Multidisciplinary Approach to Tumors of the Pancreas and Biliary Tree

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Much of the progress made against pancreatic cancer in the last several decades has been in the areas of decreased morbidity and mortality from surgical resection, and improved quality of imaging studies, thus allowing for better selection of patients most likely to benefit from surgical therapy. Unfortunately, surgical resection, although the only hope of long-term disease control, does not result in a cure for most patients. Although the introduction of gemcitabine as an active agent in pancreatic cancer initially offered hope for improved outcomes, the dismal median and 5-year survivals of patients undergoing multimodal therapy demonstrate that there remains significant need for more effective chemotherapeutic and targeted therapies in this disease.

Cystic tumors of the pancreas represent a spectrum of diseases, from benign to frankly malignant. The ability to predict an individual lesion’s risk of being malignant has improved with the advancement of cross-sectional imaging techniques and the introduction of endoscopic ultrasound (EUS) with aspiration of cyst contents for analysis, although diagnostic uncertainty still may be present in many cases. This may allow for the application of surgical resection in patients most likely to derive benefit.

Methods of early detection and effective systemic therapies are lacking for cholangiocarcinoma and gallbladder cancer and pancreatic cancer. Surgical resection offers the best hope of extended disease control, but is not possible in many cases because of the advanced stage of disease on presentation. A multidisciplinary approach to these challenging tumors can help expedite work-up and tailor available therapies to an individual patient’s needs.
Cystic lesions of the pancreas are encountered more and more frequently in clinical practice as higher-quality cross-sectional imaging studies are used for various related or nonrelated indications. These lesions encompass a spectrum of histopathologic entities, from benign with no metastatic potential to frankly malignant. Although there is no single test or combination of studies that definitively identify the malignant potential of cystic lesions of the pancreas, a rational approach to the work-up of such lesions can attempt to direct surgical therapy to those patients most likely to derive benefit.

The initial step in this process is a thorough history and physical examination, seeking to elicit current or past symptoms of pancreatitis, trauma, pancreatic insufficiency, or constitutional symptoms suggestive of malignancy. High-quality cross-sectional imaging is essential to the proper diagnostic algorithm, and may include multislice helical CT with intravenous contrast and fine cuts through the pancreas (less than or equal to 3 mm) or MRI with pre- and postgadolinium images. A comparison with prior studies, if possible, can help determine the rate of change of these lesions.

Some investigators have examined the use of 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) scanning in the work-up of cystic lesions of the pancreas. In a prospective study of 50 patients who had cystic lesions of the pancreas, Sperti and colleagues found that 16 of 17 patients (94%) who had malignant cystic neoplasms displayed increased 18-FDG uptake with standard uptake values (SUV) greater than 2.5. Of the 33 patients with benign tumors, two had increased 18-FDG uptake, for an overall specificity and accuracy of 94%. The ability of PET to distinguish benign from malignant cystic tumors of the pancreas was better than that of CT, which had a sensitivity of 65%, specificity of 88%, and overall accuracy of 80%. These findings were not corroborated by a retrospective study at Memorial Sloan-Kettering Cancer Center. In this study, 79 patients who underwent PET imaging for cystic lesions of the pancreas were reviewed. Twenty-one patients underwent resection, and 47 were followed with imaging. Increased 18-FDG uptake was seen in four of seven patients (57%) who underwent resection of a malignant cystic tumor, and in 2 of 14 (14%) of patients who had a benign tumor, for a sensitivity of 57% and a specificity of 85%. Cross-sectional imaging revealed evidence of malignancy in all patients who had malignant tumors. Thus, 18-FDG PET imaging should not be considered a routine part of the work-up for cystic lesions of the pancreas, but in a patient who has equivocal findings on cross-sectional imaging, PET may help with operative decision making. The use of the National Oncologic PET Registry established by the Centers for Medicare and Medicaid is highly encouraged.

EUS with aspiration of cyst contents has emerged as a possibly useful tool in the work-up of a cystic lesion of the pancreas. Although morphologic features seen with EUS may not allow for differentiation between benign and malignant lesions beyond that seen with standard cross-sectional imaging, analysis of cyst fluid obtained by means of fine-needle aspiration of the cyst contents may help in the decision-making process, as will be discussed.

Non-neoplastic cystic lesions of the pancreas primarily include pseudocysts, although parasitic cysts and cysts associated with congenital disease such as cystic fibrosis also may be seen. Pseudocysts may be diagnosed by history, although a history of pancreatitis does not exclude a cystic neoplasm. Further support of this diagnosis may come from serum and cystic fluid tumor markers such as carcinoembryonic antigen (CEA) and CA 19-9, which are normal in a pseudocyst. Furthermore, pseudocyst fluid is usually high in amylase and negative for tumor markers (Table 1).
<table>
<thead>
<tr>
<th></th>
<th>Pseudocyst</th>
<th>Serous Cystic Neoplasm</th>
<th>Mucinous Cystic Neoplasm</th>
<th>Intraductal Papillary Nucinous Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Any</td>
<td>60–80 y</td>
<td>30–50 y</td>
<td>60–80 y</td>
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<tr>
<td><strong>Gender</strong></td>
<td>Equal distribution</td>
<td>Female &gt; male</td>
<td>Female &gt;&gt; male</td>
<td>Equal distribution</td>
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<tr>
<td><strong>Location</strong></td>
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<td>Head &gt; body/tail</td>
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<tr>
<td><strong>Appearance on imaging</strong></td>
<td>Single cyst or multiloculated macrocystic; may have findings of chronic pancreatitis</td>
<td>Honey-combed microcystic; may have central scar; may have dominant cyst</td>
<td>Macrocystic, single or multi-loculated; thick, smooth wall; no connection to main duct</td>
<td>Polycystic lesion with dilation of pancreatic duct</td>
</tr>
<tr>
<td><strong>Cyst fluid carcinoembryonic antigen</strong></td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>Cyst fluid amylase</strong></td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Cyst fluid mucin</strong></td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>Natural history</strong></td>
<td>No malignant potential; resection indicated for diagnostic uncertainty, internal drainage for persistent symptoms</td>
<td>Invasive/metastatic disease extremely rare; resection for symptomatic or enlarging lesions, and is curative</td>
<td>Potential for invasive disease at diagnosis or with observation; resection recommended, is curative, although recurrence in 50% of patients with invasive component</td>
<td>Potential for invasive disease at diagnosis or with observation; resection recommended for main duct intraductal papillary mucinous neoplasm or branch duct &gt;3 cm; recurrence in &gt;50% of patients with invasive disease</td>
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</table>

The more common neoplastic cystic lesions of the pancreas include serous cystic neoplasms, mucinous cystic neoplasms (MCN), and intraductal papillary mucinous neoplasms (IPMN). Serous cystic neoplasms affect women more often than men at a ratio of approximately 3:1 to 4:1, and their incidence increases with age. Most of these tumors are benign, with a serous cystadenocarcinoma being a reportable event. Cross-sectional imaging findings consistent with serous cystic neoplasm include a central stellate scar, a honeycombed appearance, or a pattern sunburst calcification. When aspirated, the cyst contents demonstrate scant cellularity, a low CEA, and low CA 19-9 levels. An asymptomatic serous cyst may be observed safely. In the symptomatic patient who is a good operative candidate, resection may be indicated. Lesions larger than 4 cm or that are rapidly growing or changing in appearance also may be considered for resection. Nonstandard pancreatic resections such as enucleation, central pancreatectomy, or spleen-preserving distal pancreatectomy may be considered for serous lesions. In all cases of resected disease, patients are considered definitively treated, and further surveillance is not necessary.

MCNs most frequently are found in middle-aged women. Cross-sectional imaging shows a macrocystic lesion, which may be multiloculated and typically has a thick wall. There is no communication with the main pancreatic duct. A lesion size greater than 3 cm, the presence of mural nodules, a solid component, and calcifications are indications of malignant disease. EUS with cyst aspiration typically demonstrates viscous fluid with elevated mucin and CEA levels. Elevated serum CEA or CA 19-9 suggests malignant or invasive disease, although sensitivity is low. There is no reliable way to distinguish benign from malignant MCN, to detect malignant transformation, or to predict which lesions will go on to become malignant. Therefore, the diagnosis of MCN is an indication for resection, and a standard anatomic resection is preferred, although some authors advocate that low-risk MCNs may be treated with a less-extensive procedure. When final pathologic analysis reveals noninvasive disease, long-term disease-free survival is expected. Invasive MCN may recur in up to 50% of patients, and as such, these patients should be followed with imaging.

IMPNs, initially described in 1982, are distributed equally between men and women, and increase in incidence with increasing age. The two variants are main duct and branch duct, and the histology can range from benign adenomas to invasive disease. Any portion of the pancreas or even the entire pancreas may be affected. Cross-sectional imaging shows a polycystic lesion, with pancreatic ductal dilation in the main duct variant. Mural nodules, solid component, calcifications, and significant ductal dilation suggest malignant disease. As with MCN, there is no reliable means to discriminate between invasive and noninvasive disease, or to detect transformation. Asymptomatic branch duct lesions less than 3 cm may be followed safely with serial imaging, while all symptomatic lesions, lesions greater than 3 cm and main duct lesions should be removed with a standard anatomic resection. Intraoperative frozen section of the pancreatic duct margin should be examined with the goal of achieving a margin free of invasive disease or dysplastic epithelium. Some authors support achieving a margin free of invasive disease only; in a retrospective review of patients undergoing resection for IPMN, eight patients with noninvasive IPMN at the final surgical margin had no recurrences, with a median follow-up of 34 months. The prognosis following resection depends on the presence of invasive disease, with a 77% to 100% 5-year survival in the absence of invasive disease (median 85 months), and 5-year median survival as low as 36% with invasive disease (median 23 months). Postoperative surveillance is tailored to the risk of recurrence, with more aggressive
follow-up for patients who have invasive disease. An algorithm depicting the work-up and treatment of cystic lesions of the pancreas is presented in Fig. 1.

In summary, cystic lesions of the pancreas remain diagnostic challenges. Although data from demographics, cross-sectional imaging, serum tumor markers, and cyst fluid analysis may be helpful in determining the potential of a given lesion to harbor a malignancy, there are many cases in which these data are equivocal. In such cases, the age and comorbidities of the patient may influence the surgeon’s decision to recommend excision versus observation. The patient’s wishes may play a role in preoperative decision making also. Finally, the availability of minimally invasive techniques may alter the risk/benefit profile in favor of resection for patients in whom a preoperative diagnosis cannot be reached with certainty.

**PANCREATIC DUCTAL ADENOCARCINOMA**

Pancreatic ductal adenocarcinoma remains a formidable challenge from the standpoint of a lack of early diagnostic tests and effective therapies. Although ranking tenth in incidence of malignancies in the United States, it is the fourth most common cause of cancer-related deaths in men and women, with an estimated 37,680 new cases and 34,290 deaths expected in 2008. Complete surgical resection offers the best hope for long-term control of disease, although only approximately 30% of patients present with potentially resectable disease by imaging studies, and less than 20% of all patients ultimately undergo resection. A recent analysis of data from the National Cancer database revealed that among patients who had clinical stage 1 pancreatic cancer (T1-2N0M0), 38.2% of patients were not offered surgery, with an additional 15.5% of patients excluded for age or comorbidities. Additionally, increasing evidence shows that patients treated in high-volume centers, which largely incorporate a multidisciplinary evaluation and treatment approach, experience superior outcomes than those patients seen in lower-volume centers.

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**Fig. 1.** Algorithm for the work-up of a cystic lesion of the pancreas. Abbreviations: EUS, endoscopic ultrasound; FNA, fine-needle aspiration; H&P, history and physical; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; SCA, serous cystadenoma. *(From Katz MH, Mortenson MM, Wang H, et al. Diagnosis and management of cystic neoplasms of the pancreas: an evidence-based approach. J Am Coll Surg 2008;207(1):116; with permission.)*
Pancreatic cancer often remains asymptomatic until reaching an advanced stage. A cost-effective screening program has not been developed for the average-risk patient. Cigarette smoking, increased body mass index, high dietary fat, and exposure to beta-naphthlamine or benzidine have been associated with an increased risk of pancreatic cancer.23 A small subset of pancreatic cancer has a familial predilection, including kindreds with a p16 germline mutation or the BRCA-2 gene mutation. In these high-risk individuals, EUS may be used as a screening modality to detect early stage tumors.24

DIAGNOSIS AND WORK-UP

Triphasic dynamic-phase helical or spiral CT scanning with fine cuts through the pancreas is the recommended method for evaluating known or suspected pancreatic lesions.23 Approximately 70% to 85% of tumors will be resectable at the time of laparotomy if CT imaging demonstrates no evidence of extrapancreatic disease, no obstruction of the superior mesenteric vein (SMV)-portal vein (PV) confluence, and no tumor extension to the celiac trunk or superior mesenteric artery (SMA).25

PET has been investigated for diagnosis and staging of pancreatic malignancies. Earlier reports describe CT-PET as superior to CT in diagnosing pancreatic carcinoma (sensitivity and specificity 92% and 85% versus 65% and 62%),26 but advances in the quality of CT and MRI imaging, and the increasing use of preoperative chemotherapy or chemoradiotherapy, which mandate tissue confirmation, leave open the question as to how PET or CT-PET contribute to the work-up of a patient who has suspected pancreatic cancer.

A study of PET for staging in a series of 42 patients who had untreated pancreatic cancer found that FDG-PET imaging detected metastatic disease in 13 of 16 patients (81% sensitivity), and identified eight metastatic sites in seven patients that were not seen on CT.27 Overall, PET scanning changed the clinical staging in 5 of 42 patients (11.9%). The use of PET or CT-PET should be reserved for those patients in whom conventional imaging studies are equivocal, and it should be considered investigational. Again, the National Oncologic PET registry is recommended.3

EUS may be a useful tool in selected patients. For those patients suspected of having a pancreatic malignancy in whom no mass is seen on cross-sectional imaging, EUS may demonstrate a hypoechoic lesion consistent with a pancreatic tumor, with a sensitivity of 97% to 100%, including tumors smaller than 2 cm.28,29 EUS with fine needle aspiration biopsy (FNAB) also allows for tissue confirmation. In addition, EUS can provide greater accuracy than other imaging modalities in assessing portal vein involvement or invasion by known pancreatic tumors, thus selecting patients who may require vessel resection or who may benefit from preoperative treatment.30 EUS is the preferred method for obtaining tissue diagnosis in those patients who have unresectable disease or who will undergo preoperative treatment; however, biopsy of metastasis is appropriate in patients who have metastatic disease.31

In a patient with a clearly resectable pancreatic mass who is a good surgical candidate and is not being considered for preoperative treatment, endoscopic evaluation may not be necessary. The use of endoscopy for tissue diagnosis in this setting must be balanced with an understanding that a negative biopsy does not rule out a malignancy, and should not change the decision to proceed to surgery.23

The role of endoscopy for preoperative biliary decompression is controversial. Authors from Memorial Sloan-Kettering found an association between preoperative biliary decompression and increased risk of infections complications ($P = .022$) and death ($P = .021$) in patients undergoing biliary decompression before pancreaticoduodenectomy (PD).32 Another retrospective review of 300 patients undergoing PD—172
(57%) with preoperative biliary decompression and 93 (31%) without—found no difference in the incidence of complications, although the stent group had more wound infections \((P = .029)\). Thus, patients who have symptomatic jaundice from an obstructing peri-ampullary tumor may undergo preoperative endoscopic stent placement, particularly if surgery is to be significantly delayed. Stenting, however, is indicated for obstructed patients with cholangitis, or those undergoing preoperative therapy. In these patients, temporary plastic stents are used most commonly; however, stent changes are necessary in 6 to 12 weeks because of stent obstruction. Some authors advocate the use of metallic, self-expanding stents, even in cases of patients planned for resection.

Carbohydrate antigen 19-9 (CA 19-9) is a tumor marker associated with pancreatic adenocarcinoma. It is a derivative of the Lewis[a] blood group determinant, and as such is undetectable in patients who have a Lewis-negative blood group phenotype. In addition, CA 19-9 often is elevated in patients who have biliary obstruction, even in the absence of malignancy. Markedly elevated CA 19-9 in the nonjaundiced patient who had pancreatic cancer was found to be 84% to 88% predictive of unresectable disease in retrospective studies. Although this laboratory value should not preclude a patient who has imaging studies consistent with resectable disease from receiving aggressive treatment, it may be a useful tool in selecting patients for additional confirmatory studies or procedures to identify locally advanced or metastatic disease. In addition, CA 19-9 response to treatment is a prognostic indicator, and its rise after treatment nadir is indicative of recurrent disease.

Unrecognized occult metastatic disease may be found in as many as 25% of patients brought to the operating room for planned resection, leading many surgeons to perform diagnostic laparoscopy before exploration. This procedure may be performed in the same setting as the planned resection, or in advance to allow for analysis of peritoneal cytology. The presence of malignant cells in peritoneal washings performed at resection has been found to correlate with a median survival of 8 months, compared with 16 months for patients who have negative cytology \((P<.001)\). The survival pattern of patients who had positive cytology was comparable to those patients who had unresected metastatic disease (median survival 7 months, \(p = \) not significant). Although a staging laparoscopy is listed as a category 2B recommendation by the National Comprehensive Cancer Network (NCCN), patients most likely to benefit from its use include patients who have multiple comorbidities or those who have a high suspicion for vessel involvement or metastatic disease caused by markedly elevated CA 19-9 levels, large primaries or body/tail lesions.

**TREATMENT CONSIDERATIONS**

Complete surgical resection, either by means of PD or distal pancreatectomy with splenectomy, is the only hope for long-term survival in patients who have pancreatic cancer. Short-term outcomes for these procedures have improved significantly over the past 20 years, and data suggest that surgical mortality and overall survival are improved when pancreatic resection is performed at a high-volume institution by a surgical team that performs at least 20 resections per year. The goal of resection is complete removal of all gross and microscopic disease (R0 resection). Multiple technical aspects of PD have been studied, including extent of lymphadenectomy, method of pancreatic anastomosis, pylorus preservation, and vascular resection. A summary of these findings was presented in a prior issue of *Surgical Clinics of North America* and on the NCCN Web site.
The antimetabolite prodrug gemcitabine initially was found to have improved activity against pancreatic cancer compared with 5-FU in patients who have metastatic disease, and subsequently has been studied and incorporated into the adjuvant setting. Patients who have metastatic disease are treated best by a gemcitabine-containing regimen, depending on performance status, and ideally should be treated on a clinical trial. Locally advanced, unresectable disease may be approached with chemotherapy or chemoradiation, with the role of radiation remaining controversial in both the adjuvant setting and in patients who have locally advanced, unresectable disease. Diagnostic laparoscopy may help confirm the absence of metastatic disease in patients being considered for chemoradiation, as 37% of patients who had locally advanced, unresectable tumors were found to have metastatic disease not detected by imaging studies when submitted to staging laparoscopy.

The designation of borderline resectable tumors recently has emerged to describe a subpopulation of potentially resectable tumors with imaging features that indicate a higher likelihood of a margin-positive, or R1 resection. For tumors of the head or uncinate process, these criteria include SMV/PV impingement, SMA abutment, encasement of the gastroduodenal artery (GDA) up to its origin at the hepatic artery, limited inferior vena cava (IVC) involvement, short-segment SMV occlusion with patent vein proximally and distally, and colon or mesocolon invasion. In addition, some authors include patients who have marginal performance status, or patients who have findings on imaging studies suspicious for but not clearly diagnostic of metastatic disease into the category of borderline resectable.

Numerous studies have demonstrated the adverse impact of positive margins on survival, with median survivals ranging from 8 to 11 months in patients who had R1 or R2 resections, compared with 17 to 26 months for patients who had margin-negative (R0) resections. The goal in the management of the borderline resectable patient is to maximize the chance of an R0 resection, which may be accomplished by delivering adjuvant treatment before surgery. In addition to improving the rate of R0 resection, the use of preoperative treatment:

- Allows for the identification of patients who develop rapidly progressive disease and likely would not benefit from surgical resection
- Treats what is likely a systemic disease at diagnosis with a systemic treatment first
- May allow for more patients to complete all modalities of treatment
- May improve the efficacy of chemotherapy and radiation by delivering treatments to well-vascularized tissues
- May render a subset of patients who have locally advanced unresectable disease amenable to surgical resection

Investigators at MD Anderson have demonstrated that the use of gemcitabine and cisplatin followed by gemcitabine-based chemoradiation delivered preoperatively was tolerated by 79 of 90 (88%) patients enrolled in a phase 2 trial. Fifty-two of the patients ultimately underwent PD, and the median survival for this subgroup was 31 months, compared with 10.5 months for patients who were not resected (P<.001). In a similar phase 2 trial employing preoperative chemoradiation with gemcitabine, 11 of 85 patients were deemed unresectable at restaging, because of medical comorbidity (three) or disease progression (eight). At surgery, another nine patients were found to have evidence of metastatic disease, for a total of 20/85 (23%) patients who progressed on preoperative treatment. Median overall survival for patients undergoing resection was 34 months compared with 7.1 months for patients who did not undergo PD (<0.001). Clearly a portion of the survival advantage of this treatment paradigm is derived from selecting out patients who likely would not have benefited from...
resection. In fact, to date, no randomized prospective trial has compared preoperative versus postoperative adjuvant treatment in resectable pancreatic cancer, so the true survival advantage to this regimen is unknown.

All patients who have undergone resection of a pancreatic adenocarcinoma should be considered for adjuvant treatment, as recurrence rates for surgery alone range from 50% to 80%. In the United States, 5-FU based chemoradiotherapy has been the standard adjuvant treatment for resected pancreatic cancer, based on results from early phase 3 and single-institution studies demonstrating an improvement in median overall survival from 11 months to 20 months with the addition of 5-FU and concurrent radiation therapy. A more recent phase 3 trial randomized 538 patients who had resected pancreatic cancer to gemcitabine followed by gemcitabine plus radiation or 5-FU followed by 5-FU plus radiation. Median overall survival for the 388 patients who had pancreatic head tumors in the gemcitabine group was 20.5 months compared with 16.9 months in the 5-FU group, with 3-year survivals of 31% versus 22% ($P = .09$).

In Europe, radiation is not part of the standard treatment of pancreatic cancer. A phase 3 study from the European Study Group for Pancreatic Cancer (ESPAC) randomized 541 patients using a four-arm, $2 \times 2$ factorial design to compare the impact of chemotherapy, chemoradiation, chemoradiation plus chemotherapy, and observation on survival after resection. Adjuvant chemoradiation was found to be associated with a lower median survival compared with regimens without chemoradiotherapy (17.9 months versus 15.9 months, $P = .05$). Patients receiving chemotherapy, however, had a median survival of 20.1 months compared with 15.5 months for those patients not receiving chemotherapy ($P = .009$).

More recently, the CONKO-001 (Charite Onkologie) trial reported phase 3 data on 368 patients who had resected pancreatic cancer randomized to either 6 months of gemcitabine or observation. Disease-free survival at 3 and 5 years was 23.5% and 16% in the gemcitabine group, compared with 8.5% and 6.5% in the observation group ($P < .001$). Median overall survival was 22.8 months in the gemcitabine group compared with 20.2 months with observation ($P = .005$), with 3- and 5-year survivals of 36.5% and 21%, versus 19.5% and 9%.

Clearly the best hope for progress against pancreatic cancer remains the development of more efficacious systemic therapy. To date, targeted therapies have been largely unsuccessful in improving survival of patients who have pancreatic cancer. In a phase 3 trial, however, the epidermal growth factor receptor (EGFR) antagonist erlotinib demonstrated statistically significant improvement in overall survival in patients who had advanced or metastatic disease when given with gemcitabine, compared with gemcitabine alone (median survival 6.24 months versus 5.91 months, $P = .038$, 1-year survival 23% versus 17%, $P = .023$). The clinical significance of a 2-week improvement in overall survival remains to be clarified.

Pancreatic cancer is associated with symptoms such as pruritus from symptom-atic biliary obstruction, nausea and vomiting from duodenal obstruction, and intractable pain from perineural tumor invasion. Various palliative treatments may be considered, including biliary stenting, operative biliary or gastric bypass, and celiac plexus neurolysis. In a review of 155 patients with locally advanced or metastatic disease who had been staged with laparoscopy and thus not submitted to prophylactic bypass procedures, 98% of the patients (152 of 155) did not require subsequent palliative procedures. This suggests that laparotomy for prophylactic biliary or duodenal bypass is unnecessary. When possible, minimally invasive palliative treatments such as endoscopic biliary stenting, CT-guided celiac plexus neurolysis, or linear array EUS-guided chemical neurolysis should be employed over open surgical approaches.
BILIARY MALIGNANCIES

Tumors of the biliary tree include cholangiocarcinoma and gallbladder carcinoma. These cancers are less common than pancreatic cancer, with an estimated 9000 new cases of gallbladder and extrahepatic bile duct cancer in 2008, but they present many of the same challenges, including advanced stage at presentation and a lack of effective systemic therapies. Like pancreatic tumors, surgery offers the best hope of cure for cholangiocarcinoma and gallbladder cancer. Long-term survival remains poor in these patients, with 5-year survivals in the range of 5%.

CHOLANGIOCARCINOMA

Cholangiocarcinoma is a relatively uncommon tumor, with an incidence that increases with age and a slight male predominance. Risk factors include cirrhosis, primary sclerosing cholangitis (PSC), chronic choledocholithiasis, bile duct adenoma, choledochal cyst, biliary papillomatosis, and parasitic or typhoid infection, although many patients who develop cholangiocarcinoma have no risk factors. Cholangiocarcinoma can arise along any portion of the intra- or extrahepatic biliary tree. Tumors of the distal extrahepatic bile duct are managed in the same manner as pancreatic head cancers. Tumors of the intrahepatic bile ducts are approached in similar fashion to hepatocellular carcinoma, discussed elsewhere in this issue. The remainder of this article focuses on peri-hilar cholangiocarcinoma and cancer of the gallbladder.

The therapeutic goal of cholangiocarcinoma is a complete surgical resection with negative margins and adequate liver reserve, including inflow, outflow, and biliary drainage. As such, the preoperative work-up focuses on identifying the extent of disease within the bile ducts and the presence of metastases, which would preclude a curative resection.

Patients most commonly present with obstructive jaundice, with pain and constitutional symptoms typically occurring in more advanced disease. Physical examination may be unrevealing, or may demonstrate jaundice, right upper quadrant tenderness, or a palpable distended gallbladder, if the lesion is distal to the cystic duct. Laboratory studies are consistent with obstructive jaundice and may include a prolonged prothrombin time caused by malabsorption of fat-soluble vitamins. There are no sensitive and specific tumor markers for cholangiocarcinoma, with CA 19-9 being the most used test, in particular for screening patients who have PSC.

Ultrasoundography is frequently the first test employed, and the pattern of ductal dilation may help identify the location of the obstructing tumor. Likewise, CT scanning may reveal a pattern of ductal dilation that suggests a location of an obstructing tumor; periportal, peripancreatic, celiac or mesenteric lymphadenopathy and intrahepatic metastases also may be visible on CT. MRI with magnetic resonance cholangiopancreatography using gadolinium contrast allows for more precise assessment of the location extent of intraductal tumor involvement, the relationship of tumor to the portal vein, and the presence of lymph node or distant metastases.

Cholangiography, either by means of percutaneous or endoscopic routes, is helpful in palliating symptomatic jaundice, obtaining brush cytology specimens for tissue diagnosis, and for assessing the extent of ductal involvement. Unfortunately, bile duct cytology may be nondiagnostic in up to 50% of patients who have a cholangiocarcinoma, highlighting the need for improved diagnostic techniques in these patients.

The indications for surgical resection include a medically fit patient with no evidence of extrahepatic disease, including lymph node involvement beyond the porta hepatis, and no involvement of the contralateral bile duct beyond the secondary biliary
radicals. The goal of resection is complete removal of all gross and microscopic disease (R0 resection), as this is associated with a prolonged disease-free survival. For hilar cholangiocarcinoma, concomitant liver resection has been shown to decrease the incidence of local recurrence and should be considered in the preoperative planning. In patients who have unresectable disease, systemic treatment with 5-FU or gemcitabine-based chemotherapy may offer improvement in time to progression; however, no standard therapy has been established. Likewise, the role of adjuvant treatment is unproven and is approached best on a clinical trial. Liver-directed therapy, including transarterial chemoembolization (TACE), also may be used in patients who have unresectable or recurrent disease, and is discussed elsewhere in this issue.

Gallbladder Cancer

Gallbladder cancer remains a challenging clinical entity, both because of its insidious presentation (leading to diagnosis either at the time of cholecystectomy or upon pathologic review) and because of its relatively low incidence, approximately 5000 new cases in the United States per year. Together, these make a prospective study very difficult.

Gallbladder cancer occurs approximately three times as often in women compared with men, and the incidence increases with age, with the peak incidence occurring in the seventh decade of life. A history of gallstones, in particular larger gallstones, chronic cholecystitis, and a calcified gallbladder (porcelain gallbladder) may increase the risk of developing gallbladder cancer as much as eight times that of the general population. Gallbladder polyps are thought to progress from adenomas to carcinomas, similar to colorectal cancer, with polyp size greater than 1 cm and broad-based, sessile polyps carrying the highest risk of malignancy in a retrospective review.

The preoperative diagnosis of gallbladder cancer is made based on the appearance of a mass on imaging, which is usually ultrasonography. The sensitivity of ultrasound in detecting gallbladder cancer ranges from 50% to 85%, depending on how advanced the disease is at the time of imaging. This contributes to the high percentage of cases not recognized until the time of surgery or afterwards. A suspicious mass on ultrasound should prompt further preoperative work-up or referral. Contrast-enhanced CT or MRI is appropriate for assessing the extent of local disease, vascular invasion, and lymphadenopathy. PET, chest radiograph, and diagnostic laparoscopy can be used to evaluate for the presence of metastases before definitive resection. ERCP, MRCP, or percutaneous cholangiography may be employed in those patients presenting with jaundice, for diagnostic or palliative purposes. Tissue biopsy is not required before proceeding with surgical resection for suspected gallbladder cancer.

In patients who have preoperatively known or suspected gallbladder cancer, surgery should be performed by a team with the training and resources to complete an oncologic resection in the same setting. The goal of surgical treatment is complete cholecystectomy to a negative bile duct margin with en bloc removal of the involved liver parenchyma and a periportal lymphadenectomy. Establishing the diagnosis intraoperatively entails the use of frozen section. A recent review of 31 patients with gallbladder cancer who underwent frozen section analysis found that one patient had a cancer that was missed on frozen section, as it was located away from the polypoid lesion, and two patients had tumors staged as pT1b on frozen section later reported as pT2. The sensitivity for frozen section was 90% (28 of 31 patients), which is similar to previous studies, although a lower accuracy in diagnosing depth of
invasion was seen in earlier studies (70% of carcinoma cases had frozen section and permanent T stage agreement).69

For T1a tumors (invasion of lamina propria) found either incidentally on pathology review or at the time of cholecystectomy, no further surgery is required if the gallbladder was removed intact and the cystic duct margin is negative. For T1b lesions (invasion of muscle layer) or greater, patients should be considered for hepatic resection, lymphadenectomy, and re-excision of involved bile duct, if present.23 Although a single procedure is the ideal scenario, a review of 410 patients evaluated for gallbladder cancer at Memorial Sloan-Kettering Cancer Center did not find previous surgery to be an independent predictor of outcome (44% 5-year survival for patients treated with a single operation versus 36% for those undergoing re-resection, P = .9).70 The group presenting without prior surgery, however, had a higher proportion of stage 4 patients and more patients presenting with jaundice, indicating more advanced disease. Thus, one cannot conclude that a staged operation is equivalent to a single procedure. Some authors recommend the excision of prior port sites, but this remains controversial.71

Long-term survival for patients who have unresectable disease remains dismal, with median survival between 5 and 8 months.70 For those patients undergoing complete curative resection, 5-year overall survival ranges from 25% to 45%.72 Patients who had T2 tumors experienced a 5-year survival of 59%, compared with 21% for patients who had T3 tumors. Likewise, the presence of nodal metastases reduced 5-year survival from 54% to 16%.70,73

Because of the relative rarity of this disease and the heterogeneity of the patient population, randomized prospective data on adjuvant treatments are scarce. A single phase 3 trial from Japan compared surgery alone with surgery plus adjuvant 5-FU/mitomycin and found an improvement in 5-year survival from 14.4% to 26% (P = .04).74 A cohort of 21 patients treated at the Mayo Clinic with concurrent 5-FU and external beam radiation following potentially curative resection had an overall 5-year survival of 33%, with stage 1 to 3 patients having a 65% 5-year survival compared with 0% for stage 4 patients.75 Patients undergoing potentially curative resection of any gallbladder cancer beyond a T1, N0 tumor should be considered for adjuvant chemoradiation.

Neoadjuvant therapy has been employed in an effort to select out patients most likely to benefit from surgical therapy, and to increase the chances of a complete surgical resection.76,77 In a phase 2 study, 18 patients who had gallbladder cancer found on pathologic review underwent 5-FU based chemoradiotherapy before definitive operation. Seventeen patients completed treatment, and 13 patients ultimately underwent resection. Seven patients were alive at a median of 34 months follow-up, and none of those patients had residual disease at the time of definitive resection.77

Gemcitabine has been investigated in patients with metastatic or locally advanced unresectable gallbladder cancer with promising results. Its use in the adjuvant setting is under investigation.

SUMMARY

Tumors of the pancreas and biliary tree are approached best by a multidisciplinary team, to ensure optimal diagnostic imaging studies, expeditious staging, consideration for clinical trial participation, and tailored treatment, which may involve surgery, chemotherapy or radiation therapy. Interventional radiology and gastroenterology are essential disciplines in the multidisciplinary team, for diagnostic and therapeutic procedures such as biopsies, biliary stenting (endoscopic or percutaneous), and EUS. Gemcitabine-based chemotherapy is the most promising systemic treatment
available, but still results in recurrence and disease progression in most patients treated in an adjuvant or palliative setting, respectively. Clinical trial participation is extremely important, so that newer, hopefully more promising therapies may be studied and incorporated into clinical care.

REFERENCES


54. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of