

RADIATION THERAPY ONCOLOGY GROUP

RTOG 92-09

**PHASE I/II STUDY OF HYPERFRACTIONATED EXTERNAL BEAM IRRADIATION,
PROPHYLACTIC HEPATIC IRRADIATION WITH CONCURRENT 5-FLUOROURACIL
AND LOW DOSE FOLINIC ACID IN PATIENTS WITH UNRESECTABLE CARCINOMA OF
THE PANCREAS**

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HEPATIC IRRADIATION WITH CONCURRENT 5-FLUOROURACIL AND LOW DOSE FOLINIC ACID IN
PATIENTS WITH UNRESECTABLE CARCINOMA OF THE PANCREAS**

SCHEMA

Dose Escalations

- Only one dose level will be open at one time

| | | |
|--------------------------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| R (closed 8/8/95) | <u>Arm 1:</u> | 46 Gy to the pancreas in 34 fractions over 23 days. 40 Gy to the regional nodes in 30 fractions over 21 days. 25 Gy to whole liver in 20 fractions over 14 days. |
| E | | |
| G (opened 3/1/96) | <u>Arm 2:</u> | 49 Gy to the pancreas in 36 fractions over 24 days. 40 Gy to the regional nodes in 30 fractions over 21 days. 25 Gy to the whole liver in 20 fractions over 14 days. |
| I | | |
| S (not open) | <u>Arm 3:</u> | 55 Gy to the pancreas in 40 fractions over 28 days. 40 Gy to the regional nodes in 30 fractions over 21 days. 25 Gy to the whole liver in 20 fractions over 14 days. |
| T | | |
| E (not open) | <u>Arm 4:</u> | 61 Gy to the pancreas in 44 fractions over 30 days. 40 Gy to the regional nodes in 30 fractions over 21 days. 25 Gy to the whole liver in 20 fractions over 14 days. |
| R | | |

Radiation Therapy: Radiation will be delivered in 1.5 Gy fractions twice daily in weeks 1 and 4 (and week 5 for level 4). 1.25 Gy b.i.d. will be delivered during weeks 2 and 3. All fractions must be separated by at least 6 hours.

Chemotherapy: Leucovorin (folinic acid) 20 mg/m² rapid i.v. injection followed by 5-FU 400 mg/m² rapid i.v. injection. 5-FU and Leucovorin will be given concurrently with RT on three consecutive days during week 1, then x 3 days during week 5 and x 4 days during week 9.

Eligibility: (See Section 3.0 for details)

- Pathologically or cytologically confirmed locally unresectable ductal adenocarcinoma of the pancreas.
- Oral nutrition \geq 1200 calories/day
- WBC \geq 4,000, platelets \geq 100,000
- KPS \geq 60
- Bilateral renal function by IVP or scan
- Interval from surgery must be 2-6 weeks
- No prior radiation to the upper abdomen or systemic chemotherapy
- No distant metastases
- Tumor must be \leq 6 cm in greatest diameter
- No evidence of regional lymph node involvement except by direct extension of the primary

Required Sample Size: 104 maximum

6/12/95, 3/1/96)

Institution # _____

RTOG 92-09

Case # _____

ELIGIBILITY CHECK (6/21/93, 6/12/95)

page 1 of 2

- _____(Y) 1. Is there histologic or cytologic proof of adenocarcinoma of the pancreas?
- _____(N) 2. Is the tumor any of the types specified in 3.2.4 (islet, cystadenoma, cystadenocarcinoma, carcinoid, duodenal, periampullary or distal bile duct cancer)?
- _____(Y) 3. Is disease confined to the pancreas, contiguous organs, regional lymph nodes (by direct extension only) or adjacent peritoneum ?
- _____(N) 4. Based on CT or operative findings, is there evidence of regional lymph node involvement (including the lateral aortic nodes) other than by direct extension?
- _____(N) 5. Is the greatest tumor diameter > 6 cm by operative or imaging findings?
- _____(Y/N) 6. Is the tumor considered locally resectable?
Reason for non-surgical RX approach? _____
_____(Y) If resectable, is the patient considered a non-surgical candidate (due to medical contraindications or refusal of surgery)?
- _____(Y/N) 7. Has the patient undergone prior surgical exploration for this tumor? (If no, skip to Q10)
- _____(Y) 8. Is the interval between surgery and protocol RX per protocol specifications?
- _____(N) 9. Has the patient undergone a complete resection?
- _____(N) 10. Is there any evidence of distant metastasis?
- _____(N) 11. Any radiotherapy to the upper abdomen or prior systemic chemotherapy?
- _____(Y/N) 12. Any prior malignancy other than non-melanoma of the skin or insitu of the cervix?
_____(Y) If yes, has the patient been disease-free for > 5 years?
- _____(Y) 13. Were all mandatory studies specified in 4.3 completed?
- _____(Y) 14. Has bilateral renal function (as determined by IVP, renal scan or abdominal CT) been verified?
- _____(≥ 4) 15. What is the current WBC (per 1000)?
- _____(≥ 100) 16. What is the current platelet count (per 1000)?
- _____(≤ 1.5) 17. What is the serum creatinine?

Institution # _____

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ELIGIBILITY CHECK (6/21/93, 6/12/95)

Case # _____

- _____(Y) 18. Is the patient free of significant nausea or vomiting and able to maintain an oral intake > 1200 calories/day?
- _____(≥ 60) 19. What is the Karnofsky Performance Scale?
- _____(Y) 20. Is the patient's age ≥ 18?
- _____(Y) 21. Has a study-specific consent been signed?

| | | | |
|--|-----------------------|--|---------------------------------|
| | Patient's Name | | Sex |
| | Verifying Physician | | Race |
| | Patient ID # | | Social Security Number |
| | Referring Institution | | Zip Code (9 digit if available) |
| | Medical Oncologist | | Method of Payment |
| | Birthdate _____ | | Treatment Start Date |
| | | | Treatment Assignment |

Completed by _____

Date _____

1.0 BACKGROUND

1.1 Introduction

In the treatment of unresectable but localized carcinoma of the pancreas, randomized series from Mayo Clinic¹ and the Gastrointestinal Tumor Study Group (GITSG)² demonstrated that a combined modality program using external beam radiation therapy plus 5-fluorouracil resulted in a significantly improved survival when compared to radiation therapy alone or chemotherapy alone. In the most recent study from the Gastrointestinal Tumor Study Group, a combined irradiation/chemotherapy regimen had improved survival over a SMF (streptozocin, mitomycin-C, 5-FU) chemotherapy only arm resulting in median survival of 42 weeks with an 18 month survival of 18%.³

Following external beam radiation therapy alone or in conjunction with chemotherapy, local failure rates as well as the development of hepatic metastases remain high. In the high dose series from Thomas Jefferson University Hospital (60.0 to 67.0 Gy in 7 to 8 weeks) local failure was seen in at least 2/3 of the patients.⁴ In a Mayo series of 12 patients, 2-year actuarial local control was only 19% and 43% of the patients developed hepatic metastases following standard external beam radiotherapy.⁵

Liver metastases are also a common pattern of failure in both intraoperative radiation therapy (IORT) series for locally unresectable pancreas cancer as well as adjuvant irradiation \pm 5-FU after total resection. External beam + IORT series from MGH, Mayo and Rush Presbyterian resulted in better local control than external beam trials but still had a high incidence of liver metastases at 49%, 38%, and 52% respectively, of patients at risk.^{5,6,7} In the randomized GITSG adjuvant trial, the risk of liver metastases in the surgery alone arm was 52% and was similarly high in irradiation + 5-FU arm at 40%.⁸ In a University of Kansas series of resection \pm XRT/5-FU, the incidence of liver metastases was 44%.⁹

1.2 Chemotherapy Results

The use of adjuvant systemic chemotherapy in an attempt to control occult metastatic disease with advanced pancreatic carcinoma has been disappointing with no studies demonstrating significant benefits.³ For patients with unresectable pancreatic cancer, the survival of patients receiving 5-FU in conjunction with external beam radiotherapy has been shown to be superior to that of patients receiving external beam radiotherapy alone.^{1,2} The use of 5-FU and folinic acid in conjunction with external beam radiation therapy has not been evaluated as an adjuvant treatment in patients with locally advanced pancreatic carcinoma except for the phase I/II Mayo/NCCTG tolerance study combining external irradiation with 5-FU and low dose leucovorin for locally advanced GI cancers (including pancreas) (Gunderson-personal Communication). This was a single fraction per day pilot delivering 45-54 Gy in 1.8 Gy fractions to unresected or residual tumor \pm lymph nodes combined with 3 or 4 days of 5-FU (400 mg/m²) and leucovorin (20 mg/m²) given during weeks 1 and 5 of external beam radiotherapy followed by additional post external beam cycles of 5-FU and low dose leucovorin. The median survival of 22 patients with unresected pancreatic cancer, PS 0-1, was greater than or equal to 15 months (exploratory laparotomy not required to rule out peritoneal seeding or liver metastases).

1.3 Prophylactic Hepatic Irradiation

An additional approach in dealing with the high incidence of hepatic metastasis is prophylactic hepatic irradiation. There are limited data available on the efficiency of this treatment approach. Komaki et al. reported on 16 patients receiving high dose external beam radiation therapy to the pancreas, 61.2 Gy over 7 weeks combined with prophylactic hepatic irradiation to 23.4 Gy over 2.5 weeks combined with 5-FU. This study reported a 2-year survival of 46.7% and only two patients developed hepatic metastasis.¹¹ No complications were observed. This pilot study was followed by a Phase I/II trial by the RTOG(protocol 8801)with a larger group of patients 81 enrolled, 79 evaluable)applying 5-FU infusion instead of bolus during RT. This study reported a median survival of 8.4 months.¹² This manuscript reported preliminary results from the multi-institutional trial. Updated survival results show a 2-year survival rate of 11.5%. Raju et al. reported eight patients with unresectable pancreatic carcinoma treated with 5-FU infusion,⁴ 1000 mg/m²/one day infusion. The pancreas received 65 Gy and the liver 25 Gy in three weeks combined with 5-FU infusion¹³. All patients were alive without evidence of disease between 9 to 11 months. Toxicity was reported as minimal. It would seem appropriate to consider prophylactic hepatic irradiation as an adjuvant treatment to deal with potential microscopic involvement in the liver.

1.4 Altered Fractionation

The natural history of locally advanced pancreatic carcinoma is frequently rapid with the early emergence of distant metastases or uncontrollable primary disease. In view of the rapid natural disease history and large percentage of patients with high grade lesions, the evaluation of hyperfractionation schedules for pancreas cancer is reasonable. The tolerance of twice daily large upper abdominal external beam fields encompassing the liver, pancreas tumor, regional lymph nodes with concurrent chemotherapy is unknown. Gunderson (personal communication) has observed that the tolerance of twice a day radiation for gastric carcinoma (1.5 Gy to tumor and nodal field in the morning and 1.5 Gy to the upper abdomen in the afternoon) combined with 3-day infusion 5-FU weeks 1 and 5 to be more toxic than once daily fractionation schedules plus bolus 5-FU weeks 1 and 5 with more patients having to receive hyperalimentation during irradiation. For twice daily treatments with concurrent chemotherapy, doses of 1.25 Gy per fraction to extended upper abdominal fields and 1.5 Gy per fraction for tumor and nodal fields would seem reasonable for initial tolerance studies. Preliminary data from the RTOG study evaluating hepatic irradiation for patients with hepatic metastases indicates acceptable tolerance of 30 Gy given in 1.5 Gy b.i.d. fractions to the liver. Since the entire stomach will not be in the extended field in this pancreas pilot, 1.5 Gy b.i.d. fractions may be better tolerated than in the Mayo pilot for gastric cancer which by definition needed to include the entire stomach. An additional potential advantage of accelerated fractionation schedules for unresectable pancreas cancer is the shortened time commitment to treatment in a disease in which median survival with standard treatment is less than one year in most trials. Even the longest escalation will allow completion of all external beam radiation b.i.d. treatment within 3-4.5 weeks. Since median survival with external irradiation \pm chemotherapy ranges from only 8 to 10 months in randomized group trials, the shortened treatment schema may be more appropriate than the 6 to 10 week commitment in other schemas.

2.0 OBJECTIVES

- 2.1** To evaluate the efficacy and toxicity of hyperfractionated external beam irradiation, prophylactic hepatic irradiation with concurrent fluorouracil and low dose folinic acid in patients with unresectable adenocarcinoma of the pancreas.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (6/12/95)

- 3.1.1** Patients with pathologically or cytologically confirmed ductal adenocarcinoma of the pancreas. Diagnosis may be obtained by CT-guided needle biopsy or laparotomy. If the diagnosis is confirmed by CT needle biopsy, laparoscopy should be considered to rule out peritoneal seeding.
- 3.1.2** Patients must have locally unresectable pancreatic carcinoma.
- 3.1.2.1** This includes patients who are considered unresectable based on standard anatomic criteria, i.e., tumor fixation to portal vein or superior mesenteric vessel or other retroperitoneal structure.
- 3.1.2.2** Disease should be confined to the pancreas, contiguous organs, regional lymph nodes (by direct extension) and adjacent peritoneum.
- 3.1.2.3** Patients who are considered unresectable due to other medical conditions or who refuse surgery are eligible.
- 3.1.2.4** Tumor must be \leq 6 cm in greatest diameter based on operative or imaging findings.
- 3.1.3** Patients should be maintaining oral nutrition (greater than 1200 calories per day) and be free of significant nausea and vomiting. Intravenous hyperalimentation may be employed to supplement oral intake above 1200 calories per day.
- 3.1.4** White blood counts \geq 4,000 and platelet counts \geq 100,000.
- 3.1.5** Patients must have bilateral renal function as determined by excretory urogram (IVP) abdominal CT scan or renal scan. The serum creatinine must be \leq 1.5 mg/dl.
- 3.1.6** Karnofsky performance status \geq 60.
- 3.1.7** Study-specific informed consent must be obtained and patients must be \geq 18 years of age.
- 3.1.8** Interval from exploratory laparotomy to start of protocol treatment must be 2-6 weeks. Interval between biliary or gastric bypass surgery and study treatment must be 3-6 weeks.

3.2 Conditions for Patient Ineligibility (6/12/95)

- 3.2.1** Karnofsky less than 60.
- 3.2.2** Previous radiation therapy to upper abdomen or systemic chemotherapy.
- 3.2.3** Previous malignancy unless disease-free for greater than 5 years except for non-melanoma skin cancer or carcinoma in situ of cervix.
- 3.2.4** Islet cell carcinomas, cystadenomas, cystadenocarcinomas, carcinoid tumors, duodenal carcinomas, distal bile duct and periampullary carcinomas. (6/21/93)

- 3.2.5 Patients who have had complete surgical resection of tumor.
- 3.2.6 Evidence of metastatic disease as defined by physical exam, chest radiograph, CT scan of abdomen and if done, laparoscopy or laparotomy findings.
- 3.2.7 Failure to perform the mandatory studies in Section 4.3.
- 3.2.8 Tumor > 6 cm.
- 3.2.9 Evidence of regional lymph node involvement (*except by direct extension*) based on operative or CT findings (*including involvement of the lateral aortic lymph nodes*).

4.0 PRETREATMENT EVALUATIONS

- 4.1 Histologic or cytologic confirmation of carcinoma is required for patient inclusion in this study (CT or ultrasound biopsy, intraoperative). The preferred technique for intraoperative biopsy is a true-cut transduodenal biopsy. A shave or superficial wedge biopsy, biopsy of adjacent lymph nodes, true cut needle biopsy or fine needle aspiration biopsy are also acceptable.
- 4.2 Complete history and physical examination including weight, Karnofsky and anatomical diagram of tumor.
- 4.3 Mandatory studies: (must be done within a month of study entry)
 - 4.3.1 Chest: PA/lateral
 - 4.3.2 CT scan of the abdomen and liver with intravenous contrast
 - 4.3.3 CT scan with i.v. contrast and/or intravenous pyelogram to demonstrate location and function of kidneys (IVP can be done during simulation)
 - 4.3.4 CBC and platelets
 - 4.3.5 Liver and renal function tests (to include LDH), amylase, glucose, electrolytes, serum albumin, BUN, creatinine, and urine analysis.
- 4.4 Optional studies:
 - 4.4.1 Angiography
 - 4.4.2 Upper GI Series
 - 4.4.3 Abdominal ultrasound
 - 4.4.4 Magnetic Resonance Imaging (MRI).
 - 4.4.5 CEA and CA19-9

5.0 REGISTRATION PROCEDURES (6/21/93)

- 5.1 Patients can be registered only after pretreatment evaluation and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday-Friday, from 8:30 a.m. to 5:00 p.m.. The following information must be provided:
 - Patient's Name & ID Number
 - Institution Name & Number
 - Physician's Name
 - Eligibility Criteria Information
 - Medical Oncologist's Name
 - Patient Demographics
 - Treatment Start Date

6.0 RADIATION THERAPY

6.1 Energy Specifications

- 6.1.1 External therapy must be conducted with a supervoltage unit. Minimum acceptable photon energy is 6 MV. Minimum treatment distance to skin for SSD techniques or isocenter for SAD techniques is 80 cm.

6.2 External Beam Radiation Therapy

- 6.2.1 The external beam radiation will be initiated up to 6 weeks after diagnosis. If laparotomy without bypass has been done, treatment can be initiated as early as two weeks postoperatively; if either a biliary or gastric bypass is performed, the interval should be at least three weeks. If the patient is unable to start therapy at 6 weeks, the case should be discussed with Dr. Willett prior to registration.
- 6.2.2 Isodose distribution is mandatory in outlining the position of the spinal cord, kidney and the tumor. Efforts should be made to minimize normal tissue irradiation by utilizing CT scan information and surgical clips.
- 6.2.3 All b.i.d. radiation fractions (both pancreatic bed and upper abdominal fields) **must be separated by at least 6 hours**. Treatment times or intervals must be documented on the daily treatment record.

6.2.4 Simulation/localization and portal verification films will be obtained for each treatment field and submitted to RTOG Headquarters.

6.3 Treatment Plan (Appendix VI)

6.3.1 Week 1: Pancreatic Bed and Regional Lymphatic Irradiation (Appendix VII, Fig. 1A, IB: B, C)

6.3.1.1 Dose Levels 1,2,3,4: Three or four field technique to be utilized treating to a total dose of 15 Gy at 1.50 Gy b.i.d. The target will include the unresected or residual tumor with 3 to 5 cm margins beyond defined area of risk. The pancreaticoduodenal, portahepatic and celiac axis lymph nodes should be included (should also include suprapancreatic for body lesions).

6.3.2 Weeks 2 & 3: Whole Liver/Pancreatic Bed/Regional Lymphatics Appendix VII, Fig. 2)

6.3.2.1 Dose Levels 1,2,3,4: AP-PA techniques to 25 Gy given at 1.25 Gy b.i.d.

6.3.2.2 This field will include tumor bed and lymphatics as previously described but will also include the entire liver as defined by CT scan.

6.3.3 Week 4: Pancreatic Bed Boost (Appendix VII, Fig. 1A, IB: B' C')

6.3.3.1 Dose Levels 1,2,3,4 : Three or four field technique to be utilized treating the unresected or residual tumor with a 1.5 - 2 cm margin .

6.3.3.2 Dose Level 1: 1.5 Gy b.i.d. for two days (6.0 Gy).

6.3.3.3 Dose Level 2: 1.5 Gy b.i.d. for three days (9.0 Gy)

6.3.3.4 Dose Level 3: 1.5 Gy b.i.d. for five days (15.0).

6.3.3.5 Dose Level 4: 1.5 Gy b.i.d. for seven days (21.0).

6.3.4 External Beam Total Dose

6.3.4.1 Dose Level 1: 46 Gy to the pancreas in 34 fractions over 23 days. 40 Gy to the regional nodes in 30 fractions over 21 days. 25 Gy to whole liver in 20 fractions over 14 days .

6.3.4.2 Dose Level 2: 49 Gy to the pancreas in 36 fractions over 24 days. 40 Gy to the regional nodes in 30 fractions over 21 days. 25 Gy to whole liver in 20 fractions over 14 days .

6.3.4.3 Dose Level 3: 55 Gy to the pancreas in 40 fractions over 28 days. 40 Gy to the regional nodes in 30 fractions over 21 days. 25 Gy to whole liver in 20 fractions over 14 days .

6.3.4.4 Dose Level 4: 61 Gy to the pancreas in 44 fractions over 30 days. 40 Gy to the regional nodes in 30 fractions over 21 days. 25 Gy to whole liver in 20 fractions over 14 days .

6.4 Dose Specifications

6.4.1 For the following portal arrangements the target dose shall be specified as follows:

6.4.1.2 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

6.4.1.3 For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.

6.4.1.4 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.

6.4.1.5 For a single beam: on the central ray at the plane of rotation at the center of the target area.

6.4.1.6 For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.

6.4.1.7 Other or complex treatment arrangements: at the center of the target area.

6.5 Normal Tissue Tolerance

6.5.1 Spinal cord: **Dose must not exceed 40 Gy.**

6.5.2 Kidney: One kidney should be excluded from treatment if possible. If both total kidneys are within the extended field (liver and tumor nodal), the dose to one kidney must not exceed 15 Gy. For lesions in the head and proximal body, obliqued AP-PA fields could be used after the 15 Gy to include liver, pancreas and lymph nodes yet exclude left kidney. A CT scan and/or excretory urogram should be obtained before the start of treatment to define the renal function since at least 2/3 of one kidney must be excluded from the high dose fields. With head of pancreas lesions, one commonly has to include greater than 50% of the right kidney and therefore spare the left. For body or tail lesion, one may have to include greater than 50% of the left kidney and therefore spare the right kidney.

6.5.3 Since the entire liver will receive 25 Gy, efforts to minimize hepatic irradiation by tumor/regional nodal fields and tumor boost fields by shaping and weighting of beams (three and four fields) must be done to limit high dose irradiation to less than one third of the liver volume.

6.5.4 Treatment breaks of up to one-week are permissible. Interruption beyond one week will be a protocol violation.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 5-Fluorouracil (5-FU)

- 7.1.1** 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. The melting range of the solid is 280-284°C. At 25°C the solubility is 12.2 mg/ml in water, 5.5 mg/ml in 95% ethanol, and less than 0.1 mg/ml in chloroform. The sodium content is 8.35 mg/ml of sodium ion the molecular weight is 130.08.
- 7.1.2** Mechanism of Action The metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic 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 by continuous infusion may favor 5-FU incorporation into RNA.
- 7.1.3** Animal Tumor Data 5-FU is active in a wide range of animal neoplasms, including leukemia L1210 and adenocarcinoma 755.
- 7.1.4** Animal Toxicology Dose-limiting toxicities in rodents and large mammals are hematologic and gastroenteric side effects.
- 7.1.5** Toxicities: Nausea, vomiting, stomatitis, dermatitis, alopecia, leukopenia, thrombocytopenia, rare cerebellar ataxia.
- 7.1.6** 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 can be stored at room temperature.
- 7.1.7** Human Pharmacology 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 14 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 Leucovorin (Folinic Acid)

- 7.2.1** How Supplied: Available commercially in 50 mg vials containing desiccated powder which is reconstituted with 5 ml of water for intravenous injection.
- 7.2.2** Storage: The reconstituted powder should be given immediately unless bacteriostatic water USP is used as a diluent. In this case, the solution should be given within 7 days.
- 7.2.3** Known Side Effects and Toxicities when given in combination with 5-FU: Mild nausea and vomiting, stomatitis, anorexia, diarrhea, alopecia, myelosuppression have been observed.

7.3 Administration

- 7.3.1** Chemotherapy given concurrently with radiation: 1) Chemotherapy will be given within 2 hours after administration of radiation therapy on three consecutive days during week one of dose levels 1-4. 2) On each day of the chemotherapy, leucovorin will be given at the dose of 20 mg/m²/day by rapid i.v. injection. 5-FU at the dose of 400 mg/m² will be given by rapid i.v. injection immediately following administration of leucovorin.
- 7.3.2** Chemotherapy subsequent to radiation therapy:
- 7.3.2.1** During week 5: 5-FU and leucovorin will be administered for three consecutive days. Chemotherapy will be given provided the leukocyte count is at least 4000/mm³ and the platelet count at least 100,000/m³. If the blood counts are not at this level, weekly blood counts will be obtained and chemotherapy will be initiated when the counts have risen to acceptable levels. If after six additional weeks, the leukocyte counts and platelet counts have not risen to the above levels, additional chemotherapy will not be given. Leucovorin will be given at a dose of 20 mg/m²/day by rapid i.v. injection. 5-FU at a dose of 400 mg/m²/day will be given by rapid i.v. injection immediately following administration of leucovorin.
- 7.3.2.2** During week 9: 5-FU and leucovorin will be administered for four consecutive days. If the patients did not experience leukocyte counts less than 2000 or platelet counts of less than 50,000 or any other

severe toxicity, the second course will be given over four consecutive days. Leucovorin at a dose of 20 mg/m²/day will be given by rapid i.v. injection and 5-FU at a dose of 400 mg/m²/day will be given by rapid i.v. injection immediately following administration of leucovorin.

7.4 Dose Modifications

7.4.1 Treatment Modifications Based on Toxicity If multiple toxicities are seen, the dose administered should be based on the most severe toxicity.

7.4.2 Combined Chemotherapy and Radiation

| | <u>Toxicity Reaction</u> | <u>Treatment</u> | <u>Changes</u> |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 7.4.2.1 | During Radiation WBC < 2000 or Platelets < 50,000 3 upper stool symptoms | RT | Delay RT until counts rise above these levels and/or until vomiting subsides and/or Grades 2- stool frequency reduces to lower GI < 5/day. |
| 7.4.2.2 | <u>Chemotherapy Subsequent to Radiation</u> Prior to each course Any stomatitis Any diarrhea WBC less than 4000 or Platelets < 100,000 | 5-FU Leucovorin | Delay until stomatitis or diarrhea subsides or until counts rise above these levels |
| 7.4.2.3 | <u>During Interval After First Course</u> Mild to moderate stomatitis (Grades 1-2) Mild to moderate diarrhea (Grades 1-2) WBC 2000-3500 | 5-FU Leucovorin | Do not add 4th day of treatment to second course |
| 7.4.2.4 | Severe stomatitis (Grade ≥ 3) Severe diarrhea (Grade ≥ 3) (Greater than 6 loose stools/day) WBC < 2000 | 5-FU Leucovorin | Decrease daily 5-FU dose by 33%. |

7.5 Adverse Drug Reaction Reporting Guidelines (6/12/95)

7.5.1 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported in writing to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days and telephone to RTOG Headquarters Data Management staff and to the Study Chairman within 24 hours 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 number available 24 hours
(301) 230-2330

7.5.3 Special reporting requirements for RTOG 92-09 - The following toxicities must be called in to RTOG Headquarters within 24 hours of discovery.

7.5.3.1 Grade ≥ 3 hepatic, small bowel, large bowel, stomach or kidney

7.5.3.2 Grade ≥ 1 spinal cord

- 7.5.3.3. Any death, regardless of cause, that occurs while the patient is receiving protocol treatment or any death, regardless of cause, that occurs within one month of discontinuing protocol treatment.
- 7.5.3.4 All adverse events requiring telephone reporting are to be followed with written documentation and data forms within 10 working days.
- 7.5.3.5 Failure to comply with these additional requirements may lead to suspension of registration privileges to this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

A central review is not planned

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

| Assessment | Pretreatment Within 2 weeks of Study Entry | Weekly During RX | After RX ^e |
|-----------------------------------------------------------------------|--------------------------------------------------|------------------------|--------------------------|
| History & Physical | X | | X |
| Path Evaluation/Tumor Diagram | X | | |
| Weight & KPS | X | X | X |
| Chest, PA & LAT | X ^a | | X ^b |
| Abdomen/Liver CT Scan | X ^a | | X ^f |
| IVP ^c | X ^a | | |
| CBC & platelets | X ^a | X | X |
| LDH, amylase, glucose, creatinine, BUN, electrolytes, albumin, CA19-9 | X ^a | | X |
| Urinalysis, CEA | X ^a | | b |
| Angiography, UGI | d | | |
| Ultrasound, MRI | d | | b |
| Metastatic Evaluation (Bone, brain, liver scans) | | X ^b | X ^b |
| Toxicity Evaluation | | X | X |

- a. Within 4 weeks before study entry
- b. When appropriate for new symptoms or findings
- c. Or CT with i.v. contrast to demonstrate location and function of kidneys
- d. Optional
- e. See Section 12.1 for follow-up schedule
- f. At first follow up and then q 6 months

11.2 Nutritional Support

11.2.1 At the time of initial evaluation, nutritional evaluation will be performed to include the following as the minimum: body weight and serum albumin. Intravenous nutrition is required in all patients who have either a) loss of 10% or more of body weight in 6 months prior to admission b) or with serum albumin less than 3.2 gram/percent. Intravenous feeding should provide at least 40 calories per kilogram body weight per day as carbohydrate and/or fat in at least 1 gram protein equivalent per kilogram body weight per day and should be considered postoperatively until patients measured oral intake is at least 1800 calories per day. For patients with steatorrhea, random stool 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.

11.2.2 During the course of external beam radiation therapy, patients will be weighed weekly and serum albumin measured at least bi-weekly. Diet histories will be taken to estimate oral nutritional intake. If either of the following occur: a) weight loss of > 10% from external beam radiation, or b) serum albumin below 3 gram/percent, then adequate nutritional intake must be ensured by dietary supplements, or i.v. nutrition.

11.3 Response Definitions: Tumor identified by CT scan will be measured bidimensionally in the longest and its perpendicular diameters.

11.3.1 Complete Response (CR): Disappearance of the tumor by CT scan.

11.3.2 Partial Response (PR): 50% or greater decrease in the size of the lesion as seen on CT scan.

11.3.3 Stable Disease

11.3.3.1 No progression of primary indicator lesion.

11.3.3.2 No new areas of malignant disease.

11.3.3.3 No significant deterioration in weight, symptoms, or performance status.

11.3.4 Progressive Disease (PD): Twenty-five percent or greater increase in the size of the lesion as seen on CT scan or increase or new onset of jaundice. Nausea and vomiting from gastric outlet obstruction and a rise in serum bilirubin from progressive biliary obstruction will be considered disease progression.

11.3.4.1 Development of any new area of malignant disease. Histologic confirmation is desirable.

11.3.4.2 Measurable evidence of hepatic metastasis. Any of the following will be criteria of progression:

a) Hepatomegaly with a clearly defined liver edge extending 5 cm or more below the costal margins or xiphoid on quiet respiration. Hepatomegaly must be confirmed by CT scan.

b) A CT scan demonstrating a new and clearly defined perfusion defect measuring at least 1 cm in greatest diameter.

11.3.4.3 Pathophysiologic evidence of progression, e.g. the appearance of jaundice, ascites, pleural effusions, or neurologic findings reasonable established to be related to malignant disease (ascites and pleural effusions must have cytologic confirmation).

11.4 Post-Treatment Evaluation

11.4.1 Following completion of all treatment, patients should undergo followup with history, physical exam, liver and renal function chemistries, CEA and CA19-9.

11.4.2 CT scan should be obtained at first followup visit and then every 6 months, or unless clinically indicated.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

| <u>Item</u> | <u>Due</u> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Demographic Form (A5) Medical Oncology Treatment Planning Form (M2) | Within 1 wk of registration |
| Initial Evaluation Form (I1) Pathology Report (P1) | Within 2 wks of registration |
| <u>Preliminary Dosimetry Information:</u> RT Prescription (Protocol Treatment Form) (T2) Films (simulation and portal for pancreatic bed & regional nodes) (T3) Calculations (for above fields) (T4) | Within 1 wk of start of RT |
| Radiotherapy Form (T1) <u>Final Dosimetry Information:</u> Treatment Record for all fields (T5) Isodose Distribution for all fields (T6) Boost Film (simulation and portal for pancreatic bed boost) (T8) Supplemental Films (simulation and portal for liver/ | Within 1 week of RT end |

pancreatic bed/nodes) (TP)
Supplemental Calculations (for boost supplemental and fields)
(TL)

Chemotherapy Flowsheets (M1)

At completion of chemotherapy
for weeks 1,5 and 10 and upon
termination of treatment as

applicable.

Follow-up Form (F1)

Every 3 months from treatment
start for 1 year; q 4 months x 1
year; q 6 months x 3 years then
annually or upon observation of
toxicity described in Section 13.2
and at death.

Autopsy Report (D3)

As applicable

12.2 Timely Data Submission for Toxicity Evaluation

Timely submission of data is essential in order to meet the study's objectives for toxicity evaluation and to safely assign treatment levels. Required assessments through month 6 after the completion of protocol treatment will not be suppressed.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Objectives

The primary objectives of this study are to identify the maximum tolerated dose of hyperfractionated external beam irradiation to the pancreas and regional lymph nodes when administered with prophylactic hepatic irradiation and a concurrent chemotherapeutic regimen of leucovorin and 5-FU in patients with unresectable pancreatic cancer. Once this maximum dose is identified, indications of treatment efficacy will be examined by evaluating endpoints such as overall survival, time to disease progression, and patterns of development of metastatic disease (i.e. sites of metastatic disease and time to development of metastatic disease).

13.2 Dose-Limiting Toxicity

In a previous RTOG study (RTOG 84-05) it was shown that hepatic irradiation up to 30 Gy in 20 fractions was well tolerated. However, in the present study there is concern that the addition of the concurrent chemotherapeutic regimen and irradiation of the pancreas may increase chances for the development of hepatic toxicity. For this reason, prophylactic irradiation to the liver is limited to 25 Gy in all dose arms.

In all dose arms, severe hepatic toxicity (Grade 3 or higher) is considered the most likely toxicity that will force limitation of treatment dose. However, any other severe toxicity (Grade 3 or higher) of the small bowel, large bowel, stomach, or kidney will be considered dose-limiting if such toxicity is observed. Any incidence of spinal cord complications will also be considered a dose limiting toxicity. Reversible toxicities, such as hematologic toxicities associated with administration of chemotherapeutic agents, will not be considered dose-limiting unless efforts to resolve such toxicities fail and severe hematologic toxicity persists.

Due to the fact that hepatic toxicity is a late effect of radiation therapy and may not be observed before six months from end of radiotherapy, no patient will be considered to be free of treatment related toxicity until evaluation at six months from end of treatment. It is acknowledged that some patients may die before this evaluation point making them inevaluable for toxicity outcomes. As discussed in the following section, this will require accrual of a larger group of patients in each dose group.

13.3 Sample Size and Dose Escalation Scheme

Due to the clinical severity of a grade 3 or grade 4 hepatic toxicity or other toxicity being considered dose limiting, it was felt that evidence of toxicity at a level of 30% or above would not be acceptable. Therefore, this trial was designed to identify the maximum RT dose regimen that can be tolerated with less than a 30% chance for a patient developing a severe (Grade 3 or higher) hepatic, small bowel, large bowel, stomach, or kidney toxicity, or any grade spinal cord toxicity. By calculating discrete binomial probabilities, we can reject:

H_0 : Toxicity at a given dose $\geq 30\%$
for

H_1 : Toxicity at a given dose $< 30\%$

with 95% confidence ($\alpha = 0.05$, one-sided) if we observe dose-limiting toxicities in no more than:

**0 of the first 9 evaluable patients,
1 of the first 14 evaluable patients,
2 of the first 19 evaluable patients .**

Due to the requirement that we have six months of follow-up before we can evaluate toxicity, we will likely accrue 19 evaluable patients before a six-month evaluation is performed on the first nine patients. Further, it is likely that the study will have to be suspended between dose arms to await follow-up information. The study will be re-opened as soon as a decision can be reached on safety of the recently completed dose arm. Specifically, if after six months of follow-up on the first nine evaluable patients we have not observed any dose-limiting toxicities, the study will re-open and begin accruing patients to the next dose arm. If one toxicity is observed in the first nine evaluable patients, we will delay escalating until 14 patients are evaluable and no additional toxicities are observed. If two dose-limiting toxicities are observed, we will not escalate until appropriate follow-up is available for 19 evaluable patients. **If, at any time, three or more dose-limiting toxicities are observed, we will conclude the currently open treatment regimen is too toxic and that the previous dose arm provides the maximum tolerated dose.**

As mentioned earlier, many of the toxicities that will be considered dose-limiting can only be observed as late toxicities, approximately six months post treatment. A previous study in a comparable patient group, receiving comparable treatment, suggests an 88% six month survival rate (Komaki et al). This rate would suggest that the study would have to accrue a maximum of 22 patients per dose arm in order to obtain the required 19 evaluable patients. We should note, however, that this survival rate estimate is based on a very small group of patients and that the true survival rate may, in fact, be quite different. As a conservative estimate, allowing for a patient ineligibility rate of 10% and an 85% six month survival rate we will anticipate 75% of all patients entered to be evaluable for toxicity at six months.

Depending on the rate and pattern of accrual and patient drop-out due to death or retrospective ineligibility, the actual number of patients entered on a given arm may vary, but **at most 26 patients will be entered on any dose arm.** In order to efficiently proceed through this study, we will closely monitor patient status and dynamically compensate for patients who die (without displaying dose-limiting toxicity) before toxicity evaluation at six months is conducted. Thus, **a maximum of 104 patients will be entered on the dose-escalation phase of the study if all dose arms are opened.**

13.4 Examination of Treatment Efficacy

It is hypothesized that this group of patients will experience a two-year survival rate of 11.5% (Komaki et al).¹² With 26 patients entered onto a given dose arm, we expect at least 23 patients to be evaluable for the survival outcome (10% excluded due to retrospective determination of ineligibility). If six or more (26%) of these patients survive past two years, we will conclude, with 95% one-sided confidence, that the given treatment provides greater than an 11.5% rate of a two-year survival. Other observed survival rates will fail to reject the hypothesis that the true two-year survival rate is 11.5% .

We will examine toxicity and secondary treatment endpoints (time to disease progression, sites of failure, time to development of metastatic disease, etc.) for all eligible patients entered onto the study and use this information in the development of future trials for this patient group.

13.5 Study Accrual and Duration of Study

A survey of RTOG member institutions suggested that approximately 50 patients per year (approx. 4 patients per month) will be entered on this protocol. At this rate, the accrual phase of this study will be completed in approximately two years. If accrual falls below three patients per month the study will be re-evaluated with regard to feasibility. Follow-up will continue to allow evaluation of the three-year survival endpoint for all patients entered onto the study.

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APPENDIX I

RADIATION THERAPY ONCOLOGY GROUP

RTOG 92-09

PHASE I/II STUDY OF HYPERFRACTIONATED EXTERNAL BEAM IRRADIATION, PROPHYLACTIC HEPATIC IRRADIATION WITH CONCURRENT 5-FLUOROURACIL AND LOW DOSE FOLINIC ACID IN PATIENTS WITH UNRESECTABLE CARCINOMA OF THE PANCREAS

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have cancer of the pancreas. My doctor feels that my participation in this study may be helpful. The purpose of this clinical research study is to evaluate the effectiveness and toxicities of combined chemotherapy and radiation therapy for the treatment of my disease. It will evaluate whether giving radiation to my liver will delay the appearance of liver metastases, a common site of spread.

DESCRIPTION OF PROCEDURES

The treatment to be given to me is as follows:

I will receive radiation therapy twice a day to my pancreas, local lymph nodes (glands) and liver for four to five weeks. The daily treatments will be separated by at least six hours but can be given on an outpatient basis. Each radiation treatment takes less than five minutes. Within two hours after my radiation treatments, for three days during weeks one and five and for four days during week nine, I will receive two consecutive injections of chemotherapy intravenously (in my vein). Each chemotherapy session should last approximately 45 minutes. Although the chemotherapy doses are the same for all patients, I will be assigned to a certain dose of radiation. As more patients participate in this study, and if there are no serious side effects at one particular dose, then the dose will be increased to a higher dose for other patients. Therefore, the dose that I receive will depend on the number of patients already entered into this study and the side effects that they have experienced. The expected total duration of treatment will be about nine weeks (4-5 weeks of radiation and chemotherapy and one week of chemotherapy).

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.

Risks of Radiation: During radiation, nausea, vomiting, fatigue, weight loss, or poor digestion of food may occur. Possible long-term side effects include bleeding in the stomach or other parts of the intestinal tract and injury to the spinal cord, liver, kidney, stomach and large intestine. Radiotherapy may also cause reddening or tanning of the skin or hair loss in the treatment area. With careful radiation therapy planning and medical care, efforts to minimize these side effects will be undertaken.

Risks from Chemotherapy: 5-Fluorouracil may cause nausea, vomiting, mouth soreness, diarrhea, lowered blood counts, darkening of the skin, or excessive tearing (eyes). Hair loss is uncommon but has been seen. Leucovorin may cause nausea, vomiting, soreness of the mouth, skin rash, or lowered blood counts.

(6/21/93)

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. Acute side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

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 or 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 not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program is prevention of metastases and greater shrinkage and control of my tumor and prolongation of my life but I understand 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

Alternatives which could be considered in my case include radiation therapy alone, chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. 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 the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future. I will be provided with a written list of procedures related solely to research which would not otherwise be necessary. These will be explained to me by my physician. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

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

I understand that 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 headquarters of the Radiation Therapy Oncology Group (RTOG). 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) 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 slides, may be sent to a central office for review. 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

AJCC STAGING SYSTEM, PANCREAS

3rd Edition, 1988

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor limited to the pancreas
 - T1a Tumor 2 cm or less in greatest dimension
 - T1b Tumor more than 2 cm in greatest dimension
- T2 Tumor extends directly to the duodenum, bile duct, or peripancreatic tissues
- T3 Tumor extends directly to the stomach, spleen, colon, or 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

Distant Metastasis (M)

- MX Presence of distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Stage Grouping

| | | | |
|-----------|----------|----------|----------|
| Stage I | T1 T2 | N0 N0 | M0 M0 |
| Stage II | T3 | N0 | M0 |
| Stage III | Any T | N1 | M0 |
| Stage IV | Any T | Any N | M1 |

APPENDIX V

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting 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.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3150).
2. The Principal Investigator will also report to the Study Chairman by telephone the details of the significant reaction.
3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.
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.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), when feasible, 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 (Adverse Reaction Reports or Drug Experience Reports) submitted to NCI, IDB, FDA, or to another Cooperative Group (in the case of RTOG sponsored intergroup studies) must also be submitted to RTOG Headquarters when written documentation is required.
6. When telephone reporting is required, the Principal Investigator should have all relevant material available. See attached reporting form for the information that may be requested.
7. See the specific protocol for criteria utilized to grade the severity of the reaction.
8. The Principal Investigator when participating in RTOG sponsored intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.
9. Institutions must also meet their individual Institutional Review Board (IRB) policy with regard to their toxicity reporting procedure.
10. Failure to comply with reporting requirements in a timely manner may result in suspension of participation, of application for investigational drugs or both.

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.

An unknown adverse reaction is a toxicity thought to have resulted from the agent but had 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. Form 3500 is to be used in reporting details (see attached). 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 and 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 only a reasonable suspicion.

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

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 <u>drug</u> monitor and RTOG Headquarters. **A written report <u>may</u> 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 <u>within 24 hours</u> **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 NCI Adverse Drug Reaction Reporting Form

APPENDIX VI
ESCALATION SCHEME

APPENDIX VII
FIELD DIAGRAMS