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Improved Survival with Neoadjuvant Therapy and Resection for Adenocarcinoma of the Esophagus

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Objective
This study sought to determine the impact of preoperative chemotherapy and radiation therapy (neoadjuvant therapy) followed by resection in patients with adenocarcinoma of the esophagus.

Summary Background Data
Long-term survival in patients with carcinoma of the esophagus has been poor. An increase in the incidence of adenocarcinoma of the esophagus has been reported recently.

Methods
Fifty-eight patients with biopsy-proven adenocarcinoma of the esophagus treated at this institution from January 1951 through February 1993 were studied. Since 1989, 24 patients were entered prospectively into a multimodality treatment protocol consisting of preoperative cisplatin, 5-fluorouracil (5-FU), and leucovorin with or without etoposide, and concomitant mediastinal radiation (30 Gy). Patients were re-evaluated and offered resection.

Results
There were no deaths related to neoadjuvant therapy and toxicity was minimal. Before multimodality therapy was used, the operative mortality rate was 19% (3 of 16 patients). With multimodality therapy, there have been no operative deaths (0 of 23 patients). The median survival time in patients treated before multimodality therapy was 8 months and has yet to be reached for those treated with the neoadjuvant regimen (> 26 months, $p < 0.0001$). The actuarial survival rate at 24 months was 15% before multimodality therapy and 76% with multimodality therapy. No difference in survival was noted in neoadjuvant protocols with or without etoposide ($p = 0.827$).

Conclusions
Multimodality therapy with preoperative chemotherapy and radiation therapy followed by resection appears to offer a survival advantage to patients with adenocarcinoma of the esophagus.

The most effective treatment regimen for esophageal adenocarcinoma remains controversial. While results of resection alone have improved over time,[1-6] long-term survival has remained poor. Several authors have reported improved survival with preoperative neoadju-

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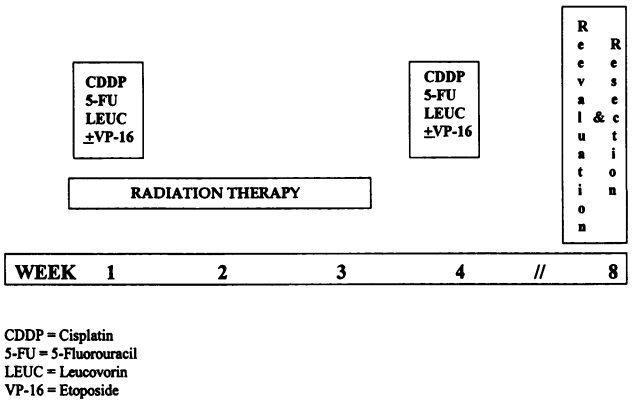
vant regimens including chemotherapy and/or radiation therapy followed by resection.[7–13] The incidence of upper gastrointestinal carcinoma, including adenocarcinoma of the esophagus, appears to be increasing.[14–16] We recently reviewed our experience with a neoadjuvant regimen composed of cisplatin-based chemotherapy and concurrent mediastinal radiation followed by resection for the treatment of esophageal carcinoma.[17] In that analysis, we found that patients with adenocarcinoma of the esophagus had a significantly improved survival compared to patients with squamous cancer treated with the same regimen. This report focuses on our experience, at a single institution, with the treatment of patients with adenocarcinoma of the esophagus and the impact of a neoadjuvant treatment regimen compared to treatment consisting of resection with or without postoperative radiation therapy or chemotherapy.

METHODS

The medical records of all patients treated for adenocarcinoma of the esophagus at the Vanderbilt University Medical Center from January 1951 through February 1993 were reviewed. All patients had histologically confirmed adenocarcinoma of the esophagus. Patients in whom the histologic type could not be precisely identified, or those in whom adenocarcinoma was thought to arise from the stomach were not considered in this review.

Since January 1989, patients were enrolled prospectively in a multimodality neoadjuvant treatment protocol. Exclusion criteria for enrollment were established prospectively and consisted of an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4, evidence of distant metastatic disease, previous chemotherapy or radiation therapy, previous malignancy, or coexisting disease rendering the patient a poor operative candidate. Five patients were assessed but excluded from the neoadjuvant protocol based on ECOG performance status. They are included in the group treated before the initiation of neoadjuvant therapy. Middle esophageal lesions were defined as those between 23 and 30 cm from the incisors on endoscopy. Preoperative staging was determined by physical examination, esophagogastroduodenoscopy, barium esophagram, chest radiograph, computed tomograms of the chest and abdomen, and bone scan.

The neoadjuvant treatment protocol is outlined in Figure 1. Patients received two cycles of chemotherapy on days 1 and 29 consisting of cisplatin (100 mg/m^2), 5-fluorouracil (5-FU) (800 mg/m^2/d × 4 days), and leucovorin (50 mg/m^2 every 6 hours × 4 days). Thirteen patients also received etoposide (25 mg/m^2). All patients received 30 Gy of concurrent radiation therapy to the involved



CDDP = Cisplatin
5-FU = 5-Fluorouracil
LEUC = Leucovorin
VP-16 = Etoposide

Figure 1. Diagnosis and method of treatment of adenocarcinoma of the esophagus by year.

esophagus and mediastinum divided into 15 fractions during the initial 3 weeks of treatment. The radiation portal was 8 cm wide and included a margin of 5 cm beyond the extent of the tumor as determined by preoperative studies. Toxicity was monitored and dose adjustments made for evidence of hematologic, renal, or gastrointestinal toxicity. Three weeks after completing the second cycle of chemotherapy, patients were re-evaluated with chest radiography, endoscopy, and computed tomography. Patients without evidence of metastatic disease were offered operation.

A pathologic complete response was defined as no evidence of tumor in the resected specimen. Statistical analysis was performed using NCSS software (NCSS, Kaysville, UT). Survival was determined from the date of entry into treatment and was estimated by the Kaplan–Meier method.[18] All patients are included in survival analyses, even operative deaths. Comparison between groups was performed using the Student's t test for unpaired variables and Fisher's exact test. Univariate regression analysis and Cox hazards regression analysis were also performed. Statistical significance was defined at a p value of less than 0.05.

RESULTS

Of 58 patients with adenocarcinoma of the esophagus, there were 52 men and 6 women. The average age of the group was 63 years (age range, 31 to 92 years). Figure 2 shows the number of patients diagnosed by year and demonstrates an increase in the number of cases of adenocarcinoma of the esophagus seen at our institution during recent years.

Dysphagia was common at presentation and occurred in 50 of the 58 patients (86%). Heartburn (26 of 58, 45%), hiatal hernia (17 of 58, 29%), and peptic ulcer disease (13 of 58, 22%) were important risk factors identi-

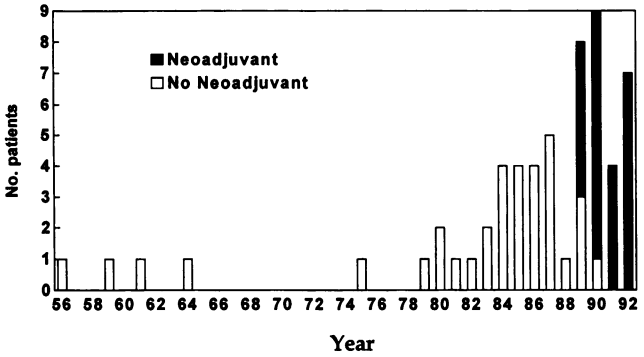


Figure 2. Preoperative neoadjuvant treatment protocol.

Table 2. TUMOR-RELATED FACTORS

	No Neoadjuvant	Neoadjuvant	p Value
Location (mid/lower)	9/25	3/21	0.324
Size ≥5 cm	68%	62%	0.782
Obstruction ≥75%	32%	21%	0.385
Barrett's	41%	42%	1.00
Cell differentiation			
Well	7	2	
Moderate	7	11	0.075
Poor	17	8	

fied in the history. Demographics and historical risk factors were similar between patients treated with preoperative neoadjuvant therapy and those treated before the initiation of neoadjuvant therapy (Table 1).

There were 12 mid-esophageal lesions and 46 distal esophageal tumors. The tumors of 24 of the 58 patients (41%) developed in the Barrett's epithelium. The tumor was 5 cm or larger in 38 of 58 patients (66%), and was associated with luminal obstruction of 75% or greater in 16 of 58 patients (28%). The tumor was judged to be well-differentiated in 9 of 52 patients (17%), moderately differentiated in 18 of 52 (35%), and poorly differentiated in 25 of 52 (48%). No tumor-related factor was different statistically for patients treated with neoadjuvant therapy or before neoadjuvant therapy (Table 2). Disease was classified according to preoperative studies as clinical stage I (18 of 58, 31%), stage II (31 of 58, 53%), or stage IV (9 of 58, 16%). All of the latter group were treated before the initiation of neoadjuvant therapy.

Thirty-four patients with adenocarcinoma of the esophagus were treated before the use of neoadjuvant therapy. Sixteen patients underwent resection. Eight patients had a transhiatal esophagectomy and six were resected through a combined abdominal and right thoracic approach. One patient had a distal esophageal resection through an isolated abdominal approach, and one patient had an esophagectomy through thoracotomy alone. Four patients had adjuvant chemotherapy, and two received postoperative radiation therapy. Nine patients had definitive radiation therapy, and four had combined radiation therapy and chemotherapy without resection. Three patients were treated with chemotherapy alone. Two patients received best supportive care only.

Table 1. PATIENT HISTORY

	No Neoadjuvant	Neoadjuvant	p Value
No. of patients	34	24	
Age in yr (mean ± SD)	65.4 ± 12.1	59.7 ± 9.6	0.060
Male/female	30/4	22/2	1.00
White/black	31/3	23/1	0.645
Dysphagia	85%	88%	1.00
Vomiting	24%	8%	0.171
Heartburn	35%	58%	0.110
Weight loss (mean ± SD)	13.1 ± 14.9	20.7 ± 17.8	0.084
Smoking (>30 pk-yrs)	62%	54%	0.598
Alcohol use (moderate/heavy)	26%	33%	0.770
Hiatal hernia	38%	17%	0.089
Peptic ulcer	29%	13%	0.202

Twenty-four patients were entered into neoadjuvant treatment. Twenty-three patients completing the protocol underwent exploration, and 21 of these patients (91%) underwent esophageal resection. This is a significantly higher resectability rate than in patients without metastatic disease treated before the use of neoadjuvant therapy (16 of 25, 64%; $p = 0.038$). Fourteen patients (67%) had transhiatal esophagectomy, and in seven (33%) the esophagus was resected using a combined abdominal and right thoracic approach. Occult liver metastases were discovered at operation in two patients who did not receive esophageal resection. In both patients there was no evidence of residual tumor in the esophagus by preoperative evaluation or at the time of operation. One patient was denied operation at the time of re-evaluation because of performance status and concurrent medical problems.

There were no deaths during preoperative therapy. Severe (grade 3 or 4) mucositis was seen in five patients (21%). Significant hematologic toxicity (leukocyte count nadir < 1000/μL) was seen in three patients (13%). Renal toxicity (transient rise in serum creatinine to > 50% of baseline) was seen in two patients (8%). Gastrointestinal toxicity including nausea, vomiting, or diarrhea was common (17 of 24, 71%), but was easily managed. Toxicity for postoperative adjuvant therapy in patients treated before 1989 included one death related to chemotherapy (8%), hematologic toxicity in two patients (17%),

Table 3. OPERATIVE RESULTS

	No Neoadjuvant	Neoadjuvant	p Value
Resectability	64%	91%	0.038
Pathologic Stage			
Stage 0	0	6	
Stage I	2	4	
Stage IIA	1	5	0.056
Stage IIB	4	2	
Stage III	8	4	
Stage IV	1	2	

severe mucositis in two patients (17%), and gastrointestinal toxicity in nine patients (75%).

Pathologic staging in 23 patients who completed neoadjuvant treatment revealed stage 0 disease (complete response to neoadjuvant therapy) in 6 patients (23%). Of patients with residual tumor at resection, four had stage I disease, five had stage IIA, two had stage IIB, four had stage III, and two had stage IV. This distribution of pathologic stage was similar to that of 14 patients who had resection before neoadjuvant therapy ($p = 0.056$, Table 3).

The 30-day hospital mortality rate in the 39 patients having operation was 8% (3 patients). Since the initiation of neoadjuvant therapy in 1989, there have been no operative deaths. There were 3 perioperative deaths in the 16 patients resected before 1989 (19% operative mortality rate). One patient died of sepsis after anastomotic leak, one died of pneumonia and sepsis, and one died after a myocardial infarction.

Major perioperative complications were uncommon. There were three anastomotic leaks: two in the neoadjuvant group and one before neoadjuvant therapy. There was one wound infection in the neoadjuvant group. Five patients experienced pneumonia: four in the group resected before neoadjuvant therapy and one after neoadjuvant therapy. Two patients each suffered a perioperative myocardial infarction and had prolonged ventilatory requirements, all in the group treated before neoadjuvant therapy.

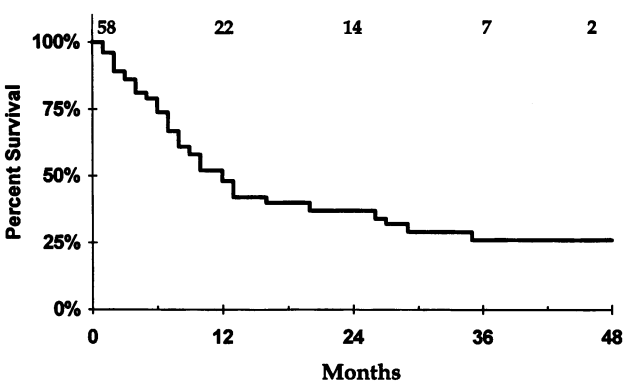


Figure 3. Actuarial survival of all patients treated for adenocarcinoma of the esophagus.

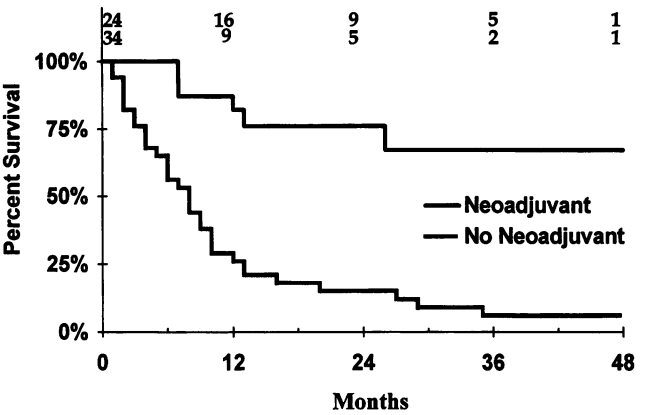


Figure 4. Actuarial survival by method of treatment.

Survival from the time of diagnosis in all patients is shown in Figure 3. The median survival time is 12 months, and the 2-year actuarial survival rate is 37%. Significant improvement is seen in patients treated with preoperative neoadjuvant therapy (Fig. 4). The median survival time was prolonged from 8 months without neoadjuvant therapy, to more than 26 months with the use of neoadjuvant therapy ($p < 0.0001$). The 2-year actuarial survival rate was 15% compared to 76% for these groups. Comparing the survival in the 16 patients receiving esophageal resection before neoadjuvant therapy to that in the 24 patients receiving multimodality neoadjuvant therapy, significantly better median survival (10 *vs.* > 26 months) and 2-year actuarial survival (19% *vs.* 76%) was seen in patients receiving preoperative neoadjuvant therapy ($p = 0.0002$).

Cox hazards regression analysis revealed that preoperative neoadjuvant therapy ($p < 0.001$) and age ($p = 0.019$) were independent predictors of improved survival. No statistical difference in survival was observed by multivariate analysis regarding sex ($p = 0.356$), race ($p = 0.650$), weight loss ($p = 0.389$), tumor size smaller than 5 cm ($p = 0.843$), presence or absence of Barrett's epithelium ($p = 0.599$), cellular differentiation ($p = 0.094$), preoperative clinical stage ($p = 0.208$), or type of surgical resection (transhiatal *vs.* combined abdominal/right thoracic approach; $p = 0.872$). Complete response to neoadjuvant therapy ($p = 0.408$) and the addition of etoposide to the neoadjuvant regimen ($p = 0.827$) did not alter survival.

Sites of late failure after neoadjuvant therapy included liver ($n = 4$), neck ($n = 2$), brain ($n = 1$), and local recurrence ($n = 1$). Causes of late deaths included cancer in

five patients and pneumonia in one patient. In patients treated before neoadjuvant therapy, sites of late recurrence included liver (n = 3), lung (n = 3), local recurrence (n = 2), bone (n = 2), neck (n = 1), and abdomen (n = 1). Causes of late deaths were cancer in 26 patients, myocardial infarction in 2 patients, and pneumonia in 1 patient.

DISCUSSION

There has been an increase in the incidence of adenocarcinoma of the esophagus in the past decade.[14–16] Adenocarcinoma of the esophagus was uncommon previously, accounting for approximately 5% of all esophageal cancers. Throughout the 1980s, the incidence of adenocarcinoma has increased to account for 50% of esophageal cancers. The National Cancer Institute[14] has published epidemiologic data showing that in this country adenocarcinoma is now as common as squamous cell carcinoma in the white male population and has more than doubled in incidence in recent years. Adenocarcinoma of the esophagus is currently the most rapidly increasing cancer in North America.

Part of this increase in adenocarcinoma may be associated with Barrett's esophagus, which is defined as an esophagus in which 3 cm or more of the distal esophagus is lined with glandular mucosa.[19,20] The first patient with adenocarcinoma arising in a columnar-lined esophagus was described by Morson and Belcher in 1952.[20] In 1975, Naef et al.[21] emphasized the malignant potential of Barrett's esophagus. Skinner[22] reported a series of 100 patients seen with Barrett's esophagus over a 17-year period. During this period, 56 patients were treated with adenocarcinoma arising in a Barrett's esophagus and 63 additional patients were treated for adenocarcinoma of the esophagus without evidence of Barrett's epithelium. Skinner[22] reports that the incidence of esophageal cancer in the white male population in the United States is 3/100,000 or 1 in 30,000 patient-years. He suggests that the risk of adenocarcinoma developing in a benign Barrett's epithelium in white men increases 500-fold because in his series of 64 patients, 4 had adenocarcinoma, for an incidence of 1 per 60 patient-years.

Twenty-four patients in our series had treatment for adenocarcinoma arising in a Barrett's esophagus. Our data do not support a difference in survival for patients with adenocarcinoma arising in Barrett's epithelium *versus* adenocarcinoma without evidence of Barrett's esophagus.

With the premalignant nature of Barrett's esophagus well established, many investigators have searched for markers of esophageal carcinoma that could facilitate earlier diagnosis and follow-up for tumor recurrence.[23–25] The onco-suppressor gene p53,[23] and various oncogenes (particularly c-*erb* B2),[24] have been studied as potential markers for carcinoma of the esophagus. Casson and colleagues identified mutations in the p53 gene in Barrett's epithelium associated with adenocarcinoma.[23] In a prospective study, they identified p53 mutations in 5 of 12 patients who had adenocarcinoma arising in Barrett's esophagus. There were no p53 mutations in ten patients with Barrett's esophagus and no evidence of carcinoma.

The poor overall survival in patients treated for esophageal carcinoma is a result of the systemic nature of the disease at diagnosis. Surgical resection provides excellent local control, but has not significantly influenced long-term survival.[1–6] Many neoadjuvant protocols exclude adenocarcinoma of the distal esophagus. Based on our previous report, there appears to be a difference in tumor response to neoadjuvant therapy between adenocarcinoma and squamous cancer of the esophagus.[17] This fact, in light of the rising incidence of the former, warrants further investigation into risk factors and different treatment regimens for the two cell types. Recent advances in the understanding of tumor biology at the level of the genome may aid in designing effective therapy for this tumor. Cisplatin-based chemotherapeutic regimens appear to be particularly efficacious in the treatment of adenocarcinoma. Several authors have shown improved survival with cisplatin-based neoadjuvant therapy before resection for treatment of adenocarcinoma of the esophagus.[7–13] Our data support these findings. Advances in the perioperative care of these patients have lowered the 30-day mortality rate, but our results confirm an improvement in the mid-term survival of these patients with neoadjuvant therapy.

Consensus regarding the optimal neoadjuvant regimen does not exist. The most efficacious drugs studied to this point include cisplatin, 5-FU, doxorubicin, and mitomycin C. Most combination chemotherapy regimens have employed cisplatin, often with 5-FU, with good response rates. There has not been a consensus as to the proper dose of 5-FU, ranging from 100 to 1000 mg/m^2 in various studies. There is some evidence that 5-FU activity may be enhanced by modulation with leucovorin,[26] and that in adenocarcinoma of the stomach and colon, higher response rates can be achieved compared to 5-FU alone.[27,28]

Concurrent radiation therapy is used by some investigators; however, it is unclear if adenocarcinoma is more radiosensitive than squamous cancer. There is no consensus as to the best, safe dose. Current recommendations are to use a dose of less than 50 Gy for neoadjuvant or adjuvant therapy, and higher doses (55 to 65 Gy) for definitive radiation therapy.

CONCLUSIONS

There appears to be a significant increase in the reported cases of adenocarcinoma of the esophagus in recent years. The epidemiologic factors associated with this change in proportion of esophageal cancers have yet to be identified. In our experience, a neoadjuvant treatment protocol including cisplatin-based chemotherapy and concurrent mediastinal radiation therapy followed by resection provided superior survival compared to our earlier treatment. This suggests that effective treatment may have to be specific for the particular histologic type of esophageal cancer. Results of prospective, randomized trials for the treatment of adenocarcinoma of the esophagus should help to define effective treatment guidelines. Given the excellent results of therapy using this protocol, we think that future randomized trials should be designed using this, or a similar regimen, as the control arm.

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Discussion

DR. ROBERT E. CONDON (Milwaukee, Wisconsin): Dr. Sawyers was kind enough to give me a copy of the manuscript before the presentation of this paper and to ask me to comment, an invitation for which I thank him. Reading the manuscript has helped me to understand the details and the data a little bit better than my initial reading of the abstract.

Our most recent presentation of the data from my department at the Medical College of Wisconsin (MCW) was made by my resident, Mark Moon, at the 1991 meeting of the Western. At that time, we reported on 93 patients with a resected adenocarcinoma of the esophagus. Our experience now is with a little more than 100 patients.

Comparison of our experience with that of the Vanderbilt