Management of pouch neoplasia: consensus guidelines from the International Ileal Pouch Consortium

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Surveillance pouchoscopy is recommended for patients with restorative proctocolectomy with ileal pouch–anal anastomosis in ulcerative colitis or familial adenomatous polyposis, with the surveillance interval depending on the risk of neoplasia. Neoplasia in patients with ileal pouches mainly have a glandular source and less often are of squamous cell origin. Various grades of neoplasia can occur in the prepouch ileum, pouch body, rectal cuff, anal transition zone, anus, or perianal skin. The main treatment modalities are endoscopic polypectomy, endoscopic ablation, endoscopic mucosal resection, endoscopic submucosal dissection, surgical local excision, surgical circumferential resection and re-anastomosis, and pouch excision. The choice of the treatment modality is determined by the grade, location, size, and features of neoplastic lesions, along with patients' risk of neoplasia and comorbidities, and local endoscopic and surgical expertise.

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Introduction

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) has become the surgical treatment of choice in patients with ulcerative colitis or familial adenomatous polyposis (FAP) who require surgery. Both ulcerative colitis and FAP are associated with an increased risk of neoplasia of the large intestine, and proctocolectomy minimises the risk for colorectal cancer.[1] However, the risk is not zero. A meta-analysis on rectal stump surgery for inflammatory bowel disease (IBD) showed that rectal cancer occurred in 2·4% (95% CI, 1·7–3·0) of patients who had a colectomy and ileal rectal anastomosis over a follow-up of 1–35 years, and pouch, rectal cuff, or anal transition zone cancer in 0·5% (95% CI 0·3–0·6) of patients who had restorative proctocolectomy and IPAA over a follow-up of 4–25 years.[2]

The term pouch neoplasia used in this document refers to any neoplastic epithelial lesions (dysplasia or cancer), related to the various ileal pouch components, including the afferent limb, pouch body, rectal cuff, and anal transition zone. The anal transition zone has been used interchangeably with anorectal remnant in the literature. The term parapouch was used to describe anatomical structures outside the pouch body, including the prepouch ileum, rectal cuff, anal transition zone, anal canal, and perianal area. Neoplasia of the ileal pouch not involving the pouch body is termed parapouch neoplasia. The International Ileal Pouch Consortium, consisting of experts in the field, was established as a task force to prepare a series of documents in the diagnosis and management of ileal pouch disorders. The focus of this document is the management of pouch neoplasia in patients with underlying IBD or FAP. Diagnosis and surveillance of pouch neoplasia have been detailed in separate documents.[3,4]

The goal of this document is to provide practical guidance for the management of pouch dysplasia and cancer and to add relevant, updated information to that provided in the previous documents.[3,4] Due to the rarity of pouch neoplasia and scarcity of published high-quality evidence, most recommendations in this document are based on case series, case reports, and expert opinion, acknowledging shared-decision making and respect for autonomy of practicing clinicians.

Data collection

Search strategy and selection criteria

The steering committee first reviewed the medical literature for each statement. We did a systematic search of MEDLINE, Google Scholar, EMBASE, and Cochrane Central Register of Controlled Trials for studies published in English from Jan 1, 2000, to May 31, 2021 (figure 1). Key search terms were "restorative proctocolectomy", "ileal pouch", "pouch", "pouchitis", "diversion pouchitis", "cuffitis", "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "familial adenomatous polyposis", "polyposis syndrome", "primary sclerosing cholangitis", "endoscopy", "pouchoscopy", "continent ileostomy", "Kock pouch", "pouch polyps", "therapy", "treatment", "polypectomy", "endoscopic mucosal resection", "endoscopic submucosal dissection", "faecal diversion", "mucosectomy", "pouch advancement", "pouch excision", and "pouch redo", "squamous cell cancer", and "squamous intraepithelial lesion". Articles describing pouchitis, cuffitis, Crohn's disease of the pouch, pouch polyps, primary sclerosing cholangitis, FAP, dysplasia, neoplasia, or cancer of the pouch; and medical, endoscopic, or surgical treatments were reviewed and relevant articles were included in this Review.

We reviewed articles that met the criteria of any professional society guidelines, randomised controlled studies (RCTs), case-controlled studies, case series, and case reports in the management of dysplasia or cancer in patients with IBD and patients with FAP for restorative

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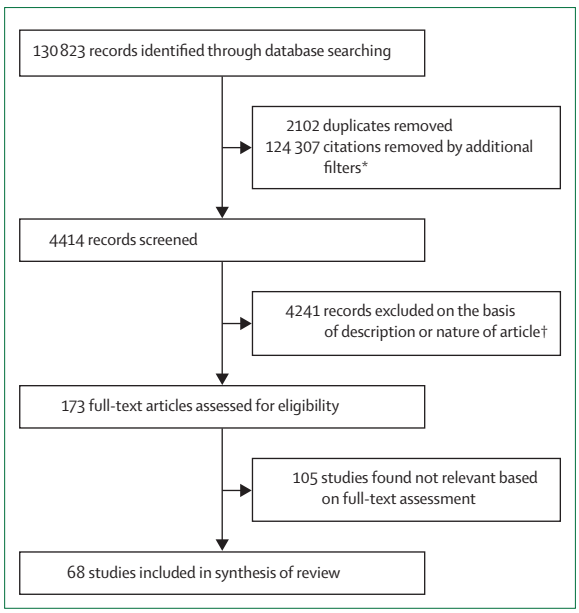

Figure 1: **PRISMA for the inclusion of relevant articles**
*Additional filters were pouchitis, cuffitis, Crohn's disease of the pouch, pouch polyps, primary sclerosing cholangitis, familial adenomatous polyposis, dysplasia, neoplasia, cancer of the pouch; and medical, endoscopic, or surgical treatment. †Excluded records comprised articles deemed not relevant on the basis of the study title or abstract; and editorials, reviews, and book chapters.

proctocolectomy and ileal pouches; case series for FAP had to number more than 50 patients to be included. Key relevant literature before the year 2000 was also included.

Consensus process and document development

Our 41-member panel consisted of leading experts in pouch disorders with different perspectives. The panel comprised 22 specialists in gastroenterology, IBD, and endoscopy, 13 surgeons (IBD or colorectal), two gastrointestinal pathologists, two gastrointestinal radiologists, one gastrointestinal oncologist, and one radiation oncologist from leading institutions in IBD and ileal pouch disorders worldwide. Inclusion criteria for the investigators required that at least two of the three criteria were met: (1) clinical practice focused on IBD, FAP, or both, with experience in ileal pouch disorders and personal experience in the diagnosis or management, or both, of pouch neoplasia; (2) publication of articles related to pouch dysplasia, neoplasia, or cancer; and (3) expertise in clinical IBD, IBD pathology, IBD radiology, or colorectal surgery. The members of the steering committee had to have experience in the management of pouch-associated, colitis-associated, or FAP neoplasia (dysplasia or cancer), publication of articles related to the diagnosis and management of inflammatory pouch disorders, pouch dysplasia, or cancer.

We used the Delphi method to guide the preparation of documents.[5] The multidisciplinary consensus group consisted of nationally or internationally renowned IBD and ileal pouch experts in medical, surgical, oncological, and pathological sciences. The steering committee generated point items based on an extensive literature review, which were first circulated among members of the steering committee via email. Multiple revisions were made according to the feedback from each committee member. The committee-approved draft was distributed among all members of the consensus group via group email, which was further revised multiple times based on comments from the members. A virtual continuing medical education-accredited consensus meeting with the first-round voting process was convened on July 25 and Aug 8, 2021. The participants voted anonymously on their agreement with the statements, provided comments, and suggested revisions. The second round of the web-based voting process for the revised statements was done within 2 months of the virtual meeting. A statement was accepted if more than 80% of participants agreed with the proposed statements. The manuscript was reviewed, re-reviewed, and approved by all members of the consensus group. Three statements were voted off by the panellists during a videoconference (appendix p 4).

This document was developed based on published literature and a consensus among expert participants in the group. We adopted the Oxford Centre for Evidence-based Medicine methodology to generate recommendations (appendix pp 1–3). We graded evidence level from 1 to 5, with 1 having the strongest evidence; and graded recommendation from A to D with A being the most highly recommended.

The consensus statements are listed in the table. The listed point statements follow the sequence of disease entities from glandular neoplasia to squamous neoplasia, lymphoproliferative disorders, and melanoma, and each disease category from the least to most invasive approaches.

Frequency, risk factors, diagnosis, and prognosis of pouch neoplasia

Various grades, morphologies, and histological types of dysplasia or cancer can occur in the pouch or parapouch, ranging from low-grade dysplasia to adenocarcinoma. Parapouch squamous cell dysplasia and squamous cell carcinoma also occur in this patient population but they are rare.

Pouch neoplasia in inflammatory bowel disease

Pouch neoplasia is not common in patients with IPAA for IBD. In a study of 3203 consecutive patients from Cleveland Clinic (Cleveland, OH, USA; 1984–2009) with a preoperative diagnosis of IBD who had restorative proctocolectomy and IPAA, 38 (1·2%) patients developed pouch neoplasia, including 11 (0·3%) with adenocarcinoma of the pouch or of the anal transition zone, or both, one (<0·1%) with pouch lymphoma, three (<0·1%) with squamous cell cancer at the anal transition zone, and 23 (0·7%) with dysplasia in the afferent limb, pouch body, cuff, or anal transition zone. The reported cumulative

		Evidence level (range 1–5)*	Grade of recommendation (range A–D)†
1. Management of neoplasia of glandular origin in IBD pouch			
1. Medical therapy			
1.1.1	Adequate medical therapy for the treatment of underlying inflammation is needed for the further clarification of indefinite for dysplasia	4	D
1.1.2	Medical treatment of inflammatory disorders of the pouch with immunomodulators or biological agents has no apparent positive or adverse effect on established dysplasia or cancer	5	D
2. Endoscopic surveillance			
1.2.1	Endoscopic surveillance with random biopsies from the pouch body, rectal cuff, and anal transition zone is recommended in all patients following ileal pouch construction for ulcerative colitis	4	C
1.2.2	Random biopsies with high-definition, white-light endoscopy or targeted biopsies with image-enhanced endoscopy can be used for detection of dysplasia	5	D
3. Endoscopic therapy			
1.3.1	Endoscopic polypectomy, endoscopic mucosal resection, or endoscopic submucosal dissections can be performed for the treatment of histology-proven low-grade dysplasia, if the lesion is unifocal and polypoid or raised, completely lifts with clear borders, and is located in the pouch body or afferent limb, or both; resections and dissections should be performed by experienced endoscopists trained in these procedures, with extreme precaution for the risk of bleeding and perforation	5	D
1.3.2	If endoscopic resection is performed, complete removal of a lesion in one piece is preferred, if feasible	5	D
1·3.3	If endoscopic polypectomy or resection is performed, adjacent mucosa should be biopsied	5	D
1.3.4	If endoscopic resection is performed, careful histopathological examination is needed to ensure the resection border is free of dysplasia; a second-look endoscopy within 4 weeks (preferably with dye-based or virtual chromoendoscopy) with biopsy is recommended if the margin is not clear; surgery (such as local excision at the examination under anaesthesia) is recommended if the border is not clear from dysplasia or there is a residual dysplastic lesion on the second look endoscopy‡	5	D
1.3.5	Endoscopic therapy is not recommended for patients with biopsy-proven adenocarcinoma located anywhere in the pouch body or parapouch area	5	D
1.3.6	Endoscopic therapy might be performed in selected patients with low-grade dysplasia in the rectal cuff or anal transition zone	5	D
1.3.7	We recommend placing a tattoo adjacent to the lesion with photo-documentation before endoscopic resection	5	D
1.3.8	Patients having multifocal, flat, non-liftable, or non-clear-bordered persistent lesions with histology-proven low-grade dysplasia of the pouch body or prepouch afferent limb, rectal cuff, or anal transition zone require surgical management	5	D
1.3.9	Patients with low-grade lesions who have had successful endoscopic therapy should have close surveillance initially at 3–6 months, then repeated at the same interval for two or three more times, or until two consecutive negative times, and yearly afterwards; recurrent or progressed dysplasia warrants surgical management‡	4	D
1.3.10	Endoscopic polypectomy, endoscopic mucosal resection, or endoscopic submucosal dissection might be attempted (but remains controversial due to a paucity of data) for the treatment of histology-proven high-grade dysplasia located in the pouch body if lesion is unifocal and polypoid or raised, and shows a discrete border, in those without risk factors for the development of pouch neoplasia (eg, the absence of precolectomy colitis-associated neoplasia or primary sclerosing cholangitis); close follow-up is necessary	5	D
1.3.11	Endoscopic polypectomy, endoscopic mucosal resection, or endoscopic submucosal dissection is not recommended for the treatment of flat or poorly demarcated lesions with histology-proven high-grade dysplasia located anywhere in the pouch body or parapouch area; histology-proven high-grade dysplasia located in the rectal cuff or anal transition zone regardless of size, shape, and border; or in those with risk factors for the development of pouch neoplasia (eg, presence of precolectomy colitis-associated neoplasia or primary sclerosing cholangitis); surgical local excision or even pouch excision should be considered recommended for these patients	5	D
4. Topical therapy			
1.4.1	Local application of bichloroacetic acid or trichloroacetic acid, which have been used for the treatment of anal squamous cell cancer, is not recommended for patients with pouch neoplasia of a glandular source	5	D
1.4.2	Infrared coagulation, argon plasma coagulation, and radiofrequency ablation are not recommended for a pouch neoplasia of glandular source	5	D

(Table continues on next page)

incidence rates for pouch neoplasia were 0·9% at 5 years, 1·3% at 10 years, 1·9% at 15 years, 4·2% at 20 years, and 5·1% at 25 years.[6] In a retrospective study using a specific Dutch pathology database, 1200 patients with IBD and IPAA were identified; 25 (1·8%) patients developed pouch neoplasia, including 16 adenocarcinomas. Cumulative

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For more on **Oxford Centre for Evidence-based Medicine methodology** see https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009

See **Online** for appendix

		Evidence level (range 1–5)*	Grade of recommendation (range A–D)†
(Continued from previous page)			
5. Surgical therapy			
1.5.1	Transanal local excision of unifocal and polypoid or raised, completely liftable, and clear-border low-grade dysplastic lesions at the pouch body, rectal cuff, or anal transitional zone can be attempted; a full circular or circumferential excision (>180-degree strip excision) with pouch advancement for multifocal dysplasia or any high-grade dysplasia in the rectal cuff or anal transitional zone might be considered‡	4	D
1.5.2	If transanal local excision of the dysplastic lesion is performed, complete resection in a single piece is preferred	5	D
1.5.3	Patients with dysplasia who had local surgical therapy should have close surveillance initially at 3–6 months (3 months for high-grade and 6 months for low-grade dysplasia), then repeated in the same interval for two or three more times, or until two consecutive negative times, and yearly afterwards; persistent or recurrent dysplasia warrants excision of the ileal pouch, rectal cuff, and anal transitional zone‡	5	D
1.5.4	If local surgical excision is performed, a careful histopathological examination is needed to ensure the resection margin is free of dysplasia; subsequent excision of the ileal pouch, rectal cuff, and anal transition zone is recommended if the margin is positive for high-grade dysplasia; these patients should be followed up closely with subsequent examination under anaesthesia	5	D
1.5.5	Pouch excision is recommended for adenocarcinoma of the rectal cuff, anal transitional zone, or other pouch locations; timely referral to a specialised centre for ileal pouch disorders is recommended for those with flat, non-liftable, non-clear-bordered low-grade, or low-grade lesions in the rectal cuff or anal transitional zone, synchronous or metachronous low-grade or high-grade dysplasia of the rectal cuff or anal transitional zone, and pouch body or afferent limb, or persistent dysplasia	4	C
1.5.6	Redo J or S pouch construction and ileal pouch–anal anastomosis might be attempted after pouch excision for dysplasia in the pouch body, rectal cuff, or anal transition zone, in selected patients	4	D
1.5.7	Surgical conversion of a pelvic pouch to a continent ileostomy using the same pouch body is contraindicated in patients with adenocarcinoma of the pouch body, rectal cuff, or anal transition zone	5	D
1.5.8	Permanent end ileostomy is required in most patients after pouch excision for neoplasia in the pouch body or parapouch areas; however, the construction of a neo-continent ileostomy might be considered in selected patients depending upon the clinical characters of the cancer	5	D
6. Tumour board and multidisciplinary approach			
1.6	A multidisciplinary approach including tumour board is recommended for pouch adenocarcinoma due to its complexity and prognosis	5	D
7. Tumour staging of pouch adenocarcinoma			
1.7.1	Serological markers such as carcinoembryonic antigen in all patients, plus cancer antigen 19-9 in those with concurrent primary sclerosing cholangitis-associated cholangiocarcinoma, should be routinely monitored after the diagnosis of adenocarcinoma	5	D
1.7.2	Tumour staging for patients with pouch adenocarcinoma includes MRI of the pelvis with contrast and CT scan of the abdomen and chest with contrast unless contraindicated	5	D
1.7.3	The role of endoscopic ultrasound in cancer staging for patients with pouch adenocarcinoma has not been defined, and until additional data becomes available, it is not recommended	5	D
1.7.4	Examination under anaesthesia with deep or punch biopsy should be considered, for any patients with suspicion of cancer who have polypoid or non-polypoid neoplastic lesions, those with long-standing non-healing fistulas, or strictures refractory to dilation or electroincision at the anastomosis, rectal cuff, or anal transition zone	5	D
1.7.5	A comprehensive histologic evaluation of endoscopically or surgically resected and excised pouch specimens is warranted, by at least one expert gastrointestinal pathologist	5	D
8. Chemoradiotherapy therapy of pouch adenocarcinoma			
1.8.1	Consultation with medical oncology and radiation oncology specialists should be obtained for patients with pouch adenocarcinoma prior to surgical intervention	5	D
1.8.2	For patients with pouch adenocarcinoma who do not have pouch excision surgery for whatever reason, the risks and benefits of radiotherapy should be carefully balanced, as pelvic radiation can result in radiation-associated pouchitis, long-term pouch dysfunction, or loss of pouch; pre-radiation faecal diversion with ileostomy is often needed	5	D
2. Management of neoplasia of squamous cell origin in IBD pouch			
1. Is surveillance for squamous cell neoplasia necessary?			
2.1	We were not able to recommend who should provide and when to start separate surveillance for neoplasia of squamous origin; however, surveillance for squamous cell neoplasia is a part of routine pouch surveillance for neoplasia; imaging enhanced endoscopy or high-resolution anoscopy might be helpful	5	D

(Table continues on next page)

		Evidence level (range 1–5)*	Grade of recommendation (range A–D)†
(Continued from previous page)			
2. Medical therapy of underlying inflammation			
2.2	It is not clear if adequate control of inflammation of the pouch, rectal cuff, or anal transition zone affects the development or outcome of squamous cell neoplasia in patients with pouches	5	D
3. Endoscopic surveillance and therapy			
2.3.1	Surveillance for squamous cell dysplasia or cancer with anal Pap smear, anoscopy, pouchoscopy, or examination under anaesthesia is recommended for patients at increased risk, such as those with a history of HPV or HIV infection, chronic, severe perianal skin excoriation, or previous squamous cell dysplasia	5	D
2.3.2	Endoscopic resection of squamous neoplasia in the pouch, rectal cuff, or anal transition zone is not recommended	5	D
4. Topical therapy			
2.4.1	The role of local application of bichloroacetic acid or trichloroacetic acid, which have been used for the treatment of anal squamous cell cancer, is not clear for patients with squamous cell cancer after ileal pouch–anal anastomosis	5	D
2.4.2	The role of infrared coagulation, argon plasma coagulation, and radiofrequency ablation in the treatment of squamous cell cancer in patients with ileal pouch–anal anastomosis is not clear	5	D
5. Surgical therapy			
2.5.1	Local surgical excision of dysplastic lesions of the squamous cell origin in patients with an ileal pouch might be performed	5	D
2.5.2	Local surgical excision of early superficial squamous cell cancer (T1N0M0) in patients with an ileal pouch might be considered based on the location and size of the lesion	5	D
2.5.3	For more advanced squamous cell cancer, management mirrors that of anal squamous cell cancer; a multidisciplinary approach, baseline pouch function, and patient preferences indicate surgical excision versus chemoradiotherapy alone; this approach can be individualised depending on the location and size of cancer, its depth, and the need for radiotherapy with or without chemotherapy	5	D
2.5.4	Redo pelvic pouch construction for patients with squamous cell cancer and ileal pouch–anal anastomosis is not recommended because of compromise on oncological resection margins	5	D
2.5.5	Surgical conversion from a failed pelvic pouch due to squamous cell neoplasia to a continent ileostomy using the same pouch body or construction of neo-continent ileostomy might be considered in selected patients	5	D
6. Tumour board and multidisciplinary approach			
2.6	A multidisciplinary approach including tumour board is recommended for advanced squamous cell cancer in patients with ileal pouches due to its complexity and prognosis	5	D
7. Tumour staging			
2.7	Tumour staging for patients with squamous cell cancer and ileal pouch–anal anastomosis includes PET scan, CT scan of the abdomen, pelvis, and chest with contrast, and, in selective cases, MRI of the pelvis with contrast might be considered; all patients should have HPV and HIV testing if the status is unknown and women should have a gynaecological examination with screening for cervical cancer	5	D
8. Immune therapy and chemoradiotherapy			
2.8.1	Patients with ileal pouch–anal anastomosis should follow the recommendation for HPV vaccine, as for the general population based on the WHO position papers on HPV, the Advisory Committee on Immunization Practices of the USA, and European Centre for Disease Control and Prevention Guidance on HPV vaccination guidelines	5	D
2.8.2	The role of immunotherapy for localised HPV-associated anal squamous cell cancer is not clear	5	D
2.8.3	Consultation with medical oncology and radiation oncology specialists should be obtained for patients with squamous cell cancer	5	D
2.8.4	For those with squamous cell cancer who do not have pouch excision surgery, the risks and benefits of radiation therapy should be carefully balanced, as pelvic radiation can result in radiation-associated pouchitis and pouch loss	5	D
3. Management of neoplasia in the pouch for familial adenomatous polyposis			
1. Medical therapy			
3.1	Chemoprevention for disease progression with medications such as sulindac, eflornithine, or a combination of both might be considered in patients with familial adenomatous polyposis after ileal pouch–anal anastomosis	1	A

(Table continues on next page)

		Evidence level (range 1–5)*	Grade of recommendation (range A–D)†
(Continued from previous page)			
2. Endoscopic surveillance and therapy			
3.2.1	Annual surveillance is recommended in patients with familial adenomatous polyposis after ileal pouch–anal anastomosis‡	4	C
3.2.2	Hot snare or cold snare polypectomy or endoscopic mucosal resection appears to be safe and feasible in the treatment of discrete pouch, rectal cuff, or anal transition zone polyps or adenomas in patients with familial adenomatous polyposis	4	C
3. Surgical therapy			
3.3.1	Excisional surgical procedures (eg, transanal circumferential excision or mucosectomy, mucosal advancement, and redo anal pouch anastomosis) are recommended for lateral spreading adenomas (ie, extensive or carpeting), or flat adenomas in the rectal cuff or anal transition zone if endoscopic removal is not feasible	5	D
3.3.2	Pouch excision is recommended for pouch adenocarcinoma in patients with familial adenomatous polyposis	5	D
4. Surveillance and management of the diverted pouch			
4.1	Optimal management of dysplasia in a long-term or permanently diverted pouch (eg, close surveillance, endoscopic mucosal resection, endoscopic submucosal dissections, or surgical pouch excision) is uncertain, due to scarce published data, personal experience, and unclear disease course; pouch excision can be the best option	5	D
5. Management of other rare malignancies of the pouch			
5.1	In patients with pouch lymphoma, obtain multidisciplinary consultation for management	5	D
5.2	We are not able to recommend a surveillance or management strategy for carcinoid tumours in the ileal pouch as these are very rare	5	D
5.3	We are not able to recommend a surveillance or management strategy for melanoma in the pouch as this is very rare	5	D
6. Surveillance and management after neoplasia diagnosis with or without endoscopic or surgical treatment			
6.1	Serological monitoring with carcinoembryonic antigen should be routinely obtained after any endoscopic or surgical therapy, including pouch-preserving procedure or pouch excision for adenocarcinoma	5	D
6.2	Endoscopic surveillance with or without image-enhanced endoscopy should be routinely performed in patients undergoing faecal diversion and revised pouch in situ or reconstructed pouch for pouch neoplasia	5	D

HPV=human papillomavirus. *Evidence level are: 1a (systematic review with homogeneity of RCTs); 1b (individual RCT); 1c (all-or-none studies); 2a (systematic review with homogeneity of cohort studies); 2b (individual cohort study); 2c (outcome research or ecological studies); 3a (systematic review with homogeneity of case-control studies); 3b (individual case-control study); 4 (case series); and 5 (expert opinion). †Grades of recommendations are: A (consistent level 1 studies), B (consistent level 2–3 studies or extrapolation from level 1 studies), C (level 4 studies or extrapolation from level 2 or 3 studies), and D (evidence or troublingly inconsistent or inconclusive studies of any level; appendix p 4). ‡The quantified duration, interval, length, or size in the recommendation is based on the agreement with relevant evidence in principle and a combined assessment of current literature and clinical adjustment of the panellists.

Table: **Consensus statements for the management of pouch neoplasia**

incidence rates for pouch neoplasia were 1·0% at 5 years, 2·0% at 10 years, 3·7% at 15 years, and 6·9% at 20 years; and for pouch carcinoma, cumulative incidence rates were 0·6% at 5 years, 1·4% at 10 years, 2·1% at 15 years, and 3·3% at 20 years.[7] In a systematic review of 35 studies of restorative proctocolectomy and IPAA for ulcerative colitis, 49 patients were reported to have adenocarcinoma, with 14 (28·6%) arising from the pouch and 33 (67·3%) from the anorectal mucosa. The pooled cumulative incidence of pouch adenocarcinoma was 0·33% (95% CI 0·31–0·34) 50 years after IBD diagnosis and 0·35% (0·34–0·36) 20 years after construction.[8] However, a study of 1723 patients with IPAA for ulcerative colitis in the national Danish Cancer Registry found two (0·1%) patients had pouch cancer during a median follow-up of 12·9 years (IQR 7·7–19·6). Compared with 8615 matched controls, the risk of overall gastrointestinal and hepatobiliary cancer following IPAA was identical to that of the comparison cohort with an incidence rate ratio of 1·1 (95% CI 0·8–1·3), raising questions for the need for routine surveillance.[9] A subsequent study was reported from Cleveland Clinic (2010–20) with a total of 9398 diagnostic or surveillance pouchoscopies in 3672 patients with a preoperative diagnosis of ulcerative colitis. 13 patients (0·1% of procedures) were found to have biopsy-proven neoplasia at the time of pouchoscopy, including seven low-grade dysplasias, all from the anal transition zone, and six (0·1%) with invasive adenocarcinoma (four at the anal transition zone and two at the pouch body).[10] Since the patients with pouch adenocarcinoma were symptomatic, the authors did not recommend surveillance pouchoscopy for asymptomatic patients.[10]

The main risk factor associated with pouch neoplasia was the presence of a preoperative diagnosis of colitis-associated neoplasia, with adjusted hazard ratios (HR) of 3·6 (95% CI 1·6–8·2) for preoperative dysplasia and 13·4 (4·0–45·5) for preoperative cancer.[6] One additional study revealed similar results; the presence of a precolectomy diagnosis of colitis-associated neoplasia was found to be a major risk factor for pouch neoplasia, with an HR

of 3·8 (1·4–10·2) for previous dysplasia and 24·7 (9·6–63·4) for previous adenocarcinoma.[7] Precolectomy colitis-associated neoplasia was also shown to be a major risk factor for pouch adenocarcinoma in the pooled analysis.[8] However, precolectomy dysplasia might not be found in the colectomy specimens in a small number of patients. Dysplasia or cancer might, however, be found in surgical specimens with colectomy performed for other indications.

The unclear disease course and the relative rarity of pouch or parapouch neoplasia in IBD have resulted in a wide variation in surveillance practice in patients with ulcerative colitis and IPAA. In a survey of clinicians caring for 272 patients with IPAA, 95 (35%) patients had never had pouchoscopy for any indication; and 191 (70%) had never undergone surveillance pouchoscopy over a median duration of pouch follow-up of 10·5 years (IQR 3·3–23·6).[11]

Histological evaluation of endoscopic or surgical specimens with regular haematoxylin and eosin stain is the gold standard for the diagnosis of epithelial neoplasia. Information on the site of the biopsy provided by the endoscopist is also crucial. There is often disagreement among pathologists in scoring colitis-associated neoplasia, even among gastrointestinal pathologists.[12] However, interobserver agreement has not been widely studied in pouchitis-associated neoplasia. In a study from a large IBD centre, interobserver agreement (κ score) between two gastrointestinal pathologists ranged from 0·60 to 0·76 for diagnosing indefinite for dysplasia (figure 2).[13,14] The agreement in low-grade dysplasia or high-grade dysplasia in the pouch between gastrointestinal pathologists has not been reported. The diagnosis of IBD-associated or pouchitis-associated dysplasia, especially indefinite for dysplasia and low-grade dysplasia, should be confirmed by a second gastrointestinal pathologist.[15,16]

The diagnosis of indefinite for dysplasia in IBD can be considered as a separate category with risk of subsequent low-grade dysplasia or high-grade dysplasia, particularly in cases with persistent diagnoses of indefinite for dysplasia after control of background inflammation.[16] Data on the natural history of indefinite for dysplasia in the pouch are scarce. However, studies focused on the colon have shown that p53 immunohistochemical staining helps predict subsequent dysplasia after indefinite for dysplasia diagnosis in the setting of IBD.[17,18] By extrapolation, p53 immunohistochemistry might be helpful in risk stratification of recurrent indefinite for dysplasia lesions in the pouch, rectal cuff, or anal transition zone (figure 2).

The evolution of pouch or parapouch neoplasia is not well defined and a sequence of chronic inflammation, dysplasia, and adenocarcinoma in the pouch or parapouch mucosa is not fully established. Pouchoscopy, currently the standard surveillance modality, can still miss dysplasia before the development of cancer.[6] In a series of 11 patients diagnosed with pouch adenocarcinoma, nine (81·8%) were detected

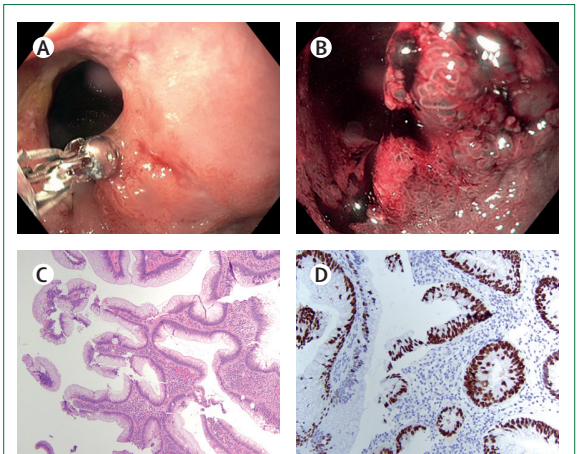

***Figure 2*: Indefinite for dysplasia in the cuff in a patient with a precolectomy diagnosis of adenocarcinoma of the caecum and multifocal high-grade and low-grade dysplasia of the sigmoid colon**
(A–B) Flat, nodular lesions at the proximal cuff on white-light and narrow-band imaging. (C) Histology of biopsy specimen showed hypermucinous features. (D) Immunohistochemistry showed overexpression of p53.

with annual surveillance at the cancer stage, rather than at the stage of low-grade dysplasia or high-grade dysplasia.[6] Furthermore, three (27·3%) patients had no visible lesions on pouchoscopy at the time of adenocarcinoma diagnosis.[6] Therefore, endoscopic surveillance, a standard of clinical practice, can still miss dysplasia. On the other hand, dysplasia does not inevitably lead to cancer, and regression of multifocal low-grade dysplasia and high-grade dysplasia in IPAA has been reported.[19] In a study evaluating the disease course in 44 patients with pouch neoplasia (including low-grade dysplasia [n=22], high-grade dysplasia [n=12], and adenocarcinoma [n=14]) family history of colorectal cancer was shown to be a risk factor associated with the persistence or progression of low-grade dysplasia. Five (41·7%) patients with high-grade dysplasia had a history of previous or synchronous pouch low-grade dysplasia and in three patients with high-grade dysplasia, the dysplasia either persisted or progressed during a median time interval of 5·4 years (IQR 2·2–9·2) . The risk for persistence or progression of dysplasia is higher with high-grade dysplasia than with low-grade dysplasia. In six (27·3%) patients with low-grade dysplasia, the dysplasia persisted or progressed over a median follow-up of 9·5 years (IQR 4·1–17·6).[20] In 14 patients with pouch adenocarcinoma, 12 (85·7%) had meta-chronous (n=2; 14·3%) or synchronous dysplasia (n=12; 85·7%).[20] The prognosis of pouch adenocarcinoma was poor. Of 14 patients with adenocarcinoma, three (21·4%) had stage I, six (42·9%) had stage II, three (21·4%) had stage III, and two (14·3%) had stage IV disease. Six of the 14 patients with pouch adenocarcinoma (42·9%) died after a median follow-up of 2·1 years (IQR 0·6–5·2).[20] According to one study, IBD-related pouch or parapouch adenocarcinomas (n=12) are more likely to show

histomorphological Crohn's-like reactions with more prominent inflammatory reactions than ulcerative colitis-associated colorectal adenocarcinomas (n=58). However, molecular features, including expression of mismatch repair (MMR) protein, p53, β-catenin, cytokeratin 7, cytokeratin 20, or CDX2 are comparable between the two groups, suggesting similar tumorigenic pathways.[21]

Pouch or parapouch squamous cell neoplasia is rare. Despite scant published data, our panellists felt that surveillance pouchoscopy in patients with IPAA can also include evaluation for dysplasia or cancer of squamous cell origin. Neoplasia of squamous cell origin includes low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell cancer. Biopsy at the rectal cuff or anal transition zone can be taken during white-light endoscopy, image-enhanced endoscopy (such as confocal endomicroscopy), or examination under anaesthesia. It is not clear whether a preoperative diagnosis of colitis-associated neoplasia increases the risk for the development of squamous neoplasia. It appears that infection with human papillomavirus (HPV) can have a role.[22] Immunohistochemistry for p16 would be helpful in difficult cases when the differential diagnosis is HSIL versus reactive changes. In situ hybridisation assay for HPV in high-risk individuals might be helpful in equivocal cases where classic viropathic changes have not been identified. High-resolution anoscopy and brushing for cytology, like its use in anal neoplasia in the general population, might be beneficial.

A recommendation for the classification of pouch or parapouch neoplasia and surveillance strategy was outlined in a previous consensus document.[3] For surveillance and management purposes, pouch or parapouch neoplasia is further classified (panel). Endoscopy plays a key role in the surveillance and management of pouch and parapouch neoplasia. Although image-enhanced endoscopy (such as dye-based and virtual chromoendoscopy) and examination under anaesthesia have been used to enhance the accuracy of surveillance, there is little evidence to support this.

Pouch neoplasia in familial adenomatous polyposis

In patients with FAP who undergo colectomy, the risk for the development of adenoma of the lower gastrointestinal tract is higher in those with ileal rectal anastomosis than IPAA or continent ileostomies. The incidence of adenoma was 85% at 5 years and 100% at 10 years follow-up for ileal rectal anastomosis and 12% at 5 years, 33% at 10 years, and 68% at 20 years of follow-up for ileal pouches.[23] Mucosectomy with hand-sewn anastomosis during restorative proctocolectomy and IPAA is indicated in some patients with FAP, especially where adenomas affect the very low rectum. Stapled anastomosis without mucosectomy is preferred for its better function in patients with a relatively clear lower rectum.[24,25] The most common locations of lower gastrointestinal neoplasia in patients who have had a colectomy for FAP are the retained rectum, after ileal rectal anastomosis, or the rectal cuff and anal transition zone, after stapled IPAA. Patients who have a hand-sewn IPAA after mucosectomy can still develop adenomas in the residual anal transition zone, the anastomosis, or parapouch area.[24] Neoplasia can also develop in the pouch itself. Targeted areas of surveillance and treatment, therefore, include the ileal pouch, rectal cuff, anal transition zone, and handsewn anastomosis itself. In a systematic review of 25 studies, the reported prevalence of adenomas in the ileal pouch varied from 6·7% to 73·9%. The risk increases from 7% to 16% after 5 years, 35–42% after 10 years, and to 75% after 15 years of follow-up.[26] In a study of 118 patients with FAP who had undergone IPAA, 57 (48·3%) had pouch adenomas at a median follow-up of 15 years after surgery and patients had pouch adenomas with high-grade dysplasia.[27] The risk factors associated with pouch adenomas were older age (>50 years) at pouch construction and the presence of advanced duodenal adenomas or presence of more than 1000 colonic adenomas at the time of colectomy.[25,27] The association between genotype (eg, *APC* mutations) and phenotype (risk of dysplasia and cancer) in patients with FAP is controversial.[28–32] Therefore, genotype-based risk stratification remains to be further investigated. Development of malignancy in the prepouch ileum is rare but might follow a rapid course.[28]

Fortunately, adenocarcinoma in IPAA is rare and adenomas in the pouch or parapouch can usually be safely managed by endoscopy. Until 2013, there were only 21 reported cases of ileal pouch carcinoma in patients with FAP and IPAA.[26] The median time from pouch construction to the detection of pouch adenocarcinoma was 10 years (range 3–20).[26] A retrospective study of 165 patients with FAP and IPAA reported dysplastic lesions in 26 patients (13 with low-grade dysplasia; eight with high-grade dysplasia; and five with adenocarcinoma) during follow-up with unclear total duration. The mean time for the detection of pouch or parapouch lesions was 14 months for low-grade dysplasia, 16 months for high-grade dysplasia, and 19 months for adenocarcinoma.[33] In the Dutch Polyposis Registry of 212 patients with FAP who had an IPAA with complete follow-up, four (1·9%) patients developed a carcinoma with a cumulative risk of 1% at 10 years.[34] Image-enhanced endoscopy is extensively used for surveillance in patients with FAP and appears to be associated with a higher than standard white-light endoscopy detection rate of pouch or parapouch neoplasia. In the 212 patients with FAP and IPAA in the Dutch Polyposis Registry, the cumulative risk of developing an adenoma in the pouch at 10-year follow-up was 45%. However, 25 (75·7%) of 33 adenomas were found in a subgroup of patients who were examined with chromoendoscopy, compared with 74 (34·9%) of 212 adenomas of the whole cohort surveyed using white-light endoscopy with or without chromoendoscopy.[34]

Panel: **Classification of the pouch and parapouch neoplasia**

Origin
- Intestinal epithelial or glandular cells from underlying inflammatory bowel disease (eg, glandular dysplasia and adenocarcinoma in the rectal cuff with underlying ulcerative colitis)
- Intestinal epithelial cells from underlying polyposis syndrome (eg, adenoma and adenocarcinoma in the pouch body with underlying familial adenomatous polyposis)
- Squamous cells (eg, anal canal squamous cell cancer or perianal fistula-related squamous cell carcinoma)
- Hematopoietic cells (eg, lymphoma)
- Melanocytes (eg, melanoma)

Configuration
- Inflammatory bowel disease
  - Polypoid (eg, adenoma)
  - Sessile or slightly raised (eg, slightly raised dysplasia or serrated lesions)
  - Flat (eg, flat dysplasia)
  - Depressed (eg, malignant ulcer)
- Familial adenomatous polyposis
  - Polypoid (eg, adenoma)
  - Flat (eg, flat adenoma)
  - Polypoid with central ulcer (eg, adenocarcinoma)

Number
- Single or unifocal
- Multiple or multifocal

Sequence
- Synchronous
- Metachronous

Location
- Prepouch efferent limb
- Pouch body
- Rectal cuff
- Anal transition zone
- Anus
- Anal or perianal fistula or sinus

Histological grade
- Intestinal epithelial origin (eg, negative for dysplasia, indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia, adenocarcinoma)
- Squamous cell origin* (eg, squamous intraepithelial neoplasia, low-grade [LSIL], condyloma acuminatum; squamous intraepithelial neoplasia, low-grade [LSIL]; squamous intraepithelial neoplasia, high-grade [HSIL]; squamous cell carcinoma including verrucous squamous carcinoma)

*Squamous cell cancer of the anus is classified based on WHO Classification of Tumours.

For more on **WHO Classification of Tumours** see https://whobluebooks.iarc.fr

For dysplasia surveillance in FAP, pouchoscopy is often performed along with upper gastrointestinal endoscopy to screen for gastroduodenal polyps, neoplasias, or malignancies. The surveillance protocol for FAP described in the guidelines from the American College of Gastroenterology (ACG)[15] is adopted by this consensus group. Lifelong endoscopic surveillance is important for the early detection of adenomas with low-grade dysplasia or high-grade dysplasia and the prevention of cancer in patients with FAP with IPAA. We previously proposed a surveillance strategy for the detection of pouch or parapouch neoplasia in a separate document.[3] The risk for the development of adenocarcinoma in patients with FAP after colectomy appears to be low, probably due to the practice of lifelong endoscopic surveillance. Only 21 cases of ileal pouch carcinoma have been recorded in the literature occurring between 3 and 20 years (median 10 years) after pouch construction in patients with FAP.[26]

The primary type of polyposis syndrome with restorative proctocolectomy and IPAA is FAP. In addition, restorative proctocolectomy and IPAA are constructed for other rare polyposis syndromes, such as juvenile polyposis, *MUTYH*-associated polyposis, and polymerase proofreading-associated polyposis with significant rectal involvement.[35,36] The incidence of pouch neoplasia in patients with these rare polyposis syndromes remains largely unknown.

Management of neoplasia of glandular origin in IBD pouch

The management algorithm for pouch neoplasia of glandular source is shown in figure 3. Surveillance pouchoscopy is recommended for patients at risk of pouch or parapouch neoplasia by our consortium,[3] the Global Interventional IBD Group,[4] and the European Crohn's and Colitis Organisation.[37] Briefly, surveillance pouchoscopy is recommended for individuals with risk factors such as the presence of precolectomy colitis-associated neoplasia as well as primary sclerosing cholangitis and chronic inflammatory disorders of the pouch (figure 4), and a family history of colorectal cancer in first-degree relatives. The surveillance interval is determined by the stratification of risk.[3,4] Routine surveillance pouchoscopy is not recommended in patients with continent ileostomies, as neoplasia is extremely rare.[3,4] All neoplasia should be evaluated and confirmed by at least one gastrointestinal pathologist.

Due to the aggressive nature of pouch neoplasia, endoscopic therapy or local surgical excision are reserved for selected patients, while pouch excision can be necessary. The approach for dysplasia versus cancer, and

neoplastic lesions in the pouch body or afferent limb versus in the rectal cuff or anal transition zone is different. For example, polypoid lesions that are amenable to endoscopic therapy are usually in the afferent limb or pouch body (figure 3). Dysplasia or cancer at the rectal cuff or anal transition zone is often flat with neoplastic lesions tending to be lateral spreading, requiring surgery.[6]

Medical therapy

The histological distinction between chronic pouchitis or cuffitis with reactive atypia and low-grade dysplasia is often difficult, leading to the use of the pathological term indefinite for dysplasia. Our expert panel speculates that adequate medical therapy with antibiotics, corticosteroids, or biological agents to control underlying inflammation and repeat surveillance biopsy with review from an expert gastrointestinal pathologist can help further clarify indefinite for dysplasia (recommendation 1.1.1, table; figure 2). The panel raised no safety concern regarding continuous use of immunomodulators or biologics in patients with pouch neoplasia, except for patients with pouch lymphoma in whom immunomodulators or anti- tumour necrosis factor biologics were not recommended. Currently, there is no evidence to suggest that medical treatment of pouchitis, Crohn's disease of the pouch, or cuffitis have a beneficial or adverse effect on disease course of established pouch or parapouch neoplasia (recommendation 1.1.2, table).

The frequency and natural history of indefinite for dysplasia have been investigated in 932 patients from a Pouch Registry, where 21 (2·3%) were diagnosed with indefinite for dysplasia at the pouch, rectal cuff, or anal transition zone. The presence of primary sclerosing cholangitis was found to be a risk factor for indefinite for dysplasia. During a mean follow-up of 19·3 months (SD 16·1), one patient with indefinite for dysplasia developed low-grade dysplasia and one evolved into high-grade dysplasia.[13] However, there are no prospective

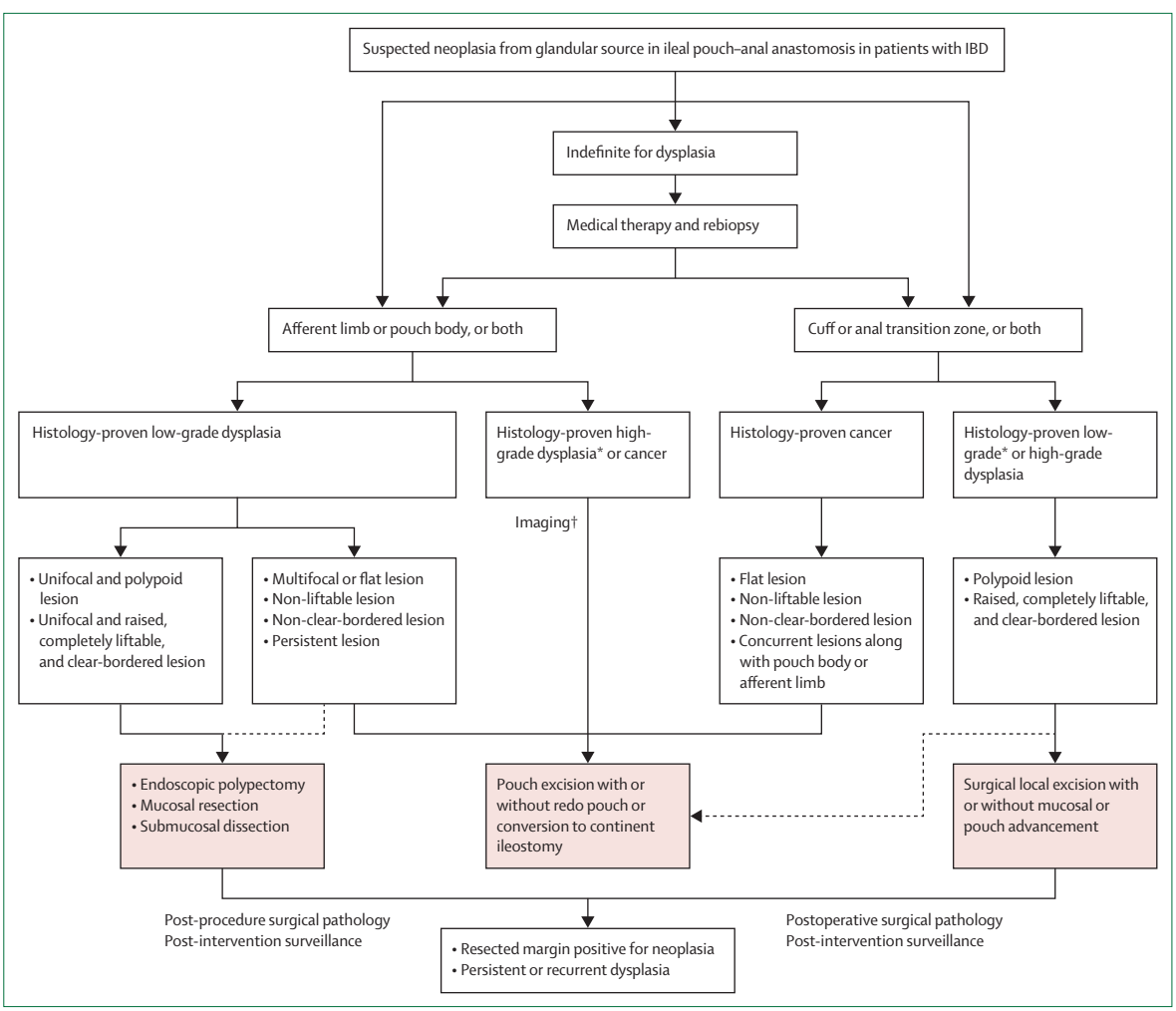

Figure 3: **Management algorithm for neoplasia of glandular source in patients with ileal pouch–anal anastomosis for IBD**
IBD=inflammatory bowel disease. *Endoscopic therapy for polypoid, liftable, and clear-bordered high-grade dysplasia in the afferent limb or pouch body, or low-grade dysplasia in the cuff or anal transition zone might be attempted in highly selected patients. †Imaging for diagnosis, staging, and monitoring.

studies on the regression of indefinite for dysplasia with anti-inflammatory therapy. It is prudent that patients with indefinite for dysplasia should have aggressive medical therapy for underlying inflammation and the patients should have closer surveillance, such as subsequent endoscopy in 3 to 6 months and every 12 months afterward. Immunohistochemical stain for p53 might be helpful in risk stratification of recurrent indefinite for dysplastic lesions in the pouch, rectal cuff, or anal transition zone (figure 2).[17]

Endoscopic surveillance

Our panel recommends pouchoscopy surveillance with random biopsies from the pouch body, rectal cuff, and anal transition zone for all patients following ileal pouch construction for ulcerative colitis (recommendation 1.2.1, table). The initiation and interval of surveillance pouchoscopy are described in a separate document from our consortium[3] and the Global Interventional IBD Group.[4] Annual surveillance endoscopy is suggested in patients with a precolectomy diagnosis of colitis-associated dysplasia or cancer and surveillance endoscopy (every 1–3 years) is suggested for patients with other purported risk factors (ie, the presence of primary sclerosing cholangitis, chronic pouchitis, chronic cuffitis, Crohn's disease of the pouch, long duration of ulcerative colitis [>8 years in total], or family history of colorectal cancer in a first-degree relative). For all other patients, the surveillance interval should be not be shorter than 3 years. For surveillance purposes, image-enhanced endoscopy is preferred, with at least three biopsies taken from the cuff or anal transition zone, along with biopsies from the afferent limb and pouch body.[3,4]

Although either anastomotic technique for IPAA can be associated with the development of cancer, stapled anastomosis without mucosectomy is preferred over mucosectomy with hand-sewn anastomosis because of its better pouch function and fewer complications. In addition, a stapled anastomosis is easier to survey than the more often stenosed hand-sewn anastomosis. Some authors have suggested that surveillance pouchoscopy might not be warranted for asymptomatic patients with IPAA for ulcerative colitis, because of the rarity of pouch neoplasia.[10] However, the IIPC has recommended routine risk-stratified pouchoscopy in both symptomatic and asymptomatic patients.[3] Proposed surveillance strategies were outlined in a separate document from our consortium.[3] A historical cohort study from the Cleveland Clinic showed that mucosectomy during pouch construction did not completely protect against pouch neoplasia.[6] Three (14·3%) of 23 patients with pouch dysplasia and six (40%) of 15 with pouch cancer had undergone mucosectomy.[6] In a systemic review with possible selection bias, pouch patients with a stapled anastomosis have an increased risk of cancer arising from the residual anorectal mucosa, although the confidence interval was wide (OR 8·0; 95% CI 1·3–48·7).[8] Similarly, pouch cancer can occur in patients with hand-sewn anastomoses with or without mucosectomy.[38] Two cohort studies (1200 patients from the Dutch Pathology Registry[7] and 3194 patients from Cleveland Clinic)[6] did not identify this as a risk factor for pouch neoplasia.

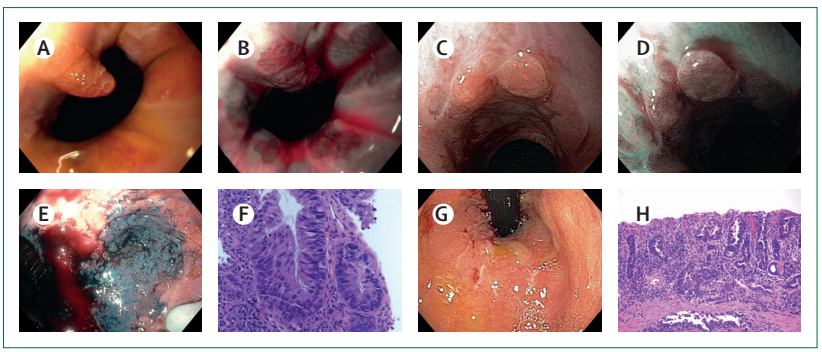

Figure 4: **Image-enhanced endoscopy and endoscopic techniques for the surveillance of pouch neoplasia in inflammatory bowel disease**
(A–B) A polypoid lesion at the anal verge enhanced by narrow-band imaging with a histologic diagnosis of indefinite for dysplasia. (C–D) Nodules at the anal transition zone with low-grade dysplasia highlighted with narrow-band imaging. (E–F) Flat lesion at the anal transition zone was highlighted by chromoendoscopy and histology showed focal high-grade dysplasia in a background of low-grade dysplasia (hematoxylin and eosin, 200×). (G–H) Retroflex view of distal pouchitis in a patient with ileal pouch-anal anastomosis and mucosectomy for a preoperative diagnosis of colitis-associated neoplasia. Histology showed invasive adenocarcinoma of the area (hematoxylin and eosin, 100×).

Although the yield of pouch dysplasia under white-light pouchoscopy appears to be low, random biopsies with high-definition white-light endoscopy or targeted biopsies with image-enhanced endoscopy can still be used for the detection of dysplasia (recommendation 1.2.2, table; figure 3). The effect of mucosal biopsy on the formation of submucosal fibrosis is theoretical and controversial. Fibrosis from biopsy has been implicated in the technical difficulty of resection. However, there are no published data on complications associated with polypectomy, endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD) or the buried neoplasia by taking mucosal biopsy. In addition, there are no published data on buried neoplasia after EMR or ESD in normal colons or ileal pouches. However, the accuracy of optical diagnosis of pouch neoplasia remains to be verified. The benefit of upfront endoscopic or surgical treatment of endoscopically suspected (white-light or image enhanced endoscopy), but not histologically proven, dysplastic lesions should be balanced with the risk of procedure-associated complications from the removal of non-neoplastic tissue.

A dysplastic lesion detected by random endoscopic biopsy warrants timely follow-up with repeat endoscopy, image-enhanced endoscopy, examination under anaesthesia, or a combination of these procedures, with extensive tissue sampling. Unifocal or multifocal dysplastic lesions might not be visible with conventional white-light endoscopy. The use of image-enhanced endoscopy and endoscopic retroflex view of the distal pouch and cuff are encouraged (figure 2, 4–5).[3] The Paris

classification was designed for the endoscopic characterisation of superficial neoplastic lesions in the colon as well as oesophagus and stomach.[39] The Paris classification might also be used to characterise the features of pouch neoplasia and guide therapy. Similarly, the Kudo classification of the pit pattern of colorectal neoplastic lesions has been used for the characterisation of colorectal polyps,[40] but its use in the management of pouch neoplasia warrants further investigation.

Endoscopic therapy

Endoscopic treatment modalities for pouch neoplasia include polypectomy, EMR, or ESD. If neoplastic lesions can be lifted by submucosal injection, the neoplasia is probably limited to the mucosa. However, non-liftable lesions do not necessarily contain tumour invasion, because submucosal fibrosis is common in IBD and potentially in chronic pouchitis as well. Similar to non-pouch IBD,[41] endoscopic polypectomy, EMR, and ESD have been used to treat pouch neoplasia. ESD has been described for the treatment of both liftable and non-liftable dysplastic lesions in ulcerative colitis.[42] Endoscopic polypectomy, EMR, or ESD can be attempted in unifocal and polypoid or raised, liftable, and clear-border low-grade dysplasia in the pouch body and afferent limb (recommendation 1.3.1, table; figure 6A–F). EMR or ESD can also be technically challenging, because of the underlying disease process of inflammation and submucosal fibrosis. EMR or ESD for treatment of lesions in the pouch body or prepouch afferent limb with a thinner wall and greater vascularity can be more difficult than in the colon or rectum. Endoscopic therapy is applied only to endoscopically visible lesions. The successful application of endoscopic treatment modalities—ie, polypectomy, EMR, or ESD—is determined by patients' underlying diseases (such as the presence of precolectomy colitis-associated neoplasia or primary sclerosing cholangitis), characteristics of the lesion (such as location, number, size, shape, border, degree of dysplasia, liftability, submucosal fibrosis, persistency), and local expertise in endoscopy and surgery (figure 4–6). ESD carries a significantly higher risk for complications (such as bleeding and perforation) than EMR. EMR and ESD are often technically challenging, and they should be performed by experienced endoscopists (recommendation 1.3.1, table).

If endoscopic resection is performed for dysplastic lesions, complete removal of a lesion in one piece is preferred (recommendation 1.3.2, table), although there are few data to inform this recommendation in the setting of pouch neoplasia. However, en-bloc resection can be technically difficult. The principle of en-bloc endoscopic resection of colitis-associated neoplasia in patients with an intact colon or rectum might apply to those with restorative proctocolectomy and IPAA.[43] The terminology of en-bloc resection in endoscopy and surgery is different. En-bloc here refers to the removal of the lesion in one piece, rather than piece-meal resection. Endoscopic en-bloc resection is performed with polypectomy, EMR, or ESD, depending on characteristics of the lesion and expertise of the endoscopist. There is no evidence to suggest that ESD has a better outcome than EMR in the treatment of pouch neoplasia, whereas ESD carries a higher risk for complications than EMR. There is a case report of a 76-year-old woman with a urinary Indiana pouch who developed colonic adenocarcinoma and was successfully treated with ESD.[44] ESD for the treatment of pouch neoplasia might be technically feasible when done by experienced endoscopists, as shown in case reports.[45,46] However, the long-term oncological outcome in ESD-treated patients has not been reported. The American Gastroenterological Association (AGA) guideline suggested that ESD had a higher rate of en-bloc resection and a lower recurrence rate for large (>2 cm) colorectal lesions than EMR.[47] However, the AGA guidelines for EMR and ESD did not specify its use for pouch neoplasia. If endoscopic polypectomy, EMR, or ESD is performed, adjacent mucosa should be biopsied because of a possible field effect of chronic mucosal inflammation-associated neoplasia (recommendation 1.3.3, table). Advances in endoscopic imaging technology with better characterisation of mucosal and pit features might replace random biopsy of the adjacent mucosa around dysplastic lesions in the future.[48] However, normal or neoplastic pit patterns in the ileal pouch mucosa in dysplasia surveillance have not been established, as normal small bowel mucosa is charaterised by villi rather than pits. The principle of margin-free resection of neoplasia following endoscopic resection of colitis-associated neoplasia in patients with an intact colon applies to those with restorative proctocolectomy and IPAA.[49] An article by Sidhu and colleagues[50] showed a reduction in residual or recurrent thermal ablation of the defect margin after EMR for treating large (≥20 mm) non-pedunculated sporadic colorectal polyps in patients

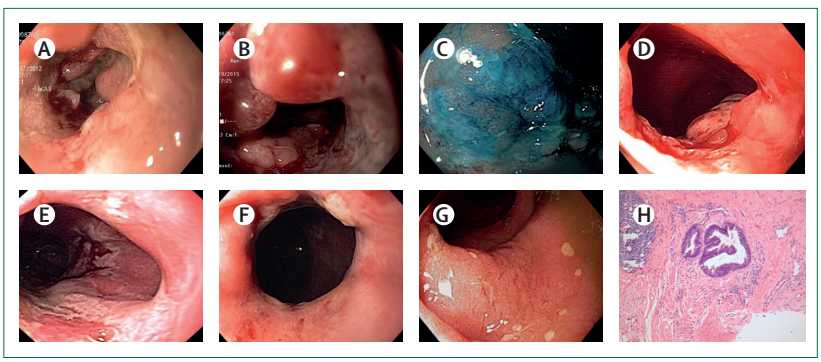

Figure 5: **Adenocarcinoma detected in chronic inflammatory disorders of the pouch or parapouch**
(A–C) Adenocarcinoma with nodular mucosa of the distal pouch and cuff which had been mistaken for Crohn's diseass. (D) Adenocarcinoma found in chronic cuffitis with inflammatory polyps. (E–F) Adenocarcinoma found in chronic cuffitis which responded to topical mesalamine therapy. (G–H) Retroflex view of distal pouchitis in a patient with ileal pouch–anal anastomosis and mucosectomy for a preoperative diagnosis of colitis-associated neoplasia. Histology showed invasive adenocarcinoma of the area (hematoxylin and eosin, 40×).

without colitis. Whether this technique reduces the risk of recurrence after resection of dysplastic lesions in ileal pouches has not been evaluated, and warrants prospective study.

Endoscopically resected specimens should be carefully examined for histopathological features, including the resection border status. A second-look endoscopy within 4 weeks with biopsy is recommended if the margin is not clear. Surgery is recommended if the border is not clear or there is a residual dysplastic lesion on the second-look endoscopy (recommendation 1.3.4, table). Our panel recommends surgery, rather than endoscopic therapy, for adenocarcinoma located anywhere in the pouch body or parapouch area (recommendation 1.3.5, table).

It seems that dysplasia in the pouch body or at the rectal cuff or anal transition zone behaves differently. Our panel suggests that dysplasia at the rectal cuff or anal transition zone can be treated similarly to colitis-associated neoplasia in IBD, in which surgical resection is preferred over endoscopic resection. The strategy of endoscopic and surgical treatment of dysplastic lesions in the pouch or parapouch areas is different. Endoscopic treatment of dysplastic lesions in the rectal cuff or anal transition zone is often difficult due to the confined space, and disease behaviour (eg, flat lesion or lateral spreading lesions).

Not all low-grade dysplastic lesions in the pouch or parapouch area persist or progress. Some of those lesions appear to regress.[20] In ulcerative colitis, multifocal low-grade dysplasia can carry a higher risk for progression than unifocal lesions.[51] Multifocal low-grade dysplastic lesions in the pouch or parapouch area might follow the same trend of progression, although there are no published data. However, it is difficult to predict which low-grade dysplastic lesions will progress or regress (or at least are not found in follow-up). Our panel felt that histopathologically confirmed low-grade dysplastic lesions should be removed if possible.

Our panellists debeted endoscopic versus surgical therapy for the treatment of low-grade dysplasia in the rectal cuff or anal transition zone. Endoscopic therapy might be performed in selected patients with unifocal, polypoid, clear-border low-grade dysplastic lesions in the rectal cuff or anal transition zone (recommendation 1.3.6, table; figure 6A–F). For further surveillance and possible additional interventions, our panel recommends that any dysplastic lesion should be marked and photo-documented before endoscopic therapy (recommendation 1.3.7, table). Our panel recommends surgical management (eg, local excision, circumferential excision with pouch advancement, or pouch excision) rather than endoscopic therapy for multifocal, flat, non-liftable, or non-clear-bordered, persistent low-grade dysplastic lesions in the prepouch afferent limb, pouch body, rectal cuff, or anal transition zone (recommendation 1.3.8, table). Endoscopically non-visible lesions detected by random biopsies might require surgery. Some patients with low-grade dysplasia, for whatever reason, might elect to have intensified surveillance. While acknowledging shared decision making and autonomy, these patients should be well informed of the risk of the development of cancer. Patients with low-grade dysplastic lesions who have undergone successful endoscopic therapy should have close surveillance (recommendation 1.3.9, table). Our panel recognised that endoscopic surveillance can be more challenging in flat or slightly raised lesions than polypoid lesions after endoscopic removal. If low-grade dysplasia persists or high-grade dysplasia or cancer is detected, the above surgical approaches are recommended.

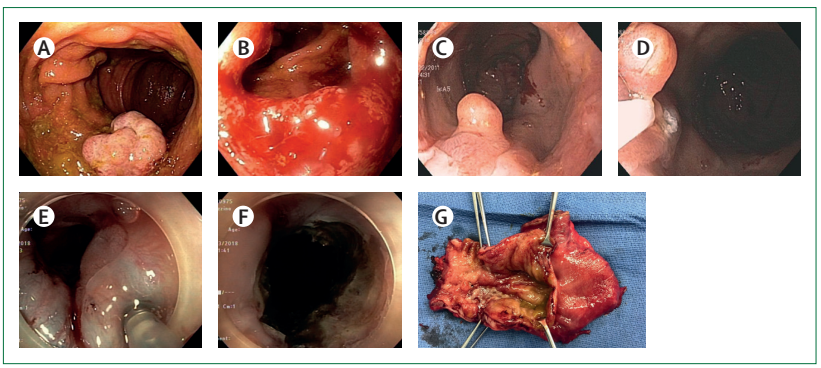

Figure 6: **Management of dysplastic lesions in the pouch or parapouch in IBD**
Endoscopic hot snare polypectomy of adenomatous lesions with low-grade dysplasia at the distal pouch body (A–B) and cuff (C–D). (E–F) Endoscopic mucosal resection of a flat lesion with low-grade dysplasia in the cuff. (G) Distal pouch adenocarcinoma after pouch excision from a patient with a preoperative diagnosis of ulcerative colitis. IBD=inflammatory bowel disease.

The management of high-grade dysplasia in the pouch or parapouch areas generated great debate among our panellists, largely due to the lack of definable clinical context and natural history. Despite the technical feasibility of endoscopic removal of high-grade dysplastic lesions, the oncological benefit of the endoscopic approach is not clear. Endoscopic polypectomy, EMR, or ESD might be attempted for the treatment of unifocal and polypoid or raised, and clear-border high-grade dysplastic lesions in the pouch body in those without risk factors for pouch neoplasia (such as a preoperative diagnosis of colitis-associated neoplasia or primary sclerosing cholangitis; recommendation 1.3.10, table). Some panellists raised concerns about the field effect of chronic inflammation-associated dysplasia. However, the panel agrees that the optimal approach should be individualised, based on the risk assessment of dysplastic lesions and patients (eg, those with precolectomy colitis-associated neoplasia or primary sclerosing cholangitis), and the expertise of endoscopists and colorectal surgeons. The presence of high-grade dysplasia in the rectal cuff or anal transition zone is often a harbinger of cancer. High-grade dysplastic lesions hardly ever regress to low-grade dysplasia, indefinite for dysplasia state, or normal mucosa. Surgery is usually required. Therefore, our panel did not recommend endoscopic polypectomy, EMR, or ESD for the treatment of flat or poorly demarcated

high-grade dysplastic lesions located anywhere in the pouch body or parapouch areas; any high-grade dysplastic lesions in the rectal cuff or anal transition zone; or patients with risk factors for the development of pouch neoplasia (recommendation 1.3.11, table; figure 3).

Topical therapy

Topical therapies, such as the application of bichloroacetic acid or trichloroacetic acid, infrared coagulation, argon plasma coagulation, and radiofrequency ablation are used for the treatment of anorectal cancer of squamous cell origin. Electrocoagulation or radiofrequency therapy might result in buried neoplastic lesions, which has been described in the endoscopic therapy of upper gastrointestinal neoplasia.[52] Therefore, these therapies are not recommended for the treatment of pouch neoplasia of a glandular source (recommendation 1.4.1, 1.4.2, table). However, some panellists have used diathermy or argon plasma coagulation therapy for flat lesions in the anal transition zone.

Surgery

Surgery is often required for the treatment of pouch neoplasia, especially neoplasia at the rectal cuff or anal transition zone, and high-grade dysplasia or adenocarcinoma in the pouch body or parapouch area. Surgical removal of the dysplastic lesions usually involves transanal excision, which is deeper than EMR or ESD. The techniques of transanal excision for the treatment of dysplasia of retained anorectal mucosa have been described.[49,53] Transanal local excision can be performed for the treatment of defined, unifocal and polypoid or raised, liftable, and clear-border low-grade dysplastic lesions at the pouch body or parapouch area. A full circular or circumferential excision with pouch advancement for multifocal dysplasia or any high-grade dysplasia in the rectal cuff or anal transition zone might be considered (recommendation 1.5.1, table; figure 3). If transanal local excision of the dysplastic lesion is performed, complete resection in a single piece is preferred (recommendation 1.5.2, table; figure 7). However, complete surgical excision of the lesion can be difficult in some patients, such as those with a short stenotic anastomosis and a narrowed rectal cuff or anus. In these patients, complete resection involves pouch advancement. Postoperative scarring of the neo-IPAA and the anal canal leads to anal stenosis and performing the procedure in two stages, first one hemicircumference and then the other, can mitigate the stenosis. Patients should be informed of the risk of recurrent dysplasia anal stenosis, the possibility of worsening faecal seepage and incontinence, and the need for ongoing surveillance.

Patients with dysplasia who undergo local surgical therapy should have close surveillance (recommendation 1.5.3, table). A careful histopathological examination of surgically excised specimens ensures that the resection margin is free of dysplasia. Re-excision of margins is recommended if the margin is positive for high-grade dysplasia. These patients should be closely monitored (recommendation 1.5.4, table).

Pouch neoplasia is one of the indications for pouch excision.[54] Pouch excision is recommended for adenocarcinoma of the pouch or parapouch area (figure 6G). Timely referral to a specialised centre for ileal pouch disorders is recommended for patients with flat, non-liftable, and non-clear-border dysplasia in the rectal cuff or anal transition zone, those with synchronous or metachronous dysplastic lesions of the pouch and parapouch area, or those with persistent dysplasia (recommendation 1.5.5, table). In a case series of 14 patients with pouch adenocarcinoma, eight (57·1%) underwent pouch excision and end ileostomy, two (14·3%) had pouch excision and construction of a continent ileostomy, three (21·4%) received palliative care, and one (7·1%) had a redo J pouch. Five (45·5%) of 11 patients with curative resection had recurrence or metastasis, and six (42·9%) patients died during a median follow-up of 2·1 years (IQR 0·6–5·2).[20] In a report of six cases with pouch adenocarcinoma, five underwent pouch excision with postoperative adjuvant chemotherapy and one had non-resectable cancer.[10] In a small case series of five patients with mid-pouch adenocarcinoma (three with underlying ulcerative colitis, one with FAP, and one with multiple malignant polyps), one died without further intervention, and four had pouch excision with or without neoadjuvant chemotherapy or chemoradiotherapy.[55]

Pouch reconstruction or conversion might be performed in patients with pouch failure by using part of the pre-existing pouch with augmentation if necessary or formation of a de-novo pouch. Surgical redo pouch might be attempted after pouch excision for benign dysplasia in the pouch body, rectal cuff, or anal transition zone in selected patients (recommendation 1.5.6, table), but is not recommended for most patients undergoing pouch excision for adenocarcinoma. There are scant published data on the outcome of pouch redo for pouch neoplasia. Of 502 patients with surgical redo pouch, ten (2%) underwent the surgery for the indication of neoplasia. However, of 101 (20%) patients who had a failed pouch redo, none with redo pouch failure resulting from the development of pouch neoplasia.[56] A separate study from the same institution included four of 12 patients with pouch high-grade dysplasia and three of 14 patients with pouch adenocarcinoma (one redo J pouch and two with J to K pouch conversion); only one patient with high-grade dysplasia had recurrent or persistent high-grade dysplasia after redo J pouch.[20] Our panel does not recommend surgical conversion of an existing pelvic pouch to a continent ileostomy using the same pouch body in patients with adenocarcinoma of the pouch, rectal cuff, or anal transition zone (recommendation 1.5.7, table).

A permanent end ileostomy is usually required in patients after pouch excision for neoplasia in the pouch

body or parapouch area. However, the construction of a neo-continent ileostomy might be considered in selected patients, depending upon the clinical characteristics of the cancer (recommendation 1.5.8, table). Patients who have had excision of a pelvic pouch for pouch dysplasia or adenocarcinoma might be a candidate for having a neo-continent ileostomy—ie, excision of the pelvic pouch and construction of a continent ileostomy using a new loop of the small bowel. Abdominopelvic resection of the pelvic pouch and construction of a neo-continent ileostomy has been described (n=2).[20] Surgical conversion to a continent ileostomy using the existing pelvic pouch was not recommended for patients with pouch excision for adenocarcinoma,[20] as pouch cancers are often advanced at the time of diagnosis.[6]

Tumour board and multidisciplinary approach

A multidisciplinary approach involving IBD gastroenterologists, colorectal surgeons, gastrointestinal radiologists, and gastrointestinal pathologists is often required in the diagnosis and management of pouch neoplasia. Tumour board review with the addition of medical and radiation oncologists is recommended for patients with adenocarcinoma of the pouch or parapouch area due to its complexity and poor prognosis (recommendation 1.6, table).

Tumour staging of pouch adenocarcinoma

The management strategy of pouch adenocarcinoma follows the principles of TNM staging system as described by the American Joint Committee on Cancer and the Union for International Cancer Control before and after endoscopic or surgical intervention. Serological markers such as carcinoembryonic antigen in all patients, along with cancer antigen 19-9 in those with concurrent primary sclerosing cholangitis-associated cholangiocarcinoma, should be monitored after the diagnosis of adenocarcinoma (recommendation 1.7.1, table). Tumour staging in pouch adenocarcinoma includes an MRI and CT scan (recommendation 1.7.2, table). The role of endoscopic ultrasound in cancer staging for patients with pouch adenocarcinoma has not been defined (recommendation 1.7.3, table). Endoscopic ultrasound is technically challenging and might be inaccurate in the setting of IPAA. Transrectal ultrasound has been used to assess neoplasia at the rectal cuff or anal transition zone.[57] However, ano–pouch ultrasound can be performed in selected patients not suitable for pelvic MRI.

Pouch cancer is prone to lateral spreading even without endoscopically visible lesions.[6] Proper tissue sampling of the malignant lesion and surrounding mucosa during pouchoscopy or examination under anaesthesia can be helpful for TNM staging. Pouchoscopy or examination under anaesthesia with deep or punch biopsy should be considered for any patients with suspicion of cancer who have polypoid or non-polypoid neoplastic lesions, those with long-standing non-healing fistulas, or refractory strictures at the anastomosis, rectal cuff, or anal transition zone (recommendation 1.7.4, table).

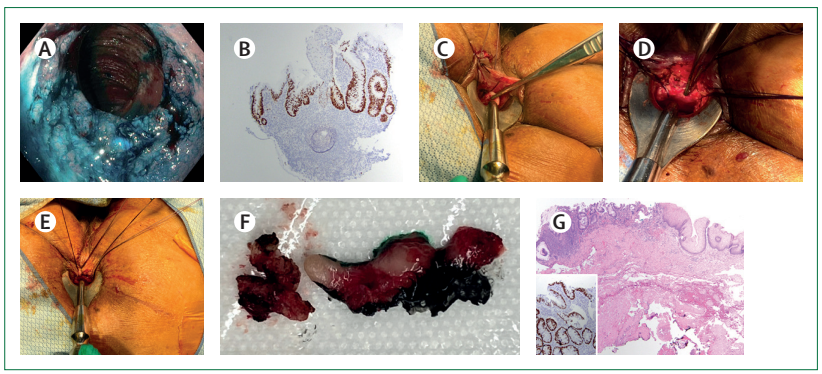

Figure 7: **Surgical excision of dysplastic lesion in the anal transition zone in a patient with underlying IBD**
(A) Flat lesion with low-grade and high-grade dysplasia in the anterior wall of the anal transition zone on chromoendoscopy. (B) Pouchoscopy biopsy of the lesion shows p53 overexpression by immunohistochemical staining (40×). (C–E) Surgical excision of the lesion followed by pouch advancement. (F) Macroscopic appearance of surgically excised anal transition zone with the dysplastic lesion. (G) Histopathology of the surgically excised dysplastic lesion (hematoxylin and eosin, 40×). The excision covered both squamous and glandular epithelia with the depth to the muscularis propria. Squamous epithelium was normal, whereas glandular mucosa showed focal high-grade dysplasia in the background of low-grade dysplasia. Immunostaining for p53 shows diffuse overexpression (inset figure, 200×). IBD=inflammatory bowel disease.

Endoscopically or surgically resected specimens should be histopathologically evaluated, assessing and documenting cancer margins, location, size, depth of invasion, degree of differentiation, lymphovascular invasion, margin involvement, tumour budding, and lymph-node involvement (recommendation 1.7.5, table). A pouch-specific or parapouch-specific cancer protocol template has not been developed. Immunohistochemistry for MMR proteins or analysis for microsatellite instability (MSI), or both, should be done to screen for Lynch syndrome and to guide anti-tumour immunotherapy. Colitis-associated neoplasia might be MSI-high due to methylation and polyposis can also result from constitutional mismatch repair deficiency (biallelic germline *MSH3* variants).[58] In addition, in patients with metastatic disease, mutational analysis for *KRAS* and *NRAS* expression should be done,[59] as patients with wild-type *RAS* might be treated with anti-epidermal growth factor receptor therapy. For advanced disease, screening for *NTRK* fusions, often done by immunohistochemistry, as well as *HER2* overexpression or amplification by immunohistochemistry, fluorescence in-situ hybridisation, or next-generation sequencing is considered.[60] Targeted drugs are available for *TRK* fusion-positive cancers and *HER2*-positive cancers.[61]

For **TNM staging** see https://www.cancer.gov/about-cancer/diagnosis-staging/staging

Chemoradiotherapy of pouch adenocarcinoma

Whether radiotherapy is indicated for pouch adenocarcinoma depends on the stage and location of cancer, the margin status, and the type of surgery. Consultation with medical oncologists and radiation oncologists with tumour board discussion should be

obtained for patients with pouch adenocarcinoma before surgical resection (recommendation 1.8.1, table).

For patients with pouch adenocarcinoma who are not eligible for pouch excisional surgery, or in whom it is not feasible, the risks and benefits of radiation therapy should be carefully balanced. Pelvic radiation can result in radiation-associated pouchitis, long-term pouch dysfunction, or loss of the pouch. Pre-radiation faecal diversion with an ileostomy can avoid the symptoms of acute radiation pouchitis but might increase the chances of long-term sequelae (recommendation 1.8.2, table). In a study of seven patients with IPAA treated by external beam radiation therapy for pelvic malignancy, most patients experienced more frequent bowel movements and incontinence.[62] Nonetheless, the use and regimen of neoadjuvant chemotherapy should be discussed in the tumour board review. There are no data that describe the adverse effects of chemotherapy on pouch function.

Management of neoplasia of squamous cell origin in IBD pouch

Squamous cell cancer and its precancerous lesions are rare in patients with IPAA, with only case reports and small case series in the literature.[63–68] In a retrospective study of 13 499 patients with ulcerative colitis, there were a total of 17 patients with ulcerative colitis and LSIL (n=3), HSIL (n=8), or squamous cell cancer (n=6). Of the six patients with squamous cell cancer, three died; one from metastatic disease, one with a malignant sheath tumour, and one from myocardial infarction.[69] At the time of anal neoplasia diagnosis, six patients had IPAA and one had ileal rectal anastomosis.[69] Most of the reported cases presented with Crohn's disease-like conditions.[64] Most squamous cell cancers in patients with pouches seem to be associated with HPV infection (figure 8E,F). However, no data compared the outcome of squamous cell cancer in the setting of IPAA between patients with and without HPV infection. Patients with HPV-positive squamous neoplasia should be tested for HIV. It is not clear how often squamous cell cancer develops from chronic wounds, fistula, or ulcers in patients with IPAA (figure 8). Treatment options for squamous cell cancer in patients with IPAA described in the literature include neoadjuvant chemoradiotherapy (fluorouracil and mitomycin), external beam radiation therapy, and pouch excision.[64–69]

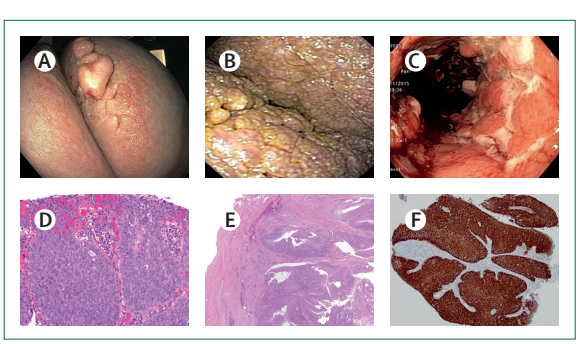

Figure 8: **Lesions at risk for squamous cell neoplasia in patients with ileal pouches for IBD**
(A–B) Perianal dermatitis and skin nodules from chronic diarrhoea. (C–D) Severe pouchitis and cuffitis with histology of biopsy showing high-grade squamous intraepithelial lesion. Histology photo courtesy of Ilyssa Gordon (Cleveland Clinic, Cleveland, OH). (E–F) Squamous cell cancer of the anal transition zone in a patient with an ileal pouch–anal anastomosis with positive immunochemistry (p16) for human papillomavirus. Histology photo courtesy of Andrew Turk (Columbia University Irving Medical Center–New York Presbyterian Hospital, New York, NY). IBD=inflammatory bowel disease.

Is surveillance for squamous cell neoplasia necessary?

At this point, we were not able to recommend who (dermatologist *vs* gynaecologist *vs* infectious disease specialist *vs* IBD specialist *vs* colorectal surgeon) should provide separate surveillance for neoplasia of squamous origin; when the surveillance should be started; and what protocol should be used. It appears that image-enhanced endoscopy can be helpful for further characterisation of squamous cell neoplasia (figure 9A,B). Our panel agrees that there is no need for a separate surveillance pouchoscopy or anoscopy for squamous cell neoplasia, but surveillance for squamous cell neoplasia can be a part of routine pouch surveillance for neoplasia from both glandular and squamous sources (recommendation 2.1, table). It appears that squamous cell cancer tends to be lateral spreading and deep, which poses a challenge for effective surveillance. For patients with purported risk factors for squamous cell cancer, such as chronic perianal skin lesions, chronic perianal fistulas, chronic cuffitis,[3] or HPV infection, surveillance pouchoscopy, anoscopy, or examination under anaesthesia can be performed. CT or MRI might also be done (figure 9). Patients with HIV infection or a history of immunosuppression are at increased risk for HPV-related squamous cell cancer of the anus, and anal Pap smear screening of squamous intraepithelial lesions is recommended.[69] The practice in patients with HIV is applied to those with IPAA and a history of HPV infection. Surveillance pouchoscopy should evaluate the anal canal, perianal skin, and fistula or sinus tract in perianal area, common locations of squamous cell neoplasia.

Medical therapy of underlying inflammation

It is not clear if adequate control of inflammation of the pouch, rectal cuff, or anal transition zone affects the development or outcome of squamous cell neoplasia in patients with IPAA (recommendation 2.2, table).

Endoscopic surveillance and therapy

Squamous cell neoplasia can be monitored by surveillance anal Pap smear, pouchoscopy, high-resolution anoscopy, or examination under anaesthesia in patients with IPAA at risk for squamous cell cancer, such as those with a history of HPV or HIV infection, chronic, severe perianal skin excoriation, or previous squamous cell dysplasia (recommendation 2.3.1, table; figure 9). Image-enhanced endoscopy, such as confocal microscopy, can be used.[70]

Squamous cell neoplasia in patients with IPAA usually requires surgery due to the location of the lesion. Endoscopic resection of squamous cell neoplasia in the pouch, rectal cuff, or anal transition zone is not recommended (recommendation 2.3.2, table).

Topical therapy

Local application of bichloroacetic acid or trichloroacetic acid, infrared coagulation, argon plasma coagulation, and radiofrequency ablation have been used for the treatment of anal squamous cell cancer. However, their role is not clear for patients with squamous cell cancer after IPAA (recommendation 2.4.1, 2.4.2, table). Nonetheless, in-situ squamous cell cancer in IPAA might be treated with topical therapy.

Surgery

The surgical management strategy for squamous cell cancer in patients with IPAA is similar to that for those without IPAA. Local surgical excision of benign squamous cell dysplasia in patients with an IPAA might be performed (recommendation 2.5.1, table), and local surgical excision of early superficial squamous cell cancer (T1N0M0) in patients with IPAA might be considered on the basis of the location and size of the lesion (recommendation 2.5.2, table).

For more advanced squamous cell cancer, management mirrors that of anal squamous cell cancer in non-pouch, non-IBD patients.[6,64] The decision on surgical excision versus chemoradiotherapy alone versus a combination of the two strategies should be individualised via a multidisciplinary approach, depending on the location and size of cancer, its depth, need for radiotherapy with chemotherapy, baseline pouch function, and patient preference (recommendation 2.5.3, table). However, there are scant published data on the surgical management of squamous cell cancer in IPAA. In one small case series of six patients with ulcerative colitis, IPAA, and anal squamous neoplasia, two patients with squamous cell cancer had pouch excision.[69]

Our panel does not recommend surgical redo J or S pouch construction in patients with squamous cell cancer in IPAA (recommendation 2.5.4, table). However, surgical conversion from a failed pelvic pouch due to squamous cell neoplasia to a continent ileostomy using the same pouch body or construction of neo-continent ileostomy might be considered in selected patients (recommendation 2.5.5, table; figure 9H).

Multidisciplinary approach and tumour board

A multidisciplinary approach is often needed for the diagnosis and management of squamous cell neoplasia. A timely referral to a specialty centre for ileal pouch disorders is recommended. A tumour board review is recommended for advanced squamous cell cancer in patients with IPAA due to its complexity and prognosis (recommendation 2.6, table).

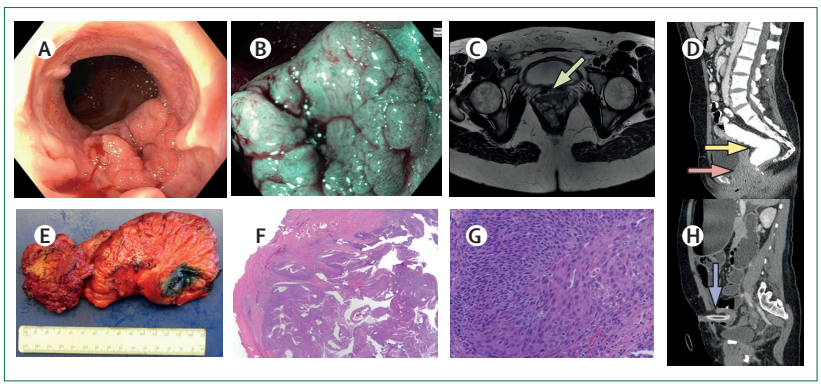

Figure 9: **Endoscopic detection and surgical management of squamous cell cancer in the anal transition zone in a patient with underlying IBD**
(A–B) Raised lesion with a central indentation enhanced by magnified endoscopy and narrow-band imaging. (C) Pelvic MRI showed invasion of lesion to the internal anal sphincter muscle (green arrow). (D) J-pouch (yellow arrow) at the time of diagnosis of cancer of the anal transition zone (red arrow). (E) Surgical excision of the J pouch. (F–G) Squamous cell cancer on surgical histopathology. (H) Construction of a new Kock pouch in the patient (blue arrow). IBD=inflammatory bowel disease.

Tumour staging

Tumour staging for patients with squamous cell cancer and IPAA includes PET, CT, and, in selected cases, MRI (figure 9C–D). All patients should undergo HPV and HIV testing if the status is unknown and women should undergo a gynaecological examination with screening for cervical cancer (recommendation 2.7, table).

Immunotherapy and chemoradiotherapy

Chemoradiotherapy is required for the treatment of squamous cell cancer with T2N0 and above. T1N0 is usually treated with surgical local excision if not too close to the sphincter, otherwise radiotherapy alone, or lower dose radiation with chemotherapy is used. A phase 2 trial of the anti-PD-1 antibody nivolumab showed safety and efficacy in metastatic squamous cell cancer of the anal canal in non-pouch patients.[71] To date, both nivolumab[71] and pembrolizumab (KEYNOTE-028 study and the larger KEYNOTE-158)[72,73] have been used for the treatment of metastatic squamous cell cancer of the anal canal in non-pouch patients.

The role of HPV vaccination for HPV-associated anal squamous cell cancer in patients with IPAA is not clear. Patients with IPAA should follow the recommendations for the HPV vaccine, as for the general population based on the guidelines from WHO, Advisory Committee on Immunization Practices of the USA, and European Centre for Disease Control and Prevention (recommendation 2.8.1, table). Quadrivalent HPV vaccine has been shown to reduce the rates of anal intraepithelial neoplasia among men who have sex with men.[74] Patients with IPAA should also follow this general HPV vaccination policy. The role of immunotherapy for localised HPV-associated anal squamous cell cancer is not clear (recommendation 2.8.2, table). Medical oncology and radiation oncology services should be consulted for patients with squamous cell cancer (recommendation 2.8.3,

table). Fluorouracil, mitomycin, and external beam radiation therapy has been used for the treatment of stage II or higher squamous cell cancer in patients with ulcerative colitis and IPAA.[69]

The risks and benefits of radiotherapy should be carefully balanced for patients with squamous cell cancer who do not have pouch excision surgery, due to concerns about radiation-associated pouchitis, poor pouch function, and pouch loss (recommendation 2.8.4, table).[63]

Management of neoplasia in the pouch for familial adenomatous polyposis

Annual surveillance pouchoscopy is recommended for patients with FAP.[3,15] The focus of this document in the setting of FAP is the management of intestinal neoplasia in the pouch body, prepouch afferent limb, rectal cuff, or anal transition zone, rather than neoplasia in the upper gastrointestinal tract. The surveillance and management of dysplastic lesions in patients with FAP who have restorative proctocolectomy and handsewn versus stapled IPAA are similar, although endoscopic surveillance and biopsy are more difficult after a handsewn IPAA. The surveillance and management of pouch neoplasia in other polyposis syndromes are outside the scope of this Review. FAP-associated desmoid tumours and endoscopic evaluation and management of polyposis in the upper gastrointestinal tract are also outside the scope of this Review.

The evolution of neoplasia in patients with FAP with a pouch occurs in two contexts: the rectal cuff and anal transition zone, and the pouch itself. Rectal cuff or anal transition zone neoplasia arises in the existing high-risk epithelium and is an immediate concern after pouch construction. The pouch is initially low-risk epithelium but becomes high risk over time as faecal stasis encourages metaplasia in the epithelium.

Medical therapy

Chemoprevention uses medical therapy to prevent polyp growth and progression to colon cancer and might be considered in patients with familial adenomatous polyposis after IPAA (recommendation 3.1, table). However, there is insufficient evidence to recommend routine medical prophylaxis of polyposis in patients with FAP. The ACG guidelines for patients with FAP recommend endoscopic surveillance of the rectum or ileal pouch yearly after colectomy or proctocolectomy.[15] Pouch polyposis could be prevented or delayed by sulindac, although there are no data to support routine prophylaxis. Pouch polyposis can be treated with sulindac or endoscopic polypectomy.[15] Sulindac is a cyclo-oxygenase (COX) 1 and COX2 inhibitor and a nonsteroidal anti-inflammatory drug, and long-term use is common in patients with desmoid disease. It is usually well tolerated. Celecoxib is a COX2 inhibitor and was initially promising for chemoprevention of adenomas in FAP, but its use is restricted by its cardiovascular complications.[75] Other reported chemoproventive agents for FAP include curcumin,[76] eicosapentaenoic acid,[77] and erlotinib.[78] There are some cases with severe pouch polyposis that cannot be controlled endoscopically for whom the only options are effective medical treatment or pouch removal. The recently described combination chemotherapy using sulindac and eflornithine offers some hope for these severely affected patients. A randomised trial of 171 patients with FAP consisted of 38 patients (22%) before colectomy, 53 (31%) with subtotal colectomy and ileal rectal anastomosis, 67 (39%) with total proctocolectomy and IPAA, and 13 (8%) with colectomy and ileostomy. 34 patients (28%) with ileorectal anastomosis or IPAA were found to have disease progression. Of these 34 patients, none of those receiving the combination therapy (n=11) required pouchectomy or proctectomy, whereas two (17%) of those receiving eflornithine alone (n=12) and one (9%) of those receiving sulindac alone (n=11) needed pouch resection or proctectomy.[79]

Endoscopic therapy

Annual surveillance is recommended in patients with FAP after IPAA (recommendation 3.2.1, table). Endoscopic polypectomy, mucosal resection, or ablation is recommended for adenomas in the afferent limb, pouch, or residual rectum, rectal cuff, or anal transition zone (figure 10).

Cancer is rare after IPAA for FAP, probably due to surveillance, short follow-up, and small bowel origin. Endoscopic polypectomy for pouch polyposis in patients with FAP is recommended by the ACG.[15] The overwhelming number of dysplastic lesions in FAP pouches have low-grade dysplasia. Although en-bloc excision should be attempted, piecemeal resection of large flat lesions with no advanced features using a hot snare is acceptable. It appears that FAP-associated pouch cancer develops earlier than cancers arising in an ileostomy.[80] However, technical aspects of endoscopic polypectomy were not detailed in the current literature, such as the size and shape of polyps. Our expert panel recommends that image-enhanced endoscopy should be used and endoscopic polypectomy or EMR be performed in polypoid or raised lesions and endoscopically liftable lesions, characterised by the Paris[39] or the narrow-band imaging–International Colorectal Endoscopic[81,82] classifications.

Most polyps or polypoid lesions in the FAP pouch can be removed endoscopically (recommendation 3.2.2, table). Cold or hot snare, hot biopsy, argon plasma coagulation, EMR, or even ESD have been used (figure 10; figure 11A–D).[83,84] A meta-analysis showed that hot snare polypectomy in the colon carried a higher risk for bleeding than cold snare polypectomy.[85] No published data compare the efficacy and safety of cold snare versus hot snare polypectomy in the pouch or small bowel. Cold snare polypectomy or EMR has been shown to effectively reduce the tumour burden of FAP in patients with ileal pouches as well as those with an

intact colon.[83] In a case series of five patients with heavy polyp burdens in the pouch body and parapouch areas, cold snare polypectomy was safe and feasible.[86] Most of the lesions in pouches are flat or relatively flat and can be effectively and safely removed by cold snare or cold EMR. Our experts felt that most small FAP-associated pouch polyps can be removed by cold snare or cold EMR for the pouch, retained rectum, or even duodenum. Hot snare resection with or without injection might be warranted for some bulky lesions in the retained rectum, some lesions near the dentate line, or lesions straddling anastomoses. Lesions with endoscopic evidence of advanced histology should be resected using electrocautery, and considered for en-bloc resection if feasible. Patients with IPAA that is carpeted with adenomas and patients with high-grade dysplasia and multiple polyps should be considered for pouch removal and followed up closely until this is accomplished (figure 11E–G).

There is scant literature on ESD for the treatment of pouch neoplasia beyond a case report.[87] Our panel raised safety concerns about the use of ESD for the treatment of neoplasia in the pouch or parapouch area in patients with FAP.

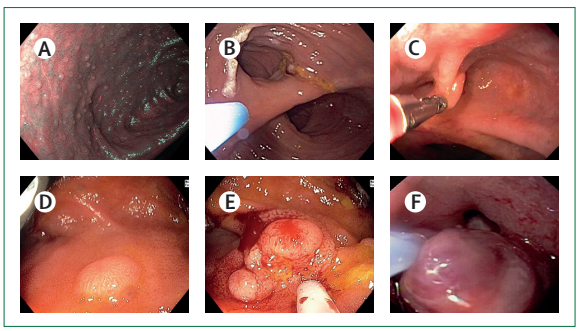

Figure 10: **Endoscopic management of adenomatous lesions of the pouch and parapouch in familial adenomatous polyposis**
(A) Narrow-band imaging showing lymphoid granules, differentiating from adenomas. (B) Argon plasma coagulation therapy. (C) Hot-biopsy therapy. (D–E) Cold snare polypectomy with transected specimen with so-called fried egg appearance of polyp and surrounding normal small bowel mucosa. (F) Hot snare polypectomy.

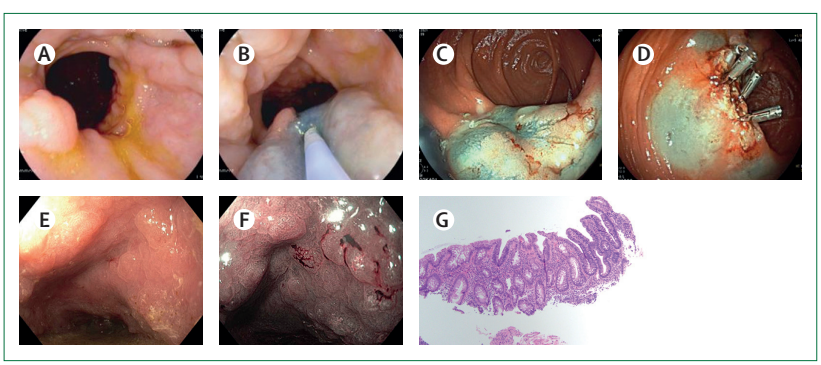

Figure 11: **Advanced management of adenomatous lesions in familial adenomatous polyposis**
(A–D) Endoscopic mucosal resection. (E–G) Extensive flat polyps in a 6 cm-long rectal cuff in a patient with ileal pouch–anal anastomosis with histolopathological confirmation of diffuse adenomas who was undergoing surgical excision of the cuff and re-anastomosis.

Surgery

Severe pouch polyposis is rare and pouch excision is seldom needed in patients with FAP. Although endoscopic therapy can be done for discrete adenomas in the rectal cuff or anal transition zone, excisional surgery (eg, transanal circumferential excision or mucosectomy, mucosal advancement, and redo anal pouch anastomosis) is recommended for extensive, lateral spreading or flat adenomas in the rectal cuff or anal transition zone, if endoscopic removal is not feasible (recommendation 3.3.1, table; figure 11E–G), although data are scarce.[86] Adenocarcinoma in the pouch or parapouch area requires pouch excision (recommendation 3.3.2, table). After pouch excision, reconstruction of a de-novo pouch might be considered in highly selected patients. Referral of these patients to centres specialising in pouch disorders for evaluation and management is highly recommended. Pouch excision without reconstruction should preferably be intersphincteric, preserving the pelvic floor, and the pelvic cavity should be filled with an omental flap if possible.

Surveillance and management of the diverted pouch

There are few published data on the development of intestinal neoplasia in diverted pouches. Surveillance of a diverted pouch can be difficult and unreliable because of the common presence of friable mucosa or diversion-associated pouchitis. In a study of 20 patients with permanently diverted pouches (18 with ulcerative colitis, one with FAP, and one with pseudo-obstruction), none had dysplasia or carcinoma in the ileal reservoir or distal to the anastomosis at a median follow-up of 12 years after restorative proctocolectomy and 3·6 years after faecal diversion.[87] Similar findings were reported in a separate study of 13 patients with a permanently diverted pouch.[88] The recommended strategy for surveillance of dysplasia in a long-term (>10 years) diverted pouch is detailed in separate documents.[3,4] Few authors in the panel have encountered cases of low-grade dysplasia, high-grade dysplasia, and adenocarcinoma in the diverted pouch. The general principle from our panel is pouch excision for confirmed dysplasia or cancer. However, consensus guidelines from the Global Interventional IBD Group recommended annual surveillance endoscopy of the diverted ileal pouch for patients with a precolectomy diagnosis of colorectal neoplasia or with previous dysplasia of the pouch and surveillance endoscopy every 1–3 years for those with potentially high risk of dysplasia, including patients with primary sclerosing cholangitis or Crohn's disease of the pouch.[4]

Optimal management of dysplasia in a long-term or permanently diverted pouch is uncertain, due to scarce published data, and unclear disease course. However, pouch excision can the best option (recommendation 4.1,

table). EMR or ESD might be attempted for polypoid or raised, clear-bordered lesions in the pouch body with close post-procedure surveillance. Flat or non-clear-bordered lesions in the pouch body or any dysplasia in the rectal cuff or anal transition zone should preferably be treated with pouch excision.

Management of other rare malignancies of the pouch

Non-Hodgkin lymphoma has been described in patients with IPAA.[6,58,89] Pouch lymphoma mostly is an incidental diagnosis or diagnosed in patients with non-specific symptoms. Most pouch lymphomas are large B-cell lymphomas.[90,91] Pouch lymphoma can be a part of lymphoproliferative disorder after immunosuppression with tacrolimus or other calcineurin inhibitors after liver transplant for primary sclerosing cholangitis. Similarly, patients with chronic refractory pouchitis or Crohn's disease of the ileoanal pouch who are receiving immunosuppressive therapy with tumour necrosis factor antagonists, with or without thiopurines, are also at risk of non-Hodgkin lymphoma. Endoscopic features of pouch lymphoma include well demarcated flat or raised lesions. Histological and immunochemical examination of biopsy specimens is the key to diagnosis. In-situ hybridisation for Epstein-Barr virus (EBV)-encoded RNA should be performed in pouch lymphoma. Non-Hodgkin lymphoma can also involve extra-pouch organs. The presence of EBV in non-Hodgkin lymphoma is often associated with immunosuppressive therapy. The literature on the treatment of non-Hodgkin lymphoma mainly describes chemotherapy, such as cyclophosphamide, adriamycin, vincristine, and prednisone.[58,91] We recommend a multidisciplinary consultation for the management of patients with pouch lymphoma (recommendation 5.1, table).

There are some case reports of carcinoid tumours of the ileal pouch in patients with ulcerative colitis.[91,92] Fortunately, neuroendocrine tumours are rare. We are not able to recommend surveillance or a management strategy for carcinoid tumours (recommendation 5.2, table). However, the management strategies of neuroendocrine tumours of the pouch or parapouch area might be similar to neuroendocrine tumours in the small bowel. Primary melanoma involving the pouch with no extra-pouch metastasis was reported in a patient with ulcerative colitis.[93] However, we are unable to recommend a surveillance or management strategy, as melanoma in the pouch is very rare (recommendation 5.3, table)

Surveillance and management after neoplasia diagnosis with or without endoscopic or surgical treatment

Patients with endoscopic or surgical excisional therapy for pouch dysplasia should be closely monitored with endoscopic surveillance. Our consortium has previously recommended that patients with low-grade dysplasia of the ileal pouch, rectal cuff, or anal transition zone who do not elect to have surgery should undergo close surveillance pouchoscopy, initially every 3–6 months and yearly after the dysplasia is cleared.[3] Patients with low-grade dysplasia or high-grade dysplasia in the pouch or parapouch area who do not have the lesion endoscopically removed for whatever reason should undergo regular pouchoscopy (recommendation 1.3.9, table). Every effort should be made to remove high-grade dysplastic lesion, as these can progress to cancer before the next interval pouchoscopy. Therefore, some panellists advocate surveillance at least every 6 months.

Patients undergoing local surgical excision for any dysplasia (low-grade dysplasia or high-grade dysplasia) should undergo close surveillance pouchoscopy (recommendation 1.5.3, table). There are no published data on the protocol for monitoring with carcinoembryonic antigen and cross-sectional imaging after excisional surgery for pouch cancer. However, serological monitoring with carcinoembryonic antigen should be routinely obtained after any endoscopic or surgical therapy including pouch-preserving procedures or pouch excision for adenocarcinoma (recommendation 6.1, table).

Endoscopic surveillance should be routinely done in patients undergoing faecal diversion and revised pouch in situ or reconstructed pouch for pouch neoplasia (recommendation 6.2, table). Image-enhanced endoscopy such as virtual chromoendoscopy or dye-based chromoendoscopy might not be reliable for surveillance due to concurrent diversion pouchitis. If malignancy is found, carcinoembryonic antigen monitoring and cross-sectional imaging are required, with frequency varying based on stage.

Conclusions

Restorative proctocolectomy with IPAA for ulcerative colitis or FAP does not completely eradicate the risk for the development of future neoplasia. The prognosis of pouch cancer is poor. Endoscopic therapy with polypectomy, mucosal resection, or submucosal dissection is mainly indicated for low-grade dysplasia in the pouch body with polypoid or raised lesions with a clear border. Low-grade dysplasia in the rectal cuff can be managed endoscopically or surgically without pouch excision. High-grade dysplasia in general or persistent low-grade dysplasia in the rectal cuff or anal transition zone usually require local surgical resection or even pouch excision in patients with ulcerative colitis. Patients with adenocarcinoma or squamous cell cancer in the pouch body or parapouch areas require pouch excision in most cases. Although adenocarcinoma of the pouch in FAP that requires pouch excision is rare, adenomatous lesions in the pouch or parapouch area can be removed with endoscopic or surgical excisional procedures. Many of the recommendations have a 5D rating. More prospective data are needed for more definitive recommendations in the management of pouch neoplasia. Until then, shared decision making with both the multidisciplinary team and the patient is a key in the management of pouch neoplasia.

Contributors

BS and RRPK conceived the Review. SA, CNB, JMC, RKC, PF, TTH, MI. RRPK, GSK, RK, XL, SL, UN, BS and SAS were on the steering committee. All authors were involved in voting, preparation, and critical review of the manuscript.

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