Benefit of postoperative adjuvant chemoradiotherapy in locoregionally advanced esophageal carcinoma

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Objective: We sought to determine whether chemoradiotherapy after esophagectomy improves survival.

Methods: From 1994 to 2000, 31 patients with locoregionally advanced esophageal carcinoma (90% pT3, 81% pN1, and 13% pM1a) received postoperative adjuvant chemoradiotherapy. Concurrently, 52 patients with advanced carcinoma underwent esophagectomy alone and survived at least 10 weeks, the time frame for adjuvant therapy. A propensity score based on demographic, tumor, and surgical factors was used to identify matched pairs to determine the association of adjuvant therapy with outcomes.

Results: For patients receiving adjuvant therapy versus esophagectomy alone, risk-unadjusted median, 1-year, and 4-year survivals were 28 versus 14 months, 68% $\pm$ 8.4% versus 60% $\pm$ 6.8%, and 44% $\pm$ 9.0% versus 17% $\pm$ 5.6%, respectively (P = .05). Similarly, risk-unadjusted median time to recurrence was 25 versus 13 months (P = .15), and median recurrence-free survival was 22 versus 11 months (P = .04). Among propensity-matched patients, median, 1-year, and 4-year survivals for those receiving adjuvant therapy versus esophagectomy were 28 versus 15 months, 60% $\pm$ 11.0% versus 65% $\pm$ 10.7%, and 44% $\pm$ 11.3% versus 0% (P = .05). Median time to recurrence was 25 versus 13 months (P = .04), and recurrence-free survival was 22 versus 10 months (P = .02).

Conclusion: In patients with locoregionally advanced esophageal carcinoma, addition of postoperative adjuvant chemoradiotherapy to esophagectomy alone doubled survival time, time to recurrence, and recurrence-free survival. Patients with locoregionally advanced carcinoma after esophagectomy should be considered for adjuvant therapy.

Postoperative adjuvant therapy provides a survival advantage in cancers of the stomach, colon, and rectum.¹⁻³ However, single-modality postoperative adjuvant therapy in esophageal cancer has been limited and potentially harmful,⁴⁻⁶ although postoperative adjuvant radiation therapy may benefit patients with advanced disease.⁷ Recent clinical experience with modern postoperative adjuvant chemoradiotherapy suggests a survival benefit compared with historical controls.^{8,9} In the absence of randomized trials, the purpose of this study was to determine whether adjuvant chemoradiotherapy after esophagectomy improves survival compared with esophagectomy alone.

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Patients and Methods

Patients

From 1994 to 2000, 31 patients with pathologically documented locoregionally advanced adenocarcinoma or squamous cell esophageal carcinoma (T3-4, N1, or M1a) underwent esophagectomy and were entered in an institutional review board–approved (IRB 4624) trial of postoperative adjuvant chemoradiotherapy. Patients were eligible for this protocol if they had not received previous radiation or chemotherapy for this cancer, had an Eastern Cooperative Oncology Group performance status of 0 or 1, a white blood cell count of $3000 \cdot \text{mm}^{-3}$ or greater, and a serum creatinine level of $2.0 \text{ mg} \cdot \text{dL}^{-1}$ or less.

During this period, 52 patients with locoregionally advanced carcinoma underwent esophagectomy alone without adjuvant therapy and survived more than 10 weeks after the operation, the time frame for postoperative adjuvant therapy (Tables 1 and 2). Data used for this study came from the Cleveland Clinic esophageal database, which has been approved for research by the institutional review board.

Esophagectomy

Esophagectomy with thoracotomy and 2-field lymphadenectomy was performed in 27 patients receiving adjuvant therapy and 46 patients receiving esophagectomy alone. Four patients receiving adjuvant therapy and 6 patients receiving esophagectomy alone had transhiatal esophagectomy and lymph node sampling. Gastrointestinal reconstruction in all patients used the stomach, with esophagogastric anastomosis done in the neck.

Postoperative Adjuvant Chemoradiotherapy

Three to 10 weeks after esophagectomy, each patient received a continuous course of external beam radiation therapy with concurrent chemotherapy. Patients received 50.4 to 59.4 Gy in 1.8-Gy once-daily fractions. Treatments were delivered using a linear accelerator with 6- to 8-MV photons at a distance of 100 cm from the source to the axis of rotation. Computed tomography–based treatment planning was used in all patients. A minimum 5-cm margin was given to the tumor bed, superiorly and inferiorly. Lymph node coverage included mediastinal and celiac lymph nodes for middle thoracic tumors and low mediastinal and celiac lymph nodes for lower thoracic tumors. The maximal spinal dose was 45 Gy, which was accomplished either by a field rearrangement after 39.6 to 41.4 Gy or by treatment with a 3-field technique from the beginning of therapy.

Concurrent with radiotherapy, each patient received two 4-day cycles of intravenous 5-fluorouracil ($1000 \text{ mg} \cdot \text{m}^{-2} \cdot \text{d}^{-1}$) and cisplatin ($20 \text{ mg} \cdot \text{m}^{-2} \cdot \text{d}^{-1}$) during the first and fourth week of adjuvant therapy. After completion of chemoradiotherapy, patients were followed at 3-month intervals.

Comparison of Outcome

Management of outcome data. Because patients had to survive esophagectomy to receive postoperative adjuvant therapy, those undergoing esophagectomy alone who died within 10 weeks of the operation were not included in this comparative study. Thus, in both groups, 10 weeks postoperatively was taken as time zero for all time-related analysis.

TABLE 1. Comparison of patients undergoing postoperative adjuvant therapy with those undergoing esophagectomy alone: Categorical variables

Variable	Adjuvant therapy (n = 31)		Esophagectomy alone (n = 52)		P value
	No.	%	No.	%	
Sex					.5
Female	3	10	8	15	
Male	28	90	44	85	
Race					.9
White	30	97	50	96	
Other	1	3	2	4	
pT					.3
pT1	2	6	2	4	
pT2	1	3	2	4	
pT3	28	90	43	83	
pT4	0	0	5	10	
pN					.6
pN0	6	19	13	25	
pN1	25	81	39	75	
pM					.4
pM0	27	87	46	88	
pM1a	4	13	4	8	
pM1b	0	0	2	4	
Histopathologic type					.9
Adenocarcinoma	26	84	43	83	
Squamous cell carcinoma	5	16	9	17	
Histopathologic grade					.97
Poorly differentiated	21	68	36	69	
Moderately differentiated	9	29	14	27	
Well differentiated	1	3	2	4	
Completeness of resection					.6
R1	8	26	11	21	
R0	23	74	41	79	
Surgical approach					.8
Thoracotomy	27	87	46	88	
Transhiatal	4	13	6	12	

Both Kaplan–Meier (nonparametric) and Cox proportional hazards analyses were used to compare survival, freedom from recurrence, and recurrence-free survival between patients receiving adjuvant therapy and those receiving esophagectomy alone. Nonparametric survival estimates were compared by using the log-rank test. Survival estimates are presented with their SE and number of patients at various intervals and as median survival.

Methods of comparisons. Outcomes were compared in 2 ways: risk unadjusted and propensity matched.

Risk-unadjusted comparison of outcomes among patients receiving postoperative adjuvant chemoradiotherapy versus esophagectomy alone was performed using the log-rank statistic.

Propensity-matched comparison was performed because selection of patients for adjuvant therapy or esophagectomy alone was not random.^{10,11} Therefore, the probability of receiving adjuvant therapy versus esophagectomy alone was estimated by logistic regression using 15 variables representing 13 patient, tumor, procedure, and experience characteristics: sex, race, age at operation, pT (T2 vs T1 and T3-4 vs T1, 2 variables), pN, total number of

TABLE 2. Comparison of patients undergoing postoperative adjuvant therapy with those undergoing esophagectomy alone: Continuous variables

Variable/group	No.	Mean $\pm$ SD	Minimum	Median	Maximum	P value
Age at operation						<.001
Adjuvant therapy	31	57 $\pm$ 10	55	33	76	
Esophagectomy alone	52	65 $\pm$ 10	66	36	90	
Total no. of resected lymph nodes						.6
Adjuvant therapy	31	17 $\pm$ 10	17	2	50	
Esophagectomy alone	52	16 $\pm$ 10	14	0	39	
Total no. of resected lymph nodes containing metastatic cancer*						.9
Adjuvant therapy	25	6.1 $\pm$ 4.7	5	1	18	
Esophagectomy alone	39	5.9 $\pm$ 5.7	3	1	27	
Date of operation (years relative to Jan 1, 1994)						<.001
Adjuvant therapy	31	4.5 $\pm$ 1.3	4.5	0.9	6.9	
Esophagectomy alone	52	2.9 $\pm$ 1.9	2.6	0.1	6.6	
Propensity score						<.001
Adjuvant therapy	31	0.56 $\pm$ 0.21	0.55	0.14	0.90	
Esophagectomy alone	52	0.26 $\pm$ 0.24	0.16	0	0.91	

*For patients with pN1 disease.

TABLE 3. Comparison of propensity-matched patients undergoing postoperative adjuvant therapy with those undergoing esophagectomy alone: Categorical variables

Variable	Adjuvant therapy (n = 20)		Esophagectomy alone (n = 20)		P value
	No.	%	No.	%	
Sex					.6
Female	2	10	3	15	
Male	18	90	17	85	
Race					.3
White	20	100	19	95	
Other	0	0	1	5	
pT					.4
pT2	1	5	1	5	
pT3	19	95	17	85	
pT4	0	0	2	10	
pN					.7
pN0	5	25	6	30	
pN1	15	75	14	70	
pM					.2
pM0	18	90	19	95	
pM1a	2	10	0	0	
pM1b	0	0	1	5	
Histopathologic type					1
Adenocarcinoma	16	80	16	80	
Squamous cell carcinoma	4	20	4	20	
Histopathologic grade					.2
Poor	10	50	15	75	
Moderate	9	45	4	20	
Well	1	5	1	5	
Completeness of resection					1
R1	4	20	4	20	
R0	16	80	16	80	
Surgical approach					.6
Thoracotomy	17	85	18	90	
Transhiatal	3	15	2	10	

lymph nodes resected, total number of resected nodes containing metastatic cancer, pM, histopathologic type (adenocarcinoma vs squamous cell carcinoma), histopathologic grade (moderately vs well and poorly vs well differentiated, 2 variables), surgical approach (thoracotomy vs transhiatal), completeness of resection (R0 vs R1), and date of operation. A propensity score was calculated for each patient from the resulting logistic regression equation. Patients undergoing each therapy were then matched by using the above propensity score.¹² Because the original 2 groups were of comparable size, there were too few esophagectomy-only patients to match every patient receiving postoperative adjuvant chemoradiotherapy. Thus, 20 well-matched pairs of patients were available for comparison of outcomes (Tables 3 and 4) by using the log-rank and hazard ratio statistics.

Presentation

Continuous variables are presented as means $\pm$ 1 SD. Survival estimates are presented as percentage $\pm$ 1 SE. For consistency with these, hazard ratios are presented with 68% confidence limits (CL).

Results

Toxicity

Toxicity of the adjuvant chemoradiotherapy is detailed in Table 5. Nutrition was well maintained during adjuvant therapy in part because 28 of the 31 patients had jejunostomy tubes in place throughout treatment. There were no toxic deaths. Unplanned hospitalizations were required in 9 patients: 3 because of uncomplicated neutropenic fever, 2 because of a venous thromboembolic event, 2 because of infections developing with adequate blood counts, and 1 each with presumably unrelated episodes of ischemic colitis and cholecystitis.

TABLE 4. Comparison of propensity-matched patients undergoing postoperative adjuvant therapy with those undergoing esophagectomy alone: Continuous variables

Variable/group	No.	Mean $\pm$ SD	Minimum	Median	Maximum	P value
Age at operation						.7
Adjuvant therapy	20	59 $\pm$ 10	58	41	76	
Esophagectomy alone	20	60 $\pm$ 10	59	36	77	
Total no. of resected lymph nodes						.4
Adjuvant therapy	20	13 $\pm$ 7	12	2	24	
Esophagectomy alone	20	15 $\pm$ 9	13	3	37	
Total no. of resected lymph nodes containing metastatic cancer*						.16
Adjuvant therapy	15	5.6 $\pm$ 3.6	5	1	14	
Esophagectomy alone	14	3.6 $\pm$ 3.8	2	1	15	
Date of operation (years relative to Jan 1, 1994)						.5
Adjuvant therapy	20	4.3 $\pm$ 1.5	4.2	0.9	6.9	
Esophagectomy alone	20	4.6 $\pm$ 1.3	4.8	2.1	6.6	
Propensity score						.9
Adjuvant therapy	20	0.49 $\pm$ 0.21	0.47	0.14	0.86	
Esophagectomy alone	20	0.49 $\pm$ 0.21	0.50	0.14	0.91	

*For patients with pN1 disease.

Outcome

Survival. For patients receiving adjuvant therapy versus esophagectomy alone, risk-unadjusted median, 1-year, and 4-year survivals were 28 months versus 14 months, 68% $\pm$ 8.4% versus 60% $\pm$ 6.8%, and 44% $\pm$ 9.0% versus 17% $\pm$ 5.6%, respectively ($P = .05$; Figure 1, A). Among propensity-matched patients, median, 1-year, and 4-year survivals in the 2 groups of patients were 28 months versus 15 months, 60% $\pm$ 11.0% versus 65% $\pm$ 10.7%, and 44% $\pm$ 11.3% versus 0%, respectively ($P = .05$; Figure 1, B). The hazard ratio of adjuvant therapy versus esophagectomy was 0.46 (CL 0.31-0.69).

Recurrence. There were 17 recurrences in patients receiving adjuvant chemoradiotherapy. One patient was alive and disease free at follow-up after resection of a solitary brain metastasis. Sixteen patients died with disease: 7 with local metastases, 7 with distant metastases, and 2 with both local and distant metastases. There were 33 cancer recurrences in patients receiving esophagectomy alone. Two were alive at follow-up, one with local and one with distant recurrence. Thirty-one died with disease: 14 with local metastases, 12 with distant metastases, and 5 with both local and distant metastases. Among the 20 propensity-matched patients receiving adjuvant therapy, 12 had recurrences, 4 local and 8 distant. Of the 20 receiving esophagectomy alone, 16 had recurrences, 6 local, 8 distant, and 2 both local and distant.

For patients receiving adjuvant therapy versus esophagectomy alone, risk-unadjusted median, 1-year, and 4-year freedoms from recurrence were 25 months versus 13 months, 65% $\pm$ 8.6% versus 53% $\pm$ 7.4%, and 44% $\pm$ 9.8% versus 23% $\pm$ 7.0%, respectively ($P = .15$; Figure 2, A). Among propensity-matched patients, median, 1-year, and 4-year freedoms from recurrence in the 2 groups of

TABLE 5. Toxicity of adjuvant chemoradiotherapy

Toxicity	No.	%
Nausea	31	100
Severe, grade 3-4	3	10
Mucositis/dysphagia	17	55
Severe, grade 3-4	6	19
Neutropenia $<1000 \cdot \text{mm}^{-3}$	9	29
With fever	3	10
Thrombocytopenia $<20,000 \cdot \text{mm}^{-3}$	2	6
Unplanned hospitalization	9	29
Toxic death	0	0

patients were 25 months versus 13 months, 60% $\pm$ 11.0% versus 50% $\pm$ 1.9%, and 40% $\pm$ 12.1% versus 0%, respectively ($P = .04$; Figure 2, B). The hazard ratio of adjuvant therapy versus esophagectomy was 0.45 (CL 0.30-0.67).

Recurrence-free survival. For patients receiving adjuvant therapy versus esophagectomy alone, risk-unadjusted median, 1-year, and 4-year recurrence-free survivals were 22 months versus 11 months, 61% $\pm$ 8.8% versus 42% $\pm$ 6.8%, and 39% $\pm$ 9.3% versus 15% $\pm$ 5.0%, respectively ($P = .04$; Figure 3, A). For propensity-matched patients, median, 1-year, and 4-year recurrence-free survivals in the 2 groups of patients were 22 months versus 10 months, 55% $\pm$ 11.1% versus 40% $\pm$ 11.0%, and 37% $\pm$ 11.6% versus 0%, respectively ($P = .02$; Figure 3, B). The hazard ratio of adjuvant therapy versus esophagectomy was 0.42 (CL 0.29-1.62).

Discussion

Rationale for Adjuvant Therapy

Single-modality preoperative adjuvant therapy (chemotherapy or radiotherapy) for esophageal carcinoma offers no

A

B

Figure 1. Survival among patients receiving adjuvant therapy compared with esophagectomy alone. *Long vertical bars* represent CLs of 1 SE. *Short vertical bars* represent censored patients. Each step in the graph represents an event. **A**, Unadjusted. Numbers of patients traced at 0, 1, and 4 years were 31, 21, and 5 in the adjuvant therapy group and 52, 31, and 5 in the esophagectomy-alone group. **B**, Propensity matched. Numbers of patients traced at 0, 1, and 4 years were 20, 12, and 3 in the adjuvant therapy group and 20, 13, and 0 in the esophagectomy-alone group.

greater survival than esophagectomy alone.¹³⁻¹⁵ Concurrent preoperative chemoradiotherapy has produced conflicting results despite complete pathologic response in up to 30% of patients.¹⁶⁻¹⁸ Single-modality postoperative adjuvant therapy has not improved survival or has been harmful,⁴⁻⁶ except for a recent report of benefit from radiation therapy for stage IIB or III tumors.⁷ However, recent phase II studies^{8,9} and this report suggest that postoperative concurrent chemoradiotherapy improves survival compared with historical controls and propensity-matched patients receiv-

A

B

Figure 2. Freedom from recurrence among patients receiving adjuvant therapy compared with esophagectomy alone. Format is as shown in Figure 1. **A**, Unadjusted. Numbers of patients traced at 0, 1, and 4 years were 31, 19, and 5 in the adjuvant therapy group and 52, 22, and 5 in the esophagectomy-alone group. **B**, Propensity matched. Numbers of patients traced at 0, 1, and 4 years were 20, 11, and 3 in the adjuvant therapy group and 20, 8, and 0 in the esophagectomy-alone group.

ing esophagectomy alone. It can be administered with acceptable toxicity and enhances local control in patients with locoregionally advanced esophageal carcinoma.

Postoperative adjuvant therapy has theoretic advantages and disadvantages. Potential advantages include the following: (1) therapy can be based on pathologic stage rather than potentially inaccurate clinical stage; (2) patients who might benefit from adjuvant therapy can be identified, avoiding toxicity in those who do not need or will not benefit from it; (3) delay resulting from induction therapy is avoided, and resection is ensured; (4) dysphagia is relieved early in treatment; (5) nutrition can be maintained with feeding

tubes placed at operation; and (6) induction therapy toxicity does not affect surgery. Potential disadvantages include the following: (1) blood supply to the resected area is reduced, decreasing delivery of chemotherapy to the locoregional tumor bed; (2) the radiation therapy target is removed at operation, complicating the definition of radiation fields; (3) postoperative complications preclude adjuvant therapy; (4) early postoperative death precludes adjuvant therapy, possibly biasing survival data; and (5) the effect of induction therapy on resectability is eliminated.

Postoperative chemoradiotherapy requires balancing advantages with disadvantages and treatment toxicity with improved survival. For the majority of patients in this report, postoperative chemoradiotherapy was advantageous. However, when to use this strategy is not clearly defined.

Treatment Strategies

A single-treatment strategy for all patients with locoregionally contained esophageal carcinoma is an outdated approach.¹⁹ Detection of cancer at an earlier stage with Barrett surveillance, accurate clinical staging, and development of new treatments allows a tailored stage-dependent approach to be used.

At one end of the cancer spectrum—high-grade dysplasia and intramucosal cancers without regional lymph node metastases—esophagectomy alone offers excellent survival.²⁰ For these patients, the toxicity of adjuvant therapy outweighs any small survival advantage.²¹

At the opposite end of the cancer spectrum—marginally operable tumors because of either bulky T3 or T4 disease or significant regional lymph node metastases (R2 resection likely)—esophagectomy alone offers no hope of cure. Induction therapy will downstage about one third of these patients, and subsequent resection will offer responders an intermediate survival.²² The survival advantage in responders far outweighs the toxicity of treatment. If nonresponders are identified after induction therapy, esophagectomy might be avoided and best palliation offered. In the future, identification of likely responders before therapy will further refine this approach.

Esophageal carcinoma between these 2 ends of the spectrum affects many patients, with variable survival after esophagectomy alone. Esophagectomy followed by postoperative adjuvant therapy should be considered in the following clinical situations: (1) patients with incorrect clinical staging who have esophagectomy and are found to have more advanced disease (T3 or N1 or M1a); (2) patients with T3 or N1 cancers (few regional nodal metastases) who appear technically resectable (R0 resection possible); and (3) patients with deep submucosal invasion (T1bN0M0) or invasion into the muscularis propria (T2N0M0) without regional nodal metastases.

Figure 3. Freedom from recurrence or death (recurrence-free survival) among patients receiving adjuvant therapy compared with esophagectomy alone. Format is as shown in Figure 1. A, Unadjusted. Numbers of patients traced at 0, 1, and 4 years were 31, 19, and 5 in the adjuvant therapy group and 52, 22, and 5 in the esophagectomy-alone group. B, Propensity matched. Numbers of patients traced at 0, 1, and 4 years were 20, 11, and 3 in the adjuvant therapy group and 20, 8, and 0 in the esophagectomy-alone group.

Strengths and Weaknesses

This is a small, single-institution, nonrandomized phase II study. Two methods of comparison were used, unadjusted and propensity matched to minimize selection bias. Results were consistent. Because esophagectomy was the first treatment, accurate pathologic stage was available for all patients and is fundamental to this comparison, unlike preoperative induction therapies in which potentially inaccurate clinical staging complicates comparisons. The absence of staging inaccuracies and good matching based on 15 variables allowed outcome comparisons to be influenced principally by postoperative adjuvant therapy. Nevertheless,

propensity matching does not guard against unknown factors. Among potential and unmeasured factors that might have influenced patient selection were subjective ones, such as vigor, mental status, ability to cooperate with and consent to treatment protocols, referral and physician bias, and the unblinded nature of the treatments. These factors influence not only nonrandomized comparisons but also randomized trials.²³

Clinical Inference

In patients with locoregionally advanced esophageal cancer in whom an R0 resection is clinically possible, the strategy of esophagectomy followed by postoperative adjuvant chemoradiotherapy should be considered. Compared with esophagectomy alone, it improves survival, decreases recurrent cancer, and increases recurrence-free survival.

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