A-91-011
76-5
MP-DC

RTOG 78-25: Revisions/Clarifications - September 11, 1979

713033

The following revisions have been made:

Schema, Item B will read as follows:

Minimum of 2000 peak pion rad to the large field plus 1500 rad boost at 100 rad/day calculated at the 80% isodose line (Maximum total 4375 at 125 rad/day at 100% isodose).

The above revisions also apply to Section 6.3 Pion Radiotherapy; Paragraph 1.

To be attached to the front of the above named protocol.

RADIATION THERAPY ONCOLOGY GROUP

RTOG 78-25

PI MESON RADIOTHERAPY* OF ADENOCARCINOMA OF THE RECTUM OR RECTOSIGMOID (INOPERABLE, NON-RESECTABLE OR RECURRENT)

Study Chairman: Morton M. Kligerman, M.D.
Site Chairman: Simon Kramer, M.D.

*Pi Meson Radiation Therapy at University of New Mexico/Los Alamos Scientific Laboratory.

Activated: June 1, 1979
Current Edition: June 1, 1979

INDEX

RADIATION THERAPY ONCOLOGY GROUP

RTOG 78-25

PI MESON RADIOTHERAPY OF INOPERABLE, SURGICALLY NON-RESECTABLE OR RECURRENT ADENOCARCINOMA OF THE RECTUM OR RECTOSIGMOID (M_0)

Stratify:

Inoperable - non-resectable vs. recurrent

RANDOMIZE

- conventional radiotherapy[a] + surgery, if feasible
- pion radiotherapy[b] + surgery, if feasible

a 850-900 rad/week (170-180 rad, 5 days/week; minimum of 2 fields/day) to the major field to a total of 4500 rad/5 wk or 5100 rad/6 wk. Boost portal to be utilized with upper dose limit dependent on findings of special small bowel films (maximum of 7000 rad/8 wk if small bowel is out of boost field).

b Minimum of 2000 peak pion rad to initial large portal. Evaluation for operation. If operation is not feasible, a boost minimum of 1300 peak pion rad to gross tumor. Pion dose to be given at a minimum of 85 peak pion rad/day. The minimum dose is approximately 2 cm peripheral to the 95% isodose line.

1.0 INTRODUCTION

1.1 Definition of the Problem

Recurrent, residual or inoperable carcinoma of the rectum poses a major problem to the oncologist. Moertel et al (1) have found the mean duration of life for patients with large bowel cancer, with proven unresectability or metastases, to be 9.5 months (median 7.0 months) from time of diagnosis, with a range of four weeks to over six years. Efforts to improve this are unquestionably necessary.

1.1.1 Cause of Death.

Opinions vary depending on the source of information. Dionne (2) claims on the basis of clinical information that nearly all patients with carcinoma of the colon and rectum die due to venous spread. Moertel (3) comments that death results from the effect of distant metastases in about 50% of patients and from local recurrence (i.e., intestinal or ureteral obstruction, recurrence plus local sepsis, etc.) in the remaining 50%. Data from autopsy series show that a majority of patients with colorectal cancer die with local problems: approximately 75% of the 125 patients reported by Taylor (4) and 25 of 34 patients discussed by Floyd, Corley and Conn (5). In the series of 180 patients with colorectal cancer reported by Cass, Pfaff and Million (6), 175 were eligible for five-year evaluation. Cancer was the known cause of death in 81 and was due to local recurrence in 50 (51.7% of those dead from cancer and 29% of the total group) without a breakdown by site.

1.1.2 Radiation Results.

1.1.2.1 Primary Radiation (standard fractionation): An expanding volume of literature reveals the marked palliative and occasional curative value of radiation for residual, inoperable

and recurrent colorectal lesions (indicating radiosensitivity). The overall response of the recurrent group is least favorable, which is not surprising since the tumor has often grown back in poorly vascularized scar tissue.

Results with recurrent disease have been fairly similar from series, i.e. good palliation but infrequent cure. Whitely et al (7) reported 80% good or excellent palliation in 102 patients with local disease treated with moderate doses (2000-2500 rad/8-12 fractions). Williams (8) treated 155 patients with doses of 6000 rad/6 weeks when feasible and reported a 5.8% five-year survival. Significant pain relief was achieved in 85%, with 57% having complete relief. Wang and Schultz (9) achieved palliation in 84% of their total 111 patients, but five-year survival was only 2/86 (2.3%) of all the recurrent group, with most long-term survivors having received 3500-5000 rad/4-5 weeks (25 patients: inoperable or residual disease). Urdaneta-Lafee and Kligerman (10) achieved significant palliation but no five-year survivals in 42 patients treated with doses ranging from 1000-6000 rad.

Although results with radiation seem to be better in those patients with inoperable (surgical or medical) and/or residual carcinoma as opposed to those with recurrence, there is need for improvement. Wang and Schultz

(9) obtained cures in 2/16 of the inoperable group, and 2/9 of the group with partial resection. Williams (8) treated 220 patients with 1-MeV energy to a usual dose of 6000 rad/6-8 weeks with a significant palliation and five-year survival in twelve (5.5%). Sklaroff (11) treated ten elderly patients who were medically inoperable. At the time of his report, five were alive and without disease from six months to nine years and an additional patient died at ten months without evidence of disease. Although the report of Urdaneta-Lafee (10) on the response of inoperable, non-resectable and recurrent rectal carcinoma gives evidence of response to radiation therapy, except in selected cases the overall survival was not encouraging due mainly to tumor found outside the treatment field. This should be reexamined in light of tumor evaluation now available through computerized tomographic scanning. The best results were reported by Rider (12) in a series of 229 patients treated at the Princess Margaret Hospital: 10% five-year survival for the total group. A "curative attempt" with doses starting as low as 3500 rad was undertaken in 65 patients with 75% referred due to inoperability, and the remainder due to patient or physician refusal of operative intervention (potentially operable). Three-year survival was approximately 42% and five-year was 29% (11/38). Doses of 4500–5000 rad/20 fractions/4 weeks yielded the best results. Many of their patients had slow regression of the lesion

following radiation with clinical and histologic persistence at a time period of one year or occasionally longer, but freedom of disease within the treated field at the three-year period.

1.1.2.2 Preoperative Radiation (unresectable carcinoma rectum): All authors except one reported increased survival when preoperative irradiation was given in low-lying operable cancer of the rectum (13). These results, along with a decrease in the percentage of positive nodes in the surgical specimens, were obtained with considerable variation in portal size and shape as well as dose. Less data is available in non-resectable or inoperable cancer of the rectum. However, Stevens and Allen (14) show a prolonged disease-free survival when inoperable patients are treated. However, in a selected group of 15 patients with inoperable and non-resectable cancer of the rectum, Kligerman (15) found preoperative irradiation to yield results similar to operable carcinoma treated by surgery only.

1.2 Rationale for Pion Radiotherapy.

The rationale for pion radiotherapy is primarily related to two factors: (1) a different biological response in the stopping region of the pion beam from that seen in conventional radiation, and (2) the capability for localizing this differential response within the target volume, largely sparing normal surrounding tissues.

With high-linear-energy-transfer (high-LET) radiation (for example, neutrons, pions, and heavy ions), there is increased irreparable damage of critical molecules (i.e., double-strand breaks in DNA), as compared to the type of damage caused by low-LET radiation (e.g., x-rays, gamma rays of cobalt, electrons, and protons). In addition, cells exposed to low-LET radiation exhibit up to three times more resistance to injury if they are not well oxygenated. Thus, hypoxic cells, large numbers of which are usually present in tumors, are less sensitive to damage than are well oxygenated cells of the tumor and the surrounding normal tissue. The dense ionization of high-LET radiation overcomes the protective effect of hypoxia, killing those cells almost as effectively as well-oxygenated cells. Further, cells are more resistant to low-LET radiation in certain phases of the cell cycle than in others. High-LET radiation reduces differences in cellular sensitivity due to cell cycle variations.

Heavy charged particles, such as pions and heavy ions, distribute their dose with a Bragg peak, a region of intense radiation which can be located in the tumor volume. In contrast, neutrons, which have no charge, deposit dose in tissue exponentially, similarly to dose absorption of the gamma rays of cobalt.

Pions have the advantages of both high-LET and low-LET radiation, because they deposit low-LET radiation as they pass through tissue (plateau region), but produce a high-LET component in the stopping (tumor) region. Due to their negative charge, the stopping pions are absorbed by the positively charged nuclei of oxygen, carbon, and nitrogen atoms. This excess energy makes the nuclei unstable and they disintegrate, producing neutrons, protons, deuterons, tritons, alpha particles, and heavy ions. These events increase the total dose in the pion stopping region and alter the biological effectiveness of the dose in that region because of the dense ionization produced mainly by the alpha particles, heavy ions, and neutrons.

Results to date of Phase I-II studies of pion radiotherapy, being conducted at the Los Alamos Meson Physics Facility (LAMPF), by the University of New Mexico Cancer Research and Treatment Center, suggest therapeutic advantages in the treatment of many advanced solid tumors with pion radiotherapy. Patients with primary and metastatic tumors of the skin, head and neck, lung, abdomen and pelvis have been irradiated with pions to assess tolerance of normal tissues and tumor response. Early studies with metastatic tumor nodules in the skin established a relative biological effectiveness (RBE) of 1.42 for pions, as compared to 100 kVp x-rays, for acute skin injury (16). Subsequently, analysis of time to regrowth of 16 nodules (primary breast) in one patient participating in that study who could be followed for 346 days suggested the possibility of therapeutic gain of 37% for pions versus x-rays (17).

An analysis of 52 evaluable tumors in 20 patients (including those in the skin metastases series) treated with pions only and followed for 3 to 22 months showed 42 tumors completely regressed, 3 tumors partially regressed, and 7 tumors did not respond, although 5 of the 7 showed no growth for 10 months (18). A more recent report on 40 patients treated for large deep-seated lesions, all of whom were followed for 6 to 15 months, showed that pion radiotherapy was well tolerated at doses ranging from 1000 to 4600 peak pion rad, delivered generally in five fractions per week with daily fraction sizes of 110 to 140 peak pion rad maximum. Complete regressions occurred in approximately half those patients treated with pions alone at maximum doses of more than 2700 peak pion rad. No complete regressions occurred in patients treated with pions alone at doses under 2700 peak pion rad. Conventional radiation and/or surgery was well tolerated by those patients requiring those treatments after pion radiotherapy. Reactions in the normal tissues within the plateau and the peak regions have been relatively mild, compared to those which would be expected with conventional radiation for similar tumor response. No patient with a pelvic

tumor has exhibited any serious untoward radiation reaction over observation times ranging up to 26 months (19). However one patient who had undergone surgical exploration was found to be non-resectable one month prior to pion radiotherapy, was re-explored one month after pion radiotherapy and again found to be non-resectable. The patient suffered complications and expired two months after the exploration.

It is estimated that some 60,000 persons die in the United States each year because of lack of tumor control at the primary site. Pions are being tested on those types of large tumors which are not well managed by any other treatment or combination of treatments to attempt to improve the survival in this group of patients. In addition, any large reduction in the body's total burden of tumor cells improves the chances for cure by conventional techniques (surgery, radiotherapy, and chemotherapy, alone or in combination). Thus, potentially, additional patients can be helped by pion radiotherapy if their large tumor masses can be eliminated or significantly reduced.

2.0 OBJECTIVES

This study is designed to determine the effect of pion radiotherapy as compared to conventional radiotherapy upon:

2.1 Local control of advanced adenocarcinomas of the rectum or rectosigmoid.

2.2 Incidence of complications and injury of normal tissues (bowel, bladder, skin, subcutaneous structures).

2.3 The occurrence of tumor shrinkage, sufficient to render an inoperable (or unresectable) cancer operable and potentially curable.

2.4 For re-explored cases, the rate of regional node sterilization.

2.5 The adjusted survival rate at 1, 2, and 3 years postmeson therapy as compared with conventional irradiation.

3.0 PATIENT SELECTION (ELIGIBILITY)

3.1 General Condition of Eligibility.

Only patients with adenocarcinoma of the rectum or rectosigmoid are eligible for this study. Their disease must be judged clinically inoperable in the opinion of the responsible surgeon or found, at operation, to be nonresectable or recurrent following surgery.

3.2 Conditions for Patient Eligibility.

In addition to the above general condition, the following conditions must be met before a patient can be admitted to the study:

3.2.1 Biopsy proof of adenocarcinoma.

3.2.2 A preliminary colostomy or ileostomy should be avoided; however, if performed will not affect patient eligibility for the study.

3.2.3 Reasonable expectation of completing the study treatment and the required follow-up examination (including travel to and treatment at Los Alamos, as well as an annual follow-up examination at the study center in Albuquerque).

3.2.4 Agreement of the patient and his physician to the conditions of the study.

3.2.5 Agreement of the patient's physician to relinquish management of the patient's treatment to the study team.

3.2.6 Understanding by the patient of the provisions of the study, and completion of the required investigational treatment consent form.

3.2.7 The patient is prepared to accept resection if following radiotherapy a surgeon deems this procedure possible.

3.2.8 Patients must not be <18 or >75 years of age, although the upper age limit can be extended for patients in unusually good physiological condition.

3.3 Conditions for Patient Ineligibility.

The following conditions are cause for exclusion of the patient from the study:

3.3.1 Biopsy proof of transitional cell carcinoma of the anus, epidermoid carcinoma of the anus, or malignant carcinoid tumor.

3.3.2 Previous radiotherapy of the primary tumor and regional adenopathy.

3.3.3 Previous chemotherapy which, in the opinion of the study team, might compromise treatment or evaluation. (All chemotherapy must be stopped 7 days before treatment can begin.)

3.3.4 Previous radiotherapy to areas overlapping the projected treatment portals.

3.3.5 Active, uncontrollable infection in the area of contemplated irradiation.

3.3.6 Medical, psychological, or other contraindication to the contemplated diagnostic or therapeutic measures and their evaluation.

3.3.7 Evidence of a second malignancy, other than skin cancer. (For patients with second malignancies other than skin cancer, the disease-free interval must exceed eight years. For patients with skin cancer, the disease must have been under control for at least three years. Skin cancer, for the purposes of this study, does not include melanoma or cancer of the lip.)

3.3.8 Karnofsky performance status < 60.

3.3.9 Evidence of distant metastases (M1).

4.0 PRETREATMENT EVALUATION

Consistent with good medical practice, the following will be performed on initial evaluation prior to admitting the patient to the study. Results of the evaluation will be used to determine patient eligibility for the study and in management of the treatment regimen.

4.1 Medical History.

4.1.1 Age.

4.1.2 Sex.

4.1.3 Race.

4.1.4 Date of onset of symptoms (month and year in which the patient first noticed the onset of definite symptoms or signs which are later explained by the disease).

4.1.5 Date (month and year) of definite diagnosis of disease.

4.1.6 Description of symptoms (weight loss, voluntary or involuntary; constipation, diarrhea, including number of stools and type, blood in stool; obstructive symptoms; pain; weakness; other).

4.1.7 Other illnesses.

4.1.8 Medications currently used.

4.1.9 Previous therapy (if any).

4.2 Physical Examination.

4.2.1 Height.

4.2.2 Weight.

4.2.3 Temperature.

4.2.4 Notation of palpable masses, organomegaly, ascites or peritonitis.

4.2.5 Performance Status (Karnofsky Function Assessment).

4.2.6 Evidence of obstruction, whether partial or complete.

4.2.7 Drawing of primary tumor (with centimeter dimensions); also, photographs, if possible.

4.3 Routine Laboratory Tests.

4.3.1 Complete blood count (with white count and differential).

4.3.2 Platelet count.

4.3.3 Urinalysis.

4.3.4 Serum alkaline phosphatase, BUN, SGOT, total protein, albumin, and creatinine.

4.3.5 Others, as indicated by the individual patient.

4.4 Routine Imaging Procedures.

4.4.1 Chest x-ray (posterior-anterior and lateral).

4.4.2 Intravenous pyelogram (except for patients allergic to contrast material).

4.4.3 Barium enema.

4.4.4 Lymphangiogram.

4.4.5 Cystogram (when invasion of bladder is suspected)

4.4.6 Liver scan.

4.4.7 CT scan, if available; if not this will be performed at the study center.

4.5 Optional Studies.

4.5.1 Immune reactivity (skin) tests.

4.5.2 Cardiopulmonary assessment if indicated to tolerate 7000 ft. altitude of Los Alamos.

4.5.3 Other studies as indicated to rule out distant metastases.

4.6 Staging Procedures.

4.6.1 Proctoscopy for tumor localization.

4.6.2 Biopsy of primary. (Note: The lesion must be adenocarcinoma.) In addition to the microscopic description and diagnosis, the pathologist is requested to use one or more of the following three designations: (1) low grade (well differentiated), (2) intermediate (moderately differentiated), or (3) high grade (poorly differentiated).

4.6.3 Proctosigmoidoscopy to establish most inferior margins of the tumor (distance between junction and distal margin of neoplasm should be recorded, i.e., less than 5 centimeters or more than 5 centimeters).

It is suggested that the patient be examined in either the knee-chest, or in the head-down position, so that the bowel is straightened out, permitting the most accurate measurement. The lateral Sims position should not be used for this purpose.

4.6.4 Clinical examination to determine circumferential involvement and extent of disease beyond rectum:

4.6.4.1 An estimate should be made as to whether the tumor involves less than one-half or more than one-half of the circumference of the rectum.

4.6.4.2 Determination of extent beyond rectum and fixation to other structures will be based on clinical examination and intravenous pyelogram results. A vaginal examination will be conducted for females.

4.6.5 Cystoscopy (when invasion of bladder is suspected).

4.6.6 Although it should be avoided if at all possible, a preliminary colostomy or ileostomy for relief of obstruction may be done.

4.6.7 Other studies as indicated (particularly to determine presence or absence of distant metastases).

4.7 Specific points to be determined during pretreatment evaluation include estimates of the following:

4.7.1 Circumferential involvement.

4.7.1.1 Less than one-half.

4.7.1.2 More than one-half.

4.7.2 Distance of most inferior margin of tumor from anorectal junction.

4.7.2.1 Less than 5.0 centimeters.

4.7.2.2 More than 5.0 centimeters.

4.7.3 Extent of disease by clinical examination.

4.7.3.1 Not fixed.

4.7.3.2 Fixed (to such structures as bladder, prostate, uterus, vagina, or sacrum).

4.7.4 Presacral soft tissue thickness on lateral x-ray study.

4.7.4.1 Less than 2 cm.

4.7.4.2 More than 2 cm.

4.7.5 Histologic Grade:

4.7.5.1 Low

4.7.5.2 Intermediate

4.7.5.3 High

5.0 ADMISSION TO STUDY AND RANDOMIZATION

Patients will be admitted to the study only after the pretreatment evaluation is completed and the eligibility criteria are met.. Copies of all necessary forms will be forwarded to RTOG Headquarters.

5.1 All therapy will be scheduled through the Cancer Research and Treatment Center in Albuquerque. It is planned to have all patients receive radiotherapy planning CT scans and localization in Los Alamos even if randomized to conventional treatment at the referring institution. Ophthalmologic examination to assess lens opacity will be performed upon admission to the study. The following steps must be completed:

5.1.1 Identification and registration (see 5.1.2) of all patients entering the participating institution with a diagnosis of adenocarcinoma of the rectum or rectosigmoid.

5.1.2 Completion of RTOG initial registry form. (Patients who are determined by their physicians as ineligible will be eliminated at this point. The RTOG initial registry form must list the reason(s) for ineligibility and be forwarded to RTOG Headquarters for use in population control).

5.1.3 Pretreatment evaluation.

5.1.4 Completion of the study entrance form (patient name and address, referring institution, referring physician, etc.).

5.1.5 Completion of patient consent form.

5.1.6 Notification to Dr. Kligerman (preferred 505/277-3539 or 505/667-7392 in Los Alamos) or his designee, of potentially eligible patients who have agreed to participate in this study.

5.2 When a patient has been fully evaluated and determined to be eligible and the forms completed as specified in 5.1, Dr. Kligerman or his designee at the pion facility will complete and submit the on-study form and will phone RTOG Headquarters and relate the following information:

5.2.1 Protocol Name.

5.2.2 Patient Name .

5.2.3 Referring institution and physician.

5.2.4 Status of primary (inoperable, unresectable, recurrent).

A project case number and treatment will be assigned by RTOG Headquarters of either:

a) conventional radiotherapy at the referring institution, or,

b) pion radiotherapy at Los Alamos. These will be confirmed by mail to Dr. Kligerman and the referring physician.

6.0 TREATMENT DETAILS

6.1 Target volume.

The target volume will be a minimum of 2 cm beyond the boundary of the gross tumor volume, or as large as needed to include that volume of tissue beyond which the radiotherapist believes microscopic tumor does not extend. However, the target volume margin will be a minimum of 5 cm along the bowel.

6.2 Conventional radiotherapy.

6.2.1 Equipment. Equipment must be 4 MeV or greater or cobalt 60. The minimum treatment distance must be 80 cm SSD or 80 cm to axis for SAD techniques.

6.2.2 Dose Time Factors. All doses will be calculated at mid-plane of the target volume which usually will be the mid-plane of the pelvis. The dose across the target volume must not be less than 10% of the mid plane dose. Dose rate will be 850-900 rad/week, 170-180 rad/day, 5 days/week and a minimum of 2 fields/day. The options will be either 4500 rad/25 fractions/5 weeks, or 5100 rad/30 fractions/6 weeks to the major volume. Other variations within the above limits of a minimum of 4500-5100 rad maximum at 850-900 rad/week will be accepted. Patients will be evaluated for operation after this dose and operated upon 3-4 weeks after the last radiotherapy treatment. If not operable or if not resectable, patients will then receive boost fields. Appropriate procedures such as bladder distension should be used to exclude as much small bowel as possible from the treatment volume. If small bowel is mobile, the dose with the

boost field should be brought to 6000 rad/7 weeks, but if immobile, to a maximum of 5000-5500 rad/6-6½ weeks. In those patients with inoperable, recurrent or gross residual disease, if the small bowel is totally out of the boost portal, it is recommended that the total dose within the boost field be carried to 6500 rad.

6.2.3 Treatment Fields. The minimum treatment field will include the primary tumor and adjacent tissue, as well as the lymph node drainage area in the pelvis and that extending along the superior hemorrhoidal vessels. The inferior boundary will be the bottom of the obturator foramen. Lateral boundaries in the true pelvis will be 1.5 cm lateral to the bony margin (iliopectineal line) at its widest point, (unless lymphangiography delineates nodes then 1 cm lateral to nodes) and in the lumbar region, the tips of the transverse processes. Superior margins will be the top of the sacroiliac joint laterally (in the pelvic region) or the top of the L_2 vertebra (in the lumbar region). For the lumbar area, the width of the field will be determined by the lymphangiogram. If not visualized, it will be at the tips of the transverse processes.

6.2.4 Boost Volume. Continuous (after large field) using standard fractionation schemes. The area and size of the boost field are dependent on operative and other diagnostic information. These fields should be as small as possible and limited to any area of residual tumor. Boost fields may be positioned per discretion of the individual radiotherapist.

6.2.5 Time Dose Modifications. Maximum acceptable delay during treatment is two weeks; in a patient with a delay of less than two weeks, the maximum acceptable dose is 5100 rads to the large pelvic field with the same rad dose/small bowel findings for the boost field as spelled out in 6.2.2. Treatment should be interrupted if counts fall below: WBC = 2,000 and/or platelets = 50,000.

6.2.6 Treatment Planning. Localizing films of each field will be taken and sent to the RTOG Office in the first week of therapy together with a copy of the treatment plan. Isodose distributions, will be submitted to RTOG Headquarters with the Radiotherapy Form at the completion of radiotherapy.

6.2.7 Dosimetry Monitoring. The Radiological Physics Center in Houston will conduct field surveys to verify the accuracy of dosimetry at each participating institution.

6.3 Pion Radiotherapy.

The tumor dose to the initial large field will be 2000 minimum peak pion rad at a daily minimum tumor dose of 85 peak pion rad. The target volume will be the same as described above under 6.2.3. The peak pion dose could be limited to the primary tumor and the local lymphatic spread in those instances where such lymphatic spread is contiguous with or near the gross tumor and which will be 2 cm from the 95% isodose line. In the latter case, the remaining drainage area will be treated prophylactically with conventional radiation to the dose level described above for conventional radiation. Patients will be evaluated for operation after this dose and operated upon 3-4 weeks after the last radiotherapy treatment. If not operable or if not resectable, patients will then receive a peak pion cone-down to the primary tumor and any known gross disease to an additional minimum 1300 peak pion rad. The boost volume will be as described under 6.2.4 above. For the pion radiotherapy, split course treatment may be needed to conform to accelerator operating schedules.

If, for whatever reason, the full prescribed dose of pion radiotherapy cannot be delivered, additive conventional radiation may be delivered to the primary field, to a dose level to be determined on an individual patient basis. Patients who receive such additive conventional therapy to the primary field will be retained on study, but will be stratified separately for statistical analysis.

7.0 ENDPOINTS OF STUDY AND RESPONSE CRITERIA

Primary endpoints will be derived from:

7.1 Patient survival time.

7.2 Quality of survival.

7.2.1 Karnofsky function assessment.

7.2.2 Subjective assessment.

7.3 Local Tumor Response.

The rate of regression of the primary tumor and regional nodes at each assessment will be determined by measurements of the primary tumor and any palpable nodes, in maximum dimensions and dimensions at right angles and when possible third dimensions; otherwise by subjective assessment percentage regression. This assessment will be performed immediately after treatment and at each follow-up visit.

7.3.1 Complete response (CR) - Complete disappearance of all measurable and palpable tumor.

7.3.2 Partial response (PR) - Tumor shrinkage greater than 50% of the product of the perpendicular diameters of the two largest dimensions.

7.3.3 Minor response (MR) - Tumor shrinkage greater than 25% but less than 50% of the product of the perpendicular diameters of the two largest dimensions.

7.3.4 No change (NC) - 25% growth to 25% shrinkage of the product of the perpendicular diameters of the two largest dimensions.

7.3.5 Progressive disease (PD) - Growth of tumor greater than 25% of the product of the perpendicular diameters of the two largest dimensions.

7.4 Response of regional node metastasis.

7.5 Incidence of distant metastasis.

7.6 Incidence of local recurrence.

7.7 Change to resectability from nonresectability.

7.8 Change to operable from inoperable.

7.9 Acute and late response of normal tissue (see Appendix III).

8.0 POST-TREATMENT EVALUATION

Parameters to be recorded at each follow up evaluation while on study include:

8.1 Medical history data (see section 4.1), including Karnofsky Status.

8.2 Physical examination including vaginal examination for female patients.

8.3 Laboratory tests, as indicated.

8.4 Imaging procedures, as indicated.

8.4.1 Chest x-ray.

8.4.2 Intravenous pyelogram (except for patients who are dye sensitive).

8.4.3 Barium enema.

8.4.4 Cystogram (when invasion of bladder is involved).

8.4.5 Liver scan.

8.4.6 CT Scan when indicated.

8.5 Proctoscopy as indicated (for patients not subsequently resected).

8.6 Cystoscopy as indicated (when invasion of the bladder is involved).

8.7 Summary of Evaluation Parameters

	Pre Treatment	At Completion	At Follow-up
History & Physical*	x	x	x
Performance Status	x	x	x
CBC, differential, platelets	x		a
Urinalysis	x		a
Blood Chemistries	x		a
Liver Enzymes	x		a
Cardiopulmonary assessment	a		
CT Scan	x	a	a
Chest x-ray	x		a
IVP**	x		a
BE	x		a
LAG	x	a***	a***
Liver Scan	x		a
Cystogram	a		a
Proctoscopy	x		a
Metastatic Survey (liver, bone, brain, etc.)	a		a
Ophthalmologic Exam	b		b

*vaginal exam for female patients

(a***) KUB or plain abdomen/pelvis radiographs as indicated

** unless contraindicated

(a) if clinically indicated

(b) Prior to treatment and yearly thereafter

(x) Required, consistent with good medical practice

9.0 FOLLOW-UP SCHEDULE

Patients receiving pion radiotherapy will receive an annual physical examination by a Study Center radiation oncologist at the study center in Albuquerque or at a regional clinic closer to the patient's home. Deaths of patients treated with either pion radiotherapy or conventional therapy will be reported.

The purpose of follow-up assessments is to determine:

9.1 Gross tumor response to treatment.

9.2 Time of distant spread and involved organs and nodes.

9.3 Long-term normal tissue effects of radiotherapy.

9.4 Time and site of local recurrence (if any) as accurately as possible.

9.5 Patient functional status during survival.

9.6 Time of survival in years.

9.7 The first day of definitive treatment is considered Day 1. Follow-up assessments should be scheduled within two weeks of the specified times and will be reported:

9.7.1 Immediately after treatment, then monthly for six months counting from Day 1.

9.7.2 Every three months for the next 18 months.

9.7.3 Every six months for the next year (when patient survival time reaches three years after Day 1).

9.7.4 If data analysis warrants, patients will continue to be followed at six-month intervals until survival reaches five years after Day 1.

9.8 If a study patient cannot return to the participating hospital where he was entered in the study, arrangements will be made to have him examined at another hospital or by his private physician and a report of this examination submitted. The following information will be recorded on the follow-up form at each visit (unless indicated otherwise):

9.8.1 Brief interim history (weight loss, abdominal pain, weakness, diarrhea, constipation, obstruction, other).

9.8.2 Physical examination: (same as 4.2).

9.8.3 Performance status (Karnofsky function assessment).

9.8.4 Laboratory tests, as indicated.

9.8.5 Imaging procedures, as indicated, (same as 8.4).

9.8.6 Ophthalmologic exam to assess lens opacity (annually).

9.8.7 Progress toward endpoints (complications, tumor response, etc.) will be recorded and reported at each follow-up visit. If a recurrence develops, a biopsy should be taken and the date of recurrence should be fixed as closely as possible. Patients receiving pion radiotherapy will receive an annual physical examination by a Study Center radiation oncologist at the Study Center in Albuquerque or at a regional clinic closer to the patient's home.

10.0 PATHOLOGY

10.1 Pathology data will be derived from:

10.1.1 Biopsy Specimens. Biopsy specimens will be examined by pathologists at the participating institutions to substantiate the diagnoses. Representative slides for patients entered onto the study will be forwarded to RTOG Headquarters for review by the study pathologist. Copies of biopsy reports will be submitted to RTOG Headquarters and the referring and/or follow-up physician.

10.1.2 Surgical Specimens. Any tissue surgically removed from anatomic sites will be examined by pathologists at the participating institutions where the surgery was performed. A description of the surgical specimen and microscopic slides will be forwarded to RTOG Headquarters for review by the study pathologist.

10.1.3 Autopsies. Autopsies should be performed on all study patients by pathologists at the participating institutions. The postmortem study should include a description of irradiated tissues and pattern of tumor spread (see Appendix IV). Autopsy reports and representative microscopic slides will be forwarded to RTOG Headquarters for review by the study pathologist.

11.0 FORMS

A copy of each study form must be submitted to RTOG Headquarters. Data will be recorded on standard forms to be supplied to each participating institution. The following records will be generated by the study team and participating institutions for storage, retrieval, and analysis.

11.1 RTOG initial registry form (submitted for both eligible and ineligible patients entering each participating institution).

11.2 On-study form.

11.3 Treatment prescription.

11.4 Localization films.

Localization films of each field will be taken and sent to the RTOG office in the first week of therapy together with a copy of the treatment plan.

11.5 Treatment summary form:

11.5.1 Radiation therapy administered (type of energy, daily schedule of treatment, maximum dose, complications during radiation therapy, a description of the lesion at the end of treatment, patient's weight at the end of treatment, performance at end of treatment, complications following therapy and their management, copies of port films and isodose curves, etc.). Isodose distributions should be attached.

11.5.2 Operative procedures and findings, if applicable (extent of disease, presence of metastases, type and extent of surgery performed, etc.).

11.5.3 Postoperative data (complications following surgery, patient weight at time of discharge, performance at time of discharge, etc.).

11.5.4 Drugs administered, if any (a description of type and dose of any drugs administered, duration, and purpose, including any chemotherapy administered in the event of lack of tumor control).

11.6 Follow-up assessment form (see Section 9.0).

11.7 Pathology forms (see Section 10.0).

11.8 Summary of forms submission.

Form	Due
Initial registry	Within two weeks of evaluation
On-study form Study entrance form Radiotherapy prescription Copies of localization films Pathology slides and report	Within two weeks of randomization
Treatment summary form Copy of radiotherapy record Copy of boost fields Isodose distribution	Within two weeks of completion of radiotherapy
Follow-up assessment	Within two days of times in 9.7
Surgery form Pathology slides and report	Within one month of surgery
Death form	Within one month of death

12.0 ADDITIONAL THERAPY ALLOWED

Therapy is to be administered as detailed in section 6.0. Subsequent therapy shall proceed at the discretion of the patient's responsible physician. Indications for subsequent therapy and the therapy performed should be documented in the patient's follow-up records.

Patients in this study may have their radiation therapy modified or interrupted as dictated by the clinical indications, such as acute bowel obstruction, or unusually severe radiation reaction not amenable to simple daily dose reduction or symptomatic treatment. A colostomy or ileostomy, although needed infrequently, should be carried out for relief of obstruction.

Patients found nonresectable at operation only will be considered for possible additional therapy (re-exploration and resection, if possible) or no additional therapy at the discretion of the individual investigator. Pathology specimens will be obtained, and the incidence of metastasis in regional nodes will be recorded.

If the primary tumor is not controlled at the primary site, subsequent therapy should proceed at the discretion of the patient's responsible physician. Clinical evidence of lack of tumor control should be documented in the patient's follow-up records.

In the event that surgery or a biopsy is performed, the excised tissue or biopsy specimen should be carefully examined by a pathologist at the participating institution, with representative slides forwarded to the study center for review by the study pathologist.

13.0 STATISTICAL CONSIDERATIONS

Based on available literature and the likelihood that only patients with more advanced tumors will be referred, members of the Committee on Human Trials of Pion Radiation Therapy, UNM/LASL, estimate the current cumulative five-year survival rate for the control cases at six percent. They believe that a survival rate of 20 percent should be sought as minimally acceptable with pion radiotherapy.

A total of 150 patients, 75 in each arm, will allow this improvement, if it exists, to be detected with high probability (90% or greater) using a one-sided test of significance with p-value of 0.05. This assumes:

1) that patient survival approximately follows a negative exponential distribution.

2) that these patients will be accrued in a period of two to three years, and a statistical analysis performed at the end of year five.

14.0 PATIENT CONSENT AND PEER JUDGMENT

All institutional, National Cancer Institute and Food and Drug Administration regulations requiring submission to the Institutional Human Experimentation committee and the use of procedures for obtaining and recording informed consent will be followed. A patient may be removed from the study at any time if the study is not in the best interest of the patient. A patient may withdraw voluntarily from the study at any time, as will be indicated in the consent form (see Appendix V).

REFERENCES

1. Moertel, C.G. and Reitemeier, R.J.: Advanced Gastrointestinal Cancer. Clinical Management and Chemotherapy. New York; Harper & Row, 1969.

2. Dionne, L.: The pattern of blood borne metastasis from carcinoma of the rectum. Cancer 18:775-81, 1965.

3. Moertel, C.G.: Alimentary Tract Cancer, Section XXIV-12 In Cancer Medicine. Lea and Febiger, 1973, 1597-1626.

4. Taylor, F.W.: Cancer of the colon and rectum -- A study of routes of metastases and death. Surgery 52:305-8, 1962.

5. Floyd, C.E., Corley, R.G. and Cohen, I.: Local recurrence of carcinoma of the colon and rectum. Am J Surg 109:153-9, 1965.

6. Cass, A.W., Pfaff, F.A. and Million, R.R.: Patterns of recurrence following surgery alone for adenocarcinoma of the colon-rectum. Cancer 37:2861-2865, 1976.

7. Whiteley, H.W., Stearns, M.W., Jr., Leaming, R.H. and Deddish, M.R.: Radiation therapy in the palliative management of patients with recurrent cancer of the rectum and colon. Surg Clin North Am 49:381-7, 1969.

8. Williams, I.G.: Radiotherapy of carcinoma of the rectum. In Cancer of the Rectum. C. Dukes, ed. Edinburgh, E. & S. Livingston, 1960, 210-219.

9. Wang, C.C. and Schultz, M.D.: The role of radiation therapy in the management of carcinoma of the sigmoid, rectosigmoid and rectum. Radiology 79:1-5, 1962.

10. Urdaneta-Lafee, N., Kligerman, M.M. and Knowlton, A.H.: Evaluation of palliative irradiation in rectal carcinoma. Radiology 104:673-7, 1972.

11. Sklaroff, D.: Radiation as primary therapy for rectal carcinoma. Am Fam Physic 8:81-5, 1973.

12. Rider, W.D.: Is the Miles operation really necessary for the treatment of rectal cancer? J Canad Assoc Radiol 26:167-75, 1975.

13. Kligerman, M.M.: Radiotherapy and rectal cancer. Cancer 39:896-900, 1977.

14. Stevens, K.R. and Allen, C.V.: Preoperative radiotherapy for adenocarcinoma of the rectosigmoid. Cancer 37:2866-2814, 1976.

15. Kligerman, M.M., and Urdaneta-Lafee, N.: Observations on fifteen selected inoperable/nonresectable cases of rectal cancer given preoperative irradiation. Am J Roentgenol Radium Ther Nucl Med 120:624-626, 1974.

16. Kligerman, M.M., Smith, A.R., Yuhas, J.M., Wilson, S.; Sternhagen, C.J., Helland, J.A., and Sala, J.M.: The relative biological effectiveness of pions in the acute response of human skin. Int J Rad Oncol Biol Phys 3:335-339, 1977.

17. Kligerman, M.M., Sala, J.M., Wilson, S., and Yuhas, J.M.: Investigation of pion treated human skin nodules for therapeutic gain. Int J Rad Oncol Biol Phys 4:263-265, 1978.

18. Kligerman, M.M., Von Essen, C.F., Khan, M.K., Smith, A.R., Sternhagen, C.J., and Sala, J.M.: Experience with pion radiotherapy. Cancer, (in press).

19. Kligerman, M.M., Wilson, S., Sala, J., von Essen, C., Tsujii, H., Dembo, J., and Khan, M.: Results of clinical applications of negative pions at Los Alamos. In Proc. Third Meeting on Fundamental and Practical Aspects of the Application of Fast Neutrons and Other High-LET Particles in Clinical Radiotherapy. Pergamon Press, Oxford, (in press).

APPENDIX I

TNM CLASSIFICATION

(American Joint Committee Staging - 1977)

The definitions of TNM categories for carcinoma of the colon and rectum follow. Each case must be assigned the highest category of T, N, and M that describes the full extent of disease in that case.

Primary Tumor (T)

- TX Depth of penetration not specified
- T0 No clinically demonstrable tumor
- TIS Carcinoma in situ (no penetration of lamina propria)
- T1 Clinically benign lesion or lesion confined to the mucosa or submucosa
- T2 Involvement of muscular wall or serosa, no extension beyond
- T3 Involvement of all layers of colon or rectum with extension to immediately adjacent structures or organs or both, with no fistula present
- T4 Fistula present along with any of the above degrees of tumor penetration
- T5 Tumor has spread by direct extension beyond the immediately adjacent organs or tissues

Nodal Involvement (N)

- NX Nodes not assessed or involvement not recorded
- N0 Nodes not believed to be involved
- N1 Regional nodes involved (distal to inferior mesenteric artery)

Distant Metastases (M)

- MX Not assessed
- M0 No (known) distant metastases
- M1 Distant metastases present (including extra-abdominal nodes; intra-abdominal nodes to proximal to mesocolon and inferior mesenteric artery (see N1); peritoneal implants, liver, lungs, and bones)
  Specify _____

Pulmonary - PUL	Lymph Nodes - LYM
Osseous - OSS	Bone Marrow - MAR
Hepatic - HEP	Skin - SKI
Brain - BRA	Eye - EYE
Pleura - PLE	Other - OTH

Add "+" to the abbreviated notation to indicate that the pathology (p) is proven.

Postsurgical Treatment Residual Tumor (R)

- R0 No residual tumor
- R1 Microscopic residual tumor
- R2 Macroscopic residual tumor; Specify _____

Stage Grouping

Stage 0

TIS NO MO
Carcinoma in situ as demonstrated by histologic examination of tissue (biopsy or other)

Stage I

Stage 1A
T0,1 NO MO
T0,1 NX MO
Tumor confined to mucosa or submucosa with no demonstrable metastasis to regional lymph nodes and no evidence of distant metastases

Stage 1B
T2 NO MO
T2 NX MO
Tumor involves muscularis but has not extended beyond serosa with no demonstrable metastasis to regional lymph nodes and no evidence of distant metastasis

Stage II

T3-5 NO MO
T3-5 NX MO
A tumor that has extended beyond the bowel wall or serosa with no demonstrable metastasis to regional lymph nodes and no evidence of distant metastasis

Stage III

Any T N1 MO
Any degree of penetration of bowel or rectal wall by tumor with metastasis to regional lymph nodes but no evidence of distant metastasis

Stage IV

Any T, Any N M1
Any degree of penetration of bowel or rectal wall by tumor with or without metastasis to regional lymph nodes and with evidence of distant metastasis

Histopathology

The predominant cancer is adenocarcinoma; pathologic diagnosis is required to utilize this classification. Tumor grading is recommended. Reference to WHO nomenclature is advised.

Other determinants of probable importance to be evaluated in prospective studies of postsurgical treatment assessment are tumor margin circumscription, histopathologic differentiation (e.g., nuclear grade, growth pattern, and mucin production) and host-cellular reaction (lymphocyte and plasma cell infiltration in and about the tumor as well as in contiguous tissues). It is essential that in each case the specific histologic type and the presence or absence of intravasal permeation (lymphatic, venous, or both) be routinely recorded.

Tumor Grade (G)

G1 Well differentiated

G2 Moderately well differentiated

G3-4 Poorly to very poorly differentiated

Use whichever indicator is most appropriate (term or G + number)

APPENDIX II

KARNOFSKY PERFORMANCE STATUS

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 process progressing rapidly.
0	Dead.

APPENDIX III

ACUTE/LATE EFFECTS SCORING

Normal Tissue Reaction Grades

1. Skin

00 Nil
01 Threshold erythema
02 Erythema < ½ field
03 Erythema ≥ ½ field
04 Dry desquamation < ½ field
05 Dry desquamation ≥ ½ field
06 Moist desquamation < ½ field
07 Moist desquamation ≥ ½ field
08 Small necrotic ulcer or slough
09 Massive acute skin necrosis
10 Unknown

2. GI Tract

0 Nil
1 Transient change of bowel habit
2 Definite change: mucosa normal
3 Minimal tenesmus and/or reddening of mucosa
4 Moderate tenesmus with mucus
5 Severe tenesmus with mucus
6 Severe tenesmus with bleeding
7 Intractable hemorrhage requiring transfusion and/or fecal diversion
8 Necrosis
9 Unknown

2a. Proctoscopic Findings

0 Nil
1 Injection
2 Dusky mucosa
3 Edema
4 Punctate hemorrhage
5 Gross bleeding

3. GU Tract

0 Nil
1 Frequency
2 Dysuria
3 Burning
4 Hematuria
5 Unknown

LATE EFFECTS

0	None
1	Lymphedema
2	Fibrosis
3	Pain
4	Ulcer
5	Pneumonitis
6	Pericarditis
7	Necrosis
8	Trismus
9	Xerostomia
10	Chronic enteritis
11	Fistula
12	Myelitis
13	Atrophy
14	Induced tumor
15	Other (specify)

APPENDIX IV

AUTOPSY PROTOCOL FOR PATIENTS TREATED WITH PION RADIATION

Histopathological data on the effects of pi mesons on normal as well as neoplastic tissues is still not extensive. For this reason these patients have enormous clinical research importance. This communication is designed to explain the basic questions we would like to try to answer and to serve as a guideline to help you in obtaining the most appropriate tissues as easily and efficiently as possible. We believe that a relatively small group of selectively localized blocks will yield more information than numerous random tissue samples.

Basically four types of specimens need to be collected of which two deal with the neoplasm per se and two with normal tissues from the treatment field. In the first place you will naturally want to assess the effects of therapy on the neoplasm within the central portion of the treatment field. Secondly it will be desirable to compare tissues from this area with those more peripherally situated at or near the margins of the treatment fields. This information will allow the therapists and physicists to assess the accuracy of localization of the field and to draw conclusions relative to dosimetry on the basis of semiquantitative histopathology.

Radiation effects upon normal tissues and organs are equally important because of potential complications of therapy. Once again there is a need to obtain separate specimens from within the treated volume and others from similar but peripheral organs or tissues that were calculated to have received a relatively low dose of radiation.

Initially we felt that the pathologist, provided with the therapy chart, could select appropriate blocks on the basis of his own judgment. In practice this has not been the case since the details of therapy, while recorded in the chart, have seldom been collated into a workable form, i.e., size and shape of fields, relative dose levels etc. Thus, on the

basis of meetings with the Human Trials Committee it was decided that the pathologist must be provided with a simplified "map" that will enable him to obtain proper sections with confidence in the course of performing his usual autopsy procedure. It is clear that this document can only be prepared by the radiation therapist and physicists during or at the conclusion of the patient's therapy.

The accompanying form includes an extremely simplified summary of therapy details together with fairly specific suggestions for tissue sampling. These suggestions are broken down into four categories as explained: 1) Several blocks from the epicenter of the treated tumor; 2) Blocks from the perimeter of the tumor; 3) Blocks from organs situated within the treated volume; 4) Blocks from tissues or organs intercepting radiation but external to the treatment field per se. A set of lettered labels is available corresponding to individual tissue sites in the lettered column as identified by the radiation therapist. The center of the form has been left blank for line drawings by the therapists. These drawings might indicate external landmarks such as tattoos or represent internal cross sections to include metal clips etc. (Initially we attempted to construct anatomically precise horizontal line drawings for each tumor included in the pi meson protocols but believe there is too much individual patient variability with regard to tumor size, configuration and orientation of treatment fields to make this practical.)

Please be assured that we will share any information generated by these studies as they pertain to this patient or to the effects of pi mesons on tissues in the most general sense. As in the case of the radiation therapists, there are pathologists from many institutions involved and we sincerely wish this to be a mutually informative effort with wide dissemination of information and findings.

PATIENT'S NAME: _____

SUMMARY OF THERAPY:	Total Dose	Date Completed	Adjuvant Chemotherapy?
High LET	_____	_____	
Low LET	_____	_____	
Other	_____	_____	

RADIATION THERAPIST: _____

PHYSICIST: _____

BLOCKS

T_C (Tumor, Central Treatment Area)

T_P (Tumor, Peripheral Treatment Area)

	OTHER SITE	ESTIMATED DOSE
A	_____	_____
B	_____	_____
C	_____	_____
D	_____	_____
E	_____	_____
F	_____	_____
G	_____	_____
H	_____	_____

T_C	A
T_C	B
T_C	C
T_C	D
T_P	E
T_P	F
T_P	G
T_P	H

APPENDIX V

PATIENT CONSENT FORM FOR

RADIATION TREATMENT OF RECTAL CANCER*

PATIENT'S NAME: _____

ADDRESS: _____

HOSPITAL/CLINIC: _____

HOSPITAL/CLINIC I.D. NUMBER: _____

1. I, _____ (Name of Patient), agree to take part in a research study to test the use of radiation to treat cancer of the rectum. Dr. Morton M. Kligerman, Dr. _____ (Name of Physician), and doctors they have chosen will do this study. Persons helping them will be supervised by a doctor at all times while treatment is being given.

2. The treatment to be given to me has been described to me by Dr. _____. It is as follows:

   a. I might receive x-ray or cobalt treatments to my abdomen and pelvis (from the top of my stomach to the top of my legs). These treatments might be given to me at the _____ (Name of Institution).

   b. I might receive negative pi meson (pion) treatments to my abdomen and pelvis (from the top of my stomach to the top of my legs). These treatments might be given to me at the Los Alamos Meson Physics Facility, Los Alamos, New Mexico.

   c. If I agree to take part in the study, I must agree to go to Albuquerque and Los Alamos, New Mexico, for tests so that my doctors can plan the best possible treatment for me.

   d. If I am chosen for pion treatment, I must agree to stay the needed time (about eight weeks) in Los Alamos for treatment.

   e. I must agree to return to the University of New Mexico Cancer Research and Treatment Center in Albuquerque for needed follow-up exams, if I am chosen for pion treatment.

   f. I understand that I will be chosen by chance for either x-ray, cobalt or pion treatment, and that my doctors cannot tell me ahead of time which treatment I will be chosen to receive.

*Sample Consent Form submitted by the Study Chairman.

3. Dr. _____ has told me that I might not feel well after these radiation treatments. Some of the things that might happe to me are:

   a. I might lose my appetite.
   b. I might have diarrhea or constipation. This is usually temporary.
   c. I might have pain when I pass water or need to pass water more often. This is usually temporary.
   d. My skin might get red and peel in the treatment area.
   e. I might lose hair in the treatment area.
   f. I might get pain or swelling in the treatment area.
   g. The number of my blood cells might be less. This could make it easier for me to get a disease caused by germs, but my blood will be tested often so that any problems can be treated quickly.
   h. I might get a narrowing in my stomach or intestine (bowel) or even a hole (not expected), but this can usually be helped by an operation.
   i. I might have weakness in my legs or lose the ability to move them, although this is not expected to happen.
   j. If I am a man, I might not be able to have sex or to father children.
   k. If I am a woman who still has monthly periods, my menstrual flow will probably stop and I will probably not be able to have children.
   l. If I am a woman, I may have a discharge from my vagina.

4. Dr. _____ has told me about the good things this research study might do for me and for other people. It will help to find out which kind of radiation is better in treating rectal cancer.

5. Dr. _____ has told me about other treatments for me.

   a. X-ray or cobalt treatment and drugs.
   b. Drugs alone.

6. Dr. _____ will answer any questions I have during the treatment.

7. I know that the treatment could harm me. No one has said that it wouldn't. I can stop treatment at any time I want to.

8. Dr. _____ is in charge of my treatment. He can change the treatment at any time, or stop it.

9. If my body is injured by the research treatment, more than or different from that explained above, I understand that any emergency medical care I need will be given to me at no cost, but I will not be paid any money. Payment for medical costs will not continue after the emergency treatment is finished.

10. I understand that by signing this paper I am not giving up my legal rights. State laws exist which may help people who think they have been treated carelessly. For information, write or call the Risk Management Division, Room 24, Lamy Building, Santa Fe, New Mexico 87503.

Date: _____ Time: _____ Place: _____

Signed: _____ Witness: _____
Name of Patient

_____ Witness: _____
Parent or Guardian When Indicated

Original: Patient Chart
cc: Patient
RTOG Headquarters