

ORIGINAL ARTICLE

## Malignant transformation of perianal and enterocutaneous fistulas is rare: results of 17 years of follow-up from The Netherlands

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### Abstract

**Objective.** Malignant transformation of fistulas has been observed, particularly in perianal fistulas in Crohn's disease (CD) patients. The prevalence of adenocarcinoma in enterocutaneous fistulas and non-CD-related fistulas, however, is unknown. We investigated adenocarcinoma originating from perianal and enterocutaneous fistulas in both CD patients and non-CD patients from nine large, mostly tertiary referral, hospitals in The Netherlands. **Methods.** Patients suffering from fistulizing disease and either dysplasia or adenocarcinoma between January 1990 and January 2007 were identified using the nationwide automated pathology database (PALGA). Clinical and histopathological data were collected and verified using hospital patient-charts and reported by descriptive statistics. The total CD-population comprised 6058 patients. **Results.** In a study-period of 17 years, 2324 patients with any fistula were reported in PALGA. In 542 patients, dysplasia or adenocarcinoma was also mentioned. After initial review and additional detailed chart review, 538 patients were excluded, mainly because the adenocarcinoma was not related to the fistula. In the remaining four patients, all suffering from CD, adenocarcinoma originating from the fistula-tract was confirmed. The malignancies developed 25 years (IQR 10–38) after CD diagnosis, and 10 years (IQR 6–22) after fistula diagnosis. Median age at time of adenocarcinoma diagnosis was 48.3 years (IQR 43–58). Only one patient had clinical symptoms indicative for adenocarcinoma. In three other patients, the adenocarcinoma was found coincidentally. **Conclusions.** Adenocarcinoma complicating perianal or enterocutaneous fistula-tracts is a rare finding. Only 4 out of 6058 CD patients developed a fistula-associated adenocarcinoma. We could not identify any malignant transformations in non-CD-related fistulas in our 17 years study-period.

**Key Words:** Adenocarcinoma, Crohn's disease, fistula

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## Introduction

Fistulas constitute a common complication of Crohn's disease (CD) and occur in 30–50% of CD patients at some time during the course of their illness [1,2]. They result from full-thickness disease rupturing into an adjacent hollow viscus or through the abdominal wall; however, the exact pathogenesis still remains unclear. Fistulas are classified according to their location and their connection with contiguous organs [3]. They can be external (e.g. perianal or enterocutaneous fistulas) or internal (e.g. enteroenteric, enterovesical, enterouterine, or enterovaginal fistulas connecting the intestine with various organs or anatomic structures).

In a few case reports, the development of adenocarcinoma in perianal fistulas complicating CD has been described [4]. A recent systematic review of literature on cancer in perianal fistulas in CD patients revealed 61 published cases [5]. The causal relation between anorectal fistulas and cancer is unknown. The diagnosis of adenocarcinoma in chronic fistulas is difficult and may be delayed further since symptoms are usually attributed to the fistula and may therefore postpone suspicion for development of adenocarcinoma [6].

Prior studies mainly focused on perianal fistulas as a complication of CD, and little is known about adenocarcinoma in enterocutaneous fistulas and in non-CD-related fistulas. A study with 17 years of follow-up after surgical management of enterocutaneous fistulas in CD did not report the occurrence of adenocarcinoma [7]. In a recent case report, we described the development of adenocarcinoma in a CD patient with a longstanding enterocutaneous fistula [8].

We hypothesized that patients with CD-related fistulas are at increased risk for malignant transformation of perianal or enterocutaneous fistulas, whereas this risk is probably not increased in patients with non-CD-related fistulas. If so, screening is probably necessary. Hence, we aimed to identify all adenocarcinomas originating from perianal and enterocutaneous fistulas in nine large hospitals (eight academic and one third-line referral hospital) in The Netherlands. Secondly, we assessed the clinical characteristics of those subjects with adenocarcinoma originating from a fistula.

## Material and methods

### *Study population*

Patients with dysplasia or adenocarcinoma in a perianal fistula or enterocutaneous fistula in The Netherlands were identified using the nationwide network and

registry of histology and cytopathology (PALGA) [9]. The PALGA database contains all pathology reports generated in the Netherlands from 1990 until the present, and it is concluded with diagnostic terms in line with SNOMED<sup>®</sup> terminology. Each subject in the database has a unique identifier which allows tracking of individual patients over time and throughout the country. The following search criteria were used for the time period January 1st, 1990 until January 1st, 2007: (colon OR rectum OR anus) AND Fistula AND (all primary carcinoma AND/OR atypia AND/OR all epithelial dysplasia AND/OR all carcinoma in situ AND/OR all micro invasive tumors).

Additionally, in a second search, the PALGA system was searched for the word "Fistula" mentioned in free text of all pathology reports from the nine participating hospitals. The participating hospitals were the Erasmus Medical Centre, Rotterdam; VU University Medical Center Amsterdam; University Medical Center Groningen; Leiden University Medical Center; Radboud University Medical Center Nijmegen; Academic Medical Center Amsterdam; University Medical Center Utrecht; Maastricht University Medical Center and Rijnstate Hospital, Arnhem.

### *Outcome parameters*

The primary outcome measure was the presence of adenocarcinoma in perianal or enterocutaneous fistulas. The secondary outcome variable was the presence of adenocarcinoma in CD-related perianal or enterocutaneous fistulas.

To delineate the definition of fistula-tract-associated adenocarcinoma, the PALGA report had to fulfill the following criteria: the fistula had to be present >6 months prior to diagnosis of adenocarcinoma, and the fistula and the adenocarcinoma had to occur in the same histology specimen. Exclusion criteria were the following: occurrence of adenocarcinoma at an anatomical localization apart from the fistula, fistula formation due to adenocarcinoma or fistulizing inflammation along with an adenocarcinoma at a separate location at distance from the fistula. If there was any doubt about the origin of the adenocarcinoma in relation to the fistula, the patient was not excluded at this stage. Of the selected patients, clinical charts and pathology reports were reviewed to confirm the diagnosis of adenocarcinoma and fistulas. An expert panel decided whether or not the fistula was already present prior to development of the adenocarcinoma.

If the diagnosis was confirmed, additional data concerning gender, age, type and cause of fistula,

disease characteristics of adenocarcinoma/dysplasia and fistula, date of onset fistula and date of adenocarcinoma, history of colonic surgery, and the presence of CD were collected. The complete medical history was assessed, including prior colonoscopies and pathology reports. If CD was present, the following data were additionally collected: date of diagnosis, date of onset symptoms attributable to CD, duration of disease, and disease characteristics including extent of disease, severity of disease, surveillance details, and CD behavior. Extent of disease was subdivided in four categories based on type and extension of inflammation: limited CD, extensive CD, ileitis terminalis, and ileocecal CD. Limited CD was defined as <50% segmental CD in the colon and extensive CD was defined as >50% segmental CD in the colon. Severity of disease was graded as mild, moderate or severe colitis based on both histological and endoscopic features. Duration of medication use before adenocarcinoma diagnosis was subdivided into four categories (0–25%, 25–50%, 50–75%, and >75% of duration of follow-up).

#### *CD population in participating centers*

The size of the CD-population per hospital was assessed using local hospital-registries at the departments of Gastroenterology and Hepatology in each hospital. All participating hospitals have a specialized IBD-clinic with a database including all their IBD-patients. The total CD-population consisted of 6058 patients.

#### *Statistical considerations*

Descriptive statistics, including medians with interquartile ranges (IQR), are reported. Statistical analysis was performed with SPSS for Windows software (version 15.0).

## **Results**

In the nine participating hospitals, 2324 patients (1193 males, 1021 females) had the diagnostic term fistula in the PALGA system (Figure 1). The primary search revealed 237 patients with both a fistula and dysplasia or adenocarcinoma (105 males, 121 females). An initial review of the excerpts excluded 112 patients. Main reasons for exclusion were: adenocarcinoma and fistula in different specimen, fistula caused by an adenocarcinoma or fistulizing inflammation along with an adenocarcinoma. In total,

125 out of 237 patients (41%) were included for detailed chart review to confirm diagnosis and collect clinical data.

The second PALGA search revealed 1136 pathology excerpts from 305 patients (146 males, 159 females) from the nine hospitals. After initial review, 61 patients remained eligible.

Summing up, 186 patients (125 patients from the first PALGA-search + 61 patients from the second search) were eligible for detailed chart review.

#### *Adenocarcinoma originating from perianal or enterocutaneous fistulas*

Of the 186 cases that were included for detailed chart review, four patients had a confirmed diagnosis of adenocarcinoma in direct association with chronic perianal or enterocutaneous fistulizing disease. Main reasons for exclusion were: fistula formation due to adenocarcinoma, or adenocarcinoma occurred at an anatomical localization apart from the fistula.

The four patients, selected out of 2324 histopathological reports, suffered from CD, and thus, none of the patients with non-CD-related fistulas were found to have developed adenocarcinoma in relation with the fistula-tract. Four out of 6058 CD patients developed adenocarcinoma originating from the fistula-tract.

#### *Patient characteristics*

Clinical data for the four patients with adenocarcinoma are summarized in Table I. All patients had persistent fistulas, which responded only partial to therapy. The median age at time of adenocarcinoma-diagnosis was 46.2 years (IQR 41–58). CD disease-characteristics of the four fistula-carcinoma patients are listed in Table II. The adenocarcinoma developed on average 22 years (IQR 9–38) after establishment of CD and 9 years (IQR 4–22) after the diagnosis of a fistula-tract as a complication of CD. In case of perianal fistula formation, the fistula was complex. Patient 4 was lost to follow-up at 4 years after adenocarcinoma diagnosis. All other patients were still alive at the end of the follow-up period (August 1st, 2008). Median follow-up time after adenocarcinoma diagnosis was 3.5 years (IQR 2–6).

*Medical history before adenocarcinoma-diagnosis.* None of the patients had major co-morbidity in their medical history or during follow-up. In two patients several surgical procedures had been performed, all because of CD-related indications. Patient 1

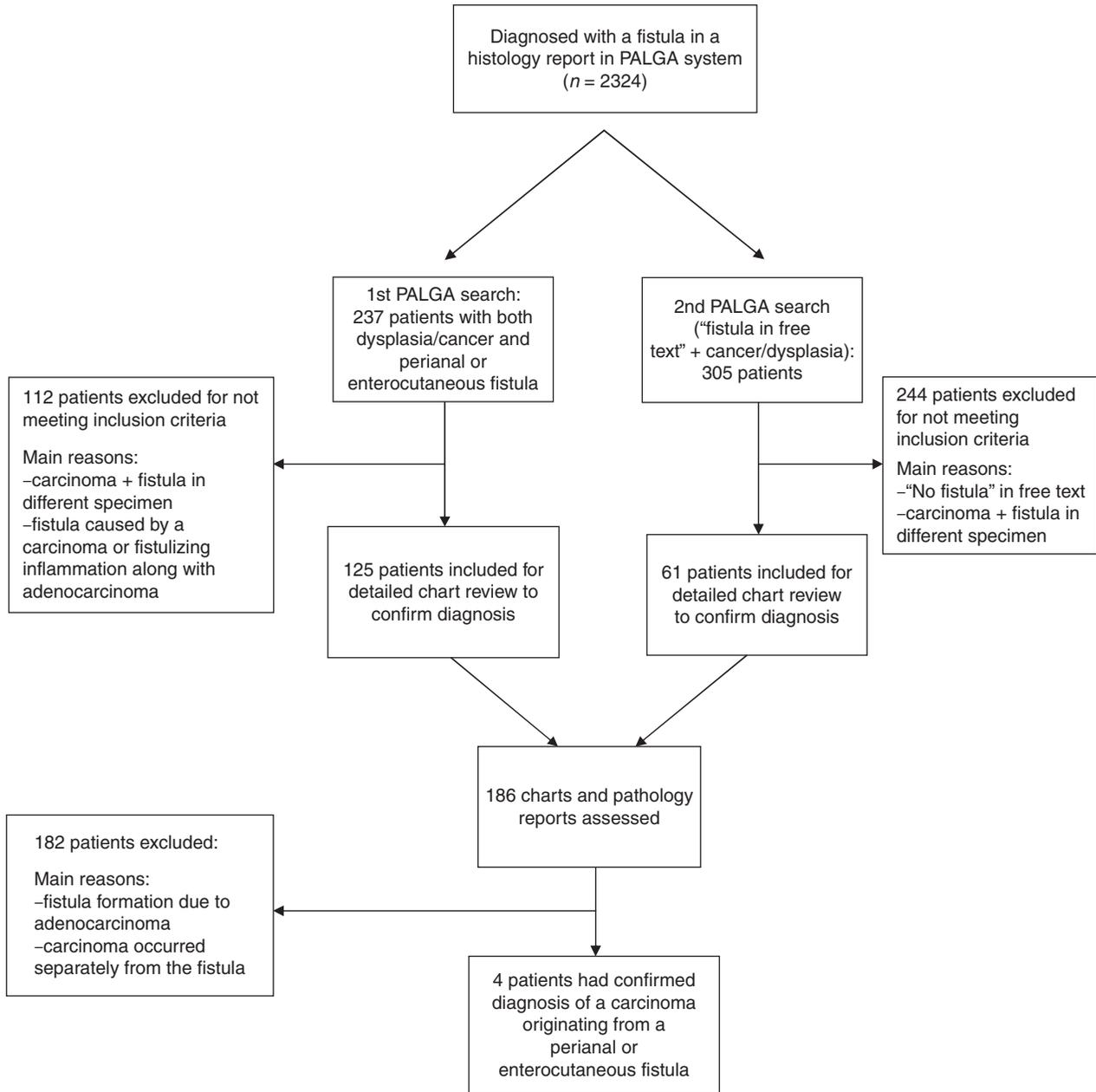


Figure 1. Flow chart study population.

underwent an ileocecal resection and re-resection 13 and 8 years before diagnosis of the adenocarcinoma, respectively, and followed by drainage of perianal abscesses 1 year before adenocarcinoma diagnosis. Patient 3 underwent a subtotal colectomy 10 years prior to adenocarcinoma diagnosis.

*Diagnosis of the adenocarcinoma.* In patient 1, abdominoperineal rectum extirpation was performed because of a persistent fistula-tract. No malignancies were found at this time. Four years after the surgery, adenocarcinoma was found in biopsies that were

taken during inspection of the area because of a persistent fistula. Revision of the initial biopsies from the resection specimen demonstrated that the tumor was already present at time of the rectum extirpation.

In patient 2, the adenocarcinoma was found coincidentally during surgery for his persistent enterocutaneous fistula. Histopathology of the resection specimen revealed a perforation of the ascending colon with localization of a well-differentiated adenocarcinoma, originating from the fistulous tract.

In patient 3, a large perianal defect was found during physical examination in the out-patient clinic.

Table I. Patient characteristics.

Patient no.	Gender	Age at diagnosis of carcinoma (years)	Duration of CD (years)	Symptoms	Duration of fistula (years)	Type of fistula	Cause of fistula	Type of carcinoma	Therapy carcinoma
1	M	41.6	20.7	None	3.8	Perianal	IBD	Adenocarcinoma	Rectum extirpation + local radiotherapy
2	M	41.5	5.4	None	5.4	Enterocutaneous	IBD	Adenocarcinoma	Right-sided hemicolectomy + chemotherapy
3	F	50.7	42	None	25	Perianal	IBD	Adenocarcinoma	Proctectomy + adjuvant radiotherapy
4	M	60.2	24.3	Purulence resulting from fistula	12.3	Perianal	IBD	Adenocarcinoma	Rectum amputation + chemotherapy

Biopsies were taken by the dermatologist and these biopsies revealed adenocarcinoma originating from the fistula-tract, consistent with an anal duct carcinoma.

Patient 4 was the only patient who had symptoms indicative, but not pathognomonic, for concurrent adenocarcinoma. This patient had a draining fistula with extensive (bloody) purulence.

## Discussion

In this large retrospective cohort study in nine large hospitals from The Netherlands we confirm that adenocarcinoma is a rare complication of longstanding fistula-formation. In our study-period of 17 years, in only four CD patients out of at least 2324 fistula-patients, an adenocarcinoma originating from the fistula-tract could be confirmed, whereas no adenocarcinoma were observed in non-CD-related fistulas. The total CD-cohort in these hospitals comprised 6058 CD patients.

The diagnosis of adenocarcinoma in chronic fistulas is difficult and is presumably delayed since symptoms usually are attributed to the fistula. Subsequently, adenocarcinoma may not be suspected and biopsy examination is usually performed only in a late stage of disease [5]. In our cohort, only one patient had symptoms that raised suspicion of concurrent adenocarcinoma. All other adenocarcinomas were diagnosed coincidentally. In patients with longstanding complex fistulas, performance of a thorough anorectal examination is hampered, due to various reasons, such as pain, anal stricturing, and limited endoscopic view. This is in line with a systematic review of literature demonstrating that on initial examination, adenocarcinoma was suspected and proven in only 20% of cases [6].

Previous reports have mainly focused on CD-related fistulas, in particular perianal fistulas. In a 14-year follow-up of more than 1000 patients, only seven patients were found to have adenocarcinomas associated with anorectal fistulas [10]. The prevalence was estimated to be only 0.7% in CD patients. Additional review of 33 other cases of anorectal adenocarcinoma demonstrated that 45% were clearly associated with fistulas [10]. Connell et al. reported four cases of adenocarcinoma in anorectal fistulas out of 1250 CD patients, which equals a prevalence of 0.3% [11]. Another systematic review of case series and reports published between 1950 and 2008 revealed 61 cases of adenocarcinomas arising in perianal fistulas in CD [6]. Contrary to previous studies, we did not restrict our cohort to CD patients, complicated by perianal fistulas. Although we combined

Table II. IBD disease characteristics.

Patient no.	Age at CD diagnosis (years)	Extent of CD	Maximum severity of CD	Medication-use during follow-up*				
				5-ASA	Immunosuppressives	Corticosteroids	Methotrexate	Anti-TNF
1	20.9	>50% segmental CD	Severe	<25%	>75%	50–75%	<25%	–
2	36.1	Ileocolic CD	Severe	>75%	50–75%	>75%	–	–
3	8.7	Ileocolic CD	Severe	–	25–50%	<25%	<25%	<25%
4	35.9	<50% segmental CD	Unknown	>75%	<25%	<25%	–	–

\*Between onset of CD and carcinoma diagnosis.

both perianal and enterocutaneous fistulas and also assessed non-CD-related fistulas, our results imply that the prevalence is lower than what was previously reported. Out of 6058 CD patients, only four patients developed adenocarcinoma in a longstanding fistula, which is by approximation calculated to be a prevalence of 0.004%.

Although our main outcome parameter was the prevalence of malignancies in external fistulas, we did search the PALGA system for malignancies in all types of fistulas, including internal fistulas. However, we could not identify any malignancies in internal fistulas and all identified malignancies in our study developed in enterocutaneous or perianal fistulas.

This is to our knowledge the first multicenter study that aimed to specifically assess the prevalence of adenocarcinoma originating from an established fistula-tract. In contrast with previous single center experiences, this study population of nine participating hospitals included all patients with an established fistula in a histopathology report. These results suggest that patients with non-CD-related fistulas are not at increased risk for developing adenocarcinoma in the fistula-tract. On the other hand, inclusion of non-CD-related fistulas might partly explain the low by approximation calculated prevalence for the development of malignancies in fistula-tracts.

This study is limited by the fact that no exact prevalence or incidence can be given. Although we are confident to have found all the fistula-associated adenocarcinoma during our study-period, we cannot give an exact number of the baseline cohort because of the following two reasons: firstly, biopsy specimens are only harvested by exception from “regular” fistulas (i.e. fistulas ascribed to a complicated course of CD), and therefore no histological data are available of the majority of this type of fistulas. As the data were gathered from a histopathological database, these series are obviously biased by having only samples from those patients from whom specimens were available following endoscopic or surgical biopsy, or from a resection specimen. Therefore, we could have missed fistulas in the total CD-population due to the design of this study. However, as histopathological data are typically gathered from almost all

malignancies, the risk that we have not characterized malignancies or dysplasia as related to fistulas in PALGA is very low.

Secondly, the total CD-population cannot be extracted from the PALGA database. Instead, local hospital registries were used to estimate the magnitude of the baseline cohort of CD patients. Although each IBD-clinic accurately records their patient-cohort and these registries are assumed to be adequately maintained, only an estimation by approximation of the prevalence of fistula-associated adenocarcinoma in CD patients can be calculated. Nevertheless, in this cohort comprising as many as 2324 patients with any fistula and an observation-period of 17 years, only four subjects developed a malignant transformation of the fistula. This implies that the estimated prevalence is unlikely to exceed 0.17% in case of patients with any manifestation of a fistula. Moreover, we estimate that the prevalence of fistula-associated adenocarcinoma in any CD patient is approximately 0.004%.

The causative relationship between anorectal fistulas and adenocarcinoma is unknown. There are two hypotheses: one suggesting that fistulas might lead to malignant transformation because of chronic inflammation of mucosa, known as “scar-tissue adenocarcinoma” [12] and another suggesting that cancer may be the cause of the fistula [13]. The latter is not supported by our study because all of our patients had a clinically established fistula for at least 5 years.

In conclusion, we demonstrated that adenocarcinoma complicating perianal or enterocutaneous fistulas is a rare phenomenon. Out of 2324 patients with a fistula, only four patients developed adenocarcinoma in the fistula-tract during an observation-period of 17 years. Only four out of 6058 CD patients developed a fistula-associated adenocarcinoma. We could not identify any malignant transformations in non-CD-related fistulas. Given this low prevalence, we believe that screening all patients with fistulas is not indicated. However, although it remains a rare complication, caution is needed since the diagnosis of concomitant adenocarcinoma formation in already established fistulas is difficult to make.

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