21 March 1972

UCM1.951211.119

TO: Faculty Committee on Research

FROM: Edward B. Silberstein, M.D.
Bernard Aron, M.D.
Eugene L. Saenger, M.D.

SUBJECT: Evaluation of the Therapeutic Effectiveness of Total and Partial Body Irradiation as Compared to Chemotherapy in Humans with Carcinoma of the Lung or Colon.

I. Purpose of the Study

The study has four goals:

1. To test the hypothesis that wide field irradiation therapy is of equal or greater efficacy compared to chemotherapy in the treatment of metastatic carcinoma of the lung or colon;

2. To test the hypothesis that chemotherapy-resistant cancers of the lung or colon may still respond to wide-field radiotherapy;

3. To develop biological indicators to determine the effectiveness of wide-field radiotherapy or chemotherapy so as to better understand the metabolic consequences of these treatments; and

4. To develop and evaluate therapeutic methods of increasing the margin of safety from toxicity following radiation or chemotherapy toxicity.

II. Introduction

The historical background of animal studies suggesting that total body irradiation is effective in the treatment of carcinoma has been reviewed by E. L. Saenger, M.D. (1). In this Phase II efficacy study, patients treated with whole or partial irradiation survived at least equally as well as patients treated with 5 fluorouracil for carcinoma of the colon metastatic to the liver (2) and with chlorambucil for carcinoma of the lung (3) and in both tumors longer than untreated patients (3,4) (Figures 1,2).

Total body radiation carries a hypothetical advantage over chemotherapy because the radiation will reach tumor tissue independently of competent vascular supply whereas treatment with chemotherapy requires a good blood supply to the target tissue.

III. Study Design

The proposed study design is that of a Phase III randomized prospective investigation.

A. Patients with metastatic carcinoma of the colon or metastatic carcinoma of the lung will be randomized to therapy with wide-field radiation therapy or chemotherapy.

1. Patients with carcinoma of the colon proven by biopsy or a laparotomy must have tumor spread beyond the areas of surgical resection, excluding regional lymph nodes resected and found to contain tumor. Patients with carcinoma of the colon with metastases above the diaphragm are also eligible. Intra-abdominal metastases must be proven by biopsy. The appearance of thoracic lesions in serial chest x-rays will be considered evidence for metastases above the diaphragm in the absence of positive cultures for tuberculosis and fungi. Patients with carcinoma of the colon will <u>not</u> be eligible if the tumor has only invaded the serosa of the colon or is found only in lymph nodes draining the tumor.

2. Patients with carcinoma of the lung will be eligible for randomization if there is: a) Stage III tumor which is localized to the chest but unresectable (including scalene node involvement) with invasion of mediastinal lymph nodes, nerves, or blood vessels. b) Stage IV. Patients with distant metastases beyond the thorax will be included for randomization except those with tumor metastatic only to the brain.

3. Patients with the above tumors will be <u>ineligible</u> for randomization if:

   a. Other significant marrow depressive therapy has been given within the past six weeks, in which case the patient will not be eligible until etiocholanolone-induced granulocyte reserve is again normal.

   b. The patient is disoriented or unable to understand the randomization between alternate treatments.

   c. Clinical judgment indicates the patient will not survive to complete an initial 6 week course of treatment.

d. Patients with hemoglobin below 9 grams per cent or hematocrit below 28%.

e. Patients with white blood counts below 3,000 or platelet counts below 100,000.

f. Patients with any form of active infection.

g. Any other active malignancy besides skin tumors.

4. Availability of patients

NEOPLASTIC DISEASE REGISTRY

New Cancer Cases in CGH

	Colon	Lung
1966	19	37
1967	35	50
1968	25	46
1969	31	48
1970	26	65
	50% CA colon is: Stage III or IV	70% CA lung is: Stage III or IV

From General Hospital alone there would be an average of 14 patients per year for the Colon Study. It may be possible to increase the size of this group by patients from elsewhere in the Medical Center if they agree to enter the study. The number of patients needed to complete the Colon study is estimated in Appendix A. It is thought desirable to make a start with this group since within 5 years the number should be adequate.

B. Patients eligible for randomization will receive complete pre-treatment evaluation:

1. Complete medical history and physical examination.

2. Roentgenographic survey.

a. Chest X-ray

b. Skull, pelvic, spine and long bone films.

3. Blood chemistry evaluation including:

a. SMA-12

b. Serum uric acid

c. Creatine phosphokinase

4. Complete blood count including reticulocyte count and platelets.

5. Evaluation of granulocyte reserves with etiocholanolone, 0.1 milligrams per kilogram.

6. Radioisotopic evaluation including bone marrow scan, liver scan, spleen scan, brain scan, and bone scan.

7. Bone marrow aspiration for evaluation of cellularity and presence of tumor cells.

8. Electrocardiogram.

9. Prothrombin time and partial thromboplastin time.

10. Urinalysis and clean catch urine culture.

11. 24 hour urine for creatinine, amylase, xanthine, hydroxyproline.

C. Patient Treatment

1. Patients with carcinoma of the colon.

a. Chemotherapy for carcinoma of the colon will be with 5 fluorouracil (5), 12-15 mg. per kilogram body weight weekly by mouth for 4 weeks. If neither response nor toxicity are observed, the dose will be increased to 15-20 mg. per kilogram for the next two weeks. The 5-FU will not be given in any week when the absolute granulocyte count is under 1,000 per cubic mm., the platelet count is less than 100,000 per cubic mm., or there is evidence of stomatitis or diarrhea.

b. The alternative treatment for carcinoma of the colon will be wide-field irradiation to be employed in the dose of 400 rads from the xiphoid process to the feet if the tumor is confined to the subdiaphragmatic area (assuming that the uppermost part of the diaphragm lies at the xiphoid process) or 200 rads total body radiation if there are metastases above and below the diaphragm. Patients receiving 200 rads total body radiation will be supported with bone marrow auto-transplantation.

2. Patients with carcinoma of the lung are staged as III or IV. Stage III patients will be randomized between therapies a., b. or c. below, after a course of localized external radiation therapy to the chest has been completed. Stage IV patients will receive either therapy a. or b.

   a. Chemotherapy employed will be chlorambucil, 0.2 mg/Kg. orally for six weeks. The dose may be reduced as low as 2 mg. per day orally to maintain platelet count over 100,000 per cubic mm. and the absolute granulocyte count to exceed 1,000 per cubic mm. Treatment will be discontinued temporarily if blood counts drop below each of these levels and resumed as soon as they rise above these levels.

   b. The radiotherapy involved will be 400 rads to the upper body (from the xiphoid process to the head) if the tumor is localized to the thorax or above, or 200-300 rads total body if the tumor has metastasized below the diaphragm.

      Total body irradiation with marrow transplantation will not be performed if bone metastases are found by scan or marrow biopsy. Partial body irradiation will be performed in this case to avoid tumor auto-transplantation.

   c. Follow up only - No treatment, until further extension of disease makes treatment necessary.

3. Radiation dose reduction.

   The total body radiation dose for carcinoma of the lung or the colon will be reduced to 150 rads if there is:

   a. An abnormal response to the etiocholanolone granulocyte mobilization test (6);

   b. Hypocellular marrow aspirate;

   c. An abnormal bone marrow scan employing technetium sulfur colloid showing decreased marrow volume.

   Partial body doses will not be altered by the above findings because of the large amount of unirradiated marrow left to provide stem cells to protect the patient.

D. Evaluation of Treatment

1. The response to the two regimens employed will be compared in terms of actuarial analysis of survival.

2. Response to the two regimens will also be compared. The appropriate forms appear in Appendix B. A patient is classified as having a response to therapy by any one of the following criteria:

   a. Complete response - disappearance of all manifestations of disease.

   b. Partial response:

      (1) Decrease by 50% or more in the longest diameter of palpable lesions employing caliper measurement.

      (2) Decrease by 50% or more of abnormal liver function tests.

      (3) Decrease by 50% or more of masses visible by roentgenography or scintiscan.

      (4) Decrease by greater than 3 centimeters in the total liver height as measured by percussion and palpation at the right midclavicular line

   c. Minimal response - less than 50% response as defined above.

   d. No response - the patient is considered a non-responder to treatment if any of the following occur:

      (1) Any lesion progresses regardless of the state of other lesions;

      (2) Any new lesions appear; or

      (3) The patient dies, regardless of the cause of death, prior to the first followup exam.

3. Palliation will also be measured by qualitative scale of treatment effect on the patient classified as follows:

   a. The patient is symptom-free and able to carry on usual daily activities;

b. Symptoms limit the patient's daily activities but is capable of self care;

c. The patient needs significant assistance with self care because of the symptoms at home or in hospital;

d. The patient is bedridden more than 50% of the time because of symptoms at home or in hospital;

e. Decrease by greater than 50% of the total analgesic dose per day (measured in milligrams of analgesic per day).

4. Patients who have had documented failure in one of the above forms of treatment by the criteria noted in D.2. above are eligible, after a six weeks rest period, for the other form of treatment, assuming that their etiocholanolone-induced granulocyte reserves return to normal.

5. Patients with complete or partial responses will be retreated with the same modality when objective tumor recurrence is found.

E. Patients will be followed weekly for the first 6-10 weeks in the Tumor Clinic of the Cincinnati General Hospital to assure uniform followup. In addition, one of the investigators (EBS) will be on call for patient problems at home and office. All tests noted in Section III,B. will be repeated no less than every 4 months. Complete blood counts are to be done weekly for the first 6 weeks of treatment. Thereafter, patients will be seen at least every 4 weeks.

IV. Toxicity

The toxicity to be expected from total body irradiation is that of bone marrow depression. The proven efficacy of bone marrow transplantation in protecting patients receiving total body radiation from the leukopenia appears in Reference 1. Pancytopenia is not a problem with partial body irradiation. Thorazine has been effective in treating post-irradiation nausea and vomiting, the frequency of which have been noted in Reference 1.

The toxicity for 5 fluorouracil and chlorambucil include marrow depression by both drugs and stomatitis and diarrhea from 5-FU. Blood counts done weekly on patients receiving chemotherapy will prevent the serious effects of thrombocytopenia and leukopenia. Patients will be instructed to call one of the physicians if stomatitis or diarrhea occur while on drug treatment.

V. Previous Work Done in this Area

Previous work in the area of total body irradiation began in 1923, and has been reviewed fully in Reference 1. This reference also includes studies referring to the chemotherapy to be employed.

VI. Methods to be Used in Procuring Consent of Subjects

Patients with either tumor who will be eligible for the above treatment will be informed on two separate occasions, with family present whenever possible, that we are comparing two forms of treatment which appear equally effective for their tumor so that the patient knows that his form of treatment will be determined randomly. Consent forms appear in Appendix C.

The form of therapy to be employed will be selected from sealed, numbered envelopes provided by the investigators and selected at random from a special file prepared prior to initiation of the study.

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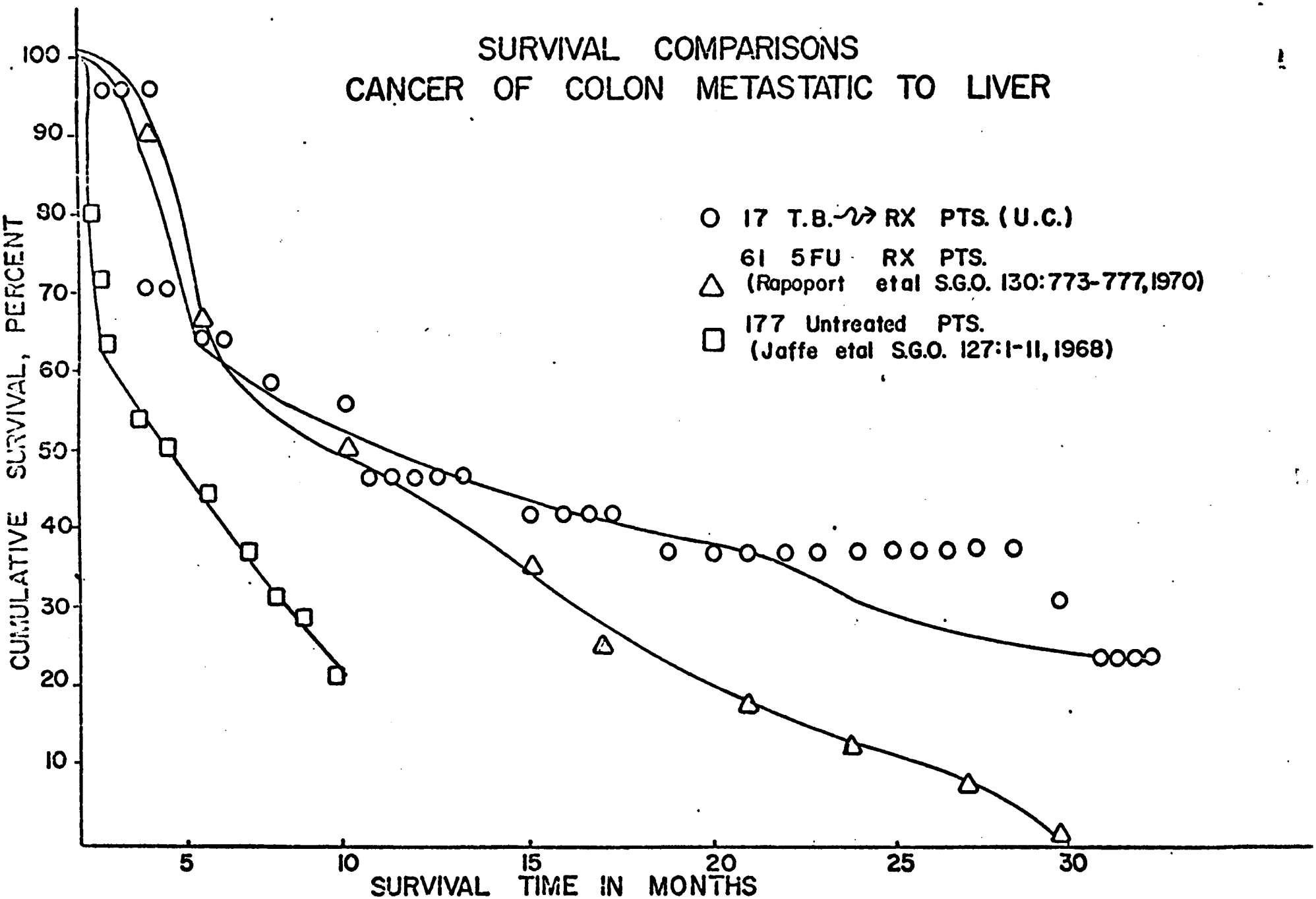
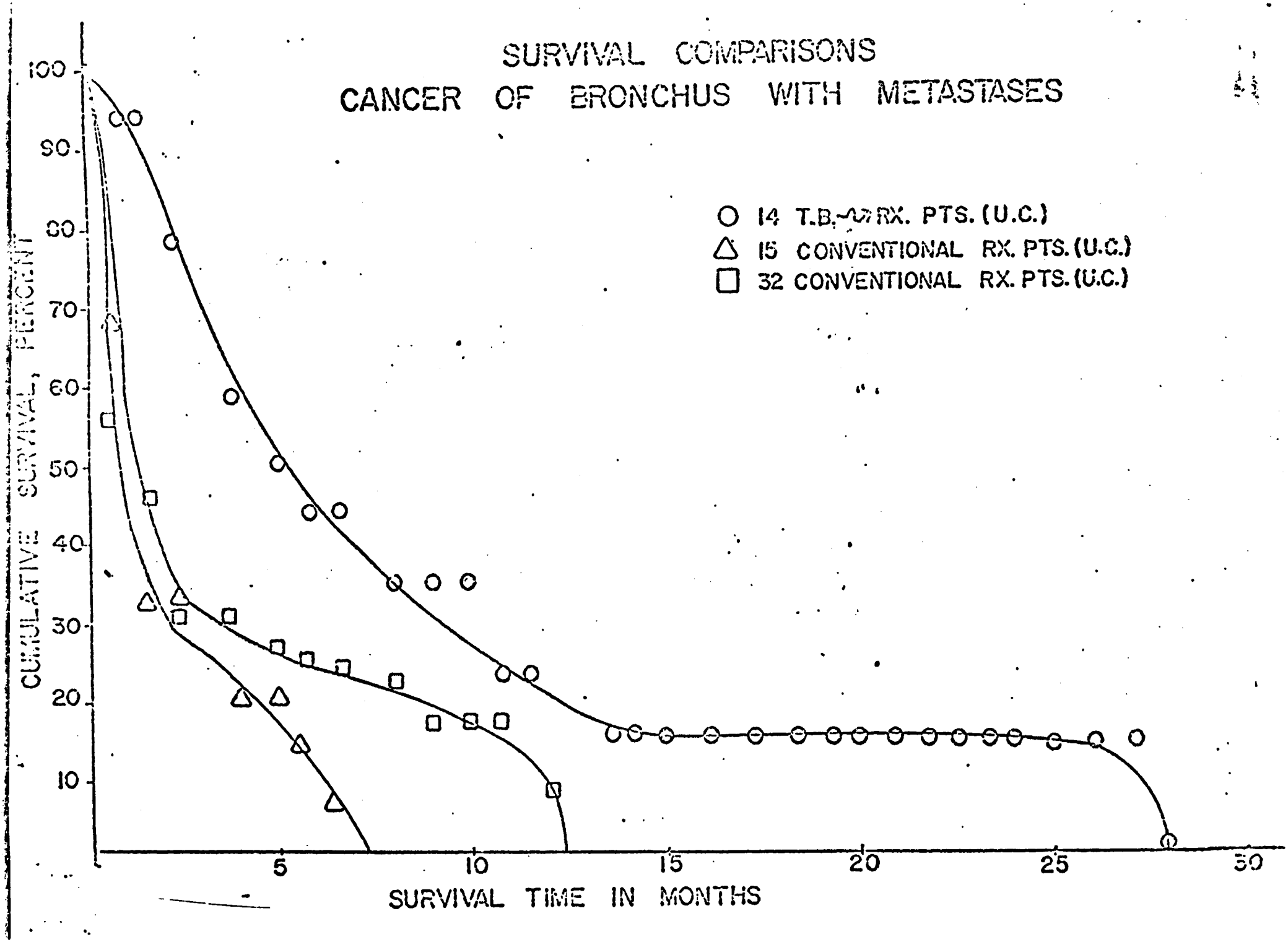
Figure 1


SURVIVAL COMPARISONS
CANCER OF COLON METASTATIC TO LIVER
17 T.B.→ RX PTS. (U.C.)
61 5FU RX PTS.
(Rapoport etal S.G.O. 130:773-777,1970)
177 Untreated PTS.
(Jaffe etal S.G.O. 127:1-11, 1968)
CUMULATIVE SURVIVAL, PERCENT
100
90
80
70
60
50
40
30
20
10
5
10
15
20
25
30
SURVIVAL TIME IN MONTHS

Figure


SURVIVAL COMPARISONS
CANCER OF BRONCHUS WITH METASTASES
14 T.B. RX. PTS. (U.C.)
15 CONVENTIONAL RX. PTS. (U.C.)
32 CONVENTIONAL RX. PTS. (U.C.)
CUMULATIVE SURVIVAL, PERCENT
100
90
80
70
60
50
40
30
20
10
5
10
15
20
25
30
SURVIVAL TIME IN MONTHS

Appendix A

ADDITIONAL SUBJECTS REQUIRED FOR TOTAL BODY IRRADIATION IN COLON WITH LIVER METASTASIS TO ESTABLISH MEDIAN SURVIVAL TIME WITHIN DESIRED LIMITS

This method estimates the number of subjects required in a given clinical trial such that the median survival will be established to within some specified interval at some level of confidence. Although the survival is a Poisson distributed variable, the distribution in time is not. Although there are some techniques available for the estimate of sample size for a given study, tacit assumption of normality of the statistic (usually the mean) is inherent in these methods.

In this case, we wish to estimate the number of subjects required to yield an uncertainty of plus or minus two months in median survival. Various objections can be raised to the application of classical techniques to this problem. However, since some experience in this particular trial is available, it is possible to use this experience to give an <u>approximate</u> <u>empirical</u> answer to the question.

Employing a known survival curve on seventeen cases (cancer of colon, metastatic to liver), the survival time rather than the fraction surviving is used as the dependent variable. In the neighborhood of the observed median for the data an uncertainty zone of plus or minus two months is erected.

Again reading survival as the dependent variable, the two curves just constructed produce an asymmetric uncertainty "flag" about the median; these came out to be $e_1 = +0.06$ and $e_2 = -0.04$, respectively. Noting that the first standard deviation of the survival about the median is given by:

$$\sqrt{\frac{p(1-p)}{N}}$$

where $p = 0.5$ and N the number of subjects, equating the values of the

above asymmetric flag will give an approximate value for N the number of subjects required:

$$N_1 = \frac{p(1-p)}{e_1} = \frac{0.25}{(.06)^2} \cong 70$$

$$N_2 = \frac{p(1-p)}{e_1} = \frac{0.25}{(.04)^2} \cong 156$$

Thus by this method between seventy and one hundred fifty-six subjects are required to establish the median survival time to within plus or minus two months. Note that this is carried out at the 68% level of confidence; for 95% confidence, between 280 and 624 subjects would be required.

Estimates of sample size based on a typical parametric test subject to alpha of 0.05 and a beta error on the order of 0.2 indicate that over 100 subjects would be required. This calculation is in reasonable agreement with the empirical estimate made above.

Appendix B

STUDY #: _____ Pt. Chart #: _____

1) Patient Name _____ Friend or Relative _____

Address _____ Address _____

Phone _____ Phone _____

2) Patient's Race ___W ___B ___Other; Sex___; Date, Birth _____; HGT. _____; WGT. _____
(M,D,Y)

3) Study Drug(s)

NAME	Dose*			
	Quantity	Units (e.g., gm)	Base (Kg)	Schedule (e.g., q.d.)
a.				
b.				
c.				
d.				
e.				

4) Primary Tumor Site _____ 5) Cell Type _____

6) Organ Involvement at Start of Therapy (Include Primary)

Skin ___No ___Yes; Lymph Nodes ___No ___Yes; Liver ___No ___Yes; CNS ___No ___Yes

Soft Tissue ___No ___Yes; Lungs ___No ___Yes; Bone ___No ___Yes; Other (specify be

7) How Metastases Proven & Date: At exploratory surgery _____ Biopsy _____ Liver Enzyme Abno
(Specify) _____

Scan _____

8) Date of Onset of Symptoms _____ Date of Tumor Diagnosis _____
(M,D,Y) (M,D,Y)

9) Prior Treatment for Cancer [Include surgery, irradiation, and drug(s)]

TREATMENT	ONSET - DATE	DURATION (Days)	AVERAGE DOSE/UNIT TIME (e.g., 3 mg. q.d.)	RESPONSE TO DRUG	
				Degree (Complete, Partial, Minimal, None, Progressive)	Duration

10) Abnormalities During Present Therapy

	Degree (Mark 0-4)*	Dose Changed? No	Dose Changed? Yes	Treatment Stopped? No	Treatment Stopped? Yes	Due to Toxicity
Blood						
Liver						
Urinary Tract						
G.I.						
Mouth						
C.N.S.						
Other (Specify)						

* 0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Life Threatening

11) New Lesions Appearing During Therapy: Site_____ Size_____ Number_____

12) Patient Response

	Date Onset Response	Date Onset Disease Progression	No Change
Measured Lesions			
Counted Lesions			

13) Other Operations and Diseases:

14) Other Medications:

NAME	DOSE	FREQUENCY

15) SURVIVAL: Alive___ Dead___ Unknown___; Autopsy ___No ___Yes; Date of Death_____ (M,D,Y); Last Seen___ (M,

SIGNATURE_____ Date_____

Patient Name _____

TUMOR FLOW SHEET

Primary Tumor Site _____ Cell Type _____

(Make entry for every day drug is given

RADIATION: Dose and Distribution OR Anti-Tumor Drug Dose for Day:	DATE																		
	2																		
	3																		
	4																		
	5																		
	6																		
OTHER THERAPY (Concurrently)	7																		
	8																		
	9																		
	10																		
	**11 Performance																		
ADVERSE REACTION A-Drug Related (0-4)*	12 Pain																		
	13 Diarrhea																		
	14 Vomiting																		
	15 Other G.I. (including liver)																		
	16 Infection (Specify)																		
	17 Bleeding																		
	18 Hair, Skin, Muc. Memb. (mouth)																		
B-Disease Related (0-4)*	19 CNS																		
	20 Respiratory																		
	21 G-U																		
	22 Cardiovascular																		

0 = none or normal
1 = mild
2 = moderate
3 = severe
4 = life threatening

** a = the patient is symptom-free and able to carry on usual activities
b = symptoms limit the patient's daily activities but is ca of self care
c = the patient needs significant assistance with self care because of the symptoms
d = the patient is bedridden more than 50% of the time beca of symptoms

Patient Name _____

Appendix B (cont.)

		DATE														
PHYSICAL FINDINGS	23	Weight Kg. lb.														
	24	Temperature														
	25	Liver (cm.) at R MCL														
	26	Spleen (cm.) (below ribs)														
	27	Other Tumor Diameter (Specify)														
	28	Other Tumor Diameter (Specify)														
LABORATORY	29	HGB/HCT														
	30	WBC (X 1000)														
	31	Polys (%)														
	32	Lymphocytes/Monocytes (%)														
	33	All Other Granulocytes (%)														
	34	Reticulocytes														
	35	Platelets (X 1000)														
	36	BUN (Mg.%)														
	37	Bilirubin (Total)														
	38	Alk. Phosphatase (mU/ml)														
	39	SGOT/LDH														
	40	Urine Protein (0-4+)														
	41	Urine Micro - Normal or Specify Abnl.														
	42	Albumin-Globulin														
Other	43	Calcium-Phosphate														
	44	Amylase (Serum)														
	45	Amylase (24 hr. urine)														
	46	Uric Acid														
	47	CPK														
	48	Prothrombin Time														
	49	OBSERVER'S INITIALS														

COMMENTS:**

SIGNATURE _____
(Senior Investigator)

DATE _____

Additional comments

Patient Name: _____

Chart #: _____

SOLID TUMOR MEASUREMENT FORM

Primary Tumor Site _____ Cell Type _____

Date Last Dose of Drug(s) _____

Date of Observation																			
Observer's Initials																			
Tissue being Measured and Coordinates																			
1.																			
2.																			
3.																			
4.																			
5.																			
6.																			
7.																			
8.																			
9.																			
10.																			
Number of Counted Lesions																			

SENIOR INVESTIGATOR'S COMMENTS: (Include complications of disease; other serious illness; complications of therapy; overall evaluation of therapeutic benefit.)

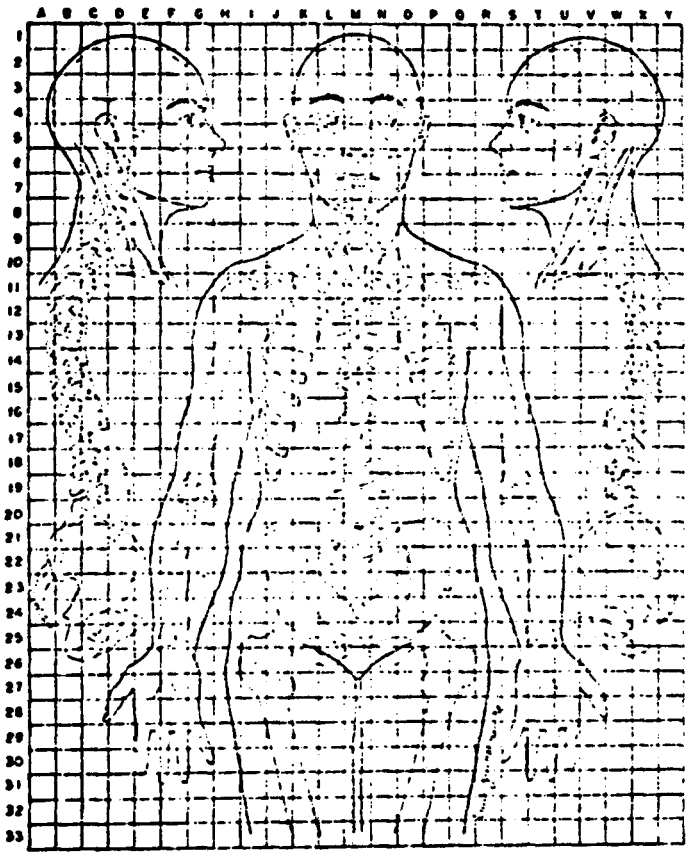
FUTURE PLANS FOR TREATMENT OF THIS PATIENT:

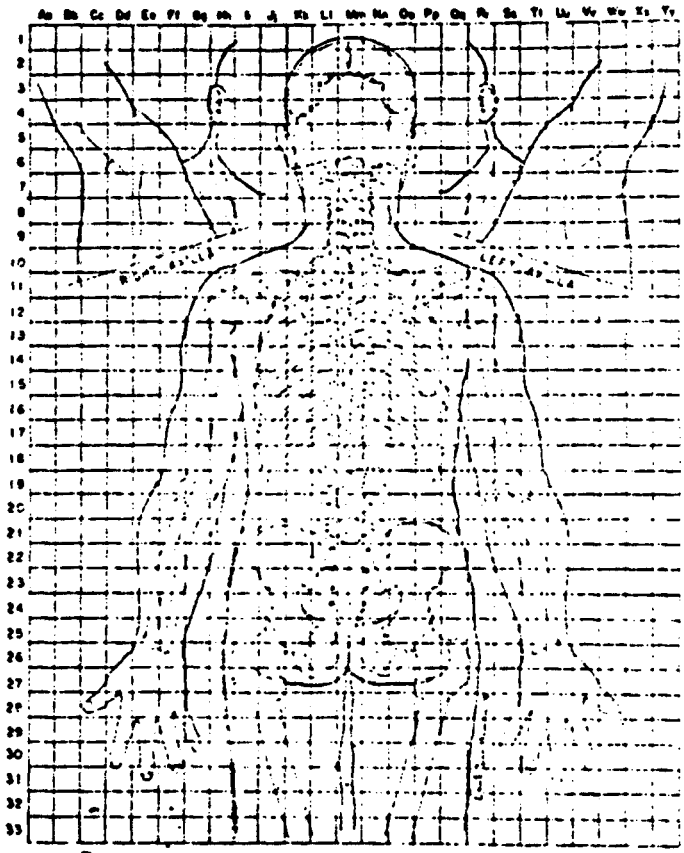
SIGNATURE _____

DATE _____

Tissue Involved – Example: lung, bone, nodes, etc.

Grid Coordinates – Horizontal and vertical grid coordinates for each measured lesion as determined from grid: For lesions not on grids – describe location under comments below.





Appendix C

UNIVERSITY OF CINCINNATI MEDICAL CENTER
FACULTY COMMITTEE ON RESEARCH
VOLUNTARY CONSENT STATEMENT

*I_____of_____
(Patient) (Normal subject)

being of the age of majority and of sound mind and body, voluntarily and without force or duress, consent to participate in a scientific investigation which is not only directed specifically to my own benefit, but also in consideration for the expected advancement of medical knowledge, which may result for the benefit of mankind.

I have been informed of and understand the nature, duration, and purpose of the study, the method and means by which it is to be conducted, the inconvenience and hazards to be expected, and the effects upon my health and person which may possibly come from participation in the experiment, as follows:

Purpose: To kill tumor cells and at the same time study the effects of radiation on blood and urine.

Procedure: Radiation of the whole body.

Risks: Radiation treatment employed is used to kill tumor cells but at the same time other, normal, cells of your body will be affected. The only cells affected which would cause any risk to you are those cells in your bone marrow. The bone marrow is a "blood factory" where white cells that fight infection, the platelets which help blood clot, and the red cells which carry oxygen to your tissues are made. The bone marrow's ability to make these cells will be decreased for four or five weeks after you receive your radiation. If you receive a dose of radiation of 200 rads or more, which your doctor will tell you, your blood counts will fall to levels where infection or bleeding could be a problem. The bleeding can be treated by transfusion of red cells and platelets and the infection by antibiotics. In addition, we prevent such low blood counts with the use of a bone marrow transplant which will be discussed with you in a separate voluntary consent statement. If your radiation dose is only given to part of the body there is no risk of danger or unusually low blood counts.

I understand that I may, at any time during the course of the experiment, revoke my consent, in writing, and withdraw from the experiment.

I acknowledge that no guarantee or assurance has been made to me as to the results that may be obtained, and I hereby waive any and all claims for liability, except for negligence, on the part of the medical personnel involved, the University of Cincinnati its Hospital and its Medical School, which otherwise might have inured to me or my heirs, as a result of this medical procedure.

I certify that I have read and am competent to understand this consent and that the explanation listed above was, in fact, made.

Volunteer_____Date_____

Investigator_____Date_____

Witness (1)_____Date_____

* Incase of subject under age, the parent or guardian should be the responsible party and should sign on his behalf.

NOTE: Copy to Patient/Normal subject, Research File and Patient's Chart.

UNIVERSITY OF CINCINNATI MEDICAL CENTER
FACULTY COMMITTEE ON RESEARCH
VOLUNTARY CONSENT STATEMENT

*I_____of_____
(Patient) (Normal subject)

being of the age of majority and of sound mind and body, voluntarily and without force or duress, consent to participate in a scientific investigation which is not only directed specifically to my own benefit, but also in consideration for the expected advancement of medical knowledge, which may result for the benefit of mankind.

I have been informed of and understand the nature, duration, and purpose of the study, the method and means by which it is to be conducted, the inconveniences and hazards to be expected, and the effects upon my health as follows:

Purpose: To prevent low blood counts following radiation of your body.

Procedure: Bone marrow transplantation.

Risks: You will be put to sleep in the operating room while approximately one pint of bone marrow is removed by needles from your pelvic bones and breast bone. No operation is performed - there is no cutting. The procedure would be painful if you were not put to sleep at this time. There is almost no risk in general anesthesia. After you awaken, your lower back and chest may be somewhat sore and will be treated with pain killers if you so desire. You will then receive your radiation treatment while lying on a stretcher and be taken back to your room. At this time, your bone marrow will be given back to you through a vein just as any blood transfusion would. The risk of receiving your own blood is zero. In the bone marrow there are many globules of fat and tiny pieces of bone all of which are filtered out of the bone marrow material which you will receive before it enters your body.

I understand that I may, at any time during the course of the experiment, revoke my consent, in writing, and withdraw from the experiment.

I acknowledge that no guarantee or assurance has been made to me as to the results that may be obtained, and I hereby waive any and all claims for liability, except for negligence, on the part of the medical personnel involved, the University of Cincinnati, its Hospital and its Medical School, which otherwise might have inured to me or my heirs, as a result of the medical procedure.

I certify that I have read and am competent to understand this consent and that the explanation listed above was, in fact, made.

Volunteer_____ Date_____

Investigator_____ Date_____

Witness (1)_____ Date_____

* Incase of subject under age, the parent or guardian should be the responsible party and should sign on his behalf.

NOTE: Copy to Patient/Normal subject, Research File and Patient's Chart.