INTRODUCTION

Pancreatic disorders represent some of the most common and feared conditions that affect the older adult population. The formulation of a management strategy for the patient with pancreatic disease requires the consideration of several issues unique to geriatrics. The ethical and philosophical issues that must be considered when confronted with malignancy also pose a challenge to healthcare providers (3). Recent innovations and management of these disorders can play an important role in improving the quality of life for those most at risk for poor outcomes (4). Evaluation and management of the older adult patient requires attention to subtle, atypical, and/or nonspecific symptoms as well as recognition of the importance of maintaining function and patience in both the interaction itself and the pace of progress (5).

Physicians must also be attentive to the need to prevent complications, especially during diagnostic and therapeutic procedures as well as when prescribing medications. The value of interventions should be determined by their effect on the patient’s independence and quality of life, and the endpoint is often improvement rather than cure (6). Thus, chronological age alone cannot justifiably be used to preclude a curative approach, especially in pancreatobiliary disease (3). Although the terms “elderly” and “older adult” are not officially defined in the scientific literature, the purpose of this article is to review pancreatic diseases with emphasis on disease and management in the older adult population, specifically those over 60–65 years of age.

PANCREATIC PHYSIOLOGY AND MORPHOLOGY IN AGING

In some but not all patients, the pancreas undergoes changes in structure and function with age. The first documented structural changes in the pancreas were noted to be duct proliferation, lobular degeneration, cavitation, and fatty replacement, and were interpreted as senile changes of the normal pancreas (7). Ductal epithelial hyperplasia and intralobular fibrosis may lead to irregularity (ectasia) and dilatation of the main pancreatic duct and secondary duct branches on endoscopic retrograde pancreatograms (8). The effect of age on pancreatic parenchyma and duct diameter is unclear, and as a result pancreatograms may be difficult to interpret in older patients (9). Additionally, the age-dependent development of fibrosis in the pancreas

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of persons who had no clinically apparent pancreatic disease and whose pancreas showed no macroscopic changes has also been documented (10).

The majority of physiological studies have consisted of relatively small sample sizes drawn from select populations (11). Most studies have not documented any decrease in pancreatic function with advancing age, although importantly arteriosclerosis may reduce pancreatic blood flow (12,13). Others have noted up to 40% reductions in enzyme and bicarbonate secretion in elderly patients compared with younger controls. Controversy continues to surround the concept that serum pancreatic enzyme levels may be elevated in the elderly patient without pancreatic disease (8). These findings do not appear to be clinically significant. Generally speaking, elderly patients are characterized by abated functional reserves of variable degree in the different organ systems (13). Whether or not clinical pancreatic insufficiency occurs as a sole consequence of aging is unknown (12).

ACUTE PANCREATITIS

In the United States, 33% of individuals who develop acute pancreatitis are older than 65-years of age (13). Older individuals have a higher incidence of gallstone pancreatitis, responsible for up to 55% of all cases (Table 1) (14). In patients over 85-years old the incidence increases up to 75%. (13,15). Although pancreatic carcinoma is a rare cause of acute pancreatitis (approximately 3% of cases), pancreatic carcinoma is much more common in elderly patients (16).

Because of the incidence of polypharmacy in the geriatric population, drug-induced pancreatitis should always be a consideration as to the etiology of pancreatitis (Table 2). Forty-four percent of men and 57% of women 65-years of age or older use five or more medications per week, whereas 12% of both men and women of this age group use ten or more medications per week (17). Class I medications (medications implicated in greater than twenty reported cases of acute pancreatitis with at least one documented case following re-exposure) relevant to the elderly population include: Valproic acid, opiates, tetracycline, cytarabine, steroids, furosemide, and sulindac. Class II medications (medications implicated in more than ten cases of acute pancreatitis) include: Octreotide, carbamazepine, acetaminophen, phenformin, enalapril and hydrochlorothiazide (18).

As clinicians, we must keep in mind that despite innumerable case reports, the validity and severity of drugs causing pancreatitis have been questioned (19). This is mostly because of the considerable underreporting of adverse drug reactions, particularly for drug-induced pancreatitis (18).

Ischemia of the pancreas is much more important in the development of acute pancreatitis in elderly

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**Table 1**

Causes of Acute Pancreatitis in the Elderly

- Gallstones
- Malignancy
- Medications
- Post-operative
- Ischemia
- Endocrine (Hypercalcemia, Hyperparathyroidism, Uremia)
- Post-ERCP
- Obstruction

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**Table 2**

Drug-Induced Pancreatitis

<table>
<thead>
<tr>
<th>Class I Medications</th>
<th>Class II Medications</th>
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<tbody>
<tr>
<td>Didanosine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Octreotide</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Pentavalent antimonials</td>
<td>Acetaminophen</td>
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<tr>
<td>Pentamidine</td>
<td>Phenformin</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Interferon alfa-2b</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Enalapril</td>
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<tr>
<td>Estrogens</td>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td>Opiates</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Erythromycin</td>
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<tr>
<td>Cytarabine</td>
<td>Cyclopenthiazide</td>
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<tr>
<td>Steroids</td>
<td>Sulfamethoxazole/Trimethoprim</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Furosemide</td>
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<td>Furosemide</td>
<td>Sulindac</td>
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Pancreatic Diseases in the Elderly

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patients than it is in younger individuals, accounting for 27% of 300 cases that demonstrated pancreatic injury following cardiac bypass surgery (20). The incidence of idiopathic acute pancreatitis increases with age as well, accounting for up to 30% of cases in patients over 60-years of age (15,21). It is presumed that many of these episodes are in fact caused by biliary microlithiasis (22). Alcohol-induced acute pancreatitis occurs in only a minority of patients above 60-years (13). Other rare causes of acute pancreatitis in the elderly include peri-operative administration of calcium chloride, Ascaris lumbricoides, and hyperlipidemia (13,23,24).

The clinical presentation of acute pancreatitis in older individuals may be atypical, and in some instances may not even be suspected (14). In two studies, in which most of the patients were older than 60-years of age, the diagnosis of acute pancreatitis was established for the first time at autopsy, and the diagnosis was not considered among 30% to 40% of patients before death (25,26). Of particular note was the absence of typical abdominal pain in 90% of these patients. In many patients, the clinical presentation was dominated by shock, organ failure, hyperglycemia and hypothermia. Fatal acute pancreatitis can occur in 28% of patients above age 60, compared with only 9% in patients below this age (27). Many other diseases can also cause elevations in amylase and lipase including: Acute cholecystitis, biliary obstruction, intestinal perforation, intestinal ischemia or infarction, and intestinal obstruction. Signs, symptoms and laboratory abnormalities (e.g., elevations in amylase and lipase) are neither entirely sensitive nor specific (28).

In older patients with organ failure of unclear origin, acute pancreatitis should be considered and searched for. Measurement of serum amylase and lipase should be supplemented by a contrast-enhanced computed tomography (CT) scan. Although most patients develop a mild, uncomplicated self-limiting form of acute pancreatitis, vigilance should be maintained for those with more serious disease, as they will exhibit more serious systemic manifestations of the disease (13). A dynamic, hypermetabolic state very similar to the sepsis syndrome, or systemic inflammatory response syndrome (SIRS), may predominate (8).

Elderly patients with acute pancreatitis and co-morbidities should be treated in a monitored environment or an intensive care unit (Table 3), depending on early stratification of the severity of their presentation using the Acute Physiology and Chronic Health Evaluation (APACHE II) and Ranson’s criteria (29).

Special emphasis should be given to fluid replacement when treating acute pancreatitis. Of note, elderly patients generally have more difficulty tolerating severe fluid imbalance, and therefore this must be taken into consideration during therapy (13). The indications for emergent ERCP with sphincterotomy is a topic of debate, but those with impending ascending cholangitis evidenced by obstructive jaundice, fever, and leukocytosis require ERCP. Additionally, patients with severe biliary pancreatitis who do not improve clinically should be considered for early ERCP (<72 hours) (30).

### CHRONIC PANCREATITIS

The age of onset of chronic pancreatitis related to alcohol consumption ranges from the late 30s to late 40s. As such, it is believed that most patients with alcoholic pancreatitis die early in life (13,31). Although the majority of cases of chronic pancreatitis are related to the consumption of alcohol, responsible for up to 85% of the disease, idiopathic “late-onset” pancreatitis is a more relevant etiology of chronic pancreatitis in the elderly, originally described as “senile” chronic pan-

<table>
<thead>
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<th>Table 3</th>
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<tr>
<td><strong>Recommended treatment in elderly patients with acute pancreatitis</strong></td>
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<tr>
<td><strong>In all patients</strong></td>
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<tr>
<td>Early admission to monitored/intensive care unit</td>
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<tr>
<td>Monitoring of vital signs</td>
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<tr>
<td>Central venous catheter placement</td>
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<tr>
<td>Aggressive fluid replacement</td>
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<tr>
<td>Urine output monitoring</td>
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<tr>
<td>Analgesic therapy</td>
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<tr>
<td>Selective prophylactic antibiotic treatment</td>
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<tr>
<td>Initial bowel rest</td>
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<tr>
<td><strong>Facultative</strong></td>
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<tr>
<td>Gastric tube (feeding)</td>
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<td>Gastric prophylaxis</td>
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creatitis (32). Among elderly patients, pain related to idiopathic pancreatitis is not as severe as it may be in younger patients, and the course of illness seems to be less progressive.

Exocrine insufficiency and endocrine insufficiency develop much more slowly amongst older patients with idiopathic pancreatitis, and fewer patients require surgical interventions for complications. It has been reported that chronic pancreatitis is the second most common cause of steatorrhea in the elderly, although the relationship of idiopathic late-onset chronic pancreatitis to the normal age-related morphological and functional abnormalities of the exocrine pancreas has not been clearly established (13,33).

Obstructive chronic pancreatitis is also a form of pancreatitis occurring more frequently in the elderly age group, usually caused by an ampullary tumor or adenocarcinoma of the pancreas (34). Obstructive chronic pancreatitis differs histologically from both alcoholic and idiopathic chronic pancreatitis in that there is the absence of calcification and protein plugs. Unlike alcoholic or idiopathic pancreatitis, the main pancreatic duct is dilated in the majority of cases (14). Pancreatic stones have been noted within the pancreatic ducts of elderly individuals as well. The stones in these patients discovered at autopsy were associated with parenchymal atrophy and fibrosis above the calculi but were not associated with signs and symptoms during life, and their significance is unclear in their contribution to the development of chronic pancreatitis (35).

Lastly, prolonged use of medications known to cause acute drug-induced pancreatitis may cause chronic pancreatitis by causing repeated or subclinical episodes of acute pancreatitis; this remains to be established (18).

Therapeutic options for chronic pancreatitis in the elderly focus on removal of offending agents (i.e. medications) and management of the three main clinical symptoms: pain, exocrine insufficiency, and endocrine insufficiency (13). Treatment of chronic pain in the elderly should be of utmost importance so as to preserve the patient’s quality of life. For cases of severe pain, nerve blockades, drainage of a hypertensive pancreatic duct system, and even pancreatic resection surgery should not be withheld in the hope of remission of pain in the future (31). If exocrine pancreatic insufficiency occurs, enzyme supplementation is the therapy of choice. Although the administration of large amounts of enzymes has provided pain relief in some patients, the rationale for using enzymes to relieve pain in chronic pancreatitis has not been generally accepted among gastroenterologists or geriatricians (36). Diabetes may also be a manifestation of late state chronic pancreatitis in the elderly, and should be treated according to the glucose level (13). Since hypoglycemic episodes are frequent in diabetes secondary to chronic pancreatitis, extreme caution is needed and it is better to avoid too rigid a control.

**PANCREATIC MALIGNANCY**

By the year 2040, more than 22% of the population in our country will be older than 65-years of age (37). This segment of the population bears the greatest burden of cancer: 55% of all malignancies and 65% of all cancer deaths occur in the elderly (38). The risk of developing pancreatic cancer dramatically increases with age, with a median age of 72-years at the time of diagnosis (39). Approximately 168,000 individuals die annually from pancreatic cancer, which ranks this cancer type as the ninth most common cause of cancer death worldwide (40). The poor prognosis of this disease is reflected by the high mortality-incidence ratio of 0.98, as 85% of patients present with disseminated or locally advanced disease (41).

Although much has been learned about the sequence of molecular derangements culminating in the development of pancreatic carcinoma, these scientific advancements have not translated into improved screening or early disease detection (42,43). The most sensitive and specific pancreatic cancer marker, CA 19-9, is not sufficiently accurate to justify its use as a screening test. CA 19-9 has a reported sensitivity of 70%–90%, a specificity of 90%, a positive predictive value (PPV) of 69%, and a negative predictive value (NPV) of 90% (44–46). The utility of CA 19-9 is further complicated by the fact that up to 10% of the Caucasian population are Lewis Antigen negative (41). Although other tumor markers are available, they have many limitations and no single marker or combination of markers serve as the gold standard for the diagnosis of pancreatic carcinoma.

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Pancreatic Adenocarcinoma

Ductal adenocarcinomas, which are responsible for more than 90% of exocrine pancreatic tumors, are typically a disease of the elderly. Pancreatic adenocarcinoma is relatively asymptomatic during its early course, though early symptoms for pancreatic cancer have been reported (41). Pain is the presenting symptom in 31% to 79% of pancreatic cancer patients (41,47–50). The abdominal pain, usually insidious, originates in the epigastric region and radiates to the sides and/or back. The pain may be worse at night and in the post-prandial period. Other presentations can be new onset diabetes mellitus and acute pancreatitis (41). A combination of anorexia and/or early satiety and asthenia has been reported in 22.3% of cancer patients compared to 0.7% of controls. The only other significant difference (aside from pruritus) was a disgust of coffee, smoking, and wine (51).

About 70% of pancreatic ductal adenocarcinomas occur in the head of the pancreas and are therefore more likely to obstruct the biliary tree, especially if tumors are larger than 2 cm (47,49,52). Jaundice is the first manifestation of pancreatic cancer depending on the site of the tumor in up to 85% of patients in some series. Detection of pancreatic carcinoma is invariably based on imaging. Contrast-enhanced CT, ideally a dual-phase CT, is the preferred imaging method for detecting and staging pancreatic cancer in most institutions (53). Contrast-enhanced MRI has been shown to be at least equivalent or even superior to dual-phase CT for detecting pancreatic cancer (54–58). Diagnostic ERCP generally is reserved for those patients suspected of harboring a pancreatic malignancy with negative or indeterminate imaging studies or if a tissue diagnosis is desired prior to surgical resection (8). In the best of hands, ERCP has a sensitivity of 90% to 97% and specificity of 81% to 90% with respect to the diagnosis of pancreatic cancer (59). Certainly, now with the advent of endosonography, this option usually precedes diagnostic ERCP for evaluation and tissue diagnosis.

The management of pancreatic adenocarcinoma depends on accurate staging. Because non-surgical treatments for pancreatic cancer have poor outcomes, appropriate staging and categorization of patients as “resectable” or “non-resectable” remains essential to allow the hope for a surgical cure while avoiding unnecessary and futile surgical resection. The high-resolution imaging capability of EUS allows excellent visualization of the primary pancreatic tumor as well as involvement of adjacent structures, including the bile duct, ampulla, and duodenum. More importantly, EUS allows imaging of adjacent vascular structures which often predicts resectability (60). EUS with histological correlates suggest that the sensitivity and specificity of vascular invasion of the vessels of the portal confluence are 66% and 59%, respectively, with accuracies reported to be between 78% and 95% without histology (61–63). In addition to cross-sectional imaging studies and EUS, further staging information can be obtained by laparoscopy and laparoscopic ultrasound if required (41).

The treatment plan for every elderly patient should take into account the patient’s general medical condition (64). The only effective curative approach for pancreatic cancer is resection (64). Resectable pancreatic cancer is defined as a pancreatic tumor without evidence of involvement of the superior mesenteric artery or celiac axis, a patent superior mesenteric-portal venous confluence, and no evidence of distant metastases (65). The predominant location of resectable tumors is usually at the head of the pancreas or peri-ampullary region. For these cases, standard pancreatoduodenectomies are the operations of choice, irrespective of the age of the patient (66).

In a study by Wagner, et al, there was no difference between two treatment groups (>70 years of age and <70 years of age) who underwent pancreatoduodenectomy in terms of their co-morbidities, use of pre-operative antibacterials, intra-operative blood loss, or length of hospital stay. Additionally, no significant difference in the rate of complications was detected and no death occurred in the older age group. In another similar study, the two comparable groups (>80 years of age and <80 years of age) who also underwent pancreatoduodenectomy were examined. Patients >80 years of age had a longer postoperative length of stay and a higher complication rate compared with younger patients but the difference in peri-operative mortality between the older and younger group was not significant. Regardless of these results, patients should be assessed individually for their fitness for surgery (64,67,68).

Radiation and chemotherapy are often administered to post-surgical patients in an attempt to prolong survival. Fluorouracil and fluorouracil-based combina-
tion regimens have been shown to be superior to observation alone or no treatment in adjuvant treatment trials (69). The ESPAC (European Study Group for Pancreatic Cancer)-1 trial of adjuvant therapy for pancreatic cancer also demonstrated a useful role for chemotherapy with fluorouracil (70). This treatment regimen was also shown to be cost-effective, and compared well with other accepted interventions in oncology (71). Because chemotherapy is never curative for metastatic disease, the palliative benefits of such therapy must be carefully weighed against its toxic effects (64). Further studies need to be conducted to define both the benefits and tolerability of radiation and chemotherapy in elderly patients with pancreatic cancer.

As many patients present with or develop biliary obstruction secondary to tumor, patients often require decompression of the biliary tree, which can be achieved through endoscopic stenting or operative bypass (41). When performed by experienced gastroenterologists, endoscopic retrograde cholangiopancreatography (ERCP) is safe in patients 90-years of age and older with few major adverse affects. Diagnostic and therapeutic outcomes are similar to those reported for younger patients (72). For the purpose of palliation, the efficacy of covered expandable metal stents for the treatment of neoplastic distal biliary obstruction has been analyzed. Isayama, et al concluded that when palliation is the goal, covered metallic stents successfully prevent tumor in-growth and were significantly superior to uncovered stents in the treatment of patients with distal malignant biliary obstruction (73,74). All patients with reasonable life expectancy should be offered these various options for palliative therapy (64).

Other Pancreatic Neoplasms: Benign and Malignant
We do acknowledge that a variety of malignancies, both primary and metastatic, may affect the pancreas (8). There are several other types of pancreatic neoplasms aside from adenocarcinoma that are rare but do merit mentioning as they tend to affect the older patient population. Those conditions affecting the elderly patient population include serous cystadenoma, mucinous cystic neoplasms (mucinous cystadenomas and mucinous cystadenocarcinomas), cystic endocrine neoplasms, acinar-cell cystadenocarcinomas, and intraductal papillary mucinous neoplasms (IPMNs).

Cystic Neoplasms of the Pancreas
Cystic neoplasms of the pancreas represent less than 10% of pancreatic neoplasms. These lesions are often asymptomatic, and are often serendipitously detected by imaging performed for the evaluation of other conditions. These cystic tumors encompass a spectrum of benign, malignant, and borderline neoplasms that are either primarily cystic or result from cystic degeneration of solid tumors.

Serous cystadenomas occur more commonly in females, who are in the seventh decade of life, and consist of almost 40% of all cystic neoplasms of the pancreas. The presence of a central scar on a CT or MRI study is a highly diagnostic feature found in approximately 20% of serous cystadenomas. Usually small and microcystic, they may grow to be quite large. They have an extremely low potential for malignant disease, and the development of serous cystadenocarcinoma is extremely rare (75). Very little information is available on the growth rate of serous cystadenomas and on the likelihood of these lesions’ producing symptoms (76). The improvement in the morbidity and mortality associated with surgery has expanded the acceptability of surgery for the preemptive treatment of benign and premalignant cystic lesions, such as these serous cystadenomas (77). Once a diagnosis has been confirmed, it is reasonable to follow the elderly patient clinically, as these lesions are most often a benign entity.

Although mucinous cystic neoplasms (MCNs) also occur more commonly in females in their fifth decade, they are often discovered later in life. They consist of approximately one-third of all cystic neoplasms of the pancreas. IPMNs, which will be discussed in the next section, and mucinous cystic neoplasms, have almost identical histological features except that mucinous cystic neoplasms have a dense mesenchymal ovarian-like stroma. It is very important to differentiate amongst these two entities, as the approach and management to each are different. Mucinous cystic neoplasms are composed of mucinous cystadenomas and mucinous cystadenocarcinomas. Current pathologic classification
distinguishes between benign, borderline, or malignant (cystadenocarcinoma) tumors based on their maximal degree of dysplasia. MCNs can have components of invasive adenocarcinoma in up to 33% of cases. As such, it is suggested that all of these tumors should be treated as premalignant lesions with possible eventual evolution to aggressive behavior if left untreated. Owing to this inherent potential for malignancy, surgical resection is advocated for all of them, and is considered curative. Five-year survival rates are excellent (>95%) for benign or borderline MCNs, and long-term survival rates are also expected for 50% to 75% of fully resected malignant tumors (78,79). Other rare types of lesions include cystic endocrine neoplasms and acinar-cell cystadenocarcinomas which in total represent less than 10% of all pancreatic cystic neoplasms, and tend to occur in the sixth to seventh decade of life.

**Intraductal Papillary Mucinous Neoplasms (IPMNs)**

IPMNs consist of only 1% of all pancreatic cancers but up to 33% of pancreatic cystic neoplasms, and usually occur in the 6th to 7th decade of life. Intraductal neoplasms can be visualized with ERCP and EUS. The appearance of mucin extrusion from a widely patent ampulla is pathognomonic of an intraductal papillary mucinous neoplasm. IPMNs exhibit different stages from adenoma to mild atypia to invasive carcinoma, but lack the ovarian stromal characteristics of mucinous cystic neoplasms (MCNs) (80). IPMNs can also be classified into two types on the basis of the site of tumor involvement, i.e. main duct type or branch type (81). Some studies have suggested that the branch-duct variant of IPMN has a somewhat lower potential for malignant disease that may not require the aggressive surgical management that other papillary mucinous neoplasms require. These patients can often be followed with serial imaging studies. Intraductal papillary mucinous neoplasms with evidence of changes to an adenomatous or borderline stage have an excellent prognosis. As such, most IPMNs have a more favorable prognosis when compared to ductal adenocarcinoma, although there have been several cases demonstrating more aggressive disease (80). As many as 19% of patients who have an intraductal papillary mucinous neoplasm require a total pancreatectomy because of extensive involvement of the pancreatic ductal system. Even with carcinoma, the five-year survival rate for IPMNs is over 50% (77). The treatment approach to IPMNs should be tailored to the pathology and the patient on a case-by-case basis.

The high-resolution imaging possible with EUS permits the identification of morphologic features of any pancreatic cystic neoplasm (77). In the past several years, endoscopy and endoscopic ultrasonography have been used to diagnose cystic lesions of the pancreas and to guide fine-needle aspiration. Endoscopic ultrasonography is currently the technique of choice for guiding the aspiration of pancreatic cystic lesions. Fluid obtained by fine needle aspiration can be examined for tumor markers and for cytologic features. With this, cytologic analysis of cyst fluid has identified cells that indicate the presence of malignant disease or a benign cystic lesion in perhaps only half of the aspirates obtained (82).

**CONCLUSION**

Pancreatic diseases in the older adult population are becoming an increasingly important aspect of gastroenterology. Technological advances in imaging and therapeutics will allow more aggressive clinical care plans in patients who as recent as five years ago would have been deemed suitable only for palliative therapy. It is estimated that by the year 2050, 23% of the United States population will be over 65-years of age (1). As this older adult population increases, 75% of healthcare expenditures will be focused on the elderly by the year 2030 (2). It is the physician’s responsibility to not only display and communicate all diagnostic and therapeutic alternatives to this population of aging patients but also to display a degree of sensitivity to patient emotions and concerns regarding appropriate levels of aggressiveness when faced with therapeutic decisions. As pancreatobiliary disorders represent some of the most common and feared conditions that affect the elderly, we believe that knowledge and awareness of the various presentations, approach, and management of these disorders in the elderly is of vital importance as well as mandatory for the practicing gastroenterologist today.
References

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