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PROGRESS REPORT ON HEAVY PARTICLE CLINICAL RADIOTHERAPY
TRIAL AT LAWRENCE BERKELEY LABORATORY JULY 1975 - JULY 1979

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LAWRENCE BERKELEY LABORATORY JULY 1975 - JULY 1979

» Joseph R. Castro, M.D.

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PROGRESS REPORT ON HEAVY PARTICLE CLINICAL RADIOTHERAPY TRIAL AT
LAWRENCE BERKELEY LABORATORY JULY 1975 - JULY 1979

BACKGROUND

The University of California Lawrence Berkeley Laboratory has a long history of interest in physics applied to biology and medicine dating back to the early clinical trials of neutron radiotherapy conducted by Stone and Lawrence. Charged particle irradiation of pituitary diseases began in 1955 with protons and deuterons later followed by plateau helium ion irradiation. Over the past 25 years, approximately 1000 patients have been so irradiated.

Beginning in 1975, the National Cancer Institute has supported pre-therapeutic biophysics and radiobiology studies directed by Doctor Cornelius A. Tobias (NIH-NCI CA15184) to prepare for a clinical trial of helium and eventually heavier charged particles in the irradiation of human cancers. Although a few patients had been irradiated with helium ions for metastatic tumors during the previous decade, a systematic clinical trial of heavy charged particle radiotherapy began in mid 1975 with Department of Energy support, augmented in 1976 by NCI support for the clinical trials (NIH-NCI CA19138). The current grant project period extends through June 30, 1982.

The principal core staff associated with the clinical radiotherapy project at LBL includes:

J. R. Castro	
J. M. Quivey	Radiotherapy

C. A. Tobias	
J. T. Lyman	Biophysics
S. Curtis	

G. T. Y. Chen	
J. T. Lyman	Radiological Physics

E. L. Alpen, Director	
Donner Laboratory	
E. J. Ainsworth	
E. Blakeley	Radiobiology
F. Ngo	
S. Curtis	

S. Pitluck
R. P. Singh

Computer Program and
Management

R. E. Walton

Chief Technologist

T. C. Peters

Program Coordinator

A number of physicians, biologists, physicists and other interested individuals in the community have acted as advisors in the development of the clinical trial under the aegis of an informal organization entitled the Bay Area Heavy Ion Association. Lawrence Berkeley Laboratory is also a special member of the Radiation Therapy Oncology Group and the Northern California Oncology Group in order to obtain assistance in protocol design, statistical services, quality control, data collection and control patient irradiation. Through an intergroup agreement, the NCOG provides referral of patients from within its geographical area and the Radiation Therapy Oncology Group will provide a means of entry for patients living in the remainder of the United States. Clinical protocols have been drawn up for irradiation of the following tumor sites:

1. Localized unresectable Carcinoma of the Pancreas (randomized)
2. Localized Carcinoma of the Esophagus (nonrandomized)
3. Advanced Carcinoma of the Uterine Cervix (randomized)
4. Localized Choroidal Melanoma (nonrandomized)
5. Phase I - Phase II radiation of miscellaneous locally advanced tumors (nonrandomized)
6. Irradiation of Metastatic Skin and Subcutaneous Nodules (nonrandomized)

The above mentioned protocols are currently employing helium ion irradiation produced at the 184-inch synchrocyclotron, with exception of the Phase I - Phase II miscellaneous sites and the skin/subcutaneous nodule studies which are conducted with heavier particles, specifically carbon, neon and argon ions produced at the Bevalac.

The 184-inch cyclotron is available virtually 52 weeks a year for biological and medical applications. With NCI support, approximately 800 hours of clinical beam time are available which should permit irradiation of approximately 100 patients per year with helium ions.

At the Bevalac, the DOE provides one-third of the available beam time for the biological and medical applications. The beam is available approximately 8 months of the year during which time radiotherapy is scheduled 4 days per week with approximately 5 hours per day available for patient irradiation. Providing that beam availability at the Bevalac can be made as reliable as at the 184-inch cyclotron, this should permit irradiation of approximately 75 patients per year with heavier particles such as carbon, neon or argon. Thus, present plans call for radiation of 200 patients per year with charged particles. The Bevalac is scheduled for a 6 month shut down in June 1981 for replacement of the accelerator liner. We hope to complete the Phase I-II pilot studies with heavy ions prior to this shut down in preparation for later Phase III trials.

In building 55, located approximately 100 meters from the Bevalac irradiation area, clinical facilities have been made available at Lawrence Berkeley Laboratory through DOE and NCI support. In addition to patient examination facilities, diagnostic x-ray simulation, CT scanning suite, offices and treatment planning computer facilities are available. A CT scanner provided through NCI support is scheduled to be installed in early 1980, which will provide the capability to scan the patients in both supine and upright positions. Since the particle beams are fixed horizontal beams, approximately 85 per cent of the patients are treated in the upright position, either seated or standing.

Isocentric, rotating patient positioners which allow patients to be treated in either the horizontal or upright position with precise daily reproducibility to within ± 2 mm are available at both accelerators. Appropriate patient support devices are available for patient immobilization and to provide a framework for compensating bolus's.

RADIOTHERAPY AND PHYSICS TREATMENT PLANNING

Under the leadership of G. T. Y. Chen, J. T. Lyman, R. P. Singh, and S. Pitluck, a computerized treatment planning system has been developed. All patients are scanned using community hospital CT scanners until the LBL scanner is installed (1980). A range shortening algorithm is utilized based on water equivalent range to convert CT numbers to electron densities. Dose distributions are then calculated on a pixel-by-pixel basis with appropriate corrections for bone and gaseous densities in the particle beam path. These dose distributions are superimposed on a gray scale CT scan display and are produced for multiple CT slice levels through the target volume. Dose distributions can be produced for any of the charged particles in use and for both the physical dose distribution in particle rads and the biologically corrected dose distributions in megavoltage photon rad equivalents (CoRE).

The equivalent rad dose distributions are based on a model developed by Doctor John Lyman, to provide equal cell killing under the spread out Bragg peak as determined by several cultured cell lines irradiated *in vitro*, notably the human kidney T1, V79 cell lines. This model is based on survival expected at the clinically utilized dose fraction size of approximately 200 photon rad equivalents per treatment. Spiral brass ridge filters are designed and fabricated to produce this level of survival under various spread out Bragg peaks ranging from 4 to 14 cm in size. Verification of equal cell killing under the Bragg peak for different particles has been obtained by E. Blakely and C. Tobias at LBL using T1 cells and by M. Raju of Los Alamos Scientific Laboratory using V79 cells in gell. This model is constantly under revision and will be changed as needed for future use. It has the advantage of providing a consistent approach to clinical irradiation with any of the charged particles produced at LBL and providing a common terminology for intercomparison with current megavoltage irradiation. To date, it has worked well with patients irradiated with helium ions over the past four years and with the initial patients treated with heavier particles such as carbon, and neon ions.

Treatment planning investigations have also included an evaluation of techniques for compensation of inhomogeneities in the beam path. For the present, relatively simple wax bolus compensating devices have been utilized in order to stop the beam at the desired depth. With the availability of CT scanning in the upright position in early 1980, more precise attempts at compensation will be made, keyed to CT scanning with the patient in treatment position. An investigation of respiratory effects has also been started in order to understand the magnitude of changes in dose distribution occurring during respiration.

Verification of the dose distribution has been made by film stack studies as well as in vivo diode measurements done where possible such as in patients with esophageal cancer irradiation.

Studies comparing irradiation with the static fixed fields with three-dimensional beam scanning techniques are also under way in preparation for later development of beam scanning at the Bevalac. Development of graphics for display of three-dimensional isodose distributions obtained by multiple CT slices at one centimeter intervals through the target volume are also under development.

A continuing programming development for the computerized treatment planning system is in progress in order to provide a faster, interactive treatment planning program.

BIOLOGY and BIOPHYSICS

Under the direction of C. A. Tobias with E. Blakely, F. Ngo, S. Curtis, E. J. Ainsworth, E. Alpen, and others, a large variety of studies into the basic biology of charged particle irradiation has been under way since 1974. These studies are divided into the areas of:

1. molecular biology,
2. normal tissue tolerance studies,
3. tumor biology studies,
4. biophysics beam development and dosimetry.

Much of this data has been reported in various journals and in LBL 5610 as well as in progress reports on the pretherapeutic study supported by NIH-NCI CA 15184. Sufficient data has been made available to begin clinical irradiation, initially with helium particles (1975) and progressing to carbon, neon, and argon ions (1977). This has included, but not been limited to: RBEs for various tissues and heavy particles; OER studies for various particles and beam configurations; studies of the treatment beam setup in order to evaluate ridge filter design and cell killing under the spread out Bragg peak; studies of normal tissue effects notably on skin, brain, spinal cord, bone marrow and intestine; studies on repair both in the broadened peak and in the plateau and beginning studies of late effects and carcinogenesis. Although this is only a partial list of biological studies, a strong core support program continues augmented

by outside users who have also provided valuable biologic data preparatory to the clinical trial.

CLINICAL STUDIES

As of July 31, 1979, 157 patients have been entered in the charged particle clinical trial at LBL. Of these, 20 patients have had all or a portion of their treatment with heavy particles including carbon, neon, or argon. The remaining 134 patients have been treated with helium ion radiotherapy alone or helium ions given in conjunction with photon therapy. When helium ions are used on conjunction with photons, the helium is usually given as a boost treatment following the photon irradiation. The total patient accrual by year is as follows:

1975 - 3
1976 - 11
1977 - 32
1978 - 65
1979 - 46 (as of 30 July 1979)

The total distribution of patients by anatomical site is:

<u>Intracranial</u>	17
Malignant Glioma	12
Other	5
<u>Thoracic</u>	21
Ca Esophagus	19
Other	2
<u>Abdomen</u>	70
Ca Pancreas	56
Ca Stomach	7
Ca Biliary Tract	7
<u>Retroperitoneal</u>	8
Para-aortic Lymph Nodes	5
Other	3
<u>Pelvis</u>	15
<u>Head and Neck</u>	14
<u>Choroidal Melanoma</u>	8
<u>Skin & Lung Nodule RBE Studies</u>	4

Of the 20 patients irradiated at the Bevalac, the following tumor sites have been irradiated:

<u>Site</u>	<u>Carbon</u>	<u>Neon</u>	<u>Argon</u>	<u>Total</u>
Ca Pancreas (Boost)	4	1		5
Brain Met/Malignant Glioma (Boost)	6			6
Advanced Head & Neck (Boost)	2	2		4
Colorectal Recurrence	1			1
Skin & Lung RBE Studies	2	1	1	4

The distribution of these patients by protocol is as follows:

Phase I - Phase II - Helium	116	(including pilot esophagus, pancreas, & stomach patients)
Phase I - Phase II - Carbon, Neon, Argon	20	(including RBE studies on skin & subcutaneous nodules-4 patients)
Total	136	

Prospective Protocols

Nonrandomized Choroidal Melanoma	NCOG/RTOG	8	
Nonrandomized Carcinoma of the Esophagus	NCOG/RTOG	7	
Randomized Carcinoma of the Pancreas	NCOG/RTOG	6 study	5 control
Randomized Carcinoma of the Uterine Cervix	NCOG/RTOG	0	
Total		21	

Protocols Under Development

Localized, unresectable gastric carcinoma
Malignant glioma of the brain
Inoperable or recurrent carcinoma of the rectum
Soft tissue sarcoma

The primary objectives of the clinical radiotherapy program are:

1. to evaluate the potential of improved dose localization particularly as exemplified by helium ion irradiation where little, if any, biologic advantage is expected, and
2. to evaluate the combined potential of improved dose localization and increased biologic effect available with heavier ions such as carbon, neon, and argon.

Because of the availability of the helium ion beam and the patient treatment facility utilized for many years for pituitary irradiation, it was possible to make modifications rapidly to provide for large field, fractionated, Bragg peak irradiation at the 184-inch cyclotron with the helium ion beam. This allowed the opportunity to gain experience with charged particle irradiation treatment techniques, patient immobilization techniques, treatment planning and dosimetry studies including the utilization of CT scanning for tumor localization and charged particle dose distributions as well as beginning studies in compensating for tissue inhomogeneities in the beam path. These treatment techniques have been directly transferable to the Bevalac facility where a similar patient positioner has been installed for human irradiation with heavier particles.

The general clinical trial design has been to begin with Phase I - Phase II studies and as rapidly as possible proceed to prospective Phase III trials. For the Phase I-II studies both with helium and now with heavier particles, we have sought patients with:

1. multiple skin and subcutaneous metastatic nodules for evaluation of skin RBE data, and
2. patients with locally advanced and/or unresectable tumors unlikely to be effectively treated by any conventional modality.

In order to facilitate intercomparison with megavoltage irradiation techniques, a conventional dose fractionation scheme has been adopted which allows the delivering of total equivalent doses in the range of 6000-7000 rads given at 200 rads equivalent per fraction, 4 fractions per week. A few exceptions to this dose specification scheme have been patients in which pulmonary nodules, subcutaneous or skin nodules have been irradiated with larger fraction sizes ranging up to 400 rads per fraction in order to obtain clinical RBE studies in 8 to 10 fractions of heavy particles.

SKIN AND RELATIVE BIOLOGIC EFFECT STUDIES

Careful observation of skin included in helium ion radiotherapy portals has revealed reactions ranging from mild erythema to dry desquamating epidermitis with patchy areas of moist epidermitis. The extent of the skin reaction depends on the dose to the skin and the location of the skin in the beam path, i.e., whether in the plateau or spread out Bragg peak. Acute helium radiotherapy reactions have been of the same severity as from similar doses of megavoltage photon radiations, utilizing an RBE of 1.2 relative to Cobalt⁶⁰ irradiation for the proximal portion of the spread out Bragg peak. Observations of skin and subcutaneous changes up to a period of 36 months has shown a similar correlation without any evidence of an increase in RBE for chronic or late skin or subcutaneous effects to date.

To estimate a RBE for carbon ion radiotherapy of the skin, a patient with Kaposi's sarcoma was irradiated to multiple fields in the lower leg utilizing graded doses of 1000, 1400, and 1700 rads given in 10 fractions and comparing the skin response of similar fields to electron beam irradiation of 2500, 3000, and 3500 rads in 10 fractions. The skin reactions were scored clinically by two independent observers and analyzed graphically in order to obtain a clinical carbon RBE for skin irradiation. The calculated RBE was 2.7 for physical doses of 300-350 rads/fraction of 10 MeV electrons and 110-130 rads/fraction of 308 MeV/u carbon ions, at approximately the mid-distal portion of the spread out Bragg peak.

One patient with metastatic nodules in both lungs from a primary carcinoma of the uterine cervix was irradiated with 8 MeV x-ray to the right lung nodules and with 400 MeV/u carbon ions to the left lung nodules. The x-ray dose was 4000 rads in 8 fractions and the carbon ion dose was 1480 rads in 8 fractions. Both treatment courses lasted 11 days. Although skin reactions could not be compared because of a coincident allergic dermatitis which required the administration of steroids, comparison of tumor regression gave an estimated RBE for carbon ions relative to 8 MeV photons of approximately 2.3 to 2.5.

One patient with subcutaneous metastases from gastric leiomyosarcoma was irradiated with 400 MeV/u neon ions while an adjacent field was irradiated with 15 MeV electrons. The applied dose was 3200 rads in 8 fractions with 15 MeV electrons and 1600 rads in 8 fractions with neon ions.

Acute skin reactions were similar in both fields suggesting a RBE of ~ 3.4 for neon skin irradiation.

CARCINOMA OF THE PANCREAS

The largest patient experience with helium ion radiotherapy at Lawrence Berkeley Laboratory has been in patients with locally advanced, unresectable carcinoma of the pancreas. Since 1975, 41 patients have completed irradiation, with a followup period of 6-42 months. Of these, 5 have no evidence of disease (Table I).

Most of these patients have been irradiated solely with helium ions delivering a total dose of 5000-6400 rads equivalent at 200 rads/fraction, 4 fractions per week over a period of 7-8 weeks. A few have had treatment (4000-4500 rads) with photons followed by helium boost therapy (1500-2000 rads). Multiport treatment plans have been utilized generally employing anterior and either one or two lateral fields. Target volumes have been designated according to tumor localization by CT scan in the supine position and barium radiographs taken in the upright position. Only a few patients have had surgical demarcation of the tumor volume by placement of metal clips. Among the earlier patients a few were accepted lacking histologic proof or with tumor extension beyond immediate peri-pancreatic lymph nodes, i.e., nodes in the porta hepatis or in the para-aortic regions. In addition, a few patients with limited metastatic nodules in the liver or omentum were irradiated. Experience has shown that such patients progress rapidly and are rarely able to complete the course of radiotherapy, much less have any significant palliation.

For patients with limited localized disease, the possibility of significant palliation and/or prolonged remission of disease is heightened, especially for patients with primary lesions in the head of the pancreas. Tolerance to particle radiotherapy has been good, with minimal morbidity usually consisting of anorexia, occasional nausea and vomiting, occasional pain possibly secondary to radiation gastritis and/or duodenitis and minimal erythematous skin reactions. Subacute and chronic effects have included significant upper gastrointestinal bleeding in 4 patients attributable to a significant portion of gastric antrum and duodenum being included in the high dose volume. Reduction of the target volume for the final 1000 rads of the 6000 rads total dose has appeared to ameliorate this problem. However, significant escalation of the total dose seems unlikely in view of the unavoidable inclusion of some portions of the stomach and duodenum in the target volume in order to encompass the pancreatic tumor.

A number of patients have been noted to have pancreatic deficiency requiring replacement of pancreatic enzymes; this appears to be attributable to the primary tumor since the pancreatic deficiency appears prior to the irradiation. Two patients have also shown signs and symptoms of mild diabetes mellitus developing 12 months post radiation and may be attributable to the radiotherapy.

The results in the pilot series of patients irradiated with helium ions have shown that the patients can tolerate the proposed treatment with minimal side effects and that reproducibility of treatment is possible. Local control appears to have been achieved in a significant number of patients. A controlled prospective study has been started to compare the results of irradiation of pancreatic cancer by helium ions with megavoltage irradiation.

CARCINOMA OF THE ESOPHAGUS

Eleven patients with localized carcinoma of the esophagus have completed irradiation with helium ions or mixtures of photons and helium ions to a dose of 6200-7000 rads given in 7-9 weeks at 200 rads/fraction, 4 fractions/week. In this small series of patients, techniques have been developed for appropriate treatment planning compensating for tissue inhomogeneities in the thorax. Four-field port arrangements have been utilized, starting with anterior-posterior fields encompassing most of the length of the esophagus and reducing the volume at 4500-5000 rads to complete the treatment through lateral or oblique portals. Although only 5 patients have had local control to date with short followup (2-6 months) the study will continue until at least 20 patients have been studied with helium ions before proceeding to a heavier particle such as carbon or neon ions.

CENTRAL NERVOUS SYSTEM

Seventeen patients with a variety of intracranial tumors have been irradiated including some with malignant glioma of the brain (12 patients), inoperable schwannoma at the base of the brain (1 patient), recurrent pinealoma (1 patient), clivus chordoma (1 patient), and metastatic brain lesions (2 patients). Of the initial 12 patients irradiated with Grade III-IV astrocytoma, 4 received carbon ions as boost therapy, 7 received helium ion irradiation as a boost and 1 was irradiated with helium ions only. Total doses ranged from 4500-6600 rads. Six patients are alive and well from 2-45 months post treatment.

HEAD AND NECK

We have had the opportunity to irradiate a small group of 11 patients with advanced neoplasms in the head and neck area, including tumors of the paranasal sinuses and advanced lesions of the tongue, floor of mouth, and pharynx. We have been able to develop particle techniques for irradiating the primary lesion as well as the lymphatic drainage in the neck, using appropriate range shortening techniques in order to minimize irradiation to the spinal cord and salivary glands. Of the initial 8 patients with primary lesions, 3 have had local control from 7-12 months or until death.

CHOROIDAL MELANOMA

A small group of 8 patients with localized ocular melanoma has been irradiated using the helium beam. The lesions have had a maximum diameter of 12 mm and have been located sufficiently far from the optic nerve or macula so as to minimize the chance of blindness secondary to the irradiation. A 1.4 cm spread out Bragg peak is utilized and the beam appropriately directed to cover the extent of the lesion as marked by surgically placed tantalum rings and ocular ultrasound examination, with a margin of 1 mm around the visible lesion. Although followup is short (1-14 months), all patients irradiated to date appear to have lesions under control. The dose has been 5585 helium rads (7000 rads equivalent) given in 5 fractions over 7-8 days.

FUTURE PLANS

Continue prospective clinical trials with helium ions.

Continue Phase I-II studies with carbon, neon, and argon ions.

Develop prospective clinical protocols for heavy particles.

Complete clinical facility with installation of vertical CT scanner.

Improve beam delivery techniques with development of 3-dimensional beam scanning.

Develop autoradioactive beam (carbon, neon) for target localization.

TABLE I

CARCINOMA OF THE PANCREAS

<u>TOTAL NUMBER OF PATIENTS</u>	41
NO BIOPSY	1
METASTATIC DISEASE (LIVER) &/OR INCOMPLETE TREATMENT	6
<u>EVALUABLE PATIENTS</u>	
ALIVE, NO EVIDENCE OF CANCER	5/34 (7,10,12,14,42 mos)
EXPIRED, INTERCURRENT DISEASE, NO EVIDENCE OF CANCER	2/34 (6,18)
LOCAL CONTROL, DM (LIVER)	3/34 (7,11,36)
PERSISTENT DISEASE $\bar{c}/\bar{s}$ DM (LIVER)	24/34 (2-12 mos)

MEAN SURVIVAL	IN 10 PATIENTS WITH CONTROL	
	<u>IN IRRADIATED AREA</u>	16 mos

<u>MEAN SURVIVAL</u>	34 PATIENTS	9 mos
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COMPLICATIONS: UPPER GI BLEEDING 4 PATIENTS