childhood and adolescence, including the maturation of cognitive and behavioral patterns (e.g., health beliefs) that affect self-management.

Long-term use of immunomodulators, which requires periodic monitoring of laboratory tests, may pose particular challenge for patients' compliance. In a study of 159 patients with CD or UC who were treated with azathioprine (AZA), 13% of the patients were found to be noncompliant based on measurement of serum metabolite concentration [33]. The noncompliant rate was even higher in patients with combination therapy of 5-ASA and immunomodulators [34]. Noncompliant patients had a higher risk for disease relapse than compliant ones [33,35]. For example, patients who were noncompliant to mesalamine therapy had a fivefold higher risk of relapse compared with patients who took at least 80% of their prescribed dose [35]. Given the problems with nonadherence, IPAA surgery may be beneficial in these patients, and may remove the need for life-long medications or minimize the use of medications in patients with good outcomes after IPAA surgery.

Adverse effects of medications

Medications used in the treatment of IBD are associated with a number of adverse effects. Sulfasalazine consists of sulfapyridine linked to 5-ASA (mesalamine and mesalazine) via an azo bond. However, its use is limited by high rates of intolerance among patients. Side effects can include headache, abdominal pain, nausea, vomiting, skin rash, fever, hepatitis, hematologic abnormalities, folate deficiency, pancreatitis, systemic lupus erythematosus and male infertility [36]. Sulfapyridine, a sulfonamide moiety has been suggested to be responsible for hypersensitivity reactions. Sulfasalazine-induced hepatotoxicity manifests as an elevation of aminotransferases, hyperbilirubinemia, and, less commonly, fever, hepatomegaly, lymphadenopathy and granulomatous liver disease [37]. Hepatotoxicity can also be a part of a hypersensitivity reaction [37].

Similarly, thiopurines (AZA and 6-mercaptopurine [6-MP]) used in the treatment of IBD are associated with liver toxicity [37]. Hepatotoxicity usually manifests as an elevation in aminotransferases, accompanied by flu-like symptoms. In some patients, it can present as an isolated cholestatic enzyme elevation. Abnormal liver function tests usually return to normal after discontinuation of the agents [37]. 6-MP/AZA-induced hepatotoxicity may occasionally be idiosyncratic in nature with a rare presentation with veno-occlusive disease [38]. Acute pancreatitis is also reported with 6-MP/AZA use in IBD. Pancreatitis is an early adverse reaction after initiation of treatment and usually occurs within 3–4 weeks of therapy. The drug-induced pancreatitis is considered to be idiosyncratic and dose independent [39]. Hepatotoxicity is also an important concern for prolonged administration of methotrexate [37].

Corticosteroids used in the management of UC are associated with severe and irreversible side effects. The frequency of adverse events in IBD patients has been reported to be as high as 555/100 patient years [40]. There are a number of short-term adverse effects, including weight gain, fluid retention, psychiatric disturbance, hyperglycemia, hypokalemia, aseptic necrosis of the bone, myopathy, immune suppression and hypertension. In addition to the myriad of short-term adverse effects, it also causes long-term effects, including skin changes, osteoporosis, cataracts and growth retardation in children [41]. Osteoporosis can occur in up to 50% of patients and result in spontaneous fractures [42]. Patients are also at risk of adrenal suppression depending on the duration, dosage and formulation used [43].

In addition, patients who are taking steroids are at increased risk of infectious complications. A meta-analysis of randomized studies of patients taking steroids found a higher rate of infections compared with placebo (relative risk: 1.4, 95% CI: 1.1–1.7) [44]. In a study from

the Mayo Clinic (MD, USA), patients who received corticosteroid therapy were approximately two- to three-times more likely than similar patients who did not receive corticosteroids to develop an opportunistic infection [45]. In the study, corticosteroid use was associated with infections of the mouth, pharynx or esophagus with candidiasis [45]. When combined with AZA/6-MP, the relative risk for opportunistic infection was higher than with corticosteroids alone, indicating a synergistic effect in the predisposition to such infections. Patients who received greater exposure to corticosteroids were exposed to a higher risk of opportunistic infections than those with lower exposures.

The use of anti-TNF agents is also associated with a number of adverse effects, including activation of latent tuberculosis, infusion reactions, hypersensitivity reactions and possible association with lymphoma [46]. Hepatosplenic T-cell lymphoma has been described in IBD patients treated with anti-TNF drugs, including infliximab and adalimumab, particularly in combination with immunomodulators [37]. However, reports from the manufacturer maintained that The Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry with a voluntary reporting system suggest that serious infection from infliximab-treated CD patients appeared to be associated with concurrent use of corticosteroids or narcotic analgesics rather than infliximab itself [47].

Since infliximab was approved by the US FDA for the treatment of moderate-to-severe UC, the agent has been used extensively in clinical practice. However, routine use of anti-TNF agents in UC may have a negative impact on postoperative course in patients who eventually fail the medical therapy and undergo restorative proctocolectomy. The risk of postoperative complications in UC patients with preoperative use of infliximab has been studied [48,49]. After adjusting for age, high-dose corticosteroids, AZA and severity of colitis, infliximab use remained significantly associated with infectious complications, with an odds ratio of 2.7 in the multivariable analysis [48]. In our study, preoperative infliximab use was also found to be associated with an increased risk for three-stage restorative proctocolectomy, instead of the traditional two-stage procedure, and increased risk of postoperative complications [49].

Cyclosporine has been used for the treatment of moderate-to-severe UC in some institutions, even in the era of biologics. In a recent multicenter study from Europe, safety of infliximab was evaluated in patients with steroid-refractory UC who did not respond to cyclosporine [50]. A total of 51 patients with steroid-refractory UC and cyclosporine failure were included. Of the 51 patients, 15 (29%) underwent colectomy within a median of 5 weeks. The rate of adverse events was 25%, including six infections, three infusional reactions, one leukopenia, one bowel perforation and one peripheral neuropathy. One death occurred in a 40-year-old man, which was caused by pneumonia after he underwent surgery 10 days after the first infliximab infusion [50].

A variety of medications used in the management of IBD can affect fertility and pregnancy, although UC itself appears to have no adverse effects on fertility in females [51] or males [52]. Among the medications, sulfasalazine has been clearly associated with male infertility and abnormalities in sperm count, motility and morphology [53]. An association between sulfasalazine use in the parent and congenital malformations in the progeny has also been described [54]. AZA and 6-MP do not appear to reduce semen quality in men with IBD [55]. Infliximab treatment in men may decrease sperm motility and morphology [56]. Congenital malformations were more commonly reported in babies of mothers with CD than those whose mothers had UC or controls (7.9 vs 3.4 vs 1.7%) [57]. In addition, use of purine analogs by both men and women treated for IBD has been associated with congenital abnormalities [58]. Association between the use of corticosteroids and stillbirth has been demonstrated [59]. However, the fertilty can also be an issue for IPAA. In general, patients with IPAA have an increased risk for infecundity. Therefore, impact of medical verus surgical therapy on fertility should be discussed with gestational-age patients.

Risk for neoplasia with medical therapy

The risk for dysplasia and cancer is one of the major concerns for UC patients. Retrospective and prospective studies have failed to conclusively resolve the question of efficacy of surveillance to decrease mortality. In addition, the cost of dysplasia surveillance in UC can be expensive. Colectomy with IPAA would be advantageous, as the diseased colon is removed. Although a small risk of malignant transformation in the ATZ remains, the risk is much lower than an intact colon left behind. A meta-analysis of published studies reported that the overall risk for

colorectal cancer was 2% after 10 years, 8% after 20 years and 18% after 30 years of diagnosis [60]. This is much higher than in patients with IPAA. In our recent study, the cumulative incidence for pouch neoplasia at 5, 10, 15, 20 and 25 years were 0.9, 1.3, 1.9, 4.2 and 5.1%, respectively [61]. Therefore, IPAA surgery offers the option of substantially reducing the risk of neoplasia in patients with UC.

While colectomy is considered as the most effective way to reduce cancer risk, the role of medical therapy in reducing the risk of neoplasia in UC is still controversial. There are several epidemiologic studies that have identified long-term 5-ASA therapy as a factor that significantly reduces the risk of developing colorectal cancer [62,63]. A meta-analysis was performed to evaluate three cohort and six case–control studies, and consisted of 334 cases of colorectal cancer, 140 cases of dysplasia and 1932 UC patients [64]. Pooled analysis demonstrated a protective association between 5-ASA use and colorectal cancer alone (odds ratio: 0.51; 95% CI: 0.37–0.69) or the combined end point of colorectal cancer and dysplasia (odds ratio: 0.51; 95% CI: 0.38–0.69) [64]. The chemopreventive effect of 5-ASAs needs to be further verified.

Limitations of surveillance colonoscopy

Patients under medical treatment will eventually need surveillance colonoscopy. Annual or biannual surveillance colonoscopy should be performed 8–10 years after diagnosis of extensive UC [65]. There are potential problems with surveillance, which could be contributed by factors such as costs, compliance and pathologic interpretation. Studies have shown that compliance to surveillance can be diminished when a patient is asymptomatic and poor compliance could increase the risk for cancer. The only study to directly address the outcomes in patients documented to be noncompliant with annual surveillance was a cohort of 121 patients with UC, in which after more than 7 years seven patients had developed cancer [66]. Two of these seven had not complied with recommendation for repeat colonoscopy or colectomy after dysplasia. The patients had quiescent disease and presented years later with obstructive symptoms related to the tumor.

However, the impact of routine surveillance colonoscopy on survival of UC patients is not clear. There are no randomized trials assessing the impact of surveillance on mortality from colorectal cancer in UC patients. However, some cohort studies of surveillance reported survival benefits. For example, a study of 41 patients with colorectal cancer arising in the setting of UC showed that the 5-year survival was 77% in UC patients on an surveillance program compared with 36% 5-year survival of those on no surveillance [67]. By contrast, some investigators questioned the usefulness of surveillance in UC patients [68]. Retrospective and prospective studies have failed to conclusively resolve the question of efficacy of surveillance to decrease mortality. In addition, the cost of detecting cancer in UC can be expensive. It was estimated that it requires approximately US$71,000 [69] or $200,000 [70] per cancer detected. Mathematical models suggest that longer intervals between surveillance colonoscopies are more cost effective until the disease duration reaches 20 years [71].

Controversy on surveillance versus colectomy for low-grade dysplasia

Based on expert opinion, patients with high-grade dysplasia, flat low-grade dysplasia or multifocal low-grade dysplasia in flat mucosa should undergo colectomy [72]. Dysplasia-associated lesion or mass arising from UC is also an indication for colectomy. There has been no consensus regarding colectomy for patients with unifocal low-grade dysplasia [72]. Box 1 summarizes the adverse long-term effects of medications.

Box 1. Long-term risks of medical management of ulcerative colitis.

- Problems with adherence to medical therapy
- Adverse effects of medications:
  - Steroids
    - Osteoporosis
    - Growth retardation in children
    - Adrenal suppression
    - Infectious complications, in particular infections of the mouth, pharynx or esophagus with candidiasis
  - Anti-TNF agents
    - Activation of latent tuberculosis
    - Possible risk of lymphoma
    - Infectious complications
  - Thiopurines
    - Hepatotoxicity
    - Infectious complications
    - Lymphoma
  - Cyclosporine
    - Infections
    - Nephrotoxicity
    - Peripheral neuropathy
- Risk of colon neoplasia with medical treatment

Improved QOL

Ileal pouch–anal anastomosis surgery was designed to improve the QOL of patients. QOL is an important measure of operative outcome with any surgery. As the usual route of defecation and continence are maintained, it is reasonable to assume that IPAA offers a clear improvement in the QOL compared with ileostomy. QOL has been studied in UC patients following surgery and different scales to measure QOL have been investigated. Following IPAA surgery, bowel function is generally acceptable, and QOL is good and comparable to that of the general population. Numerous studies have examined the effects of surgery on QOL in patients with UC [73–76]. Some studies did not assess QOL before surgery and thus QOL improvements after surgery can be presumed to be from IPAA. Nevertheless, several investigators concluded that QOL in patients after colectomy was similar to that in the general population [73–75]. Although a substantial improvement in QOL compared with the preoperative level is often observed in patients with UC after IPAA [16,17], some studies reported either minimal change in general QOL when comparing pre-IPAA with post-IPAA values [18] or a lower QOL than published norms for the general population in postsurgical patients with UC [19]. QOL is usually better in surgically than medically treated patients, particularly in patients with severe UC who have extremely poor QOL before surgery; although the degree of improvement varies depending on disease activity and severity at the time of surgery and the surgical outcome [76]. Even with surgical complications, 90% of patients with IPAA were satisfied with the procedure, 95% would undergo the procedure again and 71% of patients felt no restriction in general after IPAA [77].

Risks of IPAA

Although restorative proctocolectomy with IPAA results in good functional outcomes and improved QOL in most patients, the procedure can fail in 4–10% of patients, necessitating excision of the pouch or indefinite fecal diversion [7–10]. While the short-term causes of pouch failure are often associated with the surgical technique, the long-term causes of failure include chronic pouch sinus, chronic pouchitis, CD of the pouch and refractory cuffitis. A meta-analysis comprising 43 studies and 9317 patients reported the frequency of pouch failure to be 7% with a median follow-up period of 37 months. However, with a follow-up period of more than 60 months, the frequency increased to 9% [11]. Pelvic sepsis [12,13], chronic pouchitis and CD of the pouch [6,12,13] are the most common causes of pouch failure.

Ileal pouch–anal anastomosis surgery is associated with a number of problems that can be classified as surgical or mechanical, infectious or inflammatory, functional, dysplastic or neoplastic, and systemic complications.

Surgical complications

Anastomotic leaks

Patients with IPAA are at risk of anastomotic leaks. Anastomotic leak occurs in patients as a result of a separation that usually occurs at the pouch–anal anastomosis site or at the tip of 'J'. It occurs in 1.1% of patients [78] and patients usually present with signs of pelvic sepsis resulting from release of pouch contents [12]. Computed tomography (CT)-guided drainage may be used in mild cases; however, surgical repair is often required along with fecal diversion for more than 12 months while the patient is healing [78–80].

Pelvic sepsis & abscess

Pelvic sepsis is a detrimental complication of IPAA that commonly occurs at an early postoperative stage. Pelvic sepsis is defined as an infective process in the peripouch area or at the true pelvis distal to the pelvic inlet [12]. Immediate postoperative pelvic sepsis occurs in 5–20% of patients undergoing restorative proctocolectomy with IPAA. Patients who experience early pelvic sepsis have a cumulative incidence of pouch failure of 30% [11,12,81]. Pelvic sepsis was associated with anastomotic leak in 34%, fistulae in 25% and mortality in 3% of patients. Reported risk factors for pelvic sepsis included one-stage IPAA procedure, fulminant colitis [82], hand-sewn anastomosis [82,83] and the presence of primary sclerosing cholangitis [84]. Pelvic sepsis in the immediate postoperative period usually results from anastomotic dehiscence or in the presence of an infected pelvic hematoma. Patients can present with fever, anal pain, pelvic pressure, failure to thrive, tenesmus and discharge of pus or secondary hemorrhage through the anus. Exam under anesthesia and pelvic imaging, such as contrast pouchogram, MRI and CT, may be required to establish the diagnosis. Patients with pelvic sepsis may go on to develop sinus or fistular tracts at or around the pouch–anal anastomoses [85]. Pelvic sepsis often requires surgical intervention.

Delayed pelvic sepsis following IPAA surgery generally presents as chronic abscess formation with or without an associated fistula. Adequate drainage may be sufficient in clearing the infection. After drainage, imaging studies with contrast can be obtained to look for the presence of leaks. The absence of associated leaks on the drainage-injection study would confirm the initial diagnosis of pelvic abscess. However, patients with leaks may later develop pouch fistula or sinus [12]. If the abscess does not resolve, surgical intervention is needed.

Pouch fistulae

Patients with IPAA are at risk of fistula formation from a variety of etiologies. Fistulae may arise at any level of the pouch [86] extending into any adjacent hollow organs or to the skin [87]. Pouch fistulae may be related to CD of the pouch or may be non-CD related. Fistula at the anastomotic level can be a complication caused by an anastomotic leak or by the penetrating process of CD. Fistulae with the opening at the dentate line can be from a cryptoglandular source. However, recurrent, multiple, complex fistulae below the anastomosis level suggests a diagnosis of CD. Pouch–vaginal fistulae (PVF) are associated with significant morbidity and are one of the most common causes of pouch failure [88]. The estimated cumulative prevalence rates of PVF vary from 3 to 17% [89–94]. PVF can develop early (<6 months after IPAA) or late (>12 months after IPAA) [89]. PVF could also be a presentation of CD, and can present below or above the anastomosis as a simple or complex fistula with multiple fistulous tracts, particularly in the absence of a history of immediate postoperative pelvic abscess or pelvis sepsis [89,93]. The outcomes of medical therapy and surgical repair for PVF have been disappointing [89,95].

Strictures

Strictures are common after IPAA procedure. The strictures can be primary or secondary (i.e., anastomotic) and they are commonly located at the anastomosis, pouch inlet stricture and an afferent limb stricture. Pouch strictures were reported in 11% of patients in a large series of 1884 patients with IPAA [96]. Strictures can be fibrotic or inflammatory, and may be related to surgery-associated ischemia, concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) or CD of the pouch. Typical presentation of strictures includes symptoms related to complete or partial small bowel obstruction [96]. Cessation of NSAIDs use or treatment of CD can be initiated in appropriate patients. The use of NSAIDs is contraindicated in any form of IBD. Endoscopic treatment [97], or pouch diversion or excision may also be helpful in the management of strictures [98].

Afferent limb syndrome

Patients following IPAA surgery are at risk of afferent limb syndrome, defined by acute angulation, prolapse or intussusceptions of the afferent limb at its junction or immediately proximal to the pouch, resulting in small bowel obstruction. In a study of 567 patients with restorative proctocolectomy and IPAA, in whom 122 had one or more episodes of small-bowel obstruction, afferent limb syndrome was seen in six patients [99]. The endoscopist may notice difficulty in intubating the afferent limb. Radiographically, it is diagnosed based on evidence of small bowel dilation proximal to the level of the pouch inlet [99]. Patients with afferent limb syndrome typically require surgical relief of the obstruction.

Infertility

Patients with IBD are often young and thus most patients who undergo the IPAA surgery are faced with concerns regarding whether IPAA surgery would affect their sex life, fertility and ability to conceive. Patients who undergo IPAA surgery are at risk of infertility as the surgery involves manipulations of pelvic organs [100,101]. UC patients who underwent IPAA surgery had an approximately 20–50% lower chance of becoming pregnant and were more likely to require fertility intervention to become pregnant than those with UC treated by medical therapy [100–103]. Fecundity (i.e., the waiting time to become pregnant) in IPAA patients was increased and the cumulative rate for pregnancy was only 47% compared with 91% in the reference population [101]. A meta-analysis incorporating eight studies and a total of 528 patients reported that the infertility rate was 20% for medically treated UC versus 50% for patients with IPAA, with a relative risk for infertility of 2.42 (95% CI: 1.99–2.96) after IPAA [14]. Patients with familial adenomatous polyposis who undergo IPAA also have a reduced fertility rate, suggesting that the reduction of fertility is a consequence of the surgical procedure itself rather than underlying UC [104]. The reduction in postoperative fertility is attributed largely to occlusion of the fallopian tubes [105]. This was demonstrated in a study in which

abnormal postoperative hysterosalpingography was reported in 14 out of 21 UC patients with IPAA [105]. Therefore, female UC patients of child-bearing age should be counseled for the potential risk of infertility.

Impact of sphincter injury on pouch outcome

Sphincter injury can occur during pouch construction, particularly in patients with a history of vaginal delivery. However, in a reported series from our group, there was no difference in pouch function on long-term follow-up between the 50% of patients who had undergone vaginal delivery and the 13% who had undergone caesarean section [106]. Similar observations that there is no effect on pouch function have also been reported [107,108]. Long-term impact of sphincter injury during vaginal delivery is unknown at this time.

Sexual dysfunction

Patients with IPAA are also at risk of sexual dysfunction caused by the maneuvering of pelvic organs or nerves, which can occur or persist after IPAA. However, the majority of IPAA patients of both sexes experience good overall general satisfaction with their sex life, including the ability to achieve orgasm, which improved after surgery [109–112]. A small percent of patients can have sexual dysfunction, which may be caused by injuries to parasympathetic and sympathetic nerves during surgery, anatomic alterations, pelvic fibrosis and psychologic influence. A meta-analysis of 43 observational studies in patients with IPAA reported a pooled incidence of sexual dysfunction of 3.6% [11]. Male patients with sexual dysfunction can present with impotence or erectile dysfunction, orgasm without ejaculation or retrograde ejaculation [113–115]. While male sexual dysfunction from IPAA rarely causes infertility, preoperative semen cryopreservation may be needed, especially in patients who are undergoing a redo pouch or reoperative pelvic surgery [111]. Female sexual dysfunction can occur as a result of dyspareunia, fecal leakage during intercourse and decreased vaginal proprioception [116–118]. Therefore, both male and female patients undergoing restorative proctocolectomy should be counseled for the potential small risk of sexual dysfunction.

Portal vein thrombosis

Portal vein thrombi can be seen in UC patients before or after restorative proctocolectomy [119–121]. In a retrospective study of patients presenting postoperatively with symptoms, portal vein thrombi were found in up to 45% of CT scans performed after IPAA for UC [119]. Thrombotic complication of IPAA may be associated with an increased risk for subsequent pouchitis, as a recent study reported that 45% of selected patients with perioperative portal vein thrombosis later developed pouchitis compared with 15.4% in patients without portal vein thrombosis [121]. Our recent study also demonstrated that history of portal vein thrombosis may also be associated with risk of pouch ischemia [122]. The clinical significance of portal vein thrombosis and its effect on pouch and liver functions are under investigation by our team.

Inflammatory disorders

Patients with IPAA are susceptible to a number of inflammatory complications, including pouchitis, CD of the pouch and cuffitis, which adversely affect patient's health-related QOL [6].

Pouchitis

Pouchitis is the most frequent long-term complication of IPAA in patients with UC, with a cumulative prevalence of up to 50% [1,2,6]. Pouchitis almost exclusively affects patients with underlying UC and is rarely seen in patients with familial adenomatous polyposis. Most patients with pouchitis respond favorably to antibiotics. However, 5–19% of patients develop refractory or relapsing forms of the disease, which pose a significant management challenge for clinicians [3,123,124]. The usual presenting symptoms include increased stool frequency, urgency, incontinence, nocturnal seepage, abdominal cramps and pelvic discomfort.

For the purpose of research and clinical practice, various diagnostic criteria have been used, such as symptom assessment alone, symptom and endoscopy assessment (modified Pouch Disease Activity Index [mPDAI]) [125], or symptom and endoscopy assessment with histology evaluation (PDAI) [126], Heidelberg criteria [127] and St Marks' criteria [128]. The PDAI score is the most common criteria used in research studies. A PDAI score greater than 7 suggest a diagnosis of pouchitis [126]. Histologic features of acute inflammation include ulceration, polymorphic neutrophil infiltration and crypt abscess. Chronic histologic changes such as villous blunting and increased number of mononuclear cells in the lamina propria may frequently be seen in the pouch, reflecting adaptive changes in the ileal mucosa associated with fecal stasis [3]. These chronic histologic changes

are not necessarily indicative of active pouchitis. In clinical practice, the diagnosis of pouchitis is ideally made based on the triad of compatible symptoms, and endoscopic and histological findings, because the severity of symptoms often does not correlate with the degree of endoscopic or histologic inflammation of the pouch [128,129].

There is no uniform classification system for the classification of pouchitis. Pouchitis may be classified based on the etiology, disease duration and activity [130]. Pouchitis can also be classified based on its response to antibiotics into antibiotic-responsive, antibiotic-dependent and antibiotic-refractory pouchitis. Antibiotic-responsive pouchitis is characterized by infrequent episodes (i.e., less than four episodes per year) responding to a 2-week course of a single antibiotic. Antibiotic-dependent pouchitis is more challenging and patients often require long-term maintenance therapy to keep the disease in remission. Patients have frequent episodes (at least four episodes per year) of pouchitis or have persistent symptoms, which necessitate long-term, continuous antibiotic or probiotic therapy. Chronic antibiotic-refractory pouchitis is defined as a condition where a patient fails to respond to a 4-week course of a single antibiotic (metronidazole or ciprofloxacin), requiring prolonged therapy of 4 weeks or more, consisting of two or more antibiotics, oral or topical 5-aminosalicylate, corticosteroid therapy or oral immunomodulator therapy [127].

In the majority of patients, the etiology and pathogenesis of pouchitis are not entirely clear and are labeled as idiopathic pouchitis. By contrast, a subset of patients with pouchitis may have specific causative and pathogenetic factors that we defined as 'secondary pouchitis' [131]. Secondary causes of pouchitis should be particularly sought and ruled out in patients with chronic antibiotic-refractory pouchitis [131]. The various etiologies include *Clostridium difficile* and other infections (infectious pouchitis), *Candida*, cytomegalovirus, NSAID use (NSAID-induced pouchitis), collagen deposition of the pouch mucosa (collagenous pouchitis), ischemia (ischemic pouchitis), radiation injury (radiation pouchitis), chemotherapy (chemotherapy-associated pouchitis), concurrent autoimmune disorders (pouchitis associated with other autoimmune disorders), IgG4-pouchitis [132] and fecal diversion (diversion pouchitis) [131]. Approximately 20–30% of patients with chronic antibiotic-refractory pouchitis have identifiable secondary causes [3]. Previous studies have highlighted that in patients with underlying UC who underwent proctocolectomy and IPAA, the presence of PSC is associated with an increased risk for pouchitis (particularly chronic pouchitis) and higher long-term mortality [133,134].

Recently, a study explored tinidazole as primary prophylaxis against the development of pouchitis. The study was a randomized, double-blind, placebo-controlled clinical trial to determine if tinidazole reduces or prevents the incidence of pouchitis in UC patients at 12 months after IPAA. In this study, 38 UC patients were randomly assigned in a 2:1 ratio to receive either tinidazole 500 mg/day orally, or placebo daily within 1 month of their final stage of IPAA surgery for a total duration of 12 months [135]. Investigators reported that 8.0% of the tinidazole group developed pouchitis, compared with 38.5% of patients taking placebo. Therefore, early initiation of tinidazole may be an effective strategy to prevent pouchitis following IPAA surgery. In addition, a randomized study comparing a probiotic named VSL #3 Ok (VSL Pharmaceuticals, Inc., Gaithersburg, MD, USA), which contains viable lyophilized bacteria, including lactobacilli, bifidobacteria and streptococcus, with placebo to prevent development of initial episodes of pouchitis in patients with IPAA was carried out. The incidence of pouchitis during the first year was found to be 10 versus 40% in the probiotic-treated group and placebo group, respectively [136].

Prepouch ileitis

Ileal pouch–anal anastomosis patients are at risk of other postoperative complications including prepouch ileitis, which is defined as inflammation in the ileum immediately proximal to the pouch. This is usually seen coexisting with pouchitis, but it may occur in isolation. A recently published large study of 742 patients reported the incidence of prepouch ileitis to be 5.7% (n = 34) in patients with UC/indeterminate colitis [137]. All of these patients had varying degrees of coexisting pouch inflammation. Prepouch ileitis occurred in 13% of patients with pouch inflammation. We have recently reported that patients with PSC and IPAA have higher endoscopic and histologic activity of the afferent limb than patients without coexisting PSC [138].

Cuffitis

Cuffitis, in most cases, can be considered a residual form of UC. Patients who had undergone stapled anastomosis without mucosectomy may have an increased risk for cuffitis [139]. Clinical symptoms of cuffitis are similar to those in

pouchitis and patients frequently present with blood-mixed stools. Typical cuffitis may respond to topical 5-aminosalicylate agents or topical corticosteroids [140]. Refractory cuffitis can cause pouch failure. Chronic cuffitis may theoretically increase the risk of dysplasia or cancer at the ATZ.

CD of the pouch

One of the intriguing aspects of IPAA is that *de novo* CD of the pouch can develop after IPAA in patients with an operative classic diagnosis of UC. It was postulated by our group that the IPAA procedure may create a 'CD-friendly' environment with anastomoses, ischemia and fecal stasis. However, IPAA may be performed for highly selected, motivated patients with Crohn's colitis with no small intestinal or perianal diseases [141]. CD of the pouch may develop *de novo* weeks to years after IPAA was performed for UC despite the lack of evidence of CD in the proctocolectomy specimens. Reported cumulative frequencies of CD of the pouch ranges from 2.7 to 13% [142–148].

Crohn's disease of the pouch may be classified based on the clinical presentation into inflammatory, fibrostenotic or fistulizing phenotypes [149]. The clinical phenotypes may continue to change along the disease course with patients initially presenting with an inflammatory phenotype and later developing a fistulizing phenotype. Patients with CD of the pouch can present with symptoms elsewhere in the GI tract, including proximal small bowel and perianal location.

Crohn's disease of the pouch is diagnosed based on certain endoscopic features, including the presence of afferent limb ulcers and/or ulcerated stricture at the pouch inlet in the absence of NSAID use. The presence of ulcers or stricture in other parts of the small bowel in the absence of NSAID use also favors a diagnosis of CD [150,151]. Prepouch ileitis with diffuse pouchitis presents with endosscopic and histologic inflammation in the neoterminal ileum (typically within 10 cm of the pouch inlet) in a continuous fashion with a widely patent pouch inlet. On the other hand, CD ileitis is characterized by discrete ulcers in the distal neoterminal ileum (>10 cm beyond the pouch inlet) and ulcerated stricture at the pouch inlet.

Proximal small-bowel bacterial overgrowth

In theory, small bowel bacterial overgrowth is a norm in patients with IPAA with adaptation of the pouch. A small subset of patients with IPAA is at risk of small bowel bacterial overgrowth. Patients often present with symptoms of pouchitis; however, pouch endoscopy and histological evaluation are noncontributory, and patients often respond to empiric antibiotics [4]. There are no validated criteria to confirm the diagnosis in these patients, such as hydrogen breath tests, and the diagnosis is empiric.

Irritable pouch syndrome

Irritable pouch syndrome is the most common functional disorder of IPAA, characterized by diarrhea, abdominal pain, and urgency in the absence of endoscopic and histologic inflammation [8,152]. IPS may significantly affect the QOL in patients with IPAA [153]. While its pathogenesis is unclear, visceral hypersensitivity [154] and enterochromaffin cell hyperplasia of the pouch mucosa [155] have been demonstrated in these patients. Patients with IPS can be treated with antispasmodics, tricyclic antidepressants or belladonna/opium suppositories.

Pouch neoplasia

While total proctocolectomy with IPAA substantially reduces the risk of colitis-associated dysplasia, the procedure does not completely abolish the cancer risk, even with mucosectomy [61]. In a recently published study from our group, the cumulative incidence of pouch neoplasia at 5, 10, 15, 20 and 25 years was 0.9, 1.3, 1.9, 4.2 and 5.1%, respectively. The cumulative incidence of pouch cancer (including squamous cell carcinoma and pouch lymphoma) at 5, 10, 15, 20 and 25 years were 0.2, 0.4, 0.8, 2.4 and 3.4%, respectively. The cumulative incidence of pouch dysplasia at 5, 10, 15, 20 and 25 years was 0.8, 1.3, 1.5, 2.2 and 3.2%, respectively. A total of 38 patients (1.19%) had pouch neoplasia, including 11 (0.36%) with adenocarcinoma of the pouch and/or the ATZ, one (0.03%) with pouch lymphoma, three with squamous cell carcinoma of the ATZ, and 23 with dysplasia (0.72%) [61]. In the Cox model, the risk factor associated with pouch neoplasia was a preoperative diagnosis of UC-associated cancer or dysplasia, with adjusted hazard ratios of 13.43 (95% CI: 3.96–45.53; $p < 0.001$) and 3.62 (95% CI: 1.59–8.23; $p = 0.002$), respectively. Mucosectomy did not protect against pouch neoplasia [61].

Metabolic & systemic complications

Anemia

Anemia is common in IPAA patients, affecting approximately 17% of IPAA patients with underlying UC [156,157]. Pouch patients with anemia

typically do not have overt gastrointestinal bleeding. A recently published systematic review on the impact of anemia in restorative proctocolectomy patients reported negative effects on the patient's QOL and the substantial increase in healthcare costs secondary to anemia [158]. The etiology of anemia in these patients is likely to be multifactorial. In a study of 48 patients with a median follow-up after surgery of 9.8 years, ten patients (20.8%) had anemia and eight out of ten patients had chronic pouchitis [159]. Five patients had iron deficiency anemia, while two patients had vitamin B12 deficiency [159]. However, the study is limited by the small number of patients included – only 48 patients. A subsequent study of 18 patients identified iron-deficiency anemia in ten (55.5%) patients and pouchitis was found in 14 (77%) patients [160]. In addition, construction of IPAA involves resection of a part of the terminal ileum with reconstruction of the ileal reservoir, which predisposes patients to vitamin B12 deficiency. In a study of 150 IPAA patients measuring sequential vitamin B12, 36 (24%) had low serum B12 levels. However, 94% of these patients had a normal Schilling test and 66% had a sequential fall in vitamin B12 levels [161]. The mechanism of B12 deficiency is not clear as there was no evidence of either a defect in absorption or bacterial overgrowth to explain the low level of vitamin B12. In the study from our group of 389 patients, we did not observe any correlation between the presence of pouchitis and anemia [157]. For patients with iron deficiency, further evaluation, such as celiac serology and upper endoscopy with duodenal biopsy, is warranted. For patients with iron deficiency and/or vitamin B12 deficiency, supplement therapy is advocated.

Bone loss

Patients with IPAA are at risk of osteopenia or osteoporosis [156]. Bone loss can also be seen in patients on long-term steroids before surgery. It is not clear whether restorative proctocolectomy with IPAA has a beneficial or detrimental impact on bone mineral density (BMD). In a large series from our pouchitis clinic, low BMD (defined as a T-score of the lumbar spine, total hip or femoral neck of ≤-2.5 in postmenopausal women and in men ≥50 years of age) was common in patients with IPAA with a prevalence of 32.1% [162]. Low BMD was seen in patients with both chronic inflammatory pouch problems, and with normal pouch and IPS. None of the pouch-related factors were significant on multivariable analysis; however, advanced age, low BMI and nonuse of calcium supplement were associated with low BMD. Adverse metabolic consequences related to surgery, including malabsorption of vitamin D and K, may be related to the low BMD, and aggressive screening and use of calcium supplements may be required. Box 2 summarized the adverse long-term effects of IPAA surgery.

Although IPAA may not be the ultimate gold-standard treatment, at present it is the best option we have in IBD patients to substantially improve the QOL. However, the patient should be given detailed information regarding the different surgical options and their advantages and disadvantages, and agree to the choice of intervention and the risks involved.

Conclusion

Ileal pouch–anal anastomosis surgery has changed the outlook of patients with IBD and helps patients to maintain the usual route of defecation and continence. However, IPAA is associated with a number of risks including surgical, mechanical, inflammatory and non-inflammatory complications, which may affect the QOL in these patients. Careful selection of patients and extensive discussion regarding the realistic expectations after surgery and the risks and benefits of the IPAA surgery needs to be carried out with these patients before proceeding with surgery.

The management of patients with IBD can be challenging. How effective and safe is the medical or surgical therapy? What are the long-term benefits and risks? Will the medical therapy be effective in altering the natural history of UC and help avoid colectomy? When would be the best time for surgical intervention? Will surgical treatment with its potential complications offset its benefits in reducing the number of medicines taken and decreasing the risk of

Box 2. Long-term risks of ileal pouch–anal anastomosis.

- Pouch fistulae
- Afferent limb syndrome
- Infertility
- Portal vein thrombosis
- Pouchitis
  - Idiopathic
  - Secondary
- Prepouch ileitis
- Cuffitis
- Crohn's disease of the pouch
- Irritable pouch syndrome
- Pouch neoplasia

Box 3. Role of ileal pouch–anal anastomosis.

- Advantages of surgery
  - 'Cures' some patients
  - Decrease in dysplasia
  - Improvement in quality of life
  - Eradicates problems with adherence to life-long medications
  - Avoids adverse effects from medications
  - Avoids the risk for dysplasia and cancer with medical treatment
- Disadvantages of surgery
  - Complications from surgery including early and late complications, which can result in a decrease in quality of life
  - Risk of decreased fertility and sexual dysfunction
  - 'Losing' the colon

dysplasia or cancer? Can we predict outcomes for each individual patient? The benefits of medical therapy include preservation of intact colon and, therefore, preservation of fertility in women. The major disadvantages of medical therapy are adverse effects, costs, compliance with medications, persistent risk of colon neoplasia and potential risk of postsurgical infectious complications (particularly infliximab) once surgery is required. Restorative proctocolectomy with IPAA also has its advantages and disadvantages. Advantages of the surgery include substantial reduction of the risk of colon neoplasia, improvement in QOL, and decrease in the use of UC-related medications and their associated cost and adverse effects. The main disadvantages of surgical therapy are the risks of pouchitis, CD of the pouch, cuffitis, IPS and infertility, as well as technique-related complications such as pouch leak, pelvic abscess and pouch sinus. The risks and benefits of and alternatives to medical versus surgical therapy should be fully presented to the patient when a decision is to be made. At present, with the available evidence, we do not have conclusive support for any particular treatment. However, the introduction of IPAA has revolutionized treatment of UC. Furthermore, development of laparoscopic IPAA has set new standards of cosmesis and may decrease the risk of adhesion-related small bowel obstruction. Thus, in an appropriately chosen patient without major postoperative complications, the outcomes are excellent with well-preserved continence and a good QOL. In addition, delaying IPAA surgery in young patients planning to conceive may be a reasonable alternative in order to 'buy time' to prevent the risk of infertility. **Box 3** summarizes the advantages and disadvantages of each approach.

Future perspective

On a positive note, in the next 5 years, we speculate that with improvements in surgical techniques, such as single-port or robotic-assisted IPAA, postoperative complications may be reduced. We also believe that we will have a better understanding of the pathogenesis and natural history of pouchitis and other pouch disorders, with genetics, mucosal immunology and gut microbiology. This would give us more options for prevention and treatment of pouchitis. We believe that developments in research will further elucidate the pathogenesis pathways of pouchitis, and help design safer and more effective therapy. It is unfortunate that there are currently no US FDA-approved agents for treating pouch disorders, which has created a hurdle for routine insurance coverage for some patients. Performance of well-designed randomized controlled trials is one way to raise the awareness of pouch disorders in general and in the medical community.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Ileal pouch–anal anastomosis (IPAA) is more popular than ileostomy as the usual route of defecation and continence is maintained.
- IPAA improves quality of life in ulcerative colitis patients with dysplasia or medically refractory disease who required surgery in most clinical studies, and substantially reduces the risk of dysplasia and cancer of the colon, as well as avoiding the need for surveillance colonoscopy.
- Pouchitis is the most frequent long-term complication of IPAA in patients with ulcerative colitis, with a cumulative prevalence of up to 50%.
- Patients with IPAA are susceptible to a number of surgical, mechanical, inflammatory and noninflammatory conditions such as anastomotic leaks, pelvic sepsis, pouchitis, Crohn's disease of the pouch, cuffitis and irritable pouch syndrome, which adversely affect the outcome and compromise the patients' quality of life.
- The pouch procedure appears to be a safe operation with a low postoperative mortality rate of 0–1%.
- The advantages and disadvantages of IPAA should be discussed with eligible patients prior to surgery.

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