RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-12

A PHASE II TRIAL OF EXTERNAL IRRADIATION (50.4 GY) AND WEEKLY PACLITAXEL (TAXOL) FOR NON-METASTATIC, UNRESECTABLE PANCREATIC CANCER

Study Chairmen

Radiation Oncology
Tyvin Rich, M.D.
Univ. of Virginia
Dept. of Radiation Therapy
Health Sciences Center
Box 383
Charlottesville, VA  22908
(804) 924-9412
FAX (804) 982-3262

Medical Oncology
Howard Safran, M.D.
(401) 793-7151
FAX (401) 521-1057

Surgical Oncology
Harold Wanebo, M.D.
(401) 456-2464
FAX (401) 456-2035

Activation Date: November 9, 1998
Closure Date: March 1, 2000
Termination Date: October 5, 2005
Current Edition: June 14, 1999
Includes Revisions 1-2

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
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 Other Therapy

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 - Late Radiation Toxicity Criteria
Appendix V - Adverse Event Reporting Procedures
RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-12

A PHASE II STUDY OF EXTERNAL IRRADIATION (50.4 Gy) AND WEEKLY
PACLITAXEL (TAXOL) FOR NON-METASTATIC, UNRESECTABLE
PANCREATIC CANCER

SCHEMA

R
E
G
I  Radiation Therapy: 50.4 Gy/28 fractions (1.8 Gy per fraction) once a day in 5.5
weeks.
S
T  Chemotherapy: Paclitaxel 50 mg/m² given on days 1, 8, 15, 22, 29 and 36.
E
R

Eligibility: (See Section 3.0 for details)

- Pathologically-confirmed unresectable non-metastatic adenocarcinoma of the pancreas
- All malignant disease must be encompassable within a single irradiation field (15 x 15 cm maximum)
- Radiographically assessable.
- No prior irradiation to the planned field.
- Granulocytes ≥ 1,800/ul, platelets ≥ 100,000, bilirubin ≤ 2 mg/dL
- Creatinine < 3.0 mg% or creatinine clearance ≥ 40 ml/min.
- Oral intake ≥ 1500 calories/day
- Signed study-specific consent form

Required Sample Size: 100
Institution #
RTOG 98-12
Case #

ELIGIBILITY CHECK (11/9/98)

1. Does the patient have a pathologically-confirmed adenocarcinoma of the pancreas? (Y)
2. Does the patient have unresectable disease based on your institution’s standardized criteria of unresectability? (Y)
3. Is there evidence of metastatic disease in the major viscera or peritoneal seeding? (N)
4. Does the patient have biliary or gastroduodenal obstruction? (Y/N)
   ______ (Y) If yes, does/will the patient have drainage prior to beginning chemoradiation?
5. Is all malignant disease encompassable within a single irradiation field (15 x 15 cm maximum)? (Y)
6. Does the patient have radiographically assessable disease? (Y)
7. Has the patient had prior radiation to the planned field? (N)
8. Has the patient had prior paclitaxel or other chemotherapy? (N)
9. Has the patient had prior gemcitabine? (Y/N)
   ______ (Y) If yes, has it been completed at least 4 weeks prior to today?

The following questions will be asked at Study Registration:

1. Has the Eligibility Checklist (above) been completed? (Y)
2. Is the patient eligible for this study? (Y)
3. Date the study-specific Consent Form was signed? (must be prior to study entry) (Y)

Patient's Name
Verifying Physician
Patient ID #
Referring Institution # (if different)
Medical Oncologist
Birthdate
Sex
Race
Social Security Number
Zip Code (9 digit if available)
Method of Payment
Will any component of the patient’s care be given at a military or VA facility?
Treatment Start Date
Treatment Assignment

Completed by ________________________________ Date ________________________________

1.0 INTRODUCTION

1.1 Background and Preliminary Data
There will be an estimated 29,000 new cases of pancreatic carcinoma in 1998 in the United States and the overall 5-year survival has remained constant at < 5%. Symptomatic treatment failure especially for those with initially localized, unresectable disease occurs mainly because of local disease progression; distant metastasis also occurs frequently. Standard treatment for locally advanced disease is 5-fluorouracil (5-FU, either bolus or continuous infusion) and external beam irradiation (ExBRT, in doses of 50 to >60 Gy). The addition of the radiosensitizing chemotherapy, whether given with modest total ExBRT doses of 35 to 50 Gy or higher doses of ~60 Gy using CT guided treatment planning or radioactive seed implantation increases local control and median survival to 8 to 12 months. A new promising method of management for patients with metastatic pancreatic cancer uses Gemcitabine (difluorodeoxycytidine), but the combination of ExBRT and Gemcitabine has not been tested and it is not known whether this would be superior to 5-FU chemoradiation for the treatment of patients with localized, unresectable pancreatic cancer. A new promising chemoradiation approach is Paclitaxel (Pax) and ExBRT (PXRT).

1.1.1 The Brown University Oncology Group (BrUOG) has been a leader in the clinical development of PXRT. In a phase I study in patients with TNM stages IIIA and IIIB non-small cell lung cancer (NSCLC), an initial Pax dose of 10mg/m²/week was given by a 3 hour intravenous infusion and combined with ExBRT; subsequent Pax increments of 10 mg/m²/week were given to cohorts of three patients. Pax was administered on days 1, 8, 15, 22, 29, 36 of XRT and given with a total dose of irradiation of 60 Gy. In 27 patients the maximum tolerated dose (MTD) was 60mg/m²/week. The dose limiting toxicity was esophagitis. Only one of 27 patients developed grade 3 neutropenia. In a follow-up phase II study in 33 patients using this MTD dose with 60 Gy in NSCLC, the response rate in 29 evaluable patients was 84%. There was no difference in response rate between patients with stage IIIA and IIIB and all histologic subtypes responded. Grade 3 or 4 esophagitis occurred in 34% but only one patient required enteral nutrition by a gastrostomy tube and none required total parenteral nutrition. Two patients had grade 3 neutropenia. No patients had significant nausea.

1.1.2 For patients with locally advanced gastric or pancreatic cancers, BrUOG used a similar PXRT schedule. Patients with R-2 resections (residual disease), compromised surgical margins after resection (R-1 resections), and node positive patients were also included. Notably, several patients had poor risk factors like linitus plastica, two had failed previous chemotherapy, and seven patients had unresectable pancreatic cancers measuring >5 cm in diameter. The pancreatic target volume was defined by CT scan and covered with at least a 2 cm margin in all directions for the initial 45 Gy. The fields also included the para-aortics and porta hepatic lymph nodes.

1.1.3 Toxicity of PXRT

Three patients were not evaluable because of hypersensitivity reaction (1), pulmonary embolus (1) and recurrence of a surgical infection (1). At 60 mg/m²/week, the dose limiting toxicities were abdominal pain within the radiation field, nausea, and anorexia.

<table>
<thead>
<tr>
<th>Dosage Level</th>
<th>Paclitaxel (mg/m²/wk)</th>
<th>Gastric Cancer</th>
<th>Pancreatic Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

The median age was 70. Eligible patients had histologically documented, locally advanced, initially unresectable, gastric or pancreatic cancers. Patients with R-2 resections (residual disease), compromised surgical margins after resection (R-1 resections), and node positive patients were also included. Notably, several patients had poor risk factors like linitus plastica, two had failed previous chemotherapy, and seven patients had unresectable pancreatic cancers measuring >5 cm in diameter. The pancreatic target volume was defined by CT scan and covered with at least a 2 cm margin in all directions for the initial 45 Gy. The fields also included the para-aortics and porta hepatic lymph nodes.

<table>
<thead>
<tr>
<th>Toxicity of PXRT By Dose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/m²/wk</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>50</td>
</tr>
</tbody>
</table>
The MTD based on these data is 50 mg/m2.

1.1.4 Toxicity in the current BrUOG phase II study: Preliminary data from the BrUOG phase II PXRT study for locally advanced pancreatic cancer patients treated with 50 mg/m²/wk and 50 Gy in 5 weeks shows only one of sixteen patients with a grade 3 nausea and anorexia (6%) and one with a grade 4 hypersensitivity reaction (6%).13 No other grade 3/4 toxicities have occurred. One patient needed total parental nutrition. These data confirm the initial report of acceptable acute toxicity.

1.1.5 Treatment Response in Pancreas Cancer after PXRT:
In the phase I trial of 31 evaluable patients, treatment response was assessable radiographically in 23.12 In the 13 patients with pancreatic cancer the response rate was 31%. Five of 8 without assessable disease remain without evidence of disease at a mean follow-up of 8 months. Four patients underwent complete resection following response to PXRT including three with locally advanced gastric cancers and one with pancreatic cancer and vascular encasement. In the current phase II BrUOG study, a preliminary 30% response rate in fourteen evaluable patients confirms the initial high response rate reported in the phase I study.13

1.1.6 From these phase I and preliminary phase II data the MTD of weekly Pax and ExBRT is 50 mg/m² given once per week with conventional total doses of irradiation. These single institutional pilot data need confirmation in a larger multi-center trial with advanced disease patients who have categorically unresectable disease. The GI cancer program in RTOG will develop the use of this new radiation sensitizer in this disease and integrate this approach into a comprehensive and innovative treatment program to also include new ways of imaging pancreatic cancer, complex treatment planning and treatment delivery including 3 dimensional conformal radiation therapy and intensity modulated external beam irradiation. This first study will evaluate PXRT radiation sensitization in an RTOG multi-center phase II trial.

1.2 Correlative Studies
1.2.1 In vitro and in vivo studies indicate that radiosensitization (RS) by PXRT is dependent on the cell line (adenocarcinomas > squamous), proliferative status (log > plateau), drug concentration at the time of irradiation, length of exposure to the drug, and the time interval between drug and irradiation.14-20 These studies suggest that one mechanism of RS is based on mitotic arrest as observed in squamous cell cancers where RS is correlated with the degree and the timing of Pax induced mitotic arrest at G2/M of the cell cycle.14 However, greater RS has been seen in adenocarcinomas compared to squamous cell cancers, and this may in turn be related to differences in apoptosis induction by Pax.16 For example, in squamous cancers there is little spontaneous or XRT induced apoptosis. In contrast, RS in adenocarcinomas occurs after 34 to 48 hours which can not be explained by the mitotic arrest mechanism alone because this interval exceeds the duration of the mitotic arrest. The delayed RS in adenocarcinomas is believed to be caused by tumor reoxygenation after apoptotic clearance of paclitaxel damaged cells. This may be a common mechanism for better response to PXRT in tumors which do not have mutations in the genetic pathways controlling apoptosis.

1.2.2 The p53 gene product normally blocks cell entry into S phase in response to DNA damage and wild-type p53 function is required for the efficient activation of apoptosis in response to most chemotherapeutic agents including 5-FU, cisplatin, etoposide, Adriamycin and ionizing radiation.21-25 Clinical trials have demonstrated decreased response rates to chemotherapy in lung and colon cancers with p53 mutations however, Pax produces cytotoxicity by activating apoptosis even in the absence of p53 function in vitro and the high response rate to PXRT in NSCLC with p53 mutations is consistent with this observation.16,26 Similar high response rates to PXRT are seen in pancreatic cancer patients, where approximately two-thirds of patients have mutated p53.13 The apoptosis rates in pancreatic cancers with and without p53 mutations are presently unknown.

P16 gene alterations may have a causative role in some cases of pancreatic cancer.27 Somatic gene deletions in p16 have been detected in a familial syndrome of pancreatic cancer and melanoma.28, 29 As described below, the p16 gene is commonly mutated in most pancreatic cancer cell lines but is less commonly altered in human pancreatic cancers.30-32
Loss of normal p16 gene expression in NSCLC was found to be associated with a significantly shorter survival in patients with stage I and II tumors which were completely resected. This study suggests that p16 status is strongly predictive of metastasis in NSCLC. Similarly, loss of p16 expression in cutaneous neoplasms was strongly predictive of lymph node metastasis. p16 gene alterations confer a poor prognosis in adult T-cell leukemia. Several recent studies have indicated an association between altered p16 and more aggressive and drug-resistant tumors. Loss of p16 mediated inhibition of cell cycle progression at G1/S may interact with other genetic alterations in tumor cells and alter response to therapy. A loss in cell cycle control will also promote additional genetic changes in tumor cells because of higher mutation rates and escape from apoptosis.

Unlike p53, p16 gene alterations in primary tumors are most commonly due to gene deletions. Detection of gene deletions in primary tumor specimens is difficult because infiltration of tumor tissue by leukocytes and other normal host cells may obscure detection of gene deletions. We thus developed a novel quantitative PCR assay to detect p16 deletions locus which can be reliably applied to DNA isolated from paraffin tissue blocks.

To this end we prepared PCR primers that span p16 exon 2, the region of most reported mutations in this gene, which produce a 286 nt PCR product. These primers were chosen to amplify the p16 but not the homologous p15 locus. This was accomplished by preparing a synthetic competitive substrate lacking a Kpn I restriction enzyme site present in the native p16 sequence and adding a constant amount of this competitor to PCR reactions containing sample DNA. PCR products made from the two templates can then be distinguished by digestion with Kpn I followed by gel electrophoresis. The ratio of the intensity of the two bands reflects the number of copies of the gene present in the sample. Importantly, this ratio is insensitive to PCR conditions and allows a true estimate of the number of amplifiable gene copies present in a sample. Comparison with the results of parallel experiments using known amount of human placental DNA are used to estimate the gene copy number in the patient samples. The quality of DNA isolated from paraffin tissue blocks varies substantially, and can significantly affect this assay. To control for this variable, a second competitive PCR assay is performed using identical amounts of sample and human placental DNA with primers specific for the human Factor V gene.

1.2.3 In this phase II study, pancreatic biopsy tissue will be assessed for p53 mutations based on the preliminary BrUOG data showing p53 mutations can be assessed in needle biopsy samples. We hypothesize that wild type compared to mutated p53 tumors will respond to PXRT better because of intact mitotic and apoptotic pathways in the former. We believe future studies in the combined modality management of pancreatic cancers may benefit from this potentially important biologic understanding of treatment response.

2.0 Objectives
2.1 To determine the one-year and median survival rates after PXRT.
2.2 To determine the response rate of PXRT in unresectable pancreatic cancer in a multi-center trial.
2.3 To evaluate the acute and late treatment morbidity of paclitaxel in a multi-institutional setting.
2.4 To correlate p53 status with treatment response to PXRT.

3.0 PATIENT SELECTION
3.1 Eligibility Criteria (6/14/99)
3.1.1 Pathologically confirmed adenocarcinoma of the pancreas.
3.1.2 Patients must have unresectable disease based on institutional standardized criteria of unresectability. There must be no evidence of metastatic disease in the major viscera and no peritoneal seeding.
3.1.3 Patients with residual disease after resection (R-1 or –2, micro-and macro-scopic residual) are eligible as long as there is measurable disease on the post-operative CT or MRI scan.
3.1.4 Recurrent disease following radical surgery.
3.1.5 Patients with biliary or gastro-duodenal obstruction must have drainage prior to starting chemoradiation.
3.1.6 All malignant disease must be encompassable within a single irradiation field (15 x 15 cm maximum).
3.1.7 All patients must have radiographically assessable disease: CT with 5 mm cuts or spiral CT. A pretreatment arteriogram (HA & SMA with delayed views of portal vein) may be necessary in selected patients to determine major vascular invasion and resectability.
3.1.8 No previous irradiation to the planned field.
3.1.9 Karnofsky performance status ≥ 60. Age ≥ 18.
3.1.10 **Required Entry Laboratory Parameters:** (1/8/99)
Granulocytes ≥ 1,800/ul
Platelet count ≥ 100,000/ul
Bilirubin ≤ 2 mg/dL. Patients with elevated bilirubin due to obstruction should be stented and their bilirubin should decrease to ≤ 2 mg/dL prior to study entry.

3.1.11 The creatinine must be < 3.0 mg % or the creatinine clearance must be ≥ 40 ml/min.

3.1.12 Oral intake *(includes J-tube feedings)* of ≥ 1,500 calories/day should be maintained.

3.1.13 Signed study-specific consent form prior to study entry.

3.2 **Ineligibility Criteria**

3.2.1 Previous paclitaxel or other chemotherapy. Previous treatment with gemcitabine is acceptable as long as it has been completed at least 4 weeks prior to study entry.

3.2.2 Significant infection or other coexistent medical condition that would preclude protocol therapy.

### 4.0 PRETREATMENT EVALUATIONS

4.1 **Mandatory for Study Entry (< 4 weeks prior)**

4.1.1 History and physical, CBC, differential, platelets, SMA-7, liver function tests, chest x-ray, abdominal CT scan.

4.2 **Highly Recommended**

4.2.1 Laparoscopy and endoscopic ultrasound

4.3 **Nutritional Assessment**
The patient's weight *(kg)* and height shall be recorded upon entry into the study. Protein/caloric malnutrition shall be defined as weight loss >5% over one month or >10% over 6 months or albumin < 3.0gm/dl. Patients with poor nutritional status are defined as having a total body weight loss of > 15%. In patients with weight loss >5% in the previous six months or poor caloric intake, placement of a jejunostomy feeding tube *(PEG type or gastrojejunostomy)* for enteral nutrition may be necessary.

### 5.0 REGISTRATION PROCEDURES

5.1 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. 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
- Demographic Data
- Treatment Start Date

### 6.0 RADIATION THERAPY

#### 6.1 Total Dose

6.1.1 50.4 Gy, 28 fractions, 5.5 weeks *(1.8 Gy/day).* A cone down after 45 Gy will be performed to encompass gross or microscopic disease with a margin of 1-1.5 cm.

6.1.2 The prescription point will be designated at the intersection of the multiple beams.

6.1.3 There are no planned interruptions.

#### 6.2 Volume

6.2.1 Primary or planning CT tumor volume *(PTV)* will include the primary cancer and draining lymph nodes. The PTV is defined on CT scan with a 2 to 3 cm margin in all directions. Treatments must be individualized based on the volume and location of disease.

6.2.2 The gross tumor volume *(GTV)* will be determined with intravenous bolus contrast administration given during CT or MRI.

#### 6.3 Equipment

6.3.1 Equal to or greater than 10 MV energy.

#### 6.4 Field Borders for the Initial PTV

All fields treated will be simulated. The initial volume radiated will include the tumor as defined on CT scans, as well as areas of potential or proven nodal involvement with a 2 to 3 cm margin in all directions.
for the initial 45 Gy. The initial volume should include the level of T11 superiorly to include the celiac axis nodes. Inferior at a level of L3 or lower if necessary to encompass the entire tumor. Right lateral, the margin should include the portal, hepatic, and the common bile duct as well as the head of the pancreas with the appropriate margin. This will generally be 4-5 cm to the right of the midline. Left lateral margin should extend 2 to 3 cm beyond the tumor.

6.5 Technique
The uniformity requirement will be +/- 5% of the total dose at the prescription point within the tumor volume. The preferred technique for radiation will be a three or four field technique using anterior, posterior, left and right lateral field with the patient in a supine position. Other techniques may be used after discussing them with the radiation oncology study chair. The dose to the kidney will require careful monitoring and kidney volumes must be defined on simulation fields. The total volume of the kidney (both left and right), included in the irradiated volume (> 22.5 Gy) should not exceed 30% (or two thirds of one kidney). Since the kidneys lie posterior to the lateral fields and only the medial margin of the kidney are in the anterior posterior field, this constraint can usually be achieved. The spinal cord dose shall be limited to 45 Gy. No more than one-half of the volume of the liver should be contained within the radiation field (> 30 Gy). If severe toxicity develops during external beam radiation therapy, the course of treatment may require interruption or modification as specified in the protocol. An isodose distribution of the treatment at the central axis indicating the position of the kidney and the liver is required.

6.6 Quality Assurance Documentation
6.6.1 Within seven days after the start of treatment, the following data should be forwarded to Headquarters Quality Assurance:
• CT Scan and/or MRI showing the extent of the tumor; designating GTV including lymph nodes considered to contain tumor; RT prescription; calculations.
• Simulation films or DRR’s.
6.6.2 Within seven days after the completion of therapy treatments, the following data is to be forwarded to Headquarters Quality Assurance:
• A copy of the daily calculations and any relevant beam data associated with any modifications of treatment submission of their own treatment reports.
• A copy of the daily treatment record.
• Isodose distribution at the central axis.
• Boost films.
6.6.3 Questions concerning the radiotherapy technique should be addressed to Dr. Rich.

6.7 Toxicity
Radiation modification for hematologic toxicity:
Radiation will be held at any time if ANC < 500/ul and platelets < 50,000/ul. Blood counts will be measured twice weekly. Radiation will be resumed when blood counts are above this level.

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 Paclitaxel (Taxol)
7.1.1 Formulation: Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf-life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

7.1.2 Preparation: A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel, at the appropriate dose, will be diluted in 1000 ml of D5W, USP, in 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVP’s) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the IV fluid pathway distal to the infusion pump. Although particulate
formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

7.1.3 **Administration:** *(1/8/99)* Paclitaxel, at the appropriate dose and dilution, will be given as a 3-hour infusion. The paclitaxel is mixed in 500 or 1000 cc of D5W in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI‰ with 0.22 m in-line filter. In order to maximize radiosensitization of paclitaxel, patients will proceed with radiation 1-1/2 hours after paclitaxel infusion has been completed. Paclitaxel will be administered via an infusion control device *(pump)* using non-PVC tubing and connectors, such as the i.v. administration sets *(polyethylene or polyolefin)* which are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.

7.1.4 **Storage:** Paclitaxel vials should be stored between 2°-25°C *(36°-77°F)*.

7.1.5 **Adverse Effects:**
- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests *(SGOT, SGPT, bilirubin, alkaline phosphatase)* hepatic failure, hepatic necrosis.
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction *(MI)*, bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness.
- Neurological: Sensory *(taste)*, peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma.
- Allergy: Anaphylactoid and urticarial reactions *(acute)*, flushing, rash, pruritis.
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration *(erythema, induration, tenderness, rarely ulceration)*, radiation recall reaction.

7.1.6 **Supplier:** Commercially available.

7.2 **Schedule** *(6/14/99)*

7.2.1 This protocol will investigate the combined use of paclitaxel, 50mg/m², and radiation therapy. Paclitaxel will be delivered in the outpatient setting as an intravenous infusion over 3 hours on days 1,8,15,22,29 and 36. In order to maximize radiosensitization of paclitaxel, patients will proceed with radiation 1-1/2 hours after paclitaxel infusion has been completed.

7.2.2 Premedicate with dexamethasone 10-20mg IV 30 minutes prior to paclitaxel, diphenhydramine, 25 mg IV, 30 minutes prior to paclitaxel; ranitidine *(or other H2 blocker)*, 50 mg IV, 30 minutes prior to paclitaxel.

7.2.3 Patients will be attended by medical personnel for the first 15 minutes of infusion and then have blood pressure checked every 15 minutes for one hour, then as needed. Medications for acute management of anaphylaxis should be readily available in the location where the patient is being treated.

7.3 **Toxocities and Dose Modification of PXRT**

7.3.1 The most common toxicity of PXRT is abdominal pain, nausea, weight loss, and anorexia. Less common toxicities may include vomiting, diarrhea, neutropenia, thrombocytopenia, anemia, gastrointestinal bleeding, bowel obstruction, cutaneous eruptions, skin burns, peripheral neuropathy, arrhythmia, hypotension, anaphylactic and urticarial reactions, flushing, alopecia, skin rash, and fever and flu-like symptoms and elevated liver enzymes.

7.3.2 PXRT will be held for grade 3 or grade 4 toxicity and will not be resumed until toxicity has resolved to no greater than grade 2. If the grade ≥ 3 toxicity has not resolved after two weeks, treatment with paclitaxel will be stopped.

7.3.3 **Hematologic Toxicity:** Based on blood counts within 24 hours of treatment.

<table>
<thead>
<tr>
<th>ANC</th>
<th>PLATELETS</th>
<th>PACLITAXEL DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,800/ul</td>
<td>≥ 100,000/ul</td>
<td>Full dosage</td>
</tr>
<tr>
<td>1,000-1,799</td>
<td>75,000-99,999</td>
<td>50% dose reduction</td>
</tr>
<tr>
<td>500 - &lt; 1,000</td>
<td>50,000 - &lt; 75,000</td>
<td>Omit and repeat blood counts in one week</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>&lt; 50,000</td>
<td>Omit and repeat blood counts twice a week. Hold XRT</td>
</tr>
</tbody>
</table>

7.3.4 **Allergic Reactions:**
Discontinue paclitaxel if skin rash or anaphylaxis develop and contact study chair. A rechallenge of paclitaxel on the following week adding dexamethasone, 20 mg, the night before treatment, may be considered.
7.3.5 **Cardiac Arrhythmia:**
Stop drug administration, contact study chair.

7.3.6 **Other Toxicities:**
In the event of grade 3 or grade 4 toxicities, paclitaxel and radiation will be held until toxicity resolves to the level of grade 2. Paclitaxel dose will then be reduced by 50%. If a second episode of grade 3 or grade 4 toxicity occurs no further paclitaxel will be administered.

7.4 **RTOG Adverse Reaction Reporting**

7.4.1 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 these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

7.4.1.1 Any ADR which is both serious (*life threatening, fatal*) and *unexpected*.

7.4.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.4.1.3 Any death on study if clearly related to the commercial agent(s).

7.4.1.4 Acute myeloid leukemia (*AML*). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.4.2 The ADR report should be documented on Form FDA 3500 and mailed to the address on the form, to RTOG Headquarters and to:

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

7.4.3 Any death, regardless of cause, while patient is receiving treatment or occurring within 30 days of treatment should be reported to RTOG Headquarters by telephone.

7.4.4 Toxicities will be scored using the revised *(3/98)* NCI Common Toxicity Criteria.

8.0 **SURGERY**

8.1 **Surgical Staging**

8.1.1 Laparoscopic surgical staging is highly recommended but not mandatory prior to protocol enrollment to exclude peritoneal and hepatic metastases. At the time of initial laparoscopic exploration, the upper abdomen and peripancreatic area can be carefully assessed to determine the extent of tumor. Enlarged peripancreatic lymph nodes will be biopsied and measurements will be obtained of the tumor mass in the pancreas. The tumor area will be marked with small clips. Involvement of adjacent organs will be documented and drawings made in the patient record. Patients will be staged according to the TNM system and a staging checklist is to be completed by the surgeon.

8.1.2 In most patients an endoscopic or percutaneous biliary stent can provide the biliary bypass. A cholecystojejunostomy or choledochojenaunostomy can be done laparoscopically or laparoscopically assisted. If there is evidence of duodenal obstruction, a gastrojejunostomy should be done. For purposes of facilitating a pancreatic resection later if there is marked response, a choledochojejunostomy should be performed in the Roux-en-Y fashion in a way which permits the small bowel anastomoses and the post resection small bowel to be out of the radiation field. The bypass procedure may be done laparoscopically. A jejunostomy tube should be placed for patients with severe weight loss and inadequate nutrition as described below. In patients who had undergone laparotomies, the patient will be allowed to convalesce 2 weeks prior to the start of PXRT.

8.2 **Definitive Surgery**
All patients are to be restaged with an abdominal CT scan six weeks following completion of PXRT. In those with a marked response to treatment on the CT scan curative surgery may be attempted based on the discretion of the attending surgeon.

9.0 **OTHER THERAPY**
Not applicable to this study.

10.0 **PATHOLOGY**

10.1 **RTOG Tissue Bank**
10.1.1 Patients entered on this study must submit materials to the RTOG Tissue Bank for p53 and p16 gene assessment.

10.1.2 The following must be provided:

10.1.2.1 One H&E stained slide.

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

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

10.1.2.4 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
Dept. of Pathology
8th Ave & C Street
Salt Lake City, UT 84143
(801) 321-1929
FAX (801) 321-5020

11.0 PATIENT ASSESSMENTS

11.1 Study Parameter

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Within 4 weeks prior to study entry</th>
<th>Weekly on paclitaxel/RT</th>
<th>1-2 weeks after RX Completion</th>
<th>Follow-up (See 12.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History, Nutritional Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Xb</td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Xb</td>
</tr>
<tr>
<td>CBC, Diff, Plt</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SMA-7 (serum chemistries, BUN, creatinine)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LFTs (alk phos, SGPT)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>X</td>
<td></td>
<td>X</td>
<td>Xb</td>
</tr>
<tr>
<td>Abdominal CT</td>
<td>X</td>
<td></td>
<td>X</td>
<td>Xb</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>Xa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopic Ultrasound</td>
<td>Xa</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Highly recommended but not mandatory.
b. Every three months, CT is recommended at signs of disease progression.
c. At 6 weeks following completion of PXRT.

11.2 Complete Response (CR):
Disappearance of all measurable or evaluable disease, signs, symptoms and biochemical changes related to the tumor for > 4 weeks, during which no new lesions may appear.

11.3 Partial Response (PR):
When compared with pretreatment measurements, a reduction of >50% in sum of the products of the perpendicular diameters of all measurable lesions lasting > 4 weeks, during which no new lesions may appear, and no existing lesion may enlarge. Patients with assessable but non-measurable disease by CT scan such as those with an ill defined mass or diffuse enlargement of the pancreas are required to have a 50% decrease in radiographic abnormalities. For patients undergoing resection, pathologic residual tumor will be correlated with pretreatment tumor mass.
11.4 Disease Progression:
An increase of >25% in the sum of the products of the perpendicular diameters of any measurable lesion. No appearance of new lesions.

11.5 Stable Disease:
A < 50% reduction and < 25% increase in the sum of the products of two perpendicular diameters of all measured lesions, and the appearance of no new lesions. Stable disease must persist for > 4 weeks.

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

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td>Within 1 wk of start of RT</td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)/ or DRR’s</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Treatment Planning CT/MRI Scan (C1)</td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Monthly x 2</td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td>90 days from start of RT</td>
</tr>
<tr>
<td>Iosodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Boost Films (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy Flowsheet (M1)</td>
<td></td>
</tr>
<tr>
<td>Initial Followup Form (FS)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td></td>
</tr>
<tr>
<td>Surgery Form (S1)</td>
<td>As applicable</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints
13.1.1 Overall Survival
13.1.2 Tumor Response
13.1.3 Toxicities associated with paclitaxel and external irradiation
13.1.4 P53 and P16 evaluation

13.2 Sample Size
This protocol has two components: evaluation of a chemoradiation program and evaluation of the P53 and P16 tumor markers. The treatment objective of this study is to estimate the one-year and median survival rates for patients with non-metastatic, resectable pancreatic cancer treated with paclitaxel and external irradiation. In a prior trial for this same group of patients (RTOG 92-09), the one-year survival rate was 26.9%. This study seeks to detect a minimum of 20% improvement in the one-year survival rate as compared to the RTOG 92-09 trial at the 0.05 significance level (with a one-sided test).\(^\text{39}\) The estimated improvement was derived from institutional study.\(^\text{12}\) However, since the evaluation of the tumor markers will require more patients for adequate statistical power, this is how the study sample size will be determined.
An analysis of the Brown data suggested that the patients with P53 overexpression had poorer outcome. This study seeks to confirm the observation that was made in 30 patients, of whom half had pancreatic cancer and the other half had gastric cancer. The observed hazard ratio was 1.96. It will also evaluate the P16 marker, which had a hazard ratio of 1.16. This analysis seeks to determine if either of these have prognostic value independent of the other known factors such as performance status (KPS). For planning purposes, each marker is considered as a dichotomous variable and is subdivided into a “good” and a “poor” risk subgroup. In both the P53 and P16 analysis, mutation will be considered the “poor” risk subgroup. In the Brown group, 40% of the patients had P53 mutation, and 33% had P16 mutation. Overall survival will be the primary endpoint for this analysis. The number of events required for the evaluation of tumor markers are calculated using the equation described by Schoenfeld⁴⁰ in various hypothesized scenarios.

\[
\text{#deaths} = \frac{\left( z_{1-\alpha/2} + z_{1-\beta} \right)^2}{\left( \ln \text{HR} \right)^2 w (1-w)},
\]

where

- \( z_{1-\alpha/2} \) - normal deviate for the significance level
- \( z_{1-\beta} \) - normal deviate for the statistical power
- HR - hazard ratio expressing the increased risk of failing for the “poor” risk subgroup as compared to “good” risk subgroup.
- w - prevalence rate for patients in a subgroup

The statistical significance level was set at .05 (two-sided). Statistical power was set at .90 and .80 and hazard ratio at 2.5 and 2.0. The table below gives the number of events in each scenario.

Number of events (failures) required for various hazard ratios and statistical powers

<table>
<thead>
<tr>
<th>Hazard ratio = 2.5</th>
<th>Hazard ratio = 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistical Power</td>
</tr>
<tr>
<td></td>
<td>.90</td>
</tr>
<tr>
<td>Prevalence rate</td>
<td></td>
</tr>
<tr>
<td>.35</td>
<td>55</td>
</tr>
<tr>
<td>.40</td>
<td>52</td>
</tr>
<tr>
<td>.45</td>
<td>51</td>
</tr>
</tbody>
</table>

The study will be designed to detect a hazard ratio of 2.5 of the “poor” risk subgroup as compared with the “good” risk subgroup with 90% power. This will require 52 deaths. With 80 patients evaluable for tumor marker analysis, accrued over 20 months, with an additional 12 months of follow-up, we can expect at least 52 deaths regardless of the outcome of the treatment analysis i.e. the new treatment improved the one-year survival rate by 20% over the historical control, or it did not. The following table gives the statistical power to detect hazard ratios of 2.5 and 2.0, respectively, and the number of deaths expected under each scenario.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio = 2.5</th>
<th>Hazard ratio = 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistical Power</td>
<td>Expected # deaths</td>
</tr>
<tr>
<td>20% treatment difference</td>
<td>.927</td>
<td>55</td>
</tr>
<tr>
<td>No treatment difference</td>
<td>.963</td>
<td>67</td>
</tr>
</tbody>
</table>
Since we expect 15% of patients accrued to not have available tumor markers, and an additional 5% to be ineligible or invaluable for analysis, the total sample size required will be 100.

With 95 patients evaluable for the treatment comparison, the power to detect a 20% difference in patients treated with paclitaxel and external irradiation as compared with RTOG 92-09 is 96%. In addition, the width of a 95% confidence interval about the estimates for complete and partial response will be at most 10.9%.

13.3 Inclusion of Women and Minorities
In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 concerning inclusion of women and minority in clinical research, we have considered differences in prognosis by race and gender. In an analysis of the RTOG pancreas database, we found no difference. No other study so far has indicated any significant racial or gender differences in treatment effects for inoperable pancreatic cancer patients. These issues are not well studied. The study was designed to test the efficacy under the assumption of the same efficacy across the genders and across the races. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

13.4 Patient Accrual
The patient accrual is projected to be five cases per month, based upon the monthly accrual for RTOG 88-01 and RTOG 92-09. At this rate, it will take 20 months to reach the required total accrual of 100 cases. If the average monthly accrual is less than 1.25 patients, the study will be re-evaluated with respect to feasibility.

13.5 Suspension of Accrual Due to Morbidity
If there is any fatal treatment morbidity, the event will be reported to the study chairman for review. If there are three such fatal events, accrual will be suspended, and all data pertaining to the events will be reviewed by the study chairman and reported to the RTOG Data Monitoring Committee (DMC) for review. The results from this review will determine the future course of action.

13.6 Analysis Plans
13.6.1 Interim Analyses
Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:
   a) the patient accrual rate with a projected completion date for the accrual phase, and compliance rate of treatment delivery with respect to protocol prescription;
   b) the quality of submitted data with respect to timeliness, completeness, and accuracy;
   c) the frequency and severity of toxicities.

Through examining the above items, the RTOG DMC and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for the study, and, if necessary, the RTOG Research Strategy Committee, so that corrective action can be taken.

13.6.2 Analysis for Reporting the Study Results
Both the treatment and tumor marker analyses will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are:
   a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
   b) reporting of institutional accrual;
   c) distribution of important prognostic baseline variables – (KPS, tumor size, and location of primary);
   d) observed results with respect to the endpoints described in Section 13.1.

The estimated survival from this sample will be tested against the RTOG 92-09 trial as the historical control using a one-sided test. The median and one-year survival rates will be calculated with 95% confidence intervals.

An improvement in one-year survival of at least 15% will be considered an indication for further study of this combination.

The complete and partial response rates will be estimated with 95% confidence intervals.

The prognostic value of each tumor marker will be tested using the Cox proportional hazard model with the other prognostic factors such as KPS and location of primary as fixed covariates.
REFERENCES


Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in clinical research so I can decide whether to undergo the procedure after knowing the risks, benefits, and alternatives involved. This 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

I have been asked to take part because I have pancreatic cancer. My doctors are studying the use of the chemotherapy drug paclitaxel (Taxol) in combination with irradiation treatment. Studies suggest that with Taxol, pancreatic cancer cells may be more easily killed by radiation. In this study, I will get treatments with Taxol and irradiation to try to decrease the size of my cancer. This study is being done to determine if Taxol improves the treatment of patients with pancreatic cancer.

DESCRIPTION OF PROCEDURES

I will get Taxol by vein over three hours once a week for six straight weeks. Starting the same day as the first dose of Taxol, I will get irradiation treatments to my abdomen once a day, five days a week for five and a half weeks (28 treatments). Prior to each Taxol treatment, I will get dexamethasone, ranitidine and diphenhydramine by vein over about 5 minutes to reduce my chance of an allergic reaction to Taxol.

Blood tests, taking about two teaspoons of blood, will be done each week before the Taxol is given to check my blood counts. If my blood counts are too low, the dose of Taxol will be decreased or a dose of Taxol will be omitted. If my blood count is very low, the irradiation may also be stopped temporarily until the blood count rises. If I have a severe allergic reaction to Taxol, I will not get further doses of Taxol.

After I have finished my treatments with Taxol and radiation, I will have a CAT scan of my abdomen to see whether my tumor has changed in size. The CAT scan will be repeated every 3 months. If my cancer spreads to other parts of my body, my doctor and I will talk about other possible treatments.

RISKS AND DISCOMFORTS (1/8/99)

Cancer treatments often have side effects. The treatment used in this study 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. Side effects from Taxol and irradiation include:

FREQUENT (More than 10% of patients are expected to have these side effects):

1. Stomach pain. This usually occurs during the last three weeks of paclitaxel and radiation and generally goes away within 2-4 weeks after the treatment is finished. The stomach pain feels like a burning discomfort such as bad heartburn or an ulcer. It may make it difficult for me to eat or drink. I may get dehydrated and need to get fluids intravenously. If I am unable to eat, I temporarily may need to have a tube placed into my stomach to give me extra nourishment.

2. Nausea, loss of appetite, and weight loss.

3. Hair loss. I may lose some of my hair about three weeks after the first dose of chemotherapy. My hair will grow back after chemotherapy is stopped. Hair color will not change, but sometimes hair is curlier.
4. For women: Irregular menstrual periods. Menstrual periods may stop permanently, resulting in an inability to become pregnant. I should use appropriate contraceptive measures while I get chemotherapy.

5. For men: Decreased sperm count, which is usually temporary, but may be permanent, which may result in sterility. I should use appropriate contraceptive measures during treatment.

COMMON (1-10% of patients are expected to have these side effects):

6. Diarrhea, constipation and vomiting. If I get these side effects, I will get medicines to try to relieve them.

7. Low blood counts, susceptibility to infection and/or bleeding with possible need for a transfusion. If I develop a fever or other signs of infection when my blood counts are low, I may need to be hospitalized to get intravenous antibiotics to help my body fight the infection. Infections in patients with low blood counts are dangerous and could be fatal.

8. Sensitivity to sunlight. I should try to stay out of the sun. If I have to be in the sun, I should use sunscreen lotion and protective clothing.

RARE (Less than 1% of patients are expected to have these side effects):

9. Injury to the small bowel: bleeding and/or obstruction or pain.

10. Heart rhythm irregularities. I may feel skipped beats or palpitations which are usually temporary. I may also experience chest pain (angina). I should tell my doctor immediately if I notice this.

11. Sudden severe allergic reactions with wheezing and lowered blood pressure. If I should have an allergic reaction, it would probably happen while Taxol is being given. I would be treated right away.

12. Nervous system problems. Temporary unsteadiness when I walk, fatigue, tingling of fingers and toes, muscle weakness, drowsiness, confusion, hallucinations, agitation, or difficulty sleeping.

13. Secondary malignancies. A number of established chemotherapeutic agents have an inherent risk of causing secondary cancers and/or leukemias. Whether Taxol causes secondary malignancies is unknown. Certain agents in use today, not currently known to be associated with this risk, may be shown at a later time to result in the development of these secondary cancers and/or leukemias.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done to evaluate the effects of treatment. 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.

This study may be harmful to an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If I am a woman of childbearing age and have not been surgically sterilized (tubal ligation or hysterectomy), I should have a pregnancy test before enrolling in this study. If I am unwilling to use adequate birth control measures to prevent pregnancy, I should not participate in this study. If I should become pregnant while on this study, I must tell my doctor immediately.

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
If injury occurs as a result of this research, treatment will be available. I understand, however, I will not be reimbursed 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 contact 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 any personal benefit will result from the research program. I understand that the information obtained from this study will be used scientifically. It may possibly be helpful to others. The Possible benefits of this research program are greater shrinkage and control of my tumor and 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, or should developments occur that indicate the research program is not in my best interest the treatment would be stopped. Further treatment would be discussed.

**ALTERNATIVES**

Alternatives that could be considered in my case include radiation therapy either alone or with 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. This would probably result in continued growth of my tumor. My doctor can provide detailed information about my disease and the benefits of the various treatments available. I should feel free to discuss my disease and my prognosis with my doctor. The physician involved in my care will be available to answer any questions I have. I am free to ask my physician any questions concerning this program that I wish both now and in the future.

My physician will explain procedures related to this protocol. 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 am free to withdraw my consent to participate in research at any time. 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.

**CONFIDENTIALITY**

Records of my progress while on the study will be kept in a confidential form at this institution and in a computer file at the 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), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all the above, asked questions, received answers concerning areas I did not understand. I 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
STAGING FOR PANCREATIC CANCER
(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
<table>
<thead>
<tr>
<th>ORGAN TISSUE</th>
<th>0</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>None</td>
<td>Slight atrophy; Pigmentation change; Some hair loss</td>
<td>Patch atrophy; Moderate telangiectasia; Total hair loss</td>
<td>Marked atrophy; Gross telangiectasia</td>
<td>Ulceration</td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>None</td>
<td>Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture; &lt;10% linear reduction</td>
<td>Severe induration and loss of subcutaneous tissue; Field contracture &gt; 10% linear measurement</td>
<td>Necrosis</td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>None</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; Little mucous tissue</td>
<td>Marked atrophy with complete dryness; Severe telangiectasia</td>
<td>Ulceration</td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None</td>
<td>Slight dryness of mouth; Good response on stimulation</td>
<td>Moderate dryness of mouth; Poor response on stimulation</td>
<td>Complete dryness of mouth; No response on stimulation</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None</td>
<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
<td>Mono, para quadriplegia</td>
</tr>
<tr>
<td>BRAIN</td>
<td>None</td>
<td>Mild headache; Slight lethargy</td>
<td>Moderate headache; Great lethargy</td>
<td>Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)</td>
<td>Seizures or paralysis; Coma</td>
</tr>
<tr>
<td>EYE</td>
<td>None</td>
<td>Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma</td>
<td>Severe keratitis; Severe retinopathy or detachment</td>
<td>Panophthalmitis/Blindness</td>
</tr>
<tr>
<td>LARYNX</td>
<td>None</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
<td>Severe edema; Severe chondritis</td>
<td>Necrosis</td>
</tr>
<tr>
<td>LUNG</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances</td>
<td>Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes</td>
<td>Severe respiratory insufficiency/continuous O2/Assisted ventilation</td>
</tr>
<tr>
<td>HEART</td>
<td>None</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST Changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes; Low ORS</td>
<td>Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities</td>
<td>Tamponade/Severe heart failure/Severe constrictive pericarditis</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None</td>
<td>Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated</td>
<td>Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required</td>
<td>Necrosis/Perforation Fistula</td>
</tr>
<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None</td>
<td>Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;5 times daily; Excessive rectal mucus or intermittent bleeding</td>
<td>Obstruction or bleeding, requiring surgery</td>
<td>Necrosis/Perforation Fistula</td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver function; function tests; Serum albumin normal</td>
<td>Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites</td>
<td>Necrosis/Hepatic coma or encephalopathy</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None</td>
<td>Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%; Creatinine 1.5-2.0 mg%; Creatinine clearance &gt; 75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt;36-60 mg%; Creatinine clearance (50-74%)</td>
<td>Severe albuminuria; Severe hypertension Persistent anemia (&lt;10%); Severe renal failure; Urea &gt;60 mg% Creatinine &gt;4.0 mg% Creatinine clearance &lt; 50%</td>
<td>Malignant hypotension; Uremic coma/Urea &gt; 100%</td>
</tr>
<tr>
<td>BLADDER</td>
<td>None</td>
<td>Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria</td>
<td>Severe frequency &amp; dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (&lt; 150 cc)</td>
<td>Necrosis/Contracted bladder (capacity &lt; 100 cc); Severe hemorrhagic cystitis</td>
</tr>
<tr>
<td>BONE</td>
<td>None</td>
<td>Asymptomatic; No growth retardation; Reduced bone Density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis</td>
<td>Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis</td>
<td>Necrosis/Spontaneous fracture</td>
</tr>
<tr>
<td>JOINT</td>
<td>None</td>
<td>Mild joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement</td>
<td>Severe joint stiffness; Pain with severe limitation of movement</td>
<td>Necrosis/Complete fixation</td>
</tr>
</tbody>
</table>
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 supersede 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 (> 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 (> 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 As above
of termination of the agent.

- 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**