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Mucinous Cystic Neoplasm (Mucinous Cystadenocarcinoma of Low-Grade Malignant Potential) of the Pancreas

A Clinicopathologic Study of 130 Cases

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Mucinous cystic neoplasms (MCNs) of the pancreas are uncommon tumors. The classification and biologic potential of these neoplasms remain the subject of controversy. Attempts to classify these tumors in a similar manner to ovarian MCNs remains controversial, as even histologically benign-appearing pancreatic MCNs metastasize and are lethal. One hundred thirty cases of MCNs were identified in the files of the Endocrine Pathology Tumor Registry of the Armed Forces Institute of Pathology from the years 1979 to 1993. The pathologic features, including hematoxylin and eosin staining, histochemistry, immunohistochemistry (IHC), cell cycle analysis, and K-ras oncogene determination were reviewed. These findings were correlated with the clinical follow-up obtained in all cases. There were 130 women, aged 20–95 years (mean age at the outset, 44.6 years). The patients had vague abdominal pain, fullness, or abdominal masses. More than 95% of the tumors were in the pancreatic tail or body and were predominantly multilocular. The tumors ranged in size from 1.5 to 36 cm in greatest dimension, with the average tumor measuring >10 cm. A spectrum of histomorphologic changes were present within the same case and from case to case. A single layer of bland-appearing, sialomucin-producing columnar epithelium lining the cyst wall would abruptly change to a complex papillary architecture, with and without cytologic atypia, and with and without stromal invasion. Ovarian-type stroma was a characteristic and requisite feature. Focal sclerotic hyalinization of the stroma was noted. This ovarian-type stroma reacted with vimentin, smooth muscle actin, progesterone, or estrogen receptors by IHC analysis. There was no specific or unique epithelial IHC. K-ras mutations by sequence analysis were wild type in all 52 cases tested. Ninety percent of patients were alive or had died without evidence of disease (average follow-up 9.5 years), irrespective of histologic appearance; 3.8% were alive with recurrent disease (average 10 years after diagnosis); and 6.2% died of disseminated disease (average 2.5 years from diagnosis). Irrespective of the histologic appearance of the epithelial component, with or without stromal invasion, pancreatic MCNs should all be considered as mucinous cystadenocarcinomas of low-grade malignant potential. Pancreatic MCNs cannot be reliably or reproducibly separated into benign, borderline, or malignant categories.

Key Words: Pancreas—Mucinous cystic neoplasms—Mucinous cystadenoma—Mucinous cystadenocarcinoma—Prognostic markers—Immunohistochemistry—Histochemistry—K-ras oncogene—DNA ploidy—Prognosis.

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The term *mucinous cystic neoplasms* (MCNs) of the pancreas has been used to encompass a broad spectrum of primary tumors of the pancreas, including, but not limited to, mucinous cystadenomas,[1,8,11,13–15,17,20,24,25,30,43,45,48,52,57,62,69,75,79,82,87,88,90,96,101] mucinous cystadenocarcinomas,[1,3,4,8,9,11,15,17,18,20,22,24,25,30,37,44,52,57,79,88,90,95–97,98,101] mucinous cystic neoplasms of the pancreas with overt and latent malignancy,[5,18,21,26,31,32,36,41,50,61,68,73,83,86,94,102,103] pancreatic cysts,[48,97,106] duct ectatic tumors of various kinds,[2,10,53,71,74,85,92,101,104,105] intraductal papillary/mucinous tumors,[6,22,25,32,63,71,78,84,86,103,105] mucin-producing tumors of pancreas,[46,54,70,72,85] and adenocarcinomas with mucin production (colloid carcinoma).[9,11,22,25,90]

It is no wonder that the prognostic implications of using this general term for a specific tumor has confused the clinician, confounded the radiologist, and baffled the pathologist.

We believe that the term *MCN* should be strictly applied to an uncommon, specific type of tumor, as originally detailed by authors from our institution,[21] rather than being a vague, confusing, and all-encompassing term. These tumors are generally believed to occur much more frequently in women, in the tail of the pancreas, appearing as an encapsulated unilocular or multilocular cystic, encapsulated mass, often diagnosed by radiographic studies, lined by a columnar mucin-producing cell, and overlying an ovarian-type stroma with occasional areas of dense collagenization and surrounding pancreatic atrophy. However, in recent years, there have been several attempts to further subclassify these neoplasms into distinctive clinical, radiologic, and histopathologic entities[2,4,9,13,20,24,25,30,48,50–55,64,68,73,74,85,90,92,96] similar to the mucinous cystic tumors of the ovary or biliary system, in which the accepted histologic criteria have prognostic and treatment implications.[16,43,51,64,98] This type of classification, when applied to the pancreatic mucin-producing tumors, is confusing and frustrating. Therefore, a true analysis of the literature is virtually impossible, as many authors address only a specific characteristic of what they believe is a mucinous cystic neoplasm, lacking complete clinical, radiographic, histologic, immunophenotypic, treatment, or follow-up information. Although such studies serve as a valuable adjunct to the understanding of mucinous cystic neoplasms as a group, a more comprehensive approach using all of these parameters applied to a large group of these neoplasms was conspicuously absent from the literature. Therefore, we undertook a study of 130 MCNs, to our knowledge the largest single series of its kind (MEDLINE 1966–1998), in order to catalogue the various characteristics in a single comprehensive study. It is the intention of this study to determine whether a classification system can differentiate these neoplasms into adenomas, borderline tumors, and malignant tumors in a reproducible fashion by use of clinical symptoms, radiographic images, histomorphology, histochemical stains, immunohistochemical studies, cell cycle analysis, or K-ras oncogene determination. Furthermore, we wish to determine whether this separation yields prognostic or treatment outcomes that are statistically or clinically significant.

MATERIALS AND METHODS

One hundred forty-eight cases of MCN of the pancreas were identified in the files of the Endocrine Tumor Registry at the Armed Forces Institute of Pathology from the years 1979 to 1993. These 148 cases were identified in a review of 2574 (5.7%) benign or malignant primary pancreatic tumors seen in consultation between 1979 and 1993. For inclusion in this study, complete clinical follow-up was necessary, which was available in 130 cases. All the results are based on the 130 cases only. One hundred nine cases were obtained from civilian sources, including university medical centers and foreign contributors; 20 cases from military hospitals; and one case from a Veterans Administration Medical Center.

For a better understanding of the tumor, we used histologic criteria to artificially separate cases that had nuclear atypia (carcinoma) from cases that did not have atypia. These two groups are referred to in this article as mucinous cystic neoplasms with atypia (MCNA) and mucinous cystic neoplasms without atypia (MCNWA). Atypical features were defined as cells with an increased nuclear-to-cytoplasmic ratio, nuclear hyperchromasia, prominent nucleoli, a loss of nuclear polarity, and architectural disorganization within the papillae. Complex architecture of the papillary projections, a cribriform arrangement, or both, combined with the cytologic features, placed the tumor in the atypical category. There was a dependence on the number of sections sent in for consultation. On the basis of tumor size, if at least one section per centimeter of tumor had not been previously submitted, we would submit additional tissue, or completely embed the tumor, as material allowed.

For purposes of statistical analysis, we studied the two arbitrary groups to see whether our criteria had statistically significance differences, using the Kruskal-Wallis one-way analysis of variance, reported as the Pearson chi-square test or the Fisher exact test (two-tailed).

Hematoxylin and eosin–stained slides for all cases were reviewed. All the cases met the histologic criteria for mucinous cystic neoplasms as defined by Compagno and Oertel[21] (although none of their original cases were included in the present study). These criteria included, but were not limited to, the following (as partially stated in the introductory paragraphs): large, multicystic masses lined by columnar, mucin-producing epithelium, arranged in papillae, subtended by "ovarian-type" stroma, found mainly in the body and tail of the pancreas of middle-aged women. Adequate clinical data had to be available. Materials within the Institute's files were supplemented by a review of the patient demographics, symptoms at the outset, medical history, laboratory values, radiographic studies, surgical pathology reports, operative reports, and cancer registry records, by specific questionnaires or direct communication with the physician or the patient. Adequate follow-up was a requirement for inclusion in the study. Patients who had pseudocysts, mucin-producing adenocarcinoma, or papillary intraductal tumors were excluded from this study, as we believe those tumors to be distinct entities, easily separated by clinical and histologic review from MCNs.

Formalin-fixed, paraffin-embedded sections were stained with periodic acid–Schiff (PAS) (with and without diastase digestion), Mayer's mucicarmine, alcian blue at pH 2.5, and PAS with alcian blue. By use of the alcian blue, pH2.5/PAS staining, neutral glycoprotein stained red and sulphomucin and sialomucin stained red-purple to blue, respectively. Immunophenotypic analysis was performed in 69 cases with suitable material, according to the standardized avidin-biotin method of Hsu et al.[47] The antibody panel, listed in order of interest, is given in Table 1. Predigestion was performed for 3 minutes with 0.05% Protease VIII (Sigma Chemical Co., St. Louis, MO) in a 0.1 M phosphate buffer at a pH of 7.8 at 37°C. Antigen enhancement (recovery) was performed by use of formalin-fixed, paraffin-embedded tissue treated with a buffered citric acid solution and heated for 20 minutes in a calibrated microwave oven. Appropriate positive and negative controls were used throughout.

A positive immunoreaction was determined by chromogen deposition within the cytoplasm of the epithelial tumor cells (keratin, CAM5.2, CEA, B72.3, Dupan-2, CA19-9, chromogranin) or in the stromal cells (vimentin, smooth muscle actin, muscle specific actin, S-100 protein, CD-34). The estrogen or progesterone receptor protein immunoreactivity was determined by chromogen deposition in the nuclei of either the epithelial or stromal tumor cells, graded as a percentage of cells reactive and by intensity of reaction (0–4+). Ki67, p53, and proliferating cell nuclear antigen (PCNA) were graded as a percentage of cells demonstrating nuclear reactivity, as well as a grade of intensity (0–4+), in the epithelial (all) and stromal (PCNA) tumor cells. Collagen IV was applied in an effort to assess disruption of the stroma to determine whether there was invasion.

Tumors were studied for aneuploidy and S-phase fraction by flow cytometry, using nuclei recovered from formalin-fixed, paraffin-embedded tissue.[40] For each case, thin sections (taken before and after a 100-μ thick section) were stained with hematoxylin and eosin and reviewed to locate tumor. The thick section was dissected to maximize the neoplastic component, then deparaffinized, rehydrated, and digested in 0.1% protease XXIV solution (Sigma) with a 0.1 M TRIS buffer. The nuclei were stained with DAPI (4,6-diamino-2-phenylindol, Sigma) and were analyzed with a Partec PAS III flow cytometer (Partec GmbH, Munster, Germany). The criteria for aneuploidy were those published by Hiddemann et al.[42] Histograms with a coefficient of variation >10% for the lowest G0/G1 peak were rejected as unsuitable for analysis. Multicycle software (Phoenix Corporation, San Diego, CA) was used to calculate the S-phase fraction for each cycling population and for the entire specimen.

Point mutations in K-ras-2 were searched for in 52 cases. Mutational analysis was performed by topographic

TABLE 1. *Immunohistochemical panel*

Antigen (clone)	Primary antibody	Company	Dilution	Treatment
B72.3	mm	Biomedical Technologies (Stoughton, MA)	1:20	None
Progesterone receptor (1A6)	mm	Novocastra Laboratories (Newcastle upon Tyne, United Kingdom)	1:20	Microwave recovery
Estrogen receptor (1D5)	mm	Dako (Carpinteria, CA)	1:20	Microwave recovery
p53 (DO-7)	mm	Dako	1:400	Microwave recovery
Ki67 (MIB-1)	mm	Immunotech (Westbrook, ME)	1:20	Microwave recovery
Chromogranin (clone LK2H10)	mm	Boehringer Mannheim (Indianapolis, IN)	1:1,600	None
Carcinoembryonic antigen (CEA)	mm	Sanbio BV (Uden, Netherlands)	1:400	Enzyme digestion
CA19-9 (carbohydrate antigen 19-9)	mm	Signet Laboratories (Dedham, MA)	1:20	Enzyme digestion
DUPAN-2	mm	BioGenex Laboratories (San Ramon, CA)	1:40	Enzyme digestion
Vimentin (clone V9)	mm	BioGenex Laboratories	1:100	Microwave recovery
Smooth muscle actin (1A4)(SMA)	mm	Sigma Immuno Chemicals (St. Louis, MO)	1:8,000	None
Muscle-specific actin (HHF35)(MSA)	mm	Enzo Diagnostics (New York, NY)	1:50	None
Cytokeratin cocktail (AE1/AE3)	mm	Boehringer Mannheim	1:50	Enzyme digestion
CK-1 (LP34)	mm	Dako	1:200	Enzyme digestion
CAM5.2	mm	Becton Dickinson (Mountain View, CA)	1:200	Enzyme digestion
S-100 protein	rp	Dako	1:800	None
CD34 (Qbend/10)	mm	BioGenex Laboratories	1:80	Microwave recovery
Collagen IV	mm	Dako	1:50	Enzyme digestion
Proliferating cell nuclear antibody (PC10)(PCNA)	mm	Dako	1:200	Microwave recovery

mm, mouse monoclonal; rp, rabbit polyclonal.

microdissection with polymerase chain reaction amplification for the K-ras-2 exon 1 gene, flanking intron primers being used as previously described.[28,29,76,77] Cycle sequencing with 35S was performed by use of di-deoxy terminators and one of the amplifying primers (US Biochemical Corporation, Cleveland, OH) and subsequently run on a 6% denaturing polyacrylamide gel. Suspect mutations were subsequently reamplified and sequenced by use of a different primer.

RESULTS

Clinical

Age, Sex, and Social Habits

All of the patients (n = 130) were women (no cases occurred in men that met our criteria for inclusion as listed in Materials and Methods). Their ages ranged from 20 to 95 years (Table 2A & 2B), with an overall average age at the outset of 44.5 years. The patients with MCNWA had a mean age at the outset of 43.2 years, while patients with MCNA had a mean age of 45.63 years, without statistical significance (p = 0.211). One hundred thirteen patients were white, 12 were African American, and 5 were Asian or Indian.

Social habits were reviewed when available. Seven patients (5.4%) used to, or still continued to, smoke cigarettes only; 9 patients (6.9%) used to, or still continued to, consume alcohol only; and 27 (20.8%) patients used to, or still continued to, smoke cigarettes and consume alcohol. Sixty-two patients (47.7%) did not report ever having used tobacco or alcohol products. Alcohol and tobacco use was unknown for 25 patients (19.2%).

Symptoms and Signs

The patients experienced pain or discomfort (n = 94), usually in the epigastric or left upper quadrant region, frequently associated with an abdominal mass (n = 44) (Table 3). A few patients had a mass only (n = 12). The quality of the pain varied from dull, aching, and vague to sharp, stabbing, and cramping, either intermittent or continuous, occasionally radiating to the back. The duration of symptoms ranged from a few days to as long as 34 years. Nausea and vomiting (n = 23), diarrhea (n = 6), weight loss (n = 9), and bleeding or anemia (n = 7) were other initial symptoms, often in association with abdominal pain or mass. Seventeen patients had symptoms interpreted as those of pancreatitis, 16 of cholecystitis or cholelithiasis, 5 of diabetes mellitus, and 3 of ulcer disease, whereas only 3 patients (all with MCNA in the head of the pancreas) had jaundice, presumably related to the duct obstruction. Sixteen patients were asymptomatic, the mass having been found during routine physical examination or discovered incidentally as a radiographic abnormality.

TABLE 2A. *Age distribution of all patients with mucinous cystic tumor*

Age (yr)	MCNWA	MCNA	Total
20–29	13	7	20
30–39	15	21	36
40–49	15	18	33
50–59	9	13	22
60–69	5	9	14
70–79	2	2	4
80–89	0	0	0
90–99	1	0	1
Total	60	70	130

MCNA, mucinous cystic neoplasms with atypia; MCNWA, mucinous cystic neoplasms without atypia.

TABLE 2B. *Patient demographics and social habits*

Patient characteristics	MCNWA	MCNA	All MCNs
Number of patients	60	70	130
Age range			
Range	20–95	23–79	20–95
Mean	43.2 years	45.6 years	44.5 years
Median	42 years	44 years	43 years
Mode	37 years	37 years	37 years
Female (%)	100%	100%	100%
Race			
Caucasians	85%	89%	87%
African Americans	12%	7%	9%
Asian/Indian	3%	4%	4%
Alcohol & Tobacco Use			
Both alcohol and tobacco	20%	22%	21%
Alcohol only	7%	7%	7%
Tobacco only	5%	6%	5%
Neither	50%	45%	47%
Unknown	18%	20%	20%

TABLE 3. *Patient symptoms and signs (expressed as number of patients)*

Symptoms or signs	MCNWA	MCNA
Duration of symptoms (range)	4 days to 18 years	1 week to 12 years
Abdominal pain	42	52
Loss of weight	4	5
Nausea and vomiting	13	10
Diarrhea	2	4
Weakness and fatigue	2	1
Jaundice	0	3
Bleeding or anemia	2	5
Obesity	3	2
Fever	2	0
Tenderness	0	3
Mass	31	25
Pancreatitis	8	9
Ulcer disease	0	3
Diabetes Mellitus	1	4
Gallbladder disease	8	8
Asymptomatic	7	9

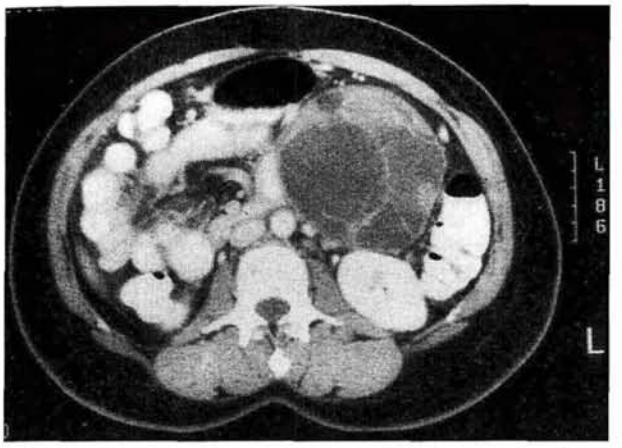

FIG. 1. Large, multicystic, encapsulated mass involving the tail of the pancreas in this computerized tomography image. Septations divide the mixed density tumor.

Diagnostic Investigations

Roentgenographic procedures were performed in the majority of patients, with computer tomography, scanning magnetic resonance imaging, and ultrasound being the most frequently used. Cross-sectional images identified a rounded, well-encapsulated, multicystic, retrogastric mass usually involving the tail or body and tail of the pancreas. Septations could be seen dividing the mucoid to hemorrhagic fluid contents of the cysts into separate cavities (Fig. 1). Calcifications were noted around the periphery within the capsule. Erosion of the organ margins or obliteration of the fat planes suggested a MCNA.

Treatment and Follow-up

Complete surgical excision was the treatment of choice. Most patients were treated by distal pancreatectomy and splenectomy (n = 86), an additional 31 patients were treated by distal pancreatectomy alone, and the remaining 13 patients by a partial pancreatectomy (n = 9) or a Whipple procedure (n = 4). One patient received postoperative chemotherapy.

Eighteen patients were initially treated with a drainage procedure into the gastrointestinal tract (stomach or jejunum) (n = 16) or to the skin (n = 2), anywhere from 1 to 34 years before the definitive surgical resection. The initial histologic appearance was interpreted as a pancreatic pseudocyst (n = 12) or as a mucinous cystadenoma (n = 6). In one case, the rupture of a cyst during surgery was followed by subsequent recurrence of the tumor. The initial biopsy specimens (many of which were available for review) contained foci of tall, columnar, mucin-secreting cells without atypia. These patients continued to have symptoms related to the tumor (given the time intervals, we cannot distinguish between growth of residual tumor or tumor recurrence) and ultimately were treated by surgical excision and complete removal of the cyst, including distal pancreatectomy and splenectomy. One of these patients received chemotherapy and subsequently died of metastatic tumor within 1 year. In 13 of the 18 recurrent cases, cytologic atypia was demonstrated at the time of definitive surgical resection. Twelve of these patients were still alive at last follow-up. The remaining 5 patients with MCNWA were also alive without evidence of disease at the last follow-up (up to 12 years).

The overall survival for mucinous cystadenocarcinoma of low grade malignant potential (MCLGMP) was excellent (Table 4). Fifty-two of 60 (86.7%) patients in the MCNWA category were alive without any evidence of disease, with an average follow-up of 8.35 years (range: 2–22 years). In three patients with MCNWA, recurrent disease had developed at the site of the original tumor (between 3 and 6 years after initial treatment), even after complete surgical excision was achieved with tumor-free surgical margins reported. Even though there had been recurrent disease, these patients were still alive from 4 to 14 years after complete surgical excision, with an average follow-up of 10 years. Four patients had died of unrelated causes, an average of 3.8 years after diagnosis. The final patient with MCNWA died of disseminated disease less than one year from the time of diagnosis, at the age of 61, despite having been treated by distal pancreatectomy.

Likewise, the overall survival for MCNA was also excellent (Table 4). Fifty-eight of 70 (84.3%) patients were alive without any evidence of disease, with an average follow-up of 9.9 years (range: 2–34 years). Two patients with MCNA had recurrent disease but, in spite of the recurrent disease, were still alive 10 and 34 years, respectively, after initial diagnosis. Three patients had died of unrelated causes an average of 1.6 years after diagnosis. Seven patients died of tumor an average of 2.7 years after diagnosis, having had both recurrent and widely metastatic disease. Only one of these patients had initially been treated by marsupialization.

Pathologic Features

Macroscopic Features

The majority of the tumors (80%) were located in the tail of the pancreas (Table 5). An additional 13.8% (n =

TABLE 4. *Patient outcome and average survival for mucinous cystic neoplasms*

Average Survival	MCNWA (60)	MCNA (70)
Alive, no evidence of disease	52 (87%) 8.4 years	59 (84%) 9.9 years
Alive, recurrent disease	3 (5%) 10 years	2 (3%) 10 & 34 years
Dead, no evidence of disease	4 (7%) 3.8 years	3 (5%) 1.6 years
Dead, recurrent or metastatic disease	1 (2%) < 1 year	7 (10%) 2.7 years

TABLE 5. *Location and size of mucinous cystic tumors*

Tumor characteristics	MCNWA	MCNA	Total number of cases
Location			
Tail of pancreas	45	59	104
Body of pancreas	3	0	3
Body and tail of pancreas	12	6	18
Head of pancreas	0	5	5
Size			
Range	1.5–26 cm	2–30 cm	1.5–30 cm
Average	10.5 cm	10.6 cm	10.58 cm
Mode	6 cm	7 cm	7 cm
Number of blocks (average)	13.3	16.4	15

18) cases occurred in both the body and the tail, while only three occurred in the body alone. Five occurred in the head of the pancreas (all MCNA). The tumors ranged from 1.5 cm (found during preoperative preparation for cholelithiasis) to 30 cm, with an average size of 10.6 cm. There was no statistically significant difference between MCNWA and MCNA based on size, although when a cutoff of 15.0 cm was used, larger tumors tended to have a worse clinical outcome ($p = 0.04$). The tumors were multilocular (only two were unilocular, and both of them had atypia and stromal invasion) with smooth, glistening external surfaces, often covered with engorged, dilated blood vessels. Sections through the macroscopic specimen demonstrated a variably thick fibrous capsule, with occasional foci of calcifications. The cysts ranged from microscopic to macroscopic, measuring ≤6 cm in greatest dimension (Fig. 2). The cyst lining was smooth and glistening to trabecular or dotted with frond-like papillary protuberances into the cyst cavity. The cysts were filled with yellow-green, thin, transparent to hazy, turbid, cream-yellow serosanguinous fluid or thick, pasty, viscous or gelatinous, opaque, brown to hemorrhagic material. Friable, necrotic debris or purulent material was adherent to the wall of the cyst or free-floating in several cases. The surrounding pancreatic tissue was generally atrophic. Cyst fluid was not tested for CEA, CA19-9, or enzyme levels in this series.

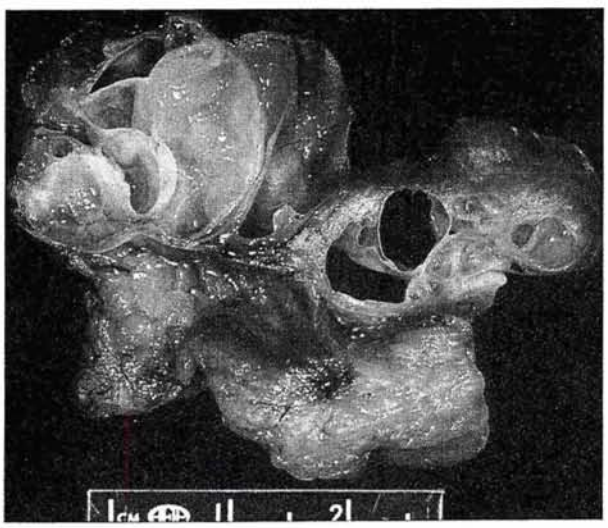

FIG. 2. Macroscopic view of a sectioned multilocular cyst, with smooth glistening cystic cavities separated by thin, transparent septations.

Microscopic Features

All tumors consisted of variable-sized cysts lined by mucin-producing columnar cells. Several sections examined were denuded of epithelium, whether the tumors were MCNWA ($n = 60$) or MCNA ($n = 70$). Therefore, many sections were often needed to demonstrate the epithelial lining, requiring the submission of additional sections, depending on the size of the tumor. Whereas the columnar cells were often the only cell type identified (usually in the tumors that had only a single epithelial layer) (Fig. 3A), goblet cells with eccentrically placed compressed nuclei, cuboidal cells with eosinophilic cytoplasm, and flattened epithelial cells could also be seen. The single row of cells seen in the MCNWA would abruptly develop a cellular pseudostratification two to seven layers thick (Fig. 3B), going on to form truly stratified papillae with variable fibrovascular cores and papillary tufts in MCNA. Cribriform and glandular arrangements were interspersed between papillary projections (Fig. 3 B and C). Nevertheless, the more complex architectural arrangements were identified in the majority of tumors classified as MCNA ($n = 59$). These changes were noted not only within a single tumor but often in the same microscopic field (Fig. 3B). Emphasis must be placed on the abrupt transition or juxtaposition of epithelium with and without atypia. Atypical features (as defined in Materials and Methods) included cells with an increased nuclear-to-cytoplasmic ratio (Fig. 3B), nuclear hyperchromasia, prominent nucleoli, a loss of nuclear polarity, and architectural disorganization in the papillae (Fig. 3D). Not all these features were identified in all the cases, and therefore it was difficult to accurately and reproducibly differentiate mild, moderate, or severe atypia. Mitotic figures were identified only in the MCNA cases, although given the number of sections examined in each case, we cannot state with certainty that there were no mitotic figures in the MCNWA cases. The number of sections examined affected the diagnosis when applied to individual cases, although in many cases, additional sections were submitted to reduce this limitation. Therefore, if two or fewer of the above cytologic criteria for atypia were present, we classified the tumor as MCNWA, while MCNA had three or more of the above criteria, as outlined in Table 6. Invasion of the stroma (Fig. 3 C-2 and E) and mucin pools with floating epithelial

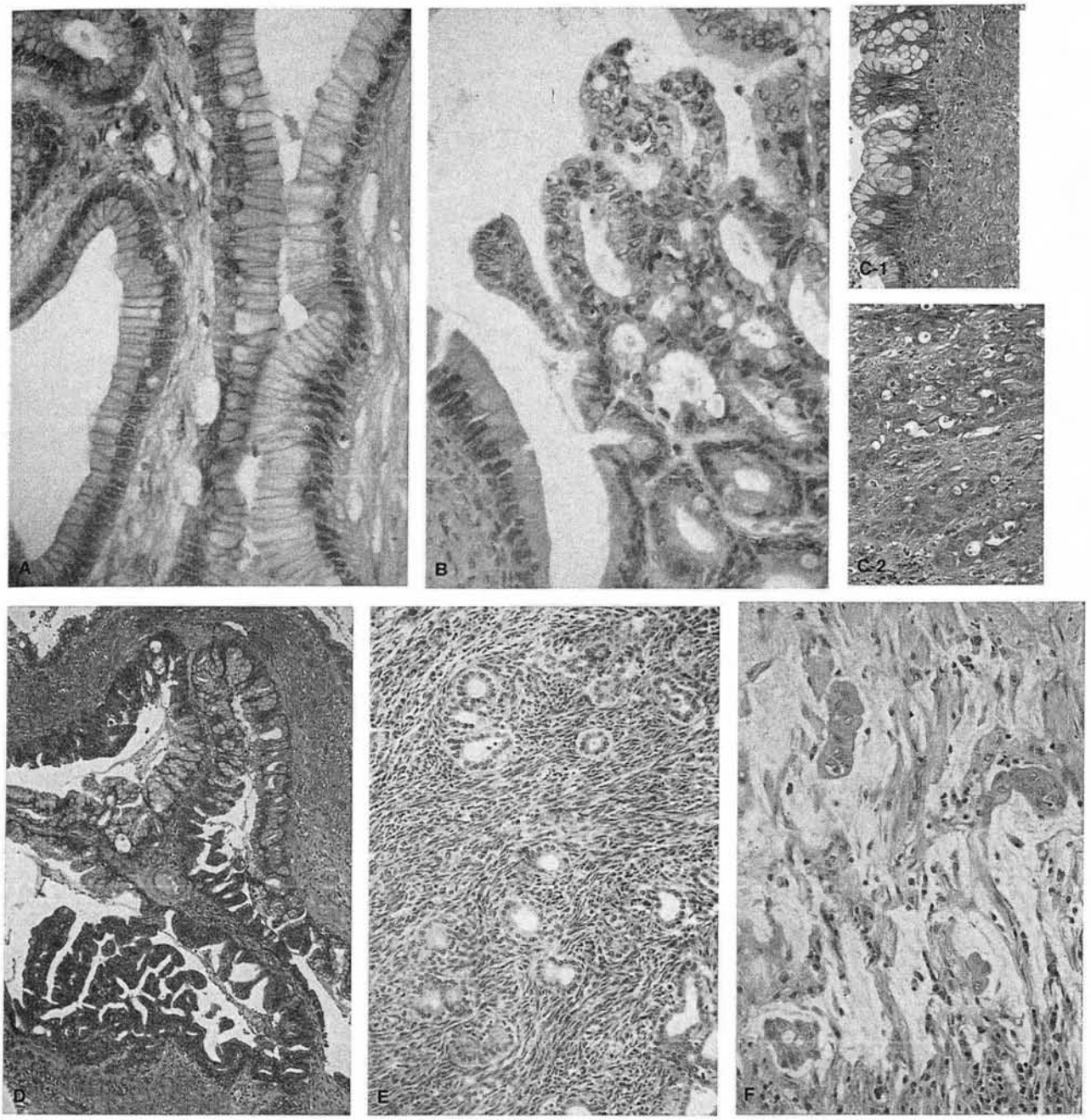

FIG. 3. (A) Tall, columnar, mucin-producing epithelium, lining cystic spaces in this mucinous cystic neoplasm without atypia (MCNWA). The stroma is scant. **(B)** The tall columnar epithelium in the lower right abruptly transitions into a pseudostratified proliferation, demonstrating a cribriform and glandular architecture. Nuclear atypia is identified in this mucinous cystic neoplasm with atypia (MCNA). Benign-appearing columnar epithelium in one field **(C-1)** was transformed abruptly into an invasive proliferation **(C-2)**. Nuclear atypicality, mitotic figures, and mucin production are readily identified in this MCNA. **(D)** Several cystic spaces are lined by benign-appearing tall columnar epithelium (right), whereas pseudostratified epithelium, complex papillae, and a cribriform architectural arrangement of the cells are noted in the rest of the MCNA. **(E)** Epithelial islands deep within the ovarian-like stroma were interpreted to represent invasive tumor (MCNA). **(F)** Atypical epithelial cells arranged in small clusters and glandular profiles surrounded by mucin pools or extravasated mucin in an area of tumor invasion (MCNA). Inflammatory elements can be seen at the periphery.

TABLE 6. *Histologic features of mucinous cystic tumors*

Feature	MCNWA (no)	MCNA (no)
Dense stroma or hyalinization	60	70
Simple lining	54	17
Cytologic atypia	29	70
Complex lining	6	53
Complex papillations	0	59
Invasion into the stroma	0	47
Mucin pools	0	22

cells (Fig. 3F), placed the tumor in the MCNA category, irrespective of cytologic or architectural features. Tumor cells or atypical glands deep in the stroma or beyond the stroma surrounded by a desmoplastic response, and tumor cells "floating" in mucin pools, were considered to represent invasion. Often, several deeper cuts, augmented by keratin immunoreactions, were necessary to confirm the epithelial nature of the isolated cells within the mucin. As noted in Table 5, the number of blocks examined was generally higher in the MCNA cases, but we believe an adequate number of sections were usually examined in both tumor categories.

Foci of endocrine cells were not identified on routine hematoxylin and eosin stain but were highlighted with chromogranin, usually in a random distribution, although perhaps in a greater frequency in areas of goblet cell metaplasia. Squamous cell metaplasia was identified in one of the MCNA cases.

Immediately subtending the epithelium was a dense, cellular, fusiform to spindle cell stroma, reminiscent of ovarian stroma (Figs. 3E and 4), identified in every case. Mitotic figures were occasionally identified within the stromal cells, although they were not specifically searched for in each case. Occasionally, the dense ovarian-type stroma was replaced by a dense collagenized stroma, almost perfectly replicating a corpus albicans of the ovary, as previously reported.[69] Calcification of the capsule as well as metaplastic bone formation was present in several cases. Hemorrhage, necrosis, and degenerative changes were identified only in MCNA. One of our cases demonstrated malignant transformation of the stroma into an undifferentiated sarcoma, in association with the malignant epithelial component (Fig. 4).

The surrounding pancreas frequently demonstrated atrophic acini, ducts, and islet of Langerhans, but true pancreatitis was conspicuous by its absence.

Histochemical Findings

The tall columnar epithelial cells demonstrated PAS-positive, diastase-resistant mucin (Fig. 5A), a pale blue reaction with alcian blue (pH 2.5), and light red to blue/purple granules with PAS and alcian blue. In areas where the cells were atypical (as defined above), much of the red granularity was lost, with a fine layer of luminal blue/purple alcian blue reactivity (at pH 2.5 with PAS) (Fig. 5B). However, there was a great deal of variability between and within cases, the differences within a given case often being quite striking. Overall, the mucin character of the epithelial tumor cells was neutral to sialated, rather than sulphated mucins of normal, uninvolved ducts.

Immunohistochemical Reactions

Although it was not necessary for the diagnosis of MCNs, a diverse panel of immunohistochemical reactions was performed (Table 7) to quantify the immunophenotype of the neoplasm, with 69 cases having sufficient material for study (25 MCNWA and 44 MCNA).

Both MCNWA and MCNA reacted with keratin, CAM5.2, CEA, DUPAN-2, and CA19-9 with a marked heterogeneity of antigen expression, weak and focal in some areas and intense and more diffuse in other areas, often variable within a single tumor. There was an accentuation of the intensity of the reactions with antibod-

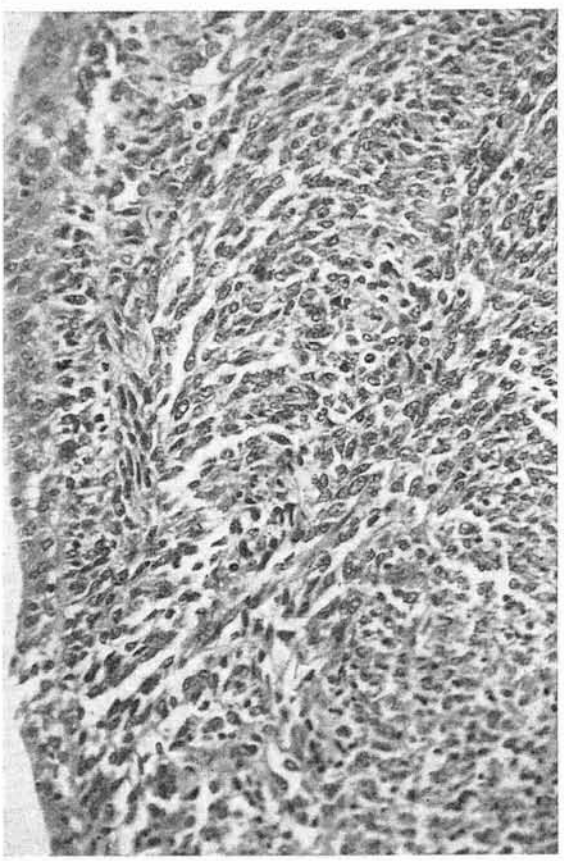

FIG. 4. Dense, spindle cell proliferation, demonstrating nuclear atypia and mitotic figures, associated with a sarcomatous transformation in a single case of mucinous cystic neoplasm with atypia.

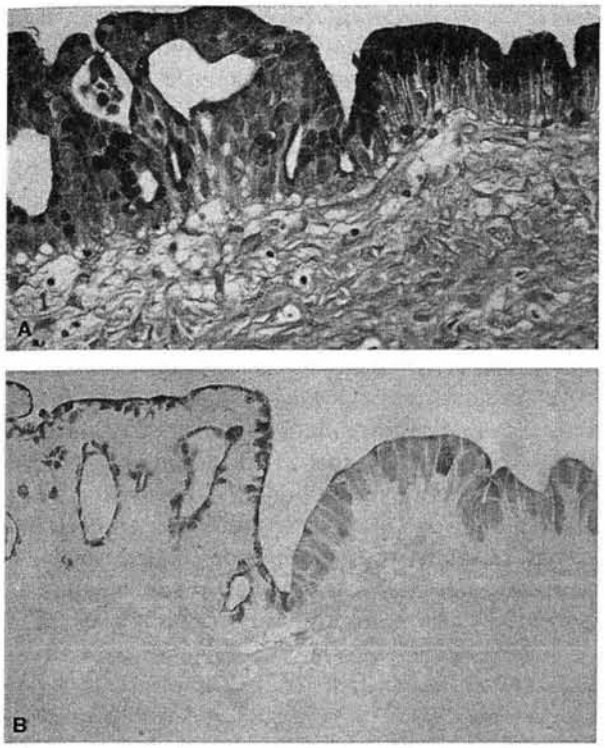

FIG. 5. (A) The character of the tall, mucin-producing cells (right) changes abruptly into a pseudostratified proliferation with less mucin production (periodic acid—Schiff [PAS] with diastase) (left) in this mucinous cystic neoplasm with atypia (MCNA). **(B)** An alcian blue with PAS reaction demonstrating a loss of red granules (left), signifying an abrupt change in the character of the epithelial mucin to neutral/sialated, rather than sulphated, as demonstrated to the right of an MCNA.

TABLE 7. *Immunohistochemical findings for mucinous cystic tumors*

Immunohistochemical antibody	MCNWA positive	MCNA positive
Keratin (epithelium)	24/24	41/41
Cam5.2 (epithelium)	24/24	41/41
CEA (epithelium)	23/23	41/41
B72.3 (epithelium)	1/24	21/44
Dupan-2 (epithelium)	24/25	41/43
CA19-9 (epithelium)	24/25	42/44
Vimentin (stroma)	22/22	40/40
Smooth muscle actin (stroma)	24/24	42/44
Muscle specific actin (stroma)	24/24	40/42
Collagen type IV (stroma)	0/22	0/40
S-100 protein (stroma)	0/22	0/40
Chromogranin (epithelium)	1/23	7/42
CD-34 (QBend)(stroma)	0/22	0/42
Estrogen receptor protein (stroma)	6/23	9/42
Progesterone receptor protein (stroma)	20/24	26/41
Ki67 (MIB-1)(epithelium)	13/24	27/43
p53 (epithelium)	6/25	22/43
PCNA (epithelium and stroma)	24/24	42/42

ies to keratin, CEA, CAM5.2, DUPAN-2, and CA19-9 at the luminal surface, with gradual supranuclear granular reactivity, extending over the rest of the cytoplasm, although the intensity, pattern, and number of cells positively identified varied within a case in similar histologic fields, as well as between cases (in areas of similar histology).

The B72.3 (TAG-72) antibody demonstrated cytoplasmic immunoreactivity in a greater number of MCNA (47.7%) cases than MCNWA (4.2%) cases. Chromogranin-positive cells were identified randomly within the epithelial cyst lining cells more frequently in MCNA cases (17%) than in MCNWA cases (4%), similar to the findings of other authors.[3,4,96] However, our overall percentage of cases with chromogranin-positive cells was lower (Table 7).

The stroma was uniformly reactive with vimentin, smooth muscle actin, and muscle-specific actin. The stromal cell nuclei in 6 cases (26%) of MCNWA and 9 cases (21%) of MCNA reacted with estrogen receptor protein, whereas 20 cases (83%) and 26 cases (63%), respectively, demonstrated immunoreactivity with progesterone receptor protein (Fig. 6A). The differences be-

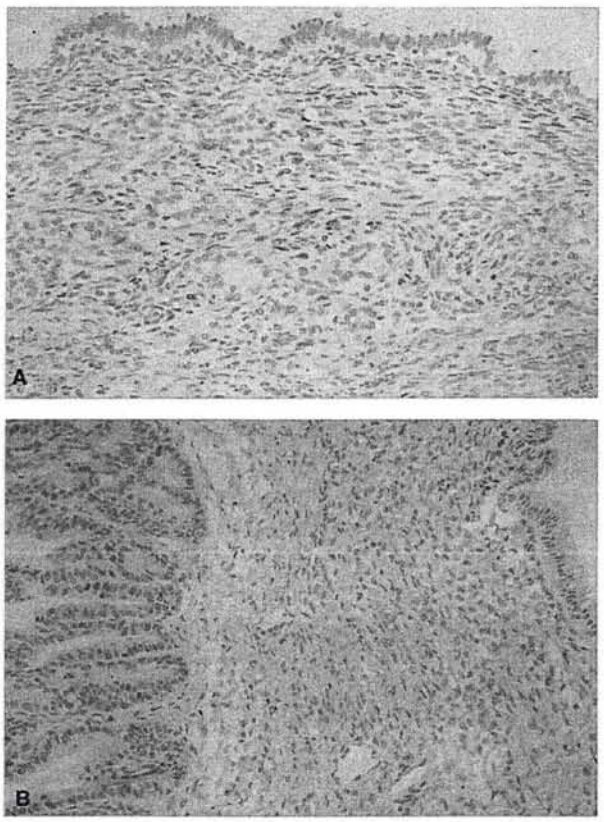

FIG. 6. (A) Nuclear immunoreactivity with the progesterone receptor antibody in the stromal nuclei, in contrast to the lack of reactivity of the overlying surface epithelium in a MCNWA. **(B)** p53 immunoreactivity is generally accentuated in the areas of atypia, while the benign-appearing epithelium does not demonstrate nuclear reactivity.

tween progesterone receptor reactivity were statistically significant ($p = 0.024$), correlating to a worse outcome with lesser or no immunoreactivity, irrespective of the tumor category (Table 8).

Proliferation markers were variably positive in the cases tested. Proliferating cell nuclear antigen, which seems to be localized to sites of DNA synthesis and is a cell cycle–regulated antigen,[38] was diffusely and strongly reactive in both the epithelial and the stromal cell nuclei in all cases tested, making this marker not useful in further assessing the nature of the tumors. Ki67 monoclonal antibodies, specifically MIB 1, react with antigens expressed in all active parts of the cell cycle.[38] The expression of Ki67 was determined as a percentage of positively reacting nuclei. Less than 10% of the cells were reactive in 50% of the MCNWA and 28% of the MCNA cases. In contrast, more than 50% of the cells were reactive in a greater number of MCNA (35%) cases than MCNWA (4%) cases. This same general staining pattern of Ki67 was replicated with the p53 immunoreaction (Table 7). The stronger the reactivity with p53, the higher the likelihood for a worse prognosis ($p = 0.041$) (Fig. 6B) (Table 8).

K-ras-2 Oncogene Determination

Not a single case of the tumors tested (25 MCNWA and 27 MCNA) demonstrated a K-ras-2 oncogene mutation. Therefore, all were wild type in the K-ras-2 oncogene.

DNA Content by Flow Cytometry

Twenty-six cases were analyzed by flow cytometry, as there was limited material available that satisfied the criteria for inclusion outlined in Materials and Methods. Twenty-three of the 26 cases analyzed were diploid, including 11 MCNWA and 12 MCNA. All the patients with diploid tumors were alive or had died without recurrence, between 2 and 17 years after presentation. Only 3 of the 26 cases analyzed were aneuploid, all occurring in MCNA. Two of these patients had died of disease 1 and 6 years, respectively, after initial diagnosis, while the third patient was alive at last follow-up without evidence of disease 12 years after initial presentation for treatment.

TABLE 8. *Potential prognostic factors for MCLGMP*

Factor evaluated	Worse prognosis
Aneuploid tumor	$p = 0.006$
Decreased/no progesterone immunoreactivity in stromal cells	$p = 0.024$
Tumor size (if greater than 15.0 cm)	$p = 0.04$
p53 (increased intensity and percent of cells immunoreactive)	$p = 0.041$
B72.3 (increased frequency of reactivity)	$p = 0.631$*
Ki67 (increased frequency and intensity of reactivity)	$p = 0.854$*

* Not statistically significant

DISCUSSION

In the years since the seminal paper on MCNs of the pancreas by Compagno and Oertel,[21] a myriad of articles on the topic have been published. These articles include new and different classifications, subclassification attempts, and the inclusion of new entities with confusingly similar sounding names.[2,9,10,22,36,46,53,54,64,70–72,74,84–86,90,92,104,105] Additionally, various clinical and radiologic findings, histochemical mucin studies, cytologic analyses, immunophenotypic expression analyses, tumor proliferation marker studies, ultrastructural examinations, and DNA ploidy analyses have been applied to the ever-expanding category of MCNs.[1,2,4,9,13,15,18–20,25,26,30–32,37,41,46,48,50,52–56,61,65,68,70,71,73,74,78,80,83,84,87,88,94,98,100,102–104,107,108] Unfortunately, the term *mucinous cystic neoplasm* has been diluted to include tumors that do not meet the definitions established earlier[4,5,21,32,43,44,61,75,95,96] or those of the World Health Organization.[59]

In general, the group of tumors encompassed by the term *MCN* are uncommon tumors, composing about 5% of our consultative cases of primary pancreatic tumors, falling at a point midway between the incidence reported in the literature (1–13%).[11,22,23,43–45,95] Mucinous cystic neoplasms occur predominantly in middle-aged women. Although all the patients in our study were women, we hasten to add that we do not believe this tumor is exclusive to women. However, the overwhelming majority of cases occur in women.[1,4,5,8,10,11,13,15,17,20,21,24,25,31–33,41,43–45,57,61,69,75,79,87,94–96,102]

The average age of 44.5 years when a patient presents for treatment is within the averages of other reports.[1,4,5,8,10,11,15,20,21,24–26,31–33,36,41,43–45,57,61,73,79,94–96,102] However, there is no statistically significant difference between the average ages of the patients with MCNWA and MCNA (Table 2), which does not match the findings published so far.[4,15,32,57] This finding supports our proposal that all these neoplasms are malignant from the beginning but display variable histologic characteristics at different times and in different patients. Many of our patients had a long history ($\leq$34 years) of episodic and intermittent symptoms before undergoing resection (Table 3). Furthermore, 18 patients were initially treated with a drainage procedure but continued to have symptoms referable to the mass, and eventually 13 of these patients demonstrated MCNA.

Our patients had a variety of other diseases (gallbladder disease [12.3%], diabetes mellitus [3.8%]), but we do not believe these associated findings form a useful pat-

tern of association with MCNs as a group. Patients in whom diabetes mellitus developed postoperatively were not included in this accounting. Only 6.9% of patients were considered to abuse alcohol or tobacco products. There was no statistically significant association with outcome ($p = 0.73$), and the percentage is insufficiently high to warrant a specific etiologic association. Our findings reflect the results of other authors.[4,5,8,13,15,20,21,24,25,32,36,43–45,48,57,63,65,74,79,82,86,87,95–97,102,107,108]

In both groups of patients, the radiographic appearances of the tumors were almost identical. The tumors usually appeared as multilocular, encapsulated, cystic masses in the tail of the pancreas, often with tumor excrescences within the lumen of the cysts. Although obliteration of the fat planes or destruction of the normal organ contours suggested a malignant tumor, this finding was not very specific, as many tumors that appeared radiographically to be benign tumors were in fact malignant on histologic examination.[5,15,20,25,30,31,37,45,48,50,52,55,62,65,68,79,82,95,96,100]

The two categories of MCNs we tried to create artificially had an almost identical average size (10.6 cm) (Table 5). Other authors have suggested a difference in size, but their tumor categories are not well defined.[5,15,79,87,90,96,102] Furthermore, the larger the tumor size (irrespective of which type), the more likely the patient is to have a worse prognosis, when >15 cm is used as the cutoff point ($p = 0.04$) (Table 8). This finding lends additional support to our theory that all of the tumors are low-grade malignancies from the start. The two groups also demonstrated a similar anatomic location (tail or body and tail of the pancreas). The only exception were the three patients with jaundice, whose tumors occurred in the head and were all MCNA. Given the overwhelming number of tumors that occur in the tail, a great deal of circumspection must be applied to those in the head of the pancreas. Thorough examination to rule out another type of tumor is mandatory. Communication with the main pancreatic duct is not usually identified in MCNs but may be observed in other types of pancreatic neoplasms.[2,10,20,32,53,54,72,74,84]

Coexistence of epithelium both with and without atypia within the same neoplasm, and frequently in an abrupt juxtaposition, suggests that the tumor may manifest different cytomorphologic characteristics at different stages of development, but probably represents a low-grade carcinoma from the outset of development. The finding of epithelium without atypia in metastatic foci certainly lends significant support to the theory the tumors may be malignant from the outset.[8] Other authors have suggested a degeneration or dedifferentiation of epithelium without atypia to epithelium with atypia, associated with malignancy.[1,4,5,8,10,15,17,21,22,24,25,32,43–45,51,63,68,73,75,79,86,95–97,102,104,105] These issues are not easily resolved, as frequently the focus of obvious carcinoma is isolated and/or small, and the only way to accurately determine the true nature of the neoplasm hinges on the number of blocks submitted or sections examined. When the tumors are large, have macroscopically visible papillations in the cysts, or demonstrate atypical epithelial features, additional sections should probably be submitted, although there may be little change in the clinical outcome of the patient based on the documentation of carcinoma. While complete sampling of the tumor is ideal, it may be difficult in routine practice (especially with large tumors). As identified in our study, there were on average more blocks embedded when the cases ultimately demonstrated areas of atypia (Table 5). Of interest—and arguably inadequately sampled—was one patient's tumor from which we did not have an adequate number of sections (only 4 sections in a 13-cm tumor) in the MCNNWA category, who died of the disease. In addition, there was no statistically significant difference in outcome according to cellular atypia ($p = 0.294$), architectural complexity ($p = 0.36$), or tumor invasion ($p = 0.201$).

As the epithelium becomes more atypical, the character of the mucin production changes from sulphated to neutral or sialated mucin, with an increase in the number of goblet cells. These reactions confirm the theories proposed by others,[5,19,39,43,49,60,80,83,101–103] in which the degree of sialomucin increases as the epithelium becomes more atypical, relative to specific grading protocols.[5,13,19,49,101,103] B72.3 (TAG-72), a glycoprotein, was demonstrated in a greater percentage of cells in MCNA (47.7%) than in MCNWA (4.2%), supporting the above theory, but the difference did not reach statistical significance in comparison with patient outcome. We did not identify a change in the mucin character of the normal or uninvolved ducts in the surrounding pancreatic parenchyma. This finding supports a similar finding by other authors for MCNs as well as other pancreatic tumor types.[60,80,101]

Although cyst fluid CEA, CA19-9, or enzyme levels were not specifically available in this series, review of the literature has shown that an increase in peripheral blood serum or cyst fluid levels of CA19-9, TAG-72, or CEA corresponds with pancreatic neoplasms, with higher results found in carcinomas,[7,27] although the results are not specific for malignancy.

We were not able to duplicate the findings of other authors with regard to the localization of CA19-9, CEA, and DUPAN-2.[39,41,49,73,91,93,102] Pancreatic cancers usually demonstrate cytoplasmic and stromal reactivity rather than apical or luminal reactivity. We did not identify stromal reactivity in our cases. The epithelial cell staining within a case spanned the spectrum from apical membrane to basolateral plasma membrane and cytoplasmic staining. Because of this variability, we did not

apply any quantitative classification scheme to the immunohistochemical localization.[39,73] There was no difference in reactivity between MCNWA and MCNA ($p = 0.615$), although invasive MCNA did demonstrate a more frequent loss of polar reactivity. Whereas nearly all tumors in both categories reacted with keratin and the various tumor-associated antigens, there was no pattern to the reactivity, nor did the reactivity demonstrate the reactive patterns of other pancreatic adenocarcinomas.[93] The immunoreaction for CA19-9 and DUPAN-2 was more intense and of superior quality than that of CEA, making interpretation of positive immunoreactivity easier for the former antibodies. The inconclusiveness of our study relates to the remarkable immunoreaction heterogeneity within a single case. In a single case there may have been luminal or cytoplasmic accentuation, but this was variable from cell to cell and from cystic space to cystic space, whereas another case with obviously malignant foci would not demonstrate the expected immunopattern. Therefore, although in theory and perhaps in aggregate the changes in immunoreactivity may be useful, when applied to an individual case the usefulness is not significant or helpful.

The original articles make reference to the subepithelial ovarian-like stroma,[5,21,32,43,63,75,82] but because all the cases in this study demonstrated this characteristic ovarian-like stroma, we believe it should be included in the diagnostic criteria for MCNs. Many published reports do not identify the stroma at all, either because they are clinical studies only, or because the tumor type is incorrect. The stromal component is usually not identified by fine needle aspiration,[18,26,37,50,56] limiting the accurate classification of MCNs. The spindled stroma is similar to the stroma found in MCNs of the ovary and biliary tree,[16,43,51,64,98] although the stroma is not required or identified in all of the biliary tumors.[16] One of our cases had a sarcomatous stroma, demonstrating nuclear pleomorphism and atypical mitotic figures. This finding has been documented in other MCNAs.[12,99,107] This sarcomatous transformation lends support to the idea the stroma is part of the tumor, not just a "bystander." The patient's outcome in our case was unaffected by the sarcomatous stroma, as she died of a widely metastatic oat cell carcinoma of the lung 4 years after the diagnosis of MCN.

The stroma was almost always reactive with vimentin, smooth muscle actin, and muscle-specific actin. These findings suggest a smooth muscle phenotype for this stroma, as suggested by other authors,[98] although others have suggested that the stroma is a metaplastic conversion of the epithelium.[107]

The stronger nuclear reactivity of the stromal component for progesterone in MCNWA than in MCNA may further support the theory that the stromal component is part of the neoplastic proliferation, not just a reactive or metaplastic phenomenon. Moreover, there seems to be a worse prognosis for patients when there is no progesterone receptor immunoreaction ($p = 0.024$) (Table 8). The estrogen receptor analysis did not demonstrate nearly as remarkable reactivity, and there was no significant decrease between MCNWA (26%) and MCNA (21%) ($p = 0.85$). None of the epithelial cells demonstrated estrogen or progesterone reactivity, which supports the findings in the literature.[58] The stroma of the fetal pancreas expresses estrogen receptors, which may account for reactivity in the stromal cells,[35] but it may also be a secondary phenomenon. Because all our patients were women, we cannot comment about the association of hormone receptor status with tumor progression or patient outcome, nor about whether these hormone receptors are present in men with this same tumor type.[98] However, these findings strongly suggest a relationship to hormonal function, at least in women. Perhaps the hormonally responsive stroma elicits a negative influence on epithelial tumor progression,[89] resulting in the significantly better prognosis for this tumor type than for other pancreatic neoplasms. Our statistically significant ($p = 0.024$) finding of a correlation between a decrease in progesterone receptor protein reactivity with a worse prognosis, may support this hypothesis (Table 8).

None of our tumors demonstrated a mutation in the K-ras oncogene. This is in sharp contrast to other tumors of the pancreas, especially those of ductal origin, which demonstrate a high mutation rate in K-ras-2 codon. Other authors[29,46,78,84,104] have demonstrated mutations in K-ras in mucin-producing tumors of the pancreas, while also demonstrating variable p53 overexpression (tumor suppressor gene product), when immunohistochemical techniques are applied (usually considered to suggest mutated p53). However, we demonstrated p53 overexpression in 41% of our cases, both with and without atypia. As the overall percentage of positive cells for p53 overexpression increased (in association with greater atypia [MCNWA = 24% vs. MCNA = 51%]), there was a statistically significant association with a worse patient outcome ($p = 0.041$) (Table 8). This finding may suggest that p53 mutations may be necessary for the development of carcinoma, with or without K-*ras* mutation.[66] Nevertheless, K-ras mutations have been identified in benign-appearing papillary-mucinous tumors, suggesting that the mutation may be an early event in tumorigenesis.[78] At the very least, it appears that abnormalities in p53 are unrelated to K-ras mutations. Furthermore, because of the distinct differences between our cases and those of the literature, it is suggested that multiple genetic alterations are responsible for tumorigenesis, expressing phenotypic heterogeneity.[46,78,84,104] The lack of oncogene mutation limits the application of K-ras-2 oncogene analysis in any attempt to separate MCNs into distinct categories (benign, borderline, or malig-

nant). The complete absence of oncogene mutation in this particular locus supports the separation of this type of tumor from ductal adenocarcinoma, which demonstrate a mutation in this oncogene with great frequency[29,46] while also separating this tumor from a more recently described ductectatic-type neoplasm.[104]

Ki67, PCNA, and B72.3 did not yield any statistically significant differences in outcome between the tumor groups assessed ($p = 0.854$, 0.499, 0.631, respectively) (Table 8).

The use of DNA flow cytometric evaluation of MCNs does yield a statistically significant difference when outcome is evaluated. The literature both supports[15,70,94] and argues against[15,88] our findings. If the tumor was diploid, the patient generally had an excellent prognosis, whereas a patient with an aneuploid tumor tended to have a worse prognosis ($p = 0.006$) (Table 8). However, there was no distinction between our artificial categories. Therefore, if the tumor is aneuploid, it may portend a worse clinical outcome. Additional ploidy studies on tumor cases with a poor outcome need to be completed to validate this result.

Cysts of the pancreas have been divided into developmental, traumatic, retention, and neoplastic cysts as well as those associated with parasites.[67,81] Obviously, the inclusion of MCNs in the neoplastic category is not met with debate. Many theories have been proposed regarding the histogenesis or differentiation of MCNs, including origin from misplaced urogenital fold epithelium, displaced alimentary-canal primordia, embryonic rests, acinar cells, ductal epithelium, and metaplastic processes.[4,13,33,43,61,69,75,83,98,106] In the truest sense of the word, neoplastic populations are capable of multidirectional differentiation, regardless of their presumed histogenesis.[34] This having been said, the presence of goblet cells and endocrine cells suggests an intestinal metaplasia/differentiation, as proposed by other authors,[3–5,43,61,83,102] further supported by ultrastructural studies.[4,107] This hypothesis could not be proved because of the marked variability in our case results.

The differential diagnosis of cystic lesions in the pancreas includes a wide variety of lesions (Table 9). Although radiographic imaging studies may help to distinguish between pseudocysts, microcystic adenomas, neuroendocrine tumors, solid and cystic epithelial neoplasms, and mucinous cystic neoplasms as general categories,[9,20,25,30,31,52,55,65,68,74,82,100] surgical excision is required for accurate diagnosis. Even though fine needle aspiration can identify the epithelial component of a tumor and accurately distinguish it from a pseudocyst,[18,26,37,50,52,56] the limited fraction of epithelium sampled can result in an incorrect interpretation, besides the complete lack of the stromal component in the aspiration material. Biopsy alone is never adequate or sufficient therapy, and complete surgical excision is therefore recommended for all cystic tumors of the pancreas.[4,5,8,18,20,21,24,25,30,32,44,45,48,50,55,57,68,74,79,82,86,90,92,95,97,100,106] Spillage of the contents of the cyst during surgery or a biopsy may lead to seeding of the abdominal cavity; therefore, caution must be exercised during the removal of these tumors.

Most of our patients' tumors occurred within the tail or the body and tail of the pancreas (Table 5), permitting a relatively easy complete surgical excision, especially in comparison with the usual pancreatic adenocarcinomas in the head of the pancreas. Our findings of an excellent prognosis associated with complete surgical excision confirm the findings of others with fewer cases than in our series.[5,15,24,32,43,45,62,79,82,86,87,90] However, as noted in other reported cases[5,20,24,36,43–45,57,62,63,75,79,82,95,97,106] and in several of our cases, marsupialization or some other drainage procedure is not a reasonable alternative. In patients who have had a drainage procedure, the tumor persists or "recurs," frequently demonstrating a greater degree of cytologic atypia. Because of the confusion in terminology in the literature, the poor prognosis reported by some authors may be due to incorrect classification of the tumor type.[8,17,20,36,44,62,63,74,79,82,87,90,92,95,97,106] Our patients treated initially by drainage and later by complete excision, as well as patients treated initially with complete surgical excision, both have a good prognosis, but the former patients had to undergo a second surgical procedure. If these patients had received a complete surgical excision initially, this additional surgery might have been averted. In summary, both MCNWA and MCNA had excellent survival statistics, without a difference between the groups, warranting the use of MCLGMP for all these tumors.

In light of the literature[5,8,15,17,20,24,32,36,43–45,48,57,62,68,75,79,82,86,92,95–97,106] and our own experience, we believe the recurrence of tumors that lack atypia and the immediate proximity of benign epithelium to markedly atypical epithelium lends support to the hypothesis that these tumors are all of low-grade malignant potential from the onset and, with the progression of time (indolent growth), display the more typical and histologically recognizable malignant features. Without close examination of the entire specimen and examination of many sections from the specimen, the true nature of the tumor

TABLE 9. *Differential diagnosis for epithelial pancreatic cystic tumors*

Pancreatic pseudocyst
Duct ectasia in pancreatitis
Mucin producing adenocarcinoma
Papillary intraductal tumors
Papillary solid and cystic epithelial neoplasm
Neuroendocrine tumors
Acinar cell cystadenocarcinoma

may be missed or understated, resulting in incomplete treatment or unnecessary surgery for persistent or recurrent disease. Therefore, on the basis of our results, we cannot support the use of the terms *cystadenoma* or *cystic neoplasm of indeterminate malignant potential.*

Therefore, we propose the use of the term *mucinous cystadenocarcinoma of low-grade malignant potential* for all the tumors in this group. None of the tumors within the MCN category should ever be regarded as truly benign, but instead as low-grade malignant tumors. Complete surgical excision of this group of pancreatic neoplasms usually results in an excellent prognosis (94% 5-year survival) without any additional therapy being indicated. Of course, clinical follow-up is suggested, often for a prolonged period, as the tumors are slow-growing and may recur after several years. □

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