Supplementary Methods

Diagnostic Criteria of Pancreatic Mucin-Producing Neoplasms

The following histologic diagnostic criteria were considered[5,6,11]: (1) MCNs: pancreatic MPNs characterized by an inner layer composed of tall mucin-producing cells surrounded by a dense ovarian-like stroma, without any macroscopic or microscopic communication with the MPD or its secondary branches; and (2) IPMNs: intraductal MPNs with tall, mucin-producing epithelium, with or without papillary projections, lacking the ovarian-like stroma. IPMNs were further classified as the following: (1) branch-duct type: when the tumor involved only branch ducts, with no macroscopic or microscopic involvement of the MPD; (2) main-duct type: when the tumor involved only the MPD; and (3) combined type: when the neoplasms involved macroscopically and/or microscopically both the MPD and its side branches.

Indeterminate mucinous lesions characterized by a mucin-producing epithelium with no ovarian-like stroma and no macroscopic or microscopic communication with the pancreatic ductal system were not included in the study.

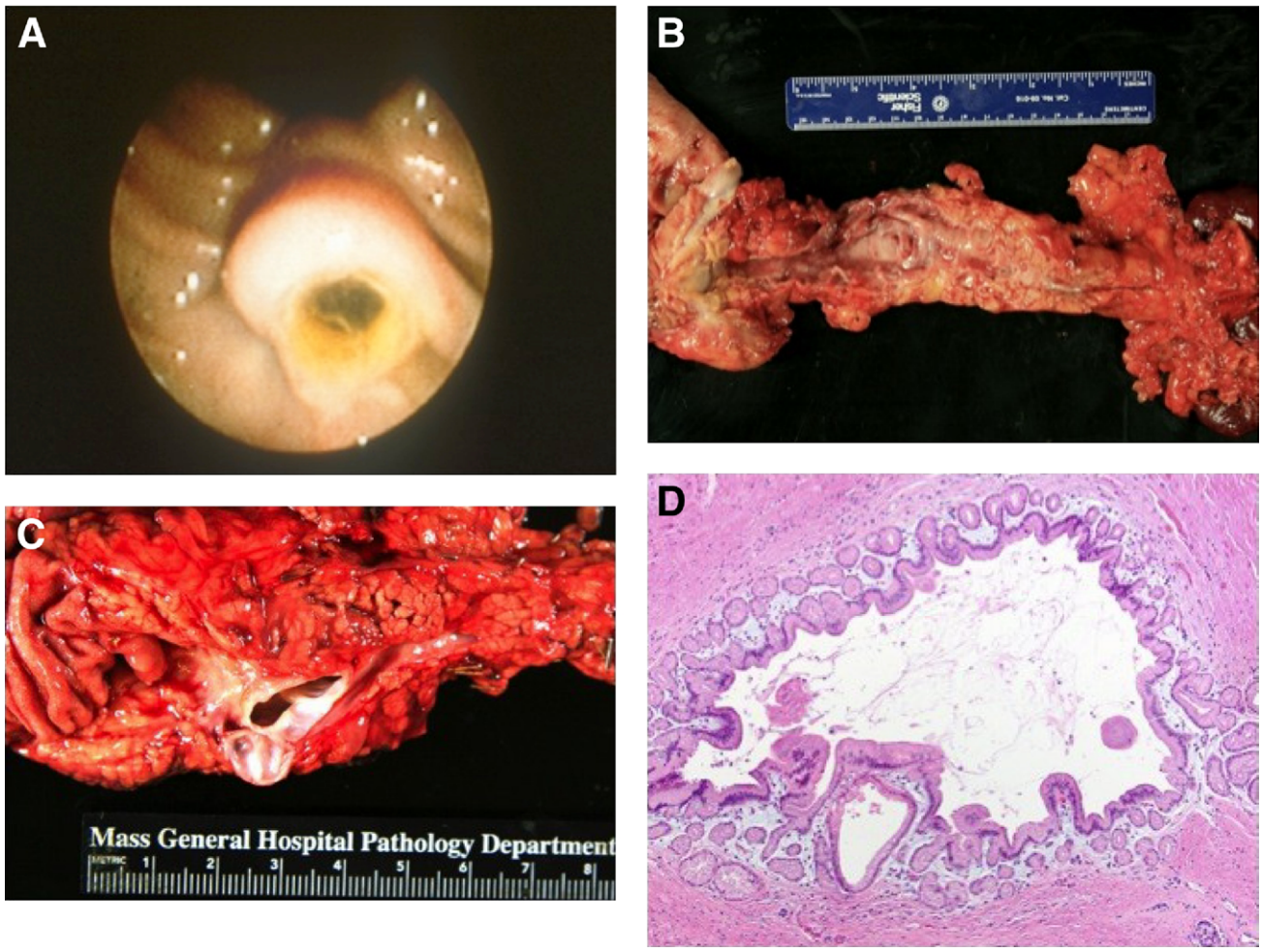
All MPNs were classified according to the World Health Organization[5,6] criteria as MCN/IPMN with mild dysplasia (adenoma), with moderate dysplasia (borderline neoplasm), with high-grade dysplasia (carcinoma in situ), or with invasive carcinoma.

Study Population

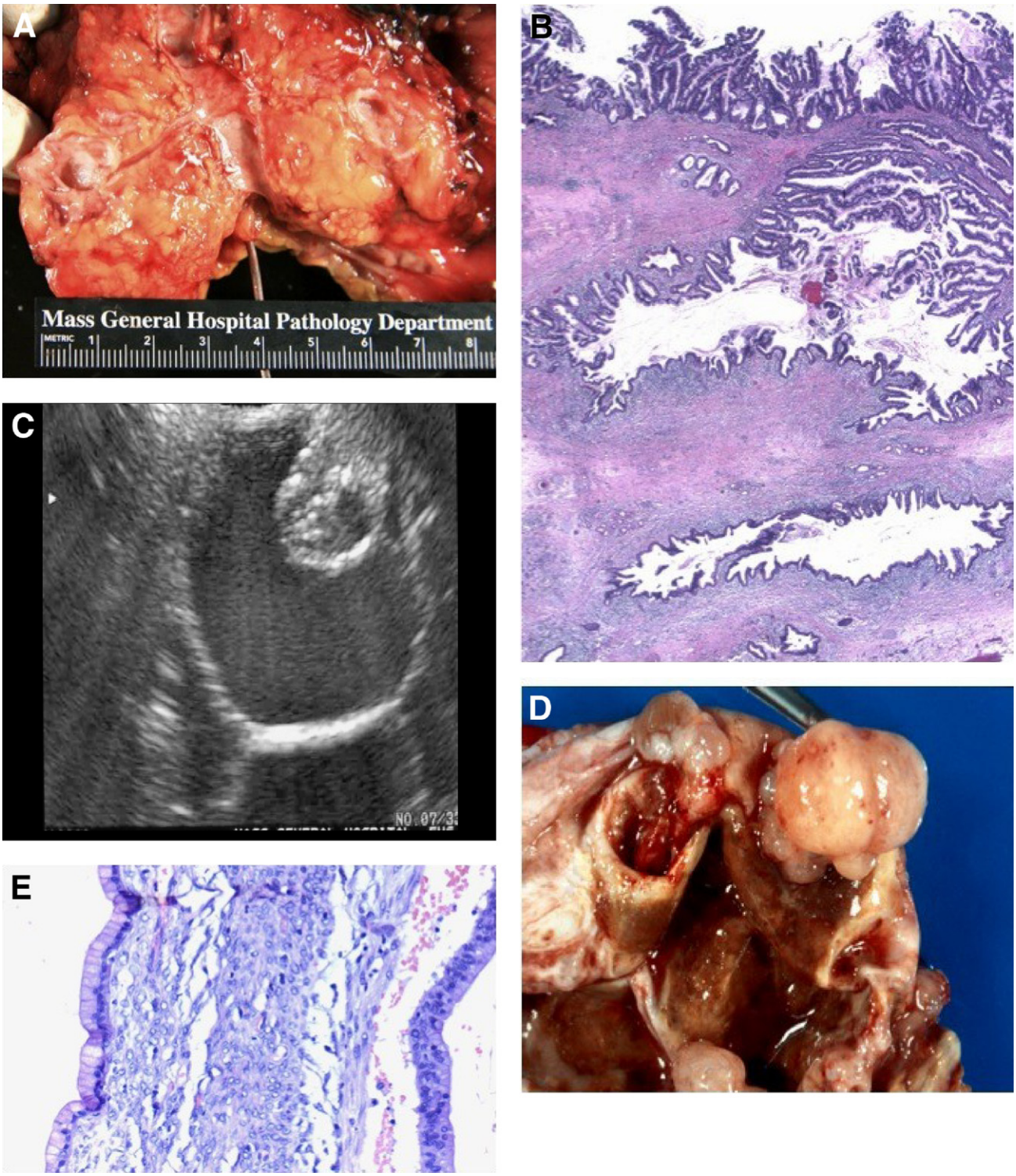
A family history of pancreatic cancer was defined as the presence of a first- or second-degree relative with a clinicopathologic history of pancreatic cancer. The presence of other malignant neoplasms was defined as the presence of previous, synchronous, or metachronous malignant tumors. The head of the pancreas and uncinate process were defined as proximal pancreas; neck-body and tail of the gland were defined as distal pancreas. The presence of different, topographically unrelated, neoplastic lesions within the gland was defined as multifocal, whereas continuous extension of the tumor along multiple segments of the gland was defined as diffuse.

The circumstances leading to the discovery of the neoplasms were categorized as follows: (1) incidental, when the neoplasm was found in an asymptomatic patient during the diagnostic work-up of an unrelated problem; (2) abdominal pain or "discomfort"; (3) other, including more specific clinical manifestations such as acute pancreatitis, new onset or worsening diabetes, weight loss, and jaundice.

After surgical resection, all patients had follow-up evaluations consisting of clinical examination, serologic assessment including tumor markers, and imaging. Imaging procedures included contrast-enhanced abdominal ultrasound, computed tomography, and magnetic resonance imaging. Patients with benign IPMNs/MCNs had yearly follow-up evaluation for at least 5 years, whereas those with invasive carcinoma were seen every 6 months for the first 2 years and yearly thereafter. Patients or their referring physicians were contacted at least yearly to determine the presence or absence of recurrence and survival.



Supplementary Figure 1. Examples of endoscopic and pathologic images of main-duct (*A, B*) and branch-duct IPMNs (*C, D*). (*A*) Endoscopic appearance of a "bulging" papilla in a main-duct IPMN. (*B*) Total pancreatectomy specimen, with a main-duct IPMN involving the entire gland. (*C*) Surgical specimen grossly showing a branch-duct IPMN, with its corresponding histopathology (*D*).

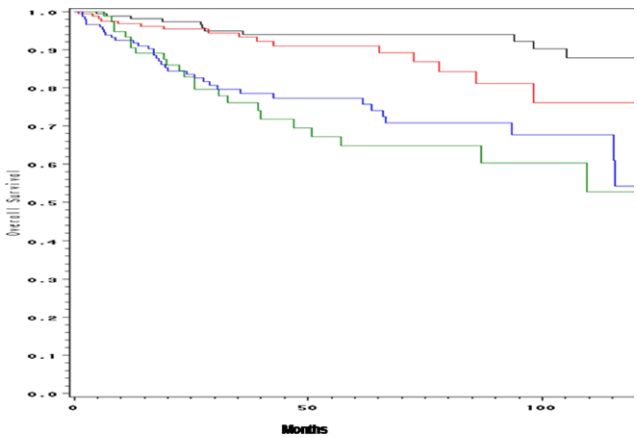


Supplementary Figure 2. Examples of endoscopic and pathologic images of combined IPMNs (*A, B*) and MCNs (*C–E*). (*A*) Surgical specimen showing a dilated main duct communicating with dilated branch-ducts. (*B*) Corresponding histopathology. (*C*) MCN features at endoscopic ultrasound, where a nodule and thick walls are clearly evident. (*D*) Surgical specimen of a left pancreatectomy performed for an MCN. (*E*) Histologic slide demonstrating the presence of ovarian-like stroma.

Supplementary Table 1. Other (Previous, Synchronous, Metachronous) Malignant Tumors in Patients With MCNs, Branch-Duct, Main-Duct, and Combined IPMNs

MCN, 15 patients (9%)	Branch-duct IPMNs, 32 patients (20%)	Main-duct IPMNs, 18 patients (22%)	Combined IPMNs, 29 patients (19.5%)
Breast carcinoma: 7	Breast carcinoma: 6	Breast carcinoma: 4	Breast carcinoma: 5
Breast carcinoma and RCC: 1	Prostate cancer: 6	Breast and ovarian cancer: 1	Prostate cancer: 5
Breast carcinoma and thyroid carcinoma: 2	Lung cancer: 4	Colonic carcinoma: 3	Colonic carcinoma: 4
Ovarian carcinoma: 1	NHL: 4	Lung cancer: 2	Lung cancer: 2
Cervical carcinoma: 2	Colonic carcinoma: 3	Prostate cancer: 2	Thyroid carcinoma: 2
CML: 1	Pancreatic ductal carcinoma: 2	Endometrioid carcinoma: 1	Pancreatic ductal carcinoma: 2
Carcinoma of the cheek: 1	Bladder cancer: 2	Gastric cancer: 1	Breast and pancreatic cancer: 1
	RCC: 1	RCC: 1	Endometrioid carcinoma: 1
	Endometrioid carcinoma: 1	Glioblastoma: 1	Ovarian and lung carcinoma: 1
	Ampullary cancer: 1	Thyroid carcinoma: 1	Larynx cancer: 1
	Carcinoma of the cheek: 1	Bladder cancer: 1	Bladder cancer: 1
	Gastric cancer: 1		Soft tissue sarcoma: 1
			Vaginal carcinoma: 1
			Carcinoma of the cheek: 1
			Pancreatic endocrine carcinoma: 1

RCC, renal cell carcinoma; CML, chronic myelogenous leukemia; NHL, non-Hodgkin's lymphoma.



Supplementary Figure 3. Overall 5-year survival (*OS*) for 557 patients with MPNs of the pancreas divided by histotype. OS was 94% for patients with MCNs (*black line*), 91% for those with branch-duct IPMNs (*red line*), 65% for patients with main-duct IPMNs (*green line*), and 77% for those with combined IPMNs (*blue line*).