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. The first evidence that the integration of chemotherapy with RT could improve outcome surfaced in the early 1980s. Several}

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

Randomized Patients (N = 129)

- Eligible Patients (n = 123)
  - Radiation Therapy Only (n = 62)
    - Received Radiation Therapy Only as Planned (n = 58)
    - Did Not Receive Treatment as Planned (n = 4)
  - Combined Modality Therapy (n = 61)
    - Received Combined Modality Therapy as Planned (n = 56)
    - Did Not Receive Treatment as Planned (n = 5)
  - Followed Up (n = 62)
    - Primary Outcome: Overall Survival
  - Lost to Follow-up (n = 0)
  - Completed Trial (n = 62)

- Registered Patients (N = 73)
  - Eligible Patients (n = 69)
    - Received Combined Modality Therapy as Planned (n = 50)
    - Did Not Receive Treatment as Planned (n = 19)
  - Followed Up (n = 69)
    - Primary Outcome: Overall Survival
  - Lost to Follow-up (n = 0)
  - Completed Trial (n = 69)

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.

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.

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

Registered Patients (N = 73)

- Eligible Patients (n = 69)
  - Did Not Receive Treatment as Planned (n = 19)
  - Combined Modality Therapy (n = 61)
    - Received Combined Modality Therapy as Planned (n = 50)
    - Did Not Receive Treatment as Planned (n = 19)
  - Followed Up (n = 69)
    - Primary Outcome: Overall Survival
  - Lost to Follow-up (n = 0)
  - Completed Trial (n = 69)

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. Nonrandomization period was from May 1990 to April 1991.

<table>
<thead>
<tr>
<th>End Points</th>
<th>Primary Outcome Measure for this Study</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary End Points</td>
<td>Patterns of treatment failure, and acute and late (ie, more than 90 days from initiation of treatment) toxic effects.</td>
<td></td>
</tr>
</tbody>
</table>

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 nously, on the first day of weeks 1, 5, 8, and 11. The patients were given a continuous infusion of fluorouracil, 1 g/m², 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.
compared with the Gray statistic. Estimates of survival rates were derived by the Kaplan-Meier method, and comparisons were made using the log-rank statistic. 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 method 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. 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).

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**Table 1. Overall Survival by Treatment Group**

<table>
<thead>
<tr>
<th>Time, y</th>
<th>No. (%) Alive Following Radiation Therapy Only (Randomized)</th>
<th>No. (%) Alive Following Combined Modality Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomized</td>
<td>Nonrandomized</td>
</tr>
<tr>
<td>0</td>
<td>62/100</td>
<td>61/100</td>
</tr>
<tr>
<td>1</td>
<td>21/34</td>
<td>32/52</td>
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<tr>
<td>2</td>
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<td>22/36</td>
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<td>3</td>
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<tr>
<td>9</td>
<td>0/3</td>
<td>4/20†</td>
</tr>
<tr>
<td>10</td>
<td>0/3</td>
<td>3/20†</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Time, y</th>
<th>Adenocarcinoma</th>
<th>Squamous Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>23/100</td>
<td>107/100</td>
</tr>
<tr>
<td>1</td>
<td>12/52</td>
<td>63/59</td>
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<tr>
<td>2</td>
<td>5/22</td>
<td>41/38</td>
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<td>3</td>
<td>4/17</td>
<td>32/30</td>
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<tr>
<td>4</td>
<td>3/13</td>
<td>27/26</td>
</tr>
<tr>
<td>5</td>
<td>3/13</td>
<td>21/21</td>
</tr>
</tbody>
</table>

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. \( P = .16 \) for adenocarcinoma vs squamous cell carcinoma.
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; 29% 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-
CHEMORADIOThERAPY OF ESOPHAGEAL CANCER


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