

# INT 0123 (Radiation Therapy Oncology Group 94-05) Phase III Trial of Combined-Modality Therapy for Esophageal Cancer: High-Dose Versus Standard-Dose Radiation Therapy

By Bruce D. Minsky, Thomas F. Pajak, Robert J. Ginsberg, Thomas M. Pisansky, James Martenson, Ritsuko Komaki, Gordon Okawara, Seth A. Rosenthal, and David P. Kelsen

**Purpose:** To compare the local/regional control, survival, and toxicity of combined-modality therapy using high-dose (64.8 Gy) versus standard-dose (50.4 Gy) radiation therapy for the treatment of patients with esophageal cancer.

**Patients and Methods:** A total of 236 patients with clinical stage T1 to T4, N0/1, M0 squamous cell carcinoma or adenocarcinoma selected for a nonsurgical approach, after stratification by weight loss, primary tumor size, and histology, were randomized to receive combined-modality therapy consisting of four monthly cycles of fluorouracil (5-FU) (1,000 mg/m<sup>2</sup>/24 hours for 4 days) and cisplatin (75 mg/m<sup>2</sup> bolus day 1) with concurrent 64.8 Gy versus the same chemotherapy schedule but with concurrent 50.4 Gy. The trial was stopped after an interim analysis. The median follow-up was 16.4 months for all patients and 29.5 months for patients still alive.

**Results:** For the 218 eligible patients, there was no significant difference in median survival (13.0 v 18.1 months), 2-year survival (31% v 40%), or local/regional failure and local/regional persistence of disease (56% v 52%) between the high-dose and standard-dose arms. Although 11 treatment-related deaths occurred in the high-dose arm compared with two in the standard-dose arm, seven of the 11 deaths occurred in patients who had received 50.4 Gy or less.

**Conclusion:** The higher radiation dose did not increase survival or local/regional control. Although there was a higher treatment-related mortality rate in the patients assigned to the high-dose radiation arm, it did not seem to be related to the higher radiation dose. The standard radiation dose for patients treated with concurrent 5-FU and cisplatin chemotherapy is 50.4 Gy.

*J Clin Oncol* 20:1167-1174. © 2002 by American Society of Clinical Oncology.

BASED ON THE RESULTS of the Radiation Therapy Oncology Group (RTOG) phase III intergroup trial RTOG 85-01, the standard therapy for patients with localized carcinoma of the esophagus selected for nonsurgical treatment is radiation therapy plus concurrent chemotherapy.<sup>1-3</sup> In that trial, patients were randomly assigned to receive four cycles of fluorouracil (5-FU) and cisplatin with radiation therapy (50 Gy) delivered concurrently with the first cycle of chemotherapy or to radiation therapy alone (64 Gy). There was a significant improvement in local/regional control and overall survival with radiation plus chemotherapy (combined-modality therapy) compared with radiation therapy alone. Despite this, the incidence of local/regional failure and local/regional persistence of disease was 47%.

In an attempt to improve these results, the intergroup INT 0122 phase II trial was designed in which the chemotherapy and radiation doses delivered in the combined-modality therapy arm of RTOG 85-01 were intensified. The regimen was modified as follows: (1) 5-FU continuous infusion was increased from 4 to 5 days; (2) total number of chemotherapy cycles was increased from four to five; (3) three cycles of full-dose neoadjuvant 5-FU and cisplatin were delivered before the start of combined-modality therapy; and (4) radiation dose was increased from 50 to 64.8 Gy.

The response, local/regional control, and survival rates for INT 0122 were similar to those reported in the combined

modality arm of RTOG 85-01. However, the incidence of treatment-related mortality was higher (9% v 2%).<sup>4,5</sup> Because of this unexpected increase in the mortality rate, this neoadjuvant treatment regimen was not pursued. Nonetheless, because the higher radiation dose was well tolerated and did not seem to be the cause of the higher mortality rate, it was used in the high-dose arm (64.8 Gy) of the present trial. The goal of our trial was to compare the survival, local/regional control, and toxicity of a combined-modality therapy regimen based on 5-FU and cisplatin using a higher dose (64.8 Gy) of radiation therapy with the same regimen using a standard dose (50.4 Gy) of radiation therapy. The

---

From the Departments of Radiation Oncology, Medicine, and Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; Statistical Office, Radiation Therapy Oncology Group, Philadelphia, PA; Division of Radiation Oncology, Mayo Clinic, Rochester, MN; Department of Radiation Oncology, M.D. Anderson Cancer Center, Houston, TX; Hamilton Regional Cancer Center, Ontario, Canada; and Sacramento Radiation Oncology Center, Sacramento, CA.

Submitted July 2, 2001; accepted October 31, 2001.

Address reprint requests to Bruce D. Minsky, MD, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021; email: minskyb@mskcc.org.

© 2002 by American Society of Clinical Oncology.

0732-183X/02/2005-1167/\$20.00

preliminary results have been published in abstract form.<sup>6</sup> The results with longer follow-up are now reported in the present study.

## PATIENTS AND METHODS

### Patient Population

Member institutions of the Radiation Therapy Oncology Group (protocol RTOG 94-05, 190 patients enrolled), Eastern Cooperative Oncology Group (protocol ECOG R9405, 34 patients enrolled), and the North Central Cancer Treatment Group (NCCTG protocol 94-40-51, 12 patients enrolled) entered patients onto this trial. The maximum number of patients treated at any one institution was 16. The RTOG served as the coordinating group and was responsible for data collection and analysis. The study was opened in June 1995 and was scheduled to accrue 298 patients. After an interim analysis by the data monitoring committee in July 1999 revealed that the chance of the high-dose arm showing a significant survival advantage compared with the standard-dose arm was 2.5% or less, the study was closed after accruing a total of 236 patients. The average monthly accrual was 4.9 patients.

### Eligibility Criteria and Pretreatment Evaluation

Enrollment was limited to American Joint Committee tumor-node-metastasis system clinical stage T1 to T4, N0/1, M0 primary squamous cell or adenocarcinoma of the cervical, mid, or distal esophagus.<sup>7</sup> Eligibility criteria included the following: age of 18 years or older, Karnofsky performance status of 60 or greater, serum creatinine below the institutional upper normal limit or creatinine clearance higher than 65 mL/min, written informed consent, bronchoscopy to exclude a tracheoesophageal fistula if the lesion was less than 30 cm from the incisors, chest/abdominal computed tomography (CT) scan revealing no evidence of metastatic disease, and adequate nutritional intake. Adequate nutritional intake was defined as ingesting either more than 1.5 times basal energy expenditure as measured by the Harris-Benedict equation or more than 1,000 calories per square meter of body-surface area (1,700 calories for the average 1.7-meter individual). Furthermore, because of the concern that the stomach could not safely tolerate 64.8 Gy, eligibility was limited to patients whose tumors did not extend to within 2 cm of the gastroesophageal junction. Therefore, most patients (85%) had squamous cell carcinomas.

Ineligibility criteria included multiple carcinomas of the esophagus, biopsy-proven invasion of the tracheobronchial tree or tracheoesophageal fistula, metastatic disease (M1), a primary tumor that extended to within 2 cm of the gastroesophageal junction, prior chemotherapy, prior thoracic radiation, surgical resection of the primary tumor, significant medical or psychiatric illnesses that, in the physician's judgment, would compromise the proposed treatment or preclude obtaining informed consent, concurrent pregnancy or lactation, history of a second malignancy other than nonmelanoma skin cancer, and cervical cancer in situ.

Clinically positive supraclavicular nodes required pathologic confirmation. Patients with cervical primary tumors with positive supraclavicular lymph nodes (defined as N1) were eligible; however, patients with noncervical primary tumors with positive supraclavicular lymph nodes (defined as M1) were ineligible. Radiographic evidence of liver metastasis and enlarged ( $\geq 1.5$  cm) retroperitoneal or celiac lymph nodes seen on CT scan required biopsy proof that there was no evidence of cancer; otherwise, the patient was ineligible.

Mandatory pretreatment evaluation included a complete history and physical examination, assessment of Karnofsky performance status,

## INT 0123

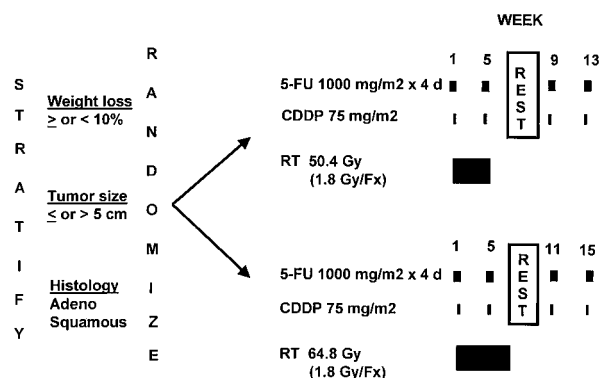


Fig 1. Treatment scheme. CDDP, cisplatin; Fx, fraction.

serum chemistry profile, complete blood cell count, chest x-ray, ECG, endoscopy with biopsy, barium swallow and upper gastrointestinal, chest, and abdominal CT scan, pulmonary function tests, and quality of life assessment using the Functional Assessment of Cancer Therapy (FACT) Head & Neck version 2. Creatinine clearance was optional. For tumors less than 30 cm from the incisor teeth, bronchoscopy was performed to exclude a tracheoesophageal fistula. Abnormal findings on CT scan suggestive of metastasis had to be accompanied by a negative biopsy. A bone scan was required for patients with an alkaline phosphatase elevated higher than 1.5 times normal. Esophageal ultrasound was strongly recommended but optional. The study was reviewed and approved by the institutional review board at the participating institutions. Written informed consent was obtained from all patients.

### Treatment Details

The treatment scheme is shown in Fig 1. Patients received four cycles of 5-FU/cisplatin plus concurrent radiation therapy. The use of colony-stimulating factors was not allowed. Radiation therapy began on day 1, concurrent with the beginning of cycle one of chemotherapy.

**Chemotherapy.** Cisplatin 75 mg/m<sup>2</sup> bolus was given over 30 minutes with adequate prehydration, mannitol, and antiemetic coverage on day 1. 5-FU 1,000 mg/m<sup>2</sup>/24 hours was given by continuous infusion on days 1 through 4 of each cycle. Each cycle of chemotherapy was repeated every 28 days. Patients had a 4-week rest after the completion of radiation and then received an additional two cycles (days 1 and 29) of chemotherapy. Therefore, cycle three of chemotherapy started on week 11 in the high-dose arm and week 9 in the standard-dose arm.

**Radiation therapy.** Radiation therapy was delivered with megavoltage equipment ( $\geq 6$  MV) using a multiple field technique. Patients were treated 5 days per week at 1.8 Gy/d.

At least two fields were treated each day, and portal films were obtained of at least two fields per week or more often if needed. Treatment could be delivered with the combination of anterior/posterior, oblique, or lateral fields, such that the dose did not vary by greater than 5% over the entire target volume. Dose inhomogeneity within the target volume of 6% to 10% was considered a minor violation and greater than 10% was scored as a major violation. The dose was prescribed to the isodose line, which covered the volume at risk. Lung inhomogeneity corrections were not used.

**Initial target volume (50.4 Gy).** The superior and inferior borders of the radiation field were 5 cm beyond the primary tumor. The lateral, anterior, and posterior borders of the field were  $\geq 2$  cm beyond the borders of the primary tumor. The tumor size was defined by endoscopic ultrasound, barium swallow, or CT scan (whichever was larger). The primary and the regional lymph nodes were included. For tumors of the cervical esophagus, the supraclavicular lymph nodes were included. A separate photon or electron boost to the supraclavicular lymph nodes was allowed to bring the total dose to 50.4 Gy.

**High-dose target volume (14.4 Gy).** Patients randomized to the high-dose arm received a cone down of 14.4 Gy to a total dose of 64.8 Gy. The intent of the cone down was to treat the primary tumor only, not the regional primary lymph nodes. The superior and inferior borders of the field were decreased to 2 cm beyond the tumor. The lateral anterior and posterior borders were the same as the initial target volume.

### Progression of Disease

Patients who developed progression of disease within the radiation target volume or developed metastatic disease were considered treatment failures. Treatment at that time was considered palliative and was at the discretion of the individual physician.

### Dose Modifications

Chemotherapy dose modifications were based on the findings on the day of treatment as well as on interim (between cycle) toxicities, whichever were greater. The National Cancer Institute cooperative group common toxicity criteria were used for acute chemotherapy toxicity. A 1-week treatment break from chemotherapy was required when grade 3 or higher toxicity was observed. Otherwise, the following modifications were made.

**Hematologic toxicity on day 1 of each chemotherapy cycle.** If the WBC was  $2,000/\text{mm}^3$  or higher but lower than  $3,000/\text{mm}^3$  or the platelet count was  $75,000/\text{mm}^3$  or greater but lower than  $100,000/\text{mm}^3$ , the dose of 5-FU and cisplatin was decreased by 50%. Radiation therapy continued. If the WBC was lower than  $2,000/\text{mm}^3$  or the platelet count was less than  $75,000/\text{mm}^3$ , both chemotherapy and radiation were held until the toxicity was no longer present.

**Hematologic toxicity between chemotherapy cycles.** If the WBC was lower than  $1,000/\text{mm}^3$  or the platelet count was  $75,000/\text{mm}^3$  or lower, the dose of 5-FU and cisplatin was decreased by 25%.

**Genitourinary toxicity (attributable to cisplatin).** If the creatinine clearance was between 55 and 65 mL/min or the serum creatinine was between 1.6 and 2 mg/100 mL, the cisplatin dose was decreased by 50%. If the creatinine clearance was less than 55 mL/min, then cisplatin was held and 5-FU was also held until the toxicity was no longer present and cisplatin could be administered again. Radiation therapy continued.

**Other toxicities.** Any other grade 3 or higher toxicity required a 1-week treatment delay. Treatment was resumed when the toxicity was grade 2 or lower. Patients with grade 3 or higher stomatitis received no additional 5-FU for that cycle, and the dose was permanently reduced for all subsequent cycles. Intercurrent (between cycle) grade 3 or higher stomatitis required a 25% permanent dose reduction.

Acute and late radiation toxicity was scored according to the RTOG morbidity scoring criteria. Radiation was also held for grade 3 or higher toxicity but was resumed when grade 3 or higher toxicity was no longer present. Patients who developed grade 3 or higher toxicities unrelated to radiation (oral mucositis, genitourinary toxicity, and hand-foot syndrome) had chemotherapy held but continued to receive radiation therapy. The radiation dose was not attenuated.

### Toxicity Assessment During Treatment

Patients were examined weekly throughout all phases of the treatment program or more often if clinically indicated. Before each chemotherapy cycle, a history, physical examination, and determination of toxicity was performed. A serum chemistry profile was performed after the completion of each chemotherapy cycle. Weekly toxicity assessment was performed during radiation therapy.

### Follow-Up Evaluation

A history and physical examination, serum chemistry profile, chest x-ray, barium swallow, and quality of life analysis was performed within 28 days after the completion of all therapy. The following were performed until the time of disease progression every 4 months for 1 year, every 6 months for 2 years, then yearly: physical examination, toxicity assessment, complete blood cell count, serum chemistry profile, chest x-ray, barium swallow and upper gastrointestinal, abdominal, and chest computed tomography scan, and quality of life assessment. Pulmonary function tests were required at 8 months. Biopsy of the primary tumor site was required at 4 months and at the time of any x-ray evidence of local or regional recurrence.

### Assessment of Primary Tumor Response

Ideally, the response of the primary tumor was determined 4 months after the completion of the last cycle of chemotherapy. Patients were scheduled to have endoscopy and biopsy. However, in patients who developed progression of disease while on treatment, the assessment was commonly performed at the time of progression.

In the absence of histologic or cytologic proof of recurrence, clinical evidence (including new masses on CT scan, new lesions on bone scan, ascites not explained by other causes, or enlarging masses by endoscopic ultrasound), although highly suspicious of recurrent or metastatic disease, did not result in a change in the patient's management. Because biopsy proof was required, this led to a search for a mass that might be biopsied.

### Patterns of Failure

Patterns of failure were defined as the first site of failure. Local/regional failure included the primary tumor and regional lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes.

### Quality Control

All radiation simulator and port films were reviewed by one physician (B.D.M.). The RTOG criteria for assessing and scoring minor and major deviations were used. The RTOG staff reviewed all radiation dosimetry and chemotherapy flow sheets.

### Statistical Analysis

The survival analysis was performed by the actuarial Kaplan-Meier method,<sup>8</sup> and differences between the curves were analyzed using the log-rank test.<sup>9</sup> The only exception to that is the outcome of time to first local/regional failure, which was estimated though the method of cumulative incidence<sup>10</sup> and Gray's test.<sup>11</sup> The time to each outcome was calculated from the date of registration. Analysis of patterns of failure was performed using crude calculations.

The estimated 2-year survival rate of the control (standard-dose) arm was based on the 36% achieved in the combined-modality therapy arm of RTOG 85-01. It was projected that increasing the radiation dose to 64.8 Gy would produce a 2-year survival of 50%. For a significance

Table 1. Pretreatment Characteristics

|                         | High Dose (64.8 Gy) |    | Standard Dose (50.4 Gy) |    |
|-------------------------|---------------------|----|-------------------------|----|
|                         | No.                 | %  | No.                     | %  |
| No. of patients         | 109                 |    | 109                     |    |
| Histology               |                     |    |                         |    |
| Squamous cell           | 95                  | 87 | 92                      | 84 |
| Adenocarcinoma          | 14                  | 13 | 17                      | 16 |
| Sex                     |                     |    |                         |    |
| Male                    | 71                  | 65 | 83                      | 76 |
| Female                  | 38                  | 35 | 26                      | 24 |
| Age, years              |                     |    |                         |    |
| Median                  | 64                  |    | 64                      |    |
| Range                   | 43-80               |    | 37-81                   |    |
| Performance status      |                     |    |                         |    |
| KPS 60-80               | 46                  | 41 | 52                      | 47 |
| KPS 90-100              | 63                  | 59 | 57                      | 53 |
| AJCC TNM clinical stage |                     |    |                         |    |
| T1                      | 6                   | 6  | 9                       | 8  |
| T2                      | 35                  | 32 | 30                      | 28 |
| T3                      | 46                  | 42 | 38                      | 34 |
| T4                      | 7                   | 6  | 10                      | 9  |
| Tx                      | 15                  | 14 | 22                      | 20 |
| N0                      | 67                  | 61 | 73                      | 66 |
| N1                      | 29                  | 27 | 18                      | 17 |
| Nx                      | 13                  | 12 | 18                      | 17 |
| Primary tumor size      |                     |    |                         |    |
| ≤ 5 cm                  | 59                  | 54 | 55                      | 50 |
| > 5 cm                  | 50                  | 46 | 54                      | 50 |
| Weight loss             |                     |    |                         |    |
| ≥ 10%                   | 44                  | 40 | 47                      | 43 |
| < 10%                   | 65                  | 60 | 62                      | 57 |
| Race                    |                     |    |                         |    |
| White                   | 75                  | 69 | 64                      | 59 |
| Hispanic                | 4                   | 4  | 4                       | 4  |
| Black                   | 26                  | 24 | 38                      | 35 |
| Asian                   | 0                   |    | 1                       | 1  |
| Native American         | 2                   | 2  | 1                       | 1  |
| Other                   | 0                   |    | 1                       | 1  |
| Prefers not to answer   | 2                   | 2  | 0                       |    |

Abbreviation: AJCC, American Joint Committee on Cancer; KPS, Karnofsky performance status; TNM, tumor-node-metastasis.

level of .05, statistical power of .80, and two-sided test, guarding against an ineligibility or unassessability of 10%, a total of 298 patients were scheduled to be entered.

### Randomization

The randomization scheme described by Zelen<sup>12</sup> was used to achieve balance in the treatment assignments among the institutions with the following three stratification variables: weight loss ( $< 10\%$  v  $\geq 10\%$ ), tumor size ( $\leq 5$  v  $> 5$  cm), and histologic cell type (adenocarcinoma v squamous). Patients were randomly assigned either to the 64.8- or 50.4-Gy arms.

## RESULTS

### Patient Characteristics and Eligibility

The pretreatment characteristics of the 218 eligible and assessable patients are listed in Table 1. The arms were well balanced for weight loss, primary tumor size, histology, sex,

race, age, performance status, clinical T stage, and clinical N stage. The median follow-up was 16.4 months for all patients and 29.5 months for those still alive.

Reasons for ineligibility in the high radiation dose arm included no bronchoscopy (four patients), tumor extended to within 2 cm of the stomach (three patients), and medically unfit to tolerate combined-modality therapy (one patient). At the time of this analysis, there was one patient with insufficient data for evaluation, leaving 109 eligible and assessable patients in the high-dose arm.

Reasons for ineligibility in the standard radiation dose arm included no bronchoscopy (four patients), tumor extended to within 2 cm of the stomach (one patient), no esophagram (three patients), and prior chest radiation therapy (one patient). At the time of this analysis, there were 109 eligible and assessable patients in the standard-dose arm.

**Table 2. Quality Review**

|                               | High Dose (64.8 Gy) |    | Standard Dose (50.4 Gy) |    |
|-------------------------------|---------------------|----|-------------------------|----|
|                               | No.                 | %  | No.                     | %  |
| Radiation therapy             |                     |    |                         |    |
| Not reviewed                  | 9                   | 8  | 6                       | 6  |
| Reviewed                      | 100                 | 92 | 103                     | 94 |
| Per protocol                  | 67                  | 67 | 86                      | 83 |
| Deviation acceptable          | 12                  | 12 | 9                       | 9  |
| Deviation unacceptable        | 3                   | 3  | 5                       | 5  |
| Incomplete RT: death          | 11                  | 11 | 1                       | 1  |
| Incomplete RT: progression    | 1                   | 1  | 0                       | 0  |
| Incomplete RT: refusal        | 6                   | 6  | 2                       | 2  |
| Chemotherapy                  |                     |    |                         |    |
| Not reviewed                  | 42                  | 39 | 45                      | 41 |
| Reviewed                      | 67                  | 61 | 64                      | 59 |
| Per protocol                  | 44                  | 66 | 44                      | 69 |
| Minor deviation, acceptable   | 10                  | 15 | 11                      | 17 |
| Major deviation, acceptable   | 10                  | 15 | 8                       | 13 |
| Major deviation, unacceptable | 3                   | 5  | 1                       | 2  |

Abbreviation: RT, radiotherapy.

### Quality Review

As seen in Table 2, the percentage of patients with complete radiation therapy information available for review at the time of the analysis was 92% in the high-dose arm and 94% in the standard-dose arm. Because of the increased incidence of treatment-related deaths in the high-dose arm, only 67% of patients received radiation according to protocol compared with 83% in the standard-dose arm. However, the incidence of acceptable deviations (12% v 9%) and unacceptable deviations (3% v 5%) was similar in both arms.

The patients with complete chemotherapy information available for review at the time of the analysis was 61% in the high-dose arm and 59% in the standard-dose arm. The percentage who received chemotherapy according to protocol guidelines was similar in the two arms (66% v 69%, respectively).

### Toxicity of Treatment

The incidence of grade 3 or higher acute and late radiation toxicity is seen in Table 3. There were a total of 11

**Table 4. Treatment-Related Deaths (grade 5)**

| Dose Received           | Toxicity                              |
|-------------------------|---------------------------------------|
| High dose (64.8 Gy)     |                                       |
| 5.4 Gy                  | Cardiac                               |
| 5.4 Gy                  | Cardiac, genitourinary                |
| 9.0 Gy                  | Cardiac, hematologic                  |
| 37.8 Gy                 | Respiratory                           |
| 43.2 Gy                 | Hematologic, infection, genitourinary |
| 50.4 Gy                 | Infection                             |
| 50.4 Gy                 | Genitourinary                         |
| 54.0 Gy                 | Infection                             |
| 61.2 Gy                 | Hematologic                           |
| 64.8 Gy                 | Infection                             |
| 64.8 Gy                 | Fistula, gastrointestinal             |
| Standard dose (50.4 Gy) |                                       |
| 50.4 Gy                 | Infection                             |
| 50.4 Gy                 | Infection                             |

treatment-related deaths (10%) in the high-dose arm compared with two (2%) in the standard-dose arm, and they are reviewed in Table 4. Of these 11 treatment-related deaths, seven occurred in patients who had received 50.4 Gy or less. Of the remaining four deaths, three occurred during the high-dose radiation portion of the treatment and one patient died of a fistula 9 months after the completion of 64.8 Gy.

### Survival

There was no significant difference in median survival (13 months [95% confidence interval, 10.5 to 19.1 months] v 18.1 months [95% confidence interval, 15.4 to 23.1 months]) or 2-year survival (31% v 40%) between the high-dose and standard-dose arms (Fig 2).

To help determine if this unexplained increase in treatment-related deaths in the high-dose arm was the factor responsible for the inferior survival rate, a separate survival analysis was performed that included only patients who received the assigned dose of radiation (Fig 3). Despite this biased analysis, there was still no survival advantage with the high-dose arm.

**Table 3. Overall Maximum Toxicity Per Patient**

| Grade | Acute Toxicity                   |    |                                      |    | Late Toxicity                   |    |                                     |    |
|-------|----------------------------------|----|--------------------------------------|----|---------------------------------|----|-------------------------------------|----|
|       | High Dose (64.8 Gy)<br>(n = 109) |    | Standard Dose (50.4 Gy)<br>(n = 109) |    | High Dose (64.8 Gy)<br>(n = 95) |    | Standard Dose (50.4 Gy)<br>(n = 99) |    |
|       | No.                              | %  | No.                                  | %  | No.                             | %  | No.                                 | %  |
| 1     | 2                                | 2  | 1                                    | 1  | 9                               | 9  | 19                                  | 20 |
| 2     | 21                               | 19 | 28                                   | 26 | 28                              | 29 | 22                                  | 22 |
| 3     | 50                               | 46 | 47                                   | 43 | 32                              | 34 | 24                                  | 24 |
| 4     | 23                               | 21 | 28                                   | 26 | 10                              | 11 | 13                                  | 13 |
| 5     | 10                               | 9  | 2                                    | 2  | 1                               | 1  | 0                                   | 0  |



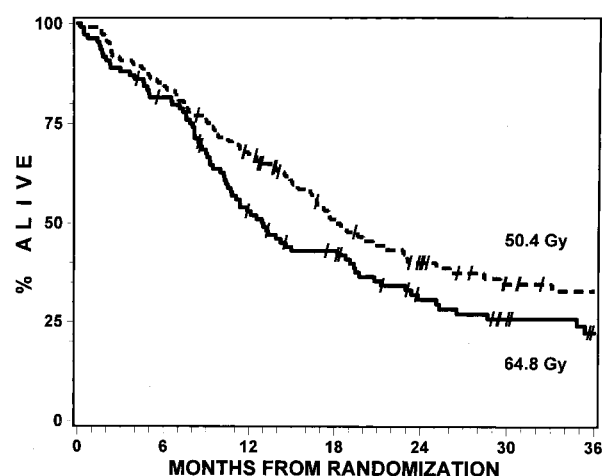


Fig 2. Overall survival according to the assigned treatment. No significant difference was observed between the two treatments.

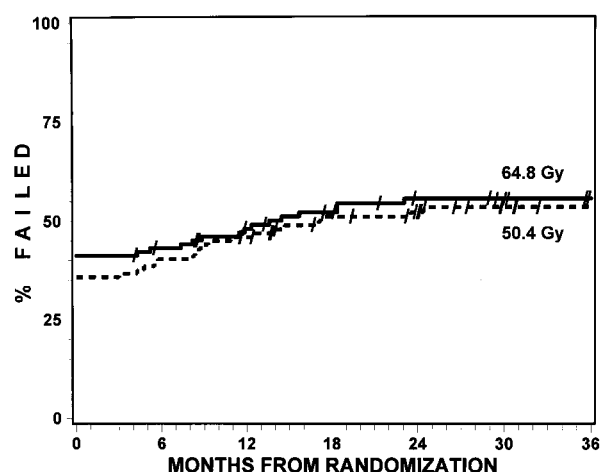


Fig 4. Time to first failure (local or regional failure and persistence) for all patients. No significant difference was observed between the two treatments.

### Patterns of Failure

The crude patterns of first failure are seen in Table 5. Although the incidence of local/regional failure and persistence of local/regional disease (50% v 55%) and distant failure (9% v 16%) was lower in the high-dose versus the standard-dose arm, this did not reach statistical significance.

The time to local or regional failure and persistence of disease is seen in Fig 4. At 2 years, the cumulative incidence of local failure was 56% for the high-dose arm versus 52% for the standard-dose arm ( $P = .71$ ).

### DISCUSSION

Because the initial report of RTOG 85-01 demonstrated an advantage in local or regional tumor control and survival

with combined-modality therapy (5-FU, cisplatin  $\times$  4 plus concurrent 50 Gy) versus radiation therapy alone (64 Gy), the standard dose of radiation has been 50 Gy. Our trial demonstrated that for patients who receive concurrent chemotherapy with radiation, higher doses of radiation therapy do not offer a local/regional control or survival advantage.

The reason for the lack of benefit in the high-dose arm is unclear. When comparing the high-dose versus low-dose arms, there was a significant prolongation of treatment time because of toxicity breaks when correcting for the number of radiation treatments as well as a significantly lower actual dose of 5-FU as a percentage of protocol dose. These factors may have contributed, in part, to the lack of benefit for patients who received high-dose versus standard-dose treatment.

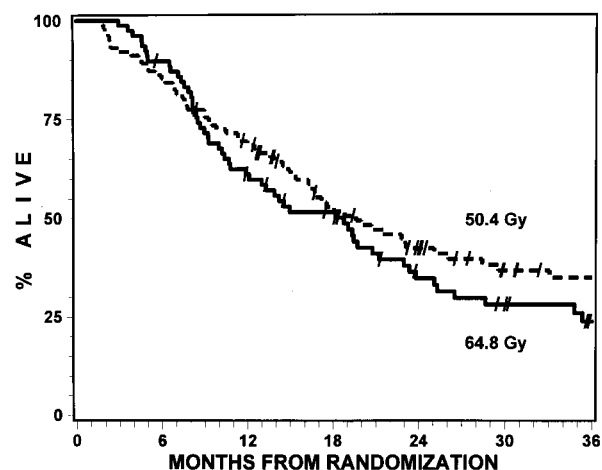


Fig 3. Survival for patients receiving the assigned dose of radiation. No significant difference was observed between the two treatments.

Table 5. Patterns of Failure

|  | High Dose<br>(64.8 Gy)<br>(n = 109) |    | Standard Dose<br>(50.4 Gy)<br>(n = 109) |    |
|--|-------------------------------------|----|---|----|
|  | No.                                 | %  | No.                                     | %  |
| Alive/no failure                         | 21                                  | 19 | 27                                      | 25 |
| Any failure                              | 88                                  | 81 | 82                                      | 75 |
| Persistent local disease                 | 36                                  | 33 | 37                                      | 34 |
| Local failure                            | 10                                  | 9  | 13                                      | 12 |
| Regional failure                         | 8                                   | 7  | 8                                       | 7  |
| Distant failure                          | 10                                  | 9  | 17                                      | 16 |
| Regional and distant failure             | 0                                   |    | 2                                       | 2  |
| Total local/regional persistence/failure | 54                                  | 50 | 60                                      | 55 |
| Treatment-related death                  | 11                                  | 10 | 2                                       | 2  |
| Second primary cancer                    | 4                                   | 4  | 1                                       | 1  |
| Cancer death/or not specified            | 3                                   | 3  | 0                                       |    |
| Dead of intercurrent disease             | 6                                   | 6  | 2                                       | 2  |

The standard radiation dose arm in our trial was similar to the combined-modality therapy arm of RTOG 85-01 with minor modifications. These modifications were made with the goal of potentially improving the tolerance of treatment. They included using 1.8-Gy rather than 2.0-Gy fractions, treatment of the primary tumor with 5-cm proximal and distal margins as opposed to 30 Gy to the whole esophagus followed by a cone down of 20 Gy to the primary tumor with 5-cm proximal and distal margins. In addition, all chemotherapy was delivered as 4-week cycles (weeks 1, 5, 9, and 11) rather than two 4-week cycles and two 3-week cycles (weeks 1, 5, 8, and 11).

There was concern that these modifications would have an adverse impact on the effectiveness of our treatment regimens. Although the incidence of local/regional failure and persistence of disease in the standard-dose arm of our trial was higher compared with the combined-modality therapy arm of RTOG 85-01 (55% *v* 46%), rates of median survival (18.1 *v* 14.1 months), 2-year survival (40% *v* 36%), grade 4 toxicity (26% *v* 20%), and treatment-related mortality (2%) were similar.

The actual doses of chemotherapy delivered as a percentage of the protocol dose in the high-dose arm were 65% for 5-FU and 75% for cisplatin, and in the standard-dose arm, the doses were 75% for 5-FU and 74% for cisplatin. However, because only 61% of patients in the high-dose arm and 59% in the standard-dose arm had complete information available for review at the time of the analysis, an accurate comparison with the combined-modality therapy arm of RTOG 85-01 was not possible.

The reason for the increased incidence of treatment related mortality in the high-dose arm compared with the standard-dose arm (10% *v* 2%) is unclear. The pretreatment characteristics were well balanced. Furthermore, because seven of the 11 treatment-related deaths in the high-dose arm occurred in patients who received 50.4 Gy or less, it is unlikely that the higher dose of radiation was responsible for the increased mortality. To help determine if this unexplained increase was the factor responsible for the inferior survival rate, a separate survival analysis was performed that included only patients who received the assigned dose of radiation (Fig 3). Despite this biased analysis, there was still no survival advantage with the high-dose arm.

With these results now known, the ideal timing for the randomization in this study may have been after the patients had reached the standard dose of 50.4 Gy rather than pretreatment. Patients could then have been assigned to receive an additional 14.4 Gy or no additional radiation. As the study was being designed, the consensus

among the study chairs was that accrual might be hampered with such a randomization. Therefore, it was decided to randomize patients before the start of treatment under the assumption that randomization would, on average, balance out the number of treatment-related deaths that might occur during the delivery of the initial 50.4 Gy. Unfortunately, this was not the case, because a substantially greater proportion of deaths occurred in the high-dose arm. This somewhat complicated the analysis and the interpretation of the trial results. However, a benefit for the higher dose could not be identified even after accounting for this imbalance.

Two prior RTOG phase II trials examined the role of increasing the radiation dose in patients selected for a nonsurgical approach. The intergroup INT 0122 (RTOG 90-12) trial enrolled 45 patients with squamous cell carcinoma who were treated with three cycles of neoadjuvant 5-FU and cisplatin followed by concurrent 5-FU, cisplatin, and 64.8 Gy.<sup>4,5</sup> The local/regional failure rate was 39%, median survival was 20 months, and 3-year survival was 30%. The overall treatment-related mortality rate was 9%; however, 5% were the sole result of the neoadjuvant component of the treatment. The RTOG 92-07 trial used a brachytherapy boost after treatment with 5-FU, cisplatin, and 50-Gy external-beam radiation therapy in 49 eligible patients with squamous cell or adenocarcinoma.<sup>13</sup> The local/regional failure rate was 63% (37% local/regional failure plus 26% local/regional persistence), the median and 2-year survival rates were 11 months and 31%, respectively, and the treatment-related mortality rate was 10%. The crude fistula rate was 12%, and the cumulative incidence was 17.5% by the end of the first year of follow-up. Therefore, neither INT 0122 nor RTOG 92-07 demonstrated improved local/regional control rates or a survival advantage with increased radiation dose level compared with RTOG 85-01. Our randomized trial confirms that dose intensification of the radiation dose above 50.4 Gy does not improve local/regional control or survival. New regimens using alternative chemotherapeutic regimens with both systemic and radiosensitization properties, such as taxanes and irinotecan, when combined with 50.4 Gy, are being actively investigated.<sup>14-16</sup>

In conclusion, our data confirm the efficacy of combined-modality therapy reported in the RTOG 85-01 trial. Intensification of the radiation dose to 64.8 Gy did not improve local/regional control or survival, and it is not recommended. For patients with esophageal cancer treated with 5-FU/cisplatin-based combined-modality therapy, the standard radiation dose is 50.4 Gy.

## REFERENCES

1. Herskovic A, Martz LK, Al-Sarraf M, et al: Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 326:1593-1598, 1992
2. Al-Sarraf M, Pajak T, Herskovic A, et al: Progress report of combined chemo-radiotherapy (CT-RT) vs radiotherapy (RT) alone in patients with esophageal cancer: An intergroup study. *Proc Am Soc Clin Oncol* 12:197, 1993 (abstr)
3. Cooper JS, Guo MD, Herskovic A, et al: Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA* 281:1623-1627, 1999
4. Minsky BD, Neuberg D, Kelsen DP, et al: Final report of intergroup trial 0122 (ECOG PE-289, RTOG 90-12): Phase II trial of neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 43:517-523, 1999
5. Minsky BD, Neuberg D, Kelsen D, et al: Neoadjuvant chemotherapy plus concurrent chemotherapy and high dose radiation for squamous cell carcinoma of the esophagus: A preliminary analysis of the phase II intergroup trial 0122. *J Clin Oncol* 14:149-155, 1996
6. Minsky BD, Berkey B, Kelsen D, et al: Preliminary results of Intergroup INT 0123 randomized trial of combined modality therapy (CMT) for esophageal cancer: Standard vs high dose radiation therapy. *Proc Am Soc Clin Oncol* 19:239a, 2000 (abstr 927)
7. American Joint Committee on Cancer: Esophagus, in Beahrs OH, Henson DE, Hutter RVP, et al (eds): *Handbook for Staging of Cancer* (ed 4). Philadelphia, PA, Lippincott, 1993, pp 75-79
8. Kaplan EL, Meier P: Nonparametric estimation for incomplete observation. *J Am Stat Assoc* 53:457-481, 1958
9. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chem Rep* 5:163-170, 1966
10. Cox DR: Regression models and life tables. *J R Stat Soc* 34:187-229, 1972
11. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 16:1141-1145, 1988
12. Zelen M: The randomization and stratification of patients to clinical trials. *J Chronic Dis* 27:365-375, 1974
13. Gaspar LE, Winter K, Kocha WI, et al: A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207). *Cancer* 88:988-995, 2000
14. Enzinger P, Ilson D, Minsky B, et al: Phase I/II neoadjuvant concurrent 96 hour Taxol, cisplatin, and radiation therapy: Promising toxicity profile and response in localized esophageal cancer. *Proc Am Soc Clin Oncol* 18:271a, 1999 (abstr 1038)
15. Safran H, Gaissert H, Akerman P, et al: Paclitaxel, cisplatin, and concurrent radiation for esophageal cancer. *Cancer Invest* 19:1-7, 2001
16. Anderson S, Ilson D, Bains M, et al: Phase I trial of cisplatin and escalating dose irinotecan given weekly with concurrent radiation in locally advanced esophageal cancer. *Proc Am Soc Clin Oncol* 20:158a, 2001 (abstr 629)