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High-LET Charged Particle Radiotherapy

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HIGH-LET CHARGED PARTICLE RADIOTHERAPY

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The Department of Radiation Oncology at UCSF Medical Center and the Radiation Oncology Department at UC Lawrence Berkeley Laboratory have been evaluating the use of high LET charged particle radiotherapy in a Phase I-II research trial ongoing since 1979. In this clinical trial, 239 patients have received at least 10 Gy (physical) minimum tumor dose with neon ions, meaning that at least one-half of their total treatment was given with high-LET charged particle therapy. Ninety-one patients received all of their therapy with neon ions.

Of the 239 patients irradiated, target sites included lesions in the skin, subcutaneous tissues, head and neck such as paranasal sinuses, nasopharynx and salivary glands (major and minor), skull base and juxtaspinal area, GI tract including esophagus, pancreas and biliary tract, prostate, lung, soft tissue and bone. Analysis of these patients has been carried out with a minimum followup period of 2 years.

TREATMENT TECHNIQUES

These patients were often treated with mixed beam modalities, including photon and helium beams, because of the limited availability of the neon ion beam. In addition, doses of neon ions were slowly escalated in the initial years in order to provide for patient safety and determine appropriate RBE values for normal tissue effects. Therefore the analysis is limited to those patients who received at least 10 Gy physical dose of neon in order to be able to make some useful estimate of high-LET effects, both on tumors and normal tissues. The RBE values utilized in planning treatment are for oxygenated normal tissues such as skin and mucosa; it has been shown experimentally that RBE values for hypoxic tumor cells are higher, and therefore it is possible that the equivalent dose to tumor was higher than those for normal tissues (1,2,3). In addition, specific normal tissues are known to have higher RBE values for high-LET irradiation, particularly CNS which is in the range of 4 to 5 (4). Thus great caution has been observed with respect to neon irradiation of brain and spinal cord, doses being limited to 10 Gy physical (approximately 45 GyE) wherever possible. There may also be higher RBE values for the GI tract than for skin and other tissues, although this has not been fully substantiated (5).

Treatment techniques consisted of multi-port irradiation delivered at the bevatron at UCLBL. Patients were treated to one field per day because of limitations on beam availability and treatment time. The dose fraction

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sizes ranged from approximately 0.9 to 2.0 Gy of neon, approximately equivalent to 2-5 Gy of megavoltage irradiation. However such equivalences are not precise and of limited use in planning high-LET therapy. The total fraction number ranged from as low as 8 to as many as 24 fractions, given 4 days per week.

Careful immobilization techniques were utilized and most patients were treated in the upright seated position since the beam is horizontal. Treatment planning was based on CT and MRI scans with a computerized treatment planning system utilized to produce isodose distributions, patient alignment and portal verification aids, appropriate tissue compensators and individual port collimators. Initially, the beam was enlarged by passing it through lead foils but this was later replaced by magnetic spreading in order to diminish fragmentation. More recently we have introduced a 2D raster scanner into clinical use as part of our program to develop dynamic conformal therapy with heavy charged particles.

Tumor doses were escalated progressively as part of this Phase I-II trial which was directed primarily at normal tissue reactions during the first several years and subsequently included analyses of tumor response. Thus it has required 10 years to accumulate sufficient numbers of patients for preliminary analysis, and to plan and implement definitive clinical trials.

RESULTS

Promising results as compared with historical results with low-LET irradiation were seen for several tumor types (6,7):

	(5 year local control, Kaplan-Maier)
1. Advanced macroscopic salivary gland carcinoma:	61%
2. Locally advanced paranasal sinus tumors:	69%
3. Locally advanced soft tissue sarcoma:	56%
4. Locally advanced bone sarcoma:	59%
5. Locally advanced prostate cancer:	75%
6. Locally advanced biliary tract cancer:	44%

As most of these patients were treated for locally advanced or recurrent tumors, and without optimal beam delivery techniques, these results show considerable potential for future treatment of selected nonresectable tumors with high-LET charged particles.

We have devised current clinical trials to explore such promising tumor sites as prostate, sarcoma and biliary tract. We expect to implement new trials in some of the GI sites in the near future when dynamic conformal heavy ion therapy is available at LBL.

Ongoing current clinical protocols are comparing locally advanced carcinoma of the prostate ("boost") treatment with neon ions against conventional therapy with megavoltage irradiation, and neon ions versus helium ions in a multi-site protocol including bone and soft tissue sarcoma, locally advanced nasopharynx cancer and locally advanced minor salivary gland tumors. A nonrandomized dose searching study is underway for

glioblastoma of the brain in which 2 dose levels of neon ions are studied, 20 versus 25 Gy. MRI studies are utilized to delineate target volumes which are limited to identifiable tumor plus the surrounding area of edema and a margin of 1 cm. For those patients receiving 25 Gy, the final 5 Gy is given only to the identifiable tumor nodule on MRI.

A biliary tract study will be opened shortly contrasting neon ions with helium ions for locally advanced biliary tract carcinoma. This is based on the data from the Phase I-II study which showed a trend to better results with neon ions although not clearly a significant improvement over those patients who received helium ion therapy for biliary tumors.

Evaluation of results for GI tumors has not as yet shown significant survival advantage over low-LET irradiation for pancreatic, gastric or esophageal tumors although local control and tolerance seemed improved. However, clinical studies with dynamic conformal heavy charged particle therapy may provide a higher rate of success since more dose to tumor may be possible without increasing the dose to the GI tract.

Other helium versus neon ion studies are ongoing in an attempt to identify which parameter of heavy ion therapy is of greatest clinical importance: Dose-localization as exemplified by protons or helium ions versus dose-localization plus high-LET biological effect as exemplified by neon ions. The genesis of these studies has been the finding that dose distribution advantages from ions such as protons or helium has marked success in treating numerous tumors in critical locations. A brief summary of some of this experience is given below.

DOSE-LOCALIZATION THERAPY WITH HELIUM IONS

Experience at UCLBL/UCSF with helium ion therapy has successfully demonstrated the advantage of charged particle dose-localization therapy in treating tumors in the eye, orbit, skull base, paranasal sinuses, juxtaspinal area, retroperitoneal space and soft tissue with high rates of local control and survival (8,9,10,11).

EYE

As of June, 1991, we have irradiated 335 patients with helium ions for localized uveal melanoma, mostly large or extra large lesions. The mean initial US height was 7 mm, with mean basal diameters of 9 x 10 mm. The doses have ranged from 48 GyE in four fractions to 80 GyE in five fractions. Treatment courses have varied in duration from 4 to 15 days.

There has been no observed dose response curve, or significant difference in results, at any of the employed dose levels which have included 48 - 50 GyE, 60 GyE, 70 GyE and 80 GyE. Although there appears to be a reasonably similar patient selection in these groups, the dose assignments have not been randomly assigned.

There have been 10 local failures including 1 patient who had a rare ring melanoma. Of the 10 patients who failed locally in the eye, 7 were felt to represent marginal misses or other technical error. In 3 patients the cause of local failure was unknown. Treatment for these patients included

enucleation in 6 patients, reirradiation in 3, and laser treatment in 1. Of the 6 patients enucleated for tumor, 5 expired from distant metastases in 13 to 42 months. One patient expired of unknown causes at 79 months post-enucleation. Four patients reirradiated or treated with laser are alive from 66 to 143 months. However, vision is poor and glaucoma exists in two of the three re-irradiated patients.

The incidence of neovascularity or glaucoma is approximately 35%. Enucleation for complications of therapy have occurred in 46 of 335 patients (14%), and in a total of 51 patients (15%) including those enucleated for recurrent tumor. Preservation of vision with 20/200 has been possible in 40% of patients and at 20/400 or better in 50%.

Distant metastases have developed in 56 of 335 patients (17%). Significant factors in development of metastases are tumor height greater than 5 mm, greatest diameter greater than 10 mm or anterior location of the tumor in the eye. Five-year survival (Kaplan-Maier) in these patients is 80% with a ten-year survival of 72%.

HEAD/NECK CHORDOMA-CHONDROSARCOMA

From 1978 through 1991, 85 patients have been irradiated for chordoma or chondrosarcoma of the skull base or cervical spine, most following partial resection. We have utilized helium ions delivering a mean dose of 67 GyE. The crude local control is 70% (59 of 85 pts) with a follow up period ranging from 2 to 163 months, median of 34 months. The projected 5 year survival by Kaplan-Maier technique is 67%. The 3 year local control (K-M) is 68% and 3 year survival is 70%.

Local control is better for chondrosarcoma than for chordoma, and in the skull base than in the cervical spine. A previous evaluation at LBL has shown a higher rate of local control for small lesions (less than 20 cc), and for those treated at time of initial diagnosis rather than post recurrence (8). Also, failures were more likely in those treated over prolonged time, that is greater than 66-72 days. A sex difference has not been demonstrated, either in incidence, level of local control or survival for non-chondroid chordoma or chondrosarcoma

Serious complications have been encountered at about the 10% level including brain and cranial nerve injury. Critical tissues most subject to injury are cranial nerves 2-8, brain stem, spinal cord and temporal lobes of brain

These results have been duplicated for other histology tumors and in other locations of the body, including some patients with soft tissue or bone sarcoma, advanced nasopharynx and minor salivary gland tumors. Since the preliminary studies were not designed to differentiate between dose-localization and high-LET effects, we believe a randomized, prospective trial between neon and helium in these tumors is indicated.

FUTURE PLANS

Future developments in order to optimize heavy ion therapy are centered around 2 main goals:

1. Development of dynamic conformal heavy charged particle therapy using a 2-D raster scanning system coupled with variable range modulation and a multi-jaw collimator. This will permit further conformation of the high dose zone to the tumor volume with additional sparing of adjacent normal tissues. This ability to further concentrate the high-LET effects in the tumor volume should reduce the possibility of normal tissue complication when using high-LET charged particles such as carbon or neon. Preliminary treatment planning comparative studies have predicted an advantage to conformal therapy but clinical studies will be needed to confirm the amount of gain.

2. Biological predictive assays are needed in order to improve the selection process for individual patients based on tumor parameters. Studies will include individual primary tumor assay comparing tumor sensitivity to low doses of high and low-LET radiation and analysis of tumor kinetics by performing potential doubling time and labeling index assays.

3. Further research into the design and fabrication of cryogenics magnets is needed to provide a smaller machine suitable for a medical center.

SUMMARY

Neon ion radiotherapy has proven to be a clinically feasible treatment modality which offers potential of improved results over conventional megavoltage irradiation in selected tumors. The treatment techniques as developed at LBL appear safe with an acceptable level of late effects. Further information is needed to improve patient selection. The biological explanation for improved results in sarcoma, prostate carcinoma and salivary gland tumors needs to be elucidated. Dynamic conformal heavy charged particle radiotherapy will further improve the therapeutic ratio allowing higher tumor doses with further sparing of normal tissues.

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