

Chemoradiotherapy of Locally Advanced Esophageal Cancer

Long-term Follow-up of a Prospective Randomized Trial (RTOG 85-01)

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THE RISK OF ESOPHAGEAL CANCER is growing; over the past 20 years the incidence rate has increased 14.8%.¹ Moreover, carcinomas of the esophagus have been among the most resistant to treatment. Mean survival following traditional therapy has approximated only 9 months. Earlam and Cuhna-Melo's² 1980 review of 122 articles describing the surgical care of 83 783 cases of squamous cell carcinoma of the esophagus revealed a paltry 5-year survival rate of 4%. Their subsequent review of the role of radiation therapy (RT) found an almost equally dismal rate of 6%.³ While improvements in technique have occurred and more modern surgical series tend to report survival rates in the 20% range, at least some investigators believe the major explanation for this has been earlier detection of tumors.⁴ The

Context Carcinoma of the esophagus traditionally has been treated by surgery or radiation therapy (RT), but 5-year overall survival rates have been only 5% to 10%. We previously reported results of a study conducted from January 1986 to April 1990 of combined chemotherapy and RT vs RT alone when an interim analysis revealed significant benefit for combined therapy.

Objective To report the long-term outcomes of a previously reported trial designed to determine if adding chemotherapy during RT improves the survival rate of patients with esophageal carcinoma.

Design Randomized controlled trial conducted 1985 to 1990 with follow-up of at least 5 years, followed by a prospective cohort study conducted between May 1990 and April 1991.

Setting Multi-institution participation, ranging from tertiary academic referral centers to general community practices.

Patients Patients had squamous cell or adenocarcinoma of the esophagus, T1-3 N0-1 M0, adequate renal and bone marrow reserve, and a Karnofsky score of at least 50.

Interventions Combined modality therapy (n = 134): 50 Gy in 25 fractions over 5 weeks, plus cisplatin intravenously on the first day of weeks 1, 5, 8, and 11, and fluorouracil, 1 g/m² per day by continuous infusion on the first 4 days of weeks 1, 5, 8, and 11. In the randomized study, combined therapy was compared with RT only (n = 62): 64 Gy in 32 fractions over 6.4 weeks.

Main Outcome Measures Overall survival, patterns of failure, and toxic effects.

Results Combined therapy significantly increased overall survival compared with RT alone. In the randomized part of the trial, at 5 years of follow-up the overall survival for combined therapy was 26% (95% confidence interval [CI], 15%-37%) compared with 0% following RT. In the succeeding nonrandomized part, combined therapy produced a 5-year overall survival of 14% (95% CI, 6%-23%). Persistence of disease (despite therapy) was the most common mode of treatment failure; however, it was less common in the groups receiving combined therapy (34/130 [26%]) than in the group treated with RT only (23/62 [37%]). Severe acute toxic effects also were greater in the combined therapy groups. There were no significant differences in severe late toxic effects between the groups. However, chemotherapy could be administered as planned in only 89 (68%) of 130 patients (10% had life-threatening toxic effects with combined therapy vs 2% in the RT only group).

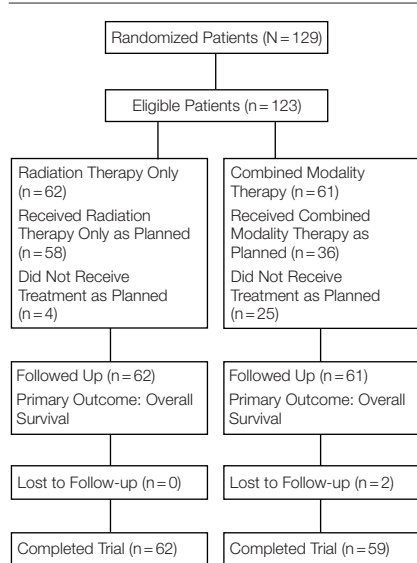
Conclusion Combined therapy increases the survival of patients who have squamous cell or adenocarcinoma of the esophagus, T1-3 N0-1 M0, compared with RT alone.

JAMA. 1999;281:1623-1627

www.jama.com

first evidence that the integration of chemotherapy with RT could improve outcome surfaced in the early 1980s. Sev-

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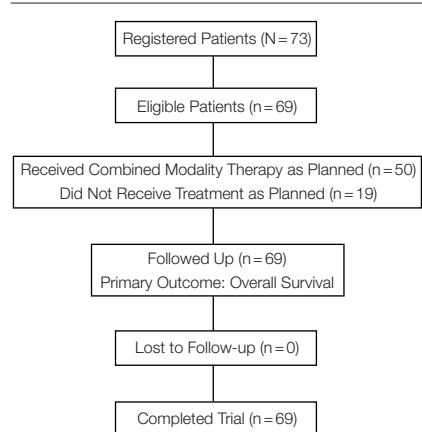
Figure 1. Progress of Patients Through the Randomized Part of the Trial

Of the 61 patients randomized to receive combined modality therapy, 37 received chemotherapy as planned and 56 received radiation therapy as planned so that 36 of the 61 received both therapies as planned. Randomization period was from January 1986 to April 1990.

eral pilot studies using cisplatin and fluorouracil suggested that median survival could be lengthened to 13 months.⁵⁻¹¹

In 1985, the Radiation Therapy Oncology Group (RTOG) launched RTOG 85-01, a prospective, randomized, phase 3 trial testing the hypothesis that concurrent chemoradiotherapy followed by adjuvant chemotherapy could improve the overall survival rate of patients who had carcinoma of the thoracic esophagus (without evidence of distant disease) compared with RT alone. Initially, the study allowed only squamous cell tumors, but adenocarcinomas were included after October 1986. To facilitate completion of the trial, the Southwest Oncology Group and the North Central Cancer Treatment Group collaboratively enrolled patients. Thus, the results reflect a diverse spectrum of patients and clinical settings for cancer care.

In early 1990, a preplanned interim analysis (detailed below) resulted in early termination of the random allocation of treatment because the group receiving combined modality therapy was surviving significantly longer.

Figure 2. Progress of Patients Through the Nonrandomized Part of the Trial

Of the 69 patients assigned to receive combined modality therapy, 52 received chemotherapy as planned and 64 received radiation therapy as planned so that 50 of the 69 received both therapies as planned. Non-randomization period was from May 1990 to April 1991.

Thereafter, a separate cohort of patients who would have been eligible for participation in the trial were prospectively registered and treated only with combined modality therapy.

Preliminary results of this trial have been published elsewhere^{12,13}; however, we report the long-term survival beyond 5 years and the first as detailed by the CONSORT statement.¹⁴

METHODS

Protocol Population

Patients were eligible for this trial if they had nondisseminated squamous or adenocarcinoma of the thoracic esophagus and a normal tracheobronchial tree, white blood cell count of at least $4.0 \times 10^9/L$, a platelet count of at least $10.0 \times 10^9/L$, serum creatinine level no greater than $133 \mu\text{mol/L}$ (1.5 mg/dL), and serum urea nitrogen level no greater than 7.85 mmol/L (22 mg/dL) (and/or creatinine clearance at least 1.0 mL/s [60 mL/min]), Karnofsky score of at least 50, no prior or concurrent other malignancy, and no prior chest irradiation or chemotherapy.

Interventions

The combined modality therapy consisted of cisplatin, 75 mg/m^2 intrave-

nously, on the first day of weeks 1, 5, 8, and 11. The patients were given a continuous infusion of fluorouracil, 1 g/m^2 , for the first 4 days of weeks 1, 5, 8, and 11. From the supraclavicular fossae to the esophagogastric junction, radiation was delivered at 30 Gy in 15 fractions over 3 weeks starting on day 1, followed by 20 Gy in 10 fractions over 2 weeks to the initial tumor length plus a 5-cm margin. The RT consisted of 50 Gy in 25 fractions over 5 weeks to the tumor plus a 5-cm margin cephalad and caudad (including the supraclavicular fossae for lesions of the middle and upper third of the thoracic esophagus) starting on day 1 and followed by 14 Gy in 7 fractions over 1.4 weeks including the initial tumor length with a 5-cm margin cephalad and caudad.

End Points

The primary outcome measure for this study was overall survival. Secondary end points were patterns of treatment failure, and acute and late (ie, more than 90 days from initiation of treatment) toxic effects.

Target Size

Target size was projected based on the estimate that 2-year survival in the group getting RT alone would be 10%. A 20% improvement in survival (ie, from 10% to 30%) was sought with combined modality therapy. A 2-tailed test was used because of the possibility that the addition of chemotherapy would be so toxic that survival would be shortened. Sample size calculations were designed to detect this difference with a type I error of .05, a statistical power of 0.90, and an assumption that up to 10% of patients subsequently would be deemed ineligible and/or have inadequate follow-up. This resulted in a total planned sample size of 150.

Statistical Analysis

The date of randomization was used as the starting point for all time to event variables. Persistence of tumor was counted as an immediate local failure. Time to local failure was estimated by the cumulative incidence approach and

compared with the Gray statistic.¹⁵ Estimates of survival rates were derived by the Kaplan-Meier method,¹⁶ and comparisons were made using the log-rank statistic.¹⁷ All statistical comparisons were made with 2-tailed tests on an intent-to-treat basis.

Prospectively Defined Stopping Rules

Interim analysis of survival data was scheduled for the next semi-annual RTOG meeting after data for 56 cases were available. The O'Brien-Fleming method¹⁸ was applied to account for multiple interim analyses. If either treatment group had a highly significant improvement in survival (log-rank test, $P < .005$), a recommendation was to be made to discontinue patient accrual.

At an interim analysis in May 1990 (90 evaluable cases had been accrued), the survival rates were statistically different at $P = .005$ (2-sided log-rank test) and favored the combined modality therapy arm. After consultation with clinicians and statisticians at the National Cancer Institute, a decision was made to suspend randomization and assign all patients to combined modality therapy.

Informed Consent

This protocol was approved by the National Cancer Institute, each of the participating national cooperative groups, and the individual review boards of each of the participating institutions. Patients provided signed informed consent prior to randomization of care.

Assignment

Randomization was done centrally at RTOG headquarters, balancing histology, tumor size, and weight loss among institutions.

RESULTS

Populations

A total of 129 patients were enrolled between January 1986 and April 1990 when a planned interim analysis revealed a difference that satisfied the "early stopping rule." Over the next

year, 73 consecutive patients were treated uniformly by chemoradiotherapy. FIGURE 1 and FIGURE 2 indicate that chemoradiotherapy had greater noncompliance than RT. All but 2 patients (lost to follow-up at 3.25 and 4.94 years) have now been followed up for a minimum of 5 years.

Analysis of pretreatment characteristics revealed no statistically significant differences in the baseline features between the randomized cohorts.¹³ The nonrandomized group had relatively fewer T2 tumors (more T1 and more T3); otherwise, the groups were not significantly different.

Survival

Long-term overall survival was associated with combined modality therapy

(TABLE 1). By 5 years, 26% (95% confidence interval [CI], 15%-37%) of the randomized combined modality group and 14% (95% CI, 6%-23%) of the nonrandomized combined modality group were alive vs none in the RT group. Our data are now sufficiently mature to conclude that 22% of the randomized combined modality group survived at least 8 years following therapy, to project that the 10-year survival rate may be as high as 20% and to observe that no deaths that occurred after 5 years were due to esophageal cancer, indicating that these patients are truly cured of their disease (not merely palliated for a longer time). There were no statistical differences in survival related to histology in those patients treated with combined modality therapy (TABLE 2).

Table 1. Overall Survival by Treatment Group*

Time, y	No. (%) Alive Following Radiation Therapy Only (Randomized)	No. (%) Alive Following Combined Modality Therapy	
		Randomized	Nonrandomized
0	62 (100)	61 (100)	69 (100)
1	21 (34)	32 (52)	43 (62)
2	6 (10)	22 (36)	24 (35)
3	0 (0)	18 (30)	18 (26)
4	0 (0)	17 (30)	13 (19)
5	0 (0)	14 (26)	10 (14)
6	0 (0)	12 (22)	6 (10)†
7	0 (0)	12 (22)	2 (6)†
8	0 (0)	10 (22)	...
9	0 (0)	4 (20)†	...
10	0 (0)	3 (20)†	...
Total dead (median, mo)	62/62 (9.3)	48/61 (14.1)	65/69 (16.7)

*Percentages are estimated. Data compiled by Kaplan-Meier method. Statistical test results of the log-rank test are: randomized comparison, $P < .001$; and combined modality therapy and radiation therapy (randomized vs nonrandomized), $P = .24$ (stratified by tumor stage). Ellipses indicate data not available because follow-up lasted less than 8 years.

†Percentages are unreliable due to the small number of people at risk.

Table 2. Survival Estimates by Histologic Type After Combined Modality Therapy*

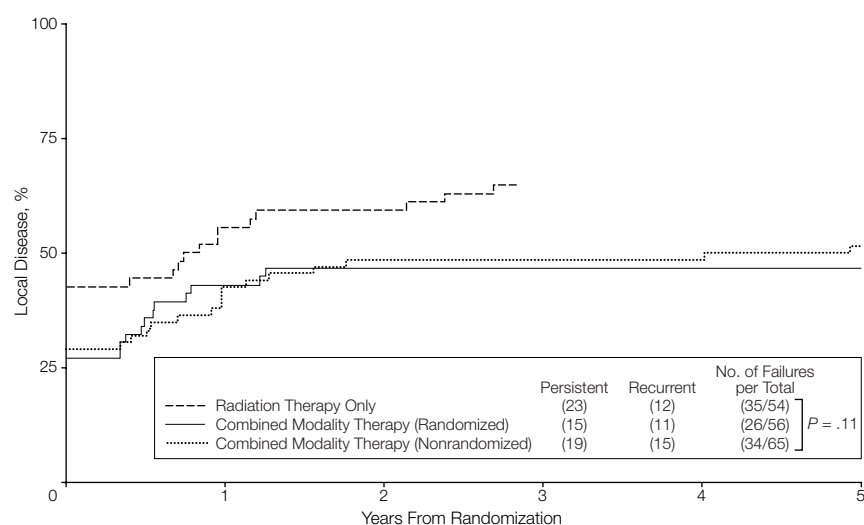
Time, y	Adenocarcinoma		Squamous Cell	
	No. (%) Alive	95% Confidence Interval, %	No. (%) Alive	95% Confidence Interval, %
0	23 (100)	...	107 (100)	...
1	12 (52)	32-73	63 (59)	50-68
2	5 (22)	5-39	41 (38)	29-48
3	4 (17)	2-33	32 (30)	21-39
4	3 (13)	0-27	27 (26)	18-34
5	3 (13)	0-27	21 (21)	13-29
Total dead (median, mo)	22/23 (12.2)		91/107 (16.9)	

*Data includes randomized and nonrandomized values combined. Percentages are estimated. Data compiled by the Kaplan-Meier method. $P = .15$ for adenocarcinoma vs squamous cell carcinoma.

Table 3. Location of Disease at First Treatment Failure*

First Failure	No. (%) Alive Following Radiation Therapy Only (Randomized)	No. (%) Alive Following Combined Modality Therapy	
		Randomized	Nonrandomized
None	0 (0)	13 (21)	4 (6)
Persistent	23 (37)	15 (25)	19 (28)
Local-regional	10 (16)	8 (13)	14 (20)
Distant only	9 (15)	5 (8)	11 (16)
Local, regional, and distant	9 (15)	5 (8)	7 (10)
Death			
Disease sites not specified	3 (5)	3 (5)	3 (4)
Other	5 (8)	10 (16)	10 (15)
Unknown	3 (5)	2 (3)	1 (1)
Total	62 (100)	61 (100)	69 (100)

*Data updated October 1, 1998. Percentages are estimated.

Figure 3. Percentage of Patients Developing Local Disease by Treatment Group in Intergroup Protocol 85-01

Time to local failure by treatment arm plotted by Kaplan-Meier method. Comparisons based on log-rank χ^2 statistic. Persistent tumors were counted as treatment failure immediately.

Table 4. Late Reactions by Treatment Group and by Anatomic Site*

Anatomic Site	Combined Modality Therapy								
	Radiation Therapy Only (Randomized) (n = 54)			Randomized (n = 52)			Nonrandomized (n = 65)		
	3	4	5	3	4	5	3	4	5
Esophagus	8	2	0	10	1	0	12	1	1
Skin	0	0	0	0	0	0	0	0	0
Lung	0	0	0	1	0	0	0	0	0
Larynx	0	0	0	0	0	0	0	0	0
Heart	3	0	0	0	0	0	0	0	0
Hematologic	0	0	0	2	1	0	4	1	0
Central nervous system	0	0	0	0	0	0	0	0	0
Other	1	0	0	0	0	0	2	0	1
Maximum severity reported per patient, No. (%)	10 (19)	2 (4)	0 (0)	13 (25)	2 (4)	0 (0)	15 (23)	2 (3)	1 (2)

*The 3, 4, 5 grading system and grades were determined by the Radiation Therapy Oncology Group scale.

Patterns of Failure

Persistence of disease was the greatest cause of treatment failure in every group of patients (TABLE 3). However, it was 40% more common in the group receiving RT alone (37% following RT only; 25% and 28% following combined modality therapy in the randomized and nonrandomized cohorts, respectively). Moreover, chemoradiotherapy appeared to prevent, not merely delay, the local growth of tumor (FIGURE 3).

Toxic Effects

Eight percent of the cohort randomly assigned to combined modality therapy experienced acute life-threatening (ie, grade 4) toxic effects on the RTOG acute morbidity scale and an additional 2% died as a direct consequence of treatment. In contrast, only 2% of patients receiving RT alone experienced acute grade 4 toxic effects and there were no fatalities due to toxic effects. Interestingly, the nonrandomized combined modality group experienced a lower grade 4 rate (4% vs 8%) and no fatalities, perhaps reflecting greater experience with this management plan (despite receiving more drugs).¹³ In contrast, once patients survived more than 90 days based on time from the beginning of treatment, there were no significant differences in (late RTOG scale) toxic effects between the groups (TABLE 4).

COMMENT

Carcinoma of the esophagus has been highly lethal even though distant metastases do not occur in the majority of patients until late in the course of their disease. Instead, carcinomas of the esophagus tend to spread axially, up and down the length of the organ and to regional lymphatics, producing their morbidity and mortality from local-regional effects. Consequently, the essential hypothesis of this trial was that concurrently administered chemotherapy would act as a promoter of the local-regional effects of RT as well as having direct cytotoxic effects on its own. The decreased incidence of per-

sistent disease seen in this trial can be viewed as evidence that this hypothesis is correct. In fact, the trial may well have handicapped the efficacy of chemoradiation by using a smaller dose of RT than was used for patients treated by RT alone (50 Gy vs 64 Gy).

In addition, chemotherapy appears to have eradicated some presumably subclinical distant metastases. Distant metastases (with or without local-regional disease) accounted for the first site of treatment failure in 30% of the RT group vs 16% in the randomized combined modality therapy group and 26% in the non-randomized combined modality therapy group. This difference was evident even though the increased life-span of patients who received chemotherapy placed them at a longer (ie, greater) risk of developing distant metastases.

The 5-year minimum follow-up of patients first reported in this article is critical for its proper interpretation. Based solely on the preliminary findings of this trial, it was tenable to think that combined modality therapy merely delays the time to failure (local, regional, or distant). The long-term durability of the multimodality therapy reported herein demonstrates that this

regimen truly cures more patients than does RT alone.

The reproducibility of the outcome in a separate, but similarly selected, group of consecutively accrued patients who were treated by combined modality therapy further demonstrates the value of chemoradiotherapy in the treatment of patients who have esophageal cancer. It seems reasonable to conclude that chemoradiotherapy now should be considered a standard of care for patients who have carcinoma of the esophagus.

Our trial did not address the potential role of surgery in combination with chemoradiotherapy. There is some evidence that chemoradiotherapy prior to surgery is feasible and more efficacious than surgery alone. For example, Walsh et al¹⁹ prospectively tested surgery alone vs multimodality therapy for esophageal adenocarcinoma (2 courses of fluorouracil and cisplatin plus concurrent RT followed by surgery). Median survival time following surgery alone was 11 months compared with 16 months following multimodal therapy ($P = .01$). Results appeared durable because 3-year survival was only 6% following surgery alone vs 32% following multimodal

therapy ($P = .01$). The authors concluded multimodal treatment is superior to surgery alone for patients with resectable adenocarcinoma of the esophagus. Since local-regional persistence of disease accounted for the majority of treatment failures in our trial, surgery might be able to eradicate some of these tumors.

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Funding/Support: Funding was provided by National Cancer Institute grants CA21661, CA32115, CA32102, and CA25224. However, the contents of this article do not necessarily represent the official views of the National Cancer Institute.

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