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Viewpoint

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Controversies in Pouch Surveillance for Patients with Inflammatory Bowel Disease

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Clinical Vignette [Abstract]

Case 1: Following 2 years of rectal blood loss, a 31-year-old male was diagnosed with ulcerative pancolitis in 1978. Initial treatment consisted of both topical and systemic 5-aminosalicylic acids [5-ASAs], and remission was achieved. In both 1984 and 1986 he was hospitalised due to exacerbations necessitating treatment with intravenous corticosteroids. The following years went well, without disease activity, under treatment with 5-ASA. In 1997, at the age of 50 years, a surveillance colonoscopy showed a stenotic process with a macroscopic irregularity in the sigmoid region. Histology revealed at least high-grade dysplasia [HGD] and signs of an invasive growth pattern which could indicate colorectal cancer [CRC]. The patient underwent restorative proctocolectomy with ileal pouch-anal anastomosis [IPAA]. Histology of the resection specimen confirmed active inflammation in the colon and rectum and a carcinoma in situ was identified in the sigmoid colon without invasive growth. This patient did not have significant comorbidities—for example primary sclerosing cholangitis [PSC]—and the CRC family history was negative. What pouch surveillance strategy should be recommended?

Case 2: A 34-year-old man presented at our inflammatory bowel disease [IBD] centre with ulcerative proctitis. Ten years later, after an initially mild disease course, his disease progressed to a pancolitis. An 11-year period with multiple exacerbations [on average every 2 year, including hospitalisation] followed and treatment consisted of topical and systemic 5-ASAs with intermittent corticosteroids. In 1998, at the age of 65 years, a two-stage restorative proctocolectomy with IPAA was performed due to disease activity refractory to systemic corticosteroids. The colectomy specimen confirmed the diagnosis of ulcerative pancolitis without evidence for colorectal dysplasia or carcinoma. Other than steroid-induced diabetes mellitus, this patient had no comorbidities. His father died from CRC at unknown age. What pouch surveillance strategy should be recommended?

Key Words: Ulcerative colitis; ileal pouch-anal anastomosis; surveillance

1. Background

Although clear and well-accepted surveillance guidelines exist for inflammatory bowel disease [IBD] patients with an intact colon, several controversies exist with respect to endoscopic surveillance of the ileal pouch-anal anastomosis IPAA. Following from our clinical vignettes, it could be questioned whether pouch surveillance is necessary at all, whether and how risk stratification should be performed, and which pouch surveillance intervals should be followed. Both the British Society of Gastroenterology [BSG] and American Gastroenterology Association [AGA] recommend regular surveillance in IBD patients with an intact colon, tailored to the individual patient's risk profile.[1,2] These strategies may reduce colorectal cancer

[CRC] incidence and mortality.[3,4] However, for IBD patients who had undergone a colectomy, guidance is less clear.

Pouch surveillance recommendations in the current IBD surveillance guidelines are lacking [AGA guideline], incomplete (American Society for Gastrointestinal Endoscopy [ASGE] guideline) or not up to date in the light of new available evidence (BSG guideline; European Crohn's and Colitis Organisation [ECCO] guideline) as shown in Table 1.[1,2,5,6] The British surveillance guidelines distinguish low [no high risk factors] and high risk (primary sclerosing cholangitis [PSC], previous colorectal neoplasia, atrophic mucosa) groups following colectomy, and recommend surveillance intervals of 5 years and 1 year, respectively.[1] However, new data with respect to risk factors for pouch carcinoma development became available in recent years. The ECCO guidelines only identify previous CRC as a very important risk factor, but subsequently propose surveillance based on risk factors as in the BSG guidelines.[5]

Lack of clear, updated, and consistent guidelines in pouch surveillance has resulted in a wide variation in daily practice. Some physicians adopt very short surveillance intervals, which may lead to unnecessary burden for patients and increased costs. In contrast, longer surveillance intervals may result in interval carcinomas. The recently updated evidence to support pouch surveillance is limited and requires careful interpretation and discussion. Here, we aim to discuss controversies regarding IPAA surveillance based on the currently available literature and suggest an approach to pouch surveillance based on up-to-date risk stratification.

2. Is Pouch Surveillance Necessary in IBD Patients?

2.1. Pro

One of the main factors that determine the benefit of a pouch surveillance strategy is the risk of developing pouch cancer. For example, it would be more useful to screen a population of which 50% will develop pouch cancer compared with a population containing almost no patients who will develop pouch cancer. As such, pouch surveillance may be of benefit in subgroups that carry a high pouch cancer risk, whereas in subgroups with a low risk profile, surveillance pouchoscopies will not be worthwhile.

The major determinant for pouch cancer development is the presence of colorectal dysplasia or carcinoma before colectomy. A recent meta-analysis showed that IBD patients with a history of colorectal dysplasia or CRC had a respectively 4.4- and 15.0-fold increase in pouch cancer risk.[7] In addition, 57.1% of pouch cancer cases in the literature had preceding colorectal neoplasia.[8] The high cumulative pouch neoplasia incidence in subgroups with previous colorectal neoplasia [29.5% after 15 years in patients with previous CRC] supports regular surveillance in these patients.[9]

The poor outcome of pouch carcinomas may also support pouch surveillance. In a previous study, 9 out of 16 patients with pouch carcinoma died within a median follow-up of 11 months [range 1–20 months].[9] Three additional patients had metastatic disease at the end of follow-up. This is in line with another study, in which 3 of 11 patients with pouch carcinoma died within 1 year of follow-up. Furthermore, alarm symptoms for pouch carcinoma can be masked due to already altered defaecation patterns, which may contribute to delayed detection and worsened outcome. Earlier detection of pouch cancers by regular endoscopic surveillance may improve the outcome.

2.2. Contra

The low overall incidence and prevalence of pouch carcinoma in IBD argues against routine pouch surveillance in all IPAA patients.

Table 1. Overview of pouch surveillance guidelines.

Guideline	Year of publication	Risk stratification		Surveillance strategy
		Yes/no	Risk categories	
AGA[2]	2010	n/a	n/a	No recommendations
BSG[1]	2010	Yes	• High risk: - Previous rectal dysplasia - Dysplasia/cancer at the time of pouch surgery - Primary sclerosing cholangitis - Type C pouch mucosa[a]	Yearly
			• Low risk: - Absence of high risk factors	5-yearly
ASGE[6]	2015	Yes	• Highest risk: - History of dysplasia or cancer.	Yearly surveillance should be considered
			• High risk: - Primary sclerosing cholangitis - Type C pouch mucosa[a] - Refractory pouchitis	Yearly surveillance may be considered
			• Other patients	No recommendations
ECCO[5]	2015	Yes	• High risk: - Dysplasia/cancer at the time of pouch surgery - Primary sclerosing cholangitis - Type C pouch mucosa[a] - Unremitting pouchitis	Yearly
			• Absence of high risk factors	No evidence that supports routine surveillance

AGA, American Gastroenterology Association; BSG, British Society of Gastroenterology; ASGE, American Society for Gastrointestinal Endoscopy; ECCO, European Crohn's and Colitis Organisation

[a]Type C pouch mucosa is defined as exhibiting permanent persistent atrophy and severe inflammation.

A meta-analysis showed a pooled cumulative incidence of pouch cancer of 3.4% 25 years after IPAA construction, which is below the general lifetime CRC risk.[7] IPAA cancers are mostly located at the anal transitional zone, and the cumulative incidence of pouch cancers originating from ileal mucosa will be even lower.[8] In addition, the incidence of precancerous lesions such as low-grade dysplasia [LGD] and high-grade dysplasia [HGD] is also low [3.0% after 20 years].[7]

When incorporating risk stratification in a pouch surveillance strategy, only those with a history of colorectal neoplasia could be identified as high risk patients. Evidence for other risk factors is less conclusive or pronounced and a combined cumulative dysplasia and carcinoma incidence of 2.2% after 15 years was shown in those without a history of colorectal neoplasia.[9] Patients with a longer IBD duration and a hand-sewn IPAA may carry an increased pouch cancer risk, but the impact of these risk factors is much lower.[7] Current factors that guide the ECCO and BSG pouch surveillance guidelines, including PSC and an atrophic pouch mucosa or pouchitis, were not identified as risk factors in the two largest IBD cohorts with IPAA reported [n = 3203 and n = 1200].[9,10] In addition, studies that only included patients with PSC pouchitis or a long-standing pouch [≥ 12 years] showed relatively low pouch carcinoma prevalences [1.5%2.4%].[11,12,13] This advocates against regular surveillance in these subgroups.

A low absolute risk for detecting pouch cancer and precancerous lesions will result in a high number needed to screen, questioning cost-efficiency of a surveillance strategy in those with a low risk profile. Many patients will need to undergo surveillance, but in most cases pouch neoplasia will not be detected. This will result in significant disadvantages, such as a financial burden for patients and health care providers, and discomfort for patients due to preparation and the endoscopic procedure. Furthermore, studies that show an improved detection and prognosis of pouch neoplasia with surveillance are lacking, and may never be performed due to the limited size of available cohorts.

3. Does Pouch Surveillance Improve the Outcome of Pouch Neoplasia?

3.1. Pro

In long-standing colonic IBD, current surveillance strategies are based on the concept of an inflammation-dysplasia-carcinoma sequence.[14] This sequence may also apply to the pathogenesis of pouch carcinoma, since patients with subsequent LGD, HGD, and pouch carcinoma have been described previously.[15] Regular pouch surveillance may result in earlier pouch neoplasia detection, with potential improved prognosis and outcome. Supportive evidence for this hypothesis is derived from a tertiary pouch referral centre performing regular surveillance pouchoscopies every 1 to 3 years at the discretion of the treating physician.[10] Of 9 patients with pouch carcinoma detected in this surveillance programme, only 1 [11%] had a stage IV cancer diagnosis, whereas in a nationwide study without routine endoscopic surveillance, 4 of 12 [33%] primary pouch carcinomas were diagnosed with stage IV disease.[9]

3.2. Contra

Although regular surveillance may result in earlier pouch neoplasia detection, it is unknown whether this strategy is sufficient to find more lesions at a precancerous stage. Typical endoscopic features of pouch neoplasia are lacking, and in many cases there are no endoscopic abnormalities at all.[9,16] Difficulties with detection of dysplasia in the pouch were confirmed by a tertiary pouch referral centre: despite regular surveillance, only 3 out of 11 patients [27.3%] were detected with dysplastic lesions preceding pouch cancer, whereas in 10 [90.9%] concurrent dysplasia was subsequently identified in the pouch excision specimen.[10]

Furthermore, it is unknown whether detection of pouch neoplasia at an earlier stage will improve outcome. For example, many dysplastic lesions never show progression to cancer or even show spontaneous regression. A previous study reported on 22 patients with LGD of the pouch. Only 3 patients demonstrated persistent LGD and 3 showed progression after a median time of 9.5 years, whereas 16 patients showed regression of LGD.[15] Similarly another study, including 21 patients with lesions of the pouch categorised as indefinite for dysplasia [IND], only showed progression to LGD in 1 patient and progression to HGD in 1 other patient during a mean follow-up of 19.3 months. In contrast, IND was not re-detected in 12 patients and 7 had persistent IND.[17]

4. Discussion

As in colorectal surveillance, direct evidence for the benefit of a pouch surveillance strategy is lacking. There are no studies evaluating the yield and the number of interval carcinomas of a particular pouch surveillance strategy, in contrast to previous studies on colorectal surveillance in IBD.[18] Furthermore, studies comparing surveillance strategies, which is for example done for colorectal surveillance recommended by the BSG and AGA guidelines, are lacking for pouch surveillance.[19] There is a need to establish a clear and well-accepted pouch surveillance guideline, reducing the wide variation in practice and allowing prospective evaluation in coming years.

Our pro-con debate has resulted in a proposed pouch surveillance strategy which is outlined in Figure 1. Given the available data, we propose a strategy based on risk stratification. Risk stratification should be based only on the presence of a history of colorectal neoplasia before colectomy which is the dominant risk factor for pouch cancer in recent studies.[7] The low absolute and relative pouch carcinoma risk in patients without previous colorectal neoplasia allows us to propose forgoing surveillance in this subgroup. Thus, in line with the current ECCO recommendations, routine surveillance of the pouch is not recommended in low risk patients.[5] However, in contrast to the BSG and ECCO guideline, the presence of PSC, atrophic pouch mucosa, or pouchitis do not guide risk stratification.[1,5] In our proposed strategy, patients with previous colorectal dysplasia or CRC are categorised into intermediate and high risk categories, respectively. The optimal surveillance interval for these categories still has to be defined. In our proposed strategy, surveillance intervals are derived from the BSG guideline for regular IBD surveillance.

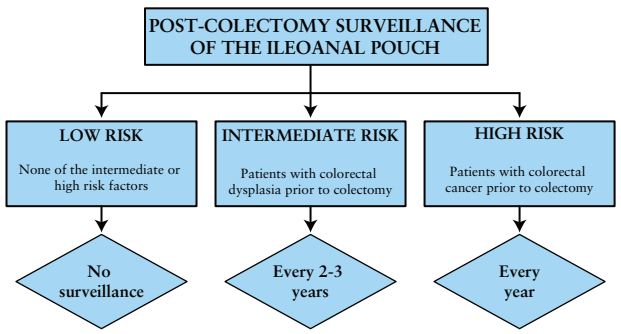

Figure 1. Proposed pouch surveillance strategy.

One of the questions that remain is how surveillance pouchoscopy should be performed. We did not incorporate this in our pro-con debate, since data from well-designed studies are lacking. Only one study investigated chromoendoscopy in 44 IPAA patients and found no increased pouch neoplasia detection rate compared with white light endoscopy.[20] In addition, the preparation for pouchoscopy is often insufficient and residual stool is a disadvantage for chromoendoscopy. By contrast, both the AGA and the BSG guidelines recommend chromoendoscopy with targeted biopsies for regular IBD surveillance.[1,2] Furthermore, evidence for a biopsy regimen in pouch surveillance is absent. Since most carcinomas arise at the anal traditional zone [67.3%], we endorse close and careful inspection of this region including random and targeted biopsies.[8] Targeted biopsies in the afferent and efferent limb and in the pouch body may be sufficient; however, evidence underlying such a strategy is currently lacking.

In addition to pouch surveillance endoscopy with biopsy, previous reports have suggested that biomarkers may also contribute to more accurate and earlier pouch neoplasia detection. As such, DNA abnormalities including aneuploidy, loss of heterozygosity, and mutations of p53, K-*ras*, and adenomatous polyposis coli genes have been studied as early biomarkers for pouch neoplasia.[21] Some studies reported DNA aneuploidy or loss of heterozygosity in patients with pouch dysplasia. However, these studies are small in size [≤ 5 patients with pouch dysplasia] and often lack a control group, not allowing us to draw clinically relevant conclusions from these data.

Several other questions are still open to debate with respect to pouch surveillance. For example, can we discontinue surveillance after a certain number of pouchoscopies without abnormalities? And what is the appropriate management of detected LGD or HGD? Although many questions remain, the implementation of a widely supported guideline for pouch surveillance is a first step towards improved surveillance in IBD patients following IPAA construction.

5. Clinical Vignette

5.1. Case 1

Based on our proposed surveillance strategy, we would categorise this patient into the high risk category recommending yearly surveillance pouchoscopies. The history of a carcinoma in situ in his sigmoid colon justifies yearly surveillance.

Indeed, this patient was followed up with pouchoscopies. He underwent a pouchoscopy in 1997, in 2001, and yearly since 2009 until 2014 [except in 2013]. A gap without surveillance of respectively 4 and 8 years was left between the first three pouchoscopies. In 2009, LGD of the pouch body was found, which regressed to normal in all following pouchoscopies.

5.2. Case 2

This patient would be categorised in the low risk category not requiring pouch surveillance, according to our proposed algorithm. Even when other factors such as a long IBD history or PSC are present, we do not recommend surveillance, in view of the low pouch cancer risk in these subgroups.

Nevertheless, this patient was frequently followed up with pouchoscopies every 2 to 3 years. He developed pouchitis once, for which he was treated with metronidazole. This did not influence the surveillance intervals. During five follow-up pouchoscopies in 14 years, no dysplasia was detected.

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Conflict of Interest

None of the authors report conflicts of interest that are relevant to the submitted manuscript.

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