Impact of Induction Concurrent Chemoradiotherapy on Pulmonary Function and Postoperative Acute Respiratory Complications in Esophageal Cancer*

Rony M. Abou-Jawde, MD; Tarek Mekhail, MD; David J. Adelstein, MD; Lisa A. Rybicki, MS; Peter J. Mazzone, MD; Marjorie A. Caroll, RN; and Thomas W. Rice, MD, FCCP

Study objective: **To evaluate the effects of induction concurrent chemoradiotherapy (cCRT) on pulmonary function and postoperative acute respiratory complications (PARCs).**
Design: **A retrospective review of our patients treated with induction cCRT to determine the impact on pulmonary function and identify predictors of PARCs. Correlations were sought between patient demographics, clinical characteristics, pre-cCRT and post-cCRT pulmonary function, radiotherapy dose, chemotherapy agents, and the development of PARCs.**
Participants: **One hundred fifty-five patients treated in three separate clinical trials were identified; 47 patients received 30 Gy (150 cGy bid) of radiation concurrently with a single course of cisplatin/5-fluorouracil (5FU), and 108 patients received 45 Gy (150 cGy bid in a split course) concurrent with two courses of either cisplatin/5FU (n = 69) or cisplatin/paclitaxel (n = 39). Esophagectomy was performed in 141 of these 155 patients following cCRT.**
Results: **cCRT was only associated with significant worsening of the diffusion capacity of the lung for carbon monoxide (DLCO), which decreased a median of 21.7% in the 45-Gy group (p = 0.007), and 8.6% in the 30-Gy group (p = 0.07). This DLCO decrease was statistically greater in the 45-Gy group than in the 30-Gy group (p = 0.02). PARCs developed in 18 patients. Percentage of predicted FEV_1 and FVC, both before and after cCRT, were both significantly higher in patients without PARCs than in patients with PARCs (p = 0.031 and p = 0.010, respectively). Post-cCRT DLCO was also significantly worse in patients with PARCs (p = 0.002). PARCs occurred significantly more often among those treated with 45 Gy (17 of 102 patients) compared to those treated with 30 Gy (1 of 39 patients) [p = 0.025]. In the 18 patients with PARCs, the median survival was only 2.1 months. This was significantly less than the 16.4-month median survival in the 123 patients who did not have PARCs (p = 0.001).**
Conclusions: **In patients treated with induction cCRT, higher radiation doses result in increasing impairment of gas exchange. PARCs were more likely in those patients with lower lung volumes, lower post-cCRT DLCO, and in those receiving higher radiation doses. These acute respiratory complications were also associated with a significant reduction in patient survival.**
(CHEST 2005; 128:250–255)

Key words: diffusion capacity of the lung for carbon monoxide; esophageal cancer; postoperative acute respiratory complication; pulmonary function; radiation therapy

Abbreviations: cCRT = concurrent chemoradiotherapy; DLCO = diffusion capacity of the lung for carbon monoxide; $\%FEV_1$ = measured FEV_1 divided by predicted FEV_1; %FVC = measured FVC divided by predicted FVC; PARC = postoperative acute respiratory complication; 5FU = 5-fluorouracil

Pathologic stage is the most important prognostic factor for survival in patients with esophageal cancer. Although surgical resection can result in a 50 to 70% overall survival in patients with stage I disease, < 15% of patients with locoregionally advanced stage III and stage IV will survive 5 years.[1–3] Furthermore, aggressive surgical resection is accompanied by significant, predominantly pulmonary morbidity and mortality.[4]

Unfortunately, most patients present with stage III and IV disease, with extension of the tumor through the esophageal wall or to regional lymph nodes. Because of the limited success achieved with surgical resection for these patients, multimodality

treatment regimens using preoperative chemotherapy, either with or without radiation, have evolved in an effort to reduce the size of the primary tumor, increase local tumor control, decrease distal recurrences, and improve overall survival.[5–8] Randomized trials[2,3,9–11] of preoperative chemotherapy or concurrent chemoradiotherapy (cCRT) have been completed but have produced inconclusive or contradictory results. In addition, although preoperative chemotherapy alone appears to be well tolerated, preoperative chemoradiotherapy has been associated with perioperative morbidity as high as 57%, and a perioperative mortality of up to 30%.[8,12–14] Many of these postoperative complications have again been pulmonary, including pneumonia, ventilator dependence, ARDS, and respiratory death.

At the Cleveland Clinic Foundation, we explored several aggressive preoperative cCRT regimens for the treatment of locoregionally advanced esophageal cancer.[7,8,15,16] We have also encountered a significant incidence of perioperative pulmonary complications. It is apparent that this preoperative cCRT has an impact on the development of these complications; however, the predictors for postoperative pulmonary morbidity are unknown. The purpose of this report is to review the effects of induction cCRT and radiation dose on pulmonary function and to identify predictors of postoperative acute respiratory complications (PARCs) in patients with esophageal cancer.

Materials and Methods

Patients treated in three clinical trials of induction cCRT and surgery for esophageal carcinoma, conducted between August 1991 and February 2001 at the Cleveland Clinic Foundation, were retrospectively reviewed. Data gathered included age, race, gender, smoking history, history of COPD, history of inhaler or steroid use, asbestos exposure, tumor histology, tumor stage, tumor location, radiation dose delivered, type of chemotherapy used, and development of PARCs.

Pulmonary function was assessed by measuring pretreatment and posttreatment FEV_1, measured FEV_1 divided by predicted FEV_1 (%FEV_1), FVC, measured FVC divided by predicted FVC (%FVC), FEV_1/FVC, and diffusion capacity of the lung for carbon monoxide (Dlco). Posttreatment pulmonary function tests were performed 3 to 4 weeks after completion of radiotherapy, just prior to surgical resection. Pre-cCRT and post-cCRT pulmonary function test results were compared. Correlations were sought between pre-cCRT and post-cCRT pulmonary function tests, radiation doses delivered, and PARCs.

PARCs are defined as the acute, serious respiratory complications that occur either directly after esophagectomy or during that hospitalization. These included postoperative pneumonia, prolonged postoperative ventilator dependency (> 2 days), discharge from the hospital receiving home oxygen, and ARDS. ARDS is defined as acute respiratory distress with a Pao_2/fraction of inspired oxygen ratio ≤ 200, and bilateral patchy airspace disease on chest radiography with no clinical evidence of volume overload.[17]

Categorical variables are summarized as frequencies and percentages. Continuous variables are summarized as the mean and SD. Changes in the individual pulmonary function tests after cCRT were analyzed using the paired t test, and changes were compared between patients receiving different doses of radiation using the t test. Univariable correlations of categorical variables with PARCs were assessed using the χ^2 test, and of the continuous variables with PARCs were assessed using the t test. Because of the small number of PARCs, multivariable analysis was limited to two-variable models. All analyses were done using statistical software (SAS version 6.12; SAS Institute; Cary, NC). All statistical tests were two sided; $p < 0.05$ was used to indicate statistical significance.

One hundred fifty-five patients treated on three separate clinical trials were identified. Forty-seven patients received 30 Gy (150 cGy bid) of radiation concurrently with a single course of cisplatin and 5-flurouracil (5FU) chemotherapy, and 108 patients received a split course of 45 Gy (24 Gy at 150 cGy bid from day 1 to day 10, concurrent with the first cycle of chemotherapy, and 21 Gy at 150 cGy bid from day 22 to day 30 concurrent with the second chemotherapy course). Chemotherapy for these patients was either cisplatin/5FU (69 patients) or cisplatin and paclitaxel (39 patients).

Esophagectomy was performed on 141 of the 155 patients. Fourteen patients did not undergo esophagectomy because of evidence of metastases ($n = 10$), failure to complete the protocol ($n = 2$), inability to tolerate cCRT ($n = 1$), and unresectability ($n = 1$).

Results

Baseline data were gathered for all patients; however, the analysis of PARCs included only those patients who underwent surgery. Clinical characteristics for our patient population are shown in Table 1 and were typical for this disease. The median age was 59 years.

Pulmonary function test results are detailed in Table 2. Changes in prechemoradiotherapy and postchemoradiotherapy pulmonary function test results are compared. Except for the Dlco ($p < 0.001$), cCRT was not associated with any significant change in pulmonary function tests. A post-cCRT decrease in Dlco was significant in the 45-Gy group (median decrease of 21.7%, $p = 0.007$), but only marginal in the 30-Gy group (median decrease of 8.6%, $p = 0.07$). This difference between the 30-Gy and 45-Gy group was also significant

*From the Departments of Hematology and Medical Oncology (Drs. Abou-Jawde, Mekhail, Adelstein, and Ms. Caroll), Biostatistics (Ms. Rybicki), Pulmonary, Allergy and Critical Care Medicine (Dr. Mazzone), and Thoracic and Cardiovascular Surgery (Dr. Rice), Cleveland Clinic Foundation, Taussig Cancer Center, Cleveland, OH.
Manuscript received April 30, 2004; revision accepted January 4, 2005.

Correspondence to: Rony Abou-Jawde, MD, 9500 Euclid Ave, Taussig Cancer Center, R35, Cleveland, OH 44195; e-mail: aboujar@cc.ccf.org