
Early Results with Combined Modality Therapy for Carcinoma of the Esophagus

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Since January 1984, 74 patients (61 men, 13 women; age range: 43–76 years) with carcinoma of the esophagus were evaluated. Fifty-two patients had squamous cell carcinoma and 22 patients had adenocarcinoma. Sixty-three patients had preoperative chemotherapy and radiation that consisted of cis-platinum and VP-16 for squamous cell carcinoma and cis-platinum 5-FU for adenocarcinoma combined with 4500–6000 rads. Thirty-four patients were staged inoperable at the completion of the 4-month treatment regimen. Eleven patients had surgery alone because they refused or were not candidates for the preoperative regimen. Twenty-nine patients completed the combined modality regimen and have had esophagogastrectomy. All patients receiving chemotherapy and radiation demonstrated improved swallowing and a dramatic reduction of tumor mass early in the course of therapy and have been able to maintain oral nutrition without other support in the posttreatment period. Of the 34 patients who had chemotherapy and radiation therapy as palliation, 18 are currently living. One patient died secondary to complications of chemotherapy, another patient died at 9 months of myocardial infarction. The remaining patients died secondary to their disease. Of the 29 patients who had radiation therapy and chemotherapy plus esophagogastrectomy, 25 are alive. There were no operative deaths. One patient died at 9 months of stroke. Three other patients had recurrence and died 1 year after surgery. Of the 11 patients who had surgery alone, two have died of the disease. Of the 29 patients who completed the integrated therapy, 10 had no evidence of residual tumor in the specimen, and in an additional five patients only microscopic foci were evident. These early results are an encouragement to continue the multidiscipline approach to carcinoma of the esophagus in the hope that the quality of life and disease-free interval, as well as ultimate survival, will be enhanced.

THE DISMAL OUTLOOK FOR SURVIVAL of carcinoma of the esophagus has remained much the same over the past decade with occasional 5-year survival being reported. More aggressive therapy and a variety

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of surgical approaches to this disease in recent years have not significantly changed the overall survival. In general, the overall 5-year survival rate in select patients has been about 15% regardless of the type of surgical therapy used.¹⁻³

Preoperative radiation as an adjunctive therapy to surgery for carcinoma of the esophagus was introduced in the 1960s and continues to be used.⁴⁵ Over the past 5 years, chemotherapeutic regimens combined with radiation were introduced in an effort to improve the surgical survival rate.⁶⁻¹⁰ In 1984, we initiated a combined modality protocol consisting of multidrug chemotherapy and radiation followed by surgery. This comprehensive approach was designed to evaluate the tumoricidal effect and, hopefully, to improve both surgical results and palliation in patients who are not surgical candidates.

Patient Population

Since 1984, 74 patients have been entered into this study (Table 1). This population includes patients with squamous cell carcinoma and adenocarcinoma of the esophagogastric junction. There were 61 men and 13 women. The white to black ratio was 3:1 for the entire group, which is a departure from reported series of patients with carcinoma of the esophagus. Fifty-two patients had squamous cell carcinoma, and of these, 31 were white. All 22 patients who had adenocarcinoma were white. In this group, seven patients had previous head and neck malignancy, one patient had colon cancer, one patient had leukemia, two patients had previous carcinoma of the kidney, and one patient had ovarian cancer (Table 2).

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TABLE 1. *Carcinoma of the Esophagus: Patient Population*

| | No. of Patients |
|----------------|-----------------|
| Total number | 74 |
| Males | 61 |
| Females | 13 |
| White | 53 |
| Black | 21 |
| Squamous cell | 52 |
| Adenocarcinoma | 22 |

TABLE 2. *Carcinoma of the Esophagus: Associated Malignancy*

| | No. of Patients |
|---------------|-----------------|
| Head and neck | 7 |
| Kidney | 2 |
| Colon | 1 |
| Leukemia | 1 |
| Ovarian | 1 |

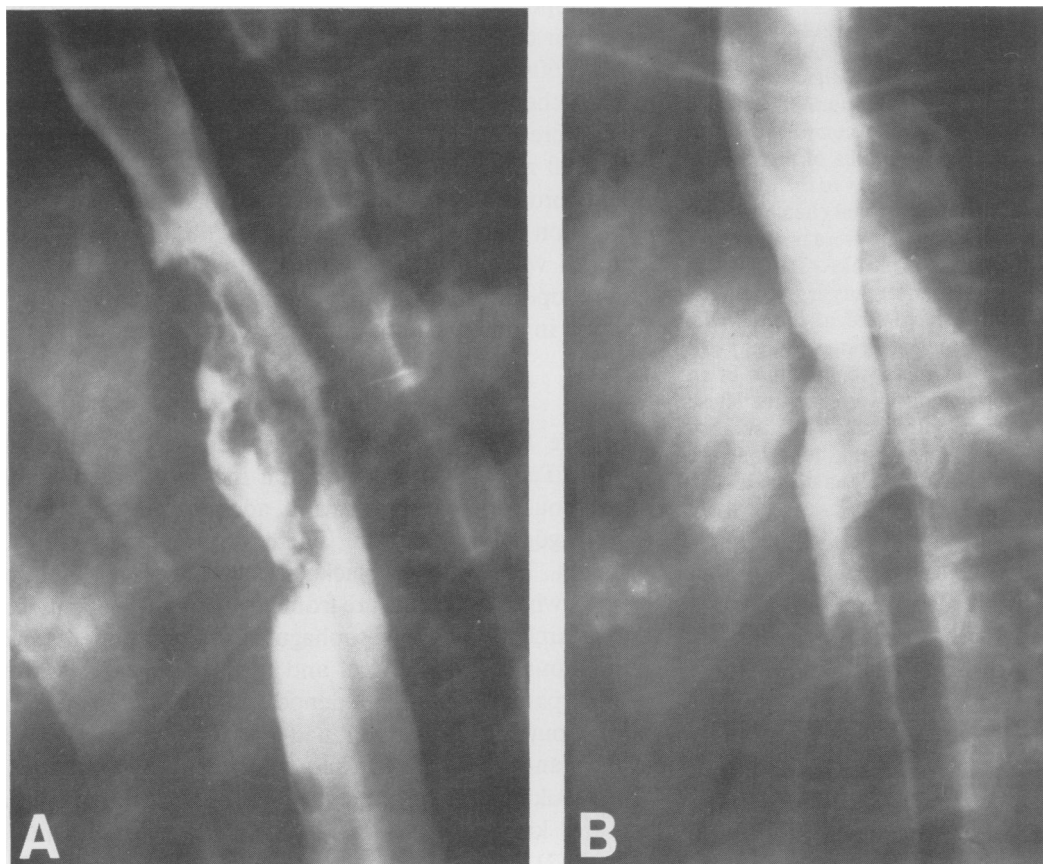
Clinical Evaluation

Patients were initially staged using chest x-rays, barium swallow, chest and upper abdominal computed tomography (CT), and a bone scan. All patients had esophagoscopy and bronchoscopy for diagnosis. At the comple-

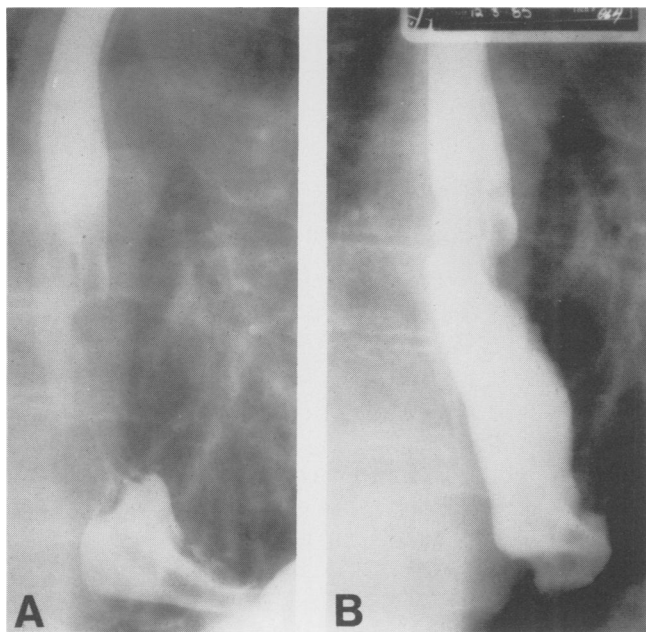
tion of treatment with chemotherapy and radiation therapy, restaging was done (Figs. 1 and 2). Patients determined to be surgical candidates had single-stage esophagectomy and reconstruction. The nonoperable group had their irradiation extended from 4500–6000 rads.

Chemotherapeutic Regimen

Once the patients were accepted for chemotherapy and radiation, they were prehydrated with 1500 mL of 5% glucose and normal saline with potassium chloride 20 mEq/L and intravenous (IV) fluids given at 150 mL/h throughout the treatment period. Those with squamous cell carcinoma had treatment with cis-platinum, 20 mg/m²/day IV for 5 days, and with VP16, 60 mg/m²/day for 5 days. Those patients with adenocarcinoma were treated with cis-platinum, 20 mg/m²/day IV for 5 days combined with 5-fluorouracil, 1000 mg/m²/day for 5 days. Antiemetic therapy consisted of Reglan® 1 mg/kg IV given before and after chemotherapy. Two courses of chemotherapy were administered 3 weeks apart, and this was followed by radiation therapy 5 days a week for 4.5 weeks for a total of 4500 rads. During the last week of radiation therapy, the patients were readmitted and received a final course of chemotherapy.



FIGS. 1A and B. A. Barium swallow of patient with squamous cell carcinoma before beginning combination therapy. B. Barium swallow at the completion of radiation and chemotherapy before surgery.



FIGS. 2A and B. A. An example of a patient with adenocarcinoma of the EG junction before chemotherapy and radiation therapy. B. The follow-up barium swallow before resection.

This therapy has been extremely well tolerated, and many patients had not only the chemotherapy but also the radiation therapy on an outpatient basis. Many patients continued to work, and the overall problems with side effects were minimal.

Therapeutic Groups

Group I comprised patients receiving chemotherapy, radiation therapy to 6000 rads, and no surgery. Group II comprised patients who completed chemotherapy, radiation therapy to 4500 rads, followed by esophagectomy and esophagogastrostomy. Group III comprised patients who had surgery without adjunctive therapy. This group could not be considered for entry either because of poor renal function or the patient's desire not to have chemotherapy and radiation.

Surgical Approach

The surgical procedure included esophagectomy and esophagogastrostomy. Although some controversy continues with regard to surgical approach, we believe there are indications for each option (Table 3).^{1,2,11,13} In the patients with lower-third lesions, the approach was through a left thoracotomy with esophagectomy, the stomach being brought up into the left chest usually just below the aortic arch, the anastomosis sewn by hand with an interrupted 3-0 silk single-layer technique. For those with middle-third lesions, the patient was approached

TABLE 3. Carcinoma of the Esophagus: Surgical Approach and Reconstruction

| | No. of Patients |
|---------------------------------|-----------------|
| Right thoracotomy | |
| Esophagogastrectomy | 17 |
| Left thoracotomy | |
| Esophagogastrectomy | 15 |
| Jejunum | 2 |
| Transhiatal esophagogastrectomy | 6 |

through a midline abdominal incision to mobilize the stomach with a combination right thoracotomy for the esophagectomy, and the anastomosis was usually done with an EEA stapler above the azygos vein in the right chest. Six patients had a transhiatal esophagectomy with the stomach being brought to the neck and the anastomosis being sewn with interrupted 3-0 silk sutures. Two patients required reconstruction with jejunum because their stomach had previously been partially resected. The jejunoesophageal anastomosis was sewn by hand in one of these patients and stapled in the other. Both of these cases were approached through the left chest.

Pathologic Findings

Pathologic findings in those patients who had chemotherapy, radiation therapy, and surgery were evaluated in 29 patients (Table 4). No residual tumor was found in 10 patients, seven of those with squamous cell carcinoma and three with adenocarcinoma. Five patients had microscopic tumor in the specimen, three of those were squamous cell and two were adenocarcinoma. Lymph nodes were positive in five of 29 patients who had esophagectomy in this group (Fig. 3).

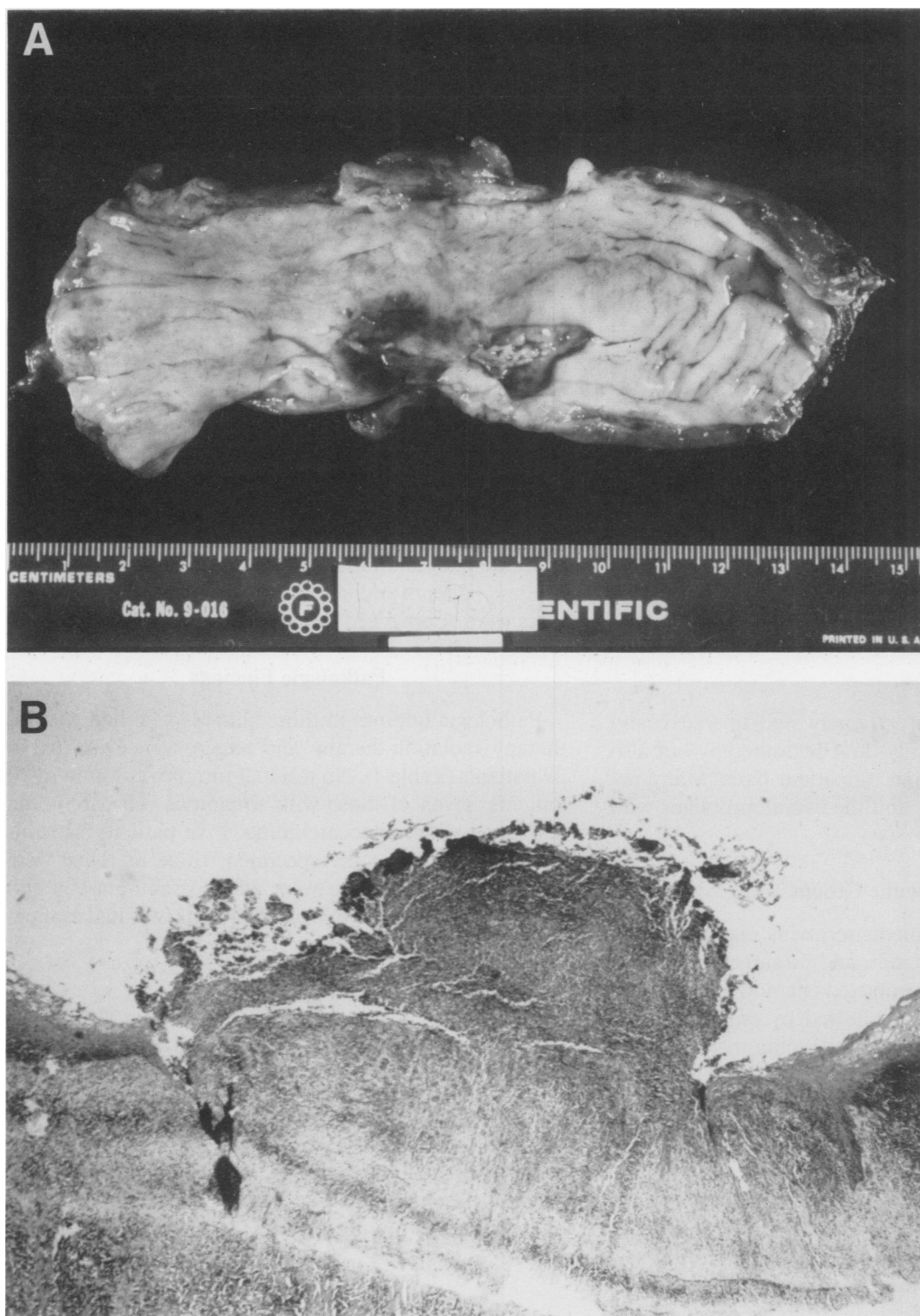
Results

Group I: Chemotherapy, Radiation Therapy (6000 rads)

In those patients receiving only chemotherapy and radiation therapy, the palliative results were excellent. The treatment schedule was well tolerated by most patients in this group. There was, however, one chemotherapy-related death. Otherwise, none of the patients needed supportive alimentation in any form other than high caloric liquids

TABLE 4. Carcinoma of the Esophagus: Chemotherapy, Radiation Therapy, and Surgery

| | Pathology (N = 29) | |
|----------------|--------------------|-------------------|
| | No Residual Tumor | Microscopic Tumor |
| Squamous cell | 7 | 3 |
| Adenocarcinoma | 3 | 2 |



FIGS. 3A and B. *A.* Gross specimen of resected esophagus in patient with squamous cell carcinoma who had been treated with radiation therapy. *B.* Low power microscopic view of the area demonstrating inflammation and ulceration but no tumor cells ($\times 25$).

taken orally. There was dramatic reversal of the catabolic nature of the process after the first dose of chemotherapy with improvement of both swallowing and appetite. None of the patients needed gastrostomy or other feeding tubes inserted during the remainder of their lives. A total of 34

patients completed treatment in this group. To date, 16 of these patients have died, with death occurring between 2 and 16 months. The longest survivor in this group is currently 16 months post-therapy with no evidence of recurrence.

Group II: Chemotherapy, Radiation Therapy (4500 rads), Surgery

Of 29 patients in Group II who had chemotherapy, radiation therapy, and surgery, two patients died within 4 months of their disease, one patient died at 9 months of a stroke, one patient died at 11 months of the disease, and one patient died at 16 months probably of the disease. The longest survival is 30 months.

Group III: Surgery Alone

In Group III, those who had surgery alone, 11 patients had esophagectomy. Two of these patients are dead, one at 17 months of her disease, the other at 26 months and the cause of death is not known. The longest survival in the surgery alone group is 32 months.

A total of 40 patients had operation without hospital mortality. One patient had an anastomotic leak in the neck that healed without difficulty. Two patients had respiratory insufficiency in the postoperative period. Two patients had anastomotic narrowing that required dilatation. Dumping syndrome occurred in two patients. Two patients had to have pyloroplasty because of poor emptying.

Discussion

Survival is shown in Figure 4 for all three groups. Although improved survival is the main treatment goal,¹⁴ we believe it is still too early for any significant long-term projections. Two initial observations should be emphasized. First, palliation with the use of chemotherapy and radiation therapy for patients who are not surgical candidates is excellent, both in adenocarcinoma and squamous cell carcinoma. This treatment modality is usually tolerated without difficulty, although the white blood count must be closely monitored. There was a single death related to leukopenia and infection in the chemotherapy group. Second, the histopathologic changes produced by the combined therapy are dramatic. The incidence of sterile specimens and only microscopic residual might well translate to significant prolongation of disease-free interval and ultimately enhance patient survival.

In the surgical group, the results have been gratifying (Fig. 5). Impressive, however, in the chemotherapy, radiation therapy, and surgery group, was the length of time required to recover from the operation, which was approximately 8 weeks compared with 4 weeks before the anorexia of the surgical experience cleared and the patient's appetite returned.

In the follow-up period, repeat staging has been done. Weight gain is usually an indicator of the current status of the patient. Those patients who are holding their weight or have gained weight post-therapy are almost invariably

Carcinoma of the Esophagus

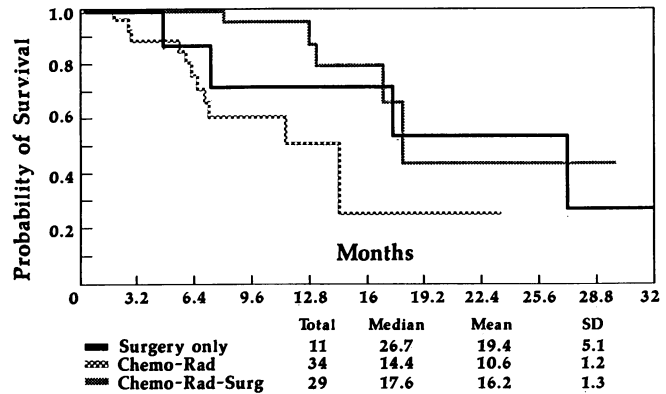


FIG. 4. This figure demonstrates the projected survival for the three groups. These curves were derived using the method of Kaplan-Meier.¹⁵

doing well without evidence of recurrence. The findings of weight loss at a return clinic visit is almost always an indication of recurrent carcinoma. Early on, we were somewhat conservative in entering patients into the protocol. Consequently, the surgery alone group was accumulated totally in the early period of the study. Over the last year, no patient has been seen who did not have chemotherapy and radiation therapy before operation. The only major medical contraindications are renal insufficiency and, therefore, the inability to take cis-platinum, or the presence of a tracheoesophageal fistula. Tracheoesophageal fistulas developed in two patients while in therapy. Neither patient required surgical management of this, both fistulas being lobar in nature. Both patients were treated with chronic antibiotics. A bypass procedure was not done because of the extensive metastatic disease in these patients.

Carcinoma of the Esophagus

Surgery + Chemo + Radiation Therapy

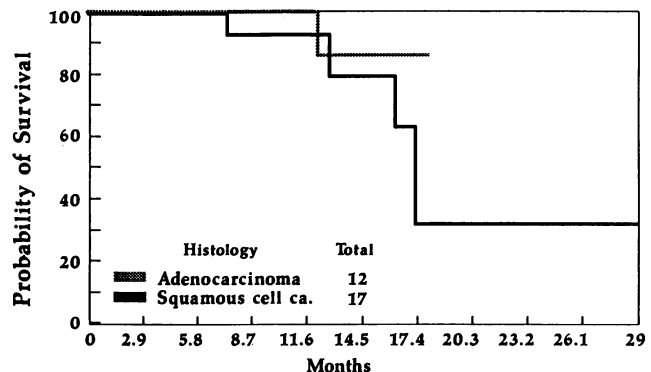


FIG. 5. This shows the survival curve for the patients with squamous cell carcinoma and adenocarcinoma who completed their chemotherapy, radiation therapy, and surgery.

Currently, the results lead us to continue the multidiscipline approach. Combination chemotherapy and radiation therapy offers safe and effective palliation. It does not adversely affect surgical morbidity or mortality. We believe that it does enhance the quality of life of these patients and perhaps with further follow-up study will demonstrate an improvement in long-term survival.

Acknowledgments

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DISCUSSION

DR. J. BRADLEY AUST (San Antonio, Texas): I am indebted to Dr. Condon for sending me a copy of his paper before this meeting. He adequately catalogues the trials and tribulations of dealing with this difficult group of patients. They are truly far advanced, but he has assumed that they can be treated surgically.

When I think about carcinoma of the esophagus, I divide patients into essentially three groups: (1) those with Stage I or Stage II disease who are potentially curable and should have a curative type of procedure; (2) those with such far advanced disease that they cannot be resected and continuity restored for successful swallowing; and (3) a vast group in between which are Stage III and IV disease, a very frustrating group, and these are the patients Dr. Condon is addressing.

Those in the first group may be helped by a radical esophagectomy such as the "Skinner" procedure, and attempt made for cure, but in Dr. Condon's group of patients it is clear that palliation was the goal, and I would not argue with Dr. Condon's philosophy that in his group of patients palliation must be the major goal of therapy.

How do you measure palliation? This is a good question. It should be balanced against operative mortality, and from my viewpoint, local recurrence, which is *prima facie* evidence of inadequate surgical resection. If we add these up in his series, the operative mortality and the local recurrence vary somewhat depending on how early deaths are counted, between about 20 and 25% of the patients. Balanced against a 2-year survival rate of 35% with an ability to swallow the major goal of therapy, I would view that he has benefited this group of patients.

The one question that I have is related to the use of the Karnofsky scale, which I think is admirable and should be used more often, but I wonder if perhaps he should add to the denominator those patients who died at surgery, so that one can compare the Karnofsky averages in patients who are treated with other forms of therapy, such as laser, to restore the swallowing mechanism.

DR. JOHN L. CAMERON (Baltimore, Maryland): I would like to confine my comments and questions primarily to the paper of Dr. Condon, although I believe they are also pertinent to those patients in Dr. Wolfe's presentation who had adenocarcinoma of the esophagus.

I believe the important issue in Dr. Condon's paper on adenocarcinoma of the esophagus is the pathogenesis.

Adenocarcinoma of the esophagus is clearly increasing in prevalence in university hospitals. Whether that is secondary to a change in referral patterns or recognition or whether there is a true increased incidence of the lesion is not clear, but I believe it is obvious that we are seeing more and more adenocarcinomas of the esophagus. This point is emphasized by Dr. Wolfe's presentation in which almost 50% of his patients had adenocarcinoma. If you look at series presented 15 and 20 years ago, the percentages of lesions that were squamous and adenocarcinoma were greatly different.

There is increasing circumstantial evidence that suggests that in virtually all patients with adenocarcinoma of the esophagus, the lesions arise from Barrett's mucosa. I would like to present briefly some of the circumstantial evidence for this that we have accumulated.

In the last 6 years we have seen 54 patients with adenocarcinoma at the gastroesophageal junction. When we examined the specimens in the routine fashion, just as in Dr. Condon's paper, approximately 25% were associated with Barrett's mucosa. However, when the specimens were totally embedded and serially sectioned, we found Barrett's mucosa in 35 of the 54 patients or an incidence of about 65%. Now, 30 of those 35 patients with clearly identifiable Barrett's mucosa were white males, and virtually all of them were heavy smokers or heavy drinkers, and most of them were both.

Dr. Condon did not comment on that in his presentation, but I would like him to tell us whether his patients were virtually all white males, heavy drinkers, and heavy smokers. That goes without saying in a V.A. population, but in his university hospital, I would like to hear the distribution.

If we take the other 19 patients in whom we could not find Barrett's mucosa, the question is: are these stomach cancers that are growing up or are they cancers that arose in Barrett's mucosa and the Barrett's mucosa has just been replaced?

Fifteen of the 19 patients were white males and virtually all were cigarette smokers and heavy drinkers, so it looks very similar to the Barrett's group.

If we look at adenocarcinoma of the body of the stomach, we have to go back over twice the time period as we did for adenocarcinoma at the GE junction because in our institution and, I am sure, in all of yours, this lesion is decreasing in prevalence unlike adenocarcinoma at the GE junction. Of 63 patients with adenocarcinoma of the body of the stomach,