High-LET Radiation Therapy of Non-small Cell Lung Cancer

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The majority of patients presenting with non-small cell lung cancer have disease that is either disseminated or too advanced locally for resection. The Radiation Therapy Oncology Group (RTOG) has demonstrated that high-dose conventional radiotherapy can improve local disease control. This has a favorable impact on long-term (not median) survival. Fast neutron radiotherapy is an innovative modality; the role of neutron treatment in improving local control for regional non-small cell lung cancer is being investigated.

Neutrons are uncharged particles. The interactions of fast neutrons in tissue produce 10-100 more ionizations per unit path length than the interactions of high-energy photons, and therefore fast neutrons are a high-LET (Linear Energy Transfer) radiation. This greater energy deposition gives rise to important radiobiologic properties of fast neutrons. High-LET radiation is better able to kill hypoxic cells. This could be important for large tumors such as lung cancer. The radiation damage caused by neutrons is less easily repaired by tumor cells; there is a reduced ability to repair both sublethal damage and potentially lethal damage. In addition, there is less variation in radiosensitivity across the cell cycle.

In the 1970s, Eichhorn* used various combinations of neutrons and photons to treat lung cancer. The neutron beam was cyclotron generated and had a mean energy of 6.2 MeV. This was a nonrandomized series in which autopsies were used to document tumor sterilization. A substantially higher proportion of patients receiving neutrons had local tumor eradication, and there was a trend of increased tumor sterilization with increasing neutron dose. The clearance rates were 33% in photon-only treated patients, 48% in patients receiving 20% of their total dose with neutrons, and 57% in patients receiving 37% of their total dose with neutrons.

Based on these early results, the RTOG designed and conducted a randomized trial of fast neutron therapy in the treatment of non-small cell lung carcinoma. Between July 1979 and March 1984, 102 evaluable patients were entered on a three-arm randomized study. Patients were randomized to receive either photon radiation therapy (60 Gray [Gy] in 30 fractions over 6 weeks), neutron radiation alone (18-20 neutron Gy in 24 fractions over 6 weeks), or mixed beam radiation therapy (a combination of 3/5 photon and 2/5 neutron radiation to a total 60 Gy equivalent in 30 fractions over 6 weeks). The randomization was stratified according to tumor size, histology, and neutron treatment facility. Thirty-nine of the evaluable cases received photons only, 29 received neutrons alone, and 34 received mixed beam treatment.

The neutron treatments in this study were delivered using low-energy, laboratory-based, fixed horizontal beam neutron generators. There were considerable problems associated with these facilities. Treatment simulation procedures and beam check films were not optimal. These beams had poor depth dose characteristics and poor skin sparing. However, at that time the laboratory-based neutron generators were the only ones available for neutron therapy.

In this study, the response of the tumor to treatment was determined by serial chest radiographs or chest CTs. A complete response was defined as the disappearance of all previously measurable tumor. A partial response was defined as the reduction by at least 50% of the product of the largest perpendicular diameters of the tumor. Because of the rapid onset of radiation fibrosis after neutron treatment, the maximum tumor response was evaluated after completing therapy.

The overall response rate (complete plus partial) was the same for all three treatment regimens (33-39%). There were no statistically significant differences in the median survival among the three treatment groups. The median survival was 7.5 months for the photon-treated group, 8.1 months for the patients in the mixed beam group, and 6.9 months for the neutron-treated group. The 3-year actuarial survival for the subgroup of patients having a complete or partial tumor response at 6 months from initiation of treatment was 12% for photon patients, 25% for the neutron patients, and 37% for the mixed beam patients. The difference in 3-year survival between the mixed beam group and the photon group was marginally significant; however, the overall differences in survival were not significant.

Treatment-related complications were graded according to the joint RTOG/EORTC scoring scheme for each organ system. The overall severe complication rate was more severe for the neutron containing treatments. The severe toxicity rates were 5.4% for the photon arm, 14.7% for the mixed beam arm, and 30.9% for the neutron arm. There were a total of 5 fatal complications, which occurred in the two neutron arms. These complications were due to pneumonia, pulmonary fibrosis, or myelitis.

A new generation of neutron treatment facilities became available in the United States in 1984. These are hospital-based clinical cyclotrons which produce high-energy neutron beams and have isocentric delivery systems. Subsequently, an RTOG randomized dose searching study was done to determine the optimal neutron dose in the thorax using 12 fractions in 4 weeks. Neutron doses of 18, 20, and 22 Gy were employed. Based on this randomized dose optimization study, 20 Gy in 12 fractions over 4 weeks was chosen as the neutron treatment for the next cooperative randomized study.

In addition, a pilot study was done at the University of Washington using both chemotherapy and radiation therapy for limited non-small cell lung cancer. The patients received two cycles of chemotherapy consisting of vinblastine-mitomycin followed in 3 weeks by vinblastine-cisplatin. Three weeks later, the patients received neutron radiation to the primary tumor plus elective whole brain radiation with photons. The target volume for the neutron radiation was...
defined as the visible margins of tumor after chemotherapy. In view of the severe pulmonary toxicity associated with neutron treatment in the first RTOG randomized study, the treatment volumes were quite economical.

Twenty-nine percent of the patients had no evident disease after treatment. In these patients there was no evidence of residual, discrete tumor after treatment, but changes were seen within the treated field that could be due to either residual tumor or fibrosis. The median survival for these patients was 13.5 months. The incidence of clinically evident pneumonitis was 11%; this was fatal in 1 patient. Another patient experienced necrosis of a lobe which also was a fatal complication. There were no instances of myelitis.

Out of 27 recurrences, 16 were locoregional only, 8 were distant only, and 3 were locoregional plus distant. The site of locoregional recurrence was scored as either in or out of the radiation field in the 19 patients experiencing locoregional failure; 40% of these recurrences were outside the radiation field. This may well have been related to the economical neutron treatment fields which were used to avoid excessive normal tissue toxicity.

In September 1986, a new neutron cooperative study was initiated. This is a phase III study of neutrons vs photons for inoperable, regional, non-small cell lung cancer. Approximately 120 patients have been entered in this study, and the expected completion date is July 1989. In this study, patients are stratified by RTOG tumor stage, weight loss, and Karnofsky Performance Status. Patients are randomized to receive either photon treatment consisting of 66 Gy in 33 fractions over 7 weeks or neutron treatment consisting of 20.4 neutron Gy in 12 fractions over 4 weeks. All patients receive prophylactic brain irradiation (36 Gy in 20 fractions). Patients on the neutron arm receive the first 10.2 Gy to the tumor volume plus a standard margin, the ipsilateral hilum and mediastinum using AP/PA fields. The gross disease is then boosted using an off-cord technique for the next 10.2 Gy. It is anticipated that this study using high-energy isocentric equipment will define the proper role of fast neutrons in the treatment of non-small cell lung cancer.

REFERENCES
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Report on the IASLC Le Havre Workshop on Combined Modality Treatment in Small Cell Lung Cancer*

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Chemotherapy is the standard treatment of SCLC, but after the initial gain observed in the 1970s, no further benefit has been obtained recently, and a majority of patients fail within 15 months. The high proportion of thoracic recurrence in patients with limited disease calls for local treatment and radiation therapy is the most common approach to be combined with chemotherapy in limited SCLC. The Le Havre Workshop focused on the fundamental and clinical aspects of the various modalities of CT and RT associations and has suggested new directions for research and therapeutic applications particularly in SCLC.¹

MATHEMATICAL MODELS

The objective of mathematical modeling is the estimation of outcome measurements using a range of parameters derived from experimental and clinical data. Combined modality treatment can be optimized by the hypotheses formulated from these measurements. Non-cross resistance may be more frequently observed than would be generally supposed because of the large variety of drugs whose effect is inhibited by common biochemical mechanisms. In experimental tumors some known parameters, such as log kill effect for RT and CT, mutation rate and mechanisms of resistance for drug treatment, normal tissue tolerance to hypoxia, and repair of sublethal damage for RT, permit development of mathematical modeling to predict responses to a simulated treatment. In human tumors, these parameters are much less known, and further research in these areas should be encouraged.

BIOLOGY

Resistance to chemotherapeutic agents as well as irradiation may be acquired, and this type of resistance is usually genetic. Numerous studies in recent years have been facilitated by the development of lung cancer lines from patients both sensitive and with acquired drug resistance. The use of spheroid tumor cells in culture is also of potential value in this regard. Monoclonal antibodies that measure target enzymes or membrane proteins and molecular probes to screen for gene amplification and mutation are now available and can be used in the study of resistant cell lines to the most common drugs given in the treatment of SCLC. Classic morphology is unable to predict CT resistance in SCLC; recent biologic advances should significantly increase our knowledge in these matters and will probably have a large impact in therapeutic management.

CONCURRENT, SEQUENTIAL, AND UNCONVENTIONAL COMBINATIONS

Chemotherapy and chest irradiation have been combined

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CHEST / 96 / 1 / JULY, 1989 / Supplement 735