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Heavy Ion Therapy: Bevalac Epoch

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Experience in high-LET particle radiotherapy dates back many years to the beginning neutron studies of Robert Stone and John Lawrence at the University of California in the late 1930's. Charged particles, although begun in the 1950's by Cornelius Tobias and John Lawrence, have been practical for use in fractionated Bragg peak cancer therapy only since the late 1970s, when CT became available for treatment planning at the Massachusetts General Hospital-Harvard Cyclotron Laboratory and the University of California Lawrence Berkeley Laboratory (UCLBL) (5). The potential of heavy ion therapy for clinical applications stems from the biological attributes of heavy ions, and the precise dose localisation possible with charged particles. Translating this into clinical use required a large effort involving biologists, physicists, physicians, accelerator physicists and engineers, computer scientists and radiation therapists (9,13,22,23)

With the development of the Bevalac complex (SuperHiLac linear accelerator + Bevatron) in the early 1970s, it became possible to have intense beams of heavy ions sufficient for timely delivery of therapeutic doses. In 1975 a collaborative clinical study was begun between University of California San Francisco Medical Center (UCSF) and UCLBL to determine the efficacy of heavy charged particles in the treatment of human cancers. In the late 1960's and 70's, intense radiobiological interest was focused on the role of hypoxia in tumor therapy and many observers expected significant biological gains from high-LET particles. Less attention was directed to the possible advantages of dose localisation although it was recognized that previous increases in the ability to deliver dose at depth had been accompanied by clinical gains in local and regional control.

Biologically, carbon, neon and similar heavy ion beams reduce the oxygen enhancement ratio and increases the Relative Biological Effectiveness (RBE) . Cells irradiated by heavy ions show less variation in cell-cycle related radiosensitivity and decreased repair of radiation injury. The physical behavior of these heavy charged particles allows precise delivery of high radiation doses to tumors while minimizing irradiation of normal tissues.

Helium and neon ions were selected as ions to be tested at LBL, representing relatively low-LET ions (helium) for their dose-distribution advantages and high-LET (neon) for both its biological and physical advantages. The use of these ions in clinical practice required an extensive pretherapeutic and supportive effort including biological studies, development of patient immobilization techniques, CT and MRI tumor targeting, and a 3D computerized treatment planning system. Progressive improvements in beam delivery and patient dosimetry techniques were essential to assure accurate and safe patient irradiations. Gradual escalation of doses were required to ascertain normal tissue tolerance and assure patient safety in introducing a new treatment modality.

The preliminary experience at LBL (1,2,3,4,5,6,7,8,25) has confirmed the usefulness of heavy charged particles in increasing tumor dose relative to normal tissues. Effective dose 10-35% higher than possible with standard techniques have been achieved with helium and neon ions and as would be expected, significant improvement in local control and survival rates have been demonstrated compared to historical data. This has been best demonstrated in tumors arising or invading the skull base, including primary chordoma-chondrosarcoma of the paraclival area, as well as tumors of the paranasal sinuses and nasopharynx (14,15). Eye and orbital tumors, salivary gland tumors, bile duct tumors, bone and soft tissue sarcoma and prostate gland tumors have also been effectively treated (17,18,21,24,26).

However, the limited availability of heavy charged particle beams due to the use of laboratory accelerators for the bulk of the clinical trials has slowed the accumulation of data relative to the merits of these forms of radiotherapy. It is likely that a further generation of use will be needed to fully resolve all of the questions related to charged particle therapeutic use, and to accumulate sufficient treated patients to have full confidence in the results.

Treatment Planning

Extensive and complex 3-D treatment planning is required for accurate charged particle therapy, using CT and MRI scanning as the prime methods of tumor localisation and target volume delineation (12). After initial evaluation which includes a careful history and physical examination, an individually constructed immobilization device to hold the patient in the desired treatment position was made, generally from perspex or thermoplastic splinting material (polyform) . A planning CT scan and/or MRI was performed with patient in the immobilization device and in treatment position whenever possible. At LBL, a CT scanner was built to scan the patient in either prone, supine or upright position. For MRI scans, a supine scanning position had to be used. To accomodate the different position, techniques for image correlation and data transfer techniques were developed at LBL to assist in treatment planning (12,13,20).

The final charged particle treatment planning was based on the CT scan, using the computerized treatment planning system developed at LBL (12); this provided the density data to account for tissue inhomogeneities in the beam path. Custom made beam shaping devices (collimators) and tissue compensators were designed and fabricated for each individual portal. Alignment aids such as digitally reconstructed beam portal radiographs and templates were created using the treatment planning system. Patient set up on the treatment machine included verification films taken daily before each treatment to assure accuracy.

At LBL, the beam energies utilized were 150/ 232 MeV/u for helium ions and 585/670 MeV/u for neon ions. Tumor doses were expressed in physical Gray and in Gray equivalent (GyE) by multiplying the charged particle beam physical dose by the RBE, representing the ratio of the photon beam dose to the charged particle beam dose required for the same late effects. For skin and most normal tissues, the RBE used for neon ions was ~ 2.5, ranging from 2.0-3.0 depending on position in beam, LET, dose fraction size, etc.

Treatment planning for heavier ions such as carbon or neon must also take into account the fragmentation tail. LET and RBE values are different in each portion of the beam profile and must be assessed in some meaningful way to plan for normal tissue late effects. Some specialised tissues have higher RBE values than skin and other tissues. The central nervous system tissue has an RBE value for neon ions of 4.5 compared to megavoltage irradiation and for the gastrointestinal tract, the RBE may also be elevated at about 3.5 .

Clinical results with Helium Ions

Skull Base:

Helium ions deposit a small amount of high_LET which must be accounted for in treatment planning but insufficiently to act biologically as heavier charged particles . Their clinical and biological effects appear to be quite similar to those reported for protons, and because they were technically easier to produce at UCLBL than protons were the mainstay of treatment with low-LET ions. During the period from 1977 through 1992, 223 patients were irradiated with helium and neon ions at UCLBL for tumors either arising in or extending to the skull base (10). 126 patients had lesions arising in the cranial base, mostly chordoma (53 pts), chondrosarcoma (27 pts), paraclival meningioma (27 pts) with 19 patients having other histologies such as osteosarcoma or neurofibrosarcoma. There were also 22 patients with primary or recurrent squamous carcinoma of the nasopharynx extending to the skull base, 44 patients with major or minor salivary gland tumors, mostly adenocarcinoma and 31 patients with squamous carcinoma of the paranasal sinuses, all with cranial base extension.

Factors of importance in irradiation of skull-based tumors include histology, site, tumor volume and whether primary or recurrent disease. Carefully planned and delivered charged particle irradiation of lesions originating in and extending to the cranial base offers an increase in tumor dose ranging from 20 to 35%, depending on location. Local control and survival appeared improved in all tumor histologies, following the ability with charged particles to deliver high tumor doses (mean of 65 Gray-equivalent) with relative sparing of the adjacent normal tissues. The Kaplan-Meier (K-M) 5 year local control was 85% for meningioma, 78% for chondrosarcoma, 63% for chordoma and 58% for other sarcoma. K-M survival rates at 5 years were 82% for meningioma, 83% for chondrosarcoma and 72% for chordoma. Nearly as high local control (58%) was seen in the other sarcoma histologies (including osteosarcoma) with K-M survival rate at 5 years of 71%.

K-M local control rates for the entire group of 126 patients with primary skull base tumors were 71% at 5 years and 57% at 10 years ; K-M survival was 77% at 5 years and 62% at 10 years. The follow up ranged from 4 to 191 months with a median of 51 and a mean of 58 months. During 1977-1986, 12 of 29 (41%) patients who had no evidence of disease had grade 3, 4 or 5 complications. From 1987 to 1992, 11 of 55 (20%) disease-free patients had grade 3, 4 or 5 complications. Seven (8%) of the 85 patients had grade 4 or 5 complications as detailed below:

In 22 patients with tumors arising in the paranasal sinuses and invading the skull base, a 5 year K-M local control rate of 60% was obtained; the 5 year K-M survival rate was 38%.

For 21 patients with minor salivary gland tumors invading the skull base treated initially, a 5 year K-M local control rate and survival rate of 68% were obtained. The mean dose was 65 GyE. Of 4 patients with recurrent minor salivary gland tumors infiltrating the skull base, all had local failure and none lived longer than 25 months. In these patients the mean dose was only 55 GyE because 3 of the 4 had previously received full dose irradiation; the other had surgery and chemotherapy.

There were 19 patients treated for major salivary gland tumors, many of whom had locally advanced (11 pts) or recurrent (5 pts) tumors, with a 5 year K-M local control rate of 58%, and a 5 year K-M survival rate of 42%. The 2 year K-M local control in the recurrent group was 50% versus 80% in the nonrecurrent patients. Similarly the 5 year K-M survival was 20% in the recurrent patients compared to 50% in the nonrecurrent patients.

Uveal Melanoma:

Proton and helium ion irradiation of uveal melanoma has now been studied for 15 years with a remarkable consistency of extremely high local control (~98%), retention of the eye (~85%), and preservation of useful vision in about 50% of patients. 347 patients were treated at LBL-UCSF from 1978-1992. These patients were studied at various dose levels from 50-80 GyE/ 4-5 fxs/ 4-16 days without a dose response being seen. In a randomized study of 184 patients comparing helium ions and 125 Iodine plaque therapy, we prospectively studied these modalities in a randomized, dynamically balanced trial (11). 184 of the patients met eligibility criteria; 86 were treated with helium ions and 98 with 125I brachytherapy. Tumors were less than 15 mm in maximum diameter and less than 10 mm in thickness. A minimum tumor dose of 70 GyE was delivered to the tumor apex. There was significantly higher local recurrence rate after 125 Iodine brachytherapy than after helium ion irradiation: (13% vs. 0%). Enucleations occurred more frequently after I 125 brachytherapy (relative risk = 1.99; 95% confidence interval; 0.78 - 5.78). More anterior segment complications occurred after helium ion irradiation.

Remaining problems to be studied including lowering the anterior chamber complications from the entry of the helium beam through further dose-searching studies, and finding effective therapy for those at risk for distant metastases (large lesions, anterior location). Currently about 20% of patients eventually succumb to clinical manifestation of presumably occult metastases at time of therapy. Nowakowski et al.(19) found 42 (16%) of 261 patients with ocular melanoma who were treated with helium ions between January 1978 and November 1986 to have developed metastatic disease. The time between start of helium ion treatment and recognition of metastatic disease ranged from 3 to 67 months (median 27 months). The mean pretreatment tumor height in the patients with metastases was 7.7 mm. All 42 patients who developed metastatic disease have died. The most common site of metastasis was the liver (n = 34). Four (10%) of the 42 patients with metastases also had local recurrence of the tumor. Multivariate analysis identified that anterior location of tumor

(p = .02), and tumor diameter greater than 10 mm (p = .0075) predicted independently the development of metastases and lack of survival.

Clinical Results With High-LET Charged Particles

Heavier particles such as carbon, neon or silicon ions have had insufficient study to prove or disprove their merits in clinical therapy. The lack of sufficient beam time and patient accrual have limited the information that can be derived from the experience although considerable knowledge was gained in the techniques, both physical and clinical, of their use. In some respects the pressure to focus on Phase III trials for the heavier particles limited the opportunity to study their use. Much effort went into trying to develop sucessful Phase III trials that might have been better spent in exploring new techniques and uses for these ions. The carbon ion beam has biological dose localisation advantages which are better than lighter ions such as protons. The ratio of dose in the tumor relative to the entrance region is maximized. Quite sharp lateral edges are present and the small fragmentation tail can be dealt with in treatment planning. Enough high-LET is present to provide significant differences in DNA damage, and supression of radiation repair. Double strand breaks are increased as is other evidence of DNA injury. These effects are maximized in the tumor by the use of the dose localisation secondary to charged particles. Slowly growing tumors seem to be effectively treated by high-LET particles; these include such histologies as salivary gland tumors, prostate gland tumors and some bone and soft tissue sarcoma. Much additional knowledge is needed on understanding the reasons for this and selecting patients likely to benefit from these therapy. Combining such therapy with sensitizing agents has barely been approached in pretherapeutic studies and deserves consideration for clinical Phase I trials. The emphasis for continuing these studies will now shift to Japan and Europe. The NIRS accelerator will be ready to begin clinical studies by late this year or early 1994. An excellent accelerator at GSI, Darmstadt could also begin clinical work in conjunction with the University of Heidelberg.

The Phase I-II clinical trial at LBL using neon ions was reviewed in 1991 by Linstadt et al.(17). A total of 239 patients who had received a minimum neon physical dose of 10 Gy (median followup for survivors 32 months) were evaluable. Compared with historical results, the 5- year actuarial disease specific survival (DSS) and local control (LC) rates suggested that neon ion treatment improved outcome for several types of tumors: advanced or recurrent macroscopic salivary gland carcinomas (DSS 59%, LC 61%); paranasal sinus tumors (DSS 69%, LC 69% for macroscopic disease); advanced soft tissue sarcomas (DSS 56%, LC 56% for macroscopic disease); macroscopic sarcomas of bone (DSS 45%, LC 59%); locally advanced prostate carcinoma (DSS 90%, LC 75%); and biliary tract carcinomas (DSS 28%, LC 44%). The treatment of malignant gliomas, pancreatic, gastric, esophageal, lung, and advanced or recurrent head and neck cancer has been less successful. By May of 1992, a total of 299 patients had completed therapy with at least 10 Gy of neon ions. These patients are still being followed and the results from the previous survey continue essentially as noted above.

Neon Ion Radiotherapy Of Prostate Cancer

High -LET charged particle conformal therapy for locally advanced prostate cancer may be beneficial for slowly growing tumors such as prostatic carcinoma. These beams offer the possibility of less radiation repair of high-LET injury as well as eliminating some of variations in sensitivity during different phases of the cell cycle. In addition, areas of hypoxia within the tumor which are resistant to low -ET treatment are less so in the presence of high-LET irradiation. Charged particle conformal therapy also allows optimal conformation of the high-dose zone to the target volume, mainly the prostate, seminal vesicles and adjacent lymphatics.

Twenty-three patients have been treated , mostly with Stage C carcinoma of the prostate. Both local control and survival appear excellent as compared to historical data for this stage of disease. Only 2 patients have died from disease, both from distant metastases. Two patients are scored as alive with local recurrence, although both are alive. In one patient the biopsy was obtained three months post completion of treatment, followed by orchiectomy and no evidence of subsequent disease. The 2nd patient had a positive biopsy in Australia,and is apparently free of disease on LH antagonists at 5 years post radiation treatment .

K-M local control and survival are projected at the 90% level at 7 years post trteatment in this small group of patients. High -LET charged particle irradiation appears to show high potential in the treatment of locally advanced prostatic cancer and may diminish the local failure rate from approximately 50% to the level of 10% or less However care must be taken in delivering this therapy. We have had 3/23 patients with rectal injuries possibly attributable to the neon ion treatment. One patient had a very large tumor and probably too large a volume was treated. Anal sphincter stricture developed leading to colostomy. Another patient developed an anterior rectal wall ulcer leading to a recto-vesical fistula requiring a colostomy/and ileal conduit. A 3rd patient had a colostomy following development of a rectal ulcer which appeared inferior to the neon target volume. These results indicate caution should be used in escalating doses in conformal therapy. A boost of neon ions for locally advanced prostate cancer after pelvic radiation therapy to 45-50 Gy should probably be in the range of 5-7 Gy or approximately 15-20 GyE.

Heavy Charged Particle Irradiation For Unfavorable Soft Tissue Sarcoma

Between 1978 and 1989, 32 patients with unfavorable soft tissue sarcoma underwent light ion (helium, neon) irradiation with curative intent at Lawrence Berkeley Laboratory (17). The tumors were located in the trunk in 22 patients and head and neck in 10. Macroscopic tumor was present in 22 at the time of irradiation. Two patients had tumors apparently induced by previous therapeutic irradiation. Follow up times for surviving patients ranged from 4-121 months (median 27 months). The overall 3-year Kaplan-Maier local control rate was 62%; the corresponding survival rate was 50%. The 3-year Kaplan-Maier control rate for patients irradiated with macroscopic tumors was 48%, while none of the patients with microscopic disease developed local recurrence (100%). The corresponding 3-year Kaplan-Maier survival rates were 40% (macroscopic) and 78% (microscopic). Patients with retroperitoneal sarcoma did

notably well; the local control rate and survival rate were 64% and 62%, respectively. Complications were acceptable; there were no radiation related deaths , while 2 patients (6%) required operations to correct significant radiation related injuries. These results appear promising compared to those achieved by low-LET irradiation, and suggest that this technique merits further investigation.

Preliminary Results In Heavy Charged Particle Irradiation Of Bone Sarcoma

Between 1979 and 1989, 17 patients with unfavorable bone sarcoma who were treated wholly or in part with heavy charged particle irradiation (helium and/or neon ions) at LBL were reviewed by Uhl et al (26) . The majority of tumors were located near critical structures such as the spinal cord or brain. Gross tumor was present in all but two patients at the time of irradiation. Six patients were treated for recurrent disease. Histologies included osteosarcoma, Ewings's sarcoma, and recurrent osteoblastoma. The followup ranged from 7 to 118 months (median 40 months). The 5-year K-M local control rate was 48%; the corresponding survival rate was 41%. Over half the patients succumbed to distant metastases despite the majority of patients receiving chemotherapy. From the results of this preliminary study, we believe that heavy charged particle irradiation can be effectively used for control of locally advanced or unresectable bone sarcoma.

Irradiation Of Bile Duct Carcinoma With Charged Particles And/Or Photons

A retrospective study by Schoenthaler et al. (24) was performed analyzing all patients with bile duct adenocarcinoma who received radiotherapy through the University of California, San Francisco and at the Lawrence Berkeley Laboratory between 1977 and 1987, a total of 62 patients. UCSF patients received photon therapy (median dose 54 Gy), and LBL patient were treated with helium and/or neon ions (median dose 60 GyE). Forty-eight patients were treated postoperatively with curative intent, 30 with photons and 18 with particles. Thirty-six patients in the study had gross residual disease; none had microscopically negative margins.The overall two year actuarial survival was 28%: 44% for particle treated patients and 18% for patients treated with photons ($p = .048$). Median actuarial survival was 23 months in particle patients and 12 months in photon patients. Local control was also improved, though less significantly, in patients treated with particles (median disease free survival 20 mos vs 4.5 mos, $p = .054$). Compared to conventional photon radiotherapy, treatment with postoperative charged particle irradiation at Lawrence Berkeley Laboratory appeared to offer a survival advantage in this non randomized series.

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