A Clinicopathologic Study of 21 Cases of Pancreatic Cystadenocarcinoma

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Cystadenocarcinomas are rare tumors of the pancreas. They are half as common as their benign counterpart—the cystadenoma. A review of 21 cases, including eight reported since 1963, revealed that most patients presented with upper abdominal pain and a large palpable upper abdominal mass. All patients had evidence of malignant degeneration occurring in a mucous cystadenoma. None had evidence of a serous cystadenoma. Grading revealed a predominance of low-grade tumors: 20 of the 21 lesions were grade 1 or 2. Cystadenocarcinomas were slightly more frequent in the head of the pancreas. Four patients had metastasis. Complete excision by distal or total pancreatectomy or Whipple pancreaticoduodenectomy is recommended. The five year survival after complete excision is 68%, and for patients with grade 1 lesions, and five year survival is 64%.

CYSTADENOCARCINOMA IS A RARE malignant tumor of the pancreas, accounting for about 1% of all pancreatic malignancies. The lesion is seen about half as frequently as its benign counterpart, the cystadenoma, according to Becker and associates.[1]

The first case reported in the American literature was by Lichtenstein in 1934.[9] He described a 44-year-old woman who at autopsy had a large papillary cystadenocarcinoma of the pancreatic tail with metastatic liver nodules and peritoneal seeds. Many isolated reports and several reviews appeared during the subsequent three decades after this initial report. Kennard in 1941[7] reviewed the world literature and added one case of papillary cystadenocarcinoma. At that time, most tumors either were biopsied only or were treated with internal or external drainage procedures or marsupialization. Sawyer and associates in 1952[12] found reports of only 29 cases of cystadenocarcinoma and added another to the literature. Most reports concerned clarifying the incidence of the tumors and assessing the malignant potential. Information on the natural history, pathogenesis, and prognosis was not forthcoming because no one institution had a large enough series with pathologic confirmation, surgical treatment, and long-term follow-up.

In 1963, Cullen, ReMine, and Dahlin[4] reported 17 acceptable cases from 42 cases of cystadenocarcinoma at the Mayo Clinic. They noted that seven of 11 patients treated by complete surgical excision survived. This experience was similar to that reported by Warren and Hardy in 1968,[13] who found that seven of 17 patients treated with resection had good results. The most recent case reports by Bilton et al.,[2] Johnson,[6] Rask,[10] and Ribet et al.[11] noted the slow-growing nature of these tumors and success after total resection of the cystadenocarcinoma.

Material

Between 1928 and 1974, there were more than 50 cases of cystadenocarcinoma of the pancreas on record in the tissue registry clinical files and autopsy files at the Mayo Clinic. The present study involves the review of 21 patients with cystadenocarcinoma. All cases accepted for review satisfied the following criteria: 1) adequate pathologic material available for review, classification, and grading; 2) primary surgical treatment at our institution; 3) follow-up of all patients and their status in 1976 or to death with cause of death being available from autopsy reports; and 4) clinical records evaluated to ascertain pertinent clinical features. Excluded from this study were cases in which 1) tissue was inadequate for classification and grading; 2) autopsy specimens were not available; 3) initial surgery was not done at our institution; 4) follow-up data or autopsy reports were not available; and 5) lesions found at autopsy were not suspected during life.

The present review adds eight new cases since the last review in 1963.[4] Four of the cases reviewed in 1963 did not satisfy the above criteria.

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TABLE 1. *Symptoms of 21 Patients With Cystadenocarcinoma of the Pancreas*

Symptom	No. of Patients
Abdominal pain	17
Loss of weight	9
Jaundice	6
Belching excessive gas	6
Nausea and vomiting	5
Bleeding	3
Diarrhea	2
Weakness and fatigue	1
Dyspnea	1
Asymptomatic	0

Clinical Findings

Age and Sex

The age range of the 21 patients (11 women and ten men) was 40–73 years, with a mean of 61.3 years: two patients were in the fifth decade, six in the sixth, ten in the seventh, and three in the eighth. The sex ratio was somewhat different from that in the previous report,[4] in which there were 13 women and four men. In patients with the benign counterpart of the cystadenocarcinoma—the cystadenoma—the average age was 55 years and the females predominated 4.6 to one. Malignant cystadenocarcinoma has not been found in any child who was in the first decade as stated by Grosfeld et al.[5] In contradistinction to Becker and coworkers' report[1] that cystadenocarcinoma occurs at a younger age than does the solid pancreatic cancer, our patients were about the same age as those with conventional solid pancreatic malignancy.

Symptoms

The most frequent symptom was pain. Seventeen patients (81%) had pain as all or part of their symptom complex at presentation (Table 1). Three patients had pain as their only complaint, and another three had pain accompanied by loss of weight and belching. Often, the pain lasted for years, but its characteristics were vague, frequently being described as an epigastric distress after meals or as mild discomfort and a feeling of upper abdominal fullness or "pressure." One patient had an eight year history of vague upper abdominal pain, and two others had symptoms for six years. In one of these patients, the distress was relieved by bending over; presumably, this allowed the stomach to move away from the upper gastrointestinal tract and relieve the compression. The localization of the pain also was often vague. One patient had periumbilical discomfort; however, in others, the pain was more constantly in the left upper quadrant.

Three patients noted that they had a palpable upper abdominal mass, one for four months and another for ten months before seeking medical attention.

Three patients, one with gross melena, had a recent history of hematemesis. At laparotomy, one patient had a profuse collateral blood supply around the cyst; another had splenic vein occlusion; and a third had hepatic metastasis.

Six patients had jaundice. At laparotomy, one had the common bile duct directly invaded by the pancreatic malignancy. Two patients with jaundice had liver metastasis, and another two had peripancreatic nodal metastasis compressing the extrahepatic biliary ducts. One patient had a large unresectable cystadenocarcinoma of the pancreatic head compressing the common bile duct. Three patients had diabetes mellitus, and no patient had a history of alcoholism or pancreatitis.

Signs

The most frequent clinical sign was a palpable abdominal mass. Twelve patients (57.2%) had a palpable mass: seven in the left upper quadrant, four in the right upper quadrant, and one in the epigastrium and right upper quadrant. In some, the mass was mobile with respiration, and masses in the left upper quadrant were commonly mistaken for enlarged spleens, as Lichtenstein did in his original report in 1934.[9] In six patients (28.5%), the cystadenocarcinoma was an incidental finding during laparotomy, while in three patients, the lesion was suspected but no mass could be palpated abdominally. The characteristics of the mass varied, but most were nontender and firm with dimensions that were large or diffuse.

Diagnostic Investigations

Fifteen patients underwent upper gastrointestinal barium study. Results were "positive" in eight (53%) ("positive" refers to the presence of an extrinsic mass deforming the barium-filled stomach and duodenum). There were no characteristic roentgenographic features of cystadenocarcinoma, and the findings were similar to those of any large retroperitoneal cystic mass. A large smooth displacement of the greater curvature of the stomach to the midline with tail lesions and a similar displacement of the stomach anteriorly with body or head lesions suggest the possibility of a benign or malignant pancreatic cyst. The high success rate of upper gastrointestinal barium studies has been noted by Warren and Hardy,[13] who found ten of 11 patients studied by upper gastrointestinal series had evidence of pancreatic enlargement. Oral or intravenous cholangiography was performed in seven cases but was not helpful in establishing the diagnosis.

Angiography, splenoportography, and radioactive and ultrasonic scanning were not used, but according

to Ribet et al.[11] angiography has been reported to be useful in preoperative planning by outlining the mesenteric vessels. Ultrasonic scanning techniques probably will be helpful in identifying the cystic nature of these tumors. The differentiation of primary cystadenoma and cystadenocarcinoma from solid pancreatic malignancy with secondary obstruction of the pancreatic duct or central necrosis still needs to be made by the surgeon and pathologist.

Associated Conditions

Seven patients had associated biliary tract disease. Five had undergone cholecystectomy for cholelithiasis, and two had cholelithiasis at laparotomy. Two patients had a duodenal ulcer, and one complained of periumbilical pain that was different from the usual ulcer pain. One patient had a gastric ulcer secondary to a pyloric ulcer. The presence of ulcers seems not to be related etiologically to the cystadenocarcinoma, although gastrin levels were not available for these patients. Except for one woman with a benign ovarian cyst, no patient had associated cystic disease of any intra-abdominal organ.

Pathologic Features of Lesion

Cystadenocarcinomas occur half as frequently as do their benign counterpart, the cystadenoma. No pancreatic cystadenocarcinoma studied had morphologic characteristics resembling the serous cystadenoma. (Cystadenomas are of two types: serous and mucinous. The mucinous cystadenoma arises from ductal epithelium while the serous type probably arises from the acinar cell. All cystadenocarcinomas have gross and histologic characteristics resembling the mucinous cystadenoma.) Pancreatic cystadenocarcinomas probably arise by malignant degeneration occurring in the benign mucinous cystadenoma. There is no associated inflammatory reaction, as is true of the pancreatic pseudocyst.

Macroscopic Findings

Pancreatic cystadenocarcinomas are rounded, lobulated, or smooth and are usually well-encapsulated lesions arising from normal pancreatic tissue. The surface may be broken by invasive tumor, as it was in eight of our cases. Most often, however, the outside appearance of the tumor gives little indication of its true malignant character.

Cystadenocarcinomas may appear anywhere in the pancreas. Unlike cystadenomas, which are more frequent in the tail of the pancreas, cystadenocarcinomas occur more frequently in the head. In our series, there were eight lesions in the head, five in the tail, four in the body and tail, one in the body, one in the body and head, and one involving the body, head, and tail. In one case, the site was unknown. There were no multiple or pedunculated cystadenocarcinomas.

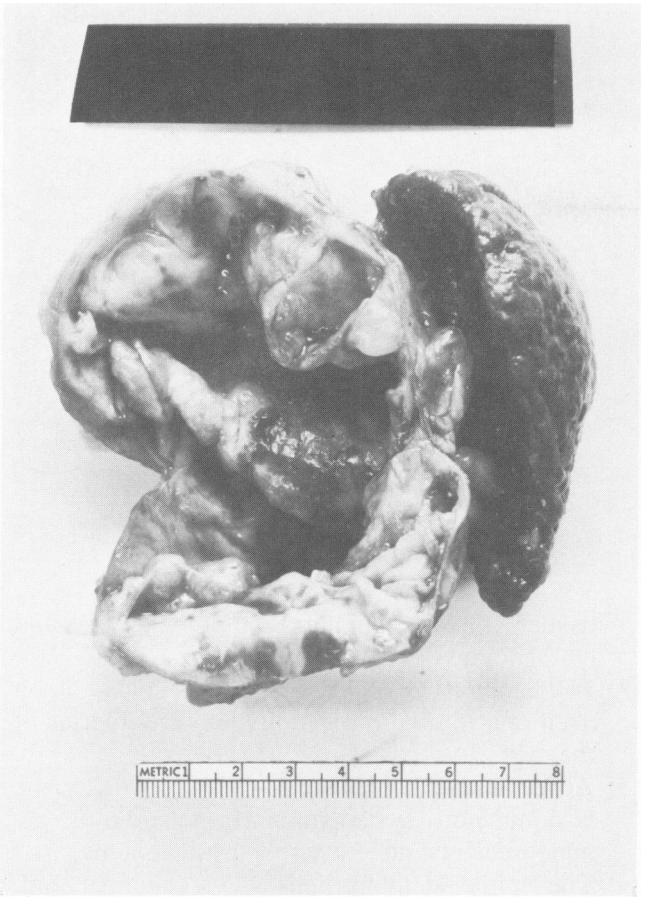

FIG. 1. Macroscopic appearance of cystadenocarcinoma of the pancreatic tail.

The size of the tumors ranged from four to 24 cm in largest diameter, with a mean of 10.1. The mean size of tumors in the head was smaller (4.9 cm) than that in the tail (12.4 cm) or body (13.6 cm).

The sectioned cystadenocarcinoma usually consisted of a large unilocular cyst into which numerous "cauliflower-like" excrescences projected (Fig. 1). Some of the larger cysts had several major subcompartments, but "honeycombing" was not seen as it is in the benign serous cystadenocarcinoma.

The fluid content was often turbid, thick, and gelatinous, and in no instances was it hemorrhagic. The surrounding pancreatic tissue usually was normal; however, six (28%) of the lesions had histologic features of old pancreatitis.

Histopathologic Features

The following microscopic features were noted:

1) The wall of the cyst varied in thickness from 2–15 mm and was composed of a fibrous connective

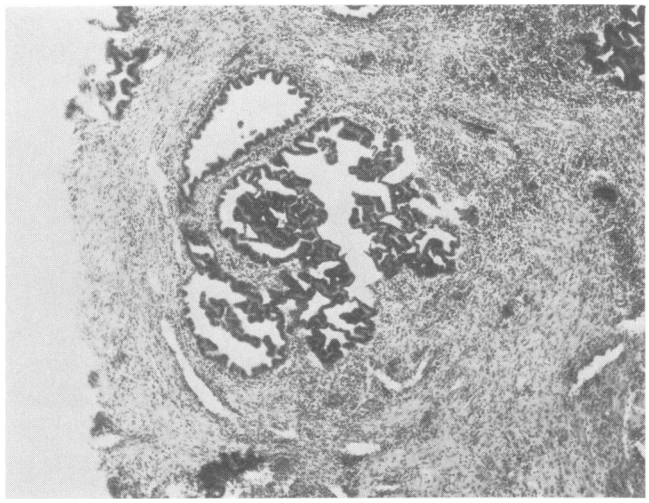

FIG. 2a. Cystadenocarcinoma of the pancreas. Areas of benign epithelial lining and malignant transition (H&E ×64).

tissue with variable infiltration of leukocytes and lymphocytes.

2) The mucous epithelial lining was folded upon itself and formed projections into the interior of the cyst.
3) All lesions had benign areas—areas characteristic of a mucinous cystadenoma. In none did the benign areas resemble a serous cystadenoma.
4) The epithelial lining cells were columnar and, within the same cyst, were interspersed with areas of frank malignancy. These areas were dedifferentiated, with epithelial "piling," loss of basal nuclear placement, and increasing pleomorphism (Fig. 2A).
5) The grading of malignancy according to Broders' classification[3] revealed predominantly well-differentiated tumors. Eleven lesions were grade 1 (Fig. 2B), nine grade 2 (Fig. 2C), and one grade 3.
6) The stroma was uniformly fibrous, with little chronic inflammatory cell infiltrate. Marked cellularity may be observed in the fibrous stroma.

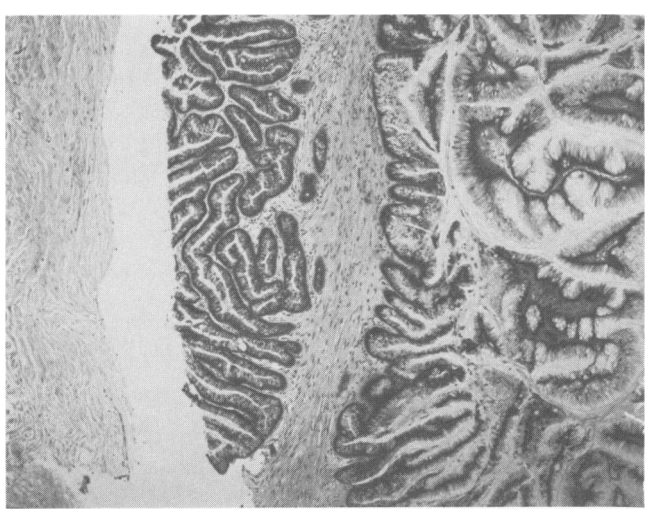

FIG. 2b. Cystadenocarcinoma of the pancreas. Grade 1 (H&E ×64).

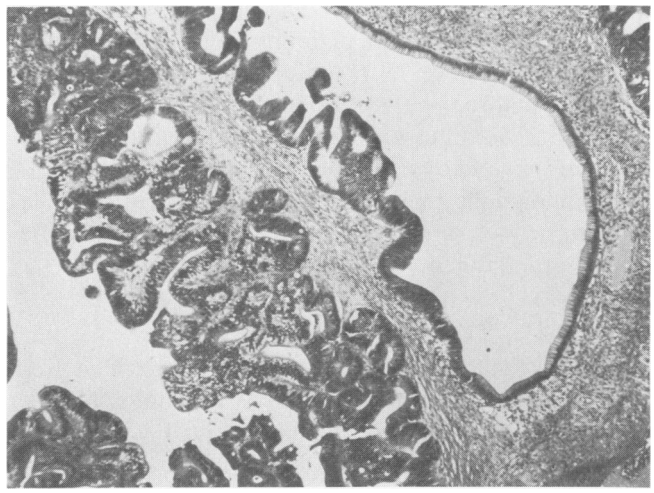

FIG. 2c. Grade 2 cystadenocarcinoma of the pancreas (H&E ×64).

Histopathologic Differentiation

The finding of a mucinous cystadenoma should alert the histopathologist to search for malignancy. Multiple samples may be required to be certain of a benign diagnosis. Needle biopsy is inadequate because the chance of obtaining only a benign portion of the tumor is highly likely. The risk of tumor cell spillage also makes biopsy less desirable. Multiple sections may be required to detect an area of malignant change, and these should be detected by the gross examination. Occasionally, the surface of the tumor is involved, and the tumor is attached to adjacent structures. Such attachment should not preclude complete excision. Local tissue and lymph nodes, if suspected of being involved, should be sampled.

Treatment and Follow-Up

Operative Considerations

The site, size, and mobility of the lesion and its relationship to vital structures, its attachment to surrounding structures, and the presence of metastasis influence the type of surgical treatment.

Four (19%) of our patients had metastasis at initial surgery: two with secondary hepatic lesions and two with metastasis confined to peripancreatic nodes. If there is local nodal metastasis, curative resective surgery is still possible. Liver metastasis precludes curative resection. However, palliative bypass surgery can be offered.

TABLE 2. *Surgical Treatment of 21 Patients With Pancreatic Cystadenocarcinoma*

Treatment	No. of Patients
Total excision with tail of pancreas and spleen	7
Whipple	4
Total pancreatectomy	3
Partial excision	3
Bypass	1
Biopsy	3
Total	21

Only rarely was the blood supply to these tumors profuse. One patient had huge, dilated veins in the retroperitoneum and had presented with upper gastrointestinal hemorrhage (requiring 18 units), presumably secondary to variceal formation by obstruction of the splenic vein from a large cystadenocarcinoma in the pancreatic tail.

For tumors in the tail or body, distal pancreatectomy, including excision of the spleen, can be performed, with hope of cure for these low-grade malignancies.

If the portal vein can be dissected free, lesions in the head of the pancreas can be treated by a Whipple type of pancreaticoduodenectomy or total pancreatectomy. Invasion and ulcers of the duodenum, as reported by Lefaucher,[8] can be surgically removed by pancreaticoduodenectomy, and the prognosis is better than that with noncystic pancreatic malignancies of the head.

The only contraindications for resective management concern the intimate relationship that these tumors may have with the mesenteric vessels or portal vein or the presence of hepatic metastasis or extensive local invasion. Smaller tumors that are suspected of not being malignant can be removed from the pancreas by partial pancreatectomy without a major pancreatic resection.

Surgical Management

Cystadenocarcinomas should be totally excised. There is no indication for internal or external damage

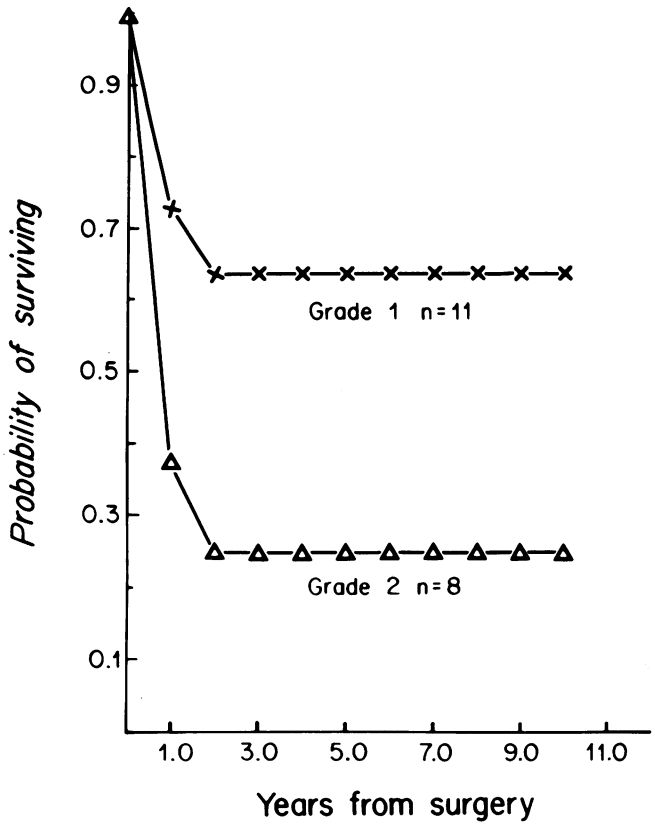

FIG. 3. Patient survival. Grade 1 cystadenocarcinoma compared with grade 2 cystadenocarcinoma.

of these cystic lesions, as there is for pancreatic pseudocysts. Unlike pseudocysts, unless there is metastasis or extensive invasion of the cyst wall by malignant infiltration, these cysts usually can be separated from the surrounding tissues. All efforts during resective procedures should be directed to removing the cyst intact, because rupture may disseminate malignant cells intraperitoneally. The various modes of treatment are shown in Table 2.

Seven patients had a curative surgical procedure—total excision along with the tail of the pancreas and spleen. Of the 14 other patients, four had Whipple

TABLE 3. *Status of Patients With Cystadenocarcinoma of Pancreas Not Resected*

Age, yr	Lesion			Treatment	Metastasis or local invasion	Follow-up
	Site	Size, cm	Grade			
47	Tail	12	2	Partial excision	Invasion of lt kidney and transverse mesocolon	Dead, 2 yr, with metastasis
73	Tail	12	2	Partial excision	. . .	Dead, 1 yr
69	Head	5	2	Partial excision	Hepatic metastasis	Dead, 5 yr
65	Total pancreas	20	1	Biopsy and bypass	Hepatic metastasis	Dead, 3 mo
65	Head	Large	2	Biopsy*	. . .	Dead, 11 yr
69	Head	5	1	Biopsy	. . .	Dead, 2 wk
59	Head	Large	1	Biopsy	. . .	Dead, 6 mo

* Lesion attached to superior mesenteric vessels and inferior vena cava, precluding resection.

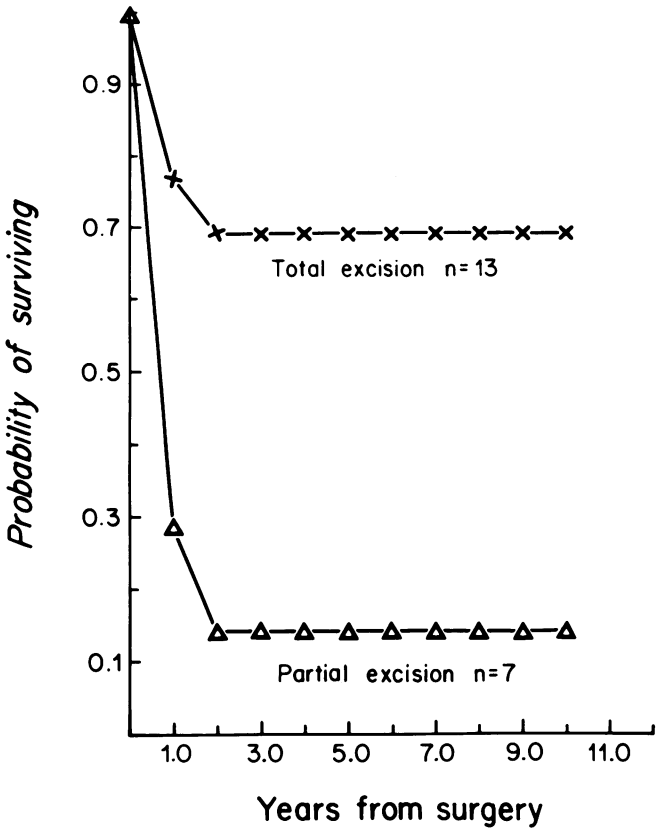

FIG. 4. Patient survival. Complete removal compared with incomplete removal.

procedure, three had total pancreatectomy, three had partial resection, one had a bypass, and three had biopsy. Detailed data on the patients who were not treated with resection are summarized in Table 3.

Results of Treatment

Follow-up data were collected from the time of surgery to death or current status in 1976. There were two postoperative deaths: one after biopsy and the other after a Whipple pancreaticoduodenectomy.

The five year survival for patients with grade 1 lesions was 64% and for those with grade 2, 24% (Fig. 3). For patients who had total excision of the tumor, the five-year survival was 68%, while for those who had partial and noncurative excision, the five year survival rate was 14% (Fig. 4).

Summary

Pancreatic cystadenocarcinoma is rare. Cystadenomas occur about twice as frequently as do cystadenocarcinomas. Eight patients with cystadenocarcinomas were surgically treated at the Mayo Clinic during the years 1963 through 1974, and 21 patients were treated surgically between 1928 and 1974. All had histologic features of benign mucous cystadenoma in portions of the cystic tumor wall. Most of the tumors were low-grade malignancies, and distribution was throughout the pancreas, although they were slightly more frequent in the head of the pancreas. Four patients had metastasis at initial surgery. Seven patients had tumors that were not treated with curative resection. For complete removal of the tumors, distal pancreatectomy, total pancreatectomy, or a Whipple pancreaticoduodenectomy is recommended. The five year survival rate after complete removal was 68%.

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