

RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-04

**A PHASE III STUDY OF PRE AND POST CHEMORADIATION 5-FU VS. PRE
AND POST CHEMORADIATION GEMCITABINE FOR POSTOPERATIVE
ADJUVANT TREATMENT OF RESECTED PANCREATIC
ADENOCARCINOMA**

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RTOG (97-04)

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INDEX

Schema

Eligibility Check

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Pretreatment Evaluations
- 5.0 Registration Procedures
- 6.0 Radiation Therapy
- 7.0 Drug Therapy
- 8.0 Surgery
- 9.0 Ancillary Therapies
- 10.0 Pathology
- 11.0 Patient Assessments
- 12.0 Data Collection
- 13.0 Statistical Considerations

References

- Appendix I - Sample Consent Form
- Appendix II - Karnofsky Performance Status
- Appendix III - Staging System
- Appendix IV - Toxicity Criteria
- Appendix V - Adverse Reaction Reporting Guidelines
- Appendix VI - Field Diagrams
- Appendix VII - Intergroup Guidelines
- Appendix VIII - Signature Page for VA facilities

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SWOG/ECOG R9704**

A PHASE III STUDY OF PRE AND POST CHEMORADIATION 5-FU VS. PRE AND POST CHEMORADIATION GEMCITABINE FOR POSTOPERATIVE ADJUVANT TREATMENT OF RESECTED PANCREATIC ADENOCARCINOMA

SCHEMA

<p>S <u>Nodal Status</u></p> <p>1. Uninvolved</p> <p>T 2. Involved</p> <p>R <u>Tumor Diameter</u></p> <p>1. < 3 cm</p> <p>A 2. ≥ 3 cm</p> <p>T <u>Surgical Margins</u></p> <p>1. Negative</p> <p>I 2. Positive</p> <p>3. Unknown</p> <p>F</p> <p>Y</p>	<p>R</p> <p>Arm 1: Pre-CRT + Chemoradiation (CRT) + Post-CRT</p> <p>A 5-FU (5-FU/RT) 5-FU</p> <p>N</p> <p>D</p> <p>O Arm 2: Pre-CRT + Chemoradiation (CRT) + Post-CRT</p> <p>Gemcitabine (5-FU/RT) Gemcitabine</p> <p>M</p> <p>I</p> <p>Z</p> <p>E</p>
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PRE-CRT CHEMOTHERAPY: Starting 3-8 weeks after definitive tumor-related surgery and within 5 business days after randomization;

Arm 1: 3 weeks of continuous infusion (CI) 5-FU at 250 mg/m²/day.

Arm 2: Gemcitabine at 1000 mg/m² once a week x 3.

CHEMORADIATION (CRT): (9/21/01) Starting 1-2 weeks after completion of pre-CRT chemotherapy and then no later than 13 weeks after definitive tumor-related surgery;

Arms 1&2: 50.4 Gy @ 1.8 Gy/fx (*field reduction at 45 Gy*) for 5.5 weeks and CI 5-FU, 250 mg/m²/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 250 mg/m²/day followed by 2 wks rest*).

Arm 2: 3 cycles of gemcitabine (*one cycle = 3 wks of gemcitabine at 1000 mg/m², once weekly followed by 1 wk rest*).

Eligibility: (*See Section 3.0 for details*)

- Localized adenocarcinoma of the pancreas following gross total resection (*i.e., removal of all gross local disease*); Stages T1-4, N0-1.
- Protocol treatment to begin within 3-8 weeks of definitive tumor-related surgery.
- KPS ≥ 60; age ≥ 18.
- Adequate oral nutrition (*e.g., ≥ 1500 calories/day*).
- WBC ≥ 3,000, platelets ≥ 100,000.
- Bilirubin and creatinine ≤ 1.5 x institutional upper limits of normal.
- SGOT ≤ 5 x institutional upper limits of normal.
- Blood samples for CA19-9 testing must be drawn ≤ 21 days prior to randomization and before the start of any protocol treatment
- Signed study-specific consent form.

Required Sample Size: 518 (9/21/01)

RTOG Institution # _____
RTOG 97-04/ECOG/SWOG R9704
RTOG Case # _____

ELIGIBILITY CHECK (4/1/99)
(Page 1 of 2)

- _____(Y) 1. Is there pathologic proof of adenocarcinoma of the pancreas?
- _____(N) 2. Is the tumor any of the types specified in Section 3.2.1 (*non-adenocarcinomas, adenosquamous carcinomas, islet cell, cystadenoma, cystadenocarcinoma, carcinoid, duodenal, ampullary, or distal bile duct cancer*)?
- _____(Y) 3. Has the patient undergone a potentially curative resection (*removal of all gross tumor*)?
- _____(N) 4. Does patient have recurrent disease following prior clearance?
- _____(Y) 5. Is the patient staged according to the AJCC staging system in Appendix III with pathologic stage T1-4,N0-1,M0 and have a tumor of the pancreatic head, neck, uncinate process, body/tail?
- _____(N) 6. Does the patient have M1 disease or NX disease?
- _____(Y/NA) 7. If the patient has reproductive potential, has he/she agreed to use an effective method of contraception?
- _____(N/NA) 8. If female, is the patient pregnant?
- _____(Y) 9. Is the interval between definitive tumor-related surgery and planned start of protocol therapy 3-8 weeks?
- _____(N) 10. Any prior radiotherapy to any site or chemotherapy?
- _____(Y/N) 11. Any prior malignancy other than non-melanoma of the skin or *in situ* of the cervix?
_____(Y) If yes, has the patient been disease-free for ≥ 5 yrs?
- _____(≥ 3.0) 12. What is the current white blood cell count (*per 1000mm³*)?
- _____(≥ 100) 13. What is the current platelet count (*per 1000 cells/mm³*)?
- _____($\leq 1.5 \times \text{IULN}^*$) 14. What is the serum creatinine (*mg% or mg/dl*)? [IULN= _____]
- _____($\leq 1.5 \times \text{IULN}^*$) 15. What is the total serum bilirubin (*mg/100ml*)? [IULN= _____]

*IULN = Institutional upper limit of normal.

(proceed to next page)

1.1 Background

Despite "potentially curative" resection for pancreatic carcinoma the 5-year survival in these patients is < 20%.¹⁻³ Even amongst the most favorable subset of patients, those with tumor diameters of < 3 cm and/or negative nodal status, the 5-year survival is no more than 36%.¹⁻⁴ 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.⁵ Amongst patients who have undergone a potentially curative resection, phase III evaluation of postoperative adjunctive chemoradiation has been limited 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-daily boluses of 5-FU at the start of week 1 and 5; followed by once weekly boluses 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.^{6,7}

1.2 Results of Adjuvant Split-Course Chemoradiation

The above *GITSG* result was duplicated in an additional cohort of 30 patients treated on a non-randomized basis with split-course chemo-radiation, achieving median and 2-year survivals of 18 months and 46% respectively, and 5-year survival of 17%, further substantiating the benefit in patients receiving this adjunctive therapy.^{7,8} 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 pancreas and periampullary region. A total of 218 patients were randomized of which 119 had pancreas cancer. Not surprisingly, therapy was well tolerated, with no grade 3 toxicities observed; while preliminary survival analysis shows no difference thus far. Among the 58 patients with pancreatic head cancer randomized to treatment, the median survival was 15.7 months and 2-year survival estimate 39% as compared to 12.9 months and 26%, respectively, for the 61 randomized to observation ($p=0.12$) (*Personal communication, Professor J. Jeekel, 2/97*). The results of this trial, while of interest, will likely not be definitive given the lack of use of maintenance therapy in the adjuvant treatment regimen, inclusion of patients with positive resection margins without stratification and lack of radiation therapy quality assurance.

1.3 Results of Adjuvant Dose-Intensive Chemoradiation

Postoperative adjunctive therapy for pancreatic carcinoma and other gastrointestinal sites have evolved into use of higher dose, non-split course, more aggressive, and potentially more toxic chemoradiation regimens as compared to that utilized in the *GITSG* study.⁹⁻¹¹ Phase III evaluation of such an approach in rectal carcinoma, with use of continuous-course irradiation to 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.¹²

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 5-FU chemotherapy, typically involving two 3-day sequences of bolus therapy. The median, 2, 3, and 5-year survival for the group was 23 months, 48%, 24%, and 12%, respectively. Five of 29 patients (17%) developed late treatment-related complications while the rate of small bowel obstruction requiring operation among those receiving > 45 Gy was 4.2% (1/24).⁹

The recently reported John Hopkins Hospital experience with chemoradiation following resection for adenocarcinoma of the pancreas includes 56 patients treated with external radiation (> 45 Gy over 5-6 weeks), and concurrent 5-FU based chemotherapy (*given either as a weekly bolus or via continuous infusion*). Despite 23% of these patients having positive resection margins, the median and actuarial 2-year survival for the group is 20 months and 35%, respectively.^{4,11}

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 venous infusion 5-FU at 300 mg/m²/day with each day of radiotherapy). The 3-year survival rate for these patients is 39%.¹³

The Eastern Cooperative Oncology Group reported the results of a phase I trial¹⁴ 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 (n=16) or bile duct (n=9). Beginning at 200 mg/m²/d, CI 5-FU was given concurrently with radiation therapy (59.4 Gy in 33 fractions over 6 to 7 weeks). Chemotherapy began on the first day of radiation 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/m² increments until dose-limiting toxicity was encountered. An additional cohort of five patients was treated at the MTD. The dose limiting toxicity was oral mucositis and the MTD of CI 5-FU was found to be 250 mg/m²/d.

1.4 Summary of Results of Adjuvant Postoperative Chemoradiation

Table 1 - Results of Adjuvant Postoperative Chemoradiation

Split-Course	Median (mos)	Survival			Late Rx Related Complications (%)
		2-Year (%)	3-Year (%)	5-Year (%)	
GITSG Randomized to Rx (N=21)	21	43	24	19	4
GITSG Registered to Rx (N=30)	18	46	•	17	
EORTC Randomized to Rx (N=58) †	15.7	34	•	•	•
Dose-Intensive	////////////////////				
Mayo (N=29)	23	48	24	12	17*
Hopkins ^o (N=56)	20	35	•	•	•
M.D.A.H. (N=19)	•	•	39	•	•

- No Data
- † No maintenance therapy given and included patients with positive margins without stratification.
- * Incidence of small bowel obstruction requiring operation with dose ≥ 45 Gy was 4.2%.
- o Included 23% of patients having positive margins.

Thus, postoperative adjuvant chemoradiation has evolved towards more dose-intensive regimens by combining modern radiotherapy techniques (continuous course radiotherapy, increased dose) and modern understanding of 5-FU pharmacology. While use of such dose-intensive regimens has become more of the community norm/standard, the 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. Evolving adjunctive chemotherapy programs may reduce the incidence of distant metastases with the potential for further improvement in patient survival.

1.5 Gemcitabine

The United States Food and Drug Administration 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 pancreatic cancer in nearly 35 years. This approval is based on the results of studies performed in patients with advanced pancreas cancer.¹⁵⁻¹⁸ Gemcitabine was generally given intravenously over 30 minutes on a weekly basis in cycles of three consecutive weeks followed by a one week rest and was well tolerated. Although objective response rates have been low, 5-11%, a modest proportion of patients, 19-39% have stabilization of disease.¹⁵⁻¹⁸ As for comparison to 5-FU, the single randomized trial of gemcitabine versus 5-FU as first line therapy in patients with advanced pancreatic cancer showed a significant, albeit modest, improvement in survival among patients treated with gemcitabine. In this randomized study of 126 chemotherapy patients with advanced/metastatic adenocarcinoma of the pancreas, the median and 1-year

survival for patients treated with gemcitabine was 5.7 months and 18%, as compared to 4.4 months and 2% ($p=0.0025$) respectively, for patients treated with 5-FU.^{18,19} These data suggest that the activity of gemcitabine in pancreatic cancer is more promising than that seen with 5-FU and its activity should be evaluated in the adjuvant setting.

1.6 Study Significance, Design, and Concept Issues

In the 20 or more years since the GITSG study was designed and initiated major improvements in surgical techniques have reduced the mortality of pancreaticoduodenectomy to about 1% or less and similarly reduced the morbidity associated with this operation. This has resulted in a much broadened scope of applicability for this operation.^{20,21} As a consequence, there is an increasing cohort of patients and families who, having successfully experienced pancreatic cancer resection with curative intent and good physiologic reserve, are not satisfied to learn of the limitations of surgery alone and the controversies and ambiguities surrounding postoperative chemoradiation adjuvant therapy. Thus, the need for the cooperative groups to return to this arena after a long hiatus is clear.

Concurrently, as discussed above, a number of phase I and II trials have suggested that higher doses of radiation, given by continuous course, can be utilized with safety and combined with continuous infusion 5-FU.^{14,22}

In addition, in rectal adjuvant therapy involving chemotherapy and radiation, the use of a sequence of chemotherapy-chemoradiotherapy-chemotherapy has been found to produce optimal results and is now routinely incorporated in intergroup postoperative adjuvant rectal trials.²³ This approach has also been incorporated into an ongoing gastric adjuvant trial. In addition to the theoretical advantages associated with this approach, systemic chemotherapy can be instituted somewhat sooner in the postoperative period than radiotherapy to the upper abdomen. Since in the past it has not been uncommon to have to delay the onset of chemoradiotherapy to the 7th or 8th postoperative week to allow for recovery of nutritional balance and surgical healing, a chemotherapy first sequence should allow significantly earlier initiation of therapy with only minimal delay in timing of radiotherapy. In fact, for patients starting chemotherapy in postoperative week 4 it is likely that chemoradiation will begin in postoperative week 8, resulting in essentially no delay over standard practice whatsoever and with a significantly earlier onset of postoperative therapy.

The use of gemcitabine following chemoradiation therapy is not anticipated to be a problem. In animal studies gemcitabine-radiation sequencing that separates the two treatments by more than a few hours does not appear to enhance radiation effects²⁴ and in preliminary data from Fox Chase Cancer Center (*personal communication, J. Hoffman, 7/97*) post chemoradiation maintenance gemcitabine has been well tolerated.

Consequently, the design of this protocol incorporates currently accepted principles for optimizing the sequencing and use of chemotherapy and radiotherapy in gastrointestinal cancer, incorporates modern radiotherapy techniques, and recognizes the improved pharmacology of continuous infusion 5-FU. The question asked in this context is: between 5-FU and gemcitabine, which drug optimizes chemotherapy effect in the pre- and post-chemoradiotherapy periods. Gemcitabine has intentionally been omitted from the chemoradiation phase because of the concern that adequate experience with concurrent irradiation and gemcitabine is not yet available to justify use in a phase III trial.

1.7 Correlative Studies

At least five studies have shown post-resectional CA19-9 values to correlate strongly with prognosis.²⁵⁻²⁹ Patients will have post-resectional (*pre-study treatment*) CA19-9 levels drawn and also have CA19-9 levels drawn as part of their routine follow-up.

A companion biomolecular basic science study is planned, with possibilities currently being evaluated.

2.0 OBJECTIVES

- 2.1 To determine whether 5-FU based chemoradiation preceded and followed by gemcitabine improves the overall survival, local-regional and distant disease control, and/or disease-free survival as compared to 5-FU based chemoradiation preceded and followed by 5-FU in the postoperative adjuvant treatment of pancreatic carcinoma.
- 2.2 To compare the acute and late toxicities between 5-FU chemoradiation preceded and followed by gemcitabine and 5-FU chemoradiation preceded and followed by 5-FU.
- 2.3 To prospectively evaluate the ability of post-resectional CA19-9 to predict survival among adjuvantly treated patients who have undergone a potentially curative resection for adenocarcinoma of the pancreas.

3.0 PATIENT SELECTION

All questions regarding patient eligibility should be directed to RTOG Headquarters.

3.1 Conditions for Patient Eligibility (4/1/99)

- 3.1.1 Histologic proof of adenocarcinoma of the pancreas prior to treatment is required.
- 3.1.2 Only those patients who have undergone a potentially curative resection (*i.e., removal of all gross tumor*) are eligible.
- 3.1.3 Patients will be staged according to the AJCC staging system (*Appendix III*) with pathologic stage T1-4, N0-1 being eligible; and have a primary tumor of the pancreas (*i.e., pancreatic head, neck, uncinate process, body/tail*).
- 3.1.4 The maximum diameter/dimension of the primary tumor, as obtained from the pathologic specimen, is required at registration as well as is the tumor status at the surgical margin (*i.e., negative, positive or unknown*).
- 3.1.5 Red cell phenotype for Lewis A and Lewis B antigens must be done.
- 3.1.5.1 If positive for either antigen, blood must be drawn for CA19-9 testing within 3 weeks prior to randomization. It may be drawn after randomization but before start of protocol treatment. Frozen samples will be forwarded to LDS Hospital per Section 10.3.
- 3.1.6 Protocol treatment must begin within 3-8 weeks (*21-56 days*) after definitive tumor-related surgery and within 5 business days after randomization.
- 3.1.7 Age ≥ 18 .
- 3.1.8 Karnofsky performance status ≥ 60 .
- 3.1.9 Before starting therapy the patient should be able to maintain adequate oral nutrition (*e.g., ≥ 1500 calories estimated caloric intake per day*) and be free of significant nausea and vomiting. If necessary, a feeding tube should be used to maintain caloric intake above 1500 calories daily.
- 3.1.10 Signed study-specific informed consent form that includes a section on the possibility of the need for deep line access (*PICC, Groshong, Hickman or Port*).
- 3.1.11 Patients must have adequate bone marrow function with WBC count of ≥ 3000 and platelet count $\geq 100,000$.
- 3.1.12 Patients must have serum bilirubin and creatinine levels ≤ 1.5 x the institutional upper limit of normal. SGOT must be less ≤ 5 x the institutional upper limit of normal.

3.2 Conditions for Patient Ineligibility

- 3.2.1 Non-adenocarcinomas, adenosquamous carcinomas, islet cell carcinomas, cystadenomas, cystadenocarcinomas, carcinoid tumors, duodenal carcinomas, distal bile duct, and ampullary carcinomas are not eligible.
- 3.2.2 Patients with M1 or NX staging are unacceptable; patients in whom regional lymph nodes cannot be identified for pathologic review are ineligible (*See Appendix III*).
- 3.2.3 Pregnant women may not participate. Women or men of reproductive potential may not participate unless they agree to use an effective contraceptive method.
- 3.2.4 Patients with recurrent disease are ineligible.
- 3.2.5 Prior radiation therapy to any site or chemotherapy.
- 3.2.6 Patients with a previous history of active malignancy within 5 years prior to study entry, except 1) *in situ* cervical carcinoma or 2) non-melanoma skin cancer.
- 3.2.7 Karnofsky performance status < 60 .

4.0 PRETREATMENT EVALUATIONS

4.1 Mandatory Studies (4/1/99)

- **To be completed within 21 days prior to randomization:**

- 4.1.1 Complete history and physical examination including weight and Karnofsky status.
- 4.1.2 Diagnostic CT scan of the abdomen and liver with intravenous contrast. **NOTE:** For patients with a documented allergy to IV contrast it is recommended they be treated with corticosteroids and Benadryl, per institutional standards, prior to CT scan. Otherwise, diagnostic magnetic resonance imaging (*MRI*) scan of the abdomen and liver is acceptable.
- 4.1.3 CBC and platelets; absolute neutrophil count will be required for patients randomized to Arm 2.
- 4.1.4 Liver and renal function tests (*i.e., total bilirubin, SGOT and creatinine*), glucose and electrolytes.
- 4.1.5 Red cell phenotype for Lewis A and B antigens must be done. If positive for either antigen, a post-resectional CA19-9 level is required. Blood may be drawn after randomization but before the start of protocol treatment. See Section 10.3 for submission information.

- **To be completed within 42 days prior to randomization:**

- 4.1.6 Chest x-ray: PA/lateral.

- 4.1.7 Evidence of at least unilateral renal function as determined by CT scan with contrast, urogram or radionuclide scan. If only a single functioning kidney is present, at least 2/3 of the functioning kidney must be excluded from any radiation port.

4.2 Optional Studies

- 4.2.1 Pregnancy test recommended for women of childbearing potential.
4.2.2 Angiography.
4.2.3 Upper GI series.
4.2.4 Abdominal ultrasound.
4.2.5 Magnetic Resonance Imaging (*MRI*).
4.2.6 CEA, PT, PTT.
4.2.7 CA19-9 level prior to definitive tumor-related surgery.
4.2.8 Nutritional consult is recommended (*see Section 11.2.1*).

5.0 REGISTRATION PROCEDURES

All institutions: If any VA facility, employees (*full or part time*), or patients will be utilized while conducting this study, Appendix VIII must be completed and submitted to RTOG prior to registering the first patient.

5.1 RTOG Members

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. Patients may also be registered via computer modem 24 hours a day, 7 days a week. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

5.2 ECOG Members

ECOG hours for registration are from 8:30 am to 4:30 pm ET.

For ECOG institutions, a signed HHS-310 Form, a copy of the institution's IRB approved informed consent document, and written justification for any changes made to the suggested informed consent in this protocol must be on file at the ECOG Coordinating Center before an ECOG institution may enter patients. The signed HHS 310, institution's informed consent, and investigator's justification for changes will be submitted to the following address:

ECOG Coordinating Center
Frontier Science
ATTN: IRB
303 Boylston Street
Brookline, MA 02146-7648
FAX (617) 632-2990

Patients must not start protocol treatment prior to registration. The eligibility checklist should be completed and signed prior to calling for registration. To register eligible patients on study, the investigator will telephone the Randomization Desk at the ECOG Coordinating Center at (617) 632-2022, Monday-Friday, between the hours of 8:30 am and 4:30 pm ET to allow time to call RTOG that same day. **ECOG members should not call RTOG directly.** The following information will be requested: a) *Protocol Number*; b) *Investigator Identification (including institution and/or affiliate name and investigator's name)*; c) *Patient identification (including patient's name or initials, chart number, social security number and demographics [sex, birth date, race, nine-digit zip code and method of payment])*; d) *Eligibility Verification*; e) *Any additional information listed in Section 5.0.* Patients must meet all of the eligibility requirements listed in Section 3.0. The randomization specialist will verify eligibility by asking questions from the checklist, and will also verify IRB approval. RTOG will forward a confirmation of treatment assignment to the ECOG Randomization Desk for routing to the ECOG participating institution.

If a patient does not receive protocol therapy, the patient may be canceled. Reasons for cancellation should be noted on the data forms and submitted to the ECOG Coordinating Center (*ATTN: DATA*) as soon as possible. The on-study form and Eligibility Checklist should also be submitted.

Note: A patient may be canceled only if no protocol therapy is administered. Written notification and an explanation must be received at RTOG as soon as this has been determined. RTOG will notify ECOG if the patient may be canceled. Once a patient has been given protocol treatment, all forms must be submitted.

5.3 Southwest Oncology Group Members (4/1/99)

Institutions will call the Southwest Oncology Group Statistical Center at 206/667-4623 between the hours of 6:30 a.m. and 1:30 p.m. Pacific Time, Monday through Friday, excluding holidays. Patients must be registered prior to the initiation of treatment, but no more than five working days prior to the planned start of treatment.

Patients must meet all eligibility requirements listed in Section 3.0. The caller must have completed the appropriate Southwest Oncology Group Registration Form. The caller must also be prepared to provide the date informed consent was obtained and the date of Institutional Review Board approval for this study. Patients will not be registered if the IRB approval date is not provided or is > 1 year prior to the date of registration. Please note: Southwest Oncology Group Institutions will follow their normal procedures for documentation of IRB approval. The caller must also provide stratification factors necessary for randomization (*Section 13.4*).

The Statistical Center will then contact the RTOG Headquarters to register and randomize the patient after which the Statistical Center will contact the institution to confirm registration. The RTOG Headquarters will forward a confirmation of treatment assignment to the Statistical Center for routing to the participating institution.

Exceptions to the current Southwest Oncology Group registration policies will not be permitted. Therefore, late registrations (*after initiation of treatment*), exceptions to eligibility requirements, participation by an institution/member not identified as eligible AND/OR cancellations will not be allowed.

6.0 RADIATION THERAPY

All questions regarding protocol treatment or dose modifications should be directed to RTOG Headquarters.

To be given concurrently with chemotherapy in both study arms, starting 1-2 weeks after completion of pre-chemoradiation chemotherapy and no later than 13 weeks after definitive tumor-related surgery. If further delay is necessary, the RTOG radiation oncology study coordinator should be notified.

NOTE: Documentation of treatment simulation films must be sent to RTOG for Quality Assurance review before radiation begins but prior to completion of pre-chemoradiation chemotherapy as per Section 6.1.8. All patients will undergo simulation within 14 days of randomization. (4/1/99)

6.1 Treatment Fields

6.1.1 Radiation Dose- Arms 1&2: Chemoradiation-50.4 Gy will be given in 28 fractions over 5 1/2 weeks at 1.8 Gy per day. A field reduction after 45 Gy is required. See Section 6.1.7, "Boost Fields".

6.1.2 Simulation must be done with the patient supine in the "arms up" position. Simulation on a diagnostic quality simulator or CT simulator that reproduces the geometry of the treatment machine is required.

6.1.3 CT scan information for nodal coverage is usually necessary; while preoperative upper GI series may also be helpful.

6.1.4 Equipment: Greater than or equal to 10 MV photons should be used whenever possible. The minimum accepted energy will be 4 MV.

6.1.5 Dose-Time Factors: All radiation fields should be treated daily with all external beam schemes.

6.1.6 A CT scan, intravenous pyelogram, or renal nuclear medicine scan must be obtained prior to treatment to ensure that functioning renal parenchyma equivalent to one whole kidney (*e.g., 2/3 of the left and 1/3 of the right*) will be excluded from all irradiation fields if possible, or at least limited to a dose of ≤ 20 Gy.

NOTE: For quality assurance purposes, renal volume(s) are required to be drawn on the simulator film of all fields used.

6.1.7 Radiation Fields (Large field-primary tumor bed plus lymph nodes). (4/1/99)

A 3 or 4 field approach is required and will be most appropriate to minimize bowel, spinal cord and kidney dose. The preoperative primary tumor extent (*as defined by preoperative imaging and operative findings, including surgical clip placement, if performed*) must be covered with a margin from the field edge of 1.5-3 cm as detailed below in "Large Fields"(f) and Section 6.1.9.1. In addition, the local/regional and para-aortic lymph nodes adjacent to the lower thoracic and upper abdominal vertebral bodies are to be included. **NOTE: For quality assurance purposes the renal and preoperative primary tumor volumes are required to be drawn on the simulator film of all fields used. Preop primary tumor volume (GTV)**

should also be outlined on the submitted CT or MRI scan (see Section 6.1.8) using an appropriate marker. This will facilitate comparison of simulation or DRR films with the axial imaging. Recommended fields are as shown in Figure 1 (Appendix VI).

- **Large Fields (9/21/01)**

As general guidelines the edges of the large fields are to be defined as follows:

- superior edge: intervertebral space T10-T11 or mid T11.
- inferior edge: intervertebral space L3-L4, depending on the preoperative studies.
- right edge: A margin of 2-3 cm is maintained on preoperative primary tumor extent. In tumors of the body or tail region the right edge may be moved to a minimum of 2 cm from the right edge of the vertebral bodies, as long as a margin of 2-3 cm is maintained on preoperative primary tumor extent, to allow sparing of the right kidney while covering nodal areas at high risk (Fig. 3 or 4, Appendix VI).
- left edge: a margin of 2-3 cm from the preoperative primary tumor extent or 2 cm from the left edge of the vertebral bodies, whichever is most lateral.
- posterior edge: should split the anterior vertebral bodies in half (Fig. 2, Appendix VI).
- anterior edge: 1.5-2 cm anterior to anterior aspect of the primary tumor as defined on preoperative CT scan and at least 3.5-4 cm anterior to the anterior edge of the vertebral bodies, whichever is most anterior, (or 1.5-2 cm anterior to nodal volumes as reconstructed from CT scan information and outlined on simulator films [recommended, but not required]).

- **Boost Fields**

A single field reduction, at 45 Gy is required, encompassing the preoperative primary tumor volume only with a field edge margin of 1.5-2 cm on all fields.

6.1.8 To assure **prospective quality assurance**, preoperative abdominal CT scan with a scout film indexed through the cuts along with simulation films of all “large fields” (primary tumor bed plus lymph nodes as per Section 6.1.7), and boost fields (as per Section 6.1.7), to be used in treatment are to be sent for **review and approval prior to completion of pre-chemoradiation chemotherapy to:**

**RTOG Dosimetry Department
1101 Market Street, 14th Floor
Philadelphia, PA 19107**

As per Sections 6.1.6 and 6.1.7, **renal and preoperative primary tumor volumes are required to be drawn on the simulator film of all fields to be used;** while the outline of nodal volumes is recommended but not required. **Preop primary tumor volume (GTV) should also be outlined on the submitted CT or MRI scan using an appropriate marker. This will facilitate comparison of simulation or DRR films with the axial imaging.** For patients whose primary tumors are non identifiable on the pre-operative CT scan, the primary tumor localization on the simulation films should be based on surgical and pathological information in conjunction with the location of the pancreas on the pre-operative CT scan. **NOTE:** A number at which the treating radiation oncologist can be easily reached for notification of approval and/or recommended modifications must be included in the mailing. Notification will be given by RTOG within 7 days of receipt of the material. **Note: all groups will send the materials directly to RTOG Headquarters, and not through their group HQ. (4/1/99)**

6.1.9 Evaluation Criteria

6.1.9.1 Field Edges (Target Volume: Large field and Boost field, defined in Section 6.1.7 and outlined in Appendix VI).

<u>AP/PA Field(s)</u>	<u>Per Protocol</u>	<u>Variation Acceptable</u>	<u>Deviation Unacceptable</u>
a) LengthInclusive of 4-5 vertebral	bodies.....	< 4 or > 5 vertebral bodies
b) Distance From Primary Tumor	2-3 cm	1-4 cm	< 1 or > 4 cm
c) Distance From Vertebral Body	2 cm	1-3 cm	< 1 or > 3 cm

<u>Lateral Fields</u>	<u>Per Protocol</u>	<u>Variation Acceptable</u>	<u>Deviation Unacceptable</u>
a) LengthSame as AP/PA	Fields.....	
b) Distance From Anterior Aspect of Primary Tumor	1.5-2 cm	0.5-3 cm	< 0.5 or > 3 cm
c) Distance From Remaining Aspect of Primary Tumor	2-3 cm	1-4 cm	< 1 or > 4 cm (9/21/01)
d) Posterior Edge	mid-vertebral bodies	+ or – 1cm from mid vertebral bodies	greater than + or - 1cm from mid vertebral bodies (9/21/01)
e) Anterior Edge Relation to Vertebral Body	3.5-4 cm	2.5-5 cm	< 2.5 or > 5 cm
f) Anterior Edge Relation to Nodal Volumes (if reconstructed from CT and outlined on simulator films)	1.5-2 cm	1-3 cm	< 1 or > 3 cm

<u>Boost Fields</u>	<u>Per Protocol</u>	<u>Variation Acceptable</u>	<u>Deviation Unacceptable</u>
Distance From Primary Tumor	1.5-2 cm	1-3 cm	< 1 or > 3 cm

NOTE: The above will be reviewed in the context of kidney sparing/shielding as required in Section 6.3.3.

6.1.9.2	<u>Dose + or – in either direction</u>	
	<u>Total Dose Variation</u>	<u>Overall Evaluation</u>
	5 %	Per Protocol
	> 5% to ≤ 10%	Variation Acceptable
	> 10%	Deviation Unacceptable

6.1.9.3	<u>Elapsed Days</u>
	Per protocol: no more than 7 break days.
	Variation, acceptable: 8 to 14 break days.
	Deviation, unacceptable: 15 or more break days.

6.2 Physical Parameters

- 6.2.1 Beam Energy - Megavoltage equipment is required with nominal photon energies ≥ 4 MV.
- 6.2.2 Treatment Distance - Minimum treatment distance to skin for SSD techniques or isocenter for SAD techniques should be at least 80 cm.
- 6.2.3 Simulation Films - To undergo prospective quality assurance and evaluation as per Sections 6.1.8 and 6.1.9.1.
- 6.2.4 Localization Films - should be obtained for each treatment field per week and made available for review.
- 6.2.5 Isodose Distribution for transverse sections through the central ray will be obtained and submitted for review. The dose delivered to the target volume must not deviate in either direction by more than 5% relative to the doses specified in Section 6.1.1. Variations will be scored per Section 6.1.9.2.
- 6.2.6 Dose Specifications - Doses will be specified as follows:
 - 6.2.6.1 For an arrangement of three or more intersecting beams: at intersection of the central ray of the beams.
 - 6.2.6.2 Other or complex treatment arrangements: at the center of the target volume. (*Note: there may be several target volumes*).
- 6.3 Critical Structure Tolerance and Treatment Breaks**
 - 6.3.1 Small Bowel and Liver - Efforts should be made to exclude the small bowel and liver as much as possible by utilizing megavoltage beams and multiple shaped ports. The liver must not have $> 60\%$ of its volume receive > 30 Gy.
 - 6.3.2 Spinal Cord - The spinal cord dose will be limited to < 45 Gy by use of posterior blocking in the lateral field(s).
 - 6.3.3 Kidneys - The equivalent of one kidney should receive ≤ 20 Gy or at least the equivalent of 2/3's of one kidney must be spared from the radiotherapy fields. If only a single functioning kidney is present at least 2/3 of the functioning kidney must be excluded from any radiation port. For head lesions, $\geq 50\%$ of the right kidney is often in the AP/PA field(s) and so $\geq 2/3$ of the left kidney should be shielded. For body or tail lesions, $\geq 50\%$ of the left kidney is often within the AP/PA field(s) and so $\geq 2/3$ of the right kidney should be shielded.
 - 6.3.4 Patients will be seen for a status check weekly during radiation therapy. Notations of tolerance, weight, and blood counts will be made. If weight loss of $> 10\%$ from pre-chemoradiation weight occurs, then adequate nutritional intake must be ensured by dietary supplements, enteral alimentation, or i.v. nutrition as deemed clinically necessary to complete protocol therapy safely.
 - 6.3.5 Unplanned Interruptions
 - 6.3.5.1 Arms 1&2: Chemoradiation - As per Sections 6.1.9.3 and 7.4.2.

7.0 DRUG THERAPY

All questions regarding protocol treatment or dose modifications should be directed to RTOG Headquarters. RTOG Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 Administration (4/1/99)

7.1.1 Pre-Chemoradiation Chemotherapy

The pre-chemoradiation chemotherapy must start 3-8 weeks after surgery and within 5 business days of randomization.

- 7.1.1.1 Treatment Arm 1: 5-FU will be given as a 3 week continuous infusion at a dose of 250 mg/m²/day for 21 consecutive days unless toxicity occurs (*see Section 7.4*).
- 7.1.1.2 Treatment Arm 2: Gemcitabine will be given once a week for 3 weeks at a dose of 1000 mg/m²/wk unless toxicity develops (*see Section 7.4*).

7.1.2 Chemoradiation - Arms 1 & 2 (9/21/01)

Chemoradiation (CI 5-FU) will begin 1-2 weeks after completion of pre-chemoradiation chemotherapy which should be within 13 weeks of definitive tumor-related surgery. If not, the Study Coordinator should be notified. All patients will need central venous access using a surgically implanted catheter (*e.g., Groshong*) or antecubital catheter (*e.g., PICC*). Anti-coagulation is suggested during CI. Acceptable anti-coagulation regimens include sodium heparin added to 5-FU such that 7500 units/24 hours is delivered to prevent catheter and venous occlusion, or warfarin 1 mg p.o. each day. Alternative institutional standard anti-coagulation regimens (*e.g., alternative heparin doses or low dose warfarin*) are acceptable and must be noted on the flow sheet. The central venous catheter will be removed following completion of the entire course of adjuvant therapy.

Day 1 through the 5.5 week duration of radiotherapy, patients will receive concomitant CI 5-FU, 250 mg/m²/day during, and limited to, the entire course of external beam radiation therapy. The CI is 7 days each week. Dose modifications are detailed in Section 7.4.

7.1.3 Post-Chemoradiation Chemotherapy

Post chemoradiation chemotherapy must start within 35 weeks of completion of chemoradiation. If further delay is deemed necessary by the treating physician, an RTOG study chair should be notified.

- 7.1.3.1** Treatment Arm 1: 5-FU - Beginning 3-5 weeks after completion of chemoradiation, patients will receive two cycles of CI 5-FU. A cycle will be defined as four weeks of CI 5-FU at 250 mg/m²/d, 7 days/week, followed by two weeks rest. Each six week period, four weeks chemotherapy and two weeks rest, will constitute one cycle. Patients will receive a total of two cycles. Dose modifications are detailed in Section 7.4.
- 7.1.3.2** Treatment Arm 2: Gemcitabine - Beginning 3-5 weeks after completion of chemoradiation, patients will receive three cycles of gemcitabine. A cycle will be defined as three weeks of gemcitabine at 1000 mg/m²/d, once weekly, followed by a one week rest. Each four week period, three weeks of chemotherapy and one week of rest, will constitute one cycle. Patients will receive a total of three cycles, 12 weeks. Dose modifications are detailed in Section 7.4.

7.2 5-Fluorouracil

- 7.2.1** Chemistry - 5-Fluorouracil is a fluorinated pyrimidine differing from the normal RNA substrate, uracil, by a fluorinated number 5 carbon. The chemical has a pH of 8.1, and the commercially available solution is buffered with NaOH to obtain an alkaline solution with a pH of around 9.0. The drug is both light sensitive and will precipitate at low temperatures or, occasionally, after a prolonged period at room temperature. Melting range of the solid is 280-284 °C. At 25 °C the solubility is 1.2 mg/ml in chloroform. The sodium content is 8.24 mg/ml and molecular weight 130.08.
- 7.2.2** Mechanism of Action - The metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridilic acid to thymidilic acid. In this fashion, 5-FU interferes with the synthesis of DNA. This creates a thymine deficiency that provides unbalanced growth and cell death. Prolonged administration of 5-FU continuous infusion may favor 5-FU incorporation into RNA.
- 7.2.3** Pharmacokinetics - 5-FU is rapidly absorbed by the tissues. Studies with radioactively labeled 5-FU administered i.v., have indicated passage of the drug through the blood-brain barrier. Intravenous administration gives a half-time of 5-7.5 minutes at a 15 mg/kg dose. Following the i.v. administration of a single 15 mg/kg dose of radioactively labeled drug, levels of 28 mcg/ml, 2-8 mcg/ml, and 0.72 mcg/ml in plasma were observed at 10 minutes, 2 hours, and 24 hours, respectively. The drug is largely catabolized in the liver and excreted in the form of nontoxic metabolites. Eighty percent of the drug is excreted as CO² from the lungs, and approximately 15% is excreted intact in the urine in 6 hours. Of this, 90% is excreted in the first hour.
- 7.2.4** Known Side Effects and Toxicities - Mild nausea and vomiting, stomatitis, anorexia, diarrhea, alopecia, hand/foot syndrome, myelosuppression, cerebellar ataxia, skin, and cardiac toxicity have been observed. The most common toxicities with continuous infusion 5-FU are mucositis and hand/foot syndrome.
- 7.2.5** Pharmaceutical Data - Each 10 ml ampule contains 500 mg of the drug (50 mg/ml), adjusted to a pH of approximately 9 with sodium hydroxide. 5-FU is commercially available and is stored at room temperature.
- 7.2.6** Supply - Commercially available.

7.3 Gemcitabine

- 7.3.1** Chemistry - Gemcitabine (*2'-deoxy-2''-difluorocytidine monohydrochloride*) is a purine analog structurally similar to cytarabine and an analog to deoxycytidine. Gemcitabine has two fluoride atoms in the geminal position of the second carbon of the ribose sugar.
- 7.3.2** Mechanism of Action - Gemcitabine inhibits DNA synthesis in tumor cells by competing with deoxycytidine triphosphate for incorporation into DNA. Gemcitabine metabolites also inhibit enzymes in DNA synthesis. Finally, gemcitabine is masked from DNA repair enzymes with the addition of one additional nucleotide after gemcitabine is in the DNA chain.
- 7.3.3** Pharmacokinetics - Gemcitabine is metabolized into active metabolites gemcitabine diphosphate and gemcitabine triphosphate. It is also metabolized to inactive compound, gemcitabine difluorouridine. Ninety-nine percent of the dose is excreted in the urine and there is negligible protein binding. The serum half life is significantly effected by decreases in creatinine clearance. However, there is no schedule for dose reduction in renal dysfunction.
- 7.3.4** Known Side Effects and Toxicities - The primary dose limiting toxicity of gemcitabine is hematological including neutropenia, anemia and thrombocytopenia. This is based on 979 patients in 22 clinical trials with various malignancies. The starting dose range was from 800-1250 mg/m² and most patients received an induction course for seven weeks of weekly treatments followed by four week cycles, three weekly treatments and one week rest. This protocol has no induction course and begins with four week cycles. Ten percent of patients discontinued therapy overall due to toxicity. Other toxicities include mild elevation in liver function tests, rare decrease in creatinine clearance, edema, nausea, vomiting, rash, constipation, diarrhea, fever, alopecia, pain, dyspnea and stomatitis.

7.3.5 Pharmaceutical Data - Gemcitabine is supplied in 200 mg and 1000 mg vials. Two hundred mg vials are reconstituted in 5 cc sodium chloride then diluted to a concentration of as low as 0.1 mg/ml if necessary for infusion. The dose is usually given over 30 minutes. One thousand mg vials are reconstituted with 25 cc sodium chloride. It is stored at room temperature until given.

7.3.6 Supply - Commercially available

7.4 Dose Modifications

Toxicities that can be directly attributable to chemotherapy will be scored as per the “*Cooperative Group Common Toxicity Criteria*” while those directly attributable to radiation will be scored according to “*RTOG Morbidity Scoring Criteria*.” Dose toxicities that cannot be directly attributable to either modality alone will be scored according to the “*Cooperative Group Common Toxicity Criteria*.”

7.4.1 Pre-Chemoradiation Chemotherapy (4/1/99)

7.4.1.1 Treatment Arm 1: 5-FU - If grade 3 or greater toxicity occurs, chemotherapy will be discontinued. Once toxicity has resolved, chemoradiation treatment will be initiated, which should be within 13 weeks of definitive tumor-related surgery, if not, an RTOG study chair should be notified. If grade 3 or greater toxicity occurs during pre-CRT chemotherapy, then when 5FU is reinitiated as part of chemoradiation, 5FU will be restarted with 20% dose reduction. This dose reduction will remain throughout the rest of therapy (*i.e. for both CRT and post-CRT chemotherapy*) unless there is further toxicity.

7.4.1.2 Treatment Arm 2: Gemcitabine - If grade 3 or greater nonhematologic toxicity occurs, chemotherapy will be discontinued. Once toxicity has resolved chemoradiation treatment will be initiated, which should be within 13 weeks of definitive tumor-related surgery, if not, an RTOG study chair should be notified. If grade 3 or greater hematologic toxicity occurs dose modifications as described in Section 7.4.6.2 should be followed.

7.4.2 Chemoradiation

7.4.2.1 Arms 1&2: Chemoradiation (CI-5-FU) - Should patients develop grade 3 or greater myelosuppression, diarrhea (*not due to pancreatic insufficiency, see Section 9.0*), or gastro-intestinal toxicity in general then 5-FU and radiation will be held for one week. If the toxicity has not resolved to grade 1 or less the treatments will be held for an additional week. When resumed, 5-FU will be restarted with 20% dose reduction. Every effort should be made to limit treatment interruptions to 1-2 weeks and therapy should definitely be restarted when toxicity has resolved to Grade 1. More than two weeks delay during chemoradiation should be discussed with an RTOG study chair.

Stomatitis will be managed with oral agents. For symptomatic stomatitis, chemotherapy will be held for 3-7 days. Radiation will continue. 5-FU will be restarted with 20% dose reduction. *This dose reduction will remain throughout the rest of the therapy unless there is further toxicity.* If further toxicity develops, the medical oncology study chair should be notified. In addition, these patients may develop hand-foot syndrome (*see Section 9.0*). In cases of grade 3 or greater hand-foot syndrome, chemotherapy will be held for one week. Radiation will continue. If not resolved to grade 1 or less chemotherapy may be held for an additional week. If not resolved in 2 weeks, the RTOG medical oncology study chair should be notified.

Otherwise upon resumption, chemotherapy will be given at 20% dose reduction for the remainder of therapy unless further toxicity is encountered. Chemotherapy is discontinued when the course of radiotherapy is completed.

7.4.3 If hemoglobin is less than 8 g/dl, it is recommended the patient receive a transfusion but neither chemotherapy nor radiation therapy will be interrupted. Erythropoietin may also be used to support hemoglobin.

7.4.4 It is recommended that a nutritionist or dietitian should be consulted/reconsulted if caloric intake declines and is associated with a weight loss $\geq 5\%$ of pre-chemoradiation weight occurs during the chemoradiation. If weight loss of $> 10\%$ from pre-chemoradiation weight occurs, then adequate nutritional intake must be ensured by dietary supplements, enteral/alimentation, or i.v. nutrition as deemed clinically necessary to complete protocol therapy safely.

7.4.5 If radiotherapy is interrupted due to treatment toxicity, chemotherapy should be delayed until radiotherapy resumes.

7.4.6 Post Chemoradiation Chemotherapy (4/1/99)

7.4.6.1 Arm 1: 5-FU - The primary toxicities of 5-FU are mucositis, diarrhea, and hand/foot syndrome. If grade 3 or greater toxicity occurs the infusion will be interrupted for one week. Once restarted the dose will be 200 mg/m². No attempt to make up dose will be undertaken. Should a patient miss more than 20 consecutive days, the patient will be removed from protocol. The same guidelines will be used for other less common toxicities such as myelosuppression.

7.4.6.2 Arm 2: Gemcitabine - The standard dose reduction guidelines for myelosuppression are as follows:

- If the pre-treatment absolute neutrophil count (ANC) is 1000 or greater and platelet count is 100,000 or greater then full dose is given.

- For ANC of 500-999 or platelet count of 50,000-99,000, 75% dose is given.
- For ANC less than 500 or platelet count less than 50,000 the dose is held until recovery. Upon resolution the dose will be 50%.
- There will be no attempt to increase gemcitabine to full dose.
- Patients with grade 3 or greater non-hematologic toxicity will have gemcitabine discontinued and not restarted until toxicities have improved to grade 2 or less. Gemcitabine will then be restarted at a 20% dose reduction. This dose reduction will remain throughout the rest of therapy. If a second episode of grade 3 or greater non-hematologic toxicity occurs, gemcitabine dose will be reduced by an additional 20%. Any other grade 3 or greater toxicity should be referred to the medical oncology study chair.

7.5 RTOG/Adverse Drug Reaction Reporting Guidelines

- 7.5.1** The following guidelines for reporting adverse drug reactions (*ADR's*) apply to any research protocol that uses commercial anticancer agents. The following *ADR's* experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days and telephoned to RTOG Headquarters Data Management and to the Study Chairman within 24 hours of discovery:
- 7.5.1.1** Any *ADR* which is both serious (*life threatening, fatal*) and unexpected.
- 7.5.1.2** Any increased incidence of a known *ADR* which has been reported in the package insert or the literature.
- 7.5.1.3** Any death on study if clearly related to the commercial agent(s).
- 7.5.2** The *ADR* report should be documented on form FDA 3500 (*Appendix V*) and mailed to:

**Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
Telephone: (24 hours) (301) 230-2330
fax (301) 230-0159**

- 7.5.3** Any death, regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 48 hours of discovery.

7.6 ECOG/Adverse Drug Reaction Reporting

- 7.6.1** All toxicities should be coded according to the RTOG Common Toxicity Criteria and the RTOG Acute Radiation Morbidity Scoring Criteria (*Appendix IV*). ECOG suggests *ADRs* to be reported on the Adverse Reaction (*ADR*) Form for Investigational Drugs (#391RF). The form must be signed by the treating investigator. However, the MedWatch (*FDA Form #3500*) is also acceptable for reporting *ADRs* on commercial arms. All *ADR* reports must be accompanied by copies of supporting documentation. In addition, your institution's Investigational Review Board must be notified.
- 7.6.2** This protocol contains COMMERCIAL AGENTS only: 5-Fluorouracil (*5-FU*) and gemcitabine. Events indicated below must be reported in the manner specified.
For:
- Any death while on treatment if clearly related to commercial agent
 - Any *ADR* which is BOTH serious (*life threatening [grade 4] or fatal [grade 5]*) AND unexpected
 - Any increased incidence of a known *ADR*
 - Occurrences of second malignancies (*include protocol reference number, time from diagnosis to development of second malignancy and any characterization of the second malignancy, such as AML-FAB sub-type, cytogenetics, etc.*)
- 7.6.3** Call the ECOG Coordinating Center within 24 hours of the event. Submit original written *ADR* form to the ECOG Coordinating Center within 5 working days of the event. In addition, a copy must be mailed to the Investigational Drug Branch (*IDB*) within 10 days and your institutional Review Board (*IRB*) must be notified.

The ECOG Coordinating Center will call the RTOG office to report *ADR* telephone calls and will forward *ADR* reports to RTOG.

	NCI/CTEP Secondary AML/MDS Report Form ¹	ECOG Second Primary Form ² (Form #630)
AML/MDS	X	

All other secondary cancers		X
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- 1 To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and to the NCI, accompanied by copies of the pathology report and when available, a copy of the cytogenetic report.
- 2 To be submitted to ECOG within 30 days of diagnosis of a new primary cancer during or after protocol treatment, regardless of relationship to protocol treatment. Not for use for reporting recurrence or metastatic disease. A copy of pathology report should be sent, if available.

NCI Telephone Number: (301) 230-2330

ECOG Telephone Number: (617) 632-3610

NCI FAX Number: (301) 230-0159

ECOG Mailing Address

NCI Mailing Address:

ECOG Coordinating Center

IDB

Frontier Science

P.O. Box 30012

ATTN: ADR

Bethesda, MD 20824

303 Boylston Street

Brookline, MA 02146-7648

7.7 Adverse Drug Reaction Reporting for Southwest Oncology Group Institutions for Commercial Agents (4/1/99)

7.7.1 ADR Reporting should be based on the Toxicity Criteria provided in the protocol. All Southwest Oncology Group Investigators are responsible for reporting of adverse drug reactions according to the NCI and Southwest Oncology Group Guidelines. Southwest Oncology Group investigators must:

7.7.2 Call the Southwest Oncology Group Operations Office at 210/677-8808 within 24 hours of any suspected adverse event deemed either drug-or treatment-related, or possibly drug-or treatment-related which meets these criteria:

- a) Any AE/ADR which is life/threatening (Grade 4) or fatal (Grade 5) and unknown. Any occurrence of secondary AML or MDS must also be reported.
- b) Any increased incidence of a known AE/ADR which has been reported in the protocol.
- c) Any AE/ADR which is fatal (Grade 5), even though known.

7.7.3 Instructions will be given as to the necessary steps to take depending on whether the reaction was previously reported, the grade (*severity*) of the reaction and study phase. The Southwest Oncology Group Operations Office will immediately notify the RTOG Office. Within 10 days of the initial telephone report, the investigator must send the completed (*original*) FDA 3500 Form (*for regimens using only commercial agents*) to the NCI:

**Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824**

In addition, within 10 days the investigator must send:

- a copy of the above report,
- copies of prestudy forms
- copies of flow sheets from prestudy through event, and
- documentation of IRB notification, to the following address:

**ADR Program
SWOG Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217**

7.7.4 At the Southwest Oncology Group Operations Office a multilayered review will be performed and pertinent findings and supporting documentation will be forwarded to the RTOG office, NCI, Study Coordinator, and Southwest Oncology Group Statistical Center.

8.0 SURGICAL GUIDELINES

8.1 Documentation of Resection

8.1.1 The following information should be sought by the surgeon at the time of resection (*a standard Whipple or pylorus-preserving pancreaticoduodenectomy is preferred for lesions of the pancreatic head, neck/uncinate process*):

- a) The margins of the resected tissue (*left lateral, bile duct*), superior and inferior are to be marked with metallic clips (*when possible*).

- b) Location of tumor in pancreas.
- c) Location of grossly involved lymph nodes.
- d) Absence of tumor in liver, absence of ascites and peritoneal tumor involvement; all suspicious areas should be biopsied or excised and evaluated for involvement by disease.

8.1.2 If tumor is adherent to and resected from adjacent structures (*e.g., a major blood vessel*), small vascular or titanium clips should be used to mark the margins of adherence. Also, resected specimens should be marked with suture at sites of adherence so pathologists may determine if radial margins are free of disease.

8.2 Patient Stratification by Surgical Margins

Patients will be stratified at randomization according to documentation of tumor status at surgical margins stated on the official pathology report. Strata will therefore include “negative”, “positive”, or otherwise not mentioned/commented on (*i.e., “unknown”*).

9.0 USE OF ANCILLARY THERAPIES

All patients need to be evaluated for the need for pancreatic enzyme replacement. Patients with evidence of pancreatic insufficiency (*i.e., diarrhea, weight loss*) should be started on enzyme replacement (*primary physician’s choice regarding which replacement*). Patients may also need either Lomotil or Imodium for diarrhea. Upper intestinal radiation may be associated with nausea and vomiting. Prophylactic serotonin antagonists should be considered. Patients should also be considered for treatment with an H₂ receptor antagonist such as cimetidine or ranitidine. If patients develop hand-foot syndrome, B₆ vitamin may be initiated at 50 mg p.o. qd.

10.0 PATHOLOGY (4/1/99)

10.1 RTOG Tissue Bank

10.1.1 Patients entered on this study must participate in the RTOG Tissue Bank for laboratory correlative studies.

10.1.2 The following must be provided:

10.1.2.1 A paraffin-embedded tissue block of the tumor obtained at surgical resection or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

10.1.2.2 Pathology report documenting that submitted block or slides contain tumor.

10.1.2.3 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.

10.1.3 RTOG will reimburse pathologists from submitting institutions \$100. per case if proper materials are submitted (*reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement*).

10.1.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).

10.1.5 Materials will be sent to:

**LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue and C Street
Salt Lake City, UT 84143
(801) 321-1929
Fax # (801) 321-5020**

10.1.6 SWOG Members

Southwest Oncology Group Institutions will submit pathology materials directly to RTOG according to Section 10.1.5. Mailing labels are available from RTOG.

10.2 ECOG Members

Paraffin blocks of the tumor tissue will be required for tumor banking. The blocks, along with the completed ECOG Pathology Material Submission Form No. 638 and RTOG Pathology Submission Form and the institutional pathology report should be submitted **within one month of study entry**. If insufficient tissue is available following diagnostic pathology to provide the paraffin block, a letter stating this must be sent to the ECOG Pathology Coordinating Office, Evanston Hospital – Room B624, 2650 Ridge Avenue, Evanston, IL 60201-1797. Include both the ECOG and the RTOG protocol number and patient number. A copy of the submission form will be sent to the ECOG Coordinating Center by the Pathology Coordinating Office. The submitting pathologist should be informed that the blocks submitted for this protocol will be banked for future laboratory studies, and therefore will not be returned to the submitting institution unless requested.

10.3 CA19-9 Testing/All Participants (4/1/99)

- 10.3.1** Red cell phenotype for Lewis A and Lewis B antigens must be obtained from your institution's laboratory.
- If the patient is positive for either antigen, draw one red top tube of blood and prepare serum within 60 minutes (*minimum 3 ml of serum after spinning*). Reminder: If patient is negative for the Lewis antigen, disregard the rest of Section 10.3.
 - Label the sample with the patient I.D., RTOG study and case numbers, and date drawn.
 - Freeze serum immediately at -20°C.
 - If necessary, sample can be maintained in the freezer for one week prior to sending it to the laboratory at LDS.
 - Sample must remain frozen until received at LDS Hospital.
 - Complete the Specimen Transmittal Form. The original must accompany the serum sample. A copy will be sent to RTOG as general data submission.
- 10.3.2** Lewis antigen is essential for detection of the CA19-9 antigen. Patients who lack the Lewis antigen cannot express CA19-9. They constitute 10-15% of the general population. Therefore, there may be two populations with low CA19-9 values: those without the Lewis antigen and those with it who have low CA19-9 because of low tumor burden. It is crucial to distinguish these groups in a study of the prognostic value of CA19-9.
- 10.3.3** CA19-9 testing for patients randomized to this study will be performed at LDS Hospital. Blood samples must be drawn up to 21 days pre-randomization. If drawn after randomization, it must be prior to the initiation of any protocol treatment. The institution must test for the Lewis antigen prior to sending the samples to LDS.
- 10.3.4** When you are ready to ship the sample(s), call Amy Furness at (801) 321-1929 to obtain information about the shipping vendor and account number to be used. You can also reach her by e-mail at ldafurne@ihc.com. Make sure the shipping vendor is aware that the sample must remain frozen until receipt at LDS or the sample cannot be used. Plan the mailing so the specimen does not arrive at LDS Hospital on a Saturday, Sunday, or holiday. The specimen must be packaged to avoid breakage, spillage, and other contamination.
- 10.3.5** Followup submissions of serum (*at first followup and annually*) will also be sent to LDS hospital.
- 10.3.6** Prepared blood samples will be shipped on dry ice to:

LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue and C Street
Salt Lake City, UT 84143
(801) 321-1929
Fax # (801) 321-5020

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (4/1/99)

Assessment	Pretreatment Within 3 Weeks before Randomization	Weekly During Treatment	At Follow-up See Note
History & Physical	X		X
Weight & KPS	X	X	X
CBC, ^k platelets	X	X ^h	X ^j
Glucose, creatinine, electrolytes, SGOT and total bilirubin	X		X ^j
Lewis Antigen	X		
CA19-9	X ^a		X ⁱ
Abdomen/liver CT scan	X		X ^j
Chest, PA & LAT	X ^b		X ^j
IVP/Nuclear scan	X ^{b,d}		
Metastatic evaluation (e.g., bone, brain, liver scans)	X ^c	X ^c	X ^c
Angiography, Upper GI Series	X ^g		
Abd. Ultrasound, MRI	X ^g		X ^c
PT, PTT ^e , CEA	X ^g		
Pregnancy Test	X ^{f,g}		
Nutritional Consult	X ^g		
Toxicity Evaluation		X	X

- a. May be done after randomization but before the start of protocol treatment. Not required if Lewis antigen is negative.
- b. Within 42 days prior to randomization.
- c. When appropriate for symptoms or findings.
- d. Or CT with i.v. contrast to demonstrate location and function of kidneys.
- e. According to institutional practice standards for heparin or warfarin prophylaxis (*see Section 7.3.2*).
- f. For women of childbearing potential.
- g. Optional - see Section 4.2.
- h. Blood counts area not required weekly between modalities, i.e. pre-CRT chemo rx and CRT or CRT and post-CRT chemo RX.
- i. At first follow-up only, and then annually thereafter. Not required if Lewis antigen was negative.
- j. At first follow-up only, then only unless clinically indicated and as appropriate for new symptoms or findings.
- k. Absolute neutrophil count is required only for patients randomized to Arm 2 and is not required during CRT.

Note: First follow-up evaluation is required at 2-4 weeks after completion of chemoradiation but prior to start of maintenance chemotherapy. Thereafter, follow-up will be q 3 months for one year, then q 6 months for two years then yearly.

11.2 Nutritional Support

11.2.1 At the time of initial evaluation, recommended nutritional evaluation should include the following as the minimum: body weight and calculation of daily oral caloric intake. For patients with steatorrhea, it is

recommended that random stool qualitative fat should be performed. If positive, patients should receive pancreatic exocrine replacement such as viokase, 3-6 tablets with meals and 1-3 tablets with snacks or equivalent should be given. Seventy-two hour fecal fat is recommended for follow-up of pancreatic replacement.

11.2.2 During the course of combined radiation and chemotherapy, patients will be weighed weekly. Diet histories will be taken to estimate oral nutritional intake. It is recommended that a nutritionist or dietitian should be consulted/reconsulted if caloric intake declines and is associated with a weight loss $\geq 5\%$ of pre-chemoradiation weight occurs during the combined radiation and chemotherapy. If weight loss of $> 10\%$ from pretreatment weight occurs, then adequate nutritional intake must be ensured by dietary supplements, enteral alimentation, or i.v. nutrition as deemed clinically necessary to complete protocol therapy safely.

11.3 Post-Treatment Evaluation

11.3.1 Following completion of all treatment, patients should undergo follow-up with a history and physical exam, as well as a CA 19-9 level (*if positive for the Lewis antigen*), based on which further investigation as needed and directed to determination of occurrence of local and/or distant disease recurrence and survival should be performed. CBC/chemistries, CXR, and abdomen/liver CT scan are required for post chemoradiation and pre-maintenance chemotherapy re-evaluation follow-up visit only (*Table 11.1*).

11.4 Criteria for Disease Progression

- local recurrence preferably proven by histology or cytology.
- positive ultrasound and/or CT scan of upper abdomen with evidence of intrahepatic disease or lymph node metastases, preferably confirmed by cytology or histology particularly for solitary liver lesions or solitary lymph node findings.
- evidence of pulmonary metastases by chest x-ray. In case of a single lesion, histological confirmation is needed.
- ascites or pleura effusion, preferably proven with positive cytology for malignant cells.
- death caused by metastases, preferably proven by histology.
- elevation in CA19-9 level will not be considered a criteria for disease progression.
- if disease progression occurs during protocol treatment, this must be noted on the data forms. Any additional therapy will be at the discretion of the treating physician.

12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission (4/1/99)

<u>Item</u>	<u>Due</u>
Demographic Form (A5) (<i>optional for non-RTOG participants</i>)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Chemotherapy Flowsheets (M1) (<i>to include pretreatment labs and the first dose of chemotherapy</i>)	
Diagnostic Pathology Report (P1) Pathology Blocks/Slides (P2)	
Serum Transmittal Form (ST) (<i>if Lewis antigen is positive</i>) Copy to RTOG, original to LDS with samples	Within 2 weeks of study entry, with first followup, then annually.
Surgery Form (S1) Operative Note (S2) Pathology Report from Surgical Resection (S5) <u>Initial Dosimetry</u> Pre-op CT Scans with a scout film indexed (C1) Pre-op CT Scan Report (C3) RT Prescription Protocol Treatment Form (T2) Simulation Films Only (T3) Calculations (T4) Boost Films (<i>simulation only</i>) (T8)	Within 3 weeks of study entry.

Post Induction Form (F0)	Within one week of end of pre-CRT chemo
Chemotherapy Flow Sheets (M1)	Within one week of 1) end of pre-CRT chemo, 2) end of chemoradiation, 3) end of first cycle of post-CRT chemo, and 4) end of second cycle of post-CRT chemo. Also upon onset of significant toxicity or death.
Radiotherapy Form (T1) Final Dosimetry Information: Daily Treatment Record (T5) Isodose Distribution (T6) Supplementary Films (TP) <i>(portal films from initial and boost films)</i>	Within 1 week of RT end
Follow-up Form (F1)	At 4 weeks after completion of chemoradiation; <i>(but prior to start of post CRT chemotherapy)</i> ; then every 3 months x 3; then q 6 months x 2 years, then annually. Also at progression/relapse and at death.
Autopsy Report (D3)	As Applicable

12.2 Quality Assurance Review

Simulation films of all fields and preoperative abdominal CT scan with a scout film indexed through the cuts. Prior to completion of pre-CRT chemo *(as per Section 6.1.8)*

12.3 ECOG Data Submission

12.3.1 *Note:* ECOG institutions should send all radiation oncology material directly to RTOG.

12.3.2 *For ECOG institutions* - originals of completed forms must be sent by the institutions to the:

ECOG Coordinating Center
Frontier Science
ATTN: DATA
303 Boylston Street
Brookline, MA 02146-7648

The RTOG case number as well as the ECOG case number should appear on every form. Investigators should retain a copy of their records. The ECOG Coordinating Center will forward the date-stamped originals to RTOG Headquarters. ECOG members should send forms directly to RTOG. RTOG forms should be used. **DO NOT use ECOG data forms except for the ECOG Pathology Material Submission Form No. 638, the ECOG Second Primary Cancer Form No. 630 and the Adverse Reaction (ADR) Form for Investigational Agents 391RF, and the NCI/CTEP Secondary AML/MDS Report Form.**

12.3.3 ECOG will attach a forms appendix to their members' version. It will be the responsibility of the institutions to copy the attached forms and to maintain a supply of available forms for data submission.

12.4 SWOG Data Submission (4/1/99)

12.4.1 *Note:* SWOG Institutions should send all radiation oncology material directly to RTOG.

12.4.2 Two copies of the original data forms as listed in Section 12.1 should be submitted at the required intervals to the Southwest Oncology Group Statistical Center, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, MP-557, P.O. Box 19024, Seattle, WA 98109-1024 for forwarding to the RTOG office. Include the RTOG protocol number and patient sequence number as well as the Southwest Oncology Group patient number. The Demographic Form (A5) is not required for SWOG members.

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints

13.1.1 Overall Survival (*Failure: Death from any cause*)

13.1.2 Disease Free Survival (*Failure: disease relapse or second primary or death without progression*);

13.1.3 Toxicity

13.2 Accrual for the Study

This is an intergroup study. From a survey of RTOG member institutions and of other participating institutions, we project an accrual rate of five patients a month. If the average monthly accrual rate is less than 4 cases, the RTOG Research Strategy Committee and the RTOG Data Monitoring Committee will evaluate the feasibility of this study.

13.3 Sample Size for the Treatment Comparison (9/21/01)

The arm containing 5-FU will be considered as the control arm for this study. Based upon previous studies, a median survival of 18 months is projected. In the phase III study for advanced pancreatic disease, a survival advantage was reported with gemcitabine as compared with 5-FU (18% vs. 2% at one year).^{18,19} If the survivals for the treatment arms in this study are assumed to follow an exponential distribution, there is a reduction of 56% in the hazard rate with gemcitabine. In light of this result, a reduction of 33% with gemcitabine is hypothesized for this study. In other words, the median survival would be 27 months. The computer software EaST for group sequential design was used for calculating the sample sizes with two planned early significance tests and with O'Brien Fleming boundary.^{30,31} Patients will enter the study uniformly over 5 years with 1.33 additional years of follow up. For significance level of .05, statistical power of .80, and a two-sided test, a total of 300 patients will be required. The final significance test would be done after 207 deaths with the two interim tests after scheduled 69 and 138 deaths. The early stopping rules will be as follows: If the normal standardized test score Z is larger than 3.35 or 2.35 on the first or second test, then the gemcitabine arm would be declared better. If $U(t)$ is smaller than .055 or 1.22 on the first or second test, then the gemcitabine arm would be declared not better. Guarding against an ineligibility/unevaluability (*no data*) rate of up to 10%, **a total of 330 patients will be entered.**

13.3.1 Background (9/21/01)

The original study design was a compromise because there was widespread concern about patient accrual. Patients with lesions other than pancreatic head lesions were added when the protocol was finalized because of this concern. The biology of pancreatic body and tail lesions is quite different than head lesions. In the chapter "Survival after Surgical Treatment of Pancreatic Cancer", in *The Pancreas*, (Beger, Warshaw, Buclee, et al., eds. Blackwell Science, 1998), Lillemoe and Cameron state, "5 year survival for pancreatic cancer of the body and tail of the pancreas is rare". Following resection, the median survival of body and tail lesions is one year or less and two and five-year actuarial survival is approximately 15-20% and 10%, respectively (*Mayo Clinic, Hopkins, Sloan Kettering*). These results are inferior to reported results with resected pancreatic head lesions.

The accrual was projected to 5 patients per month. The study opened to accrual in July 1998 and, as of March 1, 2001, 307 patients were entered for an average monthly accrual of 9.9 patients. During the last year, the accrual has dramatically increased with an average of 13.3 patients per year. Approximately 15-20% of patients entered into RTOG 97-04 have lesions other than pancreatic head lesions. Thus, the original targeted accrual for the protocol was achieved by end of April 2001. Recognizing the success of accrual to this study, an RTOG initiated proposal was made to increase the accrual goals of the study to detect a smaller difference. This proposal was subsequently endorsed by the GI intergroup mechanism. Besides RTOG, both ECOG and SWOG enter patients into this study, and their GI chairs have agreed to increase the accrual goal. A consensus also was reached about the magnitude of the increase. The RTOG DMC approved this proposed increase at its April 4 meeting, but no efficacy outcome data from study were presented. This was the first time that the DMC considered the study. In addition, the corporate sponsor, Lilly, subsequently approved the amendment.

The sample size was increased so that the study could detect a 28% reduction in hazard rate should such a difference exist with a two-sided test at significance level of 0.05 and 85% statistical power. This reduction translated into a median survival difference of 18 to 25 months (hazard ratio ~ 1.4). The sample size then became 470 analyzable patients, and yet the patient accrual would have been completed well within the originally hypothesized accrual period. In addition, the original statistical power of .80 would be maintained to compare the treatments in patients with just a head lesion. The final significance test would be performed after 355 deaths with the two interim tests scheduled after 118 and 236 deaths. The early stopping rules will be as follows: if the normal standardized test score Z is larger than 3.38 or 2.38 on the first or second test respectively, then the gemcitabine arm would be declared better. If $U(t)$ is smaller than 0.021 or 1.15 on the first or second test, then the gemcitabine arm would be declared not better. Adjusting the number of analyzable patients by 10% to account for possible ineligible or unevaluable cases, **the new targeted sample size is 518 patient entries.**

13.4 Randomization Schema

The treatment allocation will be used in a randomized permuted block within strata to balance patient factors other than institutions, as Zelen has described.³² Patients will be stratified by nodal involvement (*yes vs.*

no), tumor diameter (< 3 cm vs. = 3 cm), and tumor status at surgical margin (negative vs. positive vs. unknown) prior to randomization.

13.5 Analysis Plan for Treatment Test

13.5.1 Interim Analyses to Monitor the Study Progress:

Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase, data quality, compliance rate of treatment delivery with the distributions of important prognostic baseline variables and the frequencies and severity of the toxicities by treatment arm. They will not contain the results from the treatment comparisons with respect to the efficacy endpoints (overall survival, disease free survival, and patterns of failure).

13.5.2 Significance Testing for Early Termination

The first significance test comparing the survivals between the two treatment arms will be performed after 69th death has been reported. It is projected to occur after approximately 60% of the required sample size have entered into the study. The result will be then reported to the RTOG Data Monitoring Committee (DMC). If an early stopping rule is met, the study statistician would recommend to the DMC that the randomization be discontinued and study be immediately written up for publication.

The second significance test comparing the survivals between the two treatment arms will be performed after the 138th death has been reported. It is projected to occur after approximately 90% of the required sample size have entered into the study. The result will be then reported to the DMC. If a early stopping rule is met, the study statistician would recommend to the DMC that the randomization be discontinued and study be immediately written up for publication.

13.5.2.1 (9/21/01) Due to the change in sample size (Section 13.3.1), the two interim tests now will occur after the 118th and 236th deaths, respectively.

13.5.3 Analysis for Reporting the Initial Treatment Results: Otherwise, a major analysis will be undertaken when one of the following occurs: 1) there have been 207 total deaths on both arms; 2) there have been 114 deaths on the 5-FU containing arm where each patient has been potentially followed for a minimum of 1.33 years. It will include tabulation of all cases entered, and those excluded from the analyses with the reasons, the distribution of the important prognostic baseline variables, and observed results with respect to the endpoints mentioned in Section 13.1. The primary hypothesis for the study is whether the control and the experimental arms have different effects on overall survival. All eligible patients randomized will be included in the comparison. All eligible patients randomized will be grouped by assigned treatment arm in the analysis. The primary hypothesis of treatment benefit will be tested using the Cox proportional hazard model with the stratification factor of nodal involvement (yes vs. no), tumor diameter (< 3 cm vs. = 3 cm), and tumor status at surgical margin (negative vs. positive vs. unknown).³³ Additional analyses of treatment effect will include modifying factors such as age, sex, race, and other patient characteristics. These analyses will also use the Cox proportional hazard model. The treatment comparison on disease free survival will be analyzed in a similar fashion. The treatment comparison on the patterns of treatment failures and of 3+ grade toxicity will use the z-statistic for testing binomial proportions.

13.5.3.1 (9/21/01) The major analysis now will occur after there have been 355 deaths between the two arms, respectively, or alternatively, after there have been 177 deaths on an 5-FU arm, in which each patient potentially has been followed for a minimum of two years.

13.5.4 Inclusion of Women and Minorities

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have considered the two possible interactions (treatment by race and treatment by gender). No study so far has indicated any significant racial or gender differences in treatment effects for operable pancreatic cancer patients. These issues are not well studied.^{21,34,35} The study was designed to test the efficacy under the assumption of the same efficacy rate across the genders and the across the races. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

The distributions of genders and races are based upon review of the literature. If 55% of patients recruited in this study are males, the power to detect a 33% reduction in the hazard rate for gemcitabine is 57%. Likewise, if 45% of patients recruited in this study are females, the power to detect it is 49%. If 90% of patients recruited in this study are white, the power to detect it is 78%. Likewise, if 10% of patients recruited in this study are nonwhites, the power to detect it is 15%. The following table provides the projected distribution of gender by race:

Projected Gender and Minority Distribution

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	1		10	3	133	1	148
Male		1	13	3	164	1	182
Unknown							
Total	1	1	23	6	297	2	330

13.5.4.1 (9/21/01) Based on the current distribution of race and gender of the patients already enrolled on the study, the disposition of all patients enrolled in the future should be as follows:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female			23	8	223	6	260
Male	2	6	17	13	220		258
Unknown							
Total	2	6	40	21	385	5	518

If the ratio of sexes is approximately 1:1, the power to detect a 28% reduction in hazard rate within either gender is 51%. If 85% of patients recruited in this study are white, the power to detect a 28% reduction in hazard among such patients is 78%. Similarly, if 15% of patients recruited to this study are nonwhite, the power to detect a 28% reduction in hazard in this group is 16%.

13.6 CA19-9 Evaluation

Several published papers have reported a dramatically worse survival in pancreatic patients with elevated CA19-9 values.²⁵⁻²⁹ The patient series from Fox Chase Cancer Center was used for sensitivity analyses. At the 1997 SSO meeting, the Fox Chase investigators reported that the patients with three month post-resection CA19-9 180 u/ml had significantly worse survival.²⁹ On multivariate analysis, the three-month post-resection CA19-9 proved to be the most prognostic factor for absolute survival and disease free survival. This study seeks to confirm this observation in a multicenter trial and possibly refine their proposed cutpoint. Of 40 patients in the series, 20% were Lewis antigen negative, 27% with CA19-9 > 180 u/ml, and 53% CA19-9 < 180 u/ml. For planning purposes, the survivals for each of the groups were assumed to exponentially distributed. The treatment component of the study was designed to accrue patients for 5 years and then they would be followed for an additional 1.33 years before the final analysis is undertaken with a total of 207 deaths. Using the Fox Chase data, it is estimated that 25 patients, who are Lewis antigen negative, will be dead at the time of the final analysis. Thus, after subtracting them, there will be 182 deaths available for CA19-9 analysis. Although the patients with the elevated CA19-9 had 3.4 times increased hazard rate in the series, the statistical powers were calculated to detect at least a 2.5 and 2.0 increase respectively. The statistical significance level was set at .05 (*two-sided*) and number of deaths at 182. The statistical power was then calculated under the above conditions using the equation described by Schoenfeld.³⁶

$$\#deaths = \frac{z_a + z_b}{(\ln HR) w (1-w)}$$

z_a - normal deviate for the significance level

z_b - normal deviate for the statistical power

HR - hazard ratio

w - prevalence rate for patients with elevated CA19-9

The statistical power in both instances exceeds .99 if the CA19-9 is done at the time of the final analysis. Then statistical power was set at .90. The necessary number of deaths was determined to detect at least a 2.5 increase and a 2.00 increase respectively in the constant hazard rate for patients with evaluated CA19-9.

The calculated number of deaths was 57 and 98 for such increases respectively. Since the number of deaths at the planned two early significance tests for treatments are 67 and 134 respectively, analyses of CA19-9 as independent prognostic variable would be appropriately done at the same time. The prognostic value of CA19-9 will be tested using the Cox proportional hazard model with the other study stratification factors and assigned treatment as fixed covariates.

- 13.6.1** (9/21/01) The CA 19-9 analyses will now be performed at the same time as the revised timing of the two interim and the final tests (*Sections 13.5.2.1 and 13.5.3.1*) for treatment differences per Section 13.3.1.

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APPENDIX I (4/1/99)

RTOG 97-04 ECOG/SWOG R9704

A PHASE III STUDY OF PRE AND POST CHEMORADIATION 5-FU VS. PRE AND POST CHEMORADIATION GEMCITABINE FOR POSTOPERATIVE ADJUVANT TREATMENT OF RESECTED PANCREATIC ADENOCARCINOMA

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are to be used during my participation in clinical research so I have an opportunity to decide whether or not to undergo the procedure after knowing the risks, benefits, and alternatives. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

This study is for patients who have had a cancer of the pancreas removed. I am eligible for this study because there was no visible tumor left behind and not more than 8 weeks have passed since my operation. The purpose is to see what treatment is best to prevent this type of cancer from returning.

Past experience has shown that although it is favorable to have no visible tumor left behind and to have the tissue margins free of visible tumor cells, patients are still at risk for having a return of their tumor, either in the area of the operation or in other tissues. Patients can be given radiation treatments combined with a chemotherapy drug called 5-FU (*5-Fluorouracil*) with or without gemcitabine. There is some evidence that giving radiation treatments with 5-FU may be beneficial in preventing tumor recurrence. Gemcitabine also appears to have antitumor activity in pancreas cancer.

The purpose of this study is to find out which of the two different ways of combining radiation and chemotherapy is better for lowering the chance of tumor returning.

DESCRIPTION OF PROCEDURES

Treatment must start within 3-8 weeks after surgery. My nutritional intake will be evaluated to see if I'm getting enough to keep up my strength during treatment. If my calorie intake is low, I may need a feeding tube. My chemotherapy treatment will be determined by a process known as randomization where treatment is selected by computer. The chances of receiving either treatment are about equal. I will be treated with one of the following:

Arm 1 I will receive fluorouracil (*a chemotherapy drug*) constantly (*day and night*) by vein (*i.v.*) for three weeks. In order to get this treatment, a special i.v. tube is placed into a large vein in my neck and shoulder region or through a large vein in my arm. A small pump is used to give the drug. This pump is worn by the patient and is the size of a package of cigarettes and weighs about seven ounces. At the end of chemotherapy, I will have 1-2 weeks rest then I will start chemotherapy again but together with radiation. Radiation will be given to the area where my tumor was once a day, Monday through Friday for five and one-half weeks (*28 radiation treatments*) without a planned rest. In addition, fluorouracil is given continuously (*day and night*) by i.v. and pump seven days a week during the five and a half weeks of radiation. Once this is completed, there is a 3-5 week rest (*no treatment*) after which two cycles of fluorouracil are given. Each cycle consists of 4 weeks of fluorouracil and two weeks rest in between. After completing my treatment, I will be monitored for disease recurrence.

Arm 2 I will receive gemcitabine (*a different chemotherapy drug*) by i.v. once a week for three weeks. At the end of chemotherapy I will have 1-2 weeks rest then I will start chemotherapy again (*with fluorouracil this time*) and radiation. Radiation will be given to the area where my tumor was once a day, Monday through Friday for five and one-half weeks (*28 radiation treatments*) without a planned rest. The fluorouracil is given continuously (*day and night*) by i.v. seven days a week during the five and a half weeks of radiation. In order to get this treatment, a special i.v. tube is placed into a large vein in my neck and shoulder region or through a large vein in my arm. A small pump is used to give the drug. This pump is worn by the patient and is the size of a package of cigarettes and weighs about seven ounces. Once this is completed there is a 3-5 week rest (*no treatment*) after which I will be treated with gemcitabine again. I will get gemcitabine once each week for three

weeks followed by one week rest. This four week period is called a cycle. A total of 3 cycles of gemcitabine are given over 3 months. After completing my treatment, I will be monitored for disease recurrence.

In either arm, there can be treatment delays or interruptions, if needed, to make the treatment safer or more tolerable if there are side effects.

On both arms of the study, physical examinations and blood tests are required weekly during treatment. Some examinations, medical imaging (*that is, x-ray tests, CAT scan tests or MRI tests*), and blood tests are done before the study treatment begins and occasionally after the study treatments are completed. The type and scheduling of these tests have been planned to be as similar as possible to what most doctors would do as part of standard care. Tests will help monitor for disease recurrence. Follow-up evaluation or monitoring will be at least every 3 months for the first year after completion of treatment, then every 6 months for two years, then at least once per year. Examinations or follow-up evaluations may be done more frequently as needed for my condition or circumstances. This may include blood samples. Possible side effects from blood samples include minimal discomfort from needle punctures, possible hematoma (*black and blue marks*), and rare instances of fainting. On the days blood is drawn, 2 or 3 samples may be required. Each sample will amount to less than two teaspoons.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Radiation Therapy:

The risks of irradiation include decreased appetite, weight loss, nausea, diarrhea, abdominal cramping, lowering of blood counts with risk of bleeding, bruising, or infection, tiredness, redness of the skin, and hair loss in the treated area.

Fluorouracil (5-FU):

5-FU can cause diarrhea, a metal taste in the mouth, dry skin, dry nose, and watery eyes. The drug can cause soreness or painful ulcers of the mouth and throat. Loss of hair may result. The drug may cause thinning of the skin, nail changes, redness or darkening of the skin, rash, and increased sensitivity to the sun. 5-FU may cause decreased blood counts, usually white blood cells but also red blood cells and platelets. This can lead to an increased risk of infection, fatigue, and bleeding. Rarely, the drug can cause reversible unsteadiness upon walking, dizziness, slurred speech, or permanent headaches that continue after treatment is stopped. It has also rarely been associated with heart attack.

The special intravenous line used in all patients requires some daily care that most patients either do for themselves or get help from a family member. There is a risk of bleeding, blood clot or infection with these lines. These side effects can be serious but very rarely lead to death.

Gemcitabine:

The most common side effect of gemcitabine is decreased blood counts, usually white blood cells but also red blood cells and platelets. This can lead to an increased risk for infection, fatigue, and bleeding. Other toxicities include mild liver irritation, rare decrease in kidney function, swelling, nausea, vomiting, skin rash, constipation, diarrhea, fever, hair loss, pain, shortness of breath and sores in the mouth. While the decrease in blood cells can occur in up to one in four people, the other side effects may occur in less than one in twenty people.

It is expected that most side effects on this study will not be severe or life threatening and, while inconvenient, will respond to short treatment interruptions or changes in drug doses. However, severe or life threatening side effects may occur. My doctors will be checking closely for side effects as treatment is given and will make every reasonable effort to keep them from becoming severe. Medicines may be prescribed to help with side effects. If side effects occur, they can result in extra costs of care. This institution is not financially responsible for the cost of treating side effects resulting from the study.

Nutritional intake/appetite may be affected significantly during any of these treatments. Maintaining good nutritional intake/appetite is very important. My weight will be checked weekly while receiving radiation treatments with chemotherapy. If I experience more than 10% weight loss during the time I am receiving radiation treatment with chemotherapy, other ways of improving my nutritional intake/appetite will be considered. Placement of a feeding tube temporarily or permanently may be a possibility.

Undesired effects occurring weeks, months or years following these treatments are possible. Part of one or both of my kidneys may be permanently damaged by the radiation treatment. However, the treatments will be designed to avoid this being something that would cause a noticeable or important problem to me. Some patients treated with irradiation after surgery will develop scarring around the intestines. This occurs rarely, but can be serious or life threatening and require surgery to repair.

This study may be harmful to an unborn child. There would be significant risks to a fetus carried by a mother who is participating in this study. Therefore, participants who are still menstruating and have not been surgically sterilized should have a negative pregnancy test prior to participation in this study. The results will be made available to the study participant prior to the initiation of this study. There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____ the investigator in charge at _____. In addition, I may contact _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

It is expected that both of the treatment arms in this study will produce anti-tumor effects. It is believed that treatment on either arm would be better for most patients than no treatment at all after surgery.

It is not possible to predict whether or not any personal benefit will result from the treatment program. I understand that the information that is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program includes prolongation of my life but this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

In addition to this study, all of the following are possible choices for me after surgery:

1. No further treatment unless or until tumor problems occur again.
2. Radiation treatment to the pancreas region without drug treatment.
3. Radiation treatment to the pancreas region combined with 5-FU.
4. Chemotherapy with fluorouracil, gemcitabine or both.

I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with my doctors. The physicians involved in my care will be available to answer my questions about this program both now and in the future.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

Records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). If my hospital is an Eastern Cooperative Group member, records of my progress will also be kept in a confidential file at their Headquarters. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue, slides, and/or a small blood sample may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (*or Legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX III (4/1/99)

**STAGING FOR PANCREAS
AJCC, 5th Edition**

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 2 cm or less in greatest dimension
T2 Tumor limited to the pancreas more than 2 cm in greatest dimension
T3 Tumor extends directly into any of the following: duodenum, bile duct, peripancreatic tissues or direct invasion of the ampulla of Vater
T4 Tumor extends directly into any of the following: stomach, spleen, colon, adjacent large vessels

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
 pN1a Metastasis in a single regional lymph node
 pN1b Metastasis in multiple regional lymph nodes

Distant Metastasis (M)

- MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis, or seeding of the peritoneum, or direct extension to an organ or structure not listed in T1-3

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T1-3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supercede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone .
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- | | |
|--|--|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above |

- All life threatening (*grade 4*) events which may be due to agent. As above
 - First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.
**A written report may be required.
- ii. *Phase II, III Studies Utilizing Investigational Agents*
- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours
**A written report must be sent to RTOG within working days with a copy to IDB.
(*Grade 4 myelosuppression not reported to IDB*)
 - All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.
**A written report to follow within 10 working days.
 - All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report **in writing** to RTOG Headquarters and IDB within 10 working days.

** See attached (*if applicable to this study*) NCI Adverse Drug Reaction Reporting Form

APPENDIX VI

Field Diagrams

Figure 1: Schematic AP field, with blocking, for pancreatic head lesion.

Figure 2: Schematic lateral field, with blocking.

APPENDIX VI

Field Diagram

Figure 3: Schematic AP field, with blocking, for pancreatic body lesion.

Figure 4: Schematic AP field, with blocking, for pancreatic tail lesion.

APPENDIX VII

INTERGROUP PARTICIPATION IN RTOG STUDIES

GENERAL GUIDELINES

- I. REGISTRATION:** RTOG will be responsible for all registration/ randomizations. The procedure is:
-Each institution affiliated with a Cooperative Group will phone their group and supply the eligibility check information.
-The participating Cooperative Group will then telephone RTOG 215/574-3191 between 8:30 a.m. and 5:00 p.m. ET and supply the necessary eligibility and stratification information. RTOG will then assign a case number and treatment assignment. The participating Cooperative Group will then inform its member institution.
-RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group forwards a copy of the calendar to the participating institution.
- II. PROTOCOL DISTRIBUTION:** Each participating cooperative group is responsible for distribution of the protocol to its members. All protocol amendments will be sent by RTOG to each participating Group office for distribution to member institutions. All communication with NCI regarding this protocol will be routed through the RTOG.
- III. INSTITUTIONAL PARTICIPATION:** It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases.
- IV. CONFIRMATION/CALENDARS:** A Confirmation of Registration notice and a Data Collection Calendar is produced for each case registered and/or randomized. These will be distributed by RTOG to the appropriate cooperative group office for distribution to their members, if appropriate.

The form identification code, which appears on the Calendars in the “key” columns, is found on the form in the lower right corner.

You are expected to respond to each of the items listed either by submitting the item, by notifying us in writing that the item is not available or that the assessment was not done. The calendar may also list items that are not forms (*CT or MRI scan reports, pathology reports*) but are specific source documents. These items will be noted in the data collection section of the protocol but will not be listed on the Forms Package Index.

Additional items/forms may be required depending on events that occur e.g. if surgery was done a surgical report may be required. See the protocol for conditional requirements.

Unless specified otherwise, all patients are followed until death or termination of the study.

- V. FORMS:** Other groups will attach a forms appendix to their members' version. It will be the responsibility of the other group's member to copy the attached forms and to maintain a supply of available forms for data submission.

The Demographic Data Form (**A5**) is required on all RTOG enrollments. This form is ideally completed by the patient. Instructions are found on the form.

The RTOG assigned case and study number must be recorded on all data items submitted. Except for material which requires rapid review (*see below*), data should be routed according to the mechanism set up by the participating Group. Generally the participating group will require forms to be routed through their office and they will send the forms to:

American College of Radiology
Radiation Therapy Oncology Group - 14th Floor

- VI. LABELS:** Patient specific labels will be supplied to the participating Group for distribution to the individual institutions as patients are registered at RTOG.

When completing the labels, be specific when describing films, e.g.: "Pre-op CT Brain Scan, "Large Photon Localization Film", "Follow-up Bone Scan", etc.

Research associates are advised to consult technical staff for assistance when labeling radiotherapy films. Correct film identification is the responsibility of the institutions and is essential to maintain efficient data flow.

- VII. CANCELLATION/INELIGIBILITY:** Patients who are found to be ineligible subsequent to registration are to be followed according to plan unless you receive written instructions to the contrary.

Patients who receive no treatment whatsoever may be canceled, however, written notification and an explanation must be received at RTOG Headquarters as soon as this has been determined. We must receive this notification not later than two weeks after registration. We will notify you of the determination made regarding the status of the case and instructions regarding subsequent data submission. RTOG requires all patients in randomized trials to be followed with data submission according to protocol schedule.

- VI. RAPID REVIEW ITEMS:** Time critical data which require rapid submission must be sent directly to RTOG. These items are:

T2 - Protocol Treatment Form
T3 - Photon Localization film (*for all fields treated initially*)
T4 - Photon dose calculations (*for all fields treated initially*)

IX. REQUEST FOR STUDY INFORMATION

AND FORMS REQUEST: Requests for additional information or clarification of data will be routed through the participating Cooperative Group office for distribution to the individual institution.

The memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response.

Periodically (*generally three times per year*) computer-generated lists identifying delinquent material are prepared. These are routed by RTOG through the participating group for distribution.

X. QUESTIONS REGARDING:

**Data/Eligibility/Treatment/
Adverse Events/Data Management Procedures**

RTOG Research Associate (215) 574-3214

Forms Packets (RTOG Members)

Registration Secretary (215) 574-3191

Pathology

Pathology Clerk (801) 321-1929
(*unless specified otherwise in Section 10.0*)

Protocols/Amendments

Director, Protocol Development (215) 574-3195

**Radiotherapy data items (films,
radiographs, isodose summations,
treatment records, scans,**

Dosimetry Clerk (215) 574-3219

reports and calculations)

Randomization/Registration

Registration Secretary (215) 574-3191

If you are unable to reach the person noted, and your call is urgent, ask to speak to any HQ Research Associate.

XI. ADVERSE EVENTS AND TOXICITY

From Radiotherapy: Unusual toxicities, all grade 5 toxicities, and grade 4 toxicities in altered fractionation studies are reported by telephone within 24 hours of discovery to RTOG Headquarters, to the Group Chairman Dr. Walter Curran, to the Study Chair(s), and to the RTOG Research Associate for this study.

From Investigational Agents: Are to be reported according to NCI guidelines. In addition, RTOG Headquarters, RTOG Data Management and the Study Chair(s) are to receive notification as outlined by the NCI procedures. If telephone notification is necessary, RTOG and the Study Chair(s) must also be called.

Copies of all toxicity reports and forms submitted to NCI must be sent to RTOG Headquarters also.

From Commercial Drugs: Are to be reported according to NCI/FDA guidelines. A copy of the reports and forms submitted to FDA must be sent to RTOG.

Data Submission: Events that require telephone reporting will require current updating of data forms through the date of the event. Submit within 10 working days of the telephone call.

Second Malignancy: All second primary tumors that are diagnosed during or following protocol treatment must be reported on the study data collection forms. AML/MDS must be reported on the NCI/CTEP Secondary Reporting Form. Instructions for submission are on the data form.

APPENDIX VIII

VA Affiliations – RTOG 97-04

A Phase III Study of Pre and Post Chemoradiation 5-FU Vs. Pre and Post Chemoradiation Gemcitabine for Postoperative Adjuvant Treatment of Resected Pancreatic Adenocarcinoma

If any VA facility, employees (*full or part-time*), or patients will be utilized by the Institution or Investigator while conducting the Study, please provide acknowledgement from the director or other authorized official of the VA facility involved, by signature below, that:

- 1) the conduct of the Investigator of the research described in the protocol does not conflict with any policies of the VA or your duties to the VA;
- 2) the amount and manner of payment as described by RTOG policy does not conflict with any policies of the VA; and
- 3) the designated payee does not conflict with any policies of the VA.

APPROVED AND CONFIRMED:

(Name of VA facility)

(Signature of Authorized Official)

(Typed or Printed Name)

(Title)

(Date)

Name of RTOG Principal Investigator

RTOG Institution Name

RTOG Institution Number

***Return to Protocol Office
RTOG Headquarters
Fax 215-574-0300***