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H. MIKKEL KELLY, Administrator

TO: Members, Committee on Human Trials of Pion Radiotherapy, UNM/LASL
FROM: M. M. Kligerman, M.D. *MMK*
DATE: October 22, 1976
SUBJECT: Minutes, Vancouver Meeting

At long last, we've completed the minutes of the Vancouver meeting and the human radiobiology protocols reviewed at that meeting. I apologize that this has taken so long, but we have had two patient treatment cycles at LAMPF, three site visits from the NCI, and various other distractions since that time. I presented a paper at the PART II conference in Berkeley in September describing our most recent results with skin tests, which many of you heard. If any of you would like a copy of that paper, please let me know.

Very soon, we'll begin issuing the revised copies of those Phase III protocols which were addressed by our Committee in May. I'd like to address the remaining ones at our next meeting, and I'll be in touch with you in the near future with some suggested dates. If you have any questions about any of the attached material, please let me know.

MMK:ft
attachments

DISTRIBUTION:

John E. Antoine, M.D.
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Lt. Col. Gary W. West, M.D.
John M. Yuhas, Ph.D.

cc: James Hanley, Ph.D.
Simon Kramer, M.D., RTOG
Thomas King, Ph.D., NCI
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THE COMMITTEE ON HUMAN TRIALS OF
PION RADIATION THERAPY, UNM/LASL

Bayshore Inn
Vancouver, British Columbia
May 10-11, 1976

Present:

Morton M. Kligerman, M.D. (Chairman)
Cancer Research and Treatment Center (CRTC)
University of New Mexico
Albuquerque, New Mexico

John Antoine, M.D.
Chief, Diagnostic Oncologic Imaging, CRTC

Frederick W. George, III, M.D.
University of Southern California
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Malcolm Bagshaw, M.D.
Stanford University Medical Center
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Robert Stewart, M.D.
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F. Bing Johnson, M.D.
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Madison, Wisconsin

Joseph Castro, M.D.
Department of Radiotherapy
Mount Zion Hospital
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Lt. Col. Gary W. West, M.D.
Department of Radiation Therapy
Wilford Hall USAF Medical Center
Lackland Air Force Base, Texas

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Northeast Ohio Conjoint Radiation
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Ralph Scott, M.D.
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Seymour H. Levitt, M.D.
Department of Therapeutic Radiology
University of Minnesota Hospitals
Minneapolis, Minnesota

John M. Yuhas, Ph.D.
Biology Laboratories, CRTC

Carlos Perez, M.D.
School of Medicine
Edward Mallinckrodt Institute
of Radiology
St. Louis, Missouri

Guests:

Omar Salazar, M.D., representing
Philip Rubin, M.D.
Strong Memorial Hospital
Rochester, New York

C. Aristazabal, M.D., representing
Max Boone, M.D.
Department of Radiology
University of Arizona Medical School
Tucson, Arizona

Lloyd Skarsgaard, Ph.D., representing
J.M.W. Gibson, M.D.
TRIUMPH/British Columbia
Cancer Institute
Vancouver, B.C., Canada

Alfred R. Smith, Ph.D., representing
Charles Kelsey, Ph.D., CRTC

Lawrence Davis, M.D., representing
Simon Kramer, M.D. (RTOG)

James Hanley, Ph.D.
Statistica Consultant, RTOG

Luther Brady, M.D., representing
American Radium Society

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Biomedical Studies at LAMPF

Dr. Kligerman announced that the biomedical channel at LAMPF was again operational as of the end of March 1976, and that the physicists were obtaining information required to resume patient tests on June 13, 1976. Dr. Smith said that 30 microamps were expected for the first patient run, with 100 microamps expected by September, which would provide 30 rads per minute in a 4 x 4 x 4 cm volume. The range shifter is operational to 15 cm in depth, and a more efficient range shifter is under design. For the first patient run, the schedule will be two weeks on and one week off, although an eight-week treatment cycle is the ultimate goal. The design intensity of the accelerator is 1 milliamp, and the machine operation will be slowly escalated to that level.

Biological studies are to resume May 17, 1976, with six organ systems, beginning with single-dose experiments and progressing to two, five, and 10 fraction experiments. Those experiments requiring the longest time for achievement of measurable end points are being started first. Most of the x-ray control work is complete. The biological studies will be done with a much higher dose rate in those small volumes than was available during the initial biological studies. Biological studies are also planned to determine the effects of dose rate on relative biological effectiveness (RBE). Studies at LAMPF have already shown that once the high-LET component of a beam surpasses 10 percent, the oxygen enhancement ratio (OER) is sufficiently low to overcome protection from hypoxia. The LAMPF beam is approximately 40 percent high-LET.

Studies of inhomogeneity effects are also planned, initially with simple systems (layers of bone, fat, and muscle) and progressing to more complex systems, eventually involving the localization of body inhomogeneities with a whole-body computerized axial tomography (CAT) scanner, if sufficient funding can be obtained.

Patient studies will resume with a static beam 4 x 4 x 4 cm which can be used for peripheral masses and skin nodules. The next size contemplated is 8 x 10 x 7 for treatment of head and neck and pelvic tumors to assess the tolerance of the normal structures in these sites. After sufficient inhomogeneity data is obtained, lung nodules will be treated with the same size beam as used for skin nodules. For the coming skin experiments, the dose will be flattened to more closely match that of the control x-radiation. Flatness was sacrificed for maximum dose rate in the earlier experiment because the accelerator was operating at only 10 microamps.

Significant gains have been made in the computerized treatment planning system, such that data from the multiwire proportional counter system can be input directly and used in the treatment planning calculations.

Programs at Stanford, TRIUMF, and Berkeley

Dr. Bagshaw reported that physical dose distributions have been mapped in the pion stopping region at the Stanford facility, and have been found very symmetrical, as calculated. Magnets have been run up to 90 percent of design capacity, and two radiobiology studies with tissue culture have been conducted. The dose rate is 2 rads/min in a volume of 3 x 3 x 3 cm. The slit system has been wired into the computer. Currently, two-thirds of each production cycle are devoted to physics and one-third to radiobiology.

Reporting on the TRIUMF project, Dr. Skarsgaard said pions became available in the medical channel about a year ago, with mainly physics experiments performed

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since that time. The machine is operating at 5 microamps; design intensity is 100 microamps. Biological experiments are planned for September, when 10 microamps are expected. The pion beam will be spread by momentum selection rather than a range shifter device.

Dr. Castro reported on work with helium ions at the Berkeley cyclotron and noted that medical use of heavy ions produced by the Berkeley Bevelac is 1 to 1-1/2 years away, although biology is underway with unmodulated beams of carbon, neon, and argon ions. Skin nodule tests could start as early as this fall. The Berkeley group and the LAMPF group are searching for an appropriate treatment couch, and recently held a joint session to explore requirements. Accuracy and reproducibility within a couple of millimeters are desired. The possibility of setting up and immobilizing the patient in a module outside the treatment room and transferring him in his module to the treatment couch is under study. It is hoped that by determining whether a common couch design can be shared by the LAMPF, Berkeley, and other groups, it might be possible to develop common specifications and reduce costs to the individual facilities for each couch purchased.

Phase III Protocol Revisions

Reports were given by individuals assigned to reassess diagnostic tests (in consultation with surgeons and others particularly knowledgeable about the selected disease sites) for the various Phase III pion protocols.

Bladder. Dr. Stewart said his subcommittee recommended deletion of the statement requiring electrocardiograms for all protocols, and substituting specific tests for the 12-test chemical battery recommended. The subcommittee also recommended inclusion of squamous cell carcinoma. These and other suggestions of the subcommittee were accepted by the Committee.

Brain (Gliomas). Dr. George reported on the suggestions of his subcommittee. The difficulty of differentiating between Grade III and Grade IV tumors was discussed, and Dr. George's suggestion that a randomized study using BCNU in combination with pions and conventional radiation was reviewed. The group concurred that radiation, not BCNU, was the definitive factor in survival changes recorded in current studies. They agreed they would be willing to randomize a study with Grade III cases, but not Grade IV. However, they requested that Dr. George's subcommittee develop a staging system for gliomas. They agreed that toxicology studies of the new modality might be worthwhile. It was requested that Dr. John Antoine be added to Dr. George's subcommittee and all subcommittees to advise them on diagnostic methods for determining extent of disease.

Cervix. Dr. Castro's subcommittee suggested consideration of some test of immune reactivity, which the group decided to request when possible, but not to make mandatory. Surgical staging to determine node involvement was also discussed, but it was pointed out that this was rejected in earlier sessions as a mandatory requirement because it was impractical to expect it at all institutions. It was agreed to add the statement to all protocols that CAT scanning would be obtained when available.

Esophagus. A liver scan was suggested as part of the pretreatment evaluation by Dr. Levitt's subcommittee. A recommendation to use pions as a preoperative adjuvant was rejected until sufficient information is collected on pions alone.

Head and Neck Protocols (Oral Cavity, Oropharynx, Hypopharynx, and Larynx). Dr. West reported that his subcommittee members had not yet submitted their

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recommendations to him. (N.B.: The subcommittee has now done so, and a copy is attached.)

Osteosarcoma. Dr. Johnson's group recommended we might want to set aside osteosarcoma as a test disease, until new baseline data can be acquired from current immunological studies. The group concurred.

Prostate. Dr. Bagshaw recommended that the Stanford staging system now be dropped, and that of the International Union Against Cancer (UICC), also adopted by the American Joint Committee for Cancer Staging and End Results Reporting, be incorporated in the protocol. This recommendation was accepted. After considerable discussion, the group also elected to eliminate prostate cases with clearly positive para-aortic nodes on lymphangiography and to suspend opening the non-randomized arm. Stratification by histologic grade was also suggested and accepted. Dr. Bagshaw also noted that 5000 to 5500 rads to the whole pelvis was leading to complications. He recommended a split course regime of 2600 rads to the whole pelvis in 2.6 weeks, followed by 2000 rads in two weeks as an arc or rotation cone-down to the prostate, and ending with 2400 rads in 2.4 weeks to the whole pelvis. An alternative of 170 rads/day, 850 rads/week, to a total of 5000 rads in 6 weeks was suggested by Dr. Kligerman, followed immediately by the rotation cone down portal for an additional 2000 rads.

Rectum. Dr. Kligerman's subcommittee recommended adding a liver scan.

Stomach. Dr. Loeffler recommended the adoption of recommendations by Dr. Stanley Hoerr (see attached letter). Time was too short for review, and it was agreed that a decision would be made at the next meeting.

Human Radiobiology and Pilot Study Protocol Revisions

Superficial metastases. The protocol for skin metastases, as revised for the new series of tests, was reviewed. Dr. Kligerman noted the treatment schedule had been changed to coincide with the planned accelerator cycle, from a baseline dose of 5200 rads, 15 fractions, 19 days to 4700 rads, 13 fractions, 14 days. He said he would like to use Dr. Bagshaw's tumor nodule measuring device to try to assess tumor regression. The percentages of total dose, ranging from 50 to 91 percent, were selected by the committee at its previous meeting to ensure overlap in the dose response curves. Photographic techniques, such as including a standard gray card or red tape in the photographic field, were also discussed, as ways to improve the optical densitometric measurements from the patient photographs. A copy of the skin metastases protocol (as revised by the Human Trials Committee and as subsequently revised to meet requirements of the various human research committees at UNM and LASL) is attached.

Advanced Local and Recurrent Neoplasms. A draft protocol, adapted from one developed by Dr. Castro for the Berkeley helium/heavy ion project, was reviewed by the committee. The protocol allows for testing pions with essentially any tumor which is amenable to beams developed at LAMPF, with a view toward maximum flexibility in the pilot study phase. A copy of that protocol, as revised by the Human Trials Committee, is attached. It has been approved by the UNM Human Research Committee and is pending review by the Los Alamos Scientific Laboratory/Los Alamos Medical Center committee.

Several of those attending the meeting toured the TRIUMF facility, at the invitation of Dr. J. M. W. Gibson.

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