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Phase III Trial of Trimodality Therapy With Cisplatin, Fluorouracil, Radiotherapy, and Surgery Compared With Surgery Alone for Esophageal Cancer: CALGB 9781

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Abstract

Purpose—The primary treatment modality for patients with carcinoma of the esophagus or gastroesophageal junction has been surgery, although primary radiation therapy with concurrent chemotherapy produces similar results. As both have curative potential, there has been great interest in the use of trimodality therapy. To this end, we compared survival, response, and patterns of failure of trimodality therapy to esophagectomy alone in patients with nonmetastatic esophageal cancer.

Patients and Methods—Four hundred seventy-five eligible patients were planned for enrollment. Patients were randomly assigned to either esophagectomy with node dissection alone or cisplatin 100 mg/m^2 and fluorouracil 1,000 mg/m^2/d for 4 days on weeks 1 and 5 concurrent with radiation therapy (50.4 Gy total: 1.8 Gy/fraction over 5.6 weeks) followed by esophagectomy with node dissection.

Results—Fifty-six patients were enrolled between October 1997 and March 2000, when the trial was closed due to poor accrual. Thirty patients were randomly assigned to trimodality therapy and 26 were assigned to surgery alone. Patient and tumor characteristics were similar between groups. Treatment was generally well tolerated. Median follow-up was 6 years. An intent-to-treat analysis showed a median survival of 4.48 *v* 1.79 years in favor of trimodality therapy (exact stratified log-rank, *P* = .002). Five-year survival was 39% (95% CI, 21% to 57%) *v* 16% (95% CI, 5% to 33%) in favor of trimodality therapy.

Conclusion—The results from this trial reflect a long-term survival advantage with the use of chemoradiotherapy followed by surgery in the treatment of esophageal cancer, and support trimodality therapy as a standard of care for patients with this disease.

INTRODUCTION

Surgery has been the mainstay of treatment for patients with esophageal cancer. Radiation therapy with concurrent chemotherapy without resection results in survival outcomes that are similar to surgery, although local recurrence rates are approximately 50%. Five-year survival rates remain approximately 20% with either strategy. Adjuvant chemotherapy has not been proven to be beneficial in this disease, although there may be a differential response between adenocarcinoma and squamous cell cancers. The use of both neoadjuvant and adjuvant chemotherapy, at times coupled with radiation, have shown benefit in selected individual trials in patients with gastric and gastroesophageal junction cancers.[1,2]

There has been substantial interest in whether the use of all three modalities would be superior to surgery alone. A number of single-institution trials have been performed.[3–5] The most commonly used agents have been fluorouracil (FU) and cisplatin. Drugs such as taxanes and oxaliplatin have not demonstrated superiority to FU and cisplatin. Thus, the GI Intergroup, led by the Cancer and Leukemia Group B (CALGB), initiated a trial testing surgery alone versus trimodality therapy with radiation therapy, FU, and cisplatin in patients with nonmetastatic esophageal squamous or adenocarcinomas.

PATIENTS AND METHODS

Eligibility

Patients with histologically documented untreated squamous cell carcinoma or adenocarcinoma of the thoracic esophagus (below 20 cm) or gastroesophageal junction and with less than 2 cm distal spread into the gastric cardia were eligible. There could be no evidence of distant metastatic disease by history and physical examination; upper endoscopy with biopsy, computed tomography (CT) of the chest and upper abdomen, and pulmonary function studies were all required. Bone scan was required for alkaline phosphatase more than 3× the institutional normal value. Bronchoscopy was required if the primary tumor was adjacent to the trachea or left main stem bronchus. Patients were required to have granulocyte counts 1,800/mL, platelet count 100,000/mL, and a creatinine clearance 50 mL/min. Esophageal ultrasound (EUS) and preresection staging by thoracoscopy (ts) and laparoscopy/minilaparotomy (ls), including biopsy of celiac axis and lesser curvature, were recommended.

Tumors had to be considered surgically resectable (T1-3, NX), including regional thoracic lymph node (N1) metastases. Patients with supraclavicular lymph nodes measuring 1.5 cm by CT (not palpable) were eligible, as were patients with lymph node metastases to levels 15 to 20 (predominantly celiac axis and paracardial nodes) 1.5 cm by CT. Patients could not have previously received chemotherapy or radiation therapy for this tumor or any radiation therapy that would overlap the radiation fields required for this malignancy. Patients with previous malignancies were eligible if more than 5 years had elapsed from diagnosis without evidence of tumor recurrence.

There could be no other serious illness that would limit survival to less than 2 years, or psychiatric condition that would prevent compliance with treatment or informed consent. Patients with uncontrolled or severe cardiovascular disease, pulmonary disease, or active infections were excluded, as were pregnant patients. The protocol was approved by institutional review boards at all study sites, and informed consent was required for all patients.

Treatment Plan

Patients were randomly assigned to treatment with preoperative chemoradiotherapy followed by surgery or surgery alone. Random assignment was stratified by thoracic nodal status as determined by CT (N0; N+), prestudy staging (invasive or noninvasive), and cancer type (squamous or adenocarcinoma). Trimodality therapy began within 21 days of random assignment. Chemotherapy and radiotherapy were to begin within 24 hours of each other.

Radiotherapy (1.8 Gy/5 d/wk) was begun within 24 hours of the administration of chemotherapy, and continued for 5.5 weeks (50.4 Gy). The final 5.4 Gy treatment was given as a boost. Radiation fields extended 5 cm beyond the proximal and distal extent of tumor, and the lateral borders extended 2 cm beyond the apparent mass. Supraclavicular lymph nodes were included if the tumor extended 2 cm above the carina. If the primary tumor was in the distal third of the esophagus or if the celiac nodes were radiographically enlarged (but < 1.5 cm), the radiation fields were enlarged to include this target. The cone-down fields included the primary tumor with a 2-cm margin. Dosage was prescribed at the isocenter.

Cisplatin 100 mg/m^2 bolus intravenous infusion was given during 30 minutes on days 1 and 29 with standard prehydration and antiemetic therapy. FU 1,000 mg/m^2/day was administered as a continuous intravenous infusion for 96 hours after completion of the cisplatin on days 1 through 4 and 29 through 32.

Within 4 weeks after radiation therapy, patients were restaged with a chest and abdomen CT and repeat esophagogastroduodenoscopy. Patients with progressive or unresectable disease were removed from protocol therapy and observed for survival.

Surgery was optimally performed 3 to 8 weeks after completion of chemoradiotherapy, and within 6 weeks of randomization for patients randomly assigned to surgery alone. Resection via left chest or right chest and abdomen (Ivor-Lewis) was recommended for midesophageal- and gastroesophageal-junction cancers. Transhiatal esophagectomy was discouraged. All technically accessible lymph nodes were to be removed. The mediastinal or

deep surgical margin was marked by the surgeon and pathologist. A microscopic lateral or deep margin of less than 1 mm was considered a positive margin, and proximal and distal margins of at least 2 cm beyond gross tumor was desired.

Definition of Response

A complete pathologic response was defined as no gross or microscopic tumor in the surgical specimen using light microscopy, but not immunohistochemical stains (primary and nodes). A partial pathologic response was defined as shrinkage in tumor size compared with the original esophagogastroduodenoscopy. This was subclassified as macroscopic (evident at time of surgery) or microscopic (evident only at pathology review) residual disease. An increase in 25% of the product of perpendicular diameters at the indicator lesion, or the appearance of new lesions, was defined as progressive disease. Stable disease was defined as not qualifying as a partial or complete pathologic response or progressive disease.

Resections were defined as curative (R0) when all gross disease was removed with negative margins. Incomplete resection (R1) was defined as residual gross disease or positive surgical margins (tumor 1 mm from any margin).

Statistical Methods

The primary objective of this study was to determine whether trimodality therapy improves overall survival (OS) when compared to surgery alone. Secondary end points included response, local and distant control rates, and progression-free survival (PFS).

A target sample of 475 eligible patients was to be randomly assigned with equal probability to each treatment arm. The targeted sample size was inflated to 500 patients to account for ineligibility. Patients were grouped as previously described.

With 475 eligible patients enrolled onto the study for more than 5 years and observed for an additional 3 years, 90% power is achieved to detect a survival hazard ratio of 1.4 (two-sided $a = .05$) corresponding under exponential survival to a difference between 20% and 32% in 5-year OS. Formal interim analyses of OS were planned when 50%, 75%, and 100% of the expected number of events (n = 371) were observed.[6] Surgical mortality was to be monitored when 100, 200, 300, and 400 patients had been enrolled. Accrual would be curtailed if the mortality rate was 20% or greater on the trimodality treatment arm.

The exact χ^2 test was used to compare patient characteristics between treatment arms for categoric variables and the Van der Waerden (normal) score test was used to compare patient characteristics measured as continuous variables. OS was calculated as the time from study entry to death or date last known alive (censored). PFS was calculated from date of study entry to documented tumor progression or recurrence, death, or date last known to be progression free (censored). These time-to-event distributions were estimated using the method of Kaplan-Meier,[7] and compared using two-sided exact stratified log-rank tests.[8] Equality of the censoring distributions between treatment arms was assumed. The analyses were performed using an intent-to-treat approach, including all patients as randomly assigned regardless of eligibility or treatment. The Cox proportional hazards model[9] was used to estimate the 95% CI for the OS and PFS hazard ratios, controlling for the

stratification factors. Median follow-up was estimated among surviving patients. The recurrence site was defined as local (gastric or esophageal bed, or regional lymph nodes) or distant (supraclavicular lymph node, liver, peritoneal carcinomatosis, lung, or brain).

Patient registration, random assignment, and data collection were managed by the CALGB Statistical Center and monitored by the CALGB data safety monitoring board. In particular, central randomization was conducted by telephone via the CALGB Statistical Center Registrar, who independently confirmed eligibility but was not involved in any other aspect of the trial's conduct. Toxicity was graded according to the CALGB Expanded Common Toxicity Criteria. Analyses were based on the study database frozen on January 18, 2006, and were performed using SAS (Statistical Analysis System, Cary, NC) software. Analyses of OS and PFS were also conducted using StatXact, version 8 (Cytel Software Corp Inc, Cambridge, MA). A P value less than .05 was considered significant (Fig 1).

RESULTS

Patient and Tumor Characteristics

A total of 56 patients were enrolled onto the study between October 1997 and March 2000. Despite efforts to boost enrollment, the accrual rate to the trial remained low and the trial was closed. Thirty patients were randomly assigned to trimodality therapy and 26 were randomly assigned to surgery alone. Forty-three percent of patients were enrolled by 16 CALGB Institutions, 34% by the North Central Cancer Treatment Group, and 21% by Radiation Therapy Oncology Group.

Patient and tumor characteristics were similar between groups (Tables 1 and 2). Fifty-two patients (93%) met study eligibility criteria. Four patients failed to meet eligibility criteria, one due to T4 disease, the second due to gastric spread, the third because of two primaries, and the fourth due to lack of prestudy pulmonary function studies. Ineligible patients were included in all analyses per intent-to-treat.

Staging

Fourteen of 26 patients assigned to surgery alone were staged by EUS, and six of 26 were staged by ts/ls. Fifteen of 30 patients assigned to trimodality therapy were staged by EUS, and eight of 30 were staged by ts/ls. Patients were evaluated for stage using all staging tests available for each patient.

Toxicity

Data on grade 3 or greater toxicity were reported on 28 patients treated with preoperative therapy, and on 18 patients treated with surgery alone. Fifty-seven percent of patients receiving preoperative therapy experienced at least one occurrence of hematologic toxicity of grade 3 or greater. Nonhematologic toxicity included esophagitis/dysphagia (42%), infection (34%), and pain (24%). There was one treatment-related death due to infection (4%). Table 3 lists all grade 3 or greater toxicities reported as adverse events in at least 10% of patients treated with trimodality therapy.

Surgery

Data on surgical procedures were available for 52 patients, 26 of 30 of whom were receiving trimodality therapy and all 26 patients on the surgery-alone arm. No surgical data are available for four patients on the trimodality arm; one died from treatment-related infection before surgery, and three patients refused surgery. Of the 52 patients for whom data on surgical procedure were available, seven underwent exploration surgery only, one underwent left thoracotomy or thoracoabdominal surgery, 30 underwent Ivor-Lewis surgery, eight underwent celiotomy/right thoracotomy/cervical surgery, and six underwent transhiatal surgery. Of the seven patients who underwent exploratory surgery only, four were randomly assigned to trimodality therapy and three were assigned to surgery alone. Of the four patients assigned to trimodality therapy, two patients had metastases. No reason was provided for the exploratory-only surgery for the other two patients. Of the three patients randomly assigned to surgery alone, two had metastases and one had T4 disease.

Surgical complications were reported for 48 of the 52 patients reporting a surgical procedure (24 in each treatment arm). These complications were reported as related to surgery (Table 4), and were not reported as adverse events in Table 3. Median postoperative hospital stay was 11.5 days (range, 3 to 56 days) and 10.0 days (range, 3 to 24 days) for the trimodality and surgery-alone arms, respectively. One patient on the surgery-alone arm died within 30 days of surgery from surgical complications.

Response

Pathologic response data were available for 25 patients treated with preoperative chemoradiotherapy. The best pathologic response to neoadjuvant treatment was complete response (10 patients), partial response (microscopic; two patients), partial response (macroscopic; eight patients), stable disease (two patients), and progression (two patients). One patient was not assessable. Three of the six patients with N1 disease pretreatment were downstaged to N0 with preoperative therapy.

Survival

Median follow-up was 6 years (5.8 years after surgery alone and 6.1 years after trimodality therapy) with 57.5 and 109.9 person-years followed for the surgery alone and trimodality treatment arms, respectively. Median OS was 4.48 (95% CI, 2.4 years to not estimable) v 1.79 years (95% CI, 1.41 to 2.59 years) in favor of trimodality therapy (Fig 2). The 95% CI estimate of the OS hazard ratio is 1.46 to 5.69. Five-year OS was 39% (95% CI, 21% to 57%) v 16% (95% CI, 5% to 33%) for trimodality therapy versus surgery alone.

Median PFS was 3.47 years (95% CI, 1.31 to 4.76 years) among patients treated with preoperative chemoradiotherapy versus 1.01 years (95% CI, 0.22 to 1.46 years) among patients treated with surgery alone (Fig 3). The 95% CI estimate of the PFS hazard ratio is 1.37 to 5.32. Five-year PFS was 28% (95% CI, 12% to 47%) and 15% (95% CI, 4% to 33%) for trimodality therapy versus surgery alone. No interim analyses were performed on these end points.

Sites of recurrence were reported for nine patients on the trimodality arm and 12 on the surgery alone arm. On the trimodality arm, three patients had both local and distant recurrences, five had distant recurrence only, and one had local recurrence only. On the surgery arm, one patient had both local and distant recurrence, nine had distant recurrence only, and three had local recurrence only.

Of the 20 patients for whom data on site of recurrence were not available, nine died without documented failure, nine came off treatment for reasons other than recurrence or death, and two had no reported site of failure.

DISCUSSION

For many years, the most commonly used therapy for esophageal cancer was surgical resection alone. Radiation Therapy Oncology Group trial 8501, which compared 6,400 cGy radiation therapy alone versus 5,000 cGy with concurrent FU and cisplatin, showed 5-year survival rates of 32% v 12% in favor of combined-modality therapy.[10,11] Although survival was adequate with radiochemotherapy, local control was poor, with local failure in almost 50% of patients.

There has been great interest in the use of adjuvant chemotherapy. The GI Intergroup trial 0113 did not demonstrate an advantage to pre- and postoperative chemotherapy with FU and cisplatin compared with surgery alone. In contrast, the Medical Research Council study, using the same drugs given preoperatively, demonstrated a 3.5-month improvement in median survival.[12]

Despite the fact that surgery is more commonly used, there has been limited information to suggest that either surgery or radiation/chemotherapy is a superior approach. Stahl et al[13] randomly assigned patients with squamous cell carcinomas to either induction chemotherapy followed by radiochemotherapy and surgery, or the same induction chemotherapy followed by high-dose radiochemotherapy without surgery. There was no statistical difference in survival, but local progression-free rates were superior in the surgery cohort. Given that both surgical and nonsurgical approaches are good therapies, this raises the question about whether combining both would be superior to either modality alone.

A number of studies have been run to test the efficacy of preoperative radiochemotherapy compared with surgery alone[14–18]; FU and cisplatin were the most common drugs employed. The results have been mixed, and have not resolved the issue of whether there is a survival advantage to trimodality therapy. A recent trial from Australia[18] did not demonstrate an advantage to trimodality therapy compared with surgery alone overall, although there was a benefit for the patients with squamous cell carcinoma.

There have been a number of meta-analyses of randomized trials of surgery versus surgery and radiochemotherapy,[19–22] and these have generally shown an advantage to trimodality therapy. The most recent meta-analysis, performed by Gebski et al,[23] includes 10 studies and demonstrates a hazard ratio for mortality of 0.81 in favor of trimodality therapy.

The present study was designed to gather more information on this topic, enrolling 475 eligible patients during 5 years. Despite repeated efforts, the study investigators were unable to overcome physician biases, patient preferences, and the consequent inability to randomly assign more patients. The poor accrual led to early closure, with only 56 patients enrolled.

The results indicate a benefit in OS and PFS with trimodality therapy. There was no suggestion that operative mortality was increased by the use of trimodality therapy, and the preoperative treatment was accomplished with manageable toxicity. Although not planned, this resulted in being a trial primarily of adenocarcinoma, with only one fourth of the patients having squamous cell carcinomas.

A major limitation of this trial is the small sample size. To address this issue, CIs on median OS and PFS by treatment arm and on the OS and PFS hazard ratios were provided, and an exact permutation test was used to compare the survival end points between treatment arms. Results based on the asymptotic distributions were corroborated by the results using the exact test. The validity of the exact test relies on the assumption of equal censoring distributions between arms. Despite the curtailed study period, this assumption should be reasonable given the prospective randomized design and planned patient treatment, and follow-up. Although the accrual period was curtailed, the projected length of the follow-up period was realized. Follow-up data on PFS and OS were obtained by direct contact with participating institutions. Loss to follow-up was low (5%), with only two patients receiving trimodality therapy (at 0.27 and 2.6 years, respectively), and one patient receiving surgery alone (at 1.15 years) observed less than 3 years.

We acknowledge that there exists a publication bias for a trial of this sort in that positive trials would be published and negative trials might be ignored. Regardless, the results of this study have value in that they arise from a well-designed, cooperative-group clinical trial, and provide further evidence regarding the efficacy of trimodality therapy in this setting.

Acknowledgments

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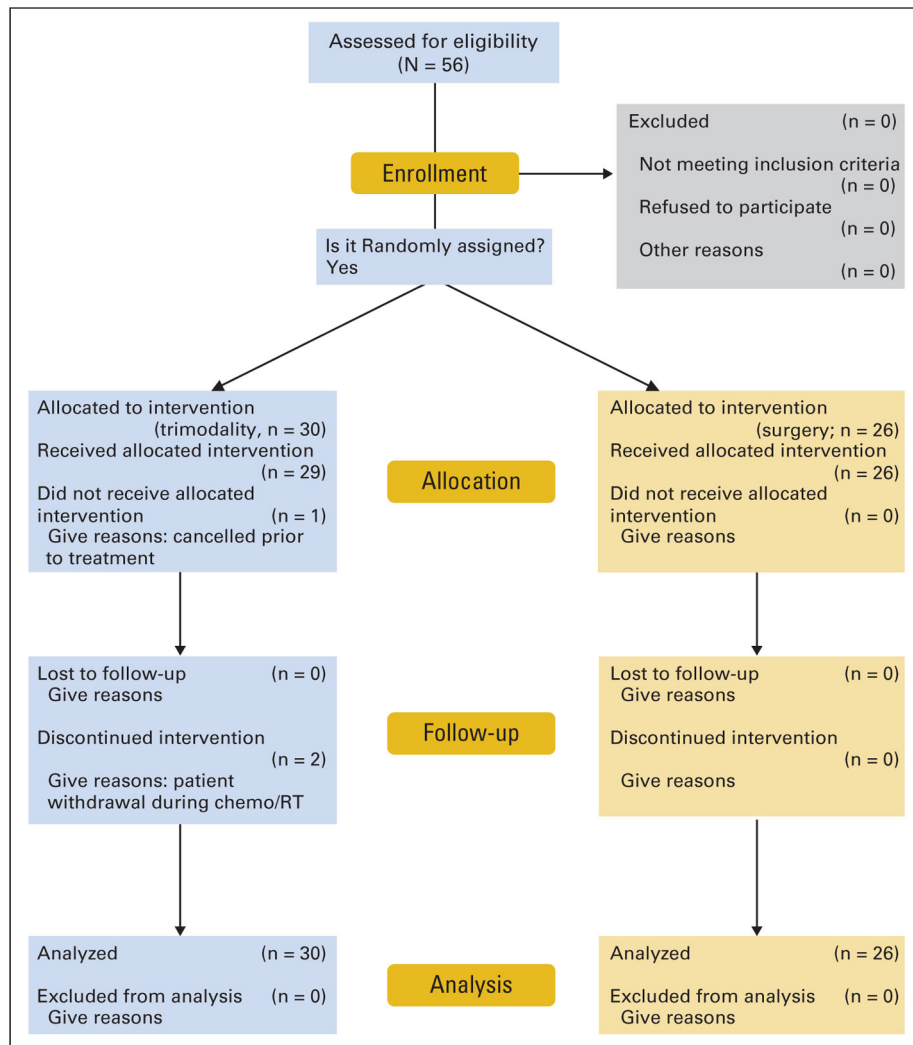
Fig 1.
CONSORT diagram.
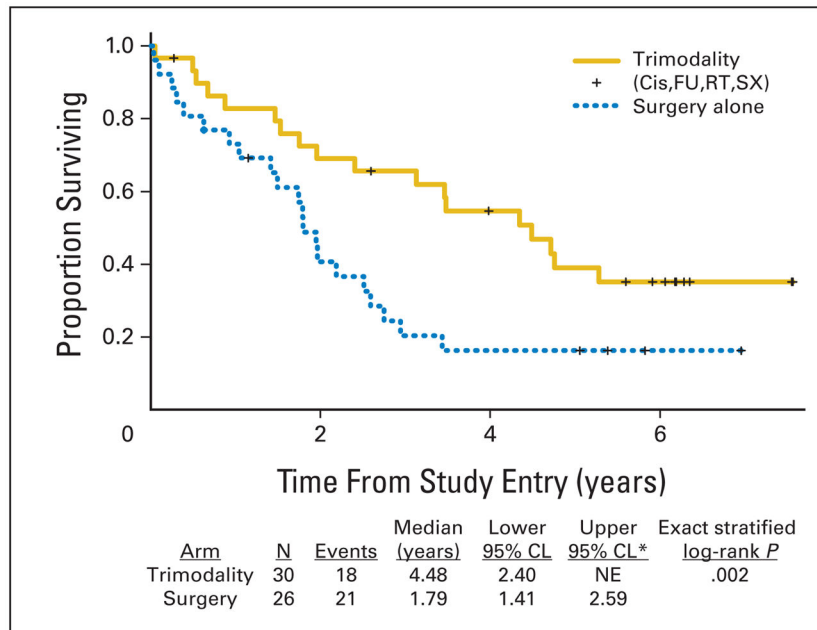
Fig 2.
Kaplan-Meier estimates of overall survival (OS) by treatment arm measured from study entry until death from any cause. (*) NE, not estimable. †Asymptotic results for OS were comparable to those obtained using the exact method.
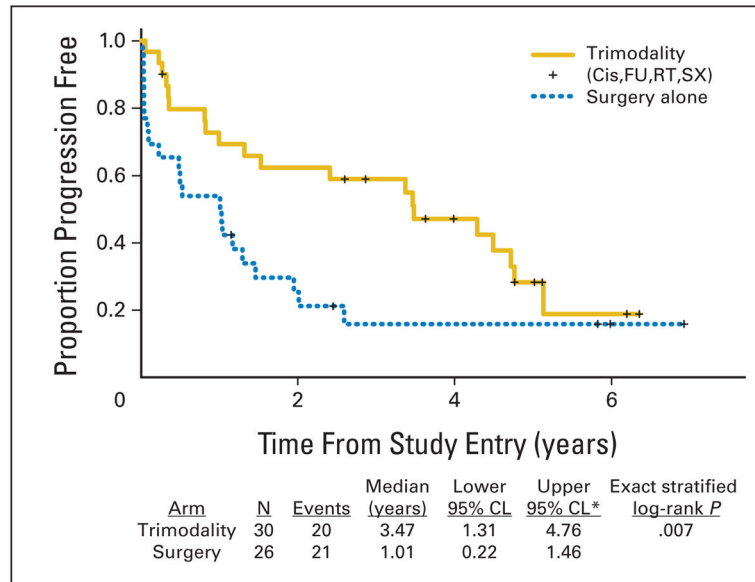
Fig 3.
Kaplan-Meier estimates of progression-free survival (PFS) by treatment arm measured from study entry until documented progression of disease or death from any cause. (*) NE, not estimable. †Asymptotic results for PFS were comparable to those obtained using the exact method.

Table 1

CALGB 9781: Patient Characteristics

Characteristic	Trimodality Therapy		Surgery Alone		Total		P*
	No.	%	No.	%	No.	%	
Sex							
Male	28	93	23	88	51	91	.65
Female	2	7	3	12	5	9	
Race/ethnicity							
White	25	83	23	88	48	86	.71
Other	5	17	3	12	8	14	
Performance status							
0	19	63	18	69	37	66	.32
1	8	27	8	31	16	29	
2	3	10	0	0	3	5	
Age, years							
Mean	60.9		61.9		61.4		.69
Median	59.9		62.2		60.7		
Range	38–77		44–76		38–77		
Tumor type							
Adenocarcinoma	23	77	19	73	42	75	1.0
Squamous	7	23	7	27	14	25	
Clinical N stage							
N0	20	67	22	85	42	75	.22
N+	10	33	4	15	14	25	
Staging method							
Noninvasive	16	53	15	58	31	55	.79
Invasive	14	44	11	42	25	45	

The header "Treatment Arm" spans the Trimodality Therapy, Surgery Alone, and Total columns.

	Treatment Arm						
	Trimodality Therapy		**Surgery Alone**		**Total**		
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	***P*** *
Albumin							
Mean	3.8		3.9		3.9		.50
Median	3.9		4.0		3.9		
Range	1.0–4.6		2.5–4.5		1.0–4.6		

Abbreviation: CALGB, Cancer and Leukemia Group B.

*
P values are associated with the exact χ^2 test for categorical variables and the Van der Waerden (normal) scores for continuous variables.

Table 2

No. of Patients Per Treatment Arm by T and N Stage

Stage		No. of Patients	
T	N	Trimodality Therapy	Surgery Alone
2	0	2	1
2	1	1	1
3	0	17	20
3	1	9	3
4	0	1	0
Unknown	0	0	1
Total		30	26

Table 3

Toxicity by Grade (3, 4, 5) for Toxicities Reported in at Least 10% of Patients on the Trimodality Treatment Arm

Toxicity	Grade 3		Grade 4		Grade 5		Total No. Reporting
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
WBC	7	25	3	11	0		28
Platelets	2	7	1	4	0		27
Hemoglobin	3	11	1	4	0		28
Granulocytes/bands	4	15	3	12	0		26
Lymphocytes	2	8	10	38	0		26
Infection	7	30	0	0	1	4	23
Nausea	3	11	0	0	0		27
Esophagitis/dysphagia	7	27	4	15	0		26
Other GI	3	14	1	5	0		21
Dysrhythmias	2	8	0	0	0		24
Pain	4	16	2	8	0		25
Weight loss	3	11	0	0	0		27

Table 4

Reported Surgical Complications (No. of occurrences) by Treatment Arm for Patients Undergoing Surgical Procedures (n = 48)

Surgical Complication	Trimodal Therapy (n = 24)	Surgery (n = 24)
Red blood count transfusion	9	4
Postoperative fever	6	8
Wound infection	3	3
Empyema	2	2
Bronchial fistula	0	1
Air leak	1	1
Atelectasis	0	2
Pneumonia with antibiotics	5	3
Respiratory failure	2	4
Splenectomy	1	0
Anastomotic strict/leak	2	0
Nerve injury	0	1
Reflux	0	1
Diarrhea	1	4
Ileus	0	1
Weight loss	5	6
Dysphagia	2	1
Tacheo-esophageal fistula	2	0
Dysrhythmia	1	2
Myocardial infarction	0	1
Deep vein thrombosis	1	0
Pulmonary embolism	1	0
Other	5	4
Postoperative death	0	1
Total postoperative, days		
Median	11.5	10.0

Surgical Complication	Trimodal Therapy (n = 24)	Surgery (n = 24)
Range	3–56	3–24