LOS ALAMOS SCIENTIFIC LABORATORY
UNIVERSITY OF CALIFORNIA
LOS ALAMOS, NEW MEXICO 87545

OFFICE MEMORANDUM

712685

: Donald M. Kerr, D-0 5/16/80

DATE: May 15, 1980

FROM : M. M. Kligerman, ADRT Klig (SW)

SUBJECT : Report to DOE

SYMBOL : ADRT

MAIL STOP: 815

MES 200

Some time ago, you requested a report on each of LASL's large research programs to submit to John Deutsch's successors at DOE. Attached is a modified version of the progress report we recently submitted to the National Cancer Institute. Since we analyze our patient data in six-month increments (as one needs at least that long to see significant changes), I felt this was the best data we could provide at this time. Please let me know if you have any questions about the attached.

MMK:mm

Attachment

REPOSITORY LANL/RC
COLLECTION Dir Ofc Files
BOX No. C-4, D-163
FOLDER MES 200 5/80-9/80

FILE BARCODE
00132842

COPIED FOR
HSPT

00132842.001

1085028

5/13/80

CLINICAL AND BIOLOGICAL STUDIES OF PION RADIOTHERAPY AT LOS ALAMOS

A. Objectives

The primary objective of this program is to conduct clinical, physical, and biological studies necessary to evaluate the efficacy, potential benefit, and role of negative pi mesons (pions) in the management of all types and stages of solid tumors not well managed by current treatment methods or combinations thereof. These studies are being conducted jointly by the University of New Mexico Cancer Research and Treatment Center and the Los Alamos Scientific Laboratory, with funding provided under a grant from the National Cancer Institute (NCI) to UNM (M. M. Kligerman, Principal Investigator), and funds for channel operations and maintenance from the U.S. Department of Energy.

Objectives for the current year were as follows:

1. Clinical Investigations. To begin Phase III studies to establish the response of primary tumors with or without limited regional spread, and of surrounding normal structures, to curative doses of pions as compared to x-rays; to continue Phase I-II studies leading to Phase III studies for additional tumor sites.

2. Physics. To continue development of the biomedical pion channel at the Los Alamos Meson Physics Facility (LAMPF), with associated hardware and software; to enhance and refine the physical understanding of pion-beam characteristics; to further develop dosimetry and calculational techniques necessary to achieve accurate dose distribution in a treatment volume of arbitrary size and location, with minimum damage to surrounding normal tissue.

3. Biology. To provide more definitive understanding of the biologic actions of pions through in-vivo and in-vitro studies of the kinetic response of normal and tumor tissues to pion, as compared to x-irradiation.

4. Administration. To provide adequate administrative and logistics support so that Phase III studies can be conducted as efficiently and as cost-effectively as possible.

B. Progress Report

1. Clinical Investigations

Phase III clinical trials were begun under protocols approved by the Radiation Therapy Oncology Group (RTOG) and the NCI Clinical Investigations Branch. They include prospective randomized comparisons of pion and photon irradiation of advanced squamous-cell carcinomas of the head and neck in certain sites (oral cavity, hypopharynx, oropharynx,

LE BARCODE
00132843

COPIED FOR
HSPT
00132843.001

1085029

and nasopharynx), inoperable or locally recurrent carcinomas of the rectum or rectosigmoid, and T3/T4 transitional-cell carcinomas of the bladder. Patient treatment under these protocols was begun in November 1979.

Phase I-II studies were continued with patients having tumors in all sites originally considered by the Committee for Human Trials of Pion Radiotherapy, UNM/LASL, to be most likely to benefit from pion therapy. The majority of patients now being accessed for Phase I-II trials have advanced carcinomas of the prostate or uterine cervix or glioblastomas and high-grade astrocytomas. An amendment to the Phase I-II protocols, approved in July 1979, allows pion irradiation to be used as boost therapy with conventional irradiation.

Phase III protocols on prostatic carcinomas and gliomas are being revised for presentation to RTOG. Cooperative ties and referral patterns are being developed with major radiotherapy centers with high caseloads in the sites under the Phase III trials to assure uniformity of treatment results on Phase III patients randomized to conventional therapy.

Because patient safety has been a primary concern in the pion program, radiation dosages to patients were initially low and were increased as experience with pion effects became available. In 1976-77, the average maximum tumor dose was 2641 rads; in 1978, 3375 rads; and 1979 (through August), 4273 rads. Average treatment volume has increased by about 50 percent from 1976 to 1979. Dose fractionation schedules have been established for each disease site.

Between November 1976 and August 1979, 108 patients--68 males and 40 females--were treated: 99 with curative intent, 72 by pions alone and the rest with a combination of modalities. Complete or partial response of tumor tissue to maximum peak pion dose was as follows: at less than 2700 rads, 52 percent; at 2700-3800 rads, 70 percent; above 3800 rads, 74 percent. As might be expected, the rate of acute and chronic reactions rises with maximum peak dosage and average daily dose. Of the 72 patients treated with pions alone in this period, 39 survive (mean follow-up, 15.5 months), of whom 30 are free of disease (mean follow-up, 13.8 months). As a result of the work on dose and reaction, the maximum peak pion dosage for most sites and situations is considered to be at 4500 rads.

Diagnostic imaging capability has been improved in two significant ways. A pion-dedicated CT scanner has been installed at the Biomedical Facility in Los Alamos, and a diagnostic CT terminal will be installed in May 1980 at the CRTC in Albuquerque. The latter will improve the timeliness of consultation. Also at the CRTC, an Octoson computer-controlled eight-transducer ultrasound scanner has been installed. This scanner has high accuracy, resolution, and reproducibility; its data, when compared with CT scan results or those of other imaging techniques, can in certain situations permit a more accurate assessment of tumor volume and extent.

COPIED FOR
HSPT
00132843.002

1085030

Pathology studies are done routinely on biopsy specimens for all patients enrolled on the pion protocols, and on materials from surgical resections done on pion patients, though the number undergoing resection after pion treatment has been small. Postmortem examinations are done on as many expiring pion patients as possible with the aim of assessing the presence or absence of tumor and its viability, and of documenting the relationship of the tumor to the treatment volume on three axes. Tissues superficial to the treated area--skin, subcutaneous tissue, muscle, and intestine--are studied, and whenever possible, tissues below the pion stopping depth, especially the spinal cord, are examined for possible evidence of injury. Unfortunately, postmortem reports are completed or pending for only 15 of 52 patients treated between November 1976 and August 1979 who subsequently expired. Of the 15, 5 were autopsies performed at CRTC, 8 were autopsies performed elsewhere with report and/or slides submitted to CRTC, and two were en-bloc specimens sent to CRTC for workup and report. Because the sample is small and the pathology various, no consistent pattern of findings has yet emerged.

2. Physics

From June 1978 to December 1979, the pion biomedical program received 5145 hours (30.6 weeks) of beam time which was used for patient treatments, radiobiology studies, beam development and characterization, and detector research. This maximally permits four patient treatment cycles of 7.5 weeks per year.

A new PDP-11/70 computer was installed for channel control, and the former channel-control computer, a PDP-11/45, was dedicated to treatment planning. Patient treatment codes were reconfigured for more efficient operation, and software was developed for a prototype dynamic treatment system. The treatment-planning code, PIPLAN, was improved through incorporation of a new, more realistic neutron-dose model and smoothed beam phase-space representations. The calculation time for a given number of rays has been decreased by more than a factor of 10 through optimization techniques. The catalog of broad beams for static treatments has been expanded to include fields up to an average of 18 x 18 cm at each of three channel momenta. Significantly better resolutions in time-of-flight identification of beam contaminants has been achieved; this information is needed for PIPLAN. Routine daily measurement and calculation of proton-beam parameters at the biomedical target are now possible, ensuring patient beam reproducibility.

Experimental research has included dosimetric and microdosimetric measurements on beams used in the radiobiology program. A simplified data-acquisition system has been developed for microdosimetry experiments, which can now be performed during beam-development periods. A definitive intercomparison of silicon-detector data and Rossi-chamber data, including Monte Carlo computer calculations, was completed. Two systems for *in-vivo* measurement of high LET were investigated: aluminum pellet activation and very small silicon detectors. In addition to measuring high-LET dose, the silicon detector, time-correlated with the range-shifter, can provide the water-equivalent thickness of the tissue in front of the detector in the patient.

COPIED FOR
HSPT

00132843.003

1085031

The first dynamic treatment with the prototype system was recently accomplished. Since the pion biomedical channel has a fixed, vertical radiation source, dynamic treatment must be achieved by moving the treatment couch through the beam in a series of steps. Currently, a beam sharply focused in one dimension is being used, and a beam focused in two dimensions is under development.

The patient immobilization and positioning (PIP) system developed at Los Alamos is being adapted for use with conventional isometric treatment machines. Frames that will permit Lightcast shells to be used on these machines are being developed and tested at CRTC in Albuquerque. The CRTC computer has been modified to accept data from the treatment-parameter monitoring system attached to the Clinac 18, and that system is now being tested. These activities should help to assure comparability of treatment results obtained from pion and conventional radiotherapy.

3. Biology

In-vitro studies with multicullular tumor spheroids (MTS) have been expanded, and investigations on late injury to normal tissue and tumors have continued. Experimental results for this reporting period can be summarized as follows:

a) Negative pions, but not positive pions, reduce the MTS growth-delay threshold. This indicates that the high-LET particles resulting from negative pion capture are critical in the observed effects of pions.

b) No difference in RBE could be detected either within or between the proximal, middle, and distal portions of 8, 11, and 14 cm (z) peaks.

c) Sulfhydryl drugs offered nearly as much protection against pions in a single-cell system as they did against x-rays. This suggests that the primary components of the beam are of a low-LET nature.

d) Pion-exposed solid tumors growing in vivo in mice showed a reduction in threshold for growth delay compared to x-rays.

e) Two-dose (24-hr) pion growth delay experiments showed less recovery than comparable x-ray studies.

f) The spinal cord continues to show higher RBEs (1.5-3.0) for pions than do the other normal tissues studied when 1 to 15 daily fractions are administered.

The shoulder-shift and threshold-reduction patterns for pion beams have been extensively confirmed. Analyses of in vivo tissues are continuing with only the spinal cord presenting cause for concern.

4. Administration

During the past year, the management of and logistic support for the pion program have been strengthened in a number of ways. LASL's

COPIED FOR
HSPT
00132843.004

1085032

naming of Dr. Kligerman as Program Manager for the pion biomedical program is resulting in better control over the work subcontracted by CRTC to LASL. Communication between the Los Alamos and Albuquerque offices has been greatly improved by a telephone-linked typing system and facsimile copier. New billing mechanisms are resulting in better collection rates. The addition of a clinical research management specialist in Los Alamos is resulting in better coordination of records and arrangements for patients, staff, and visitors.

The Biomedical Facility has been extensively modified by LASL to accommodate the new on-site CT scanner and PDP-11/70 channel-control computer, and to make more space available for treatment-related activities. Office and conference space lost in the modifications has been compensated by the addition of a modular building and a trailer situated near the Facility. Communication and safety systems were upgraded.

Three Phase III protocols were written, reformatted by RTOG, and approved by the NCI Clinical Investigations Branch. Two Phase I-II protocols implemented since 1976 were also reformatted by RTOG and submitted to the Clinical Investigations Branch for approval. A comprehensive data-collection system for Phase I-II patients has been implemented. Materials describing the Phase III program have been prepared and widely distributed to participating institutions to facilitate pion referrals.

C. Significance

A central dilemma in current cancer therapy is the inability to consistently control by any means locally advanced, primary lesions in a variety of sites. In comparison to conventional radiation therapy, pion radiation therapy offers the theoretical advantage of improved dose distribution: deposition of radiation in the region of a deep-seated tumor while sparing surrounding normal tissues. In addition, radiation in the high dose region resulting from pion star formation has the property of increased biological effectiveness per unit dose, further improving the distribution of radiation-induced injury toward the tumor site and away from sensitive normal structures.

The clinical usefulness of pion irradiation can be established only by the continuation of present trials and the addition of new Phase III trials for other sites showing promising preliminary results. LAMPF continues to be the only facility in the world capable of producing an adequate pion flux for treatment of clinically relevant volumes. Continued improvement in beam output and treatment technique, and the institution of Phase III trials for new sites such as brain and prostate, should permit a meaningful comparison to be made of the relative effectiveness of pion and conventional radiotherapy.

COPIED FOR
HSPT

00132843.005

1085033

D. Research Goals For Fiscal Year 81

1. Clinical Investigations

a. Complete preparation of a Phase III randomized protocol for Grade III-IV malignant gliomas and astrocytomas, submit the protocol to RTOG and NCI Clinical Investigations Branch for approval, begin accessing patients.

b. Complete pilot study on T3/T4 adenocarcinoma of prostate and on Stage III-A, III-B, and IV-A carcinoma of the cervix; if results suggest potential therapeutic gain, begin preparation of Phase III protocols.

c. Continue accessing and treating patients under Phase III protocols for head and neck, rectum or rectosigmoid, and bladder.

d. Continue to develop and strengthen cooperative ties and referral patterns with major radiotherapy centers to assure continued accession of appropriate patients and uniformity of treatment for Phase III control patients treated at those centers.

2. Physics

a. Upgrade computer system for improved interfacing and network-link communication; implement on-line graphics system for treatment planning; redesign scanner-control system for dosimetry.

b. Fabricate and install new range-shifter; construct new beam-profile monitor for conducting tuning studies at full beam intensity.

c. Complete calculations of late pion decays for all tunes of interest; develop new method for direct measurement of muons in the beam; develop new static beams for therapy as needed; continue development of beams for dynamic scanning; provide input data to PIPLAN and make measurements to check PIPLAN.

d. Complete development of minor hardware and software for multichannel electrometer data-acquisition system; develop range-shifter functions for each individual tune to account for differences in beam divergence; verify KERMA correction for transforming dose in tissue-equivalent plastic to dose in muscle.

e. Develop software and on-line data-acquisition systems to make silicon-detector and aluminum-activation dosimetry methods routinely applicable in clinical treatment; continue work with thermoluminescent detector to determine whether its high-temperature peak can measure high LET.

f. Remeasure and check high-LET distributions of all beam tunes used in therapy; improve LET unfolding algorithm by Monte Carlo techniques; incorporate revised total dose distributions and characterizations of pion stopping distributions into PIPLAN.

COPIED FOR
HSPT

00132843.006

1085034

g. Improve instrumentation for measuring high-energy gamma rays produced by pion capture and determine how this data can be used in routine treatment; test feasibility of using low-cost, one-dimensional Anger camera for positron detection; continue testing hardware for determination of detector configuration with optimal resolution; develop data-acquisition software.

h. Install in patient set-up room a pedestal with vertical, translational, and rotational motion to facilitate patient set-up.

i. Develop methods of calculating central-axis isodose distributions and calibration factors for each patient field.

j. Complete methods and techniques for calculating dose, range-shifter functions, and bolus design for dynamic treatments; achieve full capability to carry out dose calculations on the VAX computer; standardize the treatment-planning interface to the new on-site CT scanner; resolve the problem of crossing anatomy contour input to obtain nonambiguous interpretation; improve agreement between PIPLAN calculated dose distributions and measured dosimetry in water and Rando phantoms; design range-shifter functions that tailor the distal edge of the peak to the target volume during patient movement in dynamic treatments; implement PIPLAN into routine clinical use.

k. Develop treatment-planning methods for dynamic treatments, first for fan beams, then for spot beams focused in two dimensions.

l. Provide clinical biomedical physics support for all control patients randomized to conventional therapy; implement the patient immobilization and positioning system developed at Los Alamos on the conventional radiotherapy equipment at the CRTC in Albuquerque; continue development of a treatment-monitoring system to record patient-treatment parameters on the CRTC computer.

3. Biology

a. Complete estimates of pion RBEs for colon, kidney, and skin.

b. Refine the drop in dose in the z dimension for all patient tunes through studies with multicellular tumor spheroids.

c. Explore the nature of the elevated RBE for spinal cord.

d. Attempt to simulate pion peaks by using combinations of neutrons and x-rays.

4, Administration

a. Complete development and implementation of Phase III protocol for brain tumors.

b. Complete development and implementation of data forms for all Phase III protocols.

COPIED FOR
HSPT

1085035

00132843.007

c. Verify input data for computerized analysis of Phase I-II cases, and implement routine generation of computerized reports.

d. Complete development and dissemination of Phase III protocol procedure manual.

e. Implement systems for capture of patient encounter statistics at the Pion Biomedical Facility.

f. Refine and improve communications with radiation oncologists and physicists at participating institutions to facilitate quality control for patients assigned to conventional treatment arms of Phase III pion protocols.

Submitted by,

M. Kligerman

Morton M. Kligerman, ADRT
May 13, 1980

COPIED FOR
HSPT

00132643.008

1085036