Cancer of the Exocrine Pancreas: The Pathologic Aspects

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An estimated 24,200 patients die of pancreatic cancer each year in the United States; the cancer is now the fourth leading cause of cancer deaths in both men and women.[1,2] Adenocarcinoma of the pancreas is regarded as a devastating tumor with a relatively poor response to surgery, radiation therapy, or chemotherapy.

Because we believe that the morphologic structure of a tumor is important in studying its etiology, pathogenesis, prognosis, response to therapy, and prevention, we examined a large number of pancreatic cancers to determine if there are more morphological subtypes in pancreatic cancer than the stereotypical adenocarcinoma. If there are, it is possible that new combinations of surgery, chemotherapy, and/or radiation therapy may favorably affect one or more of the subtypes. The increasing use of computerized tomography, ultrasonography, and other imaging techniques might result in earlier diagnosis, thereby possibly increasing the life expectancy of patients with one of these tumors.

We examined 645 cases of pancreatic cancer obtained from the files of Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City (Table 1) (Figs. 1-8).[3-8]

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Duct (Ductule) Adenocarcinoma

The most common type of pancreatic cancer was an adenocarcinoma arising from cells of the duct (ductule) system. With some structural variations, this tumor made up about 75 percent of pancreatic cancers (Fig. 1) (Table 1). Although there may be further subdivisions of this type, duct adenocarcinoma will be considered the prototype of pancreatic exocrine cancer.

Site, Size, and Stage

In almost two thirds of patients with pancreatic adenocarcinoma, the tumor was located in the head of the pancreas; in the other one third, the tumor involved the body and/or tail, or diffusely infiltrated the entire organ.[4,5]

The median diameter of cancers of the head of the pancreas was five cm. Size was related to the length of survival (Table 2).[4,5]

Patients with stage I disease (cancer confined to the pancreas) made up only 14 percent of patients. In 21 percent, the cancer involved lymph nodes (stage II), and in 35 percent, metastases were present on initial clinical presentation (stage III).[4,5] A more detailed pathological staging method, based on the TNM system, has been suggested.[4]

TABLE 1
PRIMARY MALIGNANT NEOPLASMS OF THE NONENDOCRINE PANCREAS*[4]

Duct (Ductule) Cell Origin 573 patients (88.8 percent)	Duct cell carcinoma (494) Giant cell carcinoma (27) Giant cell carcinoma (osteoclastoid type) (1) Adenosquamous carcinoma (20) Adenosquamous (spindle cell) carcinoma Microadenocarcinoma (solid microglandular) (16) Mucinous ("colloid") carcinoma (9) Cystadenocarcinoma (mucinous) (5) Papillary-cystic tumor (1) Mucinous carcinoid carcinoma Carcinoid Oncocytic carcinoid Oncocytic carcinoma Oat cell carcinoma Ciliated cell carcinoma (?)
Acinar Cell Origin 8 patients (1.2 percent)	Acinar cell carcinoma (7) Acinar cell cystadenocarcinoma (1)
Mixed Cell Type 1 patient (0.2 percent)	Duct-islet cell (1) Duct-islet-acinar cell Acinar-islet cell Carcinoid-islet cell
Connective Tissue Origin 4 patients (0.6 percent)	Leiomyosarcoma (1) Malignant fibrous histiocytoma (1) Malignant hemangiopericytoma (1) "Osteogenic sarcoma" (1) Fibrosarcoma Rhabdomyosarcoma Malignant neurilemoma Liposarcoma
Uncertain Histogenesis 59 patients (9.1 percent)	Pancreaticoblastoma (simple type) Pancreaticoblastoma (mixed type) (1) Unclassified (58) Large cell (50) Small cell (7) Clear cell (1)
Malignant Lymphoma (?)	Histiocytic Plasmacytoma
Total 645 patients	

*Classification of malignant lesions of the pancreas and the relative frequency of the types at Memorial Sloan-Kettering Cancer Center in New York City. The figures were obtained from more than 500,000 surgical specimens and 13,882 autopsies. 821 patients were listed as having pancreas (nonislet) cancer; adequate clinical and pathologic material was available for study in 645 patients. Diagnoses without patient totals indicate that such a cancer did not occur in the MSKCC patients during the years of the review (1949-1978), but has been reported in the literature or was seen by us subsequent to 1978.

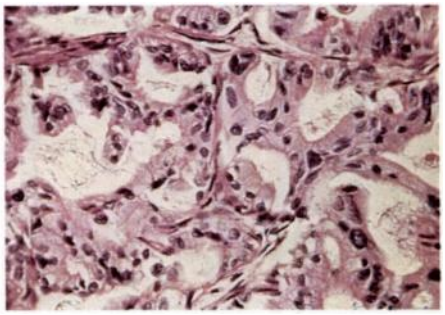

Fig. 1. Moderately well-differentiated adenocarcinoma of pancreatic duct origin. Secretion stains for mucin. (Magnification × 330.)

Tissues shown in Figs. 1–8 were fixed in formalin solution, embedded in paraffin, and stained with hematoxylin and eosin.

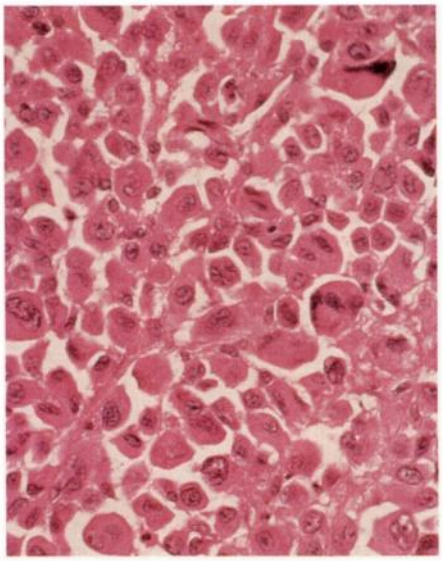

Fig. 2. Giant cell carcinoma. Large cells with heavily staining, abundant cytoplasm and huge tumor giant nuclei; latter are often bizarre in size and shape. (Magnification × 240.)

Biliary Obstruction

One of the most characteristic features of cancer of the head of the pancreas was obstruction of the biliary tract, with the development of jaundice; this occurred in two thirds of the patients. Cancers of the body and/or tail caused biliary obstruction in a markedly lower percentage of cases.[4,5]

Histological Findings

In the majority of patients, pancreatic ductal cancer was a mucin-producing adenocarcinoma, similar to the mucinous adenocarcinoma of many organs (Fig. 1) (Table 1). In the primary tumor, many minute foci of other types were apparent,[5] although in both primary and metastatic lesions the ductal adenocarcinoma predominated. Only about 10 percent of cases had no predominant morphologic pattern representing the majority of tissue examined in the primary cancer and in the metastasis. Occasionally, two or more distinct morphologic patterns were present in the primary and metastatic lesions—for example, adenosquamous carcinoma and mucinous carcinoid.

Perineural invasion occurred in at least 90 percent of cases, and in 70 percent to 80 percent of patients the lymph nodes were involved. Veins were invaded in 50 percent of patients, and the duodenum and islets were each involved in about 20 percent to 25 percent of patients.[4,5]

Marked desmoplastic response around and distal to the tumor occurred in virtually all cases. Foci of hemorrhage, necrosis, and fat necrosis, although often present, were minute and made up a surprisingly small portion of the pancreatic tissue, considering the presence of significant ductal obstruction in most cases. Some islet cells were replaced, partially or completely, by collagen.[4,5]

Lymph Node Involvement

A detailed search for lymph nodes in specimens of resected cancer of the head of the pancreas[6] showed that the groups of nodes most commonly involved were (in descending order) (Fig. 9):

- The Posterior Pancreaticoduodenal (PPD) group and the Superior Head (SH) group.

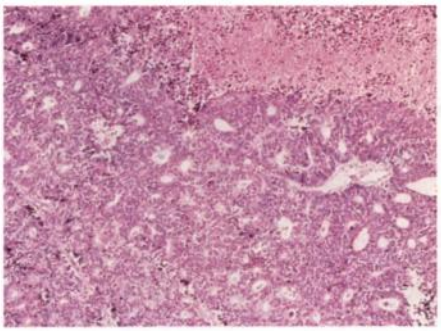

Fig. 3. Microadenocarcinoma. Focus of necrosis, many solid areas of small cells with interspersion of small glands. Some resemblance to carcinoid tumor. (Magnification × 110.)

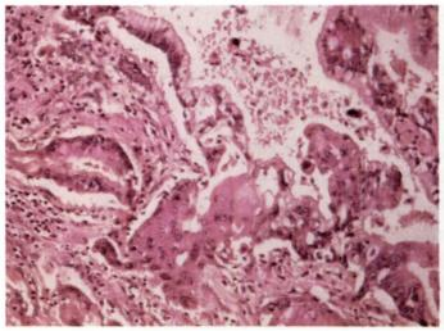

Fig. 4. Adenosquamous carcinoma. Dimorphic type with both adenocarcinoma and squamous cell carcinoma aspects. (Magnification × 150.)

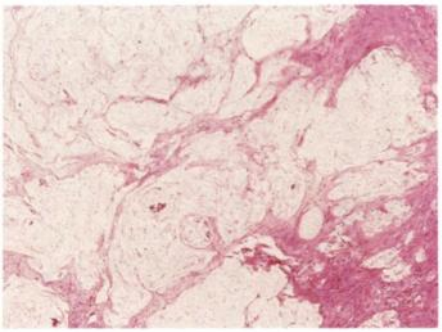

Fig. 5. Mucinous "colloid" carcinoma. Excessively large pools of mucin between septa of collagen. Relative sparsity of cancer cells. (Magnification × 150.)

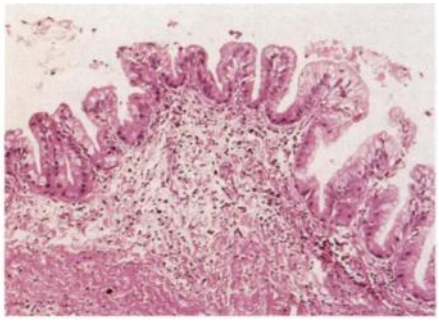

Fig. 6. Cystadenocarcinoma (mucinous). Cystic area contains mucin; cyst-wall lined with papillae of mucin-forming adenocarcinoma cells. (Magnification × 200.)

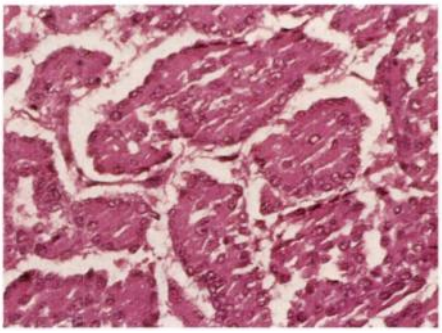

Fig. 7. Acinar cell carcinoma. Fairly well-differentiated glands. Cells have considerable eosinophilic cytoplasm containing zymogen granules. Nuclei are basally oriented. (Magnification × 150.)

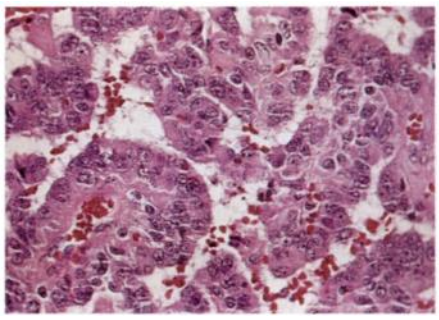

Fig. 8. Papillary-cystic tumor. Papillae with central vascular stalk, the periphery of which is lined with cells containing a considerabie amount of lightly staining cytoplasm and medium-sized nuclei with finely dispersed chromatin. Clefts and cystic spaces are between papillae. (Magnification × 150.)

- The Inferior Head (IH) and the Superior Body (SB) groups.
- The Anterior Pancreaticoduodenal (APD) group and the Inferior Body (IB) group.

Of the 18 patients with cancer of the head of the pancreas in whom a total or regional resection of the pancreas and lymph nodes was performed, there was cancer in the SB group in five patients (28 percent). Cancer was present in the IB lymph nodes of one of eight patients (13 percent) in whom IB lymph nodes were found.[6,7] These two groups of lymph nodes are not removed in the classical Whipple operation.

Metastases from Cancer of the Pancreas

Of patients with cancer of the head of the pancreas, the liver, peritoneum, and the regional nodes were the organs most involved with metastasis at hospital admission or at exploratory operation.[4,5]

In 50 patients who were later proven to have pancreatic cancer and whose primary site was unknown at the time of hospital admission (occult primary), 22 patients presented clinically with metastatic cancer of the lymph nodes, 16 of whom had cervical node involvement (Table 3).[4,5]

Cancers Metastatic to, Locally Invading, or Systemically Involving The Pancreas

In a study of 2,587 consecutive autopsies at MSKCC, 63 patients had a primary cancer of the pancreas (2.5 percent) (Table 4).[4,8] In 261 patients (10 percent), metastatic cancer was found in the pancreas. Cancers of the breast and lung and melanoma were the most common metastases to the pancreas. In 16 cases, there was invasion of the pancreas by cancers of adjacent organs, principally adenocarcinomas of the gastrointestinal tract. In 48 patients, a malignant lymphoma (including seven cases of Hodgkin's disease) involved the gland, and in 19 patients a leukemia infiltrated the pancreas.[4,8] In nine percent of patients, invading or metastatic carcinoma gave rise to signs and symptoms suggesting primary pancreatic cancer.[9]

Differential Diagnosis—Pathological

Tumors of the biliary duct systems in the region of the pancreas, and tumors of and about the ampulla of Vater are difficult, and may occasionally be impossible, to separate from those of the pancreatic duct. Since the former have a much better prognosis than the pancreatic ductal tumors, it is important for therapeutic and prognostic purposes to determine the correct site of origin (see section on ampulla-head-of-pancreas carcinoma).

For cancers involving both the lung and pancreas, it may be difficult to determine the site of origin of the cancer, even at autopsy.[10]

Chronic pancreatitis is the nonmalignant disease that most frequently causes a clinical false-positive diagnosis of pancreatic cancer.[4,7,8] Rarely, the "rock-hard" nodule felt at operation has proven to be a nodule of chronic pancreatitis.[4,9] The advent of the thin ("skinny") needle biopsy should lead to more biopsies of the gland and prevent such occurrences.

Associated Lesions

In a search for possible precursor lesions that might give rise to pancreatic cancer, we studied the pancreases of a group of patients with pancreatic cancer and compared them with a group of patients, matched for age, race, and sex, who had died of nonpancreatic cancers.[11]

In 24 percent of patients who underwent "curative" resections of the pancreas for carcinoma of the pancreas, foci of carcinoma in situ in the duct epithelium occurred separately from the main tumor area.[11] Multicentric foci of cancer scattered throughout the gland have been reported in as many as 38 percent of patients with invasive cancer of the pancreas.[12] The true incidence is probably higher, since only a small percentage of the ductal epithelium was examined.

We recently studied the ductal epithelium of five patients with extensive car-

TABLE 2
SURVIVAL AFTER WHIPPLE OPERATION FOR HEAD OF PANCREAS CANCER BY STAGE AND SIZE (25 PATIENTS)*[4]

Size (cm)	Stage I Number of Cases	Stage I Median Survival (months)
1–1.9	5	29
2–2.9	5	17
3–3.9	5	6
4–4.9	4	5
5–10	6	2
Total	25	12
< 3.0	10	23
3–10	15	4

*Operative deaths excluded.

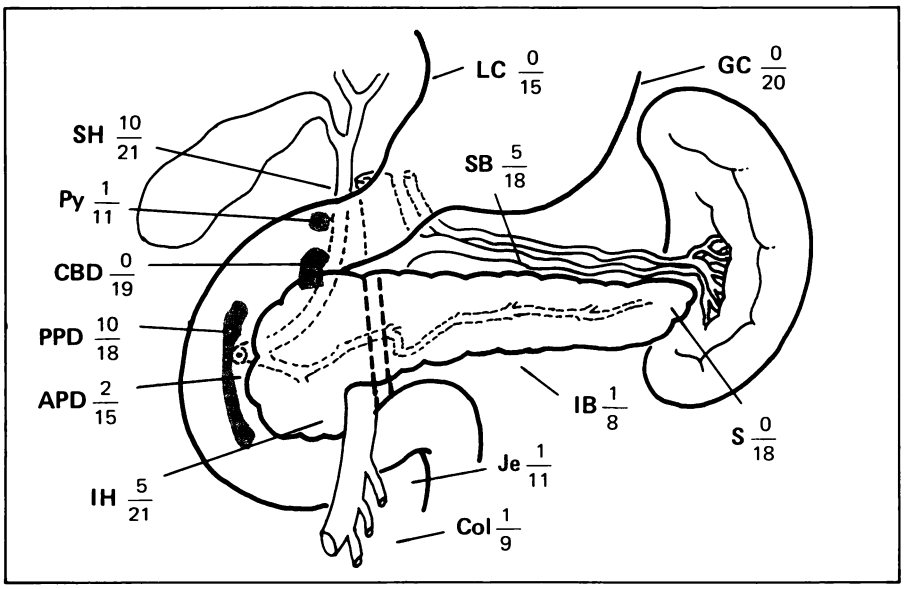

Fig. 9. Lymph node grouping (with results from dissection of 21 cancers of the head of the pancreas specimens). Denominator indicates the number of patients in whom lymph nodes of that group were found; numerator indicates the number of patients in whom lymph nodes contained microscopically verified cancer. Key for the groups of lymph nodes: SH = Superior Head, IH = Inferior Head, PPD = Posterior Pancreaticoduodenal, APD = Anterior Pancreaticoduodenal, SB = Superior Body, IB = Inferior Body, S = Splenic, GC = Greater Curvature, LC = Lesser Curvature, Py = Pylorus, CBD = Common Bile Duct, Je = Jejunum, Col = Colon. In the Whipple resection (indicated by the stippled vertical line), the SB, IB, and S groups are not usually removed. Cancer of the head of the pancreas often involves multiple groups of nodes, including SB and IB groups. Ampullary carcinoma involves the APD and PPD nodes and the SH and IH nodes, but not, in our small number of cases, the SB or IB groups.[6]

TABLE 3
INITIAL CLINICAL SITE OF METASTASIS FROM AN OCCULT PANCREATIC CANCER (50 PATIENTS)[4]

Site	Total Number of Patients	Head	Body and Tail	Site Not Specified
Lymph Nodes				
Left Neck	11	1	10	0
Right Neck	5	2	3	0
Inguinal	4	0	3	1
Axillary	1	1	0	0
Multiple Nodes	1	1	0	0
Total	22	5	16	1
Skin	8	2	6	0
Bone	8	0	6	2
Lungs	4	3	1	0
Liver	3	2	1	0
Cervix-Vagina	3	2	1	0
Brain	2	0	2	0
Total	50	14	33	3

cinoma in situ and minimal or no obvious gross invasion.[4,7,8,11] A few similar cases have been reported.[13] Two other possible precursor lesions, marked atypia (severe dysplasia) and papillary hyperplasia,[14] were found to be significantly increased in the ductal epithelium of patients with pancreatic cancer, when compared with the control group with nonpancreatic cancers.[11] The paucity of such studies emphasizes the fact that the natural history of the progression of pancreatic cancer and the role of precursor lesions are virtually unknown.

Survival

The length of survival, without regard to the type of therapy, varied with the site (longest with tumors of the head), size (longer with smaller lesions) (Table 2), and stage (longer with the lower stages).[4,5]

Of patients with cancer of the head of the pancreas, only 17 percent were alive at one year after diagnosis.[5] Of those with cancer of the body and/or tail, only one percent were alive at one year.[15] The mean survival time for stage I patients was 11 months, for stage II patients, five months, and for stage III patients, only three months.[4]

After surgery, patients with a resected stage I tumor less than three cm in diameter had a mean survival time of 23 months; patients with a resected tumor three cm or larger had a mean survival time of four months (Table 2).[4,5]

TABLE 4
AUTOPSY STUDY OF PANCREAS*
2,587 AUTOPSIES–
PANCREAS INVOLVED IN 411 PATIENTS (16 PERCENT)

Involvement of Pancreas at Autopsy (Number of Patients)	
Benign "Tumors" 4 patients (0.2 percent)	Cyst (1) Cystic pancreas (1) Islet cell adenoma (1) Serous cystadenoma (1)
Primary Malignant Neoplasms 63 patients (2.4 percent)	Duct cell carcinoma (51) Giant cell carcinoma (6) Islet cell carcinoma (4) Acinar cell carcinoma (1) Osteogenic sarcoma (1)
Invasion of Pancreas by Cancer of Adjacent Organs 16 patients (0.6 percent)	Stomach (6) Colon (3) Duodenum (2) Ovary (2) Gastroesophageal junction (1) Gallbladder (1) Retroperitoneal neurofibrosarcoma (1)
Systemic Malignant Neoplasms involving the Pancreas 67 patients (2.6 percent)	Malignant lymphoma (41) Hodgkin's disease (7) Leukemia (19)
Metastasis to Pancreas from Cancer of: 261 patients (10.1 percent)	Breast (51) Lung (49) Malignant melanoma (skin) (23) Stomach (19) Colon (19) Ovary (13) Uterine cervix (12) Esophagus (10) Neuroblastoma (various sites) (9) Other sites (56)
Total 411 patients (15.9 percent)	

*From the files of MSKCC, New York, NY, 1973–1978.[4]

The mean survival time for all patients, without regard to therapy, from the diagnosis at MSKCC to death was four months. For many patients, the diagnosis of cancer had already been made elsewhere and they were later referred to MSKCC for further treatment. The survival time from the original diagnosis of pancreatic cancer at another hospital to death at MSKCC was usually a few months longer than the four months from MSKCC diagnosis to death.

Adenocarcinoma of the pancreas is considered a devastating tumor with a relatively poor response to surgery, radiation therapy, or chemotherapy.

Five years after the MSKCC diagnosis of pancreatic cancer, there were three survivors (less than one percent of all patients with pancreatic cancer); these were patients treated by "curative" surgical resection. These patients died of cancer of the pancreas at 60, 63, and 90 months after surgery.[4,5,16]

Other Morphological Types of Pancreatic Cancer

Although the following types of pancreatic cancer were relatively less common (about 15 percent of all cases), they were distinctive morphologically,[3-5] and a few had significant clinical features (Table 5).

Giant Cell Carcinoma

This was a distinctive carcinoma of the pancreas characterized by huge cells with giant nuclei and relatively dense cytoplasm. The nuclei often assumed bizarre patterns of chromatin[3,4] (Fig. 2). The cells frequently had a spindle cell, sarcomatoid appearance.[17] The tumor was frequently seen at surgery or autopsy as a huge cyst with hemorrhagic necrotic contents. Most patients died with widespread metastases within a few weeks to months after diagnosis (Table 5).

There was also a very rare form of the cancer in which the giant cells resembled the osteoclasts of bone.[7,8,18] The prognosis for patients with this type was much better than for those with the giant cell carcinoma. We have suggested the name "giant cell carcinoma (osteoclastoid) type" for this carcinoma.

Microadenocarcinoma (Solid Microglandular, Adenocarcinoid) Carcinoma

This was a rare, intriguing cancer characterized by a large cystic and hemorrhagic tumor;[3-5] the patient usually died within a few weeks or months after diagnosis (Table 5). Histologically, the lesion suggested a carcinoid, or islet cell tumor, with many small glands containing mucin. The short survival time, however, is uncharacteristic of either a carcinoid or islet cell tumor (Fig. 3).

Adenosquamous Carcinoma

This well-recognized cancer was a combination of squamous cell carcinoma and adenocarcinoma and is known to occur in other organs (Fig. 4).[3-5] It had about the same prognosis as the ductal cell adenocarcinoma.

Mucinous (Colloid) Adenocarcinoma

This was a rare, well-known type of cancer with an inordinately excessive amount of mucin (Fig. 5).[3-5] Grossly, the neoplasm may resemble a goiter with macrofollicles containing colloid (hence the name, even though the carcinoma does not contain colloid). All of the cases occurred in men. The tumor appears to have a better prognosis than does the ductal cell carcinoma (Table 5). It is known to occur in other organs, such as the gastrointestinal tract and breast.[4]

Cystadenocarcinoma (Mucinous)

This was a large, multiloculated tumor

TABLE 5
PANCREAS CANCER DATA*

Type	Number of Cases	Median Age (year)	Sex	Number	M/F	Site**	Percent	Median Size (cm)	Survival†		
									Median (months)	One-yr. (percent)	Five-yr. (percent)
Duct Adenocarcinoma[3, 4]	380	60	M F	230 150	1.5	H BT HBT	61 18 21	5	4	17	1
Giant Cell (Pleomorphic) Carcinoma	27	62	M F	16 11	1.5	H B	50 50	11	2	0	0
Adenosquamous carcinoma	20	63	M F	15 5	3.0	H BT HBT	60 33 7	6	6	5	0
Microadenocarcinoma	16	61	M F	10 6	1.7	H BT HBT	38 44 19	14	2	0	0
Mucinous (colloid) Adenocarcinoma	9	61	M F	9 0		H BT	78 22	6	11	33	0
Cystadenocarcinoma (Mucinous)	5	54	M F	0 5		H T BT	20 60 20	16		100	40-80††
Acinar Cell Carcinoma	7	54	M F	5 2	2.5	H B HBT	43 43 14	5	7	14	0

*Demographic, pathological, and survival figures of the commonest pancreatic (nonendocrine) cancers from MSKCC.[4]
**H = Head of pancreas; B = Body of pancreas; T = Tail of pancreas.
†Exclusive of operative deaths and without regard to type of therapy.
††One patient died at 17 months and another, 60 months after operation; the third patient was alive and well three years after surgery and then was lost to follow-up; the fourth patient was alive with no evidence of disease three years after operation; the fifth patient is alive 10 years after resection of a pancreas tumor and has recently had a primary lung tumor resected.

lined by columnar mucin-producing epithelium (Fig. 6). The carcinoma occurred primarily in the body and/or tail of the pancreas in women 40 to 60 years of age. It probably arose from ductular epithelium. It had a relatively good prognosis: a five-year survival rate of at least 40 percent, if resected (Table 5).[3,4,8,19]

Acinar Cell Carcinoma

This was an uncommon cancer (less than five percent of pancreatic carcinomas) that arose from the acinar cell of the pancreas in elderly men and women (Fig. 7). It had a very poor prognosis.[3,4,7,8] It may, very rarely, produce a syndrome with subcutaneous fat necrosis, polyarthritis, and eosinophilia, possibly related to lipase and other enzymes, released from the zymogen granules of the acinar cell.[4] It has been found in children very rarely,[20] and a cystadenocarcinoma (acinar-cell type) has been reported recently.[21]

Papillary-Cystic Tumor

This uncommon, interesting tumor occurs in female patients, mostly young women, and behaves essentially like a benign tumor if resected, although a few cases have pursued a malignant course. It classically presents as a large hemorrhagic cyst in the body or tail of the pancreas. A distinctive microscopic pattern of papillae of epithelial cells (probably ductular in origin) and cystic spaces is apparent (Fig. 8). It may be more prevalent than the literature indicates, however, because Compagno et al have reported more than 50 cases.[4,7,22] We have seen six cases in consultation.[4]

Rare Cancers

Rare types of cancer of the pancreas were found in the MSKCC patients or reported in the literature[4] (Table 1). Those of epithelial origin were: duct-islet cell carcinoma, acinar-islet cell carcinoma, carcinoid-islet cell tumor, oat cell carcinoma,[23] oncocytic carcinoma,[24] mucinous carcinoid carcinoma,[4,7,8] and the pancreaticoblastoma of childhood.[4,25]

Sarcomas of the pancreas were rare, although individual cases of the common types have been reported (Table 1).

Primary malignant lymphomas, including Hodgkin's disease, of the pancreas were virtually absent, although secondary involvement of the gland was not uncommon in the disease. Leukemia involved the pancreas in a few patients (Table 4).[4,7,8]

Carcinoma of the Body and/or Tail Of the Pancreas

It has long been known that cancers of the body and/or tail of the pancreas[15] have a clinical appearance different from cancers of the head of the pancreas.[26] Jaundice occurred less frequently, widespread metastasis was found more often as the presenting sign or symptom, and the prognosis was much poorer than with cancer of the head of the pancreas. Thromboembolism was more common with cancer of the body and/or tail, and diabetes was less common than in cancer of the head of the pancreas.[4,15]

Cancers of the body and/or tail of the pancreas (Table 3) were more likely to present clinically as occult cancer[4] or as a primary cancer of the lung[10] than were cancers of the head of the pancreas. Most of the common types of carcinoma of the head of the pancreas were found in cancer of the body and/or tail, but mucinous cystadenocarcinoma occurred more often in these

Morphological classification is important as a primary marker of cancer type, but is of greater value when combined with recently introduced techniques capable of identifying antigens, types of connective tissue, enzymes, hormones, and other substances within individual cells of a tumor.

TABLE 6
SITE OF ORIGIN OF CANCER OF
THE AMPULLA-HEAD-OF-PANCREAS REGION*[27]

	Number of Patients	Percent
Pancreatic Duct (Ductule)	89	75
Ampulla (Vater)	8	7
Common Bile Duct	4	3
Duodenum	4	3
Gallbladder	2	2
Retroperitoneum	2	2
Islet Cell	1	1
Metastatic or Invasive	9	7
Total	119	100

*Postulated site of origin of cancers of the ampulla-head-of-pancreas region. Many of these tumors involved both common bile and pancreatic ducts, so that the site of origin was "best guess," based on gross and microscopic morphology.

sites than in the head of the pancreas.[4,7,8]

The survival rate for cancer of the body and/or tail was one percent at one year,[15] compared with 17 percent for cancer of the head of the pancreas.[5] One five-year survivor out of 150 patients with cancer of the body had the lesion removed incidentally, by a biopsy, at an operation for peptic ulcer.[15]

Ampulla-Head-of-Pancreas Carcinoma

With large tumors of the ampulla-head-of-the-pancreas region, it is usually difficult, and often impossible, to determine the site of origin of the tumor (Table 6).[9] Prognosis is generally better with ampullary cancer, which has a five-year survival rate of 25 percent to 40 percent,[4,27,28] compared with less than one percent for pancreatic ductal cancer.[4,5,16]

The determination of site of origin is important not only from the prognostic standpoint, but also in regard to etiology—that is, is it possible that the cancer is the result of exposure to a carcinogen(s) in bile (ampullary and/or bile duct cancer), pancreatic juice (pancreatic cancer), duodenal contents (duodenal cancer), or some combination of these factors?

With the help of gross and microscopic findings, we attempted, in a prospective study,[9] to identify the site of origin of the ampulla-head-of-the-pancreas tumors (Table 6).[4,27] Subsequently, ampullary cancer was subdivided into three classes (Fig. 10):[4,27,28] intra-ampullary, periampullary, and mixed. The last was a combination of the first two. The five-year survival figures for "curative" resection of these tumors were, respectively, 33 percent, 17 percent, and zero percent (Table 7).

The intra-ampullary tumors were relatively small, had a papillary configuration, and were mostly stage I tumors. Because they are situated in such a way

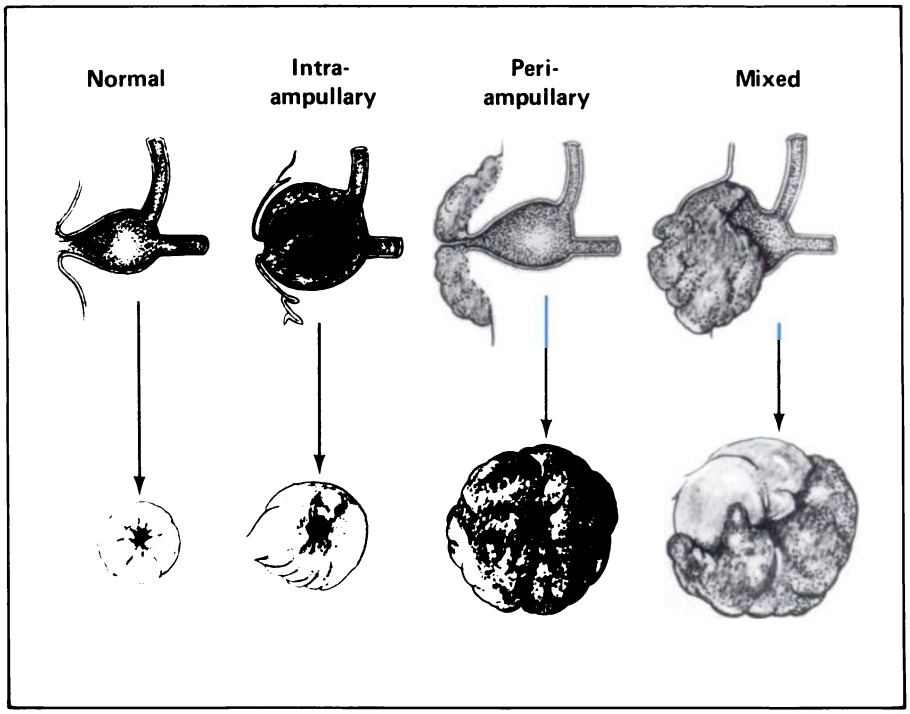

Fig.10. Classification of tumors of the ampulla-head-of-the-pancreas region: Intra-ampullary tumors are confined to the ampulla, periampullary tumors occur primarily in the duodenal mucosa around the ampulla, and those of the mixed type are both intra-ampullary and peri-ampullary.[4]

that their growth would cause obstruction of the biliary duct, these lesions may be discovered much earlier in the course of their progression than would a comparable-sized tumor of the pancreatic ducts;[7] this may account, in part, for the better survival figures.

Benign Tumors as Possible Precursors to Cancers

Because of its rarity, adenoma, or papilloma, of the pancreatic duct system was an unlikely precursor for any large number of pancreatic cancers.[4,7] Acinar cell adenoma may be a precursor of the rare acinar cell carcinoma, but none was found in the study.[4] Serous cystadenoma, a cystic tumor with watery contents,[29] was not a likely precursor of any significant number of malignant lesions.[4] A mucinous cystic tumor of the pancreas may present a problem in the separation of a mucinous cystadenoma from a mucinous cystadenocarcinoma. It is possible that the former may be a precursor of the latter. Because of the large size of these tumors, it is difficult to obtain adequate biopsy sampling, and a small focus of mucinous cystadenocarcinoma may not be included in the sampling. For this reason, it would be preferable to regard all mucinous cystic lesions as malignant and to resect them completely, if possible.[19]

Benign connective tissue tumors were very rare.[4]

Genetic Factors

Hereditable disposition does not appear to

TABLE 7
AMPULLARY CARCINOMA (MSKCC, 1949–1971)*

Type	Number	Median Size (cm)	Stage I (Percent)	"Curative" Resection (Percent)	5-Year Survival			
					Overall		"Curative" Resection†	
Intra-ampullary	20	2	65	90	5/20	(25%)	5/15	(33%)
Periampullary	8	4.5	38	88	1/8	(13%)	1/6	(17%)
Mixed	5	4.5	0	40	0/5	(0%)	0/1	(0%)
Total	33			82	6/33	(18%)	6/22	(27%)
Pancreatic duct cancer[4,5]	172	5	28	37	3/172	(1.7%)	3/51	(6%)

* A summary of the experience with 33 cases of ampullary carcinoma over a 23-year period.[4]

†Exclusive of operative mortality and other noncancer causes.

be prominent in pancreatic exocrine cancer, in contrast to some pancreatic endocrine tumors, although a small percentage of patient subsets have exhibited a hereditable tendency.[4,30] Familial pancreatitis is commonly believed to be associated with an increased risk for pancreatic cancer.

In an autopsy study of 87 patients with pancreatic ductal carcinoma, two patients were found to have an associated genetic disorder: one was a 34-year-old, white man who had familial pancreatitis, and the other was a 47-year-old, Mexican-American with epidermolysis bullosa dystrophica.[30] Patients under 50 years of age with pancreatic exocrine cancer should be investigated for the presence of associated genetic disease.

Comment

Morphological classification is important as a primary marker of types of cancer, but will be of greater value if combined with recently introduced techniques that are capable of identifying antigens, types of connective tissue, enzymes, hormones, and other substances within individual cells of a tumor.[31-38] The combinations of classical histologic and/or cytologic patterns with such techniques may determine more subtypes of cancers and lead to better correlation of these with clinical features, therapeutic response, and the biochemical aspects of tumor metabolism.

The recent advances in the unraveling of the clonal nature of experimental tumor metastases[39,40] and the relationship of mutagenesis to the cloning process[41] are pertinent to the understanding of the heterogeneity of human pancreatic cancer—that is, the multiple minor foci of morphologic subtypes seen in the primary tumor with its different predominant type.[4,5]

The presence of the same predominant histological type in both primary and metastatic cancers in most patients indicates that there is also a degree of homogeneity in human pancreatic cancer—a stabilization of clonal type.[39,40] In a minority of patients, there may be two or more predominant types; others may have a different predominant type(s) in the primary and metastatic tumors.

Carcinoma in situ has been found in up to one third of patients with invasive pancreatic cancer. Possibly, there is a significant latent period in which, eventually, the carcinoma in situ may be diagnosed with resulting better prognosis.

The presence of a heterogeneity of morphologic types as minor components and only one or two predominant types in both the primary and metastatic tumors, suggest that the host milieu probably plays a significant role in determining which clone(s) becomes predominant.

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