

CHEMOTHERAPY FOLLOWED BY SURGERY COMPARED WITH SURGERY ALONE FOR LOCALIZED ESOPHAGEAL CANCER

DAVID P. KELSEN, M.D., ROBERT GINSBERG, M.D., THOMAS F. PAJAK, PH.D., DANIEL G. SHEAHAN, M.B.,
LEONARD GUNDERSON, M.D., JOANNE MORTIMER, M.D., NORMAN ESTES, M.D., DANIEL G. HALLER, M.D.,
JAFFER AJANI, M.D., WALTER KOCHA, M.D., BRUCE D. MINSKY, M.D., AND JACK A. ROTH, M.D.

ABSTRACT

Background We performed a multi-institutional randomized trial comparing preoperative chemotherapy followed by surgery with surgery alone for patients with local and operable esophageal cancer.

Methods Preoperative chemotherapy for patients randomly assigned to the chemotherapy group included three cycles of cisplatin and fluorouracil. Surgery was performed two to four weeks after the completion of the third cycle; patients also received two additional cycles of chemotherapy after the operation. Patients randomly assigned to the immediate-surgery group underwent the same surgical procedure. The main end point was overall survival.

Results Of the 440 eligible patients with adequate data, 213 were assigned to receive preoperative chemotherapy and 227 to undergo immediate surgery. After a median possible study time of 55.4 months, there were no significant differences between the two groups in median survival: 14.9 months for the patients who received preoperative chemotherapy and 16.1 months for those who underwent immediate surgery ($P=0.53$). At one year, the survival rate was 59 percent for those who received chemotherapy and 60 percent for those who had surgery alone; at two years, survival was 35 percent and 37 percent, respectively. The toxic effects of chemotherapy were tolerable, and the addition of chemotherapy did not appear to increase the morbidity or mortality associated with surgery. There were no differences in survival between patients with squamous-cell carcinoma and those with adenocarcinoma. Weight loss was a significant predictor of poor outcome ($P=0.03$). With the addition of chemotherapy, there was no change in the rate of recurrence at locoregional or distant sites.

Conclusions Preoperative chemotherapy with a combination of cisplatin and fluorouracil did not improve overall survival among patients with epidermoid cancer or adenocarcinoma of the esophagus. (N Engl J Med 1998;339:1979-84.)

©1998, Massachusetts Medical Society.

ESOPHAGEAL carcinoma is an aggressive disease with a poor prognosis. For patients with stage 1, 2, or 3 carcinomas, surgery alone remains one standard of care. Another approach, treatment with radiation plus concurrent chemotherapy, has been shown to be superior to radiation alone.^{1,2} Chemotherapy plus radiation

but without surgery has not yet been compared in a prospective trial with surgery alone.

Because of the high rates of distant and locoregional failure, there is intense interest in combining regional therapy (such as surgery or radiation) with systemic therapy. In previous studies, chemotherapy had at least moderate effectiveness in treating metastatic disease.³ These results led to combined-therapy approaches to treating patients with localized tumors.⁴

By 1989, research data were sufficient to warrant a study of surgery alone as compared with surgery after chemotherapy. Because adenocarcinoma of the esophagus has become increasingly common, our trial included patients with either adenocarcinoma or epidermoid cancer of the esophagus.⁵

METHODS

This study involved investigators from the Radiation Therapy Oncology Group (the coordinating group), the Cancer and Acute Leukemia Group B, the Southwest Oncology Group, and the Eastern Cooperative Oncology Group. The primary objective was to compare surgery alone with preoperative and postoperative chemotherapy plus surgery. The primary end point was overall survival.

Eligibility requirements included the presence of confirmed epidermoid cancer or adenocarcinoma of the esophagus, including the gastroesophageal junction, with or without metastases in local lymph nodes and clinically limited to the locoregional area (tumor stage 1, 2, or 3; any nodal stage; and no metastasis [M0] in the tumor-node-metastasis [TNM] classification; carcinoma stage, 1 to 3). All patients were at least 18 years of age; had adequate hepatic, renal, and bone marrow reserve; and could tolerate the planned surgical procedure. Patients were ineligible if they had cervical esophageal tumors (upper border, <18 cm from the incisor teeth) or supraclavicular or other distant metastases (T4 tumors) or if they had previously undergone treatment or had previously had another primary cancer.

The pretreatment evaluation included a complete medical history and physical examination, complete blood count and platelet count, biochemical screening, radiography of the chest, barium-contrast radiography of the upper gastrointestinal tract, computed tomography of the abdomen and chest, and electrocardiography. Bronchoscopy was performed for tumors in the upper third of the esophagus. Endoscopic ultrasonography was encouraged, but not required.

The randomization scheme described by Zelen⁶ was used with

From Memorial Sloan-Kettering Cancer Center, New York (D.P.K., R.G., B.D.M.); the Radiation Therapy Oncology Group Statistical Office, Philadelphia (T.F.P.); the University of Pittsburgh, Pittsburgh (D.G.S.); the Mayo Clinic, Rochester, Minn. (L.G.); Washington University, St. Louis (J.M.); the University of Kansas, Lawrence (N.E.); the University of Pennsylvania, Philadelphia (D.G.H.); M.D. Anderson Cancer Center, Houston (J.A., J.A.R.); and the University of Western Ontario, London, Canada (W.K.). Address reprint requests to Dr. Kelsen at the Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021.

two stratification variables: weight loss (<10 percent or \geq 10 percent of body weight) and cell type as determined by histologic examination (adenocarcinoma or epidermoid cancer). Patients were randomly assigned either to undergo an immediate operation or to receive three cycles of chemotherapy with a combination of cisplatin and fluorouracil before the operation. Patients with stable disease or disease that responded to chemotherapy and in whom an R0 resection was accomplished (all margins deemed free of tumor by microscopical examination) were also to receive two cycles of chemotherapy after surgery.

Surgery

Patients who were randomly assigned to undergo only surgery underwent the operation immediately. The same operation was performed after preoperative chemotherapy in the other patients. The following surgical procedures were considered acceptable: an Ivor-Lewis esophagogastrectomy with a high intrathoracic anastomosis above the level of the azygos vein, a subtotal thoracic esophagectomy by means of a left thoracoabdominal incision with an anastomosis above the aortic arch, or a complete thoracic esophagectomy. Restoration of continuity by gastric-esophageal anastomosis or colonic interposition with a cervical anastomosis was acceptable. Transhiatal esophagectomy was acceptable only for lesions located below the carina. The proximal and distal margins had to be at least 2 cm below the gross tumor. Assessment of the margin by examination of a frozen section before completion of the operation was strongly recommended.

At the time of the esophagectomy, tissue from the lymph nodes was sampled. Removal of all accessible lymph nodes was strongly recommended to allow complete nodal staging. It was also strongly recommended that participating surgeons perform at least four esophageal resections yearly.

Resections were classified as curative when all gross tumor tissue was removed and microscopical examination revealed all margins to be free of tumor (R0). Resections were considered palliative either when microscopical examination revealed positive margins (R1; a positive margin was defined as tumor tissue at or less than 1 mm from the radial [deep], proximal, or distal margins) or when there was residual local (but not distant) gross disease (R2).

Chemotherapy

Patients assigned to chemotherapy received three cycles of cisplatin and fluorouracil before surgery. Cisplatin, at a dose of 100 mg per square meter of body-surface area, was given as a rapid intravenous infusion after prehydration on day 1. Immediately thereafter, fluorouracil was administered at a dose of 1000 mg per square meter as a continuous infusion from day 1 through day 5 (120 hours) of each cycle. The cycle was repeated beginning on days 29 and 58. Surgery was performed two to four weeks after chemotherapy. For patients with disease that was stable or responsive to treatment, postoperative chemotherapy was begun within two to six weeks after the operation. Each cycle of postoperative chemotherapy was the same as those described above, except that the cisplatin dose was 75 mg per square meter. A detailed schedule of dose reduction was prescribed. Patients with progressive disease at the primary site before surgery were not to receive postoperative chemotherapy. Surgical intervention could be performed at any time before the operation was scheduled if a repeated barium-contrast study confirmed the presence of progressive disease at the primary site, without distant metastases.

Radiation therapy was not part of the treatment plan. However, patients in whom there was a positive margin on microscopical examination, residual gross locoregional disease, or recurrence at a later date could receive radiation therapy at the discretion of the investigator. For this reason, a detailed plan of radiation therapy was included in the study protocol.

Statistical Analysis

The study was originally designed for patients with squamous-cell carcinoma. It was modified after 18 months to include pa-

tients with adenocarcinoma. A test of differences in outcome between the two cell types was also added.

The primary end point was overall survival. Secondary end points included disease-free survival, differences in survival according to cell type, effects of chemotherapy on morbidity and mortality associated with surgery, and patterns of first failures of treatment. In calculating the sample size needed to test for a difference in survival, two assumptions were made. Survival times were assumed to be distributed exponentially, without a difference in survival according to cell type. For patients assigned to surgery alone, the projected median survival was 12.5 months. The expected rate of response to chemotherapy was 50 percent, and patients assigned to both surgery and chemotherapy were projected to have a median survival of 17.3 months (a 38 percent increase in median survival as compared with surgery alone). With a P value of 0.05 indicating statistical significance (by one-sided analysis) and a statistical power of 90 percent, the accrual required to detect the hypothesized difference, regardless of cell type, was 444 patients who could be evaluated. If there was a true difference in survival according to cell type (for example, better survival in cases of adenocarcinoma than in cases of epidermoid cancer), the power to detect a 38 percent increase in median survival with 444 patients would be reduced to 87.8 percent. This sample size also gave the study a statistical power of approximately 80 percent to evaluate differences in survival between patients with adenocarcinoma and those with epidermoid cancer.

Interim analyses were planned and were performed when 50 percent, 75 percent, and 100 percent of the required sample had been enrolled. An independent data monitoring committee reviewed the results of the interim evaluations. O'Brien-Fleming criteria for early discontinuation of the trial⁷ were incorporated into the study design, but they were not satisfied at any of the interim evaluations. Informed consent was obtained from all patients before they entered the study.

Characteristics of the patients and treatments were compared by Pearson's chi-square test for discrete data and by the Wilcoxon test for continuous data.⁸ All statistical comparisons were made with two-tailed tests. Disease-free survival and overall survival were estimated according to the Kaplan-Meier method.⁹ For measures of overall survival, the comparisons were performed with the log-rank test.¹⁰ Because of the difference in the timing of the surgery in the two groups, a modification of the log-rank procedure was used to compare differences in disease-free survival.¹¹ Data on cumulative incidence were used to estimate the time to locoregional failure and the time to distant metastases.¹² The sampling test proposed by Gray was used to compare the treatment groups.¹³ The differences in overall survival between the two treatment groups were tested by the Cox proportional-hazards model.¹⁴

RESULTS

Characteristics of the Patients

From August 1990 until December 1995, a total of 467 patients at 123 institutions were registered (Table 1). Twenty-three patients were ineligible, and for four eligible patients there were no follow-up data after registration. Of the patients receiving chemotherapy, 213 of 233 were eligible and had adequate follow-up information. Similarly, of patients having only surgery, 227 of 234 were eligible. All the data received and processed through June 10, 1998, were included in the analyses. The median possible duration of participation in the study was 55.4 months (range, 29.5 to 94.1). When the analysis was restricted to surviving patients, the median duration of follow-up was 46.5 months.

TABLE 1. PATIENT CHARACTERISTICS ACCORDING TO TREATMENT GROUP AND HISTOLOGIC SUBTYPE.*

CHARACTERISTIC	TREATMENT GROUP	
	SURGERY	CHEMOTHERAPY PLUS SURGERY
Registered (no.)		
All	234	233
Epidermoid cancer	110	103
Adenocarcinoma	124	120
Eligible, with adequate follow-up data (no.)		
All	227	213
Epidermoid cancer	106	98
Adenocarcinoma	121	115
Sex (M/F)		
All	188/39	182/31
Epidermoid cancer	88/18	83/15
Adenocarcinoma	109/12	105/10
Median age (yr)		
All	61±9.4	62±9.8
Epidermoid cancer	62±9.5	62±9.1
Adenocarcinoma	62±9.4	61±10.3
Race (white/black/other)		
Epidermoid cancer	58/33/15	52/35/11
Adenocarcinoma	115/2/4	114/1/0
Loss of ≥10% of body weight (% of patients)		
All	23±7.1	23±7.3
Epidermoid cancer	31±7.4	29±8.4
Adenocarcinoma	16±6.4	17±6.0
Reason for ineligibility (no.)†		
Metastatic disease‡	4	9
Disease not operable	1	2
Previous therapy	0	4
Other	1	2

*Plus-minus values are means ±SD.

†Four additional patients (one in the surgery-only group and three in the chemotherapy-plus-surgery group) had no follow-up data after registration.

‡In most cases, metastatic disease consisted of celiac adenopathy seen on computed tomography before treatment.

The two treatment groups were well balanced with respect to major prognostic factors. Adenocarcinoma was the predominant cell type. Eighty-eight percent of the patients with adenocarcinoma were white men. By contrast, 68 of 71 black patients had epidermoid carcinoma. These data support epidemiologic studies indicating that the incidence of adenocarcinoma is rapidly increasing in white men. Substantial weight loss was seen more frequently in cases of epidermoid cancer than in cases of adenocarcinoma.

Delivery of Planned Chemotherapy

Of the 204 patients assigned to preoperative chemotherapy for whom data on chemotherapy were adequate, 144 (71 percent) received all three cycles (Table 2). Overall, 83 percent of the patients who received preoperative chemotherapy completed at least two cycles. The most common reasons for the completion of fewer than three cycles were a deci-

TABLE 2. ABILITY TO DELIVER PLANNED DOSE OF CHEMOTHERAPY.

FEATURES OF CHEMOTHERAPY DELIVERY	No. OF PATIENTS	percent of planned dose	
		CISPLATIN	FLUOROURACIL
Preoperative cisplatin-fluorouracil			
Eligible	213		
Adequate chemotherapy data	204		
Received all three cycles	144		
Received two cycles	26		
Received one cycle	32		
Received none	2		
Portion of planned preoperative dose administered			
First cycle	202	100	100
Second cycle	198	86	82
Third cycle	190	72	68
Reasons for fewer than three cycles			
Patient's or physician's choice	25		
Progression of disease	14		
Death	12		
Toxicity	3		
Other	6		
Postoperative cisplatin-fluorouracil			
Eligible	126		
Received both cycles	48		
Received one cycle	18		
Received none	60		

sion by the patient or by the physician, progression of disease, and death.

The clinical response to chemotherapy was assessed by barium-contrast radiography of the esophagus. Responses were scored as complete or partial. A minor improvement or a lack of change was not considered a response. Seven percent of the patients had complete clinical regression and 12 percent had partial clinical regression. Complete responses (T0N0M0) as assessed by pathological study were found in 2.5 percent (5 of 202) of patients who received at least one cycle of chemotherapy.

After chemotherapy, 133 patients underwent potentially curative resections (R0). Patients whose disease responded to treatment and who were undergoing curative resections were to receive two postoperative cycles of chemotherapy. However, only 52 percent received at least one cycle, and only 38 percent received both cycles. The chief reason for omitting postoperative chemotherapy was choice on the part of the physician or patient.

The major adverse effects of chemotherapy were neutropenia and mucositis (≥grade 3 toxicity in 29 percent and 25 percent of the patients, respectively). Of the patients who received chemotherapy, five (2 percent) died of causes related to treatment; four of them died of infection while they had neutropenia.

Outcome of Surgery

The median time from registration to operation was 9 days for the group undergoing only surgery

TABLE 3. SURGICAL OUTCOME AND MORTALITY AND MORBIDITY ASSOCIATED WITH SURGERY.

VARIABLE	no. of patients (%)	
	SURGERY	CHEMOTHERAPY PLUS SURGERY
Eligible patients	227	213
Surgery performed	217	171
Resections achieved*		
R0	135 (59)	133 (62)
R1	35 (15)	8 (4)
R2	33 (15)	21 (10)
None	24 (11)	51 (24)
Postoperative deaths†	13 (6)	10 (6)
Nonfatal complications		
Major	57 (26)	53 (31)
Minor	67 (31)	49 (29)
None	80 (37)	59 (35)

*Values in parentheses are the percentages of all eligible patients. Resections were classified as curative (R0), palliative (R1), or partial, without distant disease (R2).

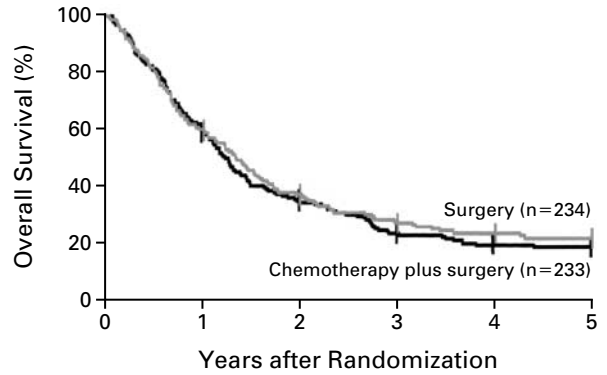
†Values in parentheses are the percentages of the patients undergoing surgery.

and 93 days for the group undergoing chemotherapy before surgery. Of the latter group, 62 percent had a potentially curative operation (R0); in those who underwent an immediate operation, residual disease was graded as absent (R0) in 59 percent (Table 3). The difference between these rates was not significant. However, the presence of a positive margin (R1) on microscopical examination was significantly more likely in patients who underwent only surgery (15 percent) than in those who received preoperative chemotherapy (4 percent, $P=0.001$).

Fewer patients in both treatment groups died during surgery than had been anticipated (Table 3). Of the patients who received chemotherapy, 10 (6 percent), as compared with 13 (6 percent) of the patients who underwent only surgery, died postoperatively. Six percent of the surgery-only group and 7 percent of the chemotherapy group died as a result of treatment ($P=0.33$), either chemotherapy or surgery.

Overall and Disease-free Survival

In an intention-to-treat survival analysis of all registered patients, the median duration of survival for patients who had chemotherapy and surgery was 14.9 months, whereas for those who had only surgery it was 16.1 months ($P=0.53$ by the log-rank test; $P=0.49$ by Cox proportional-hazards analysis, with a relative risk of death of 1.07 in the chemotherapy group; 95 percent confidence interval, 0.87 to 1.32) (Fig. 1). Survival at one year was 59 percent for those who received chemotherapy, and 60 per-



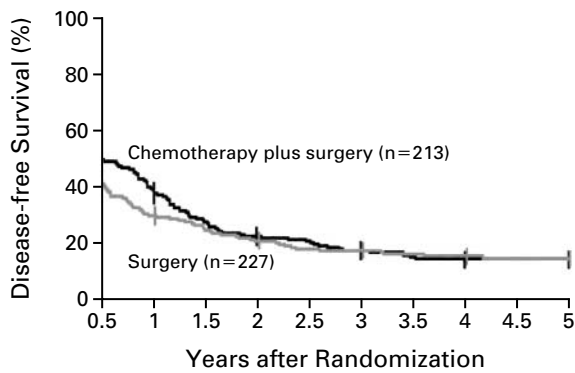
NO. OF PATIENTS AT RISK					
	0	1	2	3	4
Chemotherapy plus surgery	136	73	42	28	15
Surgery	138	81	45	27	16

Figure 1. Overall Survival of All Registered Patients.

The distribution curves represent the results of an intention-to-treat survival analysis involving all registered patients. Patients who received chemotherapy before surgery had a median survival of 14.9 months; in comparison, patients who had only surgery had a median survival of 16.1 months ($P=0.53$ by the log-rank test). Of the 233 patients receiving preoperative chemotherapy, 180 died; of the 234 not receiving it, 173 died.

cent for those who had surgery alone; at two years, survival was 35 percent and 37 percent, respectively; and at three years it was 23 percent and 26 percent. Similar results were obtained in an analysis including all patients who could be evaluated ($P=0.74$ by the log-rank test; $P=0.65$ by Cox proportional-hazards analysis, with a relative risk of death of 1.04 in the chemotherapy group; 95 percent confidence interval, 0.84 to 1.29). When only the patients who could be evaluated were considered, there was also no significant difference between the two groups in disease-free survival ($P=0.50$ by the modified log-rank test) (Fig. 2).

In a separate analysis, survival was assessed for patients with squamous-cell carcinoma and those with adenocarcinoma. When the two treatment groups were combined for each of these histologic subtypes and the subtypes were compared, there was no difference in outcome between patients with adenocarcinoma and those with epidermoid cancer. Substantial weight loss was a predictor of poor outcome. Patients who lost more than 10 percent of their body weight were significantly more likely to die ($P=0.03$ by log-rank test). When the Cox model was used to adjust for these two stratifying variables (weight loss and histologic type), the P value was 0.46. Among patients whose resection was curative, there was no significant difference in survival between those who did and those who did not undergo chemotherapy (median survival, 27.4 and 25 months, respectively).



NO. OF PATIENTS AT RISK						
Chemotherapy plus surgery	80	44	30	19	11	
Surgery	67	47	30	17	11	

Figure 2. Disease-free Survival of Eligible Patients. A landmark analysis was performed six months after randomization to adjust for the difference in the timing of surgery according to treatment group. Disease-free survival for all patients who could be evaluated did not differ significantly between the two groups (P=0.50 by Sposto's modification of the log-rank test¹¹). Of the 213 eligible patients receiving preoperative chemotherapy, 181 died; of the 227 not receiving it, 193 died.

Patterns of Failure

When the analysis was restricted to patients whose resection was curative, the frequency of first failures of therapy at a distant site of disease was slightly higher in those who underwent immediate surgery than in those who received preoperative chemotherapy (50 percent vs. 41 percent) (Table 4). Locoregional failure was equally common in patients who received preoperative chemotherapy and those who did not.

DISCUSSION

This large-scale trial of one of the most common combinations of chemotherapeutic agents used in the treatment of esophageal cancer failed to show that preoperative chemotherapy has any significant benefit when compared with surgery alone. The overall rate of clinical response to preoperative chemotherapy was only 19 percent, but chemotherapeutic regimens with similar activity in treating advanced disease in other solid-tumor cancers, such as colon cancer, have resulted in significant improvements in the rate of cure when used in an adjuvant setting.¹⁵ In our study, chemotherapy was reasonably well tolerated, no unusual adverse effects were seen, and there was no significant increase in operative morbidity and mortality. However, with the addition of chemotherapy there also was no change in survival. There are several possible explanations for this result. The first is that the regimen of chemo-

TABLE 4. PATTERNS OF FIRST FAILURE.

OUTCOME	SURGERY	CHEMOTHERAPY PLUS SURGERY
		no. (%)
Resection R0 (curative)*	129	124
Failure pattern		
Locoregional only	24 (19)	31 (25)
Local plus distant	15 (12)	9 (7)
Distant only	49 (38)	42 (34)
Any local	39 (31)	40 (32)
Any distant†	64 (50)	51 (41)

*The numbers of patients listed as having a curative resection do not include those who died postoperatively.

†The frequency of first failures at a distant site was slightly higher (P=0.21) in the surgery group than in the chemotherapy group.

therapy that we chose was unable to destroy residual regional and micrometastatic disease. However, this explanation is at variance with data from a 1992 trial¹ of an almost identical chemotherapeutic regimen used in conjunction with radiation therapy. That study evaluated 121 patients with esophageal cancer who were randomly assigned to receive a cisplatin-fluorouracil combination plus 5000 cGy of radiation or 6400 cGy of radiation alone. A significant survival advantage was observed in patients given adjuvant chemotherapy. Most patients in that trial had epidermoid carcinoma, but a subsequent report from the same investigators included additional patients with adenocarcinoma who were also assigned to receive the experimental therapy.² By contrast, in our trial, overall survival was unchanged by chemotherapy.

A more recent trial also investigated whether the addition of chemotherapy to surgery improves outcome. In this study of 160 patients with epidermoid carcinoma of the esophagus, cisplatin-etoposide chemotherapy for two to four cycles followed by a transhiatal esophagectomy was compared with transhiatal esophagectomy alone.¹⁶ A significant difference between the two regimens was noted: the median survival for patients who received combined chemotherapy and surgery was 18.5 months, as compared with 11 months for those who underwent surgery alone (P=0.002). Another recent study found that patients undergoing chemotherapy and irradiation plus surgery had a survival advantage, as well as a significant decrease in failures at distant sites, as compared with patients undergoing surgery alone.¹⁷

A second possible explanation for our negative result is that chemotherapy is an effective treatment, but inadequate amounts of cisplatin and fluorouracil were given. In our trial, only two thirds of the patients received all three planned cycles of preopera-

tive chemotherapy, and only a small group of patients received any postoperative treatment. This experience, however, is not substantially different from that of the previous trial.^{1,2}

A third possibility is that because the earlier studies involved fewer patients than the current study, the effect of systemic therapy (cisplatin-fluorouracil) used in conjunction with a regional treatment was overestimated. The study by Herskovic et al. showed significant differences at an interim analysis, but only 121 patients could be evaluated.¹ The more recent trial reported by Walsh et al. also had a small number of patients who could be evaluated (113).¹⁷ A similar approach in another recent U.S. study showed a strong trend toward improved outcome for patients receiving combined therapy. However, each group included only 50 patients, and the trial has not yet clearly shown statistically significant differences.¹⁸ Also recently, investigators in France treated 202 patients with epidermoid cancer of the esophagus with hyperfractionated radiation plus cisplatin followed by surgery or with surgery alone.¹⁹ A difference in the pattern of recurrence was noted; however, perhaps because postoperative mortality among patients receiving the combined therapy was high, there were no overall differences in outcome between the two groups. In another trial, Le Prise and colleagues compared a combination of chemotherapy and radiation therapy followed by surgery with surgery alone in 86 patients with epidermoid cancer of the esophagus.²⁰ There were no significant differences in outcome. Finally, as noted above, the positive results reported by Kok et al. were obtained in a trial that included 148 patients who could be evaluated.¹⁶

Because of these conflicting data, the role of preoperative chemotherapy and radiation therapy or preoperative chemotherapy in the treatment of esophageal cancer remains controversial. In addition to the differences between our trial and the study by Kok et al.¹⁶ (which used different chemotherapeutic regimens), the four chemotherapy-radiation studies summarized above also differ from one another. In the two negative trials, by Bosset et al. and Le Prise et al., which involved only patients with squamous-cell carcinoma, chemotherapy and radiation were given sequentially rather than concurrently.^{19,20} In the two positive (or trending toward positive) trials, by Walsh et al. and Urba et al., involving primarily patients with adenocarcinoma, chemotherapy and radiation were given concurrently.^{17,18} There were also differences in the fractionation and total dose of radiation. A new national trial will compare, on a large scale, preoperative chemotherapy plus concurrent irradiation with surgery alone.

In summary, preoperative chemotherapy with cisplatin and fluorouracil, as used in this study, failed to improve overall survival. Surgery alone remains the

standard of care for patients with locoregional esophageal cancer. Improving systemic therapy remains a high priority. In this regard, the recent identification of paclitaxel as a highly active agent in esophageal cancer has led to investigational phase I and phase 2 trials of combined therapy and combination chemotherapy for patients with esophageal cancer.²¹

Supported in part by grants (CA 21661, CA 32115, and CA 37422) from the National Cancer Institute.

Presented in part at the 1997 Meeting of the American Society of Clinical Oncology, Denver, May 17-20, 1997.

We are indebted to Adrienne Scodary, Brian Berkey, and Kathleen Parkhurst for their expert assistance in the preparation of the manuscript.

REFERENCES

- Herskovic A, Martz K, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326:1593-8.
- 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;15:277-84. [Erratum, *J Clin Oncol* 1997;15:866.]
- Kelsen DP, Ilson DH. Chemotherapy and combined-modality therapy for esophageal cancer. *Chest* 1995;107:Suppl:224S-232S.
- Ilson DH, Kelsen DP. Combined modality therapy in the treatment of esophageal cancer. *Semin Oncol* 1994;21:493-507.
- Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991;265:1287-9.
- Zelen M. The randomization and stratification of patients to clinical trials. *J Chronic Dis* 1974;27:365-75.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
- Wilcoxon F. Individual comparison by ranking methods. *Biometrics* 1945;1:80-3.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
- Sposto R, Stablein D, Carter-Campbell S. A partially grouped logrank test. *Stat Med* 1997;16:695-704.
- Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: John Wiley, 1980.
- Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141-54.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990;322:352-8.
- Kok TC, von Lanschot J, Siersema PD, von Overhagen H, Talanus HV. Neoadjuvant chemotherapy in operable esophageal squamous cell cancer: final report of a phase III multicenter randomized controlled trial. *Proc Am Soc Clin Oncol* 1997;16:277a. abstract.
- Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996;335:462-7.
- Urba S, Orringer M, Turrisi A, Whyte R, Iannettoni M, Forastiere A. A randomized trial comparing surgery to preoperative concomitant chemoradiation plus surgery in patients with resectable esophageal cancer: updated analysis. *Proc Am Soc Clin Oncol* 1997;16:277a. abstract.
- Bosset J-F, Gignoux M, Triboulet J-P, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997;337:161-7.
- Le Prise E, Etienne PL, Meunier B, et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 1994;73:1779-84.
- Ajani JA, Ilson DH, Daugherty K, Pazdur R, Lynch PM, Kelsen DP. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. *J Natl Cancer Inst* 1994;86:1086-91.