Treatment of Pancreatic Cancer

a report by

Gauri R Varadhachary, MD *and* **James L Abbruzzese, MD, FACP**

Assistant Professor, and Chairman, Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center

DOI: 10.17925/OHR.2005.00.00.1e

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death and has the highest case fatality rate. In 2004, approximately 31,860 new cases will be diagnosed, and 31,270 of affected patients are expected to die from their disease.[1] Patients usually present with advanced disease, and two-thirds of them either have locally advanced or metastatic disease. Presentation may depend on location of the primary, with more pain in patients with tumors involving the body and tail of the pancreas, and obstructive jaundice in patients presenting with pancreatic head cancer, though symptoms including weight loss, those associated with new onset diabetes, and thrombophlebitis (Trousseau's syndrome) can occur with either presentation. The majority of patients have ductal adenocarcinoma on pathology. For the few selected 15% to 20% of patients who present with a resectable tumor by radiographic criteria and undergo surgery, the five-year survival rate is only 20% and it is worse in node-positive patients.[2,3] Determining resectability is an important first step and in most cases can be accomplished by a computerized tomography (CT) scan optimized for pancreatic imaging. Based on CT scan findings (with help from endoscopic ultrasound if needed), patients can be categorized as those with potentially resectable cancer, borderline resectable cancer, unresectable locally advanced cancer, and metastatic pancreatic cancer. *Figure 1* outlines the approach to a patient with suspected pancreatic cancer.

Resectable and Borderline Resectable Pancreatic Cancer

Staging Criteria and Role of Pancreaticoduodenectomy

American Joint Committee on Cancer (AJCC) tumor, node, metastases (TNM) staging for pancreatic cancer was revised in 2002 and is presented in *Table 1*.[4] Based on this, stages 3 and 4 are considered unresectable. Resectability criteria include a clear fat plane around celiac and superior mesenteric arteries (SMA), a patent superior mesenteric vein (SMV) and portal vein, and no distant metastases. Patients are considered to have 'borderline' resectable cancer if the CT scan shows cuffing or abutment to a portion of the SMA or celiac axis, severe unilateral SMV or portal vein impingement, or gastroduodenal artery (GDA) encasement up to origin at hepatic artery. These distinctions can usually be made without a pre-operative laparoscopy or endoscopic ultrasound, although most patients, once prepared for a pancreaticoduodenectomy (Whipple procedure), do undergo intra-operative laparoscopy. An additional 20% to 40% of patients may be found to be unresectable due to a small volume of peritoneal or hepatic metastases not visualized by CT. In high-volume centers, the peri-operative mortality from pancreaticoduodenectomy is less than 2%. Even after a potentially curative resection most patients recur, and five-year survivals are rare. Important prognostic features include tumor size (<2cm), lymph node involvement, and histologic grade.[2,5] Post-operative complications include anastomotic leaks, delayed gastric emptying, thrombosis, infection, and bleeding.

Adjuvant Therapy for Resected Pancreatic Cancer

There are conflicting results from randomized controlled trials regarding the benefit of adjuvant chemoradiation. The Gastrointestinal Tumor Study Group (GITSG) conducted the first prospective study involving 22 patients. Patients were randomized to receive no adjuvant therapy versus radiation and 5-fluorouracil (5-FU). Median survival was 10.9 months for the control arm and 21 months for the treatment arm.[6] These results were replicated by the GITSG in a follow-up study with an additional 30 patients who were treated with adjuvant therapy. The registered patients demonstrated a median survival of 18 months.[7]

The European Organisation for Research and Treatment of Cancer (EORTC) randomized 114 patients with resected pancreatic cancer to receive either adjuvant concurrent chemoradiation or observation. No survival benefit was found for the adjuvant group.[8]

More recently, Neoptolemos and colleagues of the European Study Group (ESPAC) challenged the GITSG and EORTC results in their randomized study of 541

Gauri R Varadhachary, MD

James L Abbruzzese, MD, FACP

Gauri R Varadhachary, MD, is in the Department of Gastrointestinal Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston, Texas. She is a member of the American Society of Clinical Oncology. Her clinical interests center on pancreatic cancer and cancer of the unknown primary site, and she is involved in several clinical trials involving these cancers.

James L Abbruzzese, MD, FACP, is the MG and Lillie A Johnson Chair for Cancer Treatment and Research, and Chairman of the Department of Gastrointestinal Medical Oncology at the University of Texas MD Anderson Cancer Center. Dr Abbruzzese is a member of a number of numerous scientific advisory boards including the external scientific advisory board for the University of Massachusetts, and The Lustgarten Foundation for Pancreatic Cancer Research. He is a member of the American Association for Cancer Research (AACR) Research Fellowships Committee and the American Society of Clinical Oncology (ASCO) Grant Awards and Nominating Committees, among others.

Table 1: AJCC Staging of Pancreatic Cancer

Primary tumor (T)	
TX	*Primary tumor cannot be assessed*
T0	*No evidence of primary tumor*
Tis	In situ *carcinoma*
T1:	*Tumor limited to the pancreas 2cm or less in greatest dimension*
T2:	*Tumor limited to the pancreas more than 2cm in greatest dimension*
T3:	*Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery*
T4:	*Tumor involves the celiac axis or the superior mesenteric artery (unresectable tumor)*
Regional lymph nodes (N)	
NX	*Regional lymph nodes cannot be assessed*
N0	*No regional lymph node metastasis*
N1	*Regional lymph node metastasis*
Distant metastasis (M)	
MX	*Distant metastasis cannot be assessed*
M0	*No distant metastasis*
M1	*Distant metastasis*

Table 2: AJCC Stage Groupings

Stage 0	*Tis N0 M0*
Stage I A	*T1 N0 M0*
Stage I B	*T2 N0 M0*
Stage II A	*T3 N0 M0*
Stage II B	*T1–3 N1 M0*
Stage III	*T4 Any N M0*
Stage IV	*Any T Any N M1*

patients comparing adjuvant chemoradiation, chemotherapy alone, both or observation initially planned to include a 2x2 factorial design.[9] The investigators felt that this approach may restrict accrual so they expanded the study to allow two more randomization options of chemoradiotherapy or chemotherapy only. The treating physician was allowed to select the randomization option that they wished and provide information on 'background therapy'. The investigators presented data that included all three randomization arms (which was criticized for its design) and then separately presented final results that focused on the 2x2 original factorial design involving 289 patients. The final analysis on the 2x2 factorial design reported earlier this year concluded that adjuvant chemotherapy provided a survival advantage and chemoradiotherapy had a deleterious effect on survival.[10]

A recent phase II study by Picozzi et al. (Virginia Mason study) reported data on 43 patients treated with adjuvant therapy consisting of radiation and chemotherapy with 5-FU, cisplatin, and alpha-interferon.[11] This study reported a median survival of >36 months and a five-year survival of approximately 50%. A large multi-institutional study is underway to see if these results can be validated. It appears from these various studies that some form of adjuvant therapy is probably beneficial and can extend median survival by eight to 10 months. In the US, chemoradiation is still preferred, and in Europe chemotherapy alone is favored given the results of ESPAC-1.

Neoadjuvant Approach to Potentially Resectable Pancreatic Cancer

Approximately 40% of patients are unable to be treated with post-operative adjuvant therapy after a pancreaticoduodenectomy because of post-operative complications. The rationale for using neoadjuvant therapy is to shrink the tumor, which allows easier surgery, treat micrometastatic disease and give the patient the option to take the 'adjuvant' therapy with better tolerance when given pre-operatively. This approach also allows time to gauge the aggressiveness of the cancer and only takes patients with a favorable outlook to major surgery. In one study reported by Spitz et al., 142 patients with potentially resectable pancreatic cancer were treated with pre-operative versus post-operative chemoradiation.[12] They concluded that rapid fractionation pre-operative therapy resulted in similar survival, treatment toxicity, and patterns of recurrence. Rapid-fractionation pre-operative chemoradiation could be delivered over a shorter period of time compared with standard fractionation given pre- or post-operatively. Also, approximately 25% of the patients in the post-operative arm were unable to take post-operative chemoradiation due to problems with prolonged recovery. Enrollment in clinical trials should be encouraged to study this further.

Locally Advanced Unresectable Pancreatic Cancer

Pancreatic cancer is considered unresectable if the superior mesenteric artery, celiac axis, inferior vena cava, or aorta are directly involved with tumor. In most cases involvement of the superior mesenteric vein and superior mesenteric vein–portal vein confluence is also unresectable. Patients who have distant metastasis are obviously unresectable as well as patients with large/bulky peripancreatic adenopathy. A CT scan optimized for pancreatic imaging can assess resectability in most patients. Occasionally, endoscopic ultrasound or laparoscopy/laparotomy is needed. Radiation, chemotherapy, and chemoradiation are the current treatment options available and the best sequence is not clear. GITSG reported two studies (in 1979 and 1981) comparing the role of 5-FU with radiation to radiation alone.[13] Both studies reported improvement in median survival by 16–20 weeks for patients receiving chemoradiation, whereas an Eastern Cooperative

Oncology Group study (ECOG), which compared 5-FU alone with radiation plus concurrent and maintenance 5-FU, reported no difference in median survival (8.2 months for both arms) in 91 pancreatic cancer patients.[14]

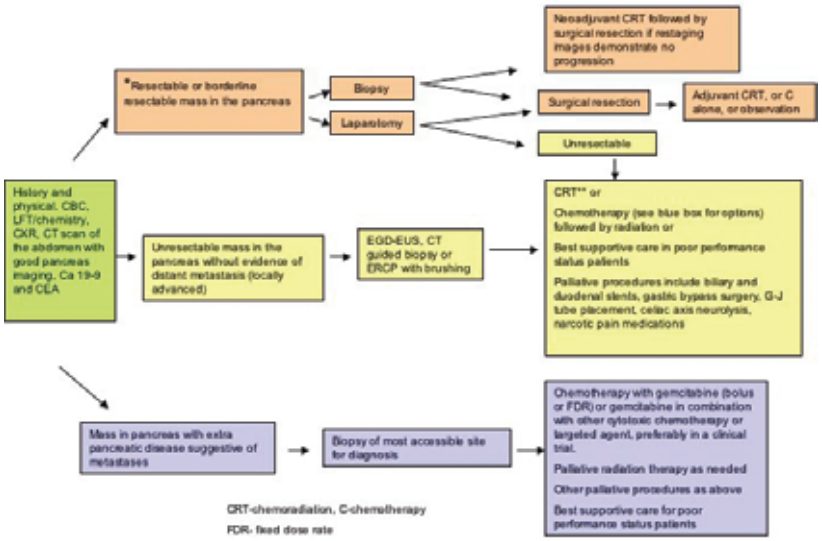
Gemcitabine has been combined with radiation in patients with locally advanced pancreatic cancer. Blackstock and colleagues reported the safety and efficacy data of twice-weekly doses of gemcitabine and concurrent radiation to the upper abdomen followed by weekly gemcitabine in patients with surgically staged, locally advanced pancreatic cancer.[15] Thirty-nine patients were evaluable for treatment response. Overall median survival was 8.2 months, and 13.5 months in 44% of patients who showed a sustained CA19-9 response. Grade III and IV hematologic toxicity occurred in 48% and 21% of patients, respectively. Grade III and IV gastrointestinal toxicities occurred in 31% and 10% of patients, respectively. This trial failed to show survival advantage with this regimen over previously reported studies. Other strategies, including bevacizumab in combination with capecitabine and radiation, are currently being studied in patients with locally advanced pancreatic cancer.

Metastatic Pancreatic Cancer

5-FU was used in metastatic pancreatic cancer for four decades prior to the availability of gemcitabine. Gemcitabine, a nucleoside analog, was the first drug to be approved by the US Food and Drug Administration (FDA) for its clinical benefit response (i.e., improvement in pain, weight loss, or performance status) rather than objective response rate or survival in patients with metastatic pancreatic cancer. In the pivotal study comparing 5-FU to gemcitabine, 24% of the gemcitabine-arm patients experienced a clinical benefit response compared with 4.8% of 5-FU-treated patients (p=0.0022). The median survival durations were 5.65 and 4.41 months for gemcitabine and 5-FU-treated patients, respectively (p=0.0025). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients.[16] Gemcitabine, given as a fixed dose rate (FDR) infusion, is associated with an increase in the intracellular gemcitabine triphosphate. In a phase II randomized trial when FDR was compared with 30-minute bolus infusion, the median survival was eight months versus five months, and one year survival was 29% versus 9% respectively.[17]

Several cytotoxic agents have been combined with gemcitabine including cisplatin, docetaxel, irinotecan, capecitabine, and oxaliplatin. Though the response rates are slightly higher no study has shown a survival benefit (survival eight to 11 months).[18-21] Studies with matrix metalloproteinase inhibitors and farnesyl transferase

Figure 1: Treatment of Algorithm for Pancreatic Cancer



inhibitors have not been very promising. Currently, other targeted agents including cetuximab, erlotinib, and bevacizumab are being studied in combination with cytotoxic therapy as first-line therapy.[22,23] There is no standard second-line therapy for pancreatic cancer despite the fact that several combinations have been tried with minimal benefit.

Non-chemotherapeutic Palliative Measures

Palliation of pain, biliary obstruction, and duodenal obstruction are important issues contributing to the optimal management of patients with pancreatic cancer. In a non-surgical setting, obstructive jaundice is palliated with either an expandable metal stent or a percutaneous trans-hepatic drainage. Metal stents are preferred to plastic stents because of longer functional life. There is no data suggesting a survival benefit for surgical bypass over non-surgical procedures if the patient has unresectable disease. Patients with duodenal obstruction (leading to gastric outlet obstruction) are candidates for palliative gastrojejunostomy, enteric stents or a gastrostomy–jejunostomy (G-J) drainage and feeding tube depending on the extent of disease, performance status, and life expectancy.

Prokinetic agents are sometimes helpful in cases of delayed gastric emptying. Pain control is of utmost importance because most patients with advanced disease have pain, which can have a very significant effect on their quality of life. Narcotic analgesia controls pain in most of the patients, and some patients are candidates for celiac axis neurolysis. Palliative radiation to the primary tumor is sometimes helpful for pain control, obstructive symptoms, or to control bleeding because of tumor invasion into the duodenum.

Summary

Pancreatic cancer is an aggressive disease with only 15% to 20% of patients with resectable disease surviving five years. Most patients present with either locally advanced or metastatic disease and have a poor median survival of six to 12 months. Gemcitabine is the current standard of care for advanced pancreatic cancer. Combining other cytotoxic agents with gemcitabine has not shown a survival advantage. The role of targeted agents is under evaluation, and perhaps a better understanding of the molecular targets and pharmacogenomics in pancreatic cancer will help to develop better treatments and select responders from non-responders thereby individualizing therapy for patients with pancreatic cancer. ■

References:

1. *Jemal A, Tiwari R C, Murray T, et al., "Cancer statistics, 2004",* CA Cancer J. Clin. *(2004), 54: pp. 8–29.*
2. *Benassai G, Mastrorilli M, Quarto G, et al., "Survival after pancreaticoduodenectomy for ductal adenocarcinoma of the head of the pancreas",* Chir. Ital. *(2000), 52: pp. 263–270.*
3. *Yeo C J, Cameron J L, Lillemoe K D, et al., "Pancreaticoduodenectomy for cancer of the head of the pancreas, 201 patients",* Ann. Surg. *(1995), 221: pp. 721–731; discussion pp. 731–733.*
4. *(AJCC) AJCoC: AJCC Cancer staging Manual, AJCC Cancer staging Manual (ed sixth edition), Springer-Verlag New York, Inc., 2002.*
5. *Lim J E, Chien M W and Earle C C, "Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients",* Ann. Surg. *(2003), 237: pp. 74–85.*
6. *Kalser M H and Ellenberg S S, "Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection",* Arch. Surg. *(1985), 120: pp. 899–903.*
7. *Gastrointestinal Tumor Study Group, "Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer",* Cancer *59: pp. 2,006–2,010, 1987.*
8. *Klinkenbijl J H, Jeekel J, Sahmoud T, et al., "Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group",* Ann. Surg. *(1999), 230: pp. 776–782; discussion pp. 782–784.*
9. *Neoptolemos J P, Dunn J A, Stocken D D, et al., "Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial",* Lancet *(2001), 358: pp. 1,576–1,585.*
10. *Neoptolemos J P, Stocken D D, Friess H, et al., "A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer",* N. Engl. J. Med. *(2004), 350: pp. 1,200–1,210.*
11. *Picozzi V J, Kozarek R A and Traverso L W, "Interferon-based adjuvant chemoradiation therapy after pancreaticoduodenectomy for pancreatic adenocarcinoma",* Am. J. Surg. *(2003), 185: pp. 476–480.*
12. *Spitz F R, Abbruzzese J L, Lee J E, et al., "Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas",* J. Clin. Oncol. *(1997), 15: pp. 928–937.*
13. *Moertel C G, Frytak S, Hahn R G, et al., "Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group",* Cancer *(1981), 48: pp. 1,705–1,710.*
14. *Klaassen D J, MacIntyre J M, Catton G E, et al., "Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study",* J. Clin. Oncol. *(1985), 3: pp. 373–378.*
15. *Blackstock A W, Tepper J E, Niedwiecki D, et al., "Cancer and leukemia group B (CALGB) 89805: phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas",* Int. J. Gastrointest. Cancer *(2003), 34: pp. 107–116.*
16. *Burris H A, 3rd, Moore M J, Andersen J, et al., "Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial",* J. Clin. Oncol. *(1997), 15: pp. 2,403–2,413.*
17. *Tempero M, Plunkett W, Ruiz Van Haperen V, et al., "Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma",* J. Clin. Oncol. *(2003), 21: pp. 3,402–3,408.*
18. *A H Ko ED, B Schillinger, A P Venook, E K Bergsland, J Allen, M A Tempero; UCSF Comprehensive Cancer Center, San Francisco, CA: A phase II study of fixed-dose rate (FDR) gemcitabine plus cisplatin for metastatic pancreatic adenocarcinoma (PanCa). Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: p. 4,107, 2004.*
19. *Rocha Lima C M, Savarese D, Bruckner H, et al., "Irinotecan plus gemcitabine induces both radiographic and CA 19-9 tumor marker responses in patients with previously untreated advanced pancreatic cancer",* J. Clin. Oncol. *(2002), 20: pp. 1,182–1,191.*
20. *Ryan D P, Kulke M H, Fuchs C S, et al., "A Phase II study of gemcitabine and docetaxel in patients with metastatic pancreatic*

carcinoma", Cancer *(2002), 94: pp. 97–103.*

21. *R. L. Fine DRF, W. Sherman, J. Chabot, R. Ennis, P. Xiao, S. Leventhal, S. Schreibman, J. F. Strauss, H. Richter; New York Presbyterian Hospital-Columbia University, New York, NY; Morristown Medical Oncology Associates, Morristown, NJ; Texas Oncology, Dallas, TX; Boca Raton Hospital, Boca Raton, FL: The GTX regimen: A biochemically synergistic combination for advanced pancreatic cancer (PC). Proc Am Soc Clin Oncol 22: page 281, 2003 (abstr 1129), 2003.*
22. *Bramhall S R, Rosemurgy A, Brown P D, et al., "Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial"*, J. Clin. Oncol. *(2001), 19: pp. 3,447–3,455.*
23. *Xiong H Q, Rosenberg A, LoBuglio A, et al., "Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II Trial"*, J. Clin. Oncol. *(2004), 22: pp. 2,610–2,616.*