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V. METHODS OF PROCEDURE

1. Analysis of tumor/normal tissue relationships with respect to selection of tumor sites for pilot studies

The initial phase of this project will stress an analysis of those tumor sites for which benefit can be expected from the improved tumor dose localization possible with helium-ion/heavy-ion beams. Our initial interest with helium ions will be directed towards evaluation of improved results primarily due to better localization of the dose, with consideration also of a slightly improved biologic response. These helium-ion studies will serve as a foundation upon which to plan later heavy-ion therapy where one does expect improved results from the greater biologic effect of these particles on the tumor as well as the comparable sparing of normal tissues through better dose localization. Considerable historical information has indicated that where an improved tumor dose localization has been achieved, local control of tumors has been higher, often with consequent improvement in survival. These considerations have been summarized by H. Suit and M. Goitein (16). They conclude that, where tumor doses of approximately 7,000 rads in 7 weeks can be delivered, local control might be only slightly improved by better dose localization, although morbidity might be diminished. Where doses of this level cannot be reached because of limitations by normal tissue tolerance, however, the improved distribution from proton therapy might allow tumoricidal doses of ~ 7,000 rads to be delivered with consequent increase in local control. Considerations for helium-ion therapy fall generally into the same classification as proton therapy because of the slightly higher RBE of 1.2 and probably only minimally improved OER of ~ 2.3 (3).

Our initial planning will thus be directed to tumor sites where an improved tumor/normal tissue dose ratio can be obtained. Suit and Goitein suggest the following sites for possible improvement in local results: carcinomata of the stomach or pancreas, retroperitoneal tissue, periaortic region, base of bladder and prostate (16). As initial tumor sites for treatment with helium ions we are considering grade III or IV astrocytomas (brain), paraaortic lymph nodes (cervix, bladder, prostate), localized pancreatic, or renal and esophageal tumors. Carcinomata of the stomach, bladder, soft tissues and the head and neck region are among the sites to be evaluated later.

In considering tumor sites to be irradiated, tissue density inhomogeneities must be recognized and the appropriate information incorporated into treatment planning. For some tumor sites adequate density information regarding such inhomogeneities may be obtained through careful imaging techniques (transverse tomography, ultrasound, standard X rays). Careful surgical exploration with precise identification and clipping of tumor volumes is an essential part of the pretreatment evaluation. Improvement in treatment planning techniques will be forthcoming with the use of computer-assisted axial tomography, which will provide accurate tissue density cross/sections for treatment planning. Helium-ion treatment compensation for inhomogeneities will be by individually prepared absorbers (bolus). For treatment with the BEVALAC heavy-ion beam, absorber materials and computer-directed energy modulation to control the depth of penetration of the extended Bragg peak can be used.

Among the patients suitable for initial feasibility studies with helium/heavy-ion irradiation are those with grade III or IV astrocytomas using "boost" therapy following whole-brain irradiation to a basic dose level of perhaps 4,000 to 4,500 rads in 5 to 6 weeks. The ability to localize the helium beam will provide significant sparing of normal brain tissue while raising the primary tumor volume dose to the equivalent of 7,000 rads in 8 weeks. Although one might not expect very great improvement in local control with helium-ion therapy, the morbidity of treatment should be less, making this site worthy of feasibility studies in preparation for heavy-ion therapy to brain tumors where a biologic advantage may be demonstrated.

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An area of greater interest is that of irradiation of periaortic lymph nodes, which are known sites of microscopic metastases from various primary sites, especially carcinoma of the uterine cervix, bladder, rectum, and prostate. To date gut tolerance has limited adequate irradiation of the lymph nodes because of a significant morbidity rate from intestinal damage with doses adequate to control tumors. The precisely defined depth-dose distribution achievable with the helium/heavy-ion beam can be effectively utilized to irradiate these nodes to at least 5,000 rads in 5 weeks with an expected decrease in morbidity. Even higher doses may be feasible because of the lower integral dose to the intestine. A simple treatment planning approach would use a direct posterior field, with appropriate compensation for vertebral bone within the treatment port; it might require combination with high-energy photon beams in order to diminish the surface dose of the single entry portal. Another disadvantage of the single posterior port is a relatively high dose to a small portion of the spinal cord and a large portion of the cauda equina. Improvement on this technique will be achieved through the use of multiple ports, appropriately weighting fields to minimize the dose to the adjacent intestine.

Localized pancreatic tumors present the same problem with regard to bowel tolerance and, in addition, require planning to minimize the radiation dose to the liver and kidneys. Surgical exploration with careful outlining of the tumor by clips would make precise dose localization possible with helium/heavy ions, using appropriately selected ports to minimize the normal tissue injury. In this manner improved local control of unresectable but relatively small pancreatic tumors is a reasonable expectation.

Localized renal tumors would be treated in the same manner as pancreatic tumors and with the same normal tissue tolerance considerations. A more complex problem arises in the case of esophageal carcinoma. Although these tumors often metastasize to abdominal lymphatics and liver, local control rates with radiotherapy also need to be improved. This could be achieved with the improved dose distribution of helium/heavy ion beams, which provide a locally higher dose while minimizing the dose to critical adjacent normal structures such as the spinal cord, heart, lung, etc. Treatment planning for esophageal cancers will require density inhomogeneity corrections for air in the trachea, the lung and bone. Adequate treatment of celiac nodes will also be feasible.

The Protocol Design Committee of the Bay Area Heavy-Ion Association will provide recommendations for tumor site selection, pretreatment evaluation, treatment guidelines for both helium/heavy-ion and control X-ray therapy and assessment during treatment. Patient availability will also have to be considered in terms of treatment capabilities in participating institutions and patient numbers. During the first year of this project, pilot studies will be conducted on selected tumors for which treatment planning and helium-ion beam capabilities are available. The number of patients to be individually studied and treated during this first year will increase as treatment capabilities increase with experience. It is our goal to proceed to controlled studies for selected sites as soon as reproducible treatment techniques are demonstrated. A considerable portion of these initial analyses can be done through existing personnel and facilities at LBL, UCSF and Stanford, as well as with the help of members of the Bay Area Heavy-Ion Association.

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2. Design of protocols for clinical trials

The Bay Area Heavy-Ion Association Protocol Design Committee is chaired by Dr. David Pistenma of the Division of Radiotherapy, Stanford University Medical School. The other members of this committee include Dr. Ted Purcell (Alta Bates Hospital), Dr. Bernard Lewinsky (Letterman General Hospital), Dr. Barry Chausser (Peninsula Hospital), Dr. Ronald Van Roy (Santa Rosa), Dr. Richard Borrison (O'Connor Hospital and Valley Medical Center, San Jose), Dr. Saul Silverman (Sacramento, CA, Univ. of Calif. at Davis), Dr. A. Rao (U.S. Naval Hospital, Oakland), and Dr. Stan Curtis (LBL).

The Protocol Design Committee has accepted the charge of defining guidelines for patient selection, evaluation and treatment. The initial monthly meetings of the Bay Area Heavy-Ion Association have been devoted to an analysis of possible tumor sites for pilot studies and the methods by which protocols for control studies might be developed. The discussions have led to the recommendation that protocols be modified from those developed by the Regional Clinical Committee and Subcommittee for Human Trials of Pion Radiation Therapy at Los Alamos Meson Physics Facility. The protocols developed at Los Alamos cover some fourteen tumor sites, all of which are suitable for treatment with helium ions or heavy ions. Additional protocols will be developed for other tumor sites that appear satisfactory for helium-ion or heavy-ion therapy. Initially the emphasis will be on feasibility studies to define treatment techniques for treating tumors with helium/heavy ions. As treatment methods are demonstrated during this initial period, randomized clinical trials will be planned and established for selected tumors. It is expected that the protocols for the randomized clinical trials will be largely accomplished within the first year of the study. This should coincide with the time at which heavy-ion radiotherapy beams become available. Some of the treatment protocols to be developed are shown in Appendix D. Others will be developed during the next year.

As these protocols are completed by the protocol design committee and approved by the principal investigator and BAHIA, they will be submitted to the LBL Human Use Advisory Committee and the University of California, Berkeley Campus Committee for the protection of human subjects. When approved, they will be opened to patients for helium ion therapy initially and for heavy ion therapy when appropriate pre-therapeutic work is completed. A control series of patients will be treated at collaborating radiation therapy facilities so that eventually a three-armed study will result; statistical advice will be needed to determine the number of patients in each arm although it is hoped that the preponderance of the study patients will be in the heavy ion therapy arm.

Not all tumor sites need to be randomized; those with survival or local control less than 10% with conventional radiotherapy techniques may be non-randomized. The initial RBE recommended by the radiobiology committee of BAHIA for use with helium ions is 1.2; in addition in many protocols helium ion doses for the initial 3-6 patients may be 20% lower than the planned level in order to be certain of no undue immediate effects. These doses will be raised to the planned level as soon as it is felt safe by the principal investigator.

All patients will have to give a voluntary, informed consent to participate in the study. This consent form to be developed will be submitted to the campus committee for protection of human subjects for their approval.

Appendices B & E list participants in the study with the current numbers of new patients seen yearly in the major participating centers. Data is also available from the California tumor registry giving the breakdown of new cancer patients in the Northern California area by site of origin of tumor.

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### 3. Tumor localization and assessment of inhomogeneities

Major problems to be encountered are those of tumor localization and the assessment of and compensation for tissue inhomogeneities. The problem of tumor localization is of paramount importance in order to effectively exploit improved dose localization provided by the sharp edges and sharp distal stopping edge of the helium/heavy-ion beam. Accurate mapping of the treatment area will therefore be needed. We plan a special effort to make use of established techniques including careful mapping and clipping of tumor extent at the time of surgery (we will encourage exploration of patients considered for heavy-ion therapy where possible); imaging techniques including standard radiographs; special X-ray procedures (vascular studies, transverse tomography, standard tomograms, etc.); ultrasonography; and isotope scanning. We will be exploring in concert with other LBL research groups and personnel, additional avenues of improved localization techniques. These include the following possibilities: 1) heavy-ion radiography; 2) helium-ion radiography; and 3) computerized transverse axial body scanning. We would expect to maintain close liaison with other particle therapy groups working on similar problems in order to exchange useful techniques. These include the Los Alamos Meson Physics Facility Pion Trial, Stanford Medical School Pion Trial, and the Massachusetts General Hospital - Harvard Medical School Proton Trial.

A major problem exists in the assessment and correction of tissue inhomogeneities traversed by the beam. The fortuitous introduction of computer-assisted transverse axial body scanners provides a means of obtaining accurate body-section density information. A similar technique, such as the heavy-ion radiographic construction method, could also provide the necessary information to perform treatment planning with full consideration of density inhomogeneities. Until this advanced instrumentation is available, existing standard radiotherapy treatment planning methodology using orthogonal X-rays, transverse tomography, surgical exploration, and standard anatomic atlases could be used to correct for inhomogeneities for selected tumors. The existing computer program for treatment planning with the 184" cyclotron will be modified to incorporate cross-sectional density information derived from computer-assisted axial transverse scanning. In the initial phase of the study representative treatment plans for several illustrative tumor sites and anatomic areas will be evaluated. These plans will serve as a reference for treatment planning for actual patients. With helium ions at the 184" cyclotron, compensation for density inhomogeneities will be made by means of an externally applied bolus. In all situations the beam energy will be decreased by the bolus so that the treatment volume receives the full dose, while the critical tissues beyond the target volume receive as small a dose as possible. Plans for treatment with the heavy-ion beams at the BEVALAC include compensation for inhomogeneities by varying the energy of the beam to give different penetration depths as well as by compensation with the externally applied bolus. Computer control will be utilized to appropriately vary the energy of the beam to stop the particles in the designated tumor volume. Autoradioactive beams (see Section V-10) will be helpful in determining the stopping power of heterogeneous tissues and for dose verification.

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#### 4. Treatment planning and implementation

We propose to proceed as follows to implement treatment of patients, first with helium ions and later with selected heavy ions:

a. Develop treatment techniques for selected tumor sites such as brain, esophagus, periaortic lymph nodes, localized pancreas for treatment with the 184"-Cyclotron, helium-ion beam (and later with the BEVALAC heavy-ion beam), utilizing large-field, fractionated, extended-Bragg-peak therapy. Development of these techniques will include such steps as preparing initial representative treatment plans utilizing phantom measurements and standard anatomic atlas cross sections, external bolus correction for inhomogeneities, and careful simulation to assure stopping the beam before vital normal structures are encountered. Correction of inhomogeneities will be greatly facilitated by use of transverse body scanner to provide electron density data in the beam path. In any event treatment will not be attempted with the helium or heavy-ion beam unless dose distribution is at least as advantageous as conventional irradiation. We expect improved dose localization over conventional techniques or we would not utilize helium/heavy-ion therapy.

b) Proceed to treatment planning for a wider variety of tumor sites.

c) Perform dosimetric and radiobiological experiments as needed to confirm treatment planning calculations.

A 930-MeV, helium-ion beam is available from the 184" Cyclotron. The physical characteristics of this beam are well known. With the addition of secondary treatment scatter within the treatment cave, maximum field size of 30-cm diameter will be obtainable. With appropriate shielding, the secondary scatter outside the beam will be quite low. The output is in the range of 150-200 rads/min.

The present ridge filter provide a 5.5-cm extended Bragg peak. RBE measurements with this ridge filter indicate an average RBE over the extended peak of 1.2, rising gradually from approximately 1.1 at the proximal portion of the peak until the distal portion of the peak, where it reaches 1.3 in the region of greatest stopping of the particles. An isosurvival ridge filter is being designed, which will correct for the variations in biological effectiveness over the extended peak.

The surface dose with this technique will be in the neighborhood of 85%, which may necessitate either combining a single helium-ion beam with a 25-MeV photon beam, or, preferably using multiple helium-ion fields.

Shaping of these fields will be accomplished by an initial collimator system followed by Cerrobend shaping placed as close to the patient as possible. This beam is horizontally directed. ISAH (Irradiation Stereotaxic Apparatus for Humans), an elaborate and versatile patient positioner, is available at the 184" Cyclotron. This allows the patient to be treated in a lying position upon a treatment table, sitting in a chair or standing upright. It has translation capabilities in three orthogonal directions as well as rotational capability in two directions. Patient immobilization will be facilitated through the use of existing face-mask techniques as well as the development of a bite-block technique suitable for head and neck (and brain) irradiation. Body casts including standard plastic techniques and newer extruded plastic methods will be utilized for other areas of the body in order to minimize patient motion. X-ray generators are available in the treatment room to verify the accuracy of the beam portals. It is expected that all of the possible methods utilized to localize the treatment volume and immobilize the patient will be explored (11)(12).

The versatility of patient positioning with ISAM should enable treatment of virtually every anatomic site, even though only a horizontal beam is available. When appropriate, this positioner will be moved to the BEVALAC facility for utilization with the heavy-ion beam. A simpler positioning apparatus will be constructed at the 184" Cyclotron as it is deemed appropriate to continue the helium-ion trial. Pretreatment evaluation of the patients will be standardized among participating institutions, but final clinical evaluation, tumor localization and treatment planning for helium-ion/heavy-ion therapy will be done at LBL.

We expect that participating radiotherapists treating control patients at their own institutions will spend half a day each week at LBL participating in the treatment planning, actual treatment and followup of study patients. This will provide maximum opportunity for consistency between treatment methods and will also provide greater reliability between comparable control and study groups.

One of the chief concerns will be to assure a truly controlled trial with comparable patient groups and careful attention to pre-treatment evaluation, set-up, treatment techniques and dosimetry. Frequent and thorough interchange of ideas, techniques and personnel will aid in this effort. It is vital that radiotherapists treating control patients participate fully in the treatment process of study patients at Berkeley to assure equal, sophisticated, best "state-of-the-art" conventional low LET radiotherapy so that no unintended bias can unduly improve the results of the patients treated with helium or heavy ions.

The Radiologic Physics Center (Houston) or a similar group if developed by the Northern California Cancer Program will visit participating institutions to verify accuracy of treatment techniques and dosimetry for control patients.

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### 5. Radiobiological verification of RBE for fractionated helium-ion beam

A great amount of radiobiological research has been performed at the Lawrence Berkeley Laboratory 184-inch Synchrocyclotron. A tabulation of much of the available information is summarized in Table I.

For the purposes of human therapeutic irradiation, the helium-ion beam will be generally used in its therapeutically-modified or "spread-out" form in which the helium-ion, Bragg-ionization curve with its single sharp peak is transformed into a flattened depth-dose distribution, so that cell killing is constant along the last 6 - 10 cm of range. This is done by interpositioning into the beam path a moving copper ridge filter (14).

It is worthwhile to examine three different portions of this spread-out Bragg curve to see how radiobiological parameters may vary.

#### Plateau region of ionization

The range of the full-energy (930-MeV), helium-ion beam is 32 cm in tissue-equivalent material. LET corresponding to this energy is 1.6 keV/micrometer. Many studies have examined biological effects in this position (or the plateau region of ionization in the spread-out Bragg peak, which has a similar average LET value).

Work has been done on human kidney cells in tissue culture by Raju *et al.* (1972); Todd *et al.* (1973); and on Chinese hamster ovary cells by Gerner and Leith (1975) (3).

It is clear that the relative biological effect in this region of ionization is unity: this is listed in Table I. In Table II, some relevant biological survival data are listed.

The work done on animal tissues is also shown in Table I. Again, the relative biological effect is essentially unity.

#### Therapeutically-modified, Bragg-peak region of ionization

In this irradiation situation (Table I), the Bragg peak has been transformed into an isodose depth profile, constant over 6 cm. For purposes of discussion, it is useful to consider two portions of the spread-out Bragg curve, the proximal and distal regions. In both regions, there will be some fraction of helium ions that are stopping and therefore exhibiting their maximum LET. This fraction of stopping to traversing particles will increase as the maximum range of the particles is approached. Biological results are again listed in Table I. Data on relative biological effectiveness, oxygen enhancement ratio, and repair of sublethal radiation damage (expressed as  $D_2-D_1/n-1$ , where  $D_2$  is the dose (given in two installments) needed to produce the same biological effect as a single dose, and where  $n$  is the number of fractions) are given.

It is evident that RBE in the proximal portion of the Bragg curve is unity or slightly greater than unity. The oxygen enhancement ratio is slightly decreased. Repair of sublethal radiation damage is also similar to that in the plateau region of ionization.

It is only in the distal region of the modified Bragg curve that change in biological effectiveness may be seen. In Table I, average increase in RBE is approximately 1.2 to 1.4, with 1.3 a reasonable mean value. It also appears that the oxygen enhancement ratio is decreased by about 30 percent of the value in the plateau region of ionization.

There also appears to be a slight reduction in ability to repair sublethal damage. Although the data are imprecise, a value of about 15 - 20% decrease in the  $D_2-D_1$  (or  $D_Q$ ) dose for the distal end of the modified Bragg ionization curve as compared to the plateau region of ionization is probably a reasonable estimate.

In Table II, we have listed some survival data on mammalian cells in tissue culture irradiated at the Lawrence Berkeley Laboratory 184-inch Cyclotron. These data are intended to explicitly present changes in survival curve parameters. Also presented is relative survival for oxic and hypoxic cells at a selected dose (300 rads). This dose level is similar to the dose per fraction that will be used clinically. It may be seen from Table II that survival at 300 rads decreases as one moves from the plateau to the modified-Bragg-peak region of ionization. This illustrates the slight increase in RBE. Also, it may be seen that survival of hypoxic cells decreases further relative to oxic cells, illustrating why OER is slightly decreased in the therapeutic modified Bragg peak.

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