[Frontiers in Bioscience 3, e186-192, November 15, 1998]

ADJUVANT THERAPY FOR PANCREATIC CANCER: CURRENT STATUS

William F. Regine, William J. John, and Mohammed Mohiuddin

Departments of Radiation Medicine and Hematology/Oncology, The University of Kentucky Medical Center and Markey Cancer, Lexington KY

Received 4/2/98 Accepted 5/5/98

TABLE OF CONTENTS

1. ABSTRACT

Only 5% to 15% of patients with pancreatic adenocarcinoma are candidates for a potentially curative resection. Evidence that postoperative adjuvant therapy improves outcome has been limited to a single randomized trial of a well tolerated split-course, 5-Flourouracil (5-FU) based, chemoradiation regimen. More aggressive regimens have since been developed and are associated with, at best, a modest improvement in patient outcome. The potentially significant morbidity associated with pancreaticoduodenectomy, which can compromise the delivery of postoperative adjuvant chemoradiation, has led to the development of preoperative (adjuvant/neoadjuvant chemoradiation) regimens in these patients. Although experience suggests that such an approach is feasible, the ultimate impact warrants further evaluation. In addition, despite evolving experiences towards more dose intensive pre or postoperative adjuvant chemoradiation regimens, the problem of distant metastases remains significant. New chemotherapeutic agents, such as gemcitabine, appear to have the potential to produce better results than those achieved over the last quarter century with 5-FU. A cooperative group study has recently been activated and is evaluating its impact in an adjuvant setting when given in addition to 5-FU based chemoradiation. In the meantime, ongoing investigations into optimal integration of different therapeutic modalities, along with advances in surgery, radiation, and systemic therapy, should lead us towards further improvements in outcomes for these patients.

2. INTRODUCTION

Despite the obvious evolution in our three major cancer treatment modalities, surgery, radiation and chemotherapy, the overall survival rate of patients with pancreatic cancer remains dismal. In the United States, the pancreatic cancer death rate has been steadily increasing and the 1997 estimated mortality rate (28,900 per/year) is expected to nearly equal its estimated incidence (29,000 per/year)(1). While this may, in part, be attributed to the limitations and less than optimal integration of our current treatment modalities, it is, in large part, due to the biologically aggressive nature of this cancer problem. Only 10-15% of patients with pancreatic cancer are able to undergo "potentially" curative resection despite which the 5-year survival in these patients is < 20% (2-7). Even amongst the most favorable subset of patients, those with tumor diameters of < 3 cm and/or negative nodal status, as well as microscopically negative margins of resection, the 5-year survival is no more than 36% (3,5-9). Studies by the Gastrointestinal Tumor Study Group (GITSG) have evaluated external beam radiation therapy with or without 5-FU in patients with locally unresectable disease. These studies have shown a definite survival advantage to the use of 5-FU in combination with radiation therapy (10). In addition, series in which the patterns of disease recurrence following pancreatic resection have been mapped suggest that both local and distant recurrences are frequent and thus the addition of chemoradiation may be beneficial (1l,12).

The current status of adjuvant therapy for pancreatic cancer is herein presented. The results of randomized trials will be discussed. Evolving institutional and cooperative group experiences will be updated.

3. POSTOPERATIVE ADJUVANT CHEMORADIATION - RANDOMIZED TRIALS

Results of adjuvant and neoadjuvant chemoradiation trials are summarized in table 1. Amongst patients who have undergone a potentially curative

Table 1 - Results of Adjuvant Chemoradiation

		SURVIVAL			
POSTOPERATIVE	Median	2-Year	3-Year	5-Year	Late Rx Related Complications
Split-Course GITSG	(mos)	(%)	(%)	(%)	(%)
Randomized to Rx (N=21)	21	43	24	19	4
GITSG Registered to Rx (N=30)	18	46	-	17	4
EORTC Randomized to Rxϕ (N=58)	17.1	37	-	-	-
Dose-Intensive					
Mayo (N=29)	23	48	24	12	17
Hopkins* (N=120)	19.5	39	-	-	-
M.D.A.H.[1] (N=19)	22	55	39	-	-
PREOPERATIVE	Median (mos)	2-Year (%)	3-Year (%)	(%)	Complications (%)
F.C.C.C.[2] (N=13)	18	-	43	-	-
M.D.A.H.[1] (N=41)	19.2	-	-	-	-
E.C.O.G.[2] (N=24)	15	25	-	-	-

-:No Data, ϕ :No maintenance therapy given and included patients with positive margins without stratification, *Included use of hepatic irradiation, 1:Included use of intraoperative irradiation, 2:Able to undergo resection.

Table 2 - Schema for RTOG/Intergroup Study #97-04 evaluation adjuvant therapy

SCHEMA

S Nodal Status
1. Uninvolved
T 2. Involved

R Tumor Diameter
1. < 3cm
A 2. ≥ 3cm

T Surgical Margins
1. Negative
I 2. Positive
3. Unknown

F
Y

R

Arm 1:Pre-CRT + Chemoradiation (CRT) + Post-CRT
A 5-FU 5-FU

N
D

O Arm 2:Pre-CRT + Chemoradiation (CRT) + Post-CRT
Gemcitabine Gemcitabine
M
I
Z
E

PRE-CRT CHEMOTHERAPY: Starting 3-6 weeks after definitive tumor related-surgery:

Arm 1: 3 weeks of continuous infusion (CI) 5-FU at 250mg/m^2/d

Arm 2: 3 weeks of Gemcitabine at 1000mg/m^2/d, once weekly

CHEMORADIATION (CRT): Starting 1-2 weeks after completion of pre-CRT chemotherapy and then no later than 12 weeks after definitive tumor-related surgery;

Arms 1&2: 50.4 Gy/ 5 1/2 wks @ 1.8 Gy/fx [field reduction at 45 Gy] and CI 5-FU, 250mg/m^2/d, during radiation.

POST-CRT CHEMOTHERAPY: Starting 3-5 weeks after completion of CRT;

Arm 1: 2 cycles of CI 5-FU (One cycle = 4 wks of CI 5-FU at 250mg/m^2/d followed by 2 wks rest) for a duration of 3 months.

Arm 2: 3 cycles of Gemcitabine (one cycle = 3 wks of Gemcitabine at 1000mg/m^2/d, once weekly followed by 1 wk rest) for a duration of 3 months.

resection, Phase III evaluation of postoperative adjunctive chemoradiation has been limited, until recently, to a single trial conducted by the GITSG which, although terminated early due to poor patient accrual, showed a statistically significant doubling in median survival and modest improvement in 5-year survival for patients receiving adjuvant split-course chemoradiation as compared to observation. Therapy involved 40 Gy in 6 weeks, with a mid 2-week break, and 3-day infusions of 5-FU at the start of weeks 1 and 5; followed by weekly infusions of maintenance 5-FU. Twenty-one patients randomized to adjuvant split-course chemoradiation had a median survival of 21 months, 2-year survival of 43%, and 5-year survival of 19%, compared to 11 months, 18% and 5%, respectively, for the observation group (p=0.03). There were no life-threatening complications or deaths attributable to therapy (l3,l4). These results were duplicated in an additional cohort of 30 patients treated on a non-randomized basis with split-course chemoradiation, achieving median and 2-year survivals of 18 months and 46% respectively, and a 5-year survival of 17%, further substantiating the benefit in patients receiving this adjunctive therapy (14-15). Only 2 of the 51 (4%) treated patients in the GITSG study developed possible late treatment related complications.

The European Organization for Research and Treatment of Cancer recently completed a Phase III trial (EORTC protocol #40891) evaluating the same split-course chemoradiation regimen as in the GITSG trial but without maintenance therapy, versus observation in patients after curative resection for cancer of the pancreatic head or periampullary region. Patients were stratified by tumor location. A total of 218 patients were randomized (110 to treatment and 108 to observation) of which 119 had pancreatic head lesions; 58 to treatment arm and 61 to observation. Not surprisingly, therapy was well tolerated, with no grade 3 toxicities observed, however, 22 patients in the treatment arm (22%) did not receive any treatment because of postoperative morbidity and patient refusal. In the treatment arm, the median survival was 24.5 months and 2-year survival was 51% compared to 19 months and 41% for the observation group (p=0.208). When analyzed by tumor location, the median and 2-year survival for patients with periampullary cancers randomized to treatment was 39.5 months and 70%, respectively, as compared to 40.1 months and 64%, respectively, for those randomized to observation (p=N.S.). In the pancreatic head cancer group patients, the median and 2-year survival for those randomized to treatment was 17.1 months and 37%, respectively, as compared to 12.6 months and 23%, respectively, for those randomized to observation (p=0.099) (16). The results of this trial, while of interest, will likely not be definitive, given the lack of use of maintenance therapy in the adjuvant regimen, the inclusion of patients with positive resection margins without stratification, the lack of radiation therapy quality assurance, and lack of statistical power. The latter two concerns can also be applied to the GITSG trial.

4. THE EVOLUTION TOWARDS MORE DOSE-INTENSIVE POSTOPERATIVE ADJUVANT CHEMORADIATION

Postoperative adjunctive therapy for pancreatic carcinoma and other gastrointestinal sites have evolved into use of higher dose, non-split course, and potentially more toxic chemoradiation regimens as compared to that utilized in the GITSG study (l7-20). Phase III evaluation of such an approach in rectal carcinoma, with use of irradiation doses of 50.4 - 54 Gy in 6 weeks combined with continuous infusion (CI) 5-FU has been associated with a significant improvement in survival when compared to a less dose-intensive chemoradiation regimen (21). Whether similar improvements can be achieved without significant upper abdominal toxicity in patients with pancreatic carcinoma, whose death rate due to disease recurrence is more exponential, needs evaluation; however, results of Phase II experiences are promising.

The Mayo Clinic experience among 29 patients treated with postoperative chemoradiation following potentially curative resection of adenocarcinoma of the pancreas is reflective of an evolution towards dose-intensive adjuvant therapy. Nine patients were treated with split-course therapy, while the remainder were treated with continuous-course therapy. The median dose of radiation used was 54 Gy with a range from 35 to 60 Gy. Twenty-seven of 29 patients also received concurrent bolus 5-FU chemotherapy. The median, 2,3, and 5-year survival for the group was 23 months, 48%, 24%, and 12%, respectively. Seventeen percent developed late treatment related complications, while the rate of small bowel obstruction requiring operation among those receiving $\geq$ 45 Gy was 4.2% (1/24) (17).

The John Hopkins Hospital evolving experience with increasingly intensive chemoradiation following resection for adenocarcinoma of the pancreas (9,19) has been recently updated in 173 patients undergoing 3 options of postoperative adjuvant therapy: 1) 99 patients receiving "standard" split-course or continuous-course radiation to doses of 40-45 Gy in conjunction with concurrent bolus 5-FU chemotherapy and followed by 4 months of maintenance 5-FU; 2) 21 patients receiving ``intensive" therapy involving continuous-course radiation of 50.4-57.6 Gy to the tumor bed and prophylactic hepatic irradiation of 23.4-27 Gy with CI 5-FU plus leucovorin concurrently and as maintenance for 4 months and, 3) 53 patients having no therapy. The “intensive" therapy group experienced increased toxicity and had no survival benefit when compared to the "standard" therapy group. However, patients receiving adjuvant therapy had a median and 2-year survival of 19.5 months and 39%, respectively, as compared to 13.5 months and 30%, respectively, for the patients who received no therapy (p=0.003) (20).

The M.D. Anderson Hospital experience with postoperative adjuvant therapy among a recently treated cohort of 19 patients made use of infusional chemoradiation

(50.4 Gy in 28 fractions over 5 1/2 weeks with CI infusion 5-FU at 300 mg/m2/day) and intraoperative electron-beam radiation therapy (10-15 Gy). The median 2 and 3-year survival for these patients is 22 months, 55%, and 39%, respectively (22).

The Eastern Cooperative Oncology Group reported the results of a Phase I trial (23) evaluating the maximum tolerated dose (MTD) of CI 5-FU with concurrent radiation in 25 patients with unresectable, residual, or recurrent carcinoma of the pancreas or bile duct. Beginning at 200 mg/m^2/d, CI 5-FU was given concurrently with radiation therapy (59.4 Gy in 33 fractions over 6 to 7 weeks). Chemotherapy began with and continued through the entire course of treatment. After each cohort of five patients had been treated and observed, the daily dose was escalated in 25-mg/m^2 increments until dose-limiting toxicity was encountered. The dose-limiting toxicity was oral mucositis and the MTD of CI 5-FU was found to be 250 mg/m^2/d.

5. THE EVOLVING EXPERIENCE OF PREOPERATIVE ADJUVANT CHEMORADIATION

Given the significant morbidity associated with pancreaticoduodenectomy, the potential for delay or inability to deliver postoperative adjuvant chemoradiation can quite commonly be problematic. This is potentially reflected in the slow patient accrual associated with the GITSG studies (14,15) and poor patient compliance noted in the EORTC trial (16). Concern of inability to deliver postoperative adjuvant chemoradiation, as well as successful pancreaticoduodenectomy following a course of preoperative radiation therapy, has led to experiences with preoperative chemoradiation prior to pancreaticoduodenectomy for patients with potentially resectable or locally advanced adenocarcinoma of the pancreas (24-26). The rationale for preoperative delivery of chemoradiation include, 1) potentially eliminating the delay effect or inability to deliver all components of combined modality therapy which can be associated with a postoperative adjuvant strategy; 2) possible avoidance of pancreaticoduodenectomy and/or laparotomy in patients who show evidence of interval development of distant disease on restaging studies or at laparotomy following preoperative chemoradiation, thus being spared the associated potential morbidity and mortality associated with surgery; 3) increased effectiveness associated with radiation therapy on well oxygenated cells that have not been surgically devascularized; 4) potentially preventing tumor cell dissemination or implantation associated with surgical manipulation and, 5) the potential for more adequate retroperitoneal dissection and reduction of the incidence of positive microscopic margins of resection (27,28).

In 1994, the Fox Chase Cancer Center (FCCC) reported on the potential feasibility of preoperative chemoradiation among 31 patients with adenocarcinoma of the pancreas (N=27) and duodenum (N=4) (29). Twenty--one patients were initially felt to be unresectable by radiographic or previous operative evaluation. Patients were preoperatively treated with radiation (50.4 Gy in 28 fractions over 5 1/2 weeks) and concurrent 5-FU (weeks 1 and 5) + mitomycin (week 1) chemotherapy. Moderate to severe (grade 3 or 4) acute toxicity was limited to 23% of the patients and 17 patients (55%) were able to undergo potentially curative resections. Among the 13 patients with pancreatic cancer able to undergo resection, the median and 3-year survival was 18 months and 43%, respectively. No late complications related to bowel obstruction or perforation were seen at a median follow-up of 4.5 years.

The M.D. Anderson Hospital recently analyzed their experience with use of preoperative adjuvant chemoradiation in 41 patients with localized adenocarcinoma of the pancreas who were deemed resectable on the basis of radiographic imaging and compared it to their previous experience using postoperative chemoradiation. At a median follow-up of 19 months in the patients receiving preoperative chemoradiation, they have found no significant differences in toxicity or survival between preoperative versus postoperative chemoradiation groups. In addition, no patients receiving preoperative chemoradiation experienced a delay in surgery because of chemoradiation toxicity (22). While the relative safety of preoperative chemoradiation has been well documented by these single institution experiences, multi-institutional evaluation of such an approach has been limited to a single cooperative group setting.

The Eastern Cooperative Oncology Group (ECOG) recently reported the results of a Phase II trial of preoperative chemoradiation for patients with resectable pancreatic adenocarcinoma (30). Preoperative chemoradiation was as that used by the FCCC group. Among 62 eligible patients, there were 2 treatment-related deaths and 27 patients (44%) experienced grade 3-5 hepatic toxicity which was as frequent and severe as hematologic toxicity. Among the 24 patients (43%; 24/53 assessable for analysis) who were able to undergo resection, the median and 2-year survival was 15 months and 25%, respectively. Thus the ultimate impact of such a treatment approach on toxicity, patterns of tumor recurrence, survival, and cost-effectiveness await additional follow-up and evaluations.

Table 1 summarizes the reviewed results of adjuvant chemoradiation. While more dose-intensive chemoradiation regimens, similar to that used in the above experiences, have become more of the community norm, an associated improvement in patient outcome has, at most, been modest. The problem of distant metastases continues to be a major factor for poor prognosis in these patients. The need for more effective chemotherapy to reduce the incidence of distant metastases, with the potential for further improvement in patient survival is clear.

6. GEMCITABINE

The United States Food and Drug Administration (FDA) recently approved Gemcitabine for use in patients with pancreatic cancer. This is the first chemotherapeutic agent since 5-FU to be approved for use in patients with

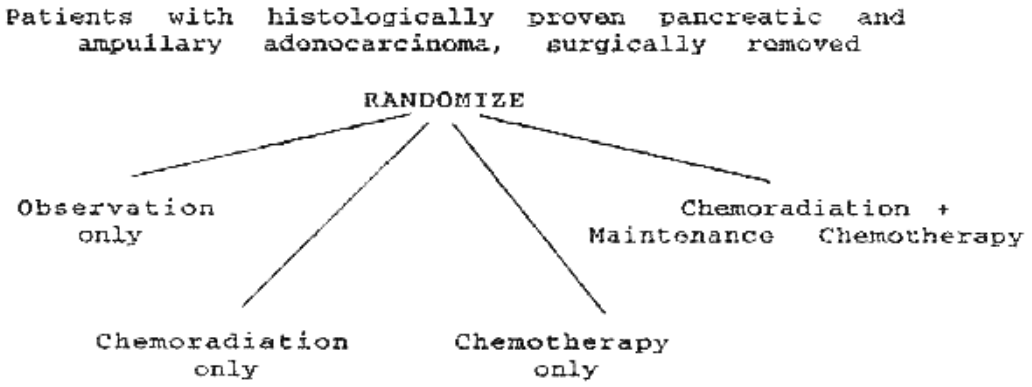

Figure 1. Design of the ESPAC adjuvant study.

pancreatic cancer in nearly 35 years. Gemcitabine is also unique in that the FDA approved the compound despite an objective response rate of 5.4% (31). The FDA approved Gemcitabine based on two registration trials in patients with symptomatic stage IV pancreas cancer (31,32). These trials introduced the concept of clinical benefit response. Pancreatic cancer patients almost always have devastating symptoms including pain and weight loss. These patients also experience declining performance status. Objective responses are also frequently difficult to assess non-invasively. Investigators combined changes in pain control, weight loss and performance status to create clinical benefit response. The FDA accepted this patient-centered endpoint for testing of gemcitabine in pancreas cancer. In the first trial investigators randomized 126 stable symptomatic patients to gemcitabine 1000 mg/m^2 weekly for seven weeks followed by a week rest then four week cycles consisting of three weekly doses of gemcitabine at 1000 mg/m^2 and one week rest (29). The other patients received bolus 5-FU. The clinical benefit response was 24% for gemcitabine and 5% for 5-FU (p=0.0022), while the objective response rate was 5% and 0%, respectively. The median survival was 5.7 months for gemcitabine and 4.4 months for 5-FU while the one-year survival was 18% and 2%, respectively (p=0.0025). In addition, patients achieving symptomatic relief did so within six weeks of initiating therapy. Symptomatic benefit lasted an average of 12 weeks. The second registration trial was a single arm Phase II trial in 63 patients who had failed 5-FU (32). Treatment was with gemcitabine at the same dose and schedule. The clinical benefit response was 27% and the one-year survival 4%. The median survival was 3.9 months. Based on these two trials the FDA approved gemcitabine to treat pancreas cancer both in front line and salvage therapy. The toxicity of gemcitabine was mild to moderate. Only 10% of patients discontinued therapy due to toxicity and the most common toxicity was myelosuppression. Other toxicities include hepatitis, nausea, vomiting, hair loss, skin rash, and fever. Gemcitabine is given as a thirty minute infusion intravenously. Gemcitabine is now used in the primary therapy for metastatic pancreas cancer. In the meantime, a Phase III evaluation of adjuvant treatment of resected pancreatic adenocarcinoma is needed to prove or disprove increased efficacy as well as establish the best "standard" adjuvant regimen for use in the community and future studies.

7. ONGOING ADJUVANT STUDIES

The Radiation Therapy Oncology Group (RTOG) study #97-04 is a Phase III Intergroup study of pre- and post-chemoradiation 5-FU versus pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment of resected pancreatic adenocarcinoma. The study was activated in July, 1998 and is thus the first American Phase III cooperative group study in nearly a quarter century (GITSG trial activated 2/74) evaluating adjuvant chemoradiation in patients with localized and resected adenocarcinoma of the pancreas. The study schema is detailed in table 1. All patients will receive the same 5-FU based chemoradiation while the study evauluates the addition of gemcitabine and its effect on overall survival, local-regional and distant disease control, and/or disease-free survival as compared to 5-FU. The study will also be the first to prospectively evaluate the ability of post-resectional CA19-9 to predict outcome among adjuvantly treated patients who have undergone a potentially curative resection for adenocarcinoma of the pancreas. In addition, a companion biomoleuclar basic science study is planned, with possibilities currently being evaluated.

As the RTOG study #97-04 begins, the European Study Group of Pancreatic Cancer (ESPAC) is expected to close, by the end of 1998. ESPAC is an adjuvant study which will have accrued nearly 500 patients with pancreatic or ampullary adenocarcinoma to a 4-arm design shown in figure 1. Patients are randomized to observation, chemoradiation only, chemotherapy only, or chemoradiation and maintenance chemotherapy. The radiotherapy and/or chemotherapy is similar to that used in the GITSG/EORTC trials. Patients are stratified according to the presence or absence of positive resection margins and the study combines two methods of quality-of-life assessment, one by the patient and one by the physicians (33).

8. PERSPECTIVE

There are many questions still remaining to be answered in the management of pancreatic cancer. Optimized integration of conventional treatment modalities of radiation, chemotherapy, and surgery still need to be established. Radiation dose, fractionation, and volume are critical issues that remain to be resolved, especially in conjunction with new cytotoxic agents which pose their own unique set of questions including mode of drug delivery, combination of drugs, and dose intensification. The use of specialized programs such as intraoperative radiation have also not been fully explored.

Evolving knowledge in the biological behavior of these tumors based on its genetic fingerprints could provide useful guides to designing customized treatment strategies. Genes such as p53, ras mutations, and c-myc expressions have been implicated in conferring enhanced resistance with chemotherapy and radiation treatment strategies. Understanding the genetic profile of pancreatic cancers will be of immense value in 1) early detection of tumors; 2) prediction of biological behavior and, 3) selection of treatment strategies including future options for gene therapy.

9. ACKNOWLEDGEMENT

We wish to thank Ms. Rita Swartz for her help in he preparation of this manuscript.

10. REFERENCES

1. S.H. Landis, T. Murray, S. Bolden, & P.A. Wingo: *CA Cancer J Clin* 48, 6-29 (1998)

2. H. Douglass: Adjuvant therapy for pancreatic cancer. *World J Surg* 19, 1701-74 (1995)

3 R.J. Geer, & M.F. Brennan: Prognostic indicators for survival after resection of pancreatic adenocarcinoma. *Am J Surg* 165, 68-73 (1993)

4. Y. Shibamoto, T. Manabe, & M. Baba: High dose, external beam and intraoperative radiotherapy in the treatment of resectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 19,605-611 (1990)

5. S.S. Nitecki, M.G. Sarr, T.V. Colby, & J.A. van Heerden: Long-term survival after resection for ductal adenocarcinoma of the pancreas.Is it really improving? *Ann Surg* 221(1), 59-66 (1995)

6. R.J. Piorkowski, S.W. Believernicht, & W. Lawrence, Jr.: Pancreatic and periampullary carcinoma: Experience with 200 patients over a 12-year period. *Am J Surg* 143, 189-192(1982)

7. B. Gudjonsson: Cancer of the pancreas: 50 years of surgery. *Cancer* 60,2284-2303 (1987).

8. M. Trede, B. Chir, G. Schwall, & H.D. Saeger: Survival after pancreaticoduodenectomy. *Ann Surg* 21(4), 447-58 (1990)

9. C.J. Yeo, J.L. Cameron, K.D.Lillemoe, J.V. Sitzman, R.H. Hruban, S.N. Goodman, W.C. Dooley, J.A. Coleman, & H.A. Pitt: Pancreaticoduodenectomy for cancer of the head of the pancreas Two hundred and one patients. *Ann of Surg* 221(6), 721-33 (1995)

10. Gastrointestinal Tumor Study Group: Therapy of locally unresected pancreatic carcinoma: A randomized comparison of high dose (6000 reds) radiation alone, moderate dose radiation (4000 rads + 5fluorouracil), and high dose radiation + 5-fluorouracil. *Cancer* 48,1705-10 (1981)

11 R. Whittington, M.P. Bryer, D.G. Haller, L.J. Solin, & E.F. Rosato: Adjuvant therapy of resected adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys* 21, 1137-43 (1991)

12. J. Tepper, G. Nardi, & H. Suit: Carcinoma of the pancreas: review of MGH experience from 1963 to 1973 - Analysis of surgical failure and implications for radiation therapy. *Cancer* 37, 1519-24 (1976)

13. M.H. Kalser, & S.S. Ellenberg: Pancreatic cancer: Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 12, 899-903 (1985)

14. H.O. Douglass, & D.M. Strablein: Ten year follow-up of first generation surgical adjuvant studies of the Gastrointestinal Tumor Study Group. In: Adjuvant therapy of cancer. 4th ed Ed: Salmon SE: Saunders, Philadelphia (1990) p. 405-415.

15. Gastrointestinal Tumor Study Group: Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer* 59, 2006-10 (1987)

16. J.H.G. Klinkenbijl, T. Shamoud, R. van Pel, M.L. Couvreur, C.H.N. Veenhof, J.P. Arnaud, A. Hennipman, J. Wils, & J. Jeekel: Radiotherapy and 5-FU after curative resection for the cancer of the pancreas and peri-ampullary region: A phase III trial of the EORTC and GITCCG. *European Journal of Cancer* 33(8), abst #1239, (1997)

17. M.L. Foo, L.L. Gunderson, D.M. Nagorney, D.C. McLlrath, J.A. van Heerden, J.S. Robinow, L.K. Kvols, G.R. Garton, J.A. Martenson, & S.S. Cha: Patterns of failure in grossly resected pancreatic ductal adenocarcinoma treated with adjuvant irradiation + 5-fluorouracil. *Int J Radiat Oncol Biol Phys* 26, 483-89 (1993)

18. M. Mohiuddin, F. Rosato, A. Schuricht, D. Barbot, W. Biermann, & R. Cantor: Carcinoma of the pancreas - The Jefferson experience 1975-1988. *Eur J Surg Onc* 20,13-20 (1994)

19. C.J. Yeo, R.H. Hruban, S.E. Kern, R.A. Abrams, L.B. Grochow, C.A. Griffin, & J.L. Cameron: Adenocarcinoma of the pancreas: Factors influencing outcome after

pancreaticoduodenectomy - The John Hopkins experience. *Cancer Bulletin* 46(6), 504-10 (1994)

20. C.J. Yeo, R.A. Abrams, L.B. Grochow, T.A. Sohn, S.E. Ord, R.H. Hruban, M.L. Zahurak, W.C. Dooley, J.A. Coleman, P.K. Sauter, H.A. Pitt, K. D. Lillemoe, & J.L. Cameron: Pancreaticoduodenectomy for pancreatic adenocarcinoma: Postoperative adjuvant chemoradiation improves survival. *Ann Surgery* 225(5), 621-36 (1997)

21. D.G. Haller, R.J. Mayer, L.L. Gunderson, & T.A. Rich: Improving adjuvant therapy for rectal cancer by combining protracted infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 331(8), 502-07 (1994)

22. F.R. Spitz, J.L. Abbruzzese, J.E. Lee, P.W.T. Pisters, A.M. Lowy, C.J. Fenoglio, K.R. Cleary, N.A. Janj an, M.S. Goswitz, T.A. Rich, & D.B. Evans: Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol* 15 (3), 928-37 (1997)

23. R. Whittington, D. Neuberg, W.J. Tester, A.B. Benson, & D.G. Haller: Protracted intravenous fluorouracil infusion with radiation therapy management of localized pancreaticobiliary carcinoma: A phase I Eastern Cooperative Group trial. *J Clin Onc* 13,227-32 (1995)

24. M.V. Pilepich, & H.H. Miller: Preoperative irradiation in carcinoma of the pancreas. *Cancer* 46, 1945 (1980)

25. G. Kopelson: Curative surgery for adenocarcinoma of the pancreas and ampulla of Vater: The role of adjuvant pre or postoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 9, 911 (1983)

26. D.B. Evans, T.A. Rich, & D.R. Byrd: Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas *Arch Surg* 127, 1335-39 (1992)

27. G.M. Fuhrman, C. Charnsangavej, & J.L. Abbruzzese: Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. *Am J Surg* 167, 104-113 (1994)

28. T. Nagakawa, I. Konishi, & K. Ueno: The results and problems of extensive surgery for carcinoma of the head of the pancreas. *Jpn J Surg* 21, 262 (1991)

29. L. Coia, J. Hoffman, R. Scher, J. Weese, L. Solin, L. Weiner, B Eisenberg, A. Paul, & G. Hanks: Preoperative chemoradiation for adenocarcinoma of the pancreas and duodenum. *Int J Radiat Oncol Biol Phys* 30 (1), 161-67 (1994)

30. J.P. Hoffman, S. Lipsitz, T. Pisansky, J.L. Weese, L. Solin, & A.B. Benson III: Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: An Eastern Cooperative Oncology Group study. *J Clin Oncol* 16(1), 317-23 (1998)

31. H.A. Burris, M.J. Moore, J. Anderson, M.R. Green, M.L. Rothenberg, M.R. Modiano, M.C. Cripps, R.K. Portenoy, A.M. Storniolo, P. Tarassoff, R. Nelson, F.A. Door, C.D. Stephens, & D.D. Van Hoff: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol* 15 (6), 2403-13 (1997)

32. M.L. Rothenberg, M.J. Moore, M .C. Cripps, J.S. Anderson, R K. Portenoy, H.A. Burris III, M.R. Green, P.G. Tarassoff, T.D Brown, E.S. Casper, A.M. Storniolo, & D.D. Von Hoff: A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. *Ann Oncol* 7, 347-53 (1996)

33. J.P. Neoptolemos, D.J. Kerr, H. Beger, K. Link, P. Pederzoli, C. Bassi, C. Dervenis, L. Fernandez-Cruz, F. Lacaine, H. Friess,& M. Ruchler: ESPAC-1 trial progress report: The European randomized adjuvant study comparing radiochemotherapy, 6 months chemotherapy and combination therapy versus observation in pancreatic cancer. *Digestion* 58, 570-577 (1997)

Key Words: Pancreatic Cancer, Adjuvant Therapy, Chemoradiation

---

Send correspondence to: William F. Regine, M.D. , University of Kentucky Medical Center , Department of Radiation Medicine , 800 Rose Street , Lexington, KY 40536-0084 , Tel: (606) 323-6486, Fax: (606) 257-4931 , E-mail:wilregi@pop.uky.edu