

Alimentary tract and pancreas

Prognosis in Crohn's disease – based on results from a regional patient group from the county of Copenhagen

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SUMMARY All patients in the county of Copenhagen (approximately 500 000 inhabitants) with Crohn's disease, $n=185$ were followed regularly between 1960 and 1978. The survival, the course of disease, the frequency of surgery, and the working capacity were estimated for the first 10 years of disease on the basis of the follow up results. The observation time ranged from 1–18 years with a median of 5.5 years for clinical observations, 5.8 years for survival, and 9.5 years for the occurrence of gastrointestinal cancer. The follow up was 100% concerning survival and cancer. The survival did not differ from that of the age- and sex-matched background population. Cancer was seen in only one of 185 patients corresponding to an annual risk of 0.06% and a cumulated risk after 10 years of 0.56, 95% confidence limits: 0.1–3.1%. The cancer was localised in the ileum. For all years, about 45% of the patients were without clinical symptoms of their disease, in 30% the clinical disease activity was low, and in 25% moderate to high. Among the patients with active disease, the course within the individual year was continuous in about one third and intermittent in about two thirds. After 10 years, 99% of the patients had experienced at least one relapse. The operation rate was 33% in the year of diagnosis, 13% in the following year, and then about 3% per year independent of whether or not the patient had been treated surgically in the past. After 10 years, 45% of the patients had not been treated surgically, 42% had had only one operation, and 13% had had two or more operations for their Crohn's disease. The working capacity was normal in about 75% of the patients for all years except the year of diagnosis. About 15–20% of the patients who had had the disease for more than five years were disabled as compared with about 4.4% of the background population. These results indicate that some of the patients with Crohn's disease run a more serious course with continuing symptoms despite of medical treatment and frequent surgical interventions. Most patients, however, remained capable for work and were able to lead a normal life.

Crohn's disease is considered a serious and taxing disease both in terms of survival and capacity to lead a normal daily life. Many patients, however, are able to lead a normal life with few relapses or with continuous mild symptoms. The exact figure for the distribution of the patients into these categories is uncertain as it demands a long term follow up of a complete regional patient group.

The aim of the present study was to evaluate the prognosis expressed as survival, operation rate, working capacity, and course and activity of the disease on the background of a regular follow up of

all patients in the county of Copenhagen (approximately 500 000 inhabitants) during 18 years.

Methods

PATIENTS

The background population was previously described in detail.¹⁻³

STUDY POPULATION

A total of 185 patients who were residents of the county of Copenhagen fulfilled the diagnostic criteria of Crohn's disease, 74 men and 111 women. The diagnostic criteria were previously described.¹

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All clinical data of the patient group at the time of diagnosis were recently published.² Sixteen patients were initially diagnosed as having ulcerative colitis, but during the course the diagnosis was changed to Crohn's disease, and conversely six patients who fulfilled the clinical criteria of Crohn's disease in the colon were shown histologically to have ulcerative colitis. The patients were included in this study for the observation years during which they fulfilled the diagnostic criteria of Crohn's disease.

One hundred and three patients were followed in this department since the time of first diagnosis. The remaining 82 were diagnosed according to the same criteria, but treated in other hospitals in the area. All clinical data have been available to the authors, and the treatment principles have been the same in the different hospitals. Table 1 gives the age of the patients and the localisation of the disease at time of diagnosis.

CLINICAL FOLLOW UP

The patients were followed regularly as outpatients at intervals of one year or less depending on the severity of symptoms. For each year of observation an assessment of clinical activity, working capacity, and treatment, both medical and surgical was made. The principles of treatment have not changed during the study period: prednisolone systemically and/or locally for exacerbation preferably in short courses of a few months' duration, but sometimes for longer periods. Sulphasalazine was used as long term treatment if the drug was tolerated. Surgical treatment was carried out in the form of limited resection of affected segments of the small and large bowel, either for obstructive symptoms or limited resection for persistent clinical activity despite intense medical treatment.

The patients were followed from the time of diagnosis until the 31 December 1978 or until death (eight patients), emigration from the area (16 patients), or termination of regular review by the patient for other personal reasons (21 patients). The clinical follow-up ranged from one to 18 years, median 5.5 years. The incidence of Crohn's disease

in the area rose during the study period¹ from 0.8 per 10⁵ inhabitants in the 1960's to 2.8 in the 1970's. Seventy four patients (40%) were observed for six years or more, and 16 patients (8.6%) have been followed for more than 10 years. At the close of the study, 151 patients were still under review.

Through the Danish Central Person Register, patients who 'dropped out' before the end of the study were traced as regards survival – that is, the survival curves comprise the total patient cohort, and through the Danish Cancer Registry the total group of patients with Crohn's disease was checked until the end of 1982 as regards occurrence of gastrointestinal cancer, yielding a median observation period for this specific variable of 9.5 years.

The definitions of working capacity and of activity and course of disease were similar to those published for ulcerative colitis.³ In patients having had intestinal resections, additional two bowel movements per day were allowed within the same degree of activity.

STATISTICAL METHODS

The follow up data were analysed using discrete failure time models with time-dependent covariates – that is, operation, course of disease, and capacity for work. The analyses were performed with the emphasis placed not only on the risk of death but also on the distribution of the covariates as described elsewhere.³⁻⁵

The risk of death was finally compared with the mortality of the population at large. For each year after diagnosis, the expected number of deaths among the patients at risk was calculated taking into account for the individual patient both sex, age, and calendar year. Finally, the deviance between the observed and expected number of deaths was evaluated on the assumption that the actual number of deaths is distributed according to a Poisson distribution.

Results

SURVIVAL

In Fig. 1 the survival of the Crohn patients is shown in relation to that of the age- and sex-matched background population. There was no significant difference between expected and observed survival, and there was no difference between the two sexes in respect to survival.

CANCER OCCURRENCE

One patient developed cancer in the ileum 13 years after diagnosis of Crohn's disease. No other gastrointestinal cancers were found among the patients.

Table 1 Total group of 185 patients with Crohn's disease. Localisation of disease at diagnosis. Age mean 33.3 years, range 4–76 years

Localisation			
Small bowel only	Both small and large bowel	Large bowel only	Duodenal or perianal localisation
58 (31%)	66 (36%)	52 (28%)	9 (5%)

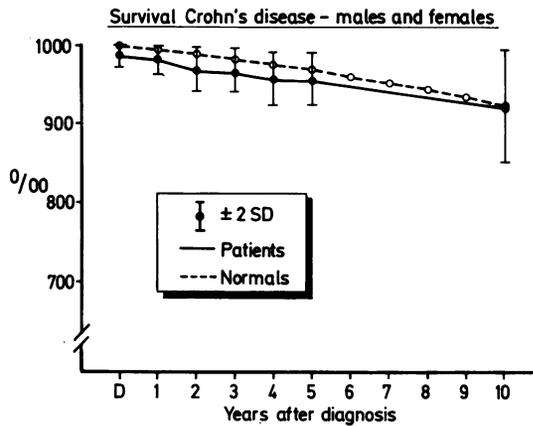


Fig. 1 Survival of patients with Crohn's disease compared with the age- and sex-matched background population.

The calculated risk of gastrointestinal cancer per year is 0.06% with 95% confidence limits: 0.01–0.31%. The cumulative risk after 10 years with Crohn's disease is 0.56% with 95% confidence limits: 0.10–3.1%.

DISEASE ACTIVITY

The distribution of the patients in different activity stages for each separate year after diagnosis is shown in Fig. 2 for all patients irrespective of treatment – that is, intestinal resection or medical

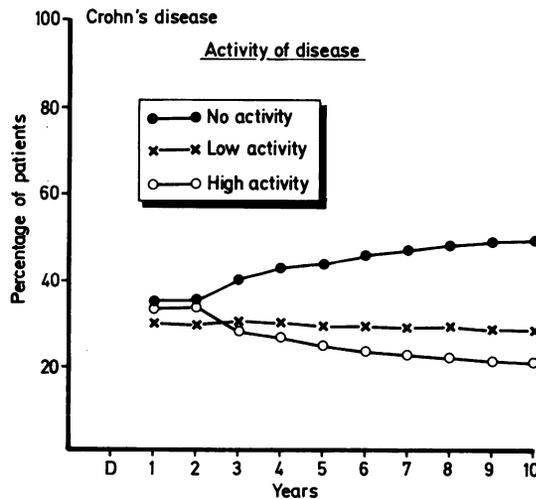


Fig. 2 Activity level in the total Crohn patient group for each separate year after diagnosis. Calculations based upon all patients alive.

treatment only. An increasing number of patients can expect to be free of symptoms with increasing duration of the disease. In the individual patient, however, the activity changed from one year to the other. The number of patients with one exacerbation only is shown in Fig. 3. After five years 6.9% and after 10 years only 1.3% of the patients had not experienced a relapse.

COURSE OF DISEASE

During each year, whether continuous, intermittent or totally inactive this is shown in Fig. 4. For all the observation years the general trend was that about 20% of the patients had continuous and about 35% intermittent symptoms, whereas the disease was clinically inactive in 45%.

OPERATION RATE

Table 2 gives the annual operation rates for the first and subsequent operations. The frequency of operation was highest in the first year with a gradual fall during the following four years. From the fifth year after diagnosis, the annual rate of operation was constant at 3% irrespective of previous surgery. In Fig. 5, the cumulative probabilities show that after 10 years with Crohn's disease 45% of the patients remained unoperated, whereas 42% were operated once and 13% twice or more.

WORKING CAPACITY

Figure 6 illustrates the distribution of the patients according to their working capacity. Except for the year of diagnosis about 75% of the patient group were fully capable for work. After five years with the disease, 12–20% of the patients were disabled as compared with 4.4% of the background population.⁶ Thus, after living five to 10 years with their disease, about 15% of the Crohn disease

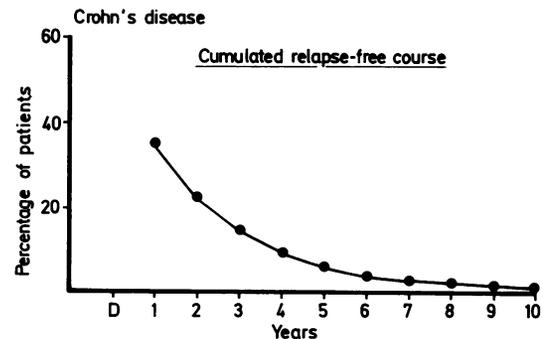


Fig. 3 Cumulative probability of a relapse-free course after the first year with Crohn's disease.

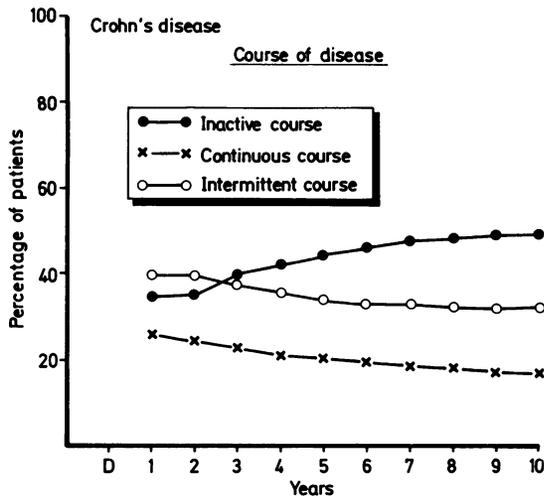


Fig. 4 Course of the disease in each separate year after diagnosis. Calculations based upon all patients alive.

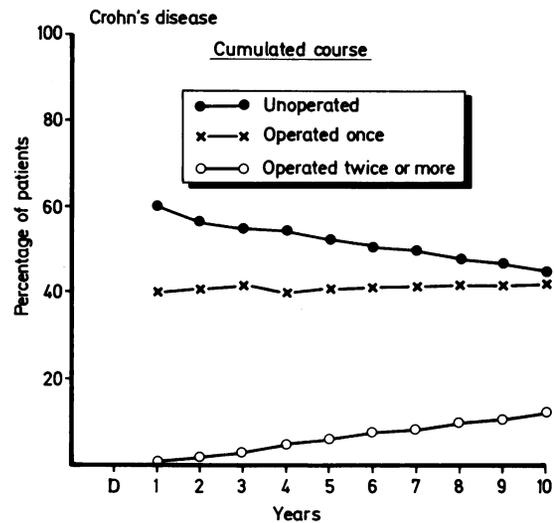


Fig. 5 Cumulative probability of one or more intestinal operations with increasing duration of Crohn's disease.

patients apparently are unable to work and thereby lead a normal social life whereas the greater part, 75%, will be socially integrated.

Discussion

To our knowledge, no complete regional patient group with Crohn's disease has hitherto been followed prospectively for a longer period. More than 99% of the patients in the region with a diagnosis of inflammatory bowel disease are included in the study.¹ The rising incidence during the study period means that most of the patients were included during the last 10 years, and only a few patients with Crohn's disease have been

followed for more than 10 years. The statistical analysis therefore was carried out only for the first 10 years after the diagnosis of Crohn's disease.

The good prognosis for survival during the first 10 years in this study contrasts with the results from Oxford⁷ where the long term follow up of 166 directly referred patients showed an increasing mortality with duration of disease and a significant

Table 2 Intestinal resections in the Crohn's disease patients

	First operation (%)	Subsequent operation(s) (%)
Year of diagnosis	33	0
1 after diagnosis	11	2
2 after diagnosis	9	0
3 after diagnosis	4	6
4 after diagnosis	4	5
5 after diagnosis	3	3
6 after diagnosis	3	3
7 after diagnosis	3	3
8 after diagnosis	3	3
9 after diagnosis	3	3
10 after diagnosis	3	3

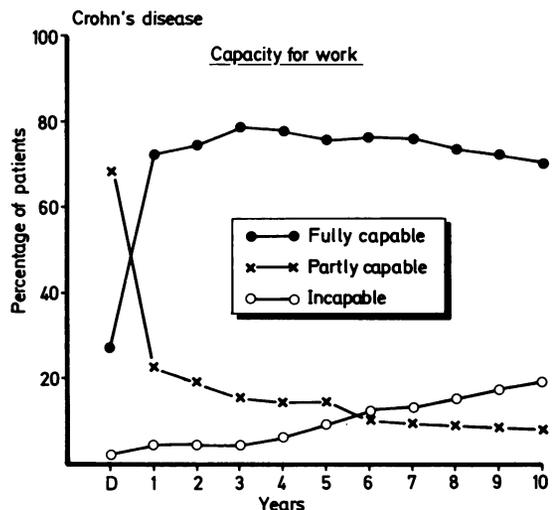


Fig. 6 Probability of being capable for work in each year after the diagnosis of Crohn's disease.

extra mortality compared with the age- and sex-matched background population. After 10 years the observed mortality was 12.6% against the expected 5.6%. The expected 10-year mortality is 7.5% in our background population and the observed one in the present study was 7.4%. The Oxford material which is not strictly regional, could well have had an excess of severe cases, explaining the more serious prognosis. Further, the study included Crohn patients from 1938 to 1970 – that is, some of the patients were in treatment before the steroid era and at a time when surgical procedures were hazardous.

An extensive but not regional study of 513 patients with Crohn's disease, who were followed from one to 35 years⁸ has been published from Birmingham. In patients below 45 years at diagnosis the mortality was three to four times higher than the expected one. In contrast with the Oxford results,⁷ the risk did not increase with the duration of the disease, but was at its highest in the first five years.

A very high mortality was reported from a Danish clinic specialising in gastroenterology with patients referred from all over the country which included, predominantly severely ill patients.⁹

The operation rate was at its highest in the year of diagnosis and was then constant at a rate of 3% per year after four years – irrespective of whether the patients had been operated on previously or not – which is in accordance with the findings from Cleveland,¹⁰ from Birmingham,¹¹ and from Leeds.¹²

Compared with ulcerative colitis,³ Crohn's disease often runs a continuous course – that is, continuous active disease in one third of the patients against one fifth of the ulcerative colitis patients. The percentage of patients with a clinically inactive disease (45%), however, is very similar to that in ulcerative colitis.

The figures for working capacity show that the majority of the patients (75%) were socially integrated. The disablement rate amounted to 20% after 10 years against 4.4% in the normal Danish population. These findings are in agreement with those of Gazzard *et al.*¹³

The occurrence of one case of intestinal cancer in our study and the calculated cumulative risk after 10 years of 0.56% is lower than the results reported from Birmingham¹⁴ and may be explained by the relatively short observation period in our study.

In conclusion this study depicts Crohn's disease as a relatively benign disease. About 75% of the

patients being able to maintain an almost normal life, whereas in a minority, the disease takes a serious course, despite intense medical and surgical treatment.

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