

Neoadjuvant Chemoradiotherapy for Esophageal Cancer

Is It Worthwhile?

Wael Z. Tamim, MD; Robert S. Davidson, MD; Robert M. Quinlan, MD; Michael A. O'Shea, MB, BCh; Richard K. Orr, MD; Richard S. Swanson, MD

Background: With promising results from several institutions, many centers began treating patients with esophageal cancer with neoadjuvant chemoradiotherapy (NC) followed by esophagectomy. This approach is demanding for the patient and has not been proved to be better than esophagectomy alone.

Objective: To assess survival time and measures of quality of life associated with NC.

Design: A retrospective review during 1990 to 1996.

Setting: The 3 tertiary academic hospitals affiliated with the University of Massachusetts Medical School, Worcester.

Participants: All patients (N = 51) with cancer of the middle or lower esophagus who were treated with NC followed by esophagectomy during this period.

Main Outcome Measures: Median and 1-, 2-, and 3-year survival times; median preoperative treatment time (first office visit for surgical consultation before beginning NC to the date of surgery), median hospital stay, and postoperative swallowing function.

Results: The median survival time of all patients was 16.3 months; 1-, 2-, and 3-year overall survival rates were

67%, 46%, and 39%, respectively. The median hospital stay was 12 days. The median postoperative treatment time was 3.3 months, which was 20% of the median survival time. Of the 51 patients, 19 were alive with a median follow-up time of 2.5 years. Twenty-nine percent of the patients had a complete pathological response with median and 1-, 2-, and 3-year survival rates of 17.5 months, 73%, 57%, and 57%, respectively. Palliation of dysphagia was excellent, with 44 (93%) of 47 operative survivors taking either a soft diet (18 [38%]) or a regular (26 [55%]) diet by the first postoperative visit.

Conclusions: Median survival time with NC followed by esophagectomy for resectable cancer of the esophagus does not appear to be significantly better than that reported for esophagectomy alone. Further, treatment time with NC consumed 20% of survival time. Examining only these outcome variables suggests that NC is not worthwhile. However, examining a longer-term outcome survival variable, such as 3-year survival time, suggests that NC followed by esophagectomy may result in greater long-term survival than that reported for esophagectomy alone. We conclude that further randomized, controlled studies are necessary before NC followed by esophagectomy is considered superior to esophagectomy alone for the treatment of resectable esophageal cancer.

Arch Surg. 1998;133:722-726

ESOPHAGEAL carcinoma is an aggressive disease with a poor prognosis. Its incidence in the United States has been increasing; it now causes about 9800 deaths per year.¹ Many institutions have been using various combinations of multimodality treatment to improve the chance of survival over that achieved with the standard of care for this disease—surgical resection alone. In the late 1980s, neoadjuvant chemoradiotherapy (NC) followed by esophagectomy became a popular approach after several favorable pilot studies were reported.

The University of Massachusetts Medical Center, Worcester, began using this approach in the late 1980s. The other 2

tertiary care affiliates of the University of Massachusetts Medical School—St Vincent's Hospital and Memorial Hospital—began using this approach in 1990. We reviewed the experience of the 3 tertiary care affiliates of the University of Massachusetts Medical School with preoperative chemoradiotherapy followed by esophageal resection for the treatment of esophageal carcinoma to assess the practicality of its application, specific survival end points, and the relief of dysphagia.

From the Department of Surgery, University of Massachusetts Medical School, Worcester.

This article is also available on our Web site: www.ama-assn.org/surgery.

PATIENTS AND METHODS

PATIENTS

Patients with carcinoma of the middle and lower thirds of the esophagus treated between July 1, 1990, and June 30, 1996, at the 3 tertiary care affiliates of the University of Massachusetts Medical School (University of Massachusetts Medical Center, St Vincent's Hospital, and Memorial Hospital) were identified retrospectively by reviewing tumor registry data and office files at the 3 institutions. The 51 patients with localized and resectable (stages I, II, and III) esophageal adenocarcinoma and squamous cell carcinoma who were treated with preoperative cisplatin, fluorouracil, and radiotherapy followed by surgery are the subjects of this study. During this period, some patients were treated with alternative combinations of surgery, chemotherapy, and radiation; they will not be included. From 1995 to the present, patients at University of Massachusetts Medical Center have been treated according to a different multimodality protocol, and they will not be included in this study.

INTERVENTIONS

Although this was not a multi-institutional protocol, chemotherapy was similar at all 3 institutions. All patients had 2 courses of preoperative chemotherapy with external beam radiotherapy between courses. Each course of chemotherapy consisted of a 4-hour infusion of cisplatin at 80 to 100 mg/m² and then a 96-hour infusion of fluorouracil at 900 mg/m². Patients typically were hospitalized for 4 to 5 days for each course.

External beam radiotherapy was administered between courses of chemotherapy for 3 to 5 weeks at total doses of 3000 to 5400 cGy. The total dose varied according

to the preference of the treating hospital: 3000 cGy at St Vincent's Hospital, 4500 cGy at Memorial Hospital, and 5400 cGy at University of Massachusetts Medical Center.

Four to 6 weeks after the end of neoadjuvant therapy, 1 of several methods of surgical resection was performed according to the surgeon's preference. The majority of patients (33 [65%]) had an Ivor Lewis thoracoabdominal esophagogastrectomy; others had either a left thoracoabdominal esophagogastrectomy or a transhiatal esophagectomy.

MAIN OUTCOME MEASURES

The main outcome measures included the median survival time, for which survival was defined as the interval from the first surgical consultation before neoadjuvant therapy until the date of the last follow-up; the median preoperative treatment time, which was the interval between the first surgical consultation before neoadjuvant therapy and the date of admission for esophageal resection; the median hospital stay, which was the time spent in the hospital for surgery; and the median follow-up time for the survivors, which was determined by using the interval between the first surgical consultation before neoadjuvant therapy and the date of last follow-up for the survivors. These outcome measures were determined for the group as a whole and for those who had a pathological complete response as well as those who had residual disease in the specimen.

Dysphagia relief was assessed by noting the diet at the first postoperative office visit.

STATISTICAL ANALYSIS

Kaplan-Meier analysis was used to calculate survival times. The log-rank test was used to compare survival rates for those with and without pathological complete response.

RESULTS

Of the 51 patients, 48 (94%) were male. The average age was 61 years (range, 34-81 years). Forty-three patients (84%) presented with dysphagia; 32 (63%) presented with weight loss. Forty-five patients (88%) smoked tobacco and 34 (67%) drank alcohol, with 6 (12%) of the group admitting to alcohol abuse. Forty-three tumors (84%) were adenocarcinomas; 8 (16%) were squamous cell carcinomas. Barrett esophagus was noted in 11 (22%) of the surgical specimens. In 43 patients (84%), the tumor was located more than 30 cm from the incisors by endoscopy; in 8 (16%) the tumors were between 25 and 30 cm from the incisors (**Table 1**).

Neoadjuvant chemoradiotherapy was tolerated well without major interruption except in 2 patients who had myelosuppression and 1 patient who had severe dysphagia. The median preoperative treatment time was 3.3 months.

The surgical mortality rate (deaths in the hospital after surgery or within 30 days of surgery) was 7.8% (4 deaths). There were no surgery-related deaths for the final 26 patients. The median hospital stay after surgery was 12 days. Dysphagia relief was excellent.

Of the survivors of surgery, 44 (93%) were taking a soft (18 [38%]) or a regular (26 [55%]) diet at the first postoperative visit. Median follow-up time for the survivors was 2.5 years.

Of the 51 patients, 15 (29%) had a pathological complete response and 36 (71%) had residual cancer in the operative specimen. The median and 3-year survival rates were 16.3 months and 38% overall, 17.5 months and 53% for those with a pathological complete response, and 15.1 months and 34% for those with residual disease in the operative specimen. The log-rank test did not demonstrate significance ($P = .5$) for the difference in survival rates between those with a pathological complete response and those with residual disease in the operative specimen (**Figure 1** and **Figure 2**).

Although median follow-up time was relatively short, of 36 patients with residual disease, 6 were alive more than 3 years from diagnosis, and 3 of these patients were alive more than 4.5 years after diagnosis. The longest-surviving patient of the entire group had residual disease at esophagectomy and was disease free 7.6 years after diagnosis. Interestingly, he developed a large squamous cell carcinoma of the proximal deep right thigh, which was his only site of metastasis (or an unusual second pri-

Table 1. Demographic Characteristics

Characteristic	No. (%) of Patients (N = 51)
Mean age, y	61
Dysphagia	48 (94)
Weight loss	43 (84)
Smoking	32 (63)
Alcohol use	45 (88)
Adenocarcinoma	43 (84)
Squamous cell carcinoma	8 (16)
Barrett esophagus	11 (22)
Tumor >30 cm from incisors	43 (84)

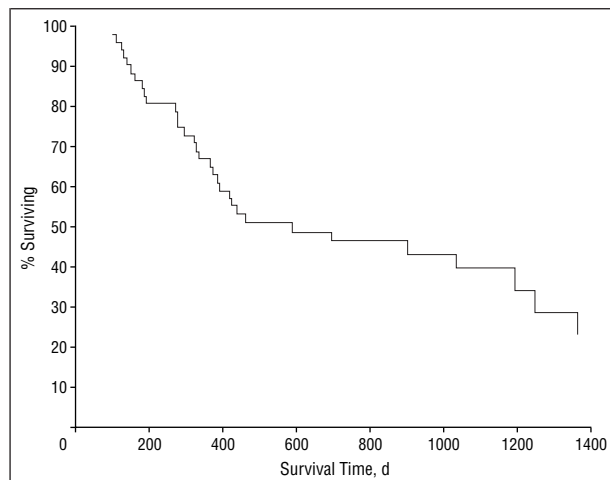


Figure 1. Overall survival curve.

mary); it eventually required a modified hemipelvectomy 2.8 years after the initial diagnosis.

When mean survival times were compared for patients with adenocarcinoma vs squamous cell carcinoma, there was not a significant difference (Table 2). Similarly, when mean survival times were compared for those who had an Ivor Lewis esophagogastrectomy vs transhiatal esophagogastrectomy, there was not a significant difference (Table 2).

COMMENT

Esophageal carcinoma is one of the most aggressive visceral cancers, with a poor prognosis and overall estimated 5-year survival rate in the range of 10%.^{2,3} The standard treatment for localized disease is surgical resection, but survival rates associated with surgery alone are poor. Swisher et al⁴ reported a median survival time of 13 months and a 3-year survival rate of 25% for patients treated with surgery alone. Ellis⁵ reported an actuarial 5-year survival rate adjusted for operative mortality and noncardiac deaths of 23.3% for patients with esophageal cancer treated with resection alone. Similar survival data for esophagectomy alone are presented in Table 3.⁵⁻⁸

Faced with low survival rates with esophagectomy alone as the treatment for esophageal cancer, several institutions have been examining methods to improve sur-

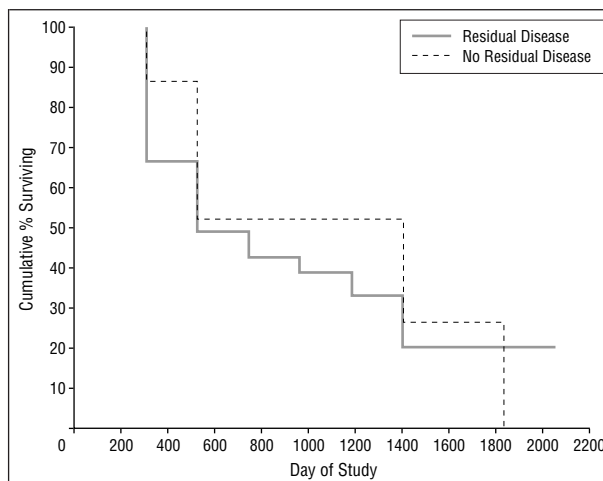


Figure 2. Cumulative survival in patients with and without residual disease.

Table 2. Influence of Histological Findings and Type of Resection on Survival for Esophageal Cancer

Histological finding	No. of Patients	Survival, d		P*
		Median	Mean	
Adenocarcinoma	31	418	551	.20
Squamous cell carcinoma	20	502	708	
Type of resection				.50
Ivor Lewis	33	467	659	
Transhiatal	8	352	539	

*By 2-tailed Student t test.

vival by using combinations of chemotherapy and radiotherapy. Some have used chemotherapy and radiation without surgery to treat this disease. At Wayne State University in Detroit, Mich, this approach yielded a median survival time of 22 months and a prohibitive toxic reaction from the chemotherapy.⁹ Al-Sarraf et al¹⁰ reported a median survival time of 17.2 months with chemotherapy and radiation without surgery. At Fox Chase Cancer Center, Philadelphia, Pa, 57 patients received chemoradiotherapy without surgery, and the median survival time was 18 months while the 5-year survival rate was 18%.¹¹ Herskovic et al¹² randomly assigned patients with resectable esophageal cancer to radiation vs chemoradiation (neither group had surgery). The median survival time was 12.5 months, and the 2-year survival rate was 38% in the chemoradiation group. Interestingly, 10 of 61 patients died before completing the 100 days of chemoradiotherapy, suggesting a 16.4% treatment-associated mortality rate. John et al¹³ reviewed the survival rates for 30 patients with esophageal cancer treated with chemoradiotherapy. The median survival time was 15 months and the 2-year survival rate was 29%.

Other investigators have combined all 3 modalities, using chemoradiation as a neoadjuvant therapy before surgical resection. Bates et al¹⁴ reported a 25.8-month median survival time and a 46% 3-year survival rate with this approach. Forastiere et al¹⁵ reported a me-

Table 3. Survival With Surgery for Esophageal Cancer

Source	Median Survival, mo	Survival, %
Gertsch et al ⁶	18	27 (3 y)*
Ellis ⁵	...†	23 (5 y)
Watson ⁷	18	26 (3 y)
El Nakadi et al ⁸	...†	24 (5 y)

*Numbers in parentheses indicate survival time.

†Ellipses indicate not specified.

dian survival time of 29 months and a 3-year survival rate of 46%. Others did not report such favorable survival results with this method (Table 4).^{4,14-19}

Our series from University of Massachusetts Medical School included 51 patients with localized and resectable esophageal cancer who were treated with NC followed by esophagectomy. Our median survival time of 16.3 months is similar to that reported by other institutions using this approach, and it is also not distinctly different from that reported for surgery alone (Tables 3 and 4). Using median survival time as the survival end point to determine the worth of this treatment suggests that NC is not obviously beneficial. The “costs” of NC are also important. Although the morbidity rate is small, NC consumed 20% of survival time. It is difficult to propose a treatment (NC) that does not seem to improve survival while the time to complete its treatment consumes one fifth of survival time.

At the same time, the value of NC may not be in improving median survival time; it may be in prolonging long-term survival. Urba et al¹⁹ recently reported preliminary results of a randomized, controlled study at the University of Michigan, Ann Arbor, comparing surgical resection with NC followed by surgical resection. Although median survival times were similar (16.9 and 17.5 months), 3-year survival rates were different: 15% for surgery alone and 32% for NC followed by surgery. Our 3-year survival rate of 38% compares favorably with the University of Michigan data for NC followed by surgery. Certainly, our data do not prove that long-term survival is improved with NC. They suggest that maturation of the University of Michigan data and further randomized, controlled trials are necessary before we can consider NC followed by esophagectomy to be superior to surgery alone.

One published randomized, controlled prospective trial did report a significant improvement in both the median survival time and the 3-year survival rate associated with NC followed by surgery as compared with surgery alone.¹⁶ In this study by Walsh et al¹⁶ from Dublin, Ireland, the median survival time was 16 months for the multimodality group as compared with 11 months for the surgical alone group; 3-year survival rates were 32% and 6%, respectively. This is an important study, but there are 2 important considerations. First, only patients with adenocarcinoma of the esophagus were eligible; patients with squamous cell carcinoma were excluded. Second, this was a small study with less than 60 patients in each arm. Clearly, the results of this study need to be reproduced before NC can be accepted as the standard of care.

Table 4. Survival With Multimodality Treatment for Esophageal Cancer

Source	Median Survival Time, mo		3-y Survival Rate, %	
	Multimodality	Surgery	Multimodality	Surgery
Nonrandomized				
Swisher et al ⁴	14	13	22	25
Bates et al ¹⁴	25.8	...*	48	...
Forastiere et al ¹⁵	29	...	46	...
Stahl et al ¹⁷	17	...	33	...
Vogel et al ¹⁸	18	...	41	...
Present series	16.3	...	38	...
Randomized				
Walsh et al ¹⁶	16	11	32	6
Urba et al ¹⁹	16.9	17.5	32	15

*Ellipses indicate not reported.

In our study, 29% of patients had a pathological complete response. This value compares favorably with that reported by others.^{4,15,16,18} Our data suggest that patients who had a pathological complete response tended to live longer than those who did not. This finding was seen by other authors.^{4,15,18} It is not clear whether improved survival with a complete response to NC is because the chemoradiotherapy was effective or whether response to chemoradiotherapy is simply a marker for favorable disease (and the subset who responded to NC would have done as well with surgery alone).

Some argue that resection is not necessary after chemoradiotherapy because those who have a complete response do not need it and those who have residual disease do so poorly that resection does not help. Our data cannot definitively address this issue, but it is interesting that our longest current survivors are those who had residual disease removed at surgery. Walsh et al¹⁶ reported that the omission of resection would have left 75% of the patients in their multimodality group with residual disease, which in 19 cases (33%) appeared to be confined to the esophagus.

Quality-of-life issues are difficult to assess when complicated treatment regimens are used to manage difficult diseases. Certainly, although most patients can complete combined-modality treatment, it is demanding for the individual patient. In our series, patients spent almost as much time in the hospital for NC (10 days for inpatient chemotherapy) as they did for the surgery (median hospital stay of 12 days). The decision to pursue NC demanded an additional 3.3 months of treatment time before surgical resection. If NC is not worthwhile—or only marginally beneficial—it would be difficult to recommend NC on the basis of the length of treatment. A short treatment time is appealing when survival time is relatively short. As most patients presented with dysphagia, an important quality-of-life issue was relief of dysphagia. In our series, most patients had relief of dysphagia after resection. Our results with relief of dysphagia compare favorably with those reported for surgery alone⁸: NC did not appear to worsen (or improve) these results.

From our data and those cited above, it is clear that NC followed by esophagectomy may improve survival over esophagectomy alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus, but the results of further randomized, controlled, prospective trials will be necessary to confirm this impression. Until we have results of these trials, NC followed by esophagectomy should be considered investigational and not the standard of care.

Presented at the New England Surgical Society Annual Meeting, Bolton Landing, NY, September 19, 1997.

Corresponding author: Richard S. Swanson, MD, Department of Surgery, University of Massachusetts Medical Center, 55 Lake Ave N, Worcester, MA 01655.

REFERENCES

- Forastiere AA, Urba SG. Preoperative treatment of esophageal cancer. *Principles Pract Oncol*. 1991;5:1-4.
- Orringer MB. Tumors of the esophagus. In: Sabiston DC Jr, Lyerly HK, eds. *Textbook of Surgery*. Philadelphia, Pa: WB Saunders Co; 1997:744-758.
- Peter JH, DeMeester Jr. Esophagus and diaphragmatic hernia. In: Schwartz SI, Shires GT, Spencer FC, eds. *Principles of Surgery*. New York, NY: McGraw-Hill Inc; 1996:109-122.
- Swisher SG, Holmes GC, Hunt KK, et al. The role of neoadjuvant therapy in surgically resectable esophageal cancer. *Arch Surg*. 1996;131:819-825.
- Ellis HF Jr. Treatment of carcinoma of the esophagus or cardia. *Mayo Clin Proc*. 1989;64:945-955.
- Gertsch P, Vautney JN, Lustenberger AA, Hamutal FK. Long-term results of transhiatal esophagectomy for esophageal carcinoma. *Cancer*. 1993;72:312-319.
- Watson A. Operable esophageal cancer: current results from the west. *World J Surg*. 1996;18:361-366.
- El Nakadi I, Houben JJ, Gay F, et al. Does esophagectomy cure a resectable esophageal cancer? *World J Surg*. 1993;17:760-765.
- Steiger Z, Franklin R, Wilson RF, et al. Eradication and palliation of squamous cell carcinoma of the esophagus with chemotherapy, radiotherapy and surgical therapy. *J Thorac Cardiovasc Surg*. 1981;82:713-719.
- Al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. *J Clin Oncol*. 1997;15:277-284.
- Cole LR, Engstrom PF, Paul AR, et al. Long-term results of infusional 5-FU, mitomycin-C and radiation of primary management of esophageal carcinoma. *Int J Radiat Oncol Biol Phys*. 1991;20:29-36.
- Herskovic A, Martz K, Al-Sarraf, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med*. 1992;326:1593-1598.
- John MJ, Flam MS, Mowry PA, et al. Radiotherapy alone and chemoradiation for nonmetastatic esophageal carcinoma: a critical review of chemoradiation. *Cancer*. 1989;63:2397-2403.
- Bates BA, Vetterbeck FC, Bernard SA, et al. Concurrent radiation therapy and chemotherapy followed by esophagectomy for localized esophageal carcinoma. *J Clin Oncol*. 1996;14:156-163.
- Forastiere AA, Orringer MB, Tamaya CP, et al. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol*. 1993;11:1118-1123.
- Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med*. 1996;335:462-467.
- Stahl M, Wilke H, Fink V, et al. Combined preoperative chemotherapy and radiotherapy in patients with locally advanced esophageal cancer: interim analysis of phase II trial. *J Clin Oncol*. 1996;14:829-837.
- Vogel SB, Mendenhall WM, Sombeck MD, et al. Downstaging of esophageal cancer after preoperative radiation and chemotherapy. *Ann Surg*. 1995;221:685-695.
- Urba S, Orringer M, Turrisi A, et al. A randomized trial comparing surgery(s) to preoperative concomitant chemoradiation plus surgery in patients (pts) with resectable esophageal cancer (CA): updated analysis. *Proc Am Soc Clin Oncol*. 1997; 16:277. Abstract 475.

IN OTHER AMA JOURNALS

JAMA

Assessing Differences in Clinical Trials Comparing Surgical vs Nonsurgical Therapy: Using Common (Statistical) Sense

George Howard, DrPH; Lloyd E. Chambless, PhD; Richard A. Kronmal, PhD

The statement of hypotheses and choice of statistical tests in clinical trials that compare surgical with nonsurgical treatment are complicated by the likelihood of excess risk in the surgical group during the perioperative period but lower risk after that compared with the more uniform risk in the nonsurgical group. Commonly used statistical survival analyses implicitly assume a constant ratio of risks in the 2 groups during the follow-up period. However, the changing pattern of risk for one treatment but not the other implies that the assessment of the relative efficacy of the treatments varies with the length of the follow-up. As such, determining whether survival curves for the 2 groups are different may not translate easily into selecting the best treatment. Alternative statements of the hypothesis based on consideration of the time horizon of patients and on clinical judgment may be more consistent with the goals of the study. Regardless of the choice of a statistical test, the choice of treatment is a decision specific to the individual patient and should be influenced by the patient's life expectancy, attitude toward taking risks, quality of life, and cost considerations. When the survival curves cross, there is a trade-off between the risk of surgery and the increase in life expectancy among the survivors of surgery. Accordingly, assessment of differences in outcomes in clinical trials comparing surgical vs nonsurgical therapy should provide both a conclusion about whether 1 treatment can reasonably be considered best for most patients and should provide information to the individual patient and physician on the expected outcome to aid in the decision-making process. *JAMA*. 1997;278:1432-1436

Reprints: George Howard, DrPH, Department of Public Health Sciences, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC.