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# PATHOLOGICAL COMPLETE REMISSION OF PANCREATIC CANCER FOLLOWING NEOADJUVANT CHEMORADIATION THERAPY

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**Abstract:**
*Neoadjuvant chemoradiotherapy followed by esophagogastrectomy has become the standard of care for patients with locally advanced esophageal cancer. This report analyses our experience with this treatment approach.*
*All patients from a single institution receiving neoadjuvant chemoradiotherapy followed by esophagogastrectomy were reviewed for operative mortality, morbidity, long-term survival, and factors affecting survival. Only patients preoperatively staged with both computed tomographic scans and endoscopic ultrasound were included.*
*There were 162 patients (142 men, 20 women), and the median age was 61 years (range, 22 to 81 years). Histopathology was adenocarcinoma in 143 patients and squamous cell in 19. Pretreatment clinical stage was II in 28 patients (17%), III in 111 (68%), and IV (M1a) in 23 (14%). Ivor Lewis esophagogastrectomy was the most common procedure, occurring in 132 patients. Operative mortality and morbidity was 4.9% and 37%, respectively. Pathologic response was complete in 42 patients (26%), near complete in 27 (17%), partial in 88 (54%), and unresectable in 5 (3%). Five-year survival for overall, complete, near complete, and partial response patients was 34%, 55%, 27%, and 27%, respectively ($p = 0.013$). Patients whose lymph nodes were rendered free of cancer showed improved overall and disease-free survival compared with patients having persistently positive lymph nodes ($p = 0.019$).*
*Esophagogastrectomy after neoadjuvant chemoradiotherapy can be performed with low mortality and morbidity. Patients with complete pathologic response have significantly improved long-term survival compared with patients with near complete and partial responses. Future efforts should be directed at understanding determinants of complete responses.*

**Key Words:** *Pathological Remission; Panceratic Cancer; Neoadjuvant Chemoradiation Therapy.*

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## INTRODUCTION:

The incidence of carcinoma of the esophagus is increasing and is the sixth leading US cause of male cancer death. Most patients present with locally advanced disease. Historically, surgery alone resulted in 5-year survival rates of 10% to 20%. Neoadjuvant chemoradiotherapy (nCRT) followed by surgical resection (nCRTSR) has become the standard of care for locally advanced esophageal cancer. This report reviews our single-institution experience with nCRTSR.

## MATERIAL AND METHOD:

Only patients whose pre-treatment staging included both computed tomography and endoscopic ultrasonography (EUS) were eligible for study. Positron emission tomography (PET) became routine at our institution in 2001. Medical records were reviewed for age, sex, symptoms, histopathology, nCRT regimen, comorbidities, operation, histopathologic response, mortality, morbidity, length of hospitalization, adjuvant therapy, and long-term survival. Mayo Foundation's Institutional Review Board approved this study. Neoadjuvant chemoradiotherapy consisted of two cycles of chemotherapy and concomitant radiotherapy. Radiotherapy included 28 daily fractions (180 cGy), 5 days/week for 5,040 cGy total dose. Chemotherapy consisted of 5-fluorouracil as a continuous 96-hour infusion (1,000 mg/m2 per day) and cisplatin (75 mg/m2 per day) as a daily bolus for 1 hour. Chemotherapy was given on the first and last 4 days of radiotherapy. A 4- to 6-week recovery period followed nCRT. Patients were considered to have completed nCRT if they finished two chemotherapy cycles and radiotherapy.

Reduction of dose during the second chemotherapy round was not considered criteria to rule nCRT incomplete. We have previously described our techniques for esophagogastrectomy. Staging was by the American Joint Committee for Cancer Staging TNM classification. Operative mortality included all deaths within 30 days of operation and those who died later but during the same hospitalization. The Social Security Death Index was used for survival data unavailable in medical records. All deaths were considered esophageal cancer related unless another cause was identified.

After esophagogastrectomy, patients were classified as

(1) complete pathologic response (CP)—microscopic absence of any viable tumor,
(2) near complete pathologic response (NCP)—microscopic foci of viable tumor cells in an otherwise necrotic specimen with no tumor remaining in resected lymph nodes, and
(3) partial pathologic response (PP)—macroscopic residual viable tumor at primary site and/or positive lymph nodes.

Descriptive statistics for categorical variables are reported as frequency and percentage, and continuous variables are reported as mean (standard deviation) or median (range) as appropriate. Long-term survival was estimated using the Kaplan–Meier survival method, and 5-year estimates and 95% confidence intervals (95% CI) are reported. The starting point in survival estimation was hospital discharge date, and date of death or last follow-up was the end point. The association of individual variables with survival was assessed using the logrank test for categorical variables and the Cox proportional hazards model for continuous variables and for the multivariate model. The multivariable model considered univariately significant variables ($p < 0.05$) with model selection using the stepwise method (backward and forward methods resulted in the same model). Disease-free survival was analyzed with similar statistical methods with unresectable patients excluded. All statistical tests were two-sided with a probability value of 0.05 for statistical significance. To report our entire experience with patients having nCRTSR, we included some previously reported patients

## RESULTS:

One hundred ninety-four patients were treated by nCRTSR. Thirty patients were excluded because they did not undergo EUS, and 2 patients were excluded for refusal to participate in research. Thus, our final cohort included 162 patients (142 men, 20 women). Median age was 61 years (range, 22 to 81 years). Comorbidities included diabetes in 14 patients, coronary artery disease in 13, and both in 4. Twenty-seven patients (16.7%) had a greater than 20 pack-year smoking history. Barrett's esophagus was present in 57 patients (35.2%). All patients had pretreatment computed tomography and EUS. Positron emission tomography became available in 2001 and was obtained in 57 patients. Histopathologic designation was adenocarcinoma in 143 patients and squamous cell in 19. Tumor location was lower esophagus in 139 patients and mid-esophagus in 23. Endoscopic ultrasonography showed suspicious lymph nodes in 150 patients (92.5%); EUS-directed fine-needle aspiration (EUS-FNA) of those lymph nodes was performed in 116 patients (71.6%). Endoscopic ultrasonography FNA was not performed if FNA necessitated primary tumor transgression. Lymph node EUS-FNA was

positive for malignancy in 92 patients (79.3%). Endoscopic ultrasonography revealed pathologically suspicious celiac axis lymphadenopathy (M1a disease) in 23 patients, and EUS-FNA was performed in 19 of these patients. Biopsied celiac lymph nodes demonstrated malignancy in 17 patients (89.5%).

*Table 1. Prechemoradiation Therapy Clinical Stage*

| TNM Classification | Stage | Patients (%) |
|---|---|---|
| T3N0M0 | IIA | 12 (7.4) |
| T1N1M0 | IIB | 1 (0.6) |
| T2N1M0 | IIB | 15 (9.4) |
| T3N1M0 | III | 105 (64.8) |
| T4N1M0 | III | 6 (3.7) |
| T1N1M1a | IVA | 1 (0.6) |
| T2N1M1a | IVA | 2 (1.2) |
| T3N1M1a | IVA | 19 (11.7) |
| T4N1M1a | IVA | 1 (0.6) |

Table 1 shows the pretreatment clinical stage of the patients. Our standard chemotherapy regimen was used in 156 patients, and 5-fluorouracil, carboplatin, and paclitaxel was used in 6 patients. Chemotherapy was completed in 145 patients (89.5%); 23 had a dose reduction during the second round. Median radiotherapy dose was 5,040 cGy (range, 1,260 to 5,400 cGy). A feeding tube was required during nCRT in 48 patients, and included an operative jejunostomy tube in 21, percutaneous endoscopic gastrostomy in 16, percutaneous endoscopic jejunostomy in 7, and a nasojejunal tube in 4. There were no feeding tube–related complications.

*Table 2. Postresection Pathologic Stage*

| TNM Classification | Stage | Patients (%) |
|---|---|---|
| T0N0M0 | 0 | 42 (25.9) |
| T1N0M0 | I | 10 (6.2) |
| T2N0M0 | IIA | 17 (10.5) |
| T3N0M0 | IIA | 16 (9.9) |
| T0N1M0 | IIB | 11 (6.8) |
| T1N1M0 | IIB | 3 (1.9) |
| T2N1M0 | IIB | 19 (11.7) |
| T3N1M0 | III | 30 (18.5) |
| TxNxM1 | IV | 5 (3.1) |
| T0N0M1 | IV | 2 (1.2) |
| T2N0M1 | IV | 1 (0.6) |
| T2N1M1 | IV | 2 (1.2) |
| T3N0M1 | IV | 1 (0.6) |
| T3N1M1 | IV | 3 (1.9) |

Thrombotic complications including deep venous thrombosis occurred in 21 patients, and pulmonary embolism occurred in 7. Deep venous thrombosis was in the upper extremity in 20 patients. Four patients with pulmonary embolism had vena cava filters placed before esophagogastrectomy. Median time interval from completion of nCRT to esophagogastrectomy was 44 days (range, 21 to 107 days). Five patients (3.1%) had unresectable cancer as a result of metastatic disease. Metastases were liver, omentum, pancreas, porta hepatis, and splenic artery lymph node in 1 patient each. Type of esophagogastrectomy was at the surgeon's discretion and included Ivor Lewis in 132 patients, extended esophagectomy (McKeown) in 22, transhiatal in 2, and left thoracoabdominal approach in 1. Anastomosis was hand-sewn in 155 patients and stapled in 7. Postoperatively, 71 patients had a feeding jejunostomy tube. Median number of lymph nodes resected was 15 (range, 3 to 50). Thirteen patients received intraoperative radiation therapy. Three patients (1.9%) had positive surgical margins.

Table 2 shows pathologic stage data; 115 patients (70.9%) were downstaged. Complete pathologic response occurred in 42 patients (25.9%), NCP in 27 (16.7%), and PP in 88 (54.3%).

There were 8 operative deaths (4.9%). Cause of death was pneumonia in 4 patients, sepsis after anastomotic leak in 3, and bleeding gastric ulcer in 1. Complications occurred in 60 patients (37.0%): atrial fibrillation in 26, pneumonia in 23, anastomotic leak in 19, wound infection in 13, chylothorax in 8, and vocal cord paralysis in 7, and myocardial infarction in 1. Regarding anastomotic leaks, 13 (68.4%) were only radiographic findings and nonoperatively managed, whereas 6 required reoperations. Five patients had successful leak repair, and 1 had esophageal exclusion. Five patients (62.5%) with chylothorax required reoperation. Seventy-one patients required blood transfusion within 48 hours of surgery. Median number of units transfused was 2 (range, 1 to 6 units). Median hospitalization was 11 days (range, 3 to 143 days). Adjuvant chemotherapy was only given to patients with unresectable cancer or those subsequently exhibiting recurrent cancer.

Given the profound impact achieving CP had on survival, univariate analysis of the same above factors was performed to determine which patients were likely to achieve CP. In that analysis, female sex (p 0.04) and squamous histopathology (p 0.0003) were predictive of CP. The small numbers of female patients and those with squamous histopathology precluded further meaningful analyses. Overall 5-year survival was 31.3% (95% CI, 23.8% to 41.0%) for patients with adenocarcinoma and 51.4% (95% CI, 30.8% to 95.8%) for patients with squamous histopathology (p 0.103). Information regarding tumor recurrence was available for 123 patients (82.5%). Recurrences occurred in 63 patients (51.2%). Median time to recurrence was 276 days (range, 46 days to 4.7 years). Recurrences were distant in 53 patients, and locoregional in 10.

## COMMENTS AND DISCUSSION:

Prognosis for patients with locally advanced esophageal cancer is grim. Neoadjuvant chemoradiotherapy followed by surgical resection has become common treatment for locally advanced esophageal cancer. Although 156 of our patients received the standard nCRT regimen, 6 patients received 5-fluorouracil, carboplatin, paclitaxel, and radiation preoperatively trial. Despite the trial's 35% CP, this protocol demonstrated significant treatment-related toxicities. Five (83.3%) of these patients required hospitalization compared with 60 (38%) having standard nCRT.

We have discontinued use of the trial regimen. Lacking a clinical trial, our approach for managing esophageal cancer has been based on clinical stage. Currently, all potentially resectable patients have computed tomography, PET, and EUS. If evidence of distant metastatic disease exists, confirmatory biopsies are performed. Endoscopic ultrasonography FNA is routinely performed on all suspicious lymph nodes provided the primary tumor is not transgressed.

Patients thought to have T1N0M0 or T2N0M0 esophageal cancer are offered esophagogastrectomy. Patients with T1N1M0, T2N1M0, T3N1M0, T3N0M0, T4N0M0, and T4N1M0 disease are offered nCRTSR, and patients with M1a disease are considered for nCRTSR. In this study, pre-treatment stage was not a significant predictor of improved survival, likely because of the small number of lymph node– negative patients. Restaging after nCRT includes computed tomography and PET. Positron emission tomography was not available for the entire study, and thus restaging did not routinely use PET. None of the ultimately unresectable patients had PET.

A CP ranging from 15% to 30% is reported in most nCRTSR series. Our 25.9% CP is similar. Our study's 5-year 55% overall and 49% disease free-survival is an improvement over the historical 10% to 20% 5-year surgery-alone survival rates; however,

the survival benefit for nCRT patients not achieving CP is difficult to elucidate. After nCRTSR, the importance of accurately stratifying patients is critical in determining prognosis. The American Joint Committee for Cancer Staging TNM classification system does not include a category for CP, making its usefulness in post-nCRTSR staging problematic. The simplest way to categorize patients after nCRTSR is whether CP is achieved, but this rationale fails to capture patient subsets with residual disease that might have improved survival. Rohatgi and colleagues have correlated treatment failure patterns with the degree of nCRT response. However, they did not consider the resected lymph node status, which traditionally is a key part of pathologic staging. Others have analysed both lymph node status and degree of pathologic response. In these reports, similar to ours, regardless of the nCRT response, pathologic lymph node–negative (N0) patients had improved survival compared with patients with residual positive lymph nodes. When patients with CP were removed from the N0 subset, survival was still superior to the N1 subset, 32 % versus 24%, although the difference was no longer significant ($p = 0.2$).

## CONCLUSION:

In conclusion, this nonrandomized, retrospective review demonstrates that nCRTSR can be performed with low mortality and morbidity. Patients with a CP have significantly improved long-term survival compared with patients having only an NCP or PP. Patients successfully downstaged from N1 to N0 lymph node status enjoy improved survival. Given the lack of data from a modern, randomized trial, these data add to the accumulated experience regarding both the efficacy and limitations of treating locally advanced esophageal cancer patients with nCRTSR. Future efforts need to be directed at understanding the determinants of achieving a CP after nCRT.

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