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External beam radiation therapy for unresectable non-small cell carcinoma of the lung has produced significant survival in patients with disease limited to one hemithorax. New approaches to improve the results of radiation treatment of these patients include interstitial implantation, the use of hypoxic cell sensitizers, biologic response modifiers, as well as changes in the technique of radiation therapy. This includes the use of modern computerized tomographic scanning technology for better definition of tumor volume as well as the use of two fractions per day in the treatment of non-small cell carcinoma of the lung. Initial results of these studies are encouraging, with an increase in patient survival suggested.

More than 135,000 new cases of bronchogenic carcinoma were diagnosed during 1983 in the United States, 80% of the non-small cell type (1). Lung cancer is the most lethal malignancy afflicting American men, and its incidence among women is rising rapidly. Approximately 117,000 deaths are attributed to this disease annually.

Only a small percentage of patients have resectable non-small cell lesions at the time of initial diagnosis; of the resected patients, only about 50% will survive more than five years (2).

For patients with pathological Stage I disease (T1 NO MO, T1 N1 MO, or T2 NO MO), the outlook for survival after surgical resection is reasonable. In a large series reported by Mountain (3), 80% were alive at one year and 55% at five years. Unfortunately, after completion of surgical staging, fewer than 20% of patients fall into this category. Of the 3-5% of patients who have Stage II disease (T2 N1 MO), median survival after surgery is only 18 months; 20-35% of patients survive for five years, depending upon histology. For patients with resectable Stage III disease, median survival is about one year; death from local tumor occurs in two thirds of these patients (2).

Radiation Therapy

The role of radiation therapy in the management of unresectable or inoperable non-small cell carcinoma has become better defined over the years. Roswit, et al (4) reported a 22% one-year survival rate for patients treated by radiation therapy with 4,000 to 6,000 cGy* in four to six weeks, as compared to a 16% one-year survival rate for a similar patient group treated with a placebo. In a randomized trial a group of patients treated with 4,000 cGy in four weeks by a combination of radiation therapy and nitrogen mustard was compared to a delayed treatment group. The one-year survival rate of both groups was 24% (5). This percentage is lower than that recently reported by the Radiation Therapy Oncology Group for inoperable non-small cell cancer (6). Further evidence for the effectiveness of radiation therapy in controlling the tumor and prolonging survival is provided by the studies of Bromley and Szur (7), Bloedorn, et al (8), and Hellman, et al (9). These studies revealed that doses from 4,700 to 6,000 cGy, when used before operation, were irradiated with complete destruction of the primary tumor in 40-60% of the cases.

Cox, et al, (10) and Eisert, et al (11) described 30% tumor clearance in patients treated with lower than 4,500 cGy, as compared to 50% with higher doses. Results were better with daily treatment five times per week rather than with one to three weekly fractions. Petrovich, et al (12), in the Veterans Administration Lung Cancer Study Group, related dose and tumor control to survival; 50% of patients who received 1,600 rets or more of radiation alone survived one year. The use of CCNU and hydroxyurea in this randomized study did not influence survival or local control.

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*The Gray (Gy) has replaced the rad as a unit of radiation dose. 1 Gray = 100 rad. 1 cGy = 1 rad.

Studies of the Radiation Therapy Oncology Group (RTOG)

Since its inception, the Radiation Therapy Oncology Group (RTOG) has carried out studies on the treatment of lung cancer. In a prospective trial, the RTOG compared four different radiation treatment schemes for inoperable localized non-small cell lung cancer: 4,000 cGy continuous, 4,000 cGy split course (two courses of treatment interrupted by a treatment-free interval), 5,000 cGy continuous, and 6,000 cGy split course. Latest available data from RTOG protocol 73-01 (6,13) indicate that the most effective dose fractionation for localized unresectable non-small cell lung cancer is 6,000 cGy delivered with a daily dose of 200 cGy per fraction, five times weekly. When compared to the other three treatment schemes of the study, a dose response curve can be suggested. An analysis of the fractionation schemes which use 200 cGy per day five days a week revealed that local failure at 4,000 cGy was 64%; at 5,000 cGy, it was 45%; and at 6,000 cGy it was 38%. Conversely, the proportion of patients who have not failed either locally or at distant sites is 18% at 4,000 cGy, 22% at 5,000 cGy, and 29% at 6,000 cGy. No distinct dose response relationship is evident for distant metastases, which develop in 37% of patients treated with 4,000 cGy; at 5,000 cGy, the relationship is 50%, and at 6,000 cGy, 46%. The higher rates for the 5,000 cGy and 6,000 cGy levels suggest that because of better local control more patients are living longer and are more likely to manifest distant metastases. Depending upon cell type, between one third and one half of patients with squamous, large cell and adenocarcinoma of the lung are expected ultimately to develop distant metastases.

Split course versus continuous irradiation

The use of daily fractionation as a continuous course compared to a split course of irradiation therapy is in dispute. In a split course a treatment-free interval is spaced between two or more treatment series of moderately high daily doses. Lee (14) and Levitt, et al (15) reported no significant advantage for the split course, while Holsti and Vuorinen (16) and Abramson and Cavanaugh (17) described a one-year survival advantage for patients treated with a 4,000 cGy split course as opposed to a 6,000 cGy continuous course. Guthrie, et al (18) found that 6,000 cGy in a split course gave a higher survival at 12 months than a 4,000 cGy split course, while Salazar, et al (19) also reported some advantage for a split course regimen. The latter authors found, however, that survival is not the optimal parameter because the development of distant metastatic disease is overwhelming. They stressed that local tumor control is the most significant result of successful therapy.

Survival after radiation therapy

Several recent studies have shown that local control by radiation therapy achieved significantly longer survival, compared to that of patients for whom local control was not possible. In a prospective RTOG trial, responding patients had significantly longer median survival than did non-responding patients (75 versus 36 weeks). The median survival for all patients according to the different treatment regimens did not differ significantly (37 to 47 weeks), but the frequency of distant metastases in adenocarcinoma and large cell undifferentiated carcinoma was twice that observed for patients who had squamous cell carcinoma. While prognostic factors include tumor size, lymph node involvement, and performance status (20,21), the RTOG data suggest that tumor cell type may also be an important prognostic factor. The prognosis is distinctly better for squamous cell carcinoma than for adenocarcinoma or large cell undifferentiated carcinoma (9,13).

Complications from radiation therapy for non-small cell carcinoma must be monitored carefully. Brady, et al (22) and Phillips and Margolis (23) determined that radiation pneumonitis occurs in approximately 50% of patients treated with 2,650 cGy in 20 fractions to the whole lung, making it necessary to reduce the volume of the irradiated lung to a minimum. Clinical symptoms are not always present despite radiographic changes. These sequellae are exaggerated by combined modality treatment which produces an increased reaction to the radiation therapy in the lung as well as in other tissues such as the esophagus.

Combination Radiation and Chemotherapy

Based on the reported effectiveness of radiation and chemotherapy in treating other cancers, such combinations have also been tried in lung cancer to minimize distant metastases as well as to assure better local control. Adjuvant chemotherapy and/or radiotherapy have contributed little to improve the excellent results in patients whose disease has been totally resected. Furthermore, combined modality approaches have been ineffective in locally advanced or inoperable disease settings (24-28). In addition to local-regional extent of the disease, failures frequently are due to distant metastases. Mohuiddin (29) reported that, at autopsy, 25% of patients with squamous cell carcinoma and 55% of patients with large cell or adenocarcinoma had distant metastases. This high frequency of distant metastases justifies the continued investigation of systemic therapy in addition to local treatment, realizing the risk of higher incidence of treatment-related side effects and complications.

New Approaches

Current studies are aimed at improving the results of radiation therapy in unresectable non-small cell carcinoma. Investigative changes in time-dose fractionation schedules include: 1) increasing total doses by one fraction per day, and 2) combining a large field treatment to the primary tumor and area of potential nodal involvement with a smaller boost field treatment limited to lymph nodes and areas grossly involved by the primary tumor. Doses of approximately 7,500 cGy, similar to those presented by Mohuiddin (29), are used in these trials. In addition, the Radiation Oncology Group is completing a pilot study in which two fractions per day of 1.2 cGy were given 4 to 6 hours apart, for a total of 5,040 cGy to a large field. Subsequently, these are increased to 6,000-7,440 cGy with small fields directed to tumor bearing areas only. This study requires the use of CT scanning and computerized treatment plans in order to minimize irradiation of normal tissues, especially lung, heart, and spinal cord. In 91 patients [including those with T4 and N3 lesions as well as smaller ones (T2, T3, N1, N2)], a one-year survival of 71% has been achieved. Complications have been acceptable; only one patient developed life-threatening pneumonitis from radiation therapy (30).

Other attempts are being made to improve therapeutic results by the use of neutrons. In an RTOG study, treatment is randomized to photons alone, neutrons alone, or a mixed photon and neutron beam. Approximately one hundred patients have been studied thus far; the results are encouraging but not decisive.

Attempts have been made to enhance radiation effect with hypoxic cell sensitizers, especially with misonidazole. A recent RTOG study employed fractionation up to 6,000 cGy accompanied by daily administration of misonidazole (0.4 mg/m^2), but no significant improvement in local control and patient survival has yet been reported. In another study, approximately one hundred patients are receiving six fractions of radiation of 600 cGy twice a week with and without administration of misonidazole (1.75 mg/m^2) on the same day; no data are yet available.

In past studies, no advantage was demonstrated in the use of the immune modifier, levamisole, in treating unresectable small cell and non-small cell carcinoma. Based on the results of a pilot study performed at Georgetown University (31), the RTOG has undertaken a study to compare the treatment of non-small cell carcinoma of the lung by radiation therapy (6,000 cGy photons) with and without supplemental administration of thymosin (0.9 mg/m^2 twice weekly) for one year after the completion of radiation.

Studies which combined radiation therapy and chemotherapy, such as VP-16 and cis-platnum, have yielded variable results. In some studies, response rates have reached 56% (32), but an RTOG study of approximately 20 patients has not produced sufficient data for analysis.

Other modalities include 1) the combination of external beam radiation therapy with administration of immunoglobulins tagged with radioactive isotopes, and 2) laser radiation for relief of obstruction of the bronchial tree in combination with radiation therapy. These procedures are too recent to be evaluated.

In summary, radiation therapy can lead to significant tumor control as well as to improved survival in patients with non-small cell carcinoma, depending on the extent of disease at presentation. Radiation alone with traditional once-a-day fractionation achieves complete regression in about 53% of T1 lesions and in 35-48% of T3 lesions. Median survival varies from 30 weeks for non-responders to 75 weeks for complete responders. The result is significantly related to performance status and other prognostic factors. Forty percent of complete responders survive for two years. New techniques have improved the one-year survival rate to 71%. However, patients who fail to respond or whose disease progresses under treatment have a very brief survival.

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