Cancer of the pancreas remains a formidable challenge in oncology. This malignancy ranks as the fourth leading cause of cancer death in the United States in 2003, with an estimated 30,700 new cases to be diagnosed and 30,000 deaths. Although gains have been achieved in the clinical management of these patients, this malignancy is rarely curable. Long-term survival is limited to patients undergoing resection. For patients with localized but unresectable malignancy, radiation therapy combined with fluorouracil, gemcitabine (Gemzar), or paclitaxel has shown modest improvements in survival and symptom palliation. However, there has been significant progress in the diagnostic evaluation of pancreatic cancer patients, which has aided clinicians in caring for these patients and in selecting therapies. The use of computed tomography, endoscopic ultrasonography, and laparoscopy techniques will be discussed. Newer techniques of radiation therapy, such as intraoperative electron-beam radiation therapy and three-dimensional conformal radiation therapy, with the integration of new biologically targeted agents may provide new avenues of research and progress in this disease.

Cancer of the pancreas is the fourth leading cause of cancer death in the United States.[1] In 2003, an estimated 30,700 new patients and approximately 30,000 deaths are expected to occur from this disease.[2] Because the etiology of the disease is poorly understood and clinical presentation is late in its natural history, cure remains elusive. For the 10% to 15% of patients undergoing resection, the 5-year survival of patients with "favorable" localized disease (ie, no lymph node metastases and disease confined to the pancreas without capsular invasion) approaches 18% to 24%.[3] For patients with advanced or metastatic disease, there are only anecdotal reports of survivors beyond 5 years. For all stages combined, the 5-year survival rate is 4%.[4] Because of these poor survival results, adjuvant and neoadjuvant treatment strategies have been investigated. New combinations of cytotoxic chemotherapy and targeted agents, and improvements in radiation therapy such as three-dimensional (3D) conformal radiation, may improve survival in patients with locally advanced pancreatic cancer. This review will highlight some of these developments. Palliation of symptoms is a major goal of therapy for patients with locally advanced or metastatic pancreatic cancer. Gastric outlet or biliary obstruction and pain are frequent and significant clinical problems, and require judicious selection of surgical, medical, and endoscopic or radiologic intervention. These procedures have been helpful in palliation and improving patient quality of life.[5,6] When resection is feasible, longterm survival may result.[3,7] For patients with locally advanced unresectable tumors, median survival is 8 to 13 months. The National Cancer Institute recommends that patients with any stage of pancreatic cancer be considered for enrollment in a clinical trial. Tumors Adjuvant Therapy

At present, surgery offers the only therapeutic means of cure for pancreatic cancer. Only 5% to 25% of patients present with tumors amenable to resection. Patients who undergo resection for localized pancreatic carcinoma have a long-term survival rate of approximately 20% and median survival of 13 to 20 months.[8] Favorable subsets include patients with resected tumors measuring less than 3 cm, no lymph node metastases, and microscopically negative surgical margins.
The Gastrointestinal Tumor Study Group (GITSG) evaluated the potential value of adjuvant therapy for patients with pancreatic cancer (Table 1). In one of the GITSG's earlier trials, patients with resected tumors who received adjuvant combination chemoradiation with fluorouracil (5-FU) and split-course radiation of 40 Gy in 20 fractions had a significant survival advantage, with a median survival of 21 months compared with 11 months for patients not receiving radiation therapy and chemotherapy after resection. These findings were confirmed in a follow-up registry trial which found that combined adjuvant radiation/5-FU therapy yielded a 2-year actuarial survival of 43% (95% confidence interval (CI) = 25%- 63%) in those patients receiving the adjuvant therapy, compared to 18% (95% CI = 5%-36%) in those who underwent surgical resection alone.[9] The European Organization for Research and Treatment of Cancer (EORTC) was unable to reproduce these positive results in a randomized trial of 218 patients with pancreas or periampullary cancers. A subset analysis of patients with primary tumors of the pancreas (114 patients) did, however, show a trend toward improved 2-year (median) and 5-year (overall) survival.[10] In this phase III trial, resected patients received either split-course irradiation (40 Gy) with concurrent 5-FU or were observed. Median survival was 19 months in observed patients compared with 24.5 months in those who received postoperative treatment ($P = .208$), with an estimated 2-year survival of 41% and 51%, respectively. Subset analysis of pancreatic cancer patients, however, showed an estimated 2-year survival of 26% for the observation patients compared to 34% for those receiving the adjuvant treatment ($P = .099$). Patients with periampullary tumors had a much higher estimated 2-year survival of 63% to 67%.

These investigators concluded that for patients undergoing surgical resection, the benefit of adjuvant therapy was limited and did not justify its routine use. A second European trial has examined various adjuvant treatment approaches, including 40-Gy splitcourse radiation therapy with concurrent and maintenance chemotherapy as well as chemotherapy alone.[11] The European Study Group for Pancreatic Cancer (ESPAC-1) phase III trial showed no survival advantage for postoperative irradiation and 5-FU chemotherapy vs no further treatment after surgery. However, a therapeutic benefit was seen for patients receiving adjuvant chemotherapy of 5-FU and leucovorin only. The ESPAC-3 trial is defining the role of adjuvant chemotherapy following curative resection of pancreatic ductal adenocarcinoma. In this study, 5-FU plus folinic acid for 24 weeks will be compared with gemcitabine (Gemzar) for 24 weeks vs no chemotherapy following surgery. The aim is to recruit 330 patients in each arm for a total of 990 patients. Enrollment is ongoing. Given conflicting results from various studies, the exact role of postoperative radiation therapy is uncertain at present. However, considering the very poor outcomes with surgery alone (15% 5-year survival) and the encouraging
Update on Combined-Modality Treatment Options for Pancreatic Cancer
Published on Physicians Practice (http://www.physicianspractice.com)

results from well-designed and controlled studies from single institutions and cooperative groups
using contemporary techniques, there is a rationale to support adjuvant therapy with radiation
therapy and 5-FU, as for other gastrointestinal carcinomas. The Radiation Therapy Oncology Group,
in conjunction with the GI Intergroup, has recently completed a phase III trial examining whether
gemcitabine improves survival over 5-FU as maintenance therapy for patients with resected
pancreatic cancer receiving radiation therapy and concurrent 5-FU. **Neoadjuvant Therapy**
In addition to postoperative treatment strategies, there has also been interest in the use of
preoperative radiation therapy and chemotherapy for patients with resectable pancreatic cancer. In
one institutional analysis of 132 patients who had received pre-operative chemoradiation (5-FU,
paclitaxel, or gemcitabine with either 45 to 50 Gy radiation at 1.8 Gy/fraction or 30 Gy at 3.0
Gy/fraction) before pancreaticoduodenectomy for adenocarcinoma of the pancreas head, a median
survival of 21 months was found for all chemoradiation combinations.[12] In this study, superior
survival was observed for women ($P = .04$) or those with no evidence of lymph node metastasis ($P = .03$). Interestingly, there was no difference in median survival between standard-fractionation
chemoradiotherapy (50.4 Gy for 5.5 weeks) and rapid-fractionation radiation therapy (30 Gy for 2
weeks). In another analysis of neoadjuvant chemoradiation therapy, patients who received
preoperative treatment of 5-FU (with or without mitomycin [Mutamycin] or gemcitabine) plus
radiation therapy (50.4 Gy) demonstrated a median overall survival of 34 months (range: 8-152
months) compared with 8 months (range: 1-14 months) for those who could not undergo surgery ($P = .005$).[13] The results of these studies have suggested specific advantages for preoperative vs
postoperative radiation therapy and chemotherapy. Some of these potential advantages include no
delay in initiation of radiation therapy (previous studies showed that 25% of patients required a
10-week delay for postoperative recovery), reduced risk of tumor cut-through, which is important
given the high rates of retroperitoneal margin involvement of these malignancies, and avoidance of
a laparotomy in patients who would not be potentially curative given the frequent development of
detectable metastases on restaging evaluation after radiation therapy and chemotherapy.

**Treatment of Unresectable Tumors** In the past, 45% of patients with newly diagnosed pancreatic
cancer presented with locally advanced disease. More recent data confirming this figure are lacking,
and it is possible that more advanced staging tools show metastatic disease early in the course of a
patient's illness, thus decreasing this percentage. In general, a tumor is considered unresectable if it
has one of the following features: (1) extensive peripancreatic lymph node involvement, (2)
encasement of the superior mesenteric vein/portal vein confluence, (3) direct involvement of the
superior mesenteric artery, inferior vena cava, aorta, or celiac axis, or (4) distant metastases.
Through a series of randomized studies published in the 1980s, chemoradiotherapy has become the
accepted standard of care for locally advanced and nonmetastatic carcinoma. **Radiation Therapy
and Chemotherapy**
A Mayo Clinic study and a series of GITSG studies performed primarily in the 1980s demonstrated
that external-beam radiation therapy (EBRT) combined with 5-FU was superior to either radiation or
chemotherapy treatment alone (Table 2).[14-17] In the Mayo Clinic study, 64 patients with
unresectable adenocarcinoma of the pancreas were randomized to 40 Gy radiation with either
concurrent 5-FU or concurrent placebo. The median survival for the chemotherapy patients was 10.4
months, compared with only 6.3 months for those receiving placebo. In a similar GITSG trial that
evaluated 194 patients with surgically confirmed unresectable and nonmetastatic disease, survival
was improved when a combined treatment of either 40 Gy for 6 weeks or 60 Gy for 10 weeks plus
5-FU (2 to 3 cycles with maintenance 5-FU after radiation) was used as compared with radiation
therapy alone using 60 Gy.[15] Combined-modality therapy using 60 Gy showed the greatest benefit
compared with combined chemotherapy with a 40-Gy dose or therapy with 60 Gy radiation alone;
the 1-year survival was 10% for radiation alone, 35% for 40 Gy combined therapy, and 46% for 60
Gy combined therapy. Follow-up GITSG studies were conducted to further clarify the benefit of
different chemotherapeutic regimens with radiation therapy in these patients. One trial was
designed to compare radiation plus either 5-FU or doxorubicin. In this trial, 157 patients were
randomized to either 60 Gy split-course EBRT with concurrent and maintenance 5-FU, or 40 Gy
continuous-course radiation with concurrent doxorubicin and maintenance doxorubicin plus 5-FU. No
survival advantage was seen with either treatment arm; however, those patients receiving
doxorubicin experienced significantly higher rates of treatment-related toxicity ($P < .05$).[16]
Another study compared the combined treatment of streptozocin (Zanosar)/mitomycin/5-FU (SMF)
chemotherapy alone to 5-FU chemotherapy plus radiation followed by adjuvant SMF chemotherapy.
This trial enrolled 48 patients randomly assigned to chemotherapy alone or chemoradiation. The 1-year
survival for patients receiving chemoradiation was 41% compared with 19% of patients receiving
In these trials, it was shown that the combination of radiation therapy and chemotherapy was superior to radiation (1-year survival, 40% vs 10%) or chemotherapy alone (1-year survival, 41% vs 19%). However, when the Eastern Cooperative Oncology Group (ECOG) performed a similar evaluation in 91 patients with locally unresectable adenocarcinoma of the pancreas, no survival benefit was shown with the use of concurrent bolus 5-FU during week 1 with 40 Gy radiation compared to 5-FU chemotherapy alone.[18] The median survival was 8.3 months with the combined treatment vs 8.2 months following treatment with 5-FU alone. The 1-year survival was 26% for patients receiving combination therapy and 32% for those receiving 5-FU. In this study, no patients received maintenance chemotherapy. With the exception of the ECOG study, conventional external-beam radiation combined with 5-FU appears to provide some survival benefit over monotherapy with radiation therapy or chemotherapy for patients with locally advanced unresectable pancreatic tumors. As a result, combined-modality therapy with 5-FU and external-beam radiation has become a frequently used treatment. While multimodality treatment with 5-FU has shown modest benefit, recent investigative efforts have moved to evaluation of gemcitabine combinations with radiation therapy. These studies have been prompted as a result of phase III trials showing efficacy of gemcitabine in the treatment of patients with metastatic pancreatic cancer.[19] In a large multicenter randomized trial of patients with locally advanced or metastatic disease, clinical benefit and median survival were significantly improved with the use of gemcitabine as compared to treatment with 5-FU (5.65 months vs 4.41 months). One-year survival was 18% with gemcitabine and 2% with 5-FU (P = .003); however, survival was not extended beyond 19 months. In an attempt to further improve these results, ECOG performed a phase III trial (E2297) of gemcitabine in combination with 5-FU vs gemcitabine alone, no significant survival benefit was observed between the single-agent or combination therapies.[20] On the other hand, a small institutional phase II study evaluating weekly gemcitabine (1,000 mg/m²) with 5-FU (2,000 mg/m²) in 23 patients for 3 consecutive weeks followed by 1 week without treatment until tumor progression occurred suggests that the gemcitabine/5-FU combination may improve 1-year survival and median survival.[21] As compared with prior results with gemcitabine alone,[20] the combination therapy demonstrated a 1-year survival rate of 30% (vs 18%) and a median survival time of 8.3 months (vs 5.65 months). Clearly, these phase II results in the metastatic setting need to be evaluated in a phase III trial to know whether there is true benefit of the combination. The Cancer and Leukemia Group B (CALGB) has released early phase II results of its chemoradiation trial in which gemcitabine was used as a radiation sensitizing agent at 40 mg/m² twice weekly in combination with 50.4 Gy radiation to the upper abdomen. With 38 evaluable patients, the study has concluded that toxicity is manageable and median survival is encouraging with chemoradiation, especially for patients with a performance status of 0, where median survival was 13.7 months as compared with 7.8 months for those with a performance status of 1 or 2.[22] The follow-up study in CALGB is evaluating weekly gemcitabine combined with infusional 5-FU during

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Radiation Dose</th>
<th>Chemotherapy Agent</th>
<th>Grade 4 Toxicities</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic[14]</td>
<td>40 Gy</td>
<td>5-FU</td>
<td>–</td>
<td>MS: 10.4 mo</td>
</tr>
<tr>
<td>GITSG[15]</td>
<td>40-60 Gy</td>
<td>5-FU</td>
<td>9%</td>
<td>1-yr survival: 35% (40 Gy), 46% (60 Gy)</td>
</tr>
<tr>
<td>GITSG[16]</td>
<td>60 Gy</td>
<td>5-FU</td>
<td>35%</td>
<td>NR</td>
</tr>
<tr>
<td>GITSG[17]</td>
<td>54 Gy</td>
<td>5-FU + SMF</td>
<td>50%</td>
<td>1-yr survival: 41%</td>
</tr>
<tr>
<td>ECOG[18]</td>
<td>40 Gy</td>
<td>5-FU</td>
<td>51%</td>
<td>MS: 8.2 mo</td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group; 5-FU = fluorouracil; GITSG = Gastrointestinal Tumor Study Group; MS = median survival; NR = not reported; SMF = streptozocin/mitomycin/5-FU.

In these trials, it was shown that the combination of radiation therapy and chemotherapy was superior to radiation (1-year survival, 40% vs 10%) or chemotherapy alone (1-year survival, 41% vs 19%). However, when the Eastern Cooperative Oncology Group (ECOG) performed a similar evaluation in 91 patients with locally unresectable adenocarcinoma of the pancreas, no survival benefit was shown with the use of concurrent bolus 5-FU during week 1 with 40 Gy radiation compared to 5-FU chemotherapy alone.[18] The median survival was 8.3 months with the combined treatment vs 8.2 months following treatment with 5-FU alone. The 1-year survival was 26% for patients receiving combination therapy and 32% for those receiving 5-FU. In this study, no patients received maintenance chemotherapy. With the exception of the ECOG study, conventional external-beam radiation combined with 5-FU appears to provide some survival benefit over monotherapy with radiation therapy or chemotherapy for patients with locally advanced unresectable pancreatic tumors. As a result, combined-modality therapy with 5-FU and external-beam radiation has become a frequently used treatment. While multimodality treatment with 5-FU has shown modest benefit, recent investigative efforts have moved to evaluation of gemcitabine combinations with radiation therapy. These studies have been prompted as a result of phase III trials showing efficacy of gemcitabine in the treatment of patients with metastatic pancreatic cancer.[19] In a large multicenter randomized trial of patients with locally advanced or metastatic disease, clinical benefit and median survival were significantly improved with the use of gemcitabine as compared to treatment with 5-FU (5.65 months vs 4.41 months). One-year survival was 18% with gemcitabine and 2% with 5-FU (P = .003); however, survival was not extended beyond 19 months. In an attempt to further improve these results, ECOG performed a phase III trial (E2297) of gemcitabine in combination with 5-FU vs gemcitabine alone, no significant survival benefit was observed between the single-agent or combination therapies.[20] On the other hand, a small institutional phase II study evaluating weekly gemcitabine (1,000 mg/m²) with 5-FU (2,000 mg/m²) in 23 patients for 3 consecutive weeks followed by 1 week without treatment until tumor progression occurred suggests that the gemcitabine/5-FU combination may improve 1-year survival and median survival.[21] As compared with prior results with gemcitabine alone,[20] the combination therapy demonstrated a 1-year survival rate of 30% (vs 18%) and a median survival time of 8.3 months (vs 5.65 months). Clearly, these phase II results in the metastatic setting need to be evaluated in a phase III trial to know whether there is true benefit of the combination. The Cancer and Leukemia Group B (CALGB) has released early phase II results of its chemoradiation trial in which gemcitabine was used as a radiation sensitizing agent at 40 mg/m² twice weekly in combination with 50.4 Gy radiation to the upper abdomen. With 38 evaluable patients, the study has concluded that toxicity is manageable and median survival is encouraging with chemoradiation, especially for patients with a performance status of 0, where median survival was 13.7 months as compared with 7.8 months for those with a performance status of 1 or 2.[22] The follow-up study in CALGB is evaluating weekly gemcitabine combined with infusional 5-FU during
radiation therapy. Paclitaxel has also been investigated in this setting due to its enhanced radiosensitizing effects in preclinical studies. A phase I study at Brown University found the maximum tolerated dose of weekly paclitaxel to be 50 mg/m^2 when given with 50 Gy of EBRT. This combination yielded a 31% response rate among 13 evaluable patients. In a follow-up phase II study, also at Brown University, this same dosing combination yielded a 26% response rate, and a 1-year survival rate of 30%.[23] Potential Surgical Resection After Chemoradiation of Locally Advanced Pancreatic Cancer

Despite improvements in survival with chemoradiation, surgery remains the only potentially curative treatment for pancreatic cancer. Chemoradiation has been employed in an effort to promote tumor regression and facilitate resection for patients with locally advanced tumors. Investigators from New England Deaconess Hospital treated 16 patients with unresectable tumors with preoperative 5-FU chemotherapy followed by 45 Gy of EBRT and infusional 5-FU. Two of the patients (13%) were able to undergo resection following treatment.[24] Similar results were found in a Duke University study in which two patients (8%) were able to be resected after first being treated with 45 Gy of EBRT and 5-FU with or without cisplatin or mitomycin.[25] A phase I dose-ranging study of twice-weekly gemcitabine (10 mg/m^2 to maximum tolerated dose of approximately 50 mg/m^2) in combination with EBRT administered to 21 patients with advanced adenocarcinoma of the pancreas found that treatment enabled surgical resection in three patients who had previously unresectable tumors.[26]

In a phase II study, weekly gemcitabine (1,000 mg/m^2) was given during an induction phase of 7 weeks, followed by a combination of weekly gemcitabine (400 mg/m^2) with 50.4 Gy radiation in 28 fractions in those who had evidence of benefit from initial chemoradiation. Three patients underwent surgical resection. Results show an overall median survival of 8 months (all groups combined). Interestingly, at the time of publication, the median survival for the chemoradiation group had not yet been reached.[27] A retrospective analysis of patients with locally advanced unresectable pancreatic cancer treated concurrently with weekly gemcitabine (250 to 500 mg/m^2) and radiation therapy (30 to 33 Gy in 10 to 11 fractions over 2 weeks) showed a median survival of 11 months with 37 of 51 patients eventually progressing.[28] While six patients were later able to undergo pancreaticoduodenectomy, the combination treatment was difficult to administer safely. Clearly, EBRT with chemotherapy offers survival benefit as well as palliation of pain associated with the tumor. In the United States, combined-modality therapy has been adopted as the standard treatment for patients with locally advanced pancreatic cancer. While these combined treatments increase median survival for patients with locally advanced carcinoma, treatment resulting in long-term survival is rare. As a result, there have been renewed efforts to enhance patient outcomes and longterm survival by improving patient selection through better staging of the disease, and to offer treatments with palliative benefits. Palliative Benefits From Chemoradiation

Despite improvements in shortterm survival with therapy, patients with locally advanced pancreatic cancer will ultimately die of their disease. It is for this reason that treatments with palliative benefits that can improve quality of life remain an important priority in the management of this disease. Unfortunately, improvements in pain, anorexia, or fatigue are not well documented in many of the studies. Pain relief has been documented in some of the larger studies, including one using intraoperative electron-beam radiation therapy where relief was obtained in 50% to 80% of patients.[29] External-beam radiation therapy with or without chemotherapy has also been associated with pain relief in 35% to 65% of patients.[15,29,30] A few other studies have reported more subtle improvements in performance status and anorexic symptoms.[29-31]

Diagnostic Tools and Patient Selection

Currently available tools for the diagnosis and staging of pancreatic cancer patients include helical computed tomography (CT) scans, endoscopic ultrasonography, MRIs, PET scans, and laparoscopy and washings. These imaging techniques have aided physicians in characterizing the tumor site, determining the feasibility of resection, and identifying the absence or presence of metastasis. After appropriate staging and definition of extent of disease, patients can then be counseled regarding available therapies and ongoing clinical trials. Computed Tomography

Computed tomography scanning of the abdomen is the most commonly used tool for diagnosis and staging. Newer-generation and higher-speed machines now provide contrast enhancement and thin-section imaging.[32] As such, motion-free high-resolution images, including 3D reconstruction of the pancreas, are available to define resectability of the lesion. A tumor may be resected if there is no extrapancreatic involvement (eg, no extensive parapancreatic lymph or distant involvement), no encasement or occlusion of the superior mesenteric vein (SMV) or SMV-portal vein confluence, and no direct involvement of the superior mesenteric artery, inferior vena cava, aorta, or celiac axis. A recent study assessing the resectability of pancreatic tumors preoperatively using CT scanning
verified the accuracy of CT scanning by finding that, with the above criteria, most tumors (> 90%) considered unresectable by CT scanning were also considered unresectable at laparotomy.[33] Similarly, a second analysis concluded that the determination of resectability of a pancreatic carcinoma was best done with dual-phase helical CT. The analysis further suggested that for improved accuracy of diagnosing lymph node involvement by pancreatic cancer, endosonography with fine-needle aspiration should be used; this is especially true in patients with suspected carcinoma, even those with negative biopsy results.[34] Combined CT/PET scan imaging is further enhancing the ability to define extent of disease. MRI scans are also being employed to aid in evaluation of the extent of pancreatic cancer. Newer imaging contrast agents may be helpful in detecting the presence of metastases, even in small lymph nodes. Ongoing improvements in all of these technologies should continue to refine the ability to stage this malignancy. **Endoscopic Ultrasound**

Endoscopic ultrasonography has proven to be useful in further characterizing the extent of the local disease.[35] This procedure allows fine-needle biopsy of the pancreatic neoplasm and regional nodes, allowing for diagnosis and staging without exploratory surgery while decreasing the potential for tumor seeding.[36] The procedure is often performed at the time of an endoscopic retrograde cholangiopancreatography for the assessment of pancreatic neoplasms.[37]

### Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Median Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massachusetts General Hospital[42] (n = 29)</td>
<td>EBRT 10-20 Gy preoperative + 30-40 Gy postoperative + IOERT 15-20 Gy ± chemotherapy</td>
<td>16.5 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Massachusetts General Hospital[43] (n = 63)</td>
<td>IOERT 15-20 Gy + EBRT (n = 22)</td>
<td>16.5 mo</td>
<td>1 yr: 77%</td>
</tr>
<tr>
<td></td>
<td>IOERT 15-20 Gy + misonidazole 3.5 g/m² (n = 41) + EBRT</td>
<td>12.0 mo</td>
<td>2 yr: 33%</td>
</tr>
<tr>
<td>Mayo Clinic[44] (n = 27)</td>
<td>EBR 50-54 Gy ± 5-FU → IOERT 20 Gy</td>
<td>14.9 mo</td>
<td>2 yr: 27%</td>
</tr>
</tbody>
</table>

**EBRT = external-beam radiation therapy; IOERT = intraoperative electron-beam radiation therapy; NR = not reported.**

### Staging

**Laparoscopy**

Staging laparoscopy allows direct visualization of the liver, peritoneum, and omentum, and can identify 1- to 2-mm metastatic nodules in patients with potentially resectable or locally advanced disease. If metastatic disease is encountered, laparotomy can be avoided. In one study of 114 patients with no evidence of metastasis by CT, laparoscopy was able to identify metastatic disease in 27 patients (~24%).[38] Interestingly, a small study of 64 patients designed to compare endoscopic sonography with helical CT for the identification and staging of pancreatic ductal adenocarcinoma found that endoscopic sonography was more accurate than helical CT (95.3% vs 89.1%). For those who underwent laparotomy (n = 43), however, helical CT more accurately predicted resectability than did endosonography (86% vs 81.4%). With the advent of new laparoscopic hand-access devices, a surgeon is now able to place a hand in the abdomen and perform functions previously possible only during open surgery.[40] Peritoneal washings may be combined with laparoscopy to assess the presence or absence of malignant cells in peritoneal fluid. For patients without visible metastases at laparoscopy but cytologic involvement in peritoneal washings, survival rates are similar to patients with macroscopic metastatic disease.[39] Laparoscopic ultrasound may be helpful in the diagnosis and staging of local pancreatic lesions.[41] With this technique, the head and body
of the pancreas are visualized by retroduodenal or infragastric approaches, respectively. When combined with laparoscopic manipulations, laparoscopic ultrasonography is able to assess the size and extent of local disease. **Improvements in Radiation Therapy**

### Intraoperative Electron-Beam Therapy

Because of the high rates of local progression following EBRT and 5-FU-based chemotherapy, many investigators have evaluated the role of intraoperative radiation therapy (IORT) in patients with locally advanced pancreatic cancer. The median survival of patients in these trials did not seem to be superior to those studies without the use of IORT. In a phase II study at Thomas Jefferson University Hospital, local failure was reported in 31% of patients. In a Mayo Clinic retrospective study of 159 patients treated similarly with 5-FU and EBRT, with some patients receiving an additional boost of IORT, local control was significantly higher at 1 year (82% vs 66%) and 2 years (48% vs 20%) in the patients receiving IORT. Nevertheless, survival was similar in both groups. It has become clear that the rapid appearance of metastatic disease offsets any improvement in local control offered by intraoperative radiation therapy (Table 3).[42-44] **Three-Dimensional Conformal Radiation Therapy**

Three-dimensional conformal radiation therapy is also being applied to treatment of patients with pancreatic cancer. This CT-based treatment is designed to allow "unconventional" beam orientations at the target site, permitting coverage with higher target volume and reduced irradiation to nontargeted tissues. For irradiation of the pancreas, it is important to reduce harmful doses to other organs such as the kidney, especially given the marked radiosensitivity of this organ. This has been successfully performed with 3D conformal radiotherapy by optimizing beam orientation and weightings to reduce the dose received by other nearby organs. By an intensity- modulated approach, the technique has been further refined so that inverse treatment planning can be performed. Here, a computer-based treatment protocol is devised, including a nonuniform radiation treatment that is delivered to the target, negating the standard trial-and-error planning approach used in the past. As these techniques evolve, it is likely that ever-increasing improvements in radiation dosing and treatment tolerance will be observed with reduced surrounding tissue morbidities. Additional techniques will likely include positron emission tomography and CT fusion.

### Newer Chemotherapeutics Combined With Radiation Therapy

New cytotoxic agents and targeted therapies are being investigated in several clinical trials. Many are being studied in combination with gemcitabine, the standard first-line agent in patients with advanced and metastatic cancer of the pancreas. Agents being evaluated include chemotherapeutic agents (eg, irinotecan [CPT-11, Camptosar-a topoisomerase I inhibitor], docetaxel [Taxotere], oxaliplatin [Eloxatin], pemetrexed [Alimta, an antifolate]); and molecularly targeted agents (eg, tipifarnib [R-115777, a farnesyltransferase inhibitor], trastuzumab [Herceptin, an anti-HER2/neu antibody], and cetuximab [Erbitux, an epidermal growth factor receptor inhibitor], and smallmolecule inhibitors of epidermal growth factor receptor, such as gefitinib [Iressa] or erlotinib [Tarceva] and bevacizumab [Avastin]). A number of approaches utilizing gene therapy are in trials. ONYX-015, an E1B 55-kD gene-deleted replication- selective adenovirus, is being studied in a phase I trial in 21 patients with locally advanced or metastatic disease. The virus is injected by endoscopic ultrasound into unresectable pancreatic carcinomas and delivered over 8 weeks at doses of 2 *10^10 to 2 *10^11 particles/treatment, combined with gemcitabine (1,000 mg/m^2) for the last 3 weeks.[45] Early results have indicated some activity: 2 of 21 patients had partial tumor regression, 2 experienced minor responses, 6 had stable disease, and 11 experienced progression or were removed from the study due to treatment toxicities. Phase II/III trials are ongoing. Immunologic approaches are also under evaluation, especially using vaccines. Here, immunotherapy is perceived as having the potential to offer alternative mechanisms of antitumor activity in an integrated approach with current regimens such as surgery or chemoradiation. For example, results of a phase I study using an interferonmodified whole-cell irradiated tumor vaccine with granulocyte-macrophage colony-stimulating factor (GM-CSF) showed that median survival with treatment was 19 weeks in 15 evaluable patients with metastatic disease; 7 patients survived > 6 months and 4 patients survived > 50 weeks.[46] The analysis also revealed a strong correlation for survival with a decrease in the marker CA 19-9 within 6 weeks of treatment, thus showing a biologic response to the vaccine that was not identified by imaging studies. Ongoing studies are underway. The effects of a novel GM-CSF- secreting pancreatic tumor vaccine for the treatment of patients with surgically resected cancer of the pancreas has also been studied.[47] In this phase I trial, 14 patients with stage I-II cancer were administered the vaccine 8 weeks after pancreaticoduodenectomy at doses of 1-50 107 vaccine cells. Twelve of the patients then received chemoradiation for an additional 6 months following surgery. Six patients completed chemoradiation treatment and received three additional monthly vaccinations. Three of the patients
have remained disease-free for at least 25 months after diagnosis. Further evaluation of the vaccine is ongoing, as it was suggested that the vaccine may induce dose-dependent systemic antitumor immune response. **Conclusion** The treatment of pancreatic cancer remains a formidable challenge. Technological advances in imaging and surgery have allowed more precise staging and administration of radiation to patients with locally advanced pancreatic cancer. Studies performed in the 1980s and 1990s have demonstrated that palliation is achievable for a high percentage of patients, especially via a combined-modality approach. For patients with good performance status, chemoradiation is the treatment of choice. For those with marginal or poor performance status, single-agent gemcitabine is a reasonable alternative to prolong survival and improve quality of life. Despite advances in palliation, the limited increase in survival benefit achieved to date warrants additional clinical trials to further improve adjuvant therapies, radiation treatment fields, and dose/fractionation combinations, and to explore the potential of novel biologic therapies.

**Disclosures:** The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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