A COMPARISON OF MULTIMODAL THERAPY AND SURGERY FOR ESOPHAGEAL ADENOCARCINOMA

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ABSTRACT

Background   Uncontrolled studies suggest that a combination of chemotherapy and radiotherapy improves the survival of patients with esophageal adenocarcinoma. We conducted a prospective, randomized trial comparing surgery alone with combined chemotherapy, radiotherapy, and surgery.

Methods   Patients assigned to multimodal therapy received two courses of chemotherapy in weeks 1 and 6 (fluorouracil, 15 mg per kilogram of body weight daily for five days, and cisplatin, 75 mg per square meter of body-surface area on day 7) and a course of radiotherapy (40 Gy, administered in 15 fractions over a three-week period, beginning concurrently with the first course of chemotherapy), followed by surgery. The patients assigned to surgery had no preoperative therapy.

Results   Of the 58 patients assigned to multimodal therapy and the 55 assigned to surgery, 10 and 1, respectively, were withdrawn for protocol violations. At the time of surgery, 23 of 55 patients (42 percent) treated with preoperative multimodal therapy who could be evaluated had positive nodes or metastases, as compared with 45 of the 55 patients (82 percent) who underwent surgery alone (P<0.001). Thirteen of the 52 patients (25 percent) who underwent surgery after multimodal therapy had complete responses, as determined pathologically. The median survival of patients assigned to multimodal therapy was 16 months, as compared with 11 months for those assigned to surgery alone (P=0.01). At one, two, and three years, 52, 37, and 32 percent, respectively, of patients assigned to multimodal therapy were alive, as compared with 44, 26, and 6 percent of those assigned to surgery, with the survival advantage favoring multimodal therapy reaching significance at three years (P=0.01).

Conclusions   Multimodal treatment is superior to surgery alone for patients with resectable adenocarcinoma of the esophagus. (N Engl J Med 1996;335: 462-7.)

D URING the past 20 years the rate of increase in the incidence of adenocarcinoma of the esophagus has outstripped that of all other tumors.[1-4] This dramatic change has been accompanied by a shift in the biologic behavior of esophageal cancer toward poorer differentiation and greater nodal involvement.[5] At the time of resection 85 to 95 percent of patients have lymph-node involvement, and after standard surgical resection fewer than 10 percent survive five years.[5,6] The role of more radical surgery is controversial, and no randomized trials have been reported. Since most patients have systemic disease at presentation,[7,8] systemic therapy may improve the outcome.

Single-drug or multidrug chemotherapy rarely induces a complete response, as determined pathologically, and does not enhance survival.[9] When patients with potentially curable cancer were treated with radiotherapy alone, the two-year survival was only 10 percent.[10] Neoadjuvant therapy given before surgery may reduce the incidence of micrometastases, increase resectability, control systemic disease, and allow accurate assessment of the completeness of the pathological response, all of which might influence decisions on postoperative treatment. A number of studies have compared the response of patients to neoadjuvant therapy with the outcome in historical control patients[11-20] and have shown that esophageal adenocarcinoma responds to treatment based on fluorouracil and radiotherapy. We report a trial in which a combination of preoperative chemotherapy and radiotherapy was compared with surgery alone.

METHODS

Patients

In May 1990, we undertook a randomized, controlled trial to compare the outcome of multimodal treatment, consisting of two courses of fluorouracil and cisplatin and 40 Gy of radiotherapy followed by surgery, with the outcome of surgery alone for esophageal adenocarcinoma. Patients who met any of the following criteria were excluded from the study: age greater than 76 years, distant metastases, carcinoma of the cervical esophagus requiring laryngectomy, leukocyte count of less than 3500 per cubic millimeter, platelet count of less than 100,000 per cubic millimeter, serum creatinine concentration above 1.4 mg per deciliter (124 μmol per liter), an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4, previous chemotherapy or radiotherapy, previous malignant condition (apart from skin cancer), coexisting disease contraindicating surgery, and social circumstances not conducive to compliance with the full treatment protocol. The study

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was approved by the St. James's Hospital Ethics Committee, and informed consent was obtained from all patients.

Preoperative Tumor Staging

The extent of the tumor was evaluated in each patient by physical examination, chest radiography, abdominal ultrasonography, and upper gastrointestinal endoscopy. Bronchoscopy was performed when indicated by symptoms, the location of the tumor, or chest radiography. Computed tomography was performed in selected patients with equivocal findings on chest radiographs or liver ultrasonograms. Isotope bone scans were occasionally performed if indicated.

Patient Monitoring

Initially the patients were hospitalized for the duration of treatment, but later in the study they were routinely admitted only for chemotherapy. Many who could commute to the radiotherapy facility received radiotherapy as outpatients. Patients were interviewed and examined daily during chemotherapy. The following hematologic and biochemical studies were performed at least twice weekly: platelet and leukocyte counts and measurements of hemoglobin and serum electrolytes, creatinine, bilirubin, alkaline phosphatase, and γ-glutamyltransferase. Arterial-blood gas analysis and pulmonary-function tests were performed at the outset and repeated when indicated.

Chemotherapy

Chemotherapy consisted of two courses of fluorouracil and cisplatin. Fluorouracil (15 mg per kilogram of body weight per day) was infused over a period of 16 hours on days 1 through 5. After one day of hydration with 2 liters of 0.9 percent saline, cisplatin (75 mg per square meter of body-surface area) was infused over a period of eight hours on day 7. This cycle was repeated in week 6.

Radiotherapy

Radiotherapy was begun on the first day of the first course of chemotherapy and given for a total of 15 days (days 1 to 5, 8 to 12, and 15 to 19). All patients were treated with megavoltage-therapy units with either 4-MV photons (Cobalt model SEM100, Fairy Engineering, or Phillips model SL75-5) or 8-MV photons (Dynaray model 10, Radiation Dynamics). The treated area extended 5 cm beyond the longitudinal margins of the tumor, as defined by endoscopic and radiologic examination, and 2 to 3 cm beyond the radial margins. Initially, all patients were treated with parallel opposed fields (anteroposterior and posteroanterior). The technique was modified in 1994 to a three-field arrangement (anterior, right-posterior, and left-posterior oblique fields) to diminish the amount of radiation to the spinal cord. With the parallel opposed fields, a midline dose of 40 Gy in 15 fractions was prescribed (2.67 Gy per fraction). With the three-field technique, a dose of 40 Gy ±10 percent in 15 fractions was delivered to the entire treatment volume (2.67 Gy per fraction) with a computerized treatment-planning system (AECL/Theratronics Therplan). There was no correction for transmission of radiation to the lungs during either treatment technique.

Surgery

Surgery was carried out eight weeks after the beginning of treatment but was delayed if the leukocyte count was less than 2500 per cubic millimeter or the platelet count was less than 100,000 per cubic millimeter. Five operative approaches were used. Tumors of the cardia were resected through an approach involving the abdomen and the left side of the chest. In selected patients total gastrectomy and distal esophagectomy were performed through an abdominal approach. Tumors of the lower third of the esophagus were resected by the Lewis–Tanner operation, and tumors of the middle third by a three-stage operation in which the esophagus was mobilized in the right side of the chest and the anastomosis performed in the neck. In patients with

poor respiratory reserve the transhiatal approach was used. Intestinal continuity was restored by placing the stomach in the posterior mediastinum. A single layer of interrupted linen sutures was used for the anastomosis. Patients were extubated in the operating room or the recovery room, returned to the intensive care unit for four days on average, and were usually discharged less than three weeks after surgery.

Treatment-Induced Toxicity

A toxic reaction was defined according to the criteria of the World Health Organization (WHO).[21] With the introduction of ondansetron early in the study for the treatment of cisplatin-induced nausea, all patients were treated prophylactically before and during the cisplatin infusion. If the leukocyte count fell below 2500 per cubic millimeter or the platelet count fell below 100,000 per cubic millimeter, chemotherapy was withheld or radiotherapy or surgery was delayed until the count recovered. An interruption in the treatment regimen of more than two weeks was considered a major deviation from the protocol.

Pathological Stage

The tumor stage was defined according to the classification of the American Joint Committee on Cancer.[22] The stage of the cancer was defined in each patient according to the location and extent of any residual disease after chemotherapy and radiotherapy. The absence of residual tumor in the resected specimen, including the lymph nodes, was defined as a complete pathological response (stage 0). The tumor was classified as stage 1 if there was residual tumor in the mucosa or submucosa and the lymph nodes were free of tumor. If residual deposits involved the muscularis propria or adventitia but the lymph nodes were free of tumor, the disease was classified as stage 2a. If there was no residual tumor in the esophagus but a tumor deposit was found in the nodes, it was classified as stage 2b. If tumor breached the esophageal wall and the lymph nodes also contained tumor, it was defined as stage 3. Stage 4 disease was defined as metastases extending beyond the regional nodes.

Statistical Analysis

Survival was measured from the date of randomization to the date of death or most recent follow-up visit. Estimates of median survival are based on the Kaplan–Meier method; group comparisons of survival involving individual variables were based on the log-rank test. For categorical data, group comparisons were based on the chi-square or Fisher's exact test. Freedman's method[23] was used to estimate the sample size required to detect an improvement in two-year survival of 20 percentage points after chemotherapy and radiotherapy over a base-line survival rate of 23 percent for surgery alone — the survival rate for adenocarcinoma in the facility at the commencement of the study. With an alpha error of 5 percent and a power of 80 percent, the number of patients required in the study was estimated to be 190. Early indications of a clinically relevant difference between treatments suggested that an interim analysis should be undertaken. The trial was closed six years after it began because a statistically significant difference between the groups was found.

RESULTS

Demographic Data

Between May 1990 and September 1995, 113 patients with adenocarcinoma of the esophagus were recruited. Fifty-eight patients were randomly assigned to receive chemotherapy and radiotherapy before surgery, and 55 were assigned to receive surgery alone. The characteristics of the patients in the two groups were similar before treatment (Table 1). While the trial was in progress an additional 45 patients

underwent resection but did not undergo randomization for the following reasons: 14 were older than 76 years, 6 had distant metastases, 3 had uncertain histologic findings, 2 had complete dysphagia, 2 had previously undergone complex esophageal surgery, 1 required laryngectomy, 1 had recurrent tumor, and 10 chose surgery or chemoradiotherapy; in 6 the reason for not undergoing randomization was not documented.

The median length of follow-up for all patients was 10 months (range, 0.1 to 59). The median follow-up for patients who died was 7.5 months (range, 0.1 to 37), whereas for patients who were still alive as of the most recent follow-up visit it was 18 months (range, 1 to 59). The median follow-up was 10 months (range, 0.1 to 59) for patients assigned to multimodal therapy and 8 months (range, 0.1 to 38) for patients assigned to surgery.

Protocol Violations

The chemoradiotherapy protocol was violated in 10 instances, and the surgery protocol in 1. Table 2 lists the protocol violations.

Treatment-Related Morbidity

Treatment-related toxicity was low, and the regimen was well tolerated. Six patients in the multimodal group (10 percent) had grade III toxic reactions, as defined by WHO criteria (three gastrointestinal, two hematologic, and one cardiac); two patients had grade IV toxic reactions (one cardiac and one gastrointestinal); and one patient had a fatal hemorrhage from the tumor bed during treatment.

Treatment was delayed in two patients because of leukopenia, which resolved within two weeks. Two patients whose ECOG performance status deteriorated did not undergo surgery and were included in the group with grade III gastrointestinal toxic reactions.

Postoperative Complications

Respiratory complications occurred in 28 patients in the multimodal group and 32 patients in the surgery group. Fourteen cardiac events occurred in the chemoradiotherapy group, as compared with 13 in the surgery group. There were two anastomotic leaks, one recurrent nerve palsy, and one chylothorax in each group; one patient in the multimodal group had severe postoperative pancreatitis, and one patient in the surgery group had a postoperative hemorrhage requiring a second operation.

Mortality during Hospitalization

Seven patients died in the hospital, for a 90-day in-hospital mortality rate of 6 percent. Of the five patients in the multimodal group who died during hospitalization, three had completed the protocol. One died of postoperative hemorrhage, one of chylothorax, and one of an anastomotic leak. Two pa-

TABLE 1. Characteristics of the Two Treatment Groups at Base Line.

Characteristic	Surgery Alone (N=55)	Multimodal Therapy (N=58)
Age (yr)		
Median	65	65
Range	37–75	47–75
	no. of patients	
Sex		
Male	44	39
Female	11	19
Tumor site		
Middle third of esophagus	5	11
Lower third of esophagus	27	31
Cardia	23	16
Type of operation		
Three stage	12	13
Lewis–Tanner	22	21
Abdomen and left side of chest	17	15
Transhiatal	2	0
Abdominal	2	2
None	0	7
Barrett's mucosa	21	22

tients did not complete the multimodal protocol. One died preoperatively of a hemorrhage from the tumor bed, and one with complete dysphagia who had surgery before completing chemoradiotherapy died postoperatively of sepsis.

Two patients assigned to surgery died of sepsis in the hospital. A chylothorax developed in one patient within three weeks after surgery, and an iatrogenic perforation occurred in the second after attempted dilatation of the tumor.

Response to Chemoradiotherapy

At the time of surgery, only 42 percent (23 of 55) of the patients in the multimodal group who could be evaluated had positive lymph nodes or metastases, as compared with 82 percent (45 of 55) of the patients in the surgery group ($P<0.001$) (Table 3). A complete pathological response occurred in 13 of the 52 patients in the multimodal group (25 percent) who underwent resection, including 1 patient who died and had no viable tumor at autopsy and 1 patient who only had high-grade dysplasia in the tumor bed. In two patients overt metastases developed during treatment.

Survival

A comparison of the two treatment groups based on the intention-to-treat principle showed a survival advantage for the multimodal group (median survival, 16 months, as compared with 11 months in the

TABLE 2. PROTOCOL VIOLATIONS LEADING TO THE WITHDRAWAL OF 11 PATIENTS
FROM THE STUDY.

PATIENT NO.	SEX/ AGE (YR)	TREATMENT RECEIVED	COMMENT	FOLLOW-UP (MO)
Assigned to chemotherapy, radiotherapy, and surgery				
1	F/75	No treatment	Died of probable myocardial infarction before treatment was initiated	0
2	M/63	Treatment interrupted	Upper gastrointestinal hemorrhage during treatment	11
3	F/70	Treatment interrupted	ECOG performance status deteriorated during treatment	5
4	M/68	Treatment interrupted	Complete dysphagia developed	0
5	M/69	Treatment interrupted	Pericarditis developed during treatment	4
6	M/73	Treatment completed	Fatal bleeding from tumor bed; no tumor at autopsy	0
7	F/75	Treatment completed	ECOG performance status deteriorated during treatment	3
8	M/40	Treatment completed	Lung metastases developed	10
9	M/60	Treatment completed	Myocardial infarction after treatment; no surgery	29
10	M/74	Treatment completed	Lung metastases developed	3
Assigned to surgery only				
11	M/64	Emergency surgery	Iatrogenic perforation, delayed referral	0.5

group treated with surgery alone; $P=0.01$ (Fig. 1). When the two groups were compared on the basis of the treatment actually received, the median survival was 32 months in the multimodal group and 11 months in the surgery group ($P=0.001$) (Fig. 2). When survival at one, two, and three years was calculated on the basis of the intention to treat, 52, 37, and 32 percent of the patients assigned to multimodal therapy were alive, as compared with 44, 26, and 6 percent of those assigned to surgery alone; the difference reached statistical significance at three years ($P=0.01$). The survival rates at three years according to the treatment actually received were 37 percent (10 of 27 patients) in the multimodal group and 7 percent (2 of 30) in the surgery group ($P=0.006$) (Table 4).

Thirteen patients in the multimodal group had a complete pathological response. One died during treatment. A 72-year-old woman died five months after surgery; there was no autopsy, but her family physician attributed her death to tumor. The remaining 11 were alive and tumor-free 43, 36, 27, 21, 21, 16, 16, 5, 4, 4, and 2 months after resection.

Nineteen patients in the multimodal group had residual disease confined to the esophagus. As of this writing the median survival for this subgroup had not been reached: 11 were alive, none with overt disease, after a median follow-up of 37 months (range, 10 to 59). Eight had died, five of proven and one of suspected recurrence, after a median survival of 8 months (range, 3 to 32). Thirteen had stage 3

disease, four of whom were alive at 54, 43, 18, and 4 months, whereas nine had died after a median of 7 months (range, 2 to 11), all but one of recurrent disease.

Ten patients assigned to surgery had disease confined to the esophagus and had a median survival of 14 months (range, 0.3 to 38). Three of these patients were alive at 25, 29, and 38 months, whereas

TABLE 3. PATHOLOGICAL STAGE OF THE
TUMOR AT THE END OF TREATMENT
ACTUALLY RECEIVED.

TUMOR STAGE	SURGERY ALONE (N=55)	MULTIMODAL THERAPY (N=58)
	no. of patients	
0	0	13*
1	2	1
2a	8	18
2b	2	7
3	38	13
4	5	3
Unknown	0	3

*One patient who completed the chemoradiotherapy protocol died before surgery, and no viable tumor was identified at autopsy. A second patient who underwent resection had no invasive cancer but had an area of high-grade dysplasia in the mucosa at the site of the tumor.
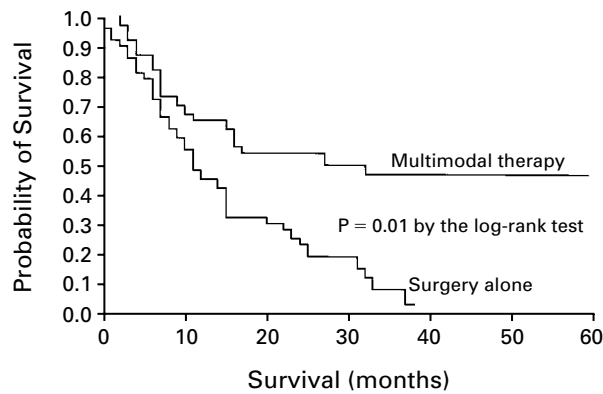
Figure 1. Kaplan–Meier Plot of Survival of Patients with Esophageal Adenocarcinoma, According to the Intention-to-Treat Analysis.
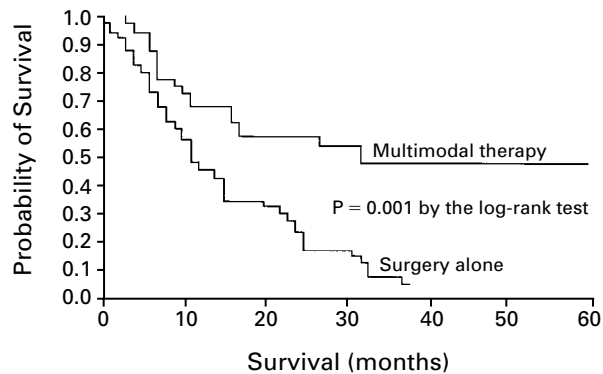

Figure 2. Kaplan–Meier Plot of Survival of Patients with Esophageal Adenocarcinoma, According to the Treatment Actually Received.

seven patients had died after a median of 11 months (range, 0.3 to 23). Thirty-eight patients had stage 3 disease; 9 of them were alive after a median follow-up of 5 months (range, 1 to 24), whereas 29 had died after a median of 10 months (range, 0.1 to 37).

DISCUSSION

In this prospective, randomized trial we compared multimodal therapy with surgery alone for esophageal adenocarcinoma. We found that 25 percent of the patients assigned to multimodal therapy had a complete pathological response after resection and 32 percent were alive at three years, whereas only 6 percent of patients treated with surgery alone lived for three years. These results support the findings of nonrandomized studies that have shown a complete pathological response in approximately 20 percent of patients treated with multimodal therapy[13,14,17-20]

and a survival advantage over historical control patients who had surgery only.

Many trials of multimodal therapy have pooled adenocarcinomas and squamous-cell tumors on the assumption that the two have a similar response to treatment. This assumption is unwarranted, because patients with adenocarcinomas have a higher incidence of lymph-node involvement (85 to 95 percent, as compared with 50 to 60 percent for those with squamous-cell carcinomas) and appear to be less sensitive to chemoradiotherapy.[13] In one randomized trial[24] of 100 patients, the 75 with adenocarcinoma were randomly assigned to chemotherapy, radiotherapy, and transhiatal resection or to resection alone. There was no difference in the estimated two-year survival between the two groups. This result may reflect the administration of a lower dose of fluorouracil than we used and a difference in attrition rates between the groups, since the survival difference in our study did not become significant until the third year.

The relative contributions of chemotherapy, radiotherapy, and surgery to the survival advantage in the multimodal group are unclear. Herskovic et al. compared chemotherapy and radiotherapy with radiotherapy alone in 121 patients, all but 15 of whom had squamous-cell carcinoma.[10] Thirty-eight percent of the patients in the multimodal group survived two years. Perhaps only patients with residual disease in the esophageal wall or local nodes benefit from resection. Unfortunately, current imaging methods cannot distinguish these patients from those with a complete pathological response.[25] In our study the omission of surgery would have left 75 percent of the patients in the multimodal group with residual disease, which in 19 cases (33 percent) appeared to be confined to the esophagus. In these patients, the residual tumor would probably have progressed. A molecular marker that reliably predicts response would greatly facilitate the process of selecting suitable candidates for surgery. The expression of epidermal growth factor receptor and that of proliferating-cell nuclear antigen have shown potential as markers in patients with squamous-cell carcinoma,[26] and the expression of c-*erb* B-2 may have a role in patients with adenocarcinoma.[27]

It is unclear whether the survival advantage in the multimodal group at three years will persist. Leichman et al. reported on a trial using cisplatin, fluorouracil, and 30 Gy of concurrently administered radiotherapy.[28] Fifteen of 21 treated patients with squamous-cell carcinoma subsequently underwent resection, of whom 5 had complete pathological responses. All those with responses subsequently died of distant metastases at 30 to 60 months.

The chemoradiotherapy regimen was well tolerated, and there were few toxic reactions. Ten patients were withdrawn from multimodal therapy because

TABLE 4. SURVIVAL THREE YEARS AFTER TREATMENT ACCORDING TO THE INTENTION TO TREAT AND ACCORDING TO THE TREATMENT ACTUALLY RECEIVED.

TYPE OF ANALYSIS	SURGERY ALONE	MULTIMODAL THERAPY	P VALUE
Intention to treat			
Including in-hospital mortality			
Survival at 3 yr — no./total (%)	2/31 (6)	10/31 (32)	0.01
Median survival — mo	11	16	0.01
Excluding in-hospital mortality			
Survival at 3 yr — no./total (%)	2/30 (7)	10/28 (36)	0.007
Median survival — mo	16	27	0.003
Actual treatment			
Including in-hospital mortality			
Survival at 3 yr — no./total (%)	2/30 (7)	10/27 (37)	0.006
Median survival — mo	11	32	0.001
Excluding in-hospital mortality			
Survival at 3 yr — no./total (%)	2/30 (7)	10/24 (42)	0.003
Median survival — mo	11	32	<0.001

of protocol violations. Two of these patients had a deterioration in ECOG performance status that was attributed to severe cisplatin-induced nausea, but the introduction of ondansetron virtually eliminated such nausea. One patient in whom complete dysphagia developed was withdrawn from the trial, but the current approach to such patients includes insertion of a stent and continuation of treatment. There were only two instances, both due to leukopenia, in which treatment or surgery had to be postponed because of side effects. The administration of colony-stimulating factor should help minimize the delay in such cases. The side effects of the preoperative treatment were severe in six patients (10 percent), life-threatening in two patients (3 percent), and fatal in one patient (2 percent); these results compare favorably with those in other recent reports.[11-20]

In conclusion, multimodal therapy followed by surgery provides a significant survival advantage over surgery alone at three years for patients with adenocarcinoma of the esophagus. Although 17 percent of the patients in the multimodal group were withdrawn because of protocol violations, direct treatment-related toxic effects were minimal. The evidence suggests that multimodal therapy should be considered in all patients with tumor confined to the esophagus and draining lymph nodes.

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