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Natural Course of Chronic Pancreatitis

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1. Introduction

In the minority of patients (i.e., 5.8% to 20%), chronic pancreatitis takes a primarily painless course (7, 8, 32, 52, 53, 76, 91). Exocrine and endocrine insufficiency are the dominating symptoms. For the majority of patients, however, pain is the decisive symptom, causing much discomfort in their daily lives. Some studies have correlated the course of pain in chronic pancreatitis with the duration of the disease, progressing exocrine and endocrine pancreatic insufficiency and morphological changes, such as pancreatic calcification and duct abnormalities. Furthermore, the course of pain has been studied following alcohol abstinence and after surgery in some groups.

Therefore, this review of the natural course of chronic pancreatitis focuses on pain but also pays attention to the course of exocrine and endocrine pancreatic insufficiency and concludes by describing the socioeconomic situation of the patients, the mortality of the disease, and the prognosis.

2. Pain decrease and duration of chronic pancreatitis

Whether progressive parenchymal destruction leads to pain decrease has been repeatedly debated (5, 6). Ammann's group has claimed that pain decreases with increasing duration of the disease (4, 7, 10). In one long-term study, 85% of 145 patients with chronic pancreatitis felt no more pain after 4.5 years (median) than at the onset of the disease (7). In another series, in which the interval between the onset of alcohol-induced chronic pancreatitis and pain relief was compared in surgically and nonsurgically treated patient groups, the curves were virtually parallel: pain relief was obtained in about 50% within 6 years and in more than 80% within 10 years from the onset of illness (11).

The reports from Zurich are at variance with the studies from Japan and Germany. Miyake et al. (91) found that only 48.2% of the patients with chronic pancreatitis became free of pain within 5 years, but 66—73% after more than 5 years. This showed that every third or fourth patient still suffered from relapsing pain attacks even after a long observation period. The Göttingen group* reported that the incidence of relapsing pain attacks decreased during the observation period, but more than half of the patients (53%) still

* Under the leadership of Prof. Dr. Werner Creutzfeldt, a group of clinicians at the University of Göttingen, Germany, began to work on the diagnosis and prognosis of pancreatic diseases, in particular chronic pancreatitis, in 1964. From the mid-1970s this group was headed by one of us (PGL). For the sake of simplicity we refer to this group as the "Göttingen group".

suffered from relapsing pain attacks even after more than 10 years of observation (76).

At present, the course of pain in alcoholic and idiopathic chronic pancreatitis remains unclarified. Layer et al. (79) investigated a group of patients with idiopathic chronic pancreatitis who had never consumed alcoholic beverages. They found that patients with early-onset pancreatitis (under 35 years of age) have a long course of severe pain from the start of their illness, whereas patients with late-onset pancreatitis (over 35 years) have a mild and often painless course. Both forms differ from alcoholic pancreatitis in having an equal gender distribution and a much slower rate of calcification. In contrast, the Göttingen group found that the course of pain is the same in alcohol- and nonalcohol-induced chronic pancreatitis (78). Even when we divided the nonalcoholic group into teetotalers and patients with little alcohol consumption, and separately compared their course of pain with alcoholics, there were no differences concerning pain relief among the three groups (77) . Further studies are required.

3. Pain decrease and progressing exocrine and endocrine pancreatic insufficiency

The Swiss group have repeatedly observed pain decrease when exocrine and endocrine pancreatic function declines (4-6, 10). Similarly, Girdwood et al. (50) reported from South Africa that pain decreased as exocrine pancreatic function deteriorated.

Conversely, groups from Denmark and Germany have reported the opposite. Thorsgaard Pedersen et al. (118) from Copenhagen found no correlation between pain and exocrine pancreatic function. The Göttingen group (76) used the secretin-pancreozymin test and fecal fat analysis to evaluate exocrine pancreatic insufficiency, whereas the Swiss group had used only indirect pancreatic function tests, i.e., chymotrypsin measurements, to evaluate exocrine pancreatic insufficiency (7). A clear-cut grading of the severity of exocrine pancreatic insufficiency was used: mild impairment was defined as reduced enzyme output; moderate impairment as a decreased bicarbonate concentration along with reduced enzyme output but normal fecal fat excretion; and severe impairment was equated with an abnormal secretin-pancreozymin test plus steatorrhea. At the end of the observation period, 141 (45%) of 311 patients with painful chronic pancreatitis had severe exocrine pancreatic insufficiency. The majority of them (81/144; 57%) still suffered from pain attacks (76).

Additionally, the course of pain was studied in correlation with endocrine pancreatic insufficiency. Endocrine pancreatic insufficiency was classified as absent, moderate (diabetes mellitus treated only by diet with or without oral medication), and severe (requiring insulin). At the end of the observation period, 117 (38%) patients were classified as having severe endocrine pancreatic insufficiency. The majority of them (69/117; 59%) still suffered from pain attacks (73, 76).

Thus, according to these results, the progression of exocrine and endocrine pancreatic insufficiency has a limited influence, if any, on the course of pain in chronic pancreatitis.

4. Pain decrease and development of morphologic changes of the pancreas (pancreatic calcifications and/or duct abnormalities)

The Swiss group (7, 10) showed an increased incidence of pancreatic calcifications, which in turn was associated with pain decrease. However, in a later survey the same group reported a regression of pancreatic calcifications in a long-term study of patients with chronic pancreatitis (12). Thus, the prognostic role of pancreatic calcifications in determining the course of pain is unclear.

Furthermore, the Swiss results are at variance with two other studies. Malfertheiner et al. (85) found that 89% of patients had pain despite pancreatic calcifications observed on computed tomography, of whom 39% had very intense pain. In the Göttingen group study, freedom of pain was significantly higher in the calcification group than in the noncalcification group. However, the majority of patients with pancreatic calcifications (56%) still had relapsing pain attacks (76).

The correlation between pain and pancreatic duct changes or pressure in the duct system is also not clear. Ebbehøj et al. (36, 37) measured pancreatic tissue fluid pressure percutaneously or intraoperatively and found a significant correlation with pain in patients with chronic pancreatitis but not with the results of endoscopic retrograde cholangiopancreatography (ERCP), i.e., regional pressure tended to be highest in the region of the pancreas with the largest but not the smallest duct diameter. Jensen et al. (63) found no correlation between pancreatic duct changes and pain. Warshaw et al. (125) found that 2 of 10 patients, one year after a lateral pancreaticojejunostomy, had no pain relief despite a patent anastomosis detected by ERCP.

Two investigations confirmed the nonparallelism between pancreatic duct changes and pain relief. Malfertheiner et al. (85) found severe pain in only 62% of patients who had advanced pancreatic duct changes demonstrated by ERCP. The Göttingen group found no significant correlation between pancreatic duct abnormalities detected by ERCP and pain in 88 patients with chronic pancreatitis (76). Severe pancreatic duct abnormalities, as defined by the Cambridge classification (13) , were present in 42 patients, but only 16 (31%) of these became free of pain. Despite a normal pancreatic duct in 14 patients, 10 (71%) suffered from persisting pain (76).

Thus, morphological changes such as pancreatic calcifications or pancreatic duct abnormalities are not necessarily helpful in determining the prognosis of chronic pancreatitis or predicting the course of pain.

Smoking has an effect on the natural course of the disease since it increases the risk of pancreatic calcification in late-onset but not early-onset idiopathic chronic pancreatitis (59).

5. Pain decrease and alcohol abuse

Since alcoholism is the leading etiologic factor in chronic pancreatitis, several studies have investigated whether alcohol abstinence influences pain or progression of the disease. Sarles and Sahel (107) reported that 50% of their patients with chronic pancreatitis experienced pain relief when alcohol abuse was discontinued, whereas Trapnell (121) reported a figure of 75% when alcohol abuse was discontinued.

Two other investigations have confirmed that abstinence can be helpful. Miyake et al. (91) demonstrated pain relief in 60% of their patients who discontinued or reduced alcohol intake, whereas spontaneous pain relief was seen in only 26% of the group who continued drinking. In a study by the Göttingen group, 66 (31%) of 214 patients with alcoholic chronic pancreatitis were motivated to stop drinking (76). Pain relief was obtained in 52% of these patients, whereas spontaneous relief in alcoholics was seen in 37%. Thus, alcohol abstinence will probably lead to some improvement of pain in every second patient with chronic pancreatitis, but why exactly abstinence helps in some cases but not in others remains to be investigated.

6. Pain decrease and intervential procedures

Interventional procedures for pain treatment in chronic pancreatitis include fragmentation of stones by extracorporeal shock wave lithotripsy (ESWL), endoscopic stone extraction, and bridging of pancreatic strictures by stent applications. Reports of the effect of these

procedures on pain are controversial and controlled studies are lacking. A large Japanese study of 555 patients who underwent ESWL for pancreatic stones report a success rate of 92.4% (fragmentation of stones) and a complete stone clearance rate after ESWL alone or in combination with interventional endoscopy of 72.6%. Symptom relief was achieved in 91.1% of the patients. Complications developed in 6.3% of the patients, including acute pancreatitis in 5.4%. A total of 504 patients were followed up for a mean of 44.3 months, during which 122 (22%) suffered stone recurrence (mean time to recurrence, 25.1 months); 22 (4.1%) required surgery (60). In another series from Japan, a total of 117 patients with pancreatic stones underwent ESWL and endoscopic treatment. Immediate pain relief was achieved in 97% and complete removal of stones in 56%. During long-term follow-up over 3 years, 70% of the patients continued to be asymptomatic (116). These results are at variance with a smaller German study in 80 patients with chronic pancreatitis, in whom ESWL was always followed by a further endoscopic procedure. Treatment success was defined as complete clearance of the main pancreatic duct or partial clearance that allowed implantation of a pancreatic stent. Successful treatment was more frequent in patients with solitary stones. The mean duration of follow-up was 40 (range 24—92) months. Pain relief and necessity for further analgesia was independent of ESWL results (1). Thus, in this study pancreatic drainage by ESWL and endoscopy had almost no effect on pain in chronic pancreatitis in the long term (1) . This finding is in sharp contrast to the results of a new, albeit retrospective study of 636 patients with idiopathic chronic pancreatitis from a high-volume tertiary-care center for endoscopy and gastrointestinal diseases in India (117). The patients were monitored after ESWL and ERCP and divided into an intermediate group (follow-up 24—60 months; n, 364) and a long-term group (follow-up >60 months; n, 272). Absence of pain was seen in 250 (68.7%) patients, mild to moderate pain in 94 (25.4%) patients, and severe pain in 20 (5.5%) patients of the intermediate group. In the long-term group, 164 (60.3%) patients had no pain, 97 (35.7%) patients had mild or moderate episodes of pain, and 11 (4.04%) patients had episodic severe pain. Recurrence of calculi was seen in 51 (14.01%) patients in the intermediate follow-up group and in 62 (22.8%) patients in the long-term group.

The Indian group freely admits that their study was single-center retrospective analysis and that visual analogue scale scores for pain an quality of life were not validated. Nevertheless, they believe the following conclusions can be drawn: Patients who have been relieved of pain during the intermediate period (2—5 years) after ESWL are likely to continue to benefit in the long term. It is probable that early intervention with ESWL and endotherapy, especially in young patients with chronic pancreatitis, alters the course of the disease. Furthermore, early ESWL could even obviate surgical intervention, although this needs to be confirmed in a randomized, controlled trial (117).

The effect of pancreatic stents on pain in chronic pancreatitis is even more controversial. Patients undergoing pancreatic duct stent placement for disrupted ducts, isolated strictures, pancreas divisum, and hypertensive pancreatic sphincters, showed subsequent ductal changes consistent with chronic pancreatitis in 36% of the cases, even though 72% of these patients had a normal initial pancreatogram (71). Furthermore, patients with preoperative endoscopic pancreatic stenting had frequent postoperative complications, mostly septic, and a prolonged hospital stay (29). A surgical review of the pitfalls and limitations of stenting in chronic pancreatitis reported that the indications for surgery in patients with a pancreatic stent were severe abdominal pain in 100%, relapsing pain attacks in 77%, and necrotizing pancreatitis in 14%. Before being selected for surgery, 4.5 ERCPs and 3.7 stent exchanges were performed per patient. Thus, from the surgical point of view, endoscopic

pancreatic duct stenting in chronic pancreatitis seems not to be indicated because of a low success rate and a substantial risk for complications (110). The same direction was taken by Holm and Matzen (56). They performed a retrospective study of patients with chronic pancreatitis and large-duct disease, who had undergone decompressing treatment with stenting, ESWL, or both. Overall, the authors observed only a small increase in weight and a small reduction in the number of opioid users. In their opinion, these changes may not be different from the natural course of the disease (56).

The latter results are in sharp contrast to a long-term outcome study of pancreatic stenting in severe chronic pancreatitis in 100 patients from Belgium. The majority of patients (70%) who responded to pancreatic stenting remained pain free after definite stent removal. However, a significantly higher restenting rate was observed in patients with chronic pancreatitis and pancreas divisum (38). Obviously, the results are also different in special subgroups. Endoscopic stenting of biliary strictures in chronic pancreatitis provided an excellent short-term but only moderate long-term result in another study from Germany. Patients without calcifications of the pancreatic head benefit from biliary stenting. However, patients with calcifications have 17-fold increased risk of failure during the course of a 12-month follow-up (66).

Of special interest are three prospective randomized trials that compared endoscopic with surgical treatment of chronic pancreatitis. Endoscopic treatment included pancreatic sphincterotomy in all and additional stenting of the pancreatic duct in 33 (52%) patients. Mean duration of stent treatment was 16 (range 12—27) months, and stents were exchanged six times (range 4—9). Surgical treatment included pancreatic resection in 61 (80%) and drainage procedures in 15 (20%) patients. Although the short-term effects were similar, the results after 5 years' follow-up showed a comparatively low rate of patients with complete absence of abdominal pain. However, the results for surgery were significantly better than for endotherapy (35). The study has been criticized for the randomization, which was agreed to by only 51.4% of the patients.

A second study was carried out in the Netherlands. The authors investigated patients with chronic pancreatitis and a distal obstruction of the pancreatic duct but without an inflammatory mass. The patients were randomly assigned to undergo endoscopic transampullary drainage (n, 19, 16 of whom underwent lithotripsy) of the pancreatic duct or operative pancreaticojejunostomy (n, 20). During the 24 months of follow-up, patients who underwent surgery, compared with those who were treated endoscopically, had lower Izbicki pain scores and better physical health summary scores. At the end of follow-up, complete or partial pain relief was achieved in 32% of patients assigned to endoscopic drainage, compared with 75% of patients assigned to surgical drainage ($p = 0.007$). Rates of complication, length of hospital stay, and changes of pancreatic function were similar in the two treatment groups, but patients receiving endoscopic treatment required more procedures than patients in the surgery group ($p > 0.001$). The authors concluded that surgical drainage of the pancreatic duct was more effective than endoscopic treatment for patients of this category (27).

The design of the study from the Netherlands was in contrast to the study by Díte et al. in the Czech Republic (35), in which the surgical arm included various operations with drainage and the endoscopic treatment did not include lithotripsy. The Dutch study thus seems to be the only one to compare two closely defined drainage options. Nevertheless, it was heavily criticized because of its short observation period. However, the authors later published a second analysis (third study) (26) . Surgery remained superior in terms of pain relief (80% vs 38%, $p = 0.042$). A total of 68% of

the patients in the endoscopy group required additional drainage, compared with 5% in the surgery group (p = 0.001). Moreover, 47% of the patients in the endoscopy group had to undergo surgery at a later date. All in all, surgical drainage should currently be preferred to endoscopic measures.

7. Pain decrease and surgery

During the course of the disease, every 2nd to 4th patient needs surgical treatment because of pain and/or organ complications, such as pancreatic pseudocysts (7, 76). The choice of the surgical procedure is dependent on the special circumstances of each patient and the expertise of the surgeon.

On the assumption that pain was caused by obstruction of pancreatic secretion into the duodenum due to inflammation or scarring, longitudinal pancreaticojejunostomy according to Partington and Rochelle (97) was once the method of choice for patients with painful chronic pancreatitis, in whom conservative treatment had not reduced the pain. It later became clear that the principal source of pain was actually inflammatory swelling of the head of the pancreas. The classic Kausch-Whipple resection, originally the standard intervention for papillary cancer of the pancreas (67, 127) was subsequently the standard operation for chronic pancreatitis with involvement of the pancreatic head over a period of decades, before being gradually replaced by the pylorus-preserving Whipple procedure (123) . Later again, various operations and their modifications were introduced to resect the head of the pancreas while preserving the duodenum.

The first duodenum-preserving resection of the head of the pancreas was introduced by Beger and coworkers in 1972 (21). The enlarged pancreatic head was resected without sacrificing the gastroduodenal and bilioduodenal passage and a drainage operation was performed comparable with the Partington-Rochelle procedure. Subtotal resection of the pancreatic head was carried out before transection of the gland above the portal vein.

A modification of this procedure was introduced by Frey (44). A limited duodenum-preserving excision of the pancreatic head was accomplished by coring out the head of the pancreas, leaving a small cuff along the duodenal wall. In contrast to the Beger procedure the pancreas was not divided above the superior mesenteric portal vein, and the main pancreatic duct was open in the body and tail of the organ (15). Later on two modifications of these operations were proposed. Groups led by Büchler combined the advantages of the Frey and Beger in the Berne procedure (51). A deep duodenal-preserving resection of the pancreatic head is accomplished according to Beger, and transection of the gland over the superior mesenteric portal vein is avoided (15).

The Hamburg procedure also combines aspects of Beger and Frey operations. Subtotal resection of the pancreatic head including the uncinate processes is carried out, but transection of the gland over the superior mesenteric portal vein is again avoided, and the excision is combined with the longitudinal V-shaped excision of the ventral aspect of the body and tail of the pancreas (14). Only a small number of randomized controlled studies have compared the different surgical procedures for the treatment of chronic pancreatitis (15).

To what extent surgical treatment influences the course of pain in different studies cannot be compared, for the following reasons:

- The definition of freedom from pain is often vague, and pain symptoms were usually not measured.
- Not all patients received the same surgical treatment for the same indication. In the past, some authors recommended not performing an indicated resection in alcoholics because of the problematic postoperative treatment of

diabetes mellitus in those patients (43, 129). It is unclear to what extent these recommendations were or are followed, if at all.

Although continued alcohol abuse distinctly worsens the effect of surgical treatment (28, 57, 80) , it is still difficult to determine whether a postoperative deterioration results from chronic pancreatitis, from continued alcohol abuse, or from the surgical treatment.

All in all, the postoperative results of a large number of studies over a period of decades show that independent of the surgical procedure freedom of pain will be obtained in up to 90% of the patients over several years of follow-up (2, 3, 15, 16, 18-20, 23-25, 30, 39-42, 45-47, 55, 58, 61, 62, 64, 70, 72, 74-76, 87, 88, 90, 93-95, 98-100, 102-106, 108, 109, 112, 113, 115, 122, 126, 128, 130) **(Table 1)**.

Only few trials compared pancreatico-duodenectomy with the later developed duodenum-preserving resection of the pancreatic head (15). Farkas et al. (39, 40) compared a modification of duodenum-preserving resection of the pancreatic head with pancreatico-duodenectomy and found that although their modified procedure did not bring about a reduction in pain compared with the other group, operation time, length of hospital stay, and morbidity were much lower and weight gain much higher. Klempa et al. (68) compared the Beger procedure with pancreaticoduodenectomy without preservation of the pylorus and found a significant benefit of the Beger procedure with regard to the postoperative hormone status. There was no difference in freedom from pain, but all patients in the Whipple group needed enzyme substitution, in contrast with only 10% of those treated according to Beger.

Büchler et al. (25) found – albeit after relatively brief follow-up –, that the Beger procedure was superior to pylorus-preserving pancreatico-duodenectomy. Patients treated according to Beger had less pain, a better quality of life, and higher body weight than those who received the “old” operation (25). Seven and 14 years later, however, these advantages had disappeared; there was no longer any truly relevant difference between the two operations (94). The authors assumed reason for the loss of the initial advantage of the the Beger procedure was that the latter may be able to delay burn-out of the gland but cannot prevent it entirely.

Only the Hamburg group compared the outcome of the Frey procedure with pylorus-preserving pancreaticoduodenectomy (61). Twenty-four months after surgery patients treated according to Frey had less pain, a better quality of life, and lower perioperative morbidity. Seven years later (114) there were no differences with regard to mortality, frequency of exocrine and endocrine pancreatic insufficiency, or need for reoperation. After a long-term follow-up (15 years) there were still no differences regarding quality of life or pain, but long-term survival was significantly better after the Frey procedure (16).

The various modifications of pancreatic head resection were compared in two controlled studies. Köninger et al. (70) compared the Beger procedure with the Berne modification and found the latter technically simpler, reflected in its significantly shorter operation times and hospital stays. The quality of life, however, was similar after both procedures.

Izbicki et al. (62) compared Beger and Frey procedures. After 1.5 years freedom from pain was the same for both interventions, but perioperative morbidity was significantly lower after the Frey procedure. Eight years after surgery there was no difference between the two groups regarding mortality, quality of life, pain, or exocrine and endocrine pancreatic insufficiency (115). Sixteen years after operation the situation remained unaltered.

Table 1. Pain freedom after different surgical procedures on the pancreas for chronic pancreatitis.

Only reports of "total freedom of pain" were included. Further stages of postoperative improvement (e. g. partly freedom of pain, etc.) were not considered. Closure of literature research June 2014

References	Surgical procedure	Mean/median observation period, years	n	Pain relief, %
Way et al.(126)	Drainage/resection	≈ 5	37	64
Lankisch et al. (75)	Drainage/resection	2 6/12	40	60
Mangold et al. (87)	Partial duodenopancreatectomy	1 8/12	44	73
	Total duodenopancreatectomy	2 10/12	18	91
	Partial left-sided resection	3 5/12	37	60
	Subtotal left-sided resection	2 10/12	17	83
Proctor et al.(100)	Pancreaticojejunostomy	11/12	22	50
Rosenberger et al. (102)	Resection	6	67	69
	Nonresective procedures	6	40	50
Lankisch et al. (74)	Pancreaticojejunostomy	3 1/12	17	76
	Resection	3 1/12	22	64
Prinz and Greenlee (99)i	Pancreaticojejunostomy	6 1/12—7 11/12	91	35
Sato et al. (109)	Pancreaticojejunostomy	6 6/12	38	68
	Left-sided resection	6 6/12	14	79
	Whipple's operation	6 6/12	9	67
Gall et al. (47)	Whipple's operation, pancreatic duct occlusion	> 1	67	93
Morrow et al. (93)	Pancreatic duct drainage	4—13	46	46
	40—80% left-sided resection	4—13	21	33
	80—95% left sided resection	4—13	8	100
	Drainage	6	46	80
	Subtotal pancreatectomy	7	21	24
Sato et al.(108)	Left-sided resection	> 6/12	21	91
	Whipple's operation	> 6/12	11	55
	Pancreaticojejunostomy	> 6/12	43	91
Bradley III (24)	Lateral pancreaticojejunostomy	5 9/12	46	28
	Caudal pancreaticojejunostomy	5 9/12	18	17
Cooper et al.(30)	Total pancreatectomy	1 6/12	83	72
Frick et al.(45, 46)	Left-sided resection	6 6/12	74	50
	Partial duodenopancreatectomy	6 6/12	62	45
	Total duodenopancreatectomy	6 6/12	22	55
	Drainage	4 7/12	156	48
Lambert et al. (72)	Duodenum-preserving total pancreatectomy	9 5/12	14	64
Rossi et al. (103)	Whipple's operation	6/12	61	72
		2	44	61
		5	33	61
		10	18	61
		15	6	83
Mannell et al. (88)	Drainage/resection	8 6/12	100	77
Stone et al. (113)	Whipple's operation	6 2/12	15	53
	Total duodenopancreatectomy	9 1/12	15	27

Table 1 continued

Beger et al. (19)	Duodenum-preserving pancreatic head resection	3 8/12	128	77
Peiper and Köhler (98)	Resection Drainage	10 10	51 24	79 65
Beger and Büchler (18)	Duodenum-preserving pancreatic head resection	3 6/12	141	77
Lankisch et al.(76)	Drainage/resection	6	70	57
Adams et al. (2)	Lateral pancreaticojejunostomy	6 4/12	62	42
Frey and Amikura (42)	Local pancreatic head resection with longitudinal pancreaticojejunostomy	6/12	50	34
Hakaim et al. (55)	Different operations: Pancreatic duct drainage 56%, left-sided resection 20%, cyst drainage 24%	5 2/12	50	30
Büchler et al. (25)	Duodenum-preserving pancreatic head resection Pylorus-preserving Whipple's operation	6/12 6/12	15 16	40 75
Fleming and Williamson (41)	Total pancreatectomy	3 6/12	40	79
Izbicki et al. (62)	Duodenum-preserving pancreatic head resection - Beger's procedure - Frey's procedure	1 6/12 1 6/12	20 22	95 94
Martin et al. (90)	Pylorus-preserving pancreaticoduodenectomy	5 3/12	45	92
Stapleton and Williamson (112)	Proximal pancreaticoduodenectomy: pylorus-preserving (n, 45), Whipple's operation (n, 7)	4 6/12	52	80
Amikura et al. (3)	Pancreaticojejunostomy Pancreaticojejunostomy plus pancreatic head resection Left-sided resection Whipple's operation	≥ 6/12 ≥ 6/12 ≥ 6/12 ≥ 6/12	69 11 37 13	75 90 80 65
Rumstadt et al. (104)	Whipple's operation	8 4/12	134	66
Traverso and Kozarek (122)	Whipple's operation Total pancreatectomy	3 6/12 3 6/12	47 10	76 76
Izbicki et al. (61)	Longitudinal pancreaticojejunostomy combined with local pancreatic head excision Pylorus-preserving pancreaticoduodenectomy	5 1/12 5 1/12	31 30	Decrease of pain score equal in both groups
Beger et al. (20)	Duodenum-preserving pancreatic head resection	5 8/12	303	88
Berney et al.(23)	Different procedures of pancreatic resection	6 4/12	68	62
Jimenez et al. (64)	Whipple's operation Pylorus-preserving pancreatic head resection	3 5/12 3 5/12	33 39	53 40
Sakorafras et al. (105)	Whipple's operation	6 7/12	66	67

Table 1 continued

White et al. (128)	Total pancreatectomy	6/12	24	82
Nealon and Matin (95)	Pancreaticojejunostomy Left-sided resection Pancreatic head resection (duodenum-preserving or pylorus-preserving pancreatic head resection	6 9/12 6 9/12 6 9/12	124 29 46	86 67 91
Sakorafas et al. (106)	Left-sided resection	6 8/12	31	49
Hutchins et al. (58)	Left-sided resection	2 10/12	84	48
Strate et al. (115)	Duodenum-preserving pancreatic head resection - Beger's procedure - Frey's procedure	8 8/12 8 8/12	34 33	No differences between both groups
Farkas et al. (40)	Duodenum-preserving pancreatic head resection (authors' modification) Pylorus-preserving Whipple's operation	1 1	40 40	85 90
Yekebas et al. (130)	"V-shaped excision" of the anterior aspects of the pancreas	11 6/12	37	89
Müller et al. (94)	Duodenum-preserving pancreatic head resection (Beger) Pylorus-preserving Whipple's operation	7 14	19 20	No differences between both groups
Farkas et al. (39)	Duodenum-preserving pancreatic head resection (authors' modification)	4	135	89
Köninger et al. (70)	Duodenum-preserving pancreatic head resection - Beger's procedure - Berne modification	2 2	26 29	Quality of life equal in both groups
Bachmann et al. (16)	Pancreaticoduodenectomy Frey's procedure	7 7	32 32	Pain control equal in both groups; lower mortality after Frey's procedure
Bachmann et al. (15)	Duodenum-preserving pancreatic head resection - Beger's procedure - Frey's procedure	8 8	38 36	Quality of life and pain control equal in both groups

Quality of life, pain control, mortality, and rates of exocrine and endocrine pancreatic insufficiency were the same in both groups (15). A metaanalysis comparing duodenum-preserving resection of the pancreatic head with pancreaticoduodenectomy was published somewhat earlier (34). There was no difference between the two procedures regarding pain relief and survival. Duodenum-preserving resection was superior to pancreaticoduodenectomy, however, because of better perioperative and early postoperative outcomes and better quality of life (34).

8. Course of exocrine pancreatic insufficiency

Exocrine pancreatic insufficiency does not play a major prognostic role. Occasionally, massive steatorrhea leading to cachexia and susceptibility

to infection has prognostic significance. Whether exocrine pancreatic insufficiency becomes worse during the course of the disease is disputed. Ammann et al. (7) found that severe exocrine pancreatic insufficiency developed within 5.65 years (median) in 122 (86.6%) of 145 patients, whereas Thorsgaard Pedersen et al. (118) observed no significant changes in exocrine pancreatic insufficiency in their patients during an observation period of 4 years. The Göttingen group found no change in the degree of severity of exocrine pancreatic insufficiency in 66 (46.2%) patients, but deterioration in 61 (42.6%) patients. Functional improvement was even seen in 16 (11.2%) of their patients, several of whom no longer required pancreatic enzyme substitution (76).

Several other studies have furnished evidence of functional improvement in cases of exocrine pancreatic insufficiency in chronic pancreatitis (22, 48, 69, 91). Improvement was observed in patients who stopped drinking and/or where exocrine pancreatic insufficiency was moderate, not severe, prior to conservative and/or surgical treatment (76).

9. Course of endocrine pancreatic insufficiency

Whereas almost all patients with chronic pancreatitis have exocrine pancreatic insufficiency to some degree at the time of diagnosis, this is not the case for endocrine pancreatic insufficiency. The Göttingen group found moderate to severe endocrine pancreatic insufficiency in all 335 patients with chronic pancreatitis, including 24 patients with painless chronic pancreatitis; however, only 260 (78%) suffered from diabetes and only 133 (40%) needed insulin treatment. After almost 10 years of observation, the incidence of diabetes had increased 10-fold in only 28 (8%) patients. However, even after this long observation period, 75 (22%) patients (i.e., every fifth patient) still had no diabetes (76).

In a large prospective cohort study, Malka et al. (86) compared patients who had undergone elective pancreatic surgery with those who had never had surgical treatment. The prevalence of diabetes mellitus did not increase in the surgical group overall, but was higher 5 years after distal pancreatectomy than after pancreatico-duodenectomy, pancreatic drainage, or cystic, biliary, or digestive drainage. There were no differences between the other surgical procedures. Pancreatic drainage did not prevent the onset of diabetes mellitus. The risk seemed to be largely caused by progression of the disease, because it increased by more than threefold after the onset of pancreatic calcifications. Endocrine complications may play a major prognostic role, especially after surgical treatment of chronic pancreatitis, because of possible hypoglycemia (82). Hypoglycemia frequently occurs after subtotal left-sided pancreatic resection (43) and may contribute to an unfavorable prognosis.

The frequency of some complications of diabetes mellitus secondary to chronic pancreatitis has been studied. Earlier investigations showed that diabetic retinopathy is a rare complication of pancreatogenic diabetes, with an occurrence rate of 7.4—18% (33, 111, 124). Gullo et al. (54) showed that the risk of retinopathy and the characteristics of this complication in patients with chronic pancreatitis and secondary diabetes are the same as for patients with type 1 diabetes. About half of the patients in each group had retinopathy; this was background, minimal, or mild to moderate without impairment of visual function. The only significant difference was the longer duration of diabetes in patients with retinopathy than in those without complication. A longer observation period may explain the higher frequency of diabetic retinopathy in this study (54) compared with the earlier investigations (33, 111, 124). Similarly, Tiengo et al. (119) and Couet et al. (31) found retinopathy in 31% and 41%, respectively, of patients with chronic pancreatitis. Furthermore, in 1995, Levitt et al. (81) showed that microvascular complications (retinopathy,

nephropathy) are equally common and severe in pancreatic diabetes and insulin-dependent diabetes mellitus.
Nondiabetic retinal lesions and retinal function abnormalities (increased threshold of dark adaptation, difficulty with night vision) are also common in patients with chronic pancreatitis, even in the absence of steatorrhea, compared with healthy controls (120). Electrocardiographic evidence of ischemic heart disease was found twice as often in genetic diabetics as in pancreatic diabetes (37% vs 18%) (65). Diabetic neuropathy was reported in about 30% of patients with chronic pancreatitis (no control group) (17).

Finally, lower extremity arterial disease occurred in 25.3% of patients with chronic pancreatitis and had the same prevalence and distribution as in idiopathic pancreatitis (131). Whether these complications have major prognostic significance has not yet been investigated.

10. Course of complications of chronic pancreatitis

The list of complications in chronic pancreatitis includes pancreatic pseudocysts and abscesses; stenosis of the common bile duct, the duodenum and the colon; development of pleural ascites; and gastrointestinal bleeding. All these complications surely have severe implications for the prognosis of the disease. However, since these have not been investigated in larger studies, their exact influence on the outcome of the disease is uncertain and they are therefore not discussed here.

11. Course of pancreatic and extrapancreatic carcinomas in chronic pancreatitis

In clinical studies, the incidence of pancreatic carcinoma in patients with chronic pancreatitis has been reported as varying from 1.4 to 2.7% (7, 9, 76, 92, 118). A multicenter historical cohort study of 2015 subjects with chronic pancreatitis involved clinical centers in six countries (83), and patients were followed for at least 2 years. The cumulative risk of pancreatic carcinoma increased noticeably and was 1.8 and 4%, respectively, 10 and 20 years after the diagnosis of chronic pancreatitis (83) **(Fig. 1)**. The risk of pancreatic carcinoma was significantly elevated in patients with chronic pancreatitis, so chronic pancreatitis has to be included in the precanceroses (83).

Unfortunately, it is very difficult to diagnose pancreatic carcinoma in chronic pancreatitis. Carcinoma of the pancreas should certainly be suspected in a patient with chronic pancreatitis if there is increasing abdominal discomfort, progressive weight loss, jaundice, and radiologic evidence including nodularity of the duodenal sweep.

Extrapancreatic carcinomas in chronic pancreatitis are not rare events and have been reported with varying incidence, from 3.9 to 12.5% (9, 76, 91, 101, 118). In some of these and other studies (9, 76, 89, 91), a considerable number of extrapancreatic carcinomas involving the upper respiratory tract (oral cavity, larynx, bronchial tree) has been observed. Since alcohol abuse is the dominating etiology of chronic pancreatitis, and because many alcoholics probably smoke, extrapancreatic carcinomas involving the upper respiratory tract may reflect the consequences of another habit abuse.

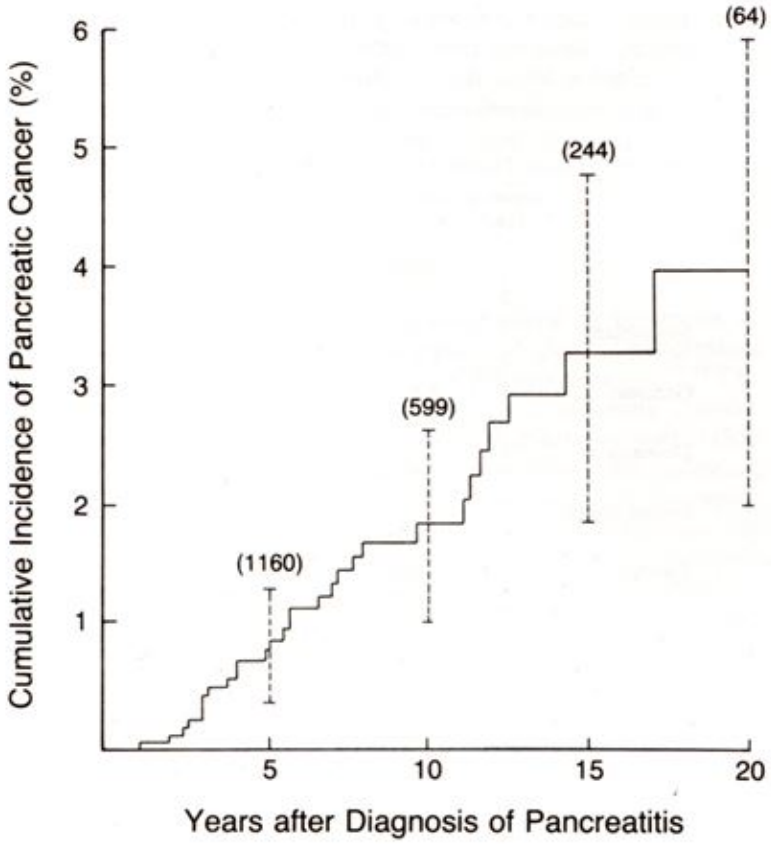

Figure 1. Cumulative incidence of pancreatic cancer in 1552 subjects with chronic pancreatitis with a minimum of 2-years' follow-up. The vertical lines represent 95% confidence intervals. In parentheses are the numbers of subjects at risk. One additional case of cancer developed after 25 years of follow-up. From Lowenfels et al. (83).

12. Socioeconomic situation in chronic pancreatitis

Some attention has been paid to the socioeconomic situation of patients with chronic pancreatitis: Gastard et al. (49) found that one out of two male patients continued to work normally, despite pain or diabetes, while one out of three was regarded as unfit for regular work, being totally incapacitated or absent from work for more than 3 months a year. The figures improved after 15 years due to the death of patients with severe forms of the disease; at this stage, 68% of the patients were working regularly, and 6% were totally incapacitated. Thorsgaard Pedersen et al. (118) found a decline during an observation period of 5 years (median). Only 15 (40%) of their 38 surviving patients still worked, whereas the remainder were either on prolonged sick-leave or retired. Miyake et al. (91) reported that while 63 (71%) of their 89 patients continued to work, almost all the other patients, who were either retired or who suffered socioeconomically, continued their alcohol abuse. The Göttingen group reported that the incidence of unemployed patients increased from 3 to 15% and the proportion of those retired from 3 to 25% during an observation period of about 11 years. Almost half of the retirements were due to chronic pancreatitis (76).

13. Mortality in chronic pancreatitis

The question of whether chronic pancreatitis affects mortality, and if so then how, was addressed by the Copenhagen Pancreatitis

Study, a prospective study of patients admitted to the five main hospitals in Copenhagen, Denmark, between 1977 and 1982. Follow-up data in 208 comprised 249 patients with definite chronic pancreatitis. These patients had a 4 times higher mortality rate than the background population. Being nonemployed or underweight had a significant impact on survival (96). Data on the mortality rate in chronic pancreatitis are difficult to interpret since etiology and mean observation times vary from study to study. Three studies with a similar observation period (median 6.3—9.8 years) revealed a general death rate of 28.8—35%, but the death rate related to chronic pancreatitis was only 12—19.8% (7, 76, 91). Continued alcohol abuse after conservative treatment and/or surgery has been associated with significantly lower survival rates (7, 41, 43, 76, 91, 129) **(Fig. 2)**.

14. Prognosis of chronic pancreatitis

The prognosis of chronic pancreatitis is independent of conservative or surgical treatment. A multicenter investigation in seven hospitals of six countries including 2015 patients with chronic pancreatitis showed that the mortality rate was 3.6 times higher than in patients without pancreatitis. The 10-year survival rate was 70%, the 20-year survival rate 45%, compared with 93% and 65%, respectively, in patients without pancreatitis.

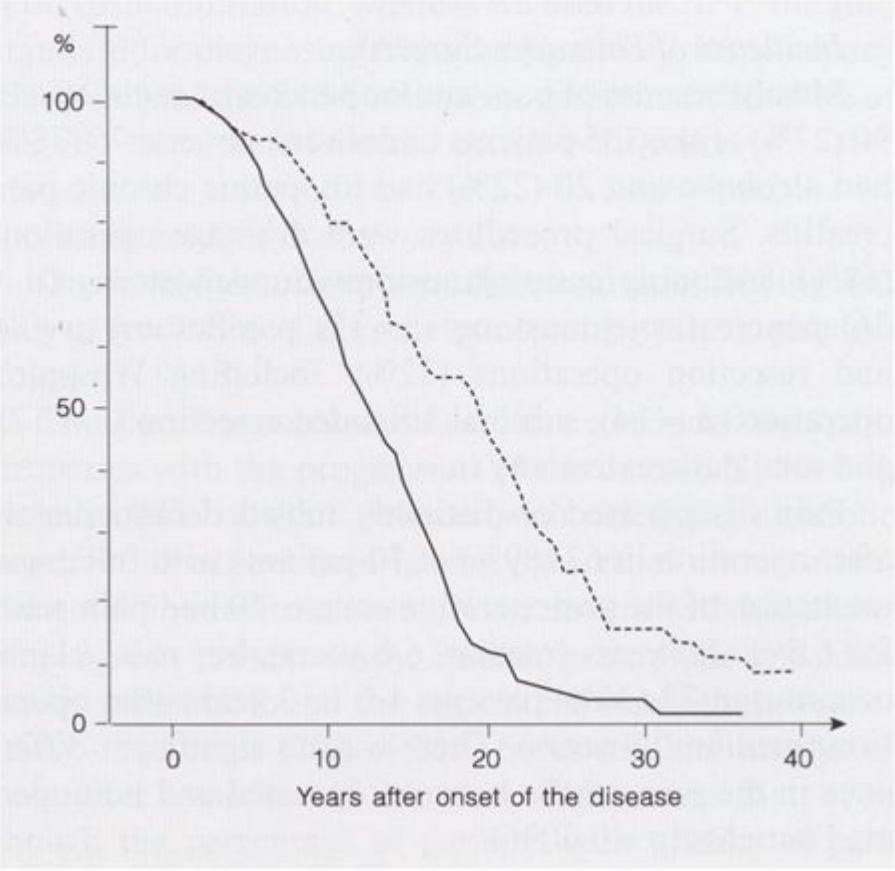

Figure 2. Cumulative survival curve for 230 patients with alcoholic (—) and 105 patients with nonalcoholic (- - -) chronic pancreatitis (p = 0.0001). The mean age of onset of the disease (i.e., first pancreatitis-related symptoms) was 37 ± 9 (mean ± SD) years in patients with alcoholic and 39 ± 17 in patients with non-alcoholic chronic pancreatitis. From Lankisch et al.(76), with permission from S. Karger AG, Basel, Switzerland.

The following factors were found:

1. Medium or high age at the time of diagniosis: the mortality rate in patients of medium or high age was 2.3-fold and 6.3-fold, respectively, compared with patients with chronic pancreatitis in whom the disease was diagnosed before the age 40.
2. Consistent alcohol abuse: hazard ration 1.6.
3. Smoking: hazard ratio 1.4.
4. Liver cirrhosis: hazard ratio 2.5.

Neither gender nor surgical history had any influence on the prognosis of the disease (84).

15. Outlook

It will not have escaped the attention of the reader that up to now there have been only a few well-performed and valid studies, and even some of these have produced partly diverging results. More controlled studies with a larger number of patients than any one single center can provide are necessary. This means we have to consider our resources and work out common criteria for the diagnosis of chronic pancreatitis and follow-up of its course. Hence, this review is not only an up-to-date survey of studies on the natural course of chronic pancreatitis but also an appeal to the readership to take up this task.

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