Interstitial Pulmonary Infiltrate following Combined Therapy for Esophageal Carcinoma*

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Seven patients with squamous cell carcinoma of the esophagus received radiation therapy in twice weekly 400 rad fractions over five weeks followed by esophagectomy. Four of these patients developed severe interstitial pulmonary infiltrates and died of pulmonary insufficiency 18-50 days after surgery. In three of these patients the infiltrates were detected within 24 hours of surgery while the infiltrate was not present until the eighth postoperative day in the fourth patient. Postmortem examination revealed widespread dilatation of interstitial and subpleural lymphatics. It is postulated that the combination of large fraction radiation therapy followed by extensive surgery resulted in lymphatic obstruction.

Carcinoma of the esophagus has an extremely poor prognosis with 80 to 90 percent of patients dying within a year, and less than 5 percent of patients surviving five years. The surgical mortality for resection of the esophageal tumor is high, and most of these patients suffer either local recurrence or metastatic disease. Preoperative irradiation may increase the number of patients who may undergo resection and decrease local recurrences. To test this modality, we began a new treatment protocol in which patients were treated with large fraction radiation therapy followed by esophagectomy. Radiation therapy was delivered in fractions of 400 rads minimum tumor dose, twice weekly for five weeks for a total of 4,000 rads. This has resulted in the development of a progressive interstitial pulmonary infiltrate in four of the seven patients treated in this manner. The radiographic appearance and presumed explanation for its occurrence is presented.

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Materials

Seven patients with squamous cell carcinoma of the esophagus were studied. They ranged in age from 61 to 65 years; all were men. The tumors were located in the middle one-third of the esophagus in four patients and the distal one-third in three patients. Each patient received twice weekly 400 rad fractions (minimum tumor dose) over five weeks for a total of 4,000 rads (uncorrected for lung trans-

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Results

Diffuse interstitial pulmonary infiltrates, unrelated to radiation therapy treatment ports, developed in four of the seven patients treated in this fashion. In three of the patients, mild interstitial changes were present 24 hours after surgery and progressed to marked infiltrates by 48 to 72 hours (Fig 1). In the fourth patient, changes did not develop until eight days after surgery and progressed gradually over the next three weeks to involve the entire lungs extensively (Fig 2). The infiltrates began in an asymmetric fashion, being more marked in one area of the lung initially, but progressively affecting all lung fields. In two patients, the left lung was initially
Forty-eight hours after esophagectomy with esophagogastrostomy an interstitial pulmonary infiltrate developed at the right base and after 72 hours progressed to involve the entire lung fields.

more severely affected (Fig 3), in one the infiltrate began in the right base (Fig 1), and in one, the infiltrate began as a bilateral process (Fig 4). Two patients received the radiosensitizing agent and two did not. In all four patients, the pulmonary infiltrates remained predominantly interstitial. There were no pleural effusions, and Kerley B lines were not present.

The patients were examined extensively for the presence of an infectious agent to explain the pulmonary findings, but none was found. No chemo-

therapy was employed, and there was no evidence of pulmonary toxicity from anesthesia. The location of the pulmonary changes did not correlate with the radiation ports. The patients became increasingly difficult to support and all died of pulmonary insufficiency 18 to 50 days after surgery.

Postmortem examinations were obtained on three of the four patients. In each case, there was extensive organizing alveolitis and interstitial fibrosis, but the most impressive finding was widespread dilatation of interstitial and subpleural lymphatics (Fig 5). A detailed description of the pathologic findings and their correlation with the radiation dose is in preparation.5

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The three patients who did not exhibit these pulmonary interstitial changes, however, have had an excellent clinical response. In two patients, no tumor was found in the primary specimen after irradiation. One of these patients is still free of disease 20 months after presentation, while the other developed a local recurrence and died 17 months after presentation. The third patient was found to have lymph node extension at surgery and died of a local recurrence at 11 months. An additional 24 patients were treated with radiation therapy in an identical fraction schedule with doses as high as 4,800 rads but without surgery. Initially, these patients were selected for treatment with radiation therapy alone because they were medically unsuitable for surgery. Later, as the pulmonary complications developed in those patients undergoing esophagectomy, the surgical arm of the protocol was abandoned. None of these patients treated with radiation therapy alone exhibited evidence of significant pulmonary toxicity despite close monitoring with chest radiographs.

**DISCUSSION**

Conventional therapies for carcinoma of the esophagus have not been effective, and the prognosis remains dismal. Surgery has a high operative mortality, particularly in patients with total esophageal obstruction or nutritional depletion. Even successful esophageal resection frequently results in local tumor recurrence or the appearance of nodal metastases. Radiation therapy provides good initial palliation, but most tumors eventually recur. The long-term results are poor with both techniques; however, surgical palliation appears more durable.

The combination of irradiation followed by esophagectomy has shown promising results, particularly in Japan. By reducing the size of the primary tumor and decreasing its extension along the esophagus, more tumors are susceptible to complete surgical resection. In many cases, distant metastases are already present, but not yet detectable. However, preoperative irradiation may reduce the dissemination caused by surgical manipulation. The development of an interstitial pulmonary infiltrate presented a perplexing clinical problem. The pulmonary findings at autopsy were interpreted as organization of unresolved edema fluid, resulting from irradiation and surgically-induced damage to mediastinal lymphatics. The pulmonary changes did not correlate with the radiation ports and the time course was also inconsistent with radiation pneumonitis.

These changes have not been previously described in patients receiving conventionally fractioned irradiation followed by esophagectomy and esophagogastrectomy. Presumably, the large fraction given our patients in order to maximize irradiation with each dose of misonidazole, contributed to this unusual postoperative complication. The combination of large fraction radiation therapy followed by extensive mediastinal surgery resulted in the lymphatic obstruction. We are unable to explain the absence of these findings in the other three patients treated in this same protocol. There was no significant difference in the radiation therapy dose or port placement; surgery was performed by the same team in all patients and was similar in extent in both groups.

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**REFERENCES**


**Figure 5. Postmortem examination of the lungs shows diffuse interstitial fibrosis and organizing alveolitis (hematoxylin and eosin, original magnification, 40x).**
Fourth Congress, International Society for Aerosols in Medicine

The Fourth Congress of the International Society for Aerosols in Medicine will be held June 9-11 in Brno, Czechoslovakia. For additional information, write; Prof. Vyskocil, Medical Faculty Hospital, Pekarska 53, CS-65691 Brno, Czechoslovakia.

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The Rocky Mountain Center for Occupational and Environmental Health at the University of Utah will present this program at The Yarrow, Park City, Utah, June 22-24. For information, contact Ms. K. Blosch, RMCOEH, University of Utah, Building 512, Salt Lake City, Utah 84112 (801:581-5710).