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9/7/77

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RESEARCH PLAN

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I. OBJECTIVES

1) Evaluate potential of helium/heavy ion radiotherapy of human cancers including analyses of radiobiologic parameters and potentially favorable tumor-normal tissue ratios.

2) Develop the physical and dosimetric bases for helium/heavy ion therapy including radiation therapy treatment planning, utilizing CT scanning.

3) Evaluate the effectiveness of helium and heavy ions relative to the best available low LET radiotherapy techniques by designing and carrying out a clinical trial of these beams in human cancers.

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V. METHODS OF PROCEDURE

1. Pilot Helium Ion Radiotherapy Study

Since July of 1975, we have been engaged in a pilot study utilizing the 934 MeV helium ion beam produced at the 184" synchrocyclotron at Lawrence Berkeley Laboratory. This helium ion beam has been used for many years, primarily using the plateau portion of the beam in a rotation technique to deliver small fraction number, high dose per fraction pituitary irradiation. In planning the pilot study of helium ion cancer radiotherapy most radiotherapists wished to use fractionation in a conventional fashion of 180-200 rads per treatment, four to five treatments per week to total doses of 5000-7000 rads in order to relate biologic effects and results more easily to ones past experience. In addition, the spread out Bragg peak would be needed in order to take fullest advantage of both the physical and biologic potential of the helium ion beam. In effect we were interested in learning treatment techniques for Bragg peak charged particle radiotherapy, techniques that could later be directly translated to the BEVALAC when we began irradiations with heavier ions such as carbon, neon or argon. The biological properties of the helium ion beam had been studied previously by Todd and others ( ) and in our initial application was summarized by Leith ( ). It was felt that little biologic advantage over low LET irradiation would be present although the observed OERs range from 1.9 to 2.3 in test conditions where x-rays gave OERs of approximately 2.5. The chief advantage appeared to lie in the physical potential of the spread out Bragg peak. Thus, the goals of the pilot study, were (and are): 1) learn treatment techniques; 2) evaluate normal tissue responses including skin and mucosal reaction; 3) study tumor responses; and 4) determine if some clinical advantage might be found in sparing of normal tissues by the favorable dose distribution characteristics of this beam.

The existing helium beam line was rapidly modified by introduction of a secondary scatterer within the medical cave. A large flat homogeneous circular field of 25 cm. diameter was obtained in which homogeneity was present to ± 2% over 90% of the field. The residual range in water of the 184" helium ion beam is 32 cm. After insertion of a secondary scatterer, ridge filter, ionization chambers, etc., the final range in tissue is about 26.5 cm. This has proven to be about the minimum range possible to irradiate a broad variety of clinical sites when one considers the path of various beam portals, particularly diagonal or oblique beams and also the bony inhomogeneities which may lie in the beam path. The dose rate is about 150-180 rads per minute so that short treatment times were available for the planned doses of approximately 200 rads per treatment. A very versatile, precise and accurate patient positioner (ISAH) was already in place which had been designed specifically for pituitary irradiation. Modification of this patient positioner to accept patients in either the supine, seated or standing positions was easily done.

After considerable discussion by a number of collaborating radiotherapists, biologists and physicists under the aegis of the Bay Area Heavy Ion Association, an informal association organized to assist in the design and conduct of the helium/heavy ion trial, we began irradiation of a pilot series of patients. More detailed information regarding this group of patients is presented in the comprehensive progress report (Section VIII of this application).

A considerable amount of useful information has been learned and may be summarized:

1. It is possible to treat most of the anatomical sites in the head and neck, trunk and extremities with the patients in a vertical position, either seated or standing. Patient immobilization and daily reproducibility has been quite good, particularly in the head and neck, where accuracy of reproducibility of ± 2 mm. has been generally obtained. In the chest and abdomen this goal has been more difficult to

achieve.

2. The clinical RBE utilized for this beam appears to be approximately 1.25 based on observation of skin, mucosal and intestinal reactions. This is somewhat lower than might be expected based on laboratory data which suggested RBEs as high as 1.8 for daily treatment doses of 150-200 rads. No unusual or unexpected clinical reactions or side effects have been encountered as yet.

3. In order to provide sufficient flexibility to irradiate different target volumes and obtain a favorable dose distribution relative to low LET radiation techniques, it is necessary to have a series of ridge filters which provide spread out Bragg peaks of different dimensions. We are currently employing a series of Bragg peaks ranging from 4 cm. to 14 cm. In addition to providing clinical flexibility, these ridge filters are designed to produce a physical dose distribution which delivers isosurvival under the Bragg peak. The calculated physical dose distribution is to produce isosurvival at approximately the 50% to 60% level per treatment taking into account the changing RBE (normal tissues) under the plateau and spread out Bragg peak. These ridge filters have been checked by Raju and have found to give essentially flat dose response curves utilizing his cell system ( ).

4. Treatment regimes of four or five fractions per week at approximately 180-200 CoRE* per fraction appear well tolerated by most patients, and in fact, better tolerated than low LET radiation, which many of them have received for the first part of their therapy course.

5. Wax bolus compensators built into light cast shells have proven to be an easy form of basic compensation for sloping surface contours and tissue inhomogeneities.

6. A more detailed and complex effort will be required to adequately assess

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*CoRE = Cobalt^{60} equivalent rads.

and compensate for tissue inhomogeneities in the beam path. This will require onsite computer assisted tomographic scanning in order to obtain the necessary tissue densities in a rapid fashion. Such scans may be required frequently or even daily because of changes in anatomical patterns such as bowel gas and/or because of tumor regression. In addition, a special unit will be required in order to scan patients in the treatment position which we estimate will be upright for 80% of our patients.

7. While patient tolerance appears improved in the sites that we have irradiated to date, a number of potential therapeutic sites have not had any pilot patients entered as yet. In addition, long term analysis of normal tissue effects requires further follow-up. Many of our patients have had short follow-up periods because of advanced and/or progressive disease. In addition, in this heterogeneous population of patients it has been impossible to adequately compare tumor response or control to that obtained with low LET radiotherapy.

Future Studies (1977-1981)

1) We would like to continue this pilot series of patients in order to study patients with the following tumor types:

1. Selected advanced head and neck tumors, such as para nasal sinuses, salivary gland tumors; certain upper aero-digestive tract sites if localized and unresectable;
2. Carcinoma of the esophagus;
3. Carcinoma of the pancreas or stomach, locally or regionally confined but unresectable;
4. Advanced carcinoma of the uterine cervix, bladder or prostate;
5. Metastatic disease to the para aortic lymph nodes;
6. Malignant glioma of the brain.

These appear to be favorable sites for charged particle irradiation and ultimately it is hoped that many of these will be opened to ramdomized studies

in which helium ion and/or heavy ion irradiation will be contrasted with low LET irradiation.

In continuing the pilot helium ion study, our current treatment plan is to deliver a full course of radiotherapy with helium ions on a four fractions per week basis, with daily doses of 180-200 CoRE to a minimum total dose of at least 6500 Co^{60} rads equivalent. Our goal is to increase the tumor or target dose relative to normal tissue doses wherever possible. We will continue to use multiple port dose distributions wherever possible in order to minimize dose to skin and internal vital structures.

The end points in the study will continue to be: 1) acute and sub-acute normal tissue response as evidenced by skin, mucosal, intestinal and connective tissue effect 2) tumor response and control; 3) late effects (fibrosis, vascular changes, necrosis tumor induction) providing patients with sufficient lifespan for long term follow-up are irradiated.

2) Some attempt will also be made to study altered time-dose fractionation schemes on a limited scale. For instance, based on the impression of improved results with combined neutron and photon irradiation in tumors of the pelvis, it may be useful to study similar combined irradiation schemes using helium ion irradiation and low LET irradiation where the doses are combined throughout the radiotherapy course instead of the helium ion irradiation being given as a boost for the last two to three weeks of treatment.

3) We will also extend our analysis of treatment techniques, particularly patient positioning, immobilization and reproducibility; use of bolus for compensation; computerized treatment planning; and utilization of CT scanning for assessing tissue inhomogeneities, electron density studies and compensation techniques. We intend to continue and extend studies of verification techniques to check on actual doses delivered in the target volume. These will include internal placement of

diodes and lithium fluoride chips whenever possible in order to verify the delivered dose. Also film stack techniques will continue to be run on selected patients as an aid to verification of the beam distribution.

Primarily we hope through these pilot studies to obtain sufficient information to open certain anatomical and tumor sites to controlled helium trials. This cannot be done until we are certain that the helium ion irradiation techniques are well understood and provide a fair basis for comparison with low LET radiation techniques. Additionally, the pilot helium ion study will continue development and refinement of treatment techniques in preparation for irradiation with heavier ions to be done at the BEVALAC.

3 Controlled Helium Ion Study

Based on information learned in the pilot helium study, we feel that we should shortly be ready to open three sites for randomized protocols. These are localized carcinoma of the pancreas and stomach, advanced carcinoma of the uterine cervix and carcinoma of the esophagus. The Protocol Development Committee of the Bay Area Heavy Ion Association has developed clinical protocols for these tumor sites among others (appendix). However, statistical consideration of the number of patients required for these clinical protocols was not thoroughly detailed at the time of their original writing. Subsequently, the radiotherapy group of Lawrence Berkeley Laboratory has become a special member of the Northern California Oncology Group, the clinical trial arm of the Northern California Cancer Program. The above mentioned protocols are in the process of being submitted to the Northern California Oncology Group for review by their statistical office and their site-specific and modality committees. Upon acceptance and statistical input, it is hoped to have these protocols opened to members of the Northern California Oncology Group by spring of 1978. The control irradiation will be done by member radiotherapy facilities and will be verified by the Radiotherapy Committee of the Northern California Oncology Group headed by Dr. Theodore Phillips. A staff physicist of the Northern California Oncology Group will ensure that the control irradiation facilities meet all required standards and adhere to the protocols.

Similarly, we propose that the same or similar protocols be submitted to the Radiation Therapy Oncology Group for their approval so that patients may be entered on a national basis. Specifically, we intend to try to make the control arm of the protocols similar in order to facilitate intercomparisons. This should allow a ready supply of patient resources both regionally and nationally.

Statistical input will be obtained from the Radiation Therapy Oncology Group as well as input into protocol design.

In addition, we expect to rely on the Northern California Oncology Group and the Radiation Therapy Oncology Group for patient accession; randomization; assistance with quality control; data collection, storage and retrieval as well as forms development.

At the present time the plan is that these protocols would be opened for helium ion irradiation versus low LET irradiation with the possibility of a third arm of heavy ions at a later date. It should also be pointed out that some protocols may be developed within the Northern California Oncology Group in which chemotherapy forms part of the treatment regime. While this may not afford the most desireable type of test vehicle for a new form of radiotherapy, it may be of value in certain tumor sites.

6. <u>Continue protocol development, statistical analysis and data storage retrieval and evaluation, expand collaborative network for heavy ion controlled trial</u>.

Up to the present time the Protocol Development Committee of the Bay Area Heavy Ion Association has developed nine protocols for use at the Lawrence Berkeley

laboratory, initially as pilot helium ion studies. Some of these protocols will eventually become randomized studies using helium ions, heavy ions and contrasting these to low LET photon techniques; others will remain non-randomized as previously mentioned, with the development of the Northern California Oncology Group, several of these protocols are in the process of being submitted to the Radiotherapy and Disease Specific Site Committees of the Northern California Oncology Group for review, approval and inclusion as official NCOG protocols.

A similar process will be carried on with the Radiation Therapy Oncology Group for selected protocols. Where possible, for common protocols we will endeavor to have common control arms with the National Neutron Trial Group. We will continue these efforts at protocol development attempting to limit the total number of heavy ion protocols to perhaps five or six clinical sites which would provide sufficient patient entry to determine the effectiveness of these beams in a timely manner. At the present time, we suggest the most likely sites to be tested will be malignant glioma of the brain, esophagus, pancreas and stomach, advanced tumors of cervix uteri, bladder and prostate and certain head and neck tumors. However, this list may well change as we look very carefully at the clinical potential of each of several heavy ions inorder to determine in which situations the tumor/normal tissue ratios are most adavntageous.

We are fortunate in having a number of collaborating radiotheapy and cancer treatment facilities in the geographic region such that the total number of new patients available to the region are in excess of 12,000 patients per year. Nevertheless many of the institutions are engaged in cooperative studies and it will be necessary to develop referral patterns and cooperative protocols very carefully in roder to avoid competition for patient resources.

In addition, as a national facility we wish to maintain access for any patient from any part of the country and hope to do this through the Radiation Therapy Oncology Group again with very carefully drawn protocols so that most if not all patients will be utilizable as study patients.

Statistical services will be obtained from the statistical offices of the

Northern California Oncology Group and Radiation Therapy Oncology Group under the direction of Dr. Byron Brown and Dr. E. Gehan, respectively. By utilizing these group offices for development of appropriate protocol forms, accession of patients, randomization procedures and handling of data, we will omit the need to develop an extensive statistical office of our own and at the same time will have access to the most sophisticated statistical techniques currently being used in cooperative trials.

We also intend to utilize the data retrieval and storage service of the University of California, Division of Radiation Oncology in order to store pertinent patient data and parameters. This system is designed especially for radiotherapy use and has been in effect for several years. It is easily adaptable to particle irradiation and allows an interactive exchange using a typewriter terminal in order to store information in the computer and obtain access to it in a usable fashion.

For quality control in randomized trials we will make use of the Radiotherapy Committee of the Northern California Oncology Group to ascertain that participating institutions adhere to protocol requirements. A Quality Assurance Subcommittee has been appointed and will have the use of appropriate physicist input through the Northern California Oncology Group.

In addition, we will rely on RTOG quality control activities already functioning where appropriate. Many of the participating radiotherapy members of BAHIA group are already members of Radiation Therapy Oncology Group and have been visited by RTOG-Radiological Physics Center for verification of dosimetric accuracy, etc., at their institutions.

Radiographs of beam portals, isodose distributions and treatment data will be required on each study patient and reviewed by either ourselves or the respective oncology group headquarters in order to be sure that control patients meet protocol requirements. A similar procedure will be done with study patients at Lawrence Berkeley Laboratory and such information forwarded to the appropriate

headquarters as is needed to ensure that the particle patients also adhere to protocol requirements. While this may not eliminate all possibilities of some bias entering the study based on more careful and detailed treatment planning at Lawrence Berkeley Laboratory, it should provide the best availagle system of comparable treatment and study groups. If necessary, we will provide specialized treatment planning at LBL for control patients at Lawrence Berkeley Laboratory, should this be necessary.

A planning study has been done at Lawrence Berkeley Laboratory for design of a specially built medical accelerator which would provide greater flexibility than the fixed horizontal beam currently available at the BEVALAC. A simiar planning effort will shortly be underway to study the possibility of beam scanning in order to provide a more flexible dose distribution with heavy ions. Until we fully research heavy ion radiotherapy treatment techniqeus and have the flexibility to provide target volume dose distributions comparable to the best available megavoltage techniques, it is not wise to begin controlled studies, except possibly limited to certainsites. It is hoepd that sufficient information will be learned during the course of this project that a definite decision on controlled heavy ion trials can be made and/or implemented.