The Role of Radiation Therapy for Carcinoma of the Lung

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A large proportion of patients with carcinoma of the lung may benefit from the use of radiation therapy. Operable patients have not been shown to benefit from preoperative irradiation, but postoperative irradiation has improved survival in those found to have involvement of hilar or mediastinal lymph nodes. Radiation therapy is the only potentially curative treatment for patients who are inoperable, but do not have distant metastasis. Control of the local tumor is very dependent upon dose-fractionation-time relationships. Patients who are relatively asymptomatic, i.e., they have a high performance status, are curable if treated promptly with radiation therapy. Small cell carcinoma requires both radiation therapy and chemotherapy. The optimal method of combining the two modalities is yet to be determined, but prophylactic cranial irradiation is necessary to control microscopic metastases that are not affected by systemic chemotherapy, and thoracic irradiation is necessary to give the highest probability of control of the primary tumor. Prophylactic cranial irradiation has also been shown to reduce the frequency of brain metastasis in patients with squamous carcinoma, large cell carcinoma, and adenocarcinoma; it may become more important in these cell types when more effective chemotherapy is developed.

A large proportion of patients with cancer of the lung will require treatment with radiation therapy some time during the course of the disease. For patients who are operable, irradiation might be considered before or after resection. Patients who have locally advanced disease or who are medically inoperable, receive irradiation alone or in combination with chemotherapy as the definitive approach to their disease. Approximately half of all patients with carcinoma of the lung present with distant metastases and require radiation therapy for the palliation of distressing symptoms. The palliative role of radiation therapy is well-recognized and is widely utilized. It will not be discussed further as the emphasis in what follows is on the role of radiation therapy in patients with localized disease.

RADIATION THERAPY IN PATIENTS WITH OPERABLE CARCINOMA OF THE LUNG

Candidates for definitive treatment by resection include those with Stage I and Stage II squamous cell, large cell, and adenocarcinoma, whose pulmonary function will permit a lobectomy or pneumonectomy. For such patients, irradiation might be considered as a preoperative or postoperative adjuvant to resection. Preoperative irradiation was justified on the basis of short-term studies which showed apparent

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sterilization of tumor in resected specimens after irradiation [1]. A national cooperative trial of the Veterans Administration Surgical Adjuvant Group was undertaken on this basis. More than 90 percent of the patients were treated with conventional X-irradiation as this study was conducted before most institutions had supervoltage equipment. Furthermore, patients with small cell carcinoma were included in the trial. The results showed a similar survival for patients who actually underwent resection following the irradiation compared to those with resection alone. The radiation therapy was associated with a higher complication rate, and the investigators concluded that preoperative irradiation did not contribute favorably to the outcome of patients with carcinoma of the lung [2].

Postoperative irradiation should be considered in any patient where the risk of microscopic residual disease is high. Patients with squamous cell carcinoma who have undergone a “curative” resection are more likely than patients with the other cell types to have persistent local disease without evidence of distant metastases [3]. To date, there is no evidence to suggest any benefit from postoperative irradiation for patients who are free of regional lymph node metastases. In fact, one study [4] showed a decreased survival in patients with negative nodes who received postoperative irradiation. Patients with metastases in para-bronchial, hilar, and mediastinal lymph nodes have an increased probability of long-term survival if they receive postoperative irradiation [5,6,7,8]. An ongoing randomized trial of the EORTC [9] shows a slight survival advantage for irradiated patients with positive lymph nodes, but it is not statistically significant. However, this trial does not show any disadvantage in survival for patients with negative nodes who received postoperative irradiation.

The oft-quoted work of Smart [10] confirmed the ability of radiation therapy to control localized tumors that otherwise would have been operable. As will be apparent from results in patients with inoperable disease, there is little doubt that irradiation can control limited intrathoracic tumors. However, at present, there is no reason to prefer irradiation to resection except for patients whose pulmonary function would not permit the appropriate operation.

IRRADIATION FOR PATIENTS WITH INOPERABLE CANCER OF THE LUNG

Effective irradiation of patients with inoperable or unresectable bronchial carcinoma, in addition to providing palliation, prolongs survival. If the tumor in the chest is controlled, the median survival is doubled [11]. Higher doses of irradiation are associated with the higher probability of local control [11]. As confirmation that the local tumor is a major determinant of survival, increasing doses of irradiation have a direct correlation with increased survival [12]. There is a natural concern that higher doses of irradiation might lead to more damage of the normal lung. However, morbidity from irradiation is more a function of the volume irradiated than the dose. Doses above 2,500 rad in 2½ weeks consistently produce pneumonitis and subsequent scarring within the irradiated volume. The utilization of individualized blocks that protect all normal lung possible (Fig. 1A) permits high doses of irradiation to be delivered to a restricted volume with a minimum of late effects (Fig. 1B). The additional justification for definitive irradiation in patients with inoperable but localized disease is the finite curability of such patients. Several authors [13,14,15,16,17] have reported three-year survival rates between 7 and 12 percent. With a more selected patient population, careful, high-dose irradiation results in a higher probability of survival. In a group of 197 patients with histologically or
cytologically confirmed carcinoma of the lung of all cell types [18], short-term survival was related to the ability to control the intrathoracic disease. Among the 92 patients with a performance status of 80 to 100 patients, those whose intrathoracic tumor was controlled had a five-year disease-free survival rate of 22 percent. No patient with persistent or recurrent thoracic disease lived beyond 27 months [19].

FIG. 1A. Treatment volume for a 61-year-old woman with large cell carcinoma compressing trachea and right upper lobe bronchus. Minimum tumor dose was 6,300 rad in 35 fractions in seven weeks (maximum dose in spinal cord limited to 4,500 rad in five weeks by use of oblique fields).

FIG. 1B. Chest film three years after treatment; patient is free of any evidence of cancer.
IRRADIATION FOR PATIENTS WITH SMALL CELL CARCINOMA

Small cell carcinoma of the lung has been recognized for many years to be strikingly responsive to irradiation. It is also very responsive to chemotherapy, and very effective drug combinations have been developed in the past decade [20]. The literature that has developed in the past decade is too vast to review in detail. The impressive responses to chemotherapy led to the assumption that thoracic irradiation was unnecessary. This assumption was tested in a prospective trial with highly effective chemotherapy in which thoracic irradiation was withheld unless there was failure of complete response or recurrence after complete response. Local recurrences developed in 48 percent of these patients [21]. It is apparent that thoracic irradiation is essential at some point in the management of patients with localized small cell carcinoma, and the same can be said for patients with disseminated disease who respond completely. An interaction of the thoracic irradiation with chemotherapy has been demonstrated [22]. Relatively low doses of irradiation that would be ineffective alone are able to control the thoracic disease when combined with effective chemotherapy. With adequate irradiation in combination with chemotherapy, the local recurrence rate can be reduced to 15 percent.

The importance of dissemination of small cell carcinoma to the central nervous system has been recognized, but the magnitude of the problem has been underestimated. The lengthening survival of patients with small cell carcinoma because of effective chemotherapy has resulted in a much higher rate of spread to the CNS than even autopsy studies would have suggested [23]. Prophylactic cranial irradiation, with doses between 2,500 and 3,000 rad in two weeks, has reduced the frequency of brain metastasis in several series [24]. A comparison of the risk of brain metastasis related to survival and the use of prophylactic cranial irradiation shows that the probability of brain metastasis does not continue to rise as patients live longer in the prophylactically treated group (Fig. 2). This indicates that the microscopic amounts of tumor are completely eliminated.
PROPHYLACTIC CRANIAL IRRADIATION FOR ALL CELL TYPES

Prophylactic cranial irradiation (PCI) has become a standard part of the management of patients with small cell carcinoma in most institutions. The risk of brain metastasis has become fully apparent in patients with small cell carcinoma, but it has only recently been recognized as a problem of equal magnitude in patients with large cell carcinoma and adenocarcinoma [25]. A recently completed, randomized prospective trial of the Veterans Administration Lung Group investigated the role of PCI in conjunction with thoracic irradiation, without chemotherapy, in patients with carcinoma of the lung of all cell types. The dose used was 2,000 rad in 10 fractions in two weeks. This dose, in the absence of chemotherapy, did not significantly reduce the frequency of brain metastasis in patients with small cell carcinoma. However, patients with "non-small cell" carcinoma did have a statistically significant reduction ($p = .038$) in the frequency of brain metastasis for patients who received PCI [26]. Therefore, there may be an increasingly important role for prophylactic cranial irradiation in patients with these cell types.

CONCLUSION

The role of radiation therapy in the current management of patients with carcinoma of the lung is evolving and expanding. In addition to a beneficial effect for patients with distressing symptoms, irradiation also has a role in operable patients and those who are inoperable but still have localized disease. Patients with resectable disease who are found to have involvement of regional lymph nodes benefit from the systematic administration of postoperative irradiation. Patients with inoperable but localized disease have a prolongation of survival from thoracic irradiation, a survival which is closely associated with the dose of irradiation administered; a small proportion of these patients can be cured. The consistent use of thoracic irradiation is also important in the management of patients with small cell carcinoma, as is prophylactic cranial irradiation; when combined with effective chemotherapy, the prospects for long-term disease-free survival for patients with small cell carcinoma are improving.

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