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Perianal Fistulizing Crohn's Disease–Associated Anorectal and Fistula Cancers: Systematic Review and Expert Consensus

Serre-Yu Wong,[1,*] Cathy Rowan,[2,*] Elvira Diaz Brockmans,[3] Cindy C. Y. Law,[1] Elisabeth Giselbrecht,[1] Celina Ang,[4] Sergey Khaitov,[5] David Sachar,[1] Alexandros D. Polydorides,[6] Leon Shin-han Winata,[7] Bram Verstockt,[8] Antonino Spinelli,[9,10] David T. Rubin,[11] Parakkal Deepak,[12] Dermot P. B. McGovern,[13] Benjamin D. McDonald,[11] Phillip Lung,[14] Lilli Lundby,[15] Amy L. Lightner,[16] Stefan D. Holubar,[17] Luke Hanna,[18,19] Carla Hamarth,[20] Jeroen Geldof,[21] Anders Dige,[22] Benjamin L. Cohen,[23] Michele Carvello,[9,10] Cristiana Bonifacio,[24] Gabriele Bislenghi,[25] Corina Behrenbruch,[26] David H. Ballard,[27] Emre Altinmakas,[28] Shaji Sebastian,[29] Phil Tozer,[19,30,31] Ailsa Hart,[18,19] and Jean-Frederic Colombel[1]

[1]Department of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Department of Gastroenterology, Beaumont Hospital, Dublin, Ireland; [3]Department of Medicine, Universidad Iberoamericana, Santo Domingo, Dominican Republic; [4]Department of Oncology, Icahn School of Medicine at Mount Sinai, New York, New York; [5]Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, New York; [6]Department of Pathology, Molecular and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [7]Medical Imaging, St. Vincent's Hospital, Melbourne, Australia; [8]Department of Gastroenterology, University Hospitals of Leuven, Leuven, Belgium; [9]Department of Biomedical Sciences, Humanitas University, Milan, Italy; [10]IRCCS Humanitas Research Hospital, Milan, Italy; [11]University of Chicago Medicine Inflammatory Bowel Disease Center, Chicago, Illinois; [12]Department of Gastroenterology, Washington University School of Medicine in St. Louis, St. Louis, Missouri; [13]The F. Widjaja Foundation Inflammatory Bowel Disease Institute, Cedars-Sinai Medical Center, Los Angeles, California; [14]Radiology Department, St. Mark's Hospital and Academic Institute, London, United Kingdom; [15]Department of Surgery, Pelvic Floor Unit, Aarhus University Hospital, Aarhus, Denmark; [16]Department of Colorectal Surgery, Scripps Clinic, San Diego, California; [17]Department of Colorectal Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, Ohio; [18]IBD Unit, St. Mark's Hospital and Academic Institute, London, United Kingdom; [19]Imperial College London, London, United Kingdom; [20]Department of Radiology, University of Chicago Medicine, Chicago, Illinois; [21]Department of Gastroenterology and Hepatology, University Hospital Ghent, Ghent, Belgium; [22]Department of Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [23]Department of Gastroenterology, Hepatology, and Nutrition, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, Ohio; [24]Radiology Department, IRCCS Humanitas Research Hospital, Milan, Italy; [25]Department of Abdominal Surgery, University Hospitals Leuven, Leuven, Belgium; [26]Department of Colorectal Surgery, St. Vincent's Hospital, Melbourne, Australia; [27]Mallinckrodt Institute of Radiology, Washington University School of Medicine in St. Louis, St. Louis, Missouri; [28]Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, New York; [29]IBD Unit, Hull University Teaching Hospitals NHS Trust, Hull, United Kingdom; [30]Department of Colorectal Surgery, St. Mark's Hospital and Academic Institute, London, United Kingdom; and [31]Robin Phillips Fistula Research Unit, St. Mark's Hospital and Academic Institute, London, United Kingdom

BACKGROUND & AIMS: **Perianal fistulizing Crohn's disease (PFCD)-associated anorectal and fistula cancers are rare but often devastating diagnoses. However, given the low incidence and consequent lack of data and clinical trials in the field, there is little to no guidance on screening and management of these cancers. To inform clinical practice, we developed consensus guidelines on PFCD-associated anorectal and fistula cancers by multidisciplinary experts from the international TOpClass consortium.**

*Authors share co-first authorship.

Abbreviations used in this paper: AAC, anal adenocarcinoma; CD, Crohn's disease; CRC, colorectal cancer; CRT, chemoradiotherapy; CT, computed tomography; EUA, exam under anesthesia; HPV, human papillomavirus; IBD, inflammatory bowel disease; MA, mucinous adenocarcinoma; MRI, magnetic resonance imaging; PET, positron emission tomography; PFCD, perianal fistulizing Crohn's disease; SCCA, squamous cell carcinoma of the anus.

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METHODS: **We conducted a systematic review by standard methodology, using the Newcastle-Ottawa Scale quality assessment tool. We subsequently developed consensus statements using a Delphi consensus approach.**

RESULTS: **Of 561 articles identified, 110 were eligible, and 76 articles were included. The overall quality of evidence was low. The TOpClass consortium reached consensus on 6 structured statements addressing screening, risk assessment, and management of PFCD-associated anorectal and fistula cancers. Patients with long-standing (>10 years) PFCD should be considered at small but increased risk of developing perianal cancer, including squamous cell carcinoma of the anus and anorectal carcinoma. Risk factors for squamous cell carcinoma of the anus, notably human papilloma virus, should be considered. New, refractory, or progressive perianal symptoms should prompt evaluation for fistula cancer. There was no consensus on timing or frequency of screening in patients with asymptomatic perianal fistula. Multiple modalities may be required for diagnosis, including an examination under anesthesia with biopsy. Multidisciplinary team efforts were deemed central to the management of fistula cancers.**

CONCLUSIONS: **Inflammatory bowel disease clinicians should be aware of the risk of PFCD-associated anorectal and fistula cancers in all patients with PFCD. The TOpClass consortium consensus statements outlined herein offer guidance in managing this challenging scenario.**

Keywords: Inflammatory Bowel Disease; Perianal Fistulizing Crohn's Disease; Anorectal Cancer.

Perianal fistulizing Crohn's disease (PFCD) affects approximately 20% of patients with Crohn's disease (CD).[1] PFCD is associated with a more aggressive disease course and more impaired quality of life than in patients with CD without perianal fistula.[2,3]

Moreover, in addition to an increased risk of colorectal cancer (CRC) (relative risk, 2.4; 95% confidence interval, 1.56–4.36) associated with CD, patients with PFCD are at increased risk of cancers in the perianal region, near or involving perianal fistula tracts, which we refer to as PFCD-associated anorectal and fistula cancers.[4–6]

Given the relative rarity compared with CD-associated CRC, there are few data to guide clinicians in screening, diagnosis, and management of these cancers.

The Treatment Optimization and Classification of Perianal Crohn's Disease (TOpClass) consortium is a large collaborative group of perianal CD researchers, which developed following an international project to reclassify perianal CD.[7] Expansion of the group has incorporated gastroenterologists, colorectal surgeons, and gastrointestinal radiologists who have active research output in the field of perianal CD and/or high-volume clinical practices in perianal disease care. We performed a systematic review of the existing literature on PFCD-associated anorectal and fistula cancers and developed consensus statements to guide clinicians and promote further research in this area.

Methods

Systematic Review

A literature search was performed for articles referring to perianal CD and associated malignancies. PubMed and PubMed Central databases were searched on June 20, 2022, January 16, 2023, and January 8, 2024. Data extraction was performed by 3 investigators. Quality assessment was performed using the Newcastle-Ottawa Scale.[8] See Supplementary Methods for full details.

Development of Consensus Statements

Consensus statements were developed by investigators from the Icahn School of Medicine at Mount Sinai and presented to the TOpClass consortium, including 10 gastroenterologists, 8 surgeons, and 6 radiologists. The first round of voting took place online during July and August 2023. The consensus statements were amended based on voting results and comments made by the expert panel. The second round of voting took place during a virtual meeting in September 2023. Further amendments were made until >70% consensus was reached (ie, "strongly agree" or "agree"). See Supplementary Methods for full detail.

Results

Systematic Review

Of 561 articles identified (Figure 1), 110 were eligible and 76 were included in the review (Supplementary Table 1). Most identified studies were retrospective, mainly case reports and case series. By the Newcastle-Ottawa Scale, the overall quality of evidence was low (Figure 2 and Supplementary Table 2).

Nomenclature of cancers of the perianal region in patients with PFCD has not been established. For clarity, we define them according to anatomy and histologic type. PFCD-associated fistula cancers directly involve perianal fistulas. PFCD-associated anorectal cancers do not directly communicate with perianal fistulas. Both

sites may be squamous cell carcinoma of the anus (SCCA) or adenocarcinoma. In our literature review, we adhere to these terms; in cases where the terminology is unclear, we use terms from the original articles.

The data and basic rationale for the 6 consensus statements (Figure 2) are presented within the following domains: epidemiology, risk factors, clinical presentation, diagnostic modalities, staging and prognosis, and treatment and outcomes.

What You Need to Know

Background

Perianal fistulizing Crohn's disease-associated anorectal and fistula cancers are rare but often devastating diagnoses. There is little guidance on screening and management of these cancers.

Findings

An international group of perianal fistulizing Crohn's disease experts conducted a systematic review of the literature and developed six consensus statements on screening and management of these cancers.

Implications for patient care

We provide practical guidance on whom to screen, how to evaluate, and how to manage perianal fistulizing Crohn's disease-associated anorectal and fistula cancers.

Epidemiology and Risk Factors for Perianal Fistulizing Crohn's Disease–Associated Anorectal and Fistula Cancers

A 2011 meta-analysis of intestinal cancers estimated overall incidence of "cancers arising from CD-associated fistulae" to be 0.2/1000 patient-years.[9] A review of the epiIIRN Cohort, an Israeli population-based database of patients with inflammatory bowel disease (IBD), concluded that the risk of anorectal cancer was significantly higher in patients with perianal CD than non-perianal CD (odds ratio, 4.67; 95% confidence interval, 1.51–14.27; $P = .01$).[10] In a retrospective cohort study of patients with PFCD, the rate of malignancy found in fistula tract biopsies was 0.79% (biopsies were obtained either because of clinical suspicion or as standard practice of the surgeon). Approximately 50% of cases were squamous cell carcinoma and 50% were adenocarcinoma.[11]

One risk factor for PFCD-associated cancers reported across many studies is PFCD duration. A retrospective case-control study of 40 patients diagnosed with PFCD-associated cancers (2005–2019) found that patients who developed cancer were diagnosed with CD at a younger age (22.7 ± 8.4 vs 27.0 ± 10.1 years; $P = .04$) and had longer duration of disease (25.8 ± 9.0 vs 19.6 ± 10.4 years; $P = .006$).[12] A similar pattern is repeated in numerous case reports and cohort studies.[13–20,21,22] Although data reporting time from fistula onset to PFCD-associated cancer are sparse, the median time from calculable data is 12 years and the mean is 13 years. Hence, we define long-standing disease as >10 years for Statements 1 and 2.

Perianal Fistulizing Crohn's Disease–Associated Anal Cancer

Anal cancer includes SCCA and anal adenocarcinoma (AAC). Although 1 retrospective case-control study of anal cancer showed no significant association between anal cancer and IBD[23] subsequent studies provide compelling evidence to the contrary.[6,10]

Squamous Cell Carcinoma of the Anus

Risk factors reported for SCCA in patients with CD include smoking, young age at diagnosis, complex perianal disease, long-standing perianal fistula, HIV status, immunosuppression, receptive anal intercourse, high-risk human papillomavirus (HPV) variants, chronically active colitis, chronic perianal fistula, and stricturing phenotype.[23–47]

High-risk HPV variants, abnormal anal cytology, and SCCA in men who have sex with men have been reported in patients with PFCD, suggesting that HPV vaccination and anal cancer screening should be considered in this population.[37,38,40–42,48] In addition, although there are no data for patients with IBD, receptive anal intercourse has been associated with anal cancer risk in men and women and is considered a risk factor by the American Cancer Society.[30–33] Because HPV vaccines are prophylactic vaccines, we recommend following clinical guidelines, such as the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (see Supplementary data for full discussion of HPV).[49,50]

Colonic/Rectal Adenocarcinoma

CRC is well-documented as occurring significantly more commonly in patients with CD and PFCD than in those without.[10,51–53,54,55]

Of published cases of PFCD-associated anorectal and fistula cancers that describe histologic type, 41/93 (44%) reported adenocarcinoma cases were mucinous adenocarcinoma (MA), a distinct subtype.[15,56–64] This is a higher rate from that reported in the general population where MA accounts for 10%–20% of CRC cases and 2%–3% of anorectal cancers.[56,65,66] One case report describes an anal MA arising from rectal tissue at the site of a previously repaired rectovaginal fistula.[67] Because CRC occurring in patients with IBD is apparently more often mucinous than in the general population,[19,68] it remains to be determined whether the higher rate of MA is specific to PFCD. Finally, other,

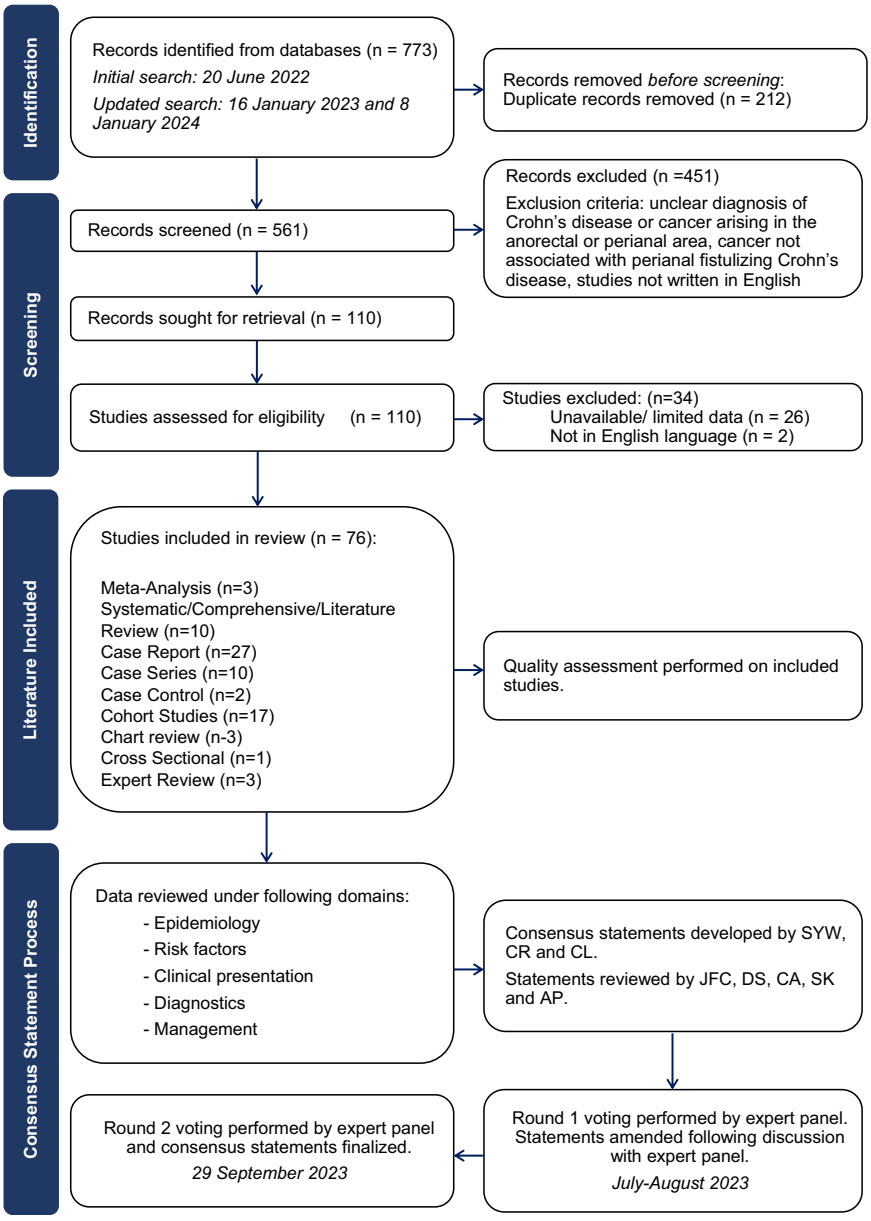

Figure 1. Search strategy schematic based on PRISMA criteria.

rarer tumors that have been reported in patients with PFCD include neuroendocrine tumors, hydroadenocarcinoma arising from the perianal eccrine glands, and adenocarcinoid rectal tumors.[69–71]

Clinical Presentation

It is difficult to distinguish benign PFCD and anorectal strictures from PFCD-associated anorectal and fistula cancers based on clinical presentation alone, because of significant overlap in symptoms (Table 1).[72,73] We include substatements for Statement 3 to prompt clinicians to evaluate for anorectal and fistula cancers in patients with PFCD who either have refractory or progressive perianal symptoms, or are asymptomatic but subsequently develop new perianal symptoms. In addition, a subgroup of patients diverted for PFCD continue to have a rectal remnant with fistula in situ. These patients may have a relative lack of symptoms that would otherwise alert physicians to an evolving malignancy and therefore require vigilance.[20,72,74,75]

Diagnostic Evaluation

A consistent theme is the challenge in detecting malignancy in patients with PFCD.[13] Indeed, cancer may first be recognized intraoperatively.[27] There are insufficient data to inform a screening strategy and given that cases of PFCD-associated anorectal and fistula cancers have been reported in asymptomatic patients, most participants in our expert panel agreed that patients with PFCD with persistent, yet quiescent, fistulas should have routine clinical evaluation of their fistulas with at least a physical examination, with or without magnetic

Statement 1. *Patients with longstanding (>10 years) persistent PFCD should be considered at a small but increased risk of developing PFCD-associated anorectal and fistula cancers, which may be squamous cell cancer of the anus (SCCA) or adenocarcinoma, including mucinous adenocarcinoma.* *47% Strongly Agree, 53% Agree*
Statement 2. *In patients with longstanding PFCD, risk factors for SCCA should be taken into account. Human papilloma viruses (HPV) testing for high-risk variants, anal cytology, and age-appropriate HPV vaccination should be considered.* *58% Strongly Agree, 25% Agree, 17% Neutral*
Statement 3. 3a. Refractory or progressive perianal symptoms (including pain, discharge, stricture, or swelling), particularly in patients with longstanding PFCD, should prompt evaluation for PFCD-associated anorectal and fistula cancers. 3b. In patients with quiescent longstanding PFCD, the emergence of new perianal symptoms (including pain, discharge, stricture, or swelling), should prompt evaluation for PFCD-associated anorectal and fistula cancers. *40% Strongly Agree, 60% Agree*
Statement 4. *Asymptomatic PFCD patients with persistent fistula should have clinical evaluation with or without MRI imaging as indicated to assess for PFCD-associated anorectal and fistula cancer. There is no consensus on the timing or frequency of evaluation.* *20% Strongly Agree, 53% Agree, 20% Neutral, 7% Disagree*
Statement 5. To evaluate for PFCD-associated anorectal and fistula cancers, multiple modalities may be required when there is a high index of clinical suspicion. These include MRI pelvis and EUA with biopsy, wherein multiple attempts at sampling may be necessary. Other modalities may need to be considered as needed/available (such as EUS or cytology of effluent from fistula). *57% Strongly Agree, 43% Agree*
Statement 6. We recommend that staging and management of PFCD-associated cancer follow current best practice guidelines used for patients with anal or rectal cancer without IBD in a multidisciplinary setting to ensure that treatments for both the cancer and IBD are optimized. *83% Strongly Agree, 17% Agree*

Figure 2. Summary of consensus for screening and management of fistula cancer from the TOpClass consortium.

resonance imaging (MRI). However, there was no consensus on timing or frequency of such evaluation. This point is addressed in Statement 4 to remind clinicians that persistent fistulas should not be neglected in their clinical evaluations, even when a patient is feeling well.

Next we focus on diagnostic accuracy of tissue diagnostics and imaging modalities. Of note, there are differences in approach should SCCA versus adenocarcinoma be suspected. For example, exam under anesthesia (EUA) is more likely to be diagnostic for SCCA upfront, and MRI and positron emission tomography/computed tomography (PET-CT) used for staging of SCCA. However, adenocarcinoma often requires a combined MRI/EUA approach for initial diagnosis.

Tissue Diagnosis

EUA with biopsy is essential in tissue diagnosis for PFCD-associated anorectal and fistula cancers.[12,14,27,58,76,77] Moreover, repeated EUA with biopsy may be required to confirm the diagnosis.[11] Endoscopy may allow for biopsy but plays a limited role.[78] In 1 case series, 35% of PFCD-associated anorectal and fistula cancers were diagnosed through endoscopic evaluation.[12]

Several strategies to obtain tissue were used in a single-center series describing surveillance in high-risk patients with CD.[79] Of 72 patients with PFCD, the rate of CRC was 6.19% (7 of 113 examinations), including 5 rectal cancers, and 2 "anal fistula" cancers. The detection rates were 1.85% (1/113) with core-needle biopsy, 5.56% (5/113) with endoscopic biopsy, and 5.88% (2/113) with excisional biopsy. Importantly, in this series 6 cases were diagnosed at an early stage.[79]

Imaging

MRI of the pelvis is the most common modality used as a first step in imaging for suspected PFCD-associated cancers. However, distinguishing between active inflammation and malignant transformation, let alone defining the radiologic features of these malignancies, presents a considerable challenge.[80,81]

A retrospective review of MRI characteristics of PFCD-associated anorectal and fistula cancers (n = 4 MA; n = 2 SCCA) found that irregular inner wall contour and delayed enhancement of internal tissue were common to all 6 cases.[82] Cystic collection with lobulated external border and delayed enhancement of internal tissue was described in all 4 cases of MA. The presence of adenopathy or solid mass were less helpful in distinguishing benign disease from malignancy transformation.[82,83] Five of the 6 cases were not identified on preoperative imaging limiting interpretation.[82] A detailed description of MRI features is included in Supplementary Methods.

Table 1. Summary of the Clinical Presentation of Patients with Fistula-Associated Malignancy

	No. of patients	Age	Gender	CD duration (*y*)	Fistula duration (*y*)	Symptoms	Type of fistula cancer
Vernava[74]	N = 1	48	Male	>20		Persistent drainage from fistula (after proctectomy)	n = 1 moderately differentiated adenocarcinoma
Bahadursingh et al[108]	N = 1	60	Male	29		Open sore on left buttock and posterior thigh draining pus and stool	n = 1 SCC
Hayashi et al[72]	N = 4	42	Male	14		Anal stenosis and ongoing perianal pain after sigmoid colostomy	n = 1 poorly differentiated adenocarcinoma with signet cells
		30	Male	13		Perianal pain	n = 1 mucinous adenocarcinoma
		46	Male	9		Abdominal fullness	n = 1 mucinous adenocarcinoma with lymph node metastases
		33	Female	16		None, a stenotic lesion found on surveillance colonoscopy	n = 1 mucinous adenocarcinoma
Devon et al[106]	N = 14	49 (mean)	n = 6 male, n = 8 female	22.7 (mean)	Evidence of perianal CD (mean, 6.9; range, 1–20 y) before their cancer diagnosis	Increasing or intractable pain	n = 11 adenocarcinomas (8 mucinous or colloid subtypes) n = 3 SCC
Iesalnieks et al[20]	N = 6	44	Male	24	23	Anal discharge	n = 1 mucinous anal adenocarcinoma
		45	Male	26	26	Anal discharge, pain, fever, weight loss	n = 1 mucinous anal adenocarcinoma
		37	Male	26	26	Anal discharge and bleeding, fecal urgency	n = 1 mucinous anal adenocarcinoma
		66	Male	42	28	Anal discharge and pain	n = 1 mucinous anal adenocarcinoma
		49	Female	33	16	Painful defecation, weight loss	n = 1 mucinous anal adenocarcinoma
		46	Female	25	10	Anal discharge, anal and abdominal pain, fecal incontinence, weight loss	n = 1 mucinous anal adenocarcinoma

Table 1. Continued

	No. of patients	Age	Gender	CD duration (*y*)	Fistula duration (*y*)	Symptoms	Type of fistula cancer
Slesser et al[109]	N = 26	42 (median)	CD patients: 3 male, 17 female			Anal pain in 12 (66.7%) cases, perianal fistula-associated symptoms 17%, rectal bleeding 11%, anal lump 5%	n = 26 SCC
Maejima et al[67]	N = 1	50	Female	33		Perianal pain of several months' duration	n = 1; 2 types of adenocarcinoma diagnosed in single lesion (well-differentiated tubular adenocarcinoma and mucinous adenocarcinoma)
Shwaartz et al[11]	N = 19	50[a] (mean)	n = 11 female, n = 8 male	25.4 (mean)	6	n = 9 asymptomatic; n = 5 perianal pain; n = 1 labial mass; n = 4 no record of presenting symptoms	n = 9 SCC, n = 10 adenocarcinoma
Lightner et al[94]	N = 7	50 (mean)	n = 5 female; n = 2 male	20 (mean)		n = 3 perianal pain, n = 4 bleeding	n = 7 SCC of the anus stage 0 (n = 1), stage I (n = 1), stage II (n = 1), stage III (n = 2), stage IV (n = 1), and unknown (n = 1)
Pareja-Lopez[69]	N = 1	42	Male	20		Painful inguinal lymphadenopathy	n = 1 perianal eccrine hydroadenocarcinoma
Ehrl et al[102]	N = 1	54	Male	20		Discharge of stool through perianal fistula, weight loss, large inflammatory tumor at perianal region with multiple discharging perianal fistulas	n = 1 verrucous carcinoma
Weingarden et al[105]	N = 1	55	Male	17		New perianal fistula 4 mo after first presentation with drainage; cancer presentation was a perianal swelling and mass	n = 1 anal squamous cell
Palmieri et al[12]	N = 40		n = 22 male, n = 18 female	25.8		n = 17 perianal pain, n = 1 weight loss, n = 31 chronic fistula activity	n = 13 adenocarcinoma, n = 20 mucinous adenocarcinoma, n = 7 SCC

Table 1. Continued

	No. of patients	Age	Gender	CD duration (*y*)	Fistula duration (*y*)	Symptoms	Type of fistula cancer
Baars et al[104]	N = 4	48.5 y[a] (mean)	n = 3 male, n = 1 female	23.1[a] (mean)	11.6[a]	Only 1 patient had clinical symptoms indicative for adenocarcinoma In 3 other patients, the adenocarcinoma was found coincidently	n = 4 adenocarcinoma
Sakanaka et al[110]	N = 1	40	Male	26		Perianal mass	n = 1 SCC
Boaz et al[111]	N = 16	61.8 (mean)	n = 14 male, n = 2 female			Increasing perianal pain, elevated WBC and CRP	n = 12 adenocarcinoma of rectum, n = 4 SCC or adenosquamous cell carcinoma of anus
Ky et al[112]	N = 7	47 (mean)	n = 3 male, n = 4 female	Range, 8–50	Range 3–50	n = 4 severe pain, n = 1 persistent fistula, n = 1 persistent fistula and severe pain, n = 1 anal ulcer, n = 1 rectovaginal fistula	n = 4 SCC, n = 3 adenocarcinoma
Harpain et al[95]	N = 7	46	n = 5 male, n = 2 female	27 (mean, SD ± 9)	20 (mean, SD ± 13)	n = 3 secretions and pain, n = 4 pain	n = 1 SCC, n = 6 adenocarcinoma
Inoue et al[100]	N = 1	49	Male	24	5	Abdominal pain, diarrhea, circumferential protruding lesion with anal stenosis	Mucinous adenocarcinoma
Kaneshiro et al[73]	N = 1	37	Male	23	—	Anal stricture, anemia, pain	Mucinous adenocarcinoma
Ganapathy et al[64]	N = 1	49	Female	29	20	Abdominal pain, weight loss, diarrhea and perianal pain	Mucinous adenocarcinoma

CD, Crohn's disease; CRP, C-reactive protein; CRT, chemoradiotherapy; SCC, squamous cell carcinoma; SD, standard deviation; WBC, white blood count.
[a]Mean age calculated from patient characteristics in original paper.

CT and ultrasound have relatively low sensitivity for malignant transformation, especially because these lesions often occur in areas of active inflammation.[84,85] Similar challenges exist with PET-CT. Although PET-CT can detect inflammation in CD, even perianal fistulas without malignancy have increased fluorodeoxyglucose uptake.[80,81] PET-CT may have a role in detecting metastatic disease from non-MA. Otherwise, its current utility beyond staging of SCCA for nodal metastases is not fully established in the absence of suspected or proven distant metastasis.[86]

There may be variable approaches based on histologic type. For primary SCCA, MRI and, to a lesser extent, endoanal ultrasound and perineal ultrasound are recommended. MRI provides essential information on tumor size, location, and nodal involvement. Radiologic evaluation of MA is also challenging.[20] It can mimic a perianal abscess on CT and MRI, further complicating interpretation. However, MA typically has a microcystic composition with high signal intensity on T2-weighted images, with less diffusion restriction on high b value diffusion-weighted imaging compared with an abscess of non-MA adenocarcinoma. Thus, whereas MRI findings in MA remain to be fully delineated, there may be differences that distinguish this histologic subtype.

We acknowledge the difficulty in identifying PFCD-associated cancers using available imaging modalities. A high index of suspicion is required, and subtle changes, such as the presence of soft tissue in a fistula tract, should raise the possibility of malignant transformation.[86] Statement 5 is intended as a general approach, recognizing that MRI and EUA are current mainstays in many centers, that multiple attempts may be required, and that diagnostics may evolve over time.

Treatment

The staging of SCCA and AAC uses the tumor-node-metastasis (TNM) classification.[87] Management of SCCA and AAC follow distinct pathways but generally combine surgical intervention, chemotherapy, and radiotherapy and influenced by the stage and extent of cancer, patient's comorbidities and IBD status, and goals of care.

Squamous Cell Carcinoma

The current standard of care for localized SCCA is curative radiotherapy with 5-fluorouracil and mitomycin-C (Wayne State or Nigro Protocol).[87,88] Definitive chemoradiotherapy (CRT) enables sphincter preservation in most patients, with 5-year colostomy-free and overall survival rates of 72% and 78%, respectively.[89] Capecitabine is increasingly used instead of 5-fluorouracil given greater ease of administration, lower incidence of myelosuppression, and fewer treatment delays with comparable results.[90] In selected cases of early anal margin cancers (T1N0M0), local excision can be attempted instead, with adjuvant CRT given if adequate margins are not achieved. Patients who cannot tolerate CRT may benefit from radiotherapy alone. Abdominoperineal resection is reserved for persistent or recurrent disease but may be considered instead of CRT as primary treatment in special cases (eg, prior pelvic radiation).[87]

Radiotherapy now uses narrower therapeutic windows, decreasing the risk of local injury, but it is unclear if the fistula tract should be included in the window and to what extent. Clinical trials are currently evaluating the efficacy and safety of checkpoint inhibitors in combination with standard-of-care CRT, or as consolidation therapy after CRT for high-risk SCCA.[88]

Patients with metastatic SCCA and an adequate functional status can be treated with systemic taxane, platinum ± fluoropyrimidine-containing chemotherapy. Following progression on first-line chemotherapy, immunotherapy can be considered based on phase II studies demonstrating safety and activity in the chemorefractory setting.[91] Selected patients may also benefit from radiation for symptom palliation. If systemic therapy cannot be tolerated, then supportive care is recommended.

Adenocarcinoma

AAC is treated similarly to rectal adenocarcinoma. The optimal treatment strategy is unclear, or if indeed it can be extrapolated to PFCD-associated AAC.[92,93] Most receive long-course neoadjuvant CRT with capecitabine. Those with T3-4 and/or node-positive cancers may receive neoadjuvant fluoropyrimidine and platinum-based chemotherapy and abdominoperineal resection, with or without adjuvant chemotherapy.[92] Metastatic AAC is treated similarly to metastatic CRC.[88] MA is treated using similar protocols to non-MA. Overall survival is lower in MA, and neoadjuvant CRT is less successful in downstaging MA.[65]

Management and Outcomes

Management and outcomes of SCCA, AAC, and rare PFCD-associated cancers in patients with IBD are summarized in Tables 2–4. Despite guidelines recommending CRT as first-line therapy for localized SCCA, a variety of treatment options including surgery alone or in combination with chemotherapy were used. Lightner et al[94] described a 56% 5-year disease-free survival rate. Most cases were stage 3 or higher at diagnosis. A retrospective Canadian study reported 33% 3-year mortality.[11] However, because staging information was reported inconsistently, there are not enough data available to evaluate differences in treatment response and outcomes. Earlier diagnosis may result in superior long-term outcomes, although this remains understudied.

Of the 117 cases of AAC in patients with IBD, most cases received surgery with or without adjuvant chemo/

Table 2. Treatment and Outcomes of IBD Patients with Squamous Cell Carcinoma of the Anus

Study	N	N with fistula	Age (median)	Stage	Intervention	Median follow-up	Recurrence	Median overall survival	Overall survival (%)	Management of IBD
Kuhlgatz et al[48]	1	1	53	T1N0M0	CRT with 5-FU and MMC followed by APR	3 mo after last surgery	3 mo (local recurrence at resection margin requiring surgical revision)	Was well 3 mo after last resection	100% (3 mo)	—
Benjelloun et al[99]	1	1	47	Advanced locoregional disease	Palliation	3 mo	—	3 mo	—	—
Osone et al[113]	1	1	68	T3N0M0	Surgery (APR)	875 d	No	Alive after 875 d	—	—
Shwaartz et al[11]	9	9	50	—	Nigro protocol = 4, Nigro protocol then APR = 2, surgery then Nigro protocol = 2, died before therapy = 1	>3 y	No recurrence in 6 of 9 patients after 3 y	3 of 9 patients died within 3 y	—	—
Quera et al[114]	1	1	33	—	Surgery	—	—	—	—	Physicians decided to not initiate biologic therapy after surgery
Weingarden et al[105]	1	1	55	—	CRT	—	Recurrence after 2 mo	—	—	Restarted adalimumab and 6MP 1 mo after CRT
Lightner et al[94]	7	5	51	Stage 1 = 1 Stage 2 = 1 Stage 3 = 3 Stage 4 = 1 Unknown = 1	CRT (Nigro protocol) = 7	2.5 y	2 of 7 patients	—	56% disease-free survival after 5 y	—
Kang et al[75]	1	1	43	M0	CRT	—	—	—	—	—
Devon et al[106]	3	3	46	—	Surgery + adjuvant CRT	26 mo	—	1 of 3 patients died within 26 mo	—	—
Boaz et al[111]	1	1	57	T4N1M0	Neoadjuvant CR + surgery (APR)	21 mo	—	Patient died within 21 mo	0% within 21 mo	—

Table 2. Continued

Study	N	N with fistula	Age (median)	Stage	Intervention	Median follow-up	Recurrence	Median overall survival	Overall survival (%)	Management of IBD
Sakanaka et al[110]	1	1	40	T3N0M0	CRT	24 mo	No recurrence	No recurrence	100%	—
Ky et al[112]	4	4	47 (mean)	—	n = 3 CRT; n = 1 neoadjuvant CRT + APR	12 y	n = 1 recurrence	n = 1 deceased at 6 mo; n = 1 deceased at 3.5 y	50%	—
Harpain et al[95]	1	1	41	T2N0M0	Surgery (APR)	—	—	—	—	—

5-FU, 5-fluorouracil; APR, abdominoperineal resection; CR, chemoradiation; CRT, chemoradiotherapy; IBD, inflammatory bowel disease; MMC, mitomycin-C.

radiotherapy. Follow-up data were sparse and limited in duration. Overall, prognosis of AAC in those with IBD seems to be poor.[95] In Ogawa et al,[62] 75% of patients (T4M0 = 2; M1 = 2) died within 23 months of diagnosis. In Iesalnieks et al[20] (T3 = 4; T4 = 2), 67% patients died within 35 months. Case reports of patients with early stage disease seemed to have better outcomes.[59]

To our knowledge, there are currently no guidelines regarding the management of SCCA and AAC in patients with IBD. Data are limited because many studies do not report management of IBD therapy during cancer treatment and/or IBD-specific outcomes, and most clinical trials exclude patients with IBD with past malignancies.

The risk of IBD flare and complications must be balanced with the risks of infection, cancer progression, and cancer recurrence. Treatment with immunotherapy also requires careful consideration because certain checkpoint inhibitors have been associated with immune-mediated colitis.[96] However, referral to a tertiary center may be beneficial in these cases, because alteration of oncologic care may not always be necessary. ECCO has provided guidelines for management of IBD therapy in patients undergoing cancer treatment.[97] Multidisciplinary collaboration in planning cancer treatment and monitoring IBD are crucial to ensure that patients receive the best possible treatment.

Discussion

Although PFCD-associated anorectal and fistula cancers are rare, there are salient considerations to help identify patients and pursue timely and appropriate diagnostic evaluation and treatment. There are several points to highlight. First, we suggest the following risk factors be used to identify patients at highest risk for PFCD-associated cancer: long-standing perianal fistula (>10 years), HPV status, and smoking.[11,13,15,17,19,20,27,58–60,64,71,75,76,79,95,98–106] Additional individuals at risk include people living with HIV, solid-organ transplant recipients, men who have sex with men, and those who practice receptive anal intercourse. Of note, several of our expert panelists would consider HPV vaccination in all patients with PFCD.[107]

Second, symptoms are nonspecific and some patients present asymptomatically. Therefore, anorectal and/or PFCD-associated cancer should be on the differential for new or refractory perianal symptoms, particularly in those with long-standing disease.

Third, diagnosis can be challenging and may require persistence by clinicians incorporating multiple modalities and repeated tissue sampling if the index of suspicion is high. Finally, management of fistula cancers truly relies on a multidisciplinary approach to ensure optimal care.

A limitation to this work is the overall limited data. There is lack of standardized terminology and histo-anatomic classification of these cancers with relation to perianal fistula. Finally, in the literature, whether a given

Table 3. Treatment and Outcomes of Patients with IBD with Anal Adenocarcinomas

Study	N	N with fistula	Age (median)	Stage	Intervention	Median follow-up	Recurrence	Median overall survival	Overall survival (%)	Management of IBD
Papaconstantinou et al[57]	1	1	40	T4N1	Surgery (APR)	—	3 mo (bone metastases)	—	—	—
De Souza et al[58]	1	1	71		Surgery (APR) + adjuvant chemotherapy (Xeloda)	—	6 mo (scrotal and inguinal lesions)	—	—	CD in remission; azathioprine held
Devroe et al[115]	1	1	70	—	Surgery (APR) + adjuvant chemotherapy (5-FU)	—	—	Patient died after 5 cycles of chemotherapy	—	RT not provided because of concerns regarding CD in remaining bowel
Smith et al[15]	1	1	79	Localized	Surgery (APR with vulvectomy)	—	—	—	—	—
Ehrl et al[102]	1	1	54	Localized	Surgery (APR with wide excision of perineal tumor)	—	—	—	—	—
Sogawa et al[103]	1	1	40	T2N0M0	Surgery (APR)	42 mo	No	42 mo	100% (42 mo)	—
Zefelippo et al[76]	4	4	44.5	T4N0M0 T3N0M0 T3N0M0 T4N2M0	Surgery + adjuvant chemotherapy (for all 4 cases)	—	2 of 4 patients (after 4 y, 20 mo)	1 patient died after 53 mo; 1 patient was free of recurrence after 1 y of follow-up	—	—
Scharl et al[59]	1	1	45	T2N0M0	Neoadjuvant CRT followed by surgery	4 y	No	No recurrence after 4 y of follow-up	100% (4 y)	Experience CD flare during CRT; budesonide and MTX postsurgery
Kim et al[116]	8	8	39	T3 = 6 T4 = 2	Surgery + CRT (6), surgery + chemotherapy (2)	30.5 mo	—	3 of 8 patients died (after 7 mo, 30 mo, 22 mo)	—	—
Kodama et al[101]	23	23	40	Stage 1 = 1 Stage 2= 12 Stage 3 = 4 Stage 4 = 6	—	—	—	—	—	—
Osone et al[113]	3	3	47	T2N0M0 = 1 T3N0MO = 1 T4N0M1 = 1	Neoadjuvant CRT + surgery (APR) = 2, APR only = 1	330 d	3 of 3 patients (175 d, 569 d, 330 d)	1 patient died after 237 d, 2 patients alive after 1269 and 520 d	—	—
Ogawa et al[62]	4	4	33.5	M1 = 2, T4M0 = 2	Surgery + adjuvant RT = 1, surgery + adjuvant CRT = 2, palliation = 1	N/A	2/4	3 of 4 patients died within 23 mo (23 mo, 5 mo, 14 mo)	1 of 4 patients alive after 63 mo without recurrence	—

Table 3. Continued

Study	N	N with fistula	Age (median)	Stage	Intervention	Median follow-up	Recurrence	Median overall survival	Overall survival (%)	Management of IBD
Iesalnieks et al[20]	6	6	45.5	T3 = 4 T4 = 2	Surgery + adjuvant CRT = 4, surgery + neoadjuvant CRT = 1, surgery only = 1	12 mo	5/6	4 of 6 patients died within 35 mo	1 patient alive with recurrence at 55 mo, 1 patient alive without recurrence at 19 mo	—
Freeman et al[60]	1	1	18	—	Surgery + RT	8 mo	N/A	Patient died after 8 mo	0%	—
Maejima et al[67]	1	1	50	T1N0M0	Surgery (APR)	18 mo	No	N/A	No recurrence after 18 mo	Was on IFX for 4 y before diagnosis, restarted IFX 1 mo after surgery
Fornaro et al[61]	1	1	60	T3 (stage 2)	Surgery (patient refused adjuvant CRT)	—	—	—	—	—
Baars et al[104]	4	4	46.2	—	Surgery + adjuvant RT = 2, surgery + adjuvant CRT = 2	3.5 y	1 of 4 patients	3 of 4 patients (1 lost to follow-up after recurrence diagnosed)	—	—
Shwaartz et al[11]	10	10	55[a]	M1 = 1, M0 = 9	Neoadjuvant CRT then surgery = 4, surgery then chemotherapy = 3, chemotherapy alone = 1, unknown 2	3 y (follow up available in only 5 of 10 patients)	1 of 5 patients developed metastases, 3 patients were recurrence free	1 of 5 patients died within 3 y	—	—
Lee et al[52]	17	10 of 17	30.2	Stage 1 = 3 Stage 2 = 6 Stage 3 = 1 Stage 4 = 6 (rectal cancer = 15)	Surgery = 16, preoperative or postoperative RT = 8	5 y	7 patients (41.2%) alive without recurrence at the latest follow-up date	—	52.6% 5-y survival	—
Pareja Lopez et al[69]	1	1	42	T4N1M0	Neoadjuvant chemotherapy + surgery	—	—	—	—	—
Massit et al[77]	1	1	36	—	Inoperable, received CRT	—	—	Patient died shortly after receiving CRT	—	—
Alcade Vargas et al[14]	1	1	50	—	Surgery (APR with radical cystoprostatectomy) + adjuvant chemotherapy	—	—	—	—	—
Devon et al[106]	11	11	48	—	Surgery + adjuvant CRT= 7, surgery + adjuvant RT = 1, neoadjuvant CRT + surgery = 2, refused treatment = 1	15.5 mo	—	3 of 11 patients dead within 15.5 mo	—	—
Vernava[74]	1	1	48	M0	Surgery	—	—	—	—	—

Table 3. Continued

Study	N	N with fistula	Age (median)	Stage	Intervention	Median follow-up	Recurrence	Median overall survival	Overall survival (%)	Management of IBD
Boaz et al[111]	3	3	63	T2N0M0= 1, T4N1M0 = 1, T4N0M0= 1	Surgery (APR) = 1, CRT = 1, neoadjuvant CR + surgery (APR) = 1	7 mo	—	No patients died during follow-up	—	—
Ky et al[112]	N = 3	N = 3	47 (mean)	—	n = 2 APR; n = 1 neoadjuvant CRT +APR	—	—	n = 1 deceased at 3.5 y	—	—
Harpain et al[95]	N = 6	N = 6	—	—	n = 6 APR + neoadjuvant/ adjuvant CRT	—	—	33% 5 y survival	—	—
Inoue et al[100]	N = 1	N = 1	49	cT4N0M0, cStage IIIB	Laparoscopic sigmoid colostomy; CRT followed by laparoscopic total pelvic exenteration, colonic conduit diversion, extensive perineal resection, and reconstruction	—	No recurrence within 6 mo after operation	—	—	—

5-FU, 5-fluorouracil; APR, abdominoperineal resection; CD, Crohn's disease; CR, chemoradiation; CRT, chemoradiotherapy; IBD, inflammatory bowel disease; IFX, infliximab; MMC, mitomycin-C; N/A, not applicable; RT, radiotherapy.
[a]Median calculated based on ages provided for 9 patients (1 unknown).

Table 4. Treatment and Outcomes of Patients with IBD with Rectal Neuroendocrine Tumor, Hydroadenocarcinoma, and Adenocarcinoid Tumors

Study	N	N with fistulas	Age (median)	Histology	Stage	Intervention	Median follow-up	Recurrence	Median overall survival
Suzuki et al[71]	1	1	39	Neuroendocrine	G1	Incidental finding in surgical specimen (was completely resected)	—	—	—
Judd et al[70]	1	1	48	Neuroendocrine/adenocarcinoid	—	Surgery (APR) + adjuvant chemotherapy	2 y	Yes, metastases after 2 y	—
Pareja-Lopez et al[69]	1	1	42	Hydroadenocarcinoma	—	Neoadjuvant chemotherapy; surgery	—	—	—

APR, abdominoperineal resection; IBD, inflammatory bowel disease.

cancer is directly invading the fistula tract or in proximity to a fistula without direct invasion is often not clearly defined.

These TOpClass consortium consensus statements represent a launching point for future studies and discussion. Although the goal was to guide clinicians, this manuscript highlights major knowledge gaps on PFCD-associated cancers. Areas for future research include the epidemiology of PFCD-associated anorectal and fistula cancers addressing the true incidence and demographic factors, such as ethnicity, race, or sex differences; establishing clinical-histologic classifications; characterization of outcomes of fistula cancer; the role of imaging; identification of key radiologic findings; and efficacy of diagnostic techniques. Finally, little is known of the pathophysiology of fistula-associated cancers, including how CD or fistula biology alone affect susceptibility or whether medications may play a role.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2024.05.029.

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Correspondence
Address correspondence to: Serre-Yu Wong, MD, PhD, One Gustave L. Levy Place, Box 1069, New York, New York, 10029. e-mail: Serre-Yu.Wong@mountsinai.org.

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CRediT Authorship Contributions

Serre-Yu Wong, MD, PhD (Conceptualization: Lead; Formal analysis: Lead; Investigation: Lead; Methodology: Lead; Project administration: Lead; Resources: Lead; Supervision: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead; Expert panel member: Equal)

Cathy Rowan (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Investigation: Lead; Methodology: Lead; Supervision: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead; Expert panel member: Equal)

Elvira Diaz Brockmans (Data curation: Equal; Investigation: Equal; Methodology: Equal; Writing – review & editing: Equal; Expert panel member: Equal)

Cindy C.Y. Law (Data curation: Equal; Formal analysis: Equal; Investigation: Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; Expert panel member: Equal)

Elisabeth Giselbrecht (Data curation: Equal; Investigation: Equal; Methodology: Equal; Visualization: Equal; Writing – review & editing: Equal)

Celina Ang (Writing – review & editing: Equal; Expert panel member: Equal)

Sergey Khaitov (Writing – review & editing: Equal; Expert panel member: Equal)

David Sachar (Writing – review & editing: Equal; Expert panel member: Equal)

Leon Shin-han Winata (Writing – review & editing: Equal; Expert panel member: Equal)

Bram Verstockt (Writing – review & editing: Equal; Expert panel member: Equal)

Antonino Spinelli (Writing – review & editing: Equal; Expert panel member: Equal)

David T. Rubin (Writing – review & editing: Equal; Expert panel member: Equal)

Parakkal Deepak (Writing – review & editing: Equal; Expert panel member: Equal)

Dermont P.B. McGovern (Writing – review & editing: Equal; Expert panel member: Equal)

Benjamin D. McDonald (Writing – review & editing: Equal; Expert panel member: Equal)

Phillip Lung (Writing – review & editing: Equal; Expert panel member: Equal)

Lilli Lundby (Writing – review & editing: Equal; Expert panel member: Equal)

Amy L. Lightner (Writing – review & editing: Equal; Expert panel member: Equal)

Stefan D. Holubar (Writing – review & editing: Equal; Expert panel member: Equal)

Luke Hanna (Writing – review & editing: Equal; Expert panel member: Equal)

Carla Hamarth (Writing – review & editing: Equal; Expert panel member: Equal)

Jeroen Geldof (Writing – review & editing: Equal; Expert panel member: Equal)

Anders Dige (Writing – review & editing: Equal; Expert panel member: Equal)

Benjamin L. Cohen (Writing – review & editing: Equal; Expert panel member: Equal)

Michele Carvello (Writing – review & editing: Equal; Expert panel member: Equal)

Cristiana Bonifacio (Writing – review & editing: Equal; Expert panel member: Equal)

Gabriele Bislenghi (Writing – review & editing: Equal; Expert panel member: Equal)

Corina Behrenbruch (Writing – review & editing: Equal; Expert panel member: Equal)

David H. Ballard (Writing – review & editing: Equal; Expert panel member: Equal)

Emre Altinmakas (Writing – review & editing: Equal; Expert panel member: Equal)

Shaji Sebastian (Writing – review & editing: Equal; Expert panel member: Equal)

Phil Tozer (Writing – review & editing: Equal; Expert panel member: Equal)

Alisa Hart (Writing – review & editing: Equal; Expert panel member: Equal)

Jean-Frederic Colombel (Conceptualization: Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; Expert panel member: Equal)

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Supplementary Methods

Literature Search Strategy

A structured search of the PubMed and PubMed Central databases was carried out from inception to the date of last search, in accordance with PRISMA guidelines. PubMed and PubMed Central databases were searched on June 20, 2022, using MeSH terms and following the PICO model. The search was updated on January 16, 2023, and January 8, 2024.

Key words were selected following the PICO model:

- Population: Patients with PFCD
- Intervention: None
- Comparison: Patients with PFCD that developed PFCD-associated anorectal or fistula cancers and patients without PFCD
- Outcome: PFCD-associated anorectal and fistula cancer incidence, risk factors, and treatment outcomes

The search was performed in free text and using MeSH. The following free text search was used:

1. Fistula Associated Cancer in Perianal Fistulizing Crohn's Disease.
2. Perianal Fistula-Associated Cancer in Crohn's Disease.
3. Rectal Cancer in Perianal Crohn's Disease.
4. Anal Cancer in Perianal Crohn's Disease.

In MeSH search, the following search details were included: 'Fistula'/ 'Fistulizing' / 'neoplasms'/ 'cancer'/ 'Perianal'/ 'Anal'/ 'Rectal'/ 'Crohn's Disease'/ 'Crohn's'/ 'perianal fistula'/ 'anal fistula'/ 'carcinoma'/ 'Perianal Cancer'/ 'rectal cancer,'' either singly or in combination.

For each individual database the relevant controlled vocabulary corresponding to the previously mentioned keywords was applied. Therefore, the search strategy was customized to each database and included standardized subject terms and the previously mentioned keywords.

Manual search: Bibliographies within articles were searched manually for additional studies.

Selection Criteria

Randomized controlled trials, cohort studies, cross-sectional studies, case reports, case series, meta-analyses, chart reviews, and expert opinions were eligible for inclusion. The abstracts were assessed by the predetermined inclusion and exclusion criteria:

- Inclusion criteria
  - Patient with Crohn's disease who developed a tumor originating within or around a perianal fistula
- Exclusion criteria
  1. Unclear diagnosis of Crohn's disease
  2. Unclear diagnosis of cancer arising from the perianal region
  3. Cancer not associated with perianal fistulizing Crohn's disease
  4. Studies written in languages other than English

After removal of duplicate references, 3 investigators (CR, EB, EG) independently performed an initial screening of titles and abstracts. Potentially relevant articles were reviewed in full to determine eligibility for inclusion according to predetermined criteria. Disagreement on eligibility was resolved by a fourth reviewer (CL).

Data Extraction

Data extraction was performed independently by 3 investigators (CR, CL, EB). The following data were collected: title, journal, year and month of publication, author; study design; risk factors; study numbers, patient demographics; Crohn's disease duration and phenotype; type of cancer; method of diagnosis and staging; and treatment and outcomes.

Quality Assessment

Quality assessment of cohort studies and case-control publications was performed using the Newcastle-Ottawa Scale.[8] The areas assessed included selection bias, selection of control subjects, management of confounders, data collection methods, reporting of withdrawals and drop-outs, and adequacy of follow-up. Each component was graded according to Newcastle-Ottawa Scale guidelines and studies were then categorized as being of good, fair, or poor quality.

Development of Consensus Statements

The consensus statements were developed by a group of IBD physicians experienced in the care of patients with perianal Crohn's disease (SYW with 10 years' experience; CR and CL with 5–10 years' experience) following a literature review, described in detail previously. The statements spanned the domains of risk factors for fistula cancer, clinical presentation, diagnosis, treatment, and outcomes. These statements were discussed and refined through collaboration with both surgical and medical IBD experts (JFC, SK, DS, each of whom have >20 years IBD experience).

The first round of voting took place using an online platform during July and August 2023. A panel of 24 experts on perianal CD in the TOpCLASS consortium, including 10 gastroenterologists, 8 surgeons, and 6 radiologists, participated. The original consensus statements were amended based on voting results and comments made by the expert panel. The second round of voting took place during a virtual meeting in September 2023 (Zoom Video Communications, Inc, San Jose, CA). Two members of the panel voted after the live meeting. Participants voted using a Likert scale (strongly agree, agree, neutral, disagree, strongly disagree). Eight statements were considered during the second round of voting with 7 statements accepted. Further amendments were made until greater than 70% consensus was reached (ie, "strongly agree" or "agree").

Supplementary Data

Human Papillomavirus and Perianal Fistulizing Crohn's Disease–Associated Cancers

HPV are commonly found and associated with cervical carcinoma and SCCA. High-risk HPV variants include HPV-16 and HPV-18.[37] A study of more than 60,000 patients determined that patients with IBD had a significantly higher age-standardized incidence of HPV-related cancers, including anal cancers, than non-IBD counterparts.[38] Anal cytology identified HPV in 15.6% of patients with anal CD, with no association with immunosuppressants.[39] In another study, 58% of anal cancer samples from women with a history of largely self-reported anal fissures and fistulas, with or without CD, were positive for high-risk HPV strains.[23] A prospective study included 31 patients with CD and assessed for HPV and anal pathology. There was a high rate (28/31; 90.3%) of HPV detection with 25 patients (80.6%) harboring single or multiple HPV strains including high-risk variants, 48.4% had abnormal anal cytology by the Bethesda system, and 61.3% had abnormal anal pathology on biopsy (AIN 1-3) with 6.5% having a high-grade squamous intraepithelial lesion on anal pathology (AIN 2-3).[40] A single-center retrospective case series of 18 patients with IBD (7 CD) found that all 6 cases of SCCA were in patients with CD, and 50% were associated with HPV-16 and p16 overexpression.[41] Others have reported SCCA in patients with CD with and without HPV.[42,48]

The CDC's Advisory Committee on Immunization Practices recommends HPV vaccination at age 11–12 years and catch-up vaccination through 26 years. Those aged 27 and older with least likelihood to have prior HPV exposure (ie, limited or no prior sexual experience) can also be considered for HPV vaccination.[49,50]

Magnetic Resonance Imaging Features in Perianal Fistulizing Crohn's Disease–Associated Cancers

MRI is often the first imaging used in the investigation of patients with PFCD, with and without suspected PFCD-associated cancers. The key sequences of MRI pelvis perianal fistula protocol contains small field of view T2 turbospin echo through the anal canal, used for assessment of various histologic subtypes of PFCD-associated cancers. On small field of view T2-weighted MRI, PFCD-mucinous adenocarcinoma commonly has -T2 hyperintense signal extending in fistula tracts and prior abscess cavities. PFCD-SCCA often manifests T2 intermediate signal mass at the superficial aspect of a chronic wound or fistula tract in the subcutaneous fat surrounding the anal canal. A low rectal cancer adenocarcinoma without mucinous histology often has a contiguous T2 intermediate signal mass involving the low rectum, anal canal, and perianal fistula.