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

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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 FEV1 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.

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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; %FEV1 = measured FEV1 divided by predicted FEV1; %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.\(^5\)\(^\text{–}\)\(^8\) Randomized trials\(^2\)\(^\text{–}\)\(^9\)\(^\text{–}\)\(^11\) 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, perioperative results. In addition, although preoperative chemoradiotherapy has been associated with perioperative morbidity as high as 57%, and a perioperative mortality of up to 30%.\(^8\)\(^,\)\(^12\)\(^\text{–}\)\(^14\) 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 (DL\(_{CO}\)). 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 \(\chi^2\) 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-fluorouracil (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 (30 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 DL\(_{CO}\) (p < 0.001), cCRT was not associated with any significant change in pulmonary function tests. A post-cCRT decrease in DL\(_{CO}\) 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.
The univariable pulmonary function test correlates of PARCs are tabulated in Table 3. Post-cCRT DLCO was predictive of PARCs. Lower pre-cCRT and post-cCRT FEV₁, %FEV₁, FVC, and % FVC were similarly predictive of PARCs.

The pretreatment and posttreatment percentage of predicted FEV₁ and FVC, and the posttreatment DLCO remained independent predictors for PARCs when analyzed in two-variable, multivariable models with the radiation therapy dose (p values ranging from 0.022 to 0.06). This analysis must be interpreted with caution, however, given the relatively small number of PARCs that developed.

**Discussion**

Even after surgery alone,¹,² patients with locoregionally advanced stage III and IV esophageal cancer acquire postoperative pulmonary complications up to 30% of the time.¹⁸,¹⁹ Several investigators have attempted to predict for the development of postoperative pulmonary complications in such patients. An FEV₁ < 65% of predicted,¹⁹ lower vital capacity,¹⁸ history of pulmonary disease, age and general physical performance assessed by exercise testing,²⁰ and preoperative peak expiratory flow rate of < 65% predicted²¹ have been shown to predict postoperative pulmonary complications in patients undergoing esophagectomy alone.

Studies¹,²² using neoadjuvant chemotherapy in locoregionally advanced esophageal cancer have produced mixed results with respect to survival outcomes. However, there seems to be no increase in the postoperative pulmonary complications after neoadjuvant therapy.

Despite widespread enthusiasm for the use of induction cCRT followed by surgical resection, randomized trials²² have also been inconclusive. This enthusiasm has been tempered by the observed

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*Data are presented as No. (%).

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<th>Table 2—Pulmonary Function Tests*</th>
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*Data are presented as mean ± SD (No.).†Paired t test, based on patients with both a pre-cCRT and post-cCRT value.
incidence of PARCs, which in some studies\textsuperscript{8,9,19,23,24} has been significantly increased, while in others\textsuperscript{6,25,26} appears to be quite similar to what is seen after esophagectomy alone. It remains unclear which patient is most likely to acquire a postoperative pulmonary complication after this kind of treatment.

As expected, we found that the pre-cCRT and post-cCRT FEV\textsubscript{1} and FVC were both significantly lower in those patients who acquired PARCs. The DLCO was the only pulmonary function test to change significantly after radiation therapy. Higher radiation dose was associated with a significant drop in the post-cCRT DLCO, and PARCs were significantly increased in patients treated with a higher radiation dose and those who had lower DLCO. The development of PARCs was associated with a significant reduction in survival, suggesting a detrimental effect of the higher radiation dose in this setting.

DLCO is a measurement that can assess disease affecting the alveolar-capillary bed or the pulmonary vasculature.\textsuperscript{27} Radiation-induced lung injuries are common especially with doses > 40 Gy. Alveolitis and radiation pneumonitis are examples of relatively acute radiation-induced lung injury, with secondary inflammation of the alveolar-capillary membrane. Hence, a fall in DLCO may actually be the early reflection of such an injury, and this may help explain why this measurement was the only one that changed significantly in the 45-Gy group. Few studies have actually looked at the DLCO as a preoperative marker for pulmonary complications after esophagectomy. Duprat et al\textsuperscript{28} found that a drop in DLCO prior to esophagectomy in patients treated with cisplatin, bleomycin, and radiation was significantly associated with prolonged mechanical ventilation.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
Variables & PARCs & \multicolumn{2}{c|}{Mean ± SD} \\
\hline
Before cCRT & & \multicolumn{2}{c|}{p Value} \\
\hline
FEV\textsubscript{1}, L & Yes (n = 18) & 2.5 ± 0.75 & 0.007 \\
& No (n = 121) & 3.05 ± 0.8 & \\
%FEV\textsubscript{1} & Yes (n = 17) & 78.5 ± 17.4 & 0.031 \\
& No (n = 120) & 88.6 ± 18.0 & \\
FVC, L & Yes (n = 11) & 3.32 ± 0.97 & 0.010 \\
& No (n = 73) & 4.13 ± 0.94 & \\
%FVC & Yes (n = 11) & 83.3 ± 16.4 & 0.010 \\
& No (n = 73) & 96.2 ± 15.0 & \\
\hline
After cCRT & & \multicolumn{2}{c|}{p Value} \\
\hline
FEV\textsubscript{1}, L & Yes (n = 17) & 2.61 ± 0.70 & 0.020 \\
& No (n = 112) & 3.10 ± 0.81 & \\
%FEV\textsubscript{1} & Yes (n = 17) & 80.9 ± 16.3 & 0.035 \\
& No (n = 111) & 90.7 ± 17.9 & \\
FVC, L & Yes (n = 9) & 3.44 ± 0.95 & 0.048 \\
& No (n = 66) & 4.12 ± 0.96 & \\
%FVC & Yes (n = 9) & 86.4 ± 16.6 & 0.049 \\
& No (n = 65) & 96.8 ± 14.3 & \\
DLCO, % & Yes (n = 12) & 58.0 ± 18 & 0.002 \\
& No (n = 74) & 79.0 ± 22 & \\
\hline
\end{tabular}
\caption{Univariable Correlations of Pulmonary Function Tests With PARCs}
\end{table}

\FIGURE 1. Median overall survival for patients with PARCs.
postoperatively and a significant increase in the incidence of ARDS. Similarly Nagamatsu et al. found that a lower preoperative percentage of DLco in patients undergoing esophagectomy only was a significant predictor of postoperative cardiopulmonary complication rates.

DLco has also been assessed in patients with lung cancer and found to be predictive of morbidity and mortality, and quality of life after pulmonary resection. Videtic et al. also reported a lower DLco to be predictive of increased treatment-related toxicity and a need for treatment interruptions in patients with lung cancer treated with cCRT. There are, however, no recent studies in patients with esophageal cancer treated with induction cCRT that have actually looked at DLco as a possible marker for PARCs. We found that DLco was the only pulmonary function test that changed significantly after induction cCRT, a change that was also worse in the group receiving more radiation; and a lower DLco proved to be a significant predictor of PARCs, which in turn significantly reduced survival.

Our results however, should be interpreted with caution. They represent outcomes from a retrospective analysis of our experience in three prospective clinical trials. Because of the retrospective nature of this study, some of the pulmonary function test data, particularly the pretreatment DLco values, were missing. We were unable to identify any systematic reason for this missing data. Instead, it appeared to reflect the clinical habits of the individual physicians involved.

CONCLUSION

cCRT-treated patients who acquire PARCs have lower pre-cCRT and post-cCRT FEV1 and FVC. A lower post-cCRT DLco is predictive of PARCs. Those receiving higher doses of radiation therapy as part of induction cCRT have a greater decrease in DLco and more PARCs than those treated with lower radiation doses. Patients acquiring PARCs have a significantly shortened survival, and we do not recommend the use of this schedule of radiation therapy to a dose of 45 Gy in the neoadjuvant cCRT setting. Rather than the traditional spirometry and lung volume measurements, a decrease in DLco may be the best early marker of acute radiation-induced lung injury and can help better predict for the development of PARCs.

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