

Outcomes with Esophageal Cancer Radiation Therapy

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Purpose: Esophageal cancer is the seventh leading cause of cancer death worldwide and is responsible for 4% of the cancer deaths in the United States annually. Changing epidemiologic patterns and expanded treatment options have brought this often deadly cancer to the forefront.

Methods and Materials: To characterize epidemiological changes, the effect of treatment advances, and patient outcomes over time, we retrospectively reviewed 756 consecutive esophageal cancer cases treated between 1985 to 2003 at The University of Texas M. D. Anderson Cancer Center in Houston. For purposes of evaluation, cases were divided into four cohorts of approximately 5 years each. Men make up 75% or more of the patients with esophageal cancer, most patients have adenocarcinoma in the gastroesophageal junction, and almost 75% have stage II or III disease.

Results: Three-year overall survival improved from 16.7% (1985–1989) to 35.2% (2000–2003). By multivariate Cox regression analysis, significant reductions in relative risk were associated with having good performance status (relative risk [RR] = 0.68 [95% confidence interval (CI) = 0.56–0.83]; $p < 0.001$), being treated in the most recent interval (2000–2003) than in the first (1985–1989) (RR = 0.63 [95% CI = 0.44–0.88]; $p = 0.007$), with improved therapies, including induction chemotherapy plus concurrent chemoradiotherapy (RR = 0.68 [CI = 0.56–0.84]; $p < 0.001$), explaining the reductions.

Conclusion: Although fully delineated comparisons must await incorporation and study of data through 2007, this analysis suggests that multimodality management that has been adapted in recent years may be associated with the improvements in out-

comes of these cases of largely stage II and III esophageal adenocarcinoma found at the gastroesophageal junction.

Key Words: Esophageal neoplasms, Radiotherapy, Radiation therapy, Treatment outcome, Outcome assessment (health care).

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One of the world's deadliest cancers, esophageal cancer has been demanding more attention in the last three decades because of changing epidemiologic patterns and expanded treatment options.^{1–4} Worldwide, esophageal cancer is the seventh leading cause of cancer death, and its 5-year relative survival rate in the United States is 14.9%.^{1,5} It represents the seventh most deadly cancer in U.S. men, responsible for 4% of all cancer deaths annually.¹ In men, incidence is highest in China (21.6/100,000), some African nations (19.2–12.5/100,000), and Kazakhstan (19.1/100,000). In the United States, incidence is 2.1/100,000 in men and 1.2/100,000 in women and increasing, and in 2008, 16,470 new cases are anticipated along with 14,280 deaths.^{1,4,6}

Pathogenesis of esophageal cancer remains largely undefined, but an increase in the incidence of adenocarcinoma and a shift to a predominately lower esophageal gastroesophageal junction location have caused associations to be drawn to gastroesophageal reflux and Barrett esophagus, conditions recognized as risk factors along with achalasia, tobacco and/or alcohol use, caustic injury, a history of cancer and cancer treatment.³

Advancements in imaging technology such as 2-fluoro-2-deoxy-D-glucose-positron emission tomography (PET) scanning and endoscopic sonography allow more accurate staging and have led to better selection of patients for different treatment modalities. New chemotherapy drugs and new combinations may have had a significant impact on controlling distant metastasis. Also advancing control are radiation technique improvements, specifically three-dimensional conformal radiotherapy techniques, which allow better strategic targeting of tumor volume and improved sparing of normal tissue and thus an increased therapeutic ratio.⁷

In this report, we review our experience at The University of Texas M. D. Anderson Cancer Center, from 1985 to December 2003, where we included 765 consecutive patients with primary esophageal cancer who received radiotherapy as the sole treatment or as a compo-

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ment of multimodal therapy. The purpose of this study was to characterize changes in the epidemiology of esophageal cancer, identify changes in the diagnostic process and in treatment, and analyze the impact of these changes on long-term outcome using multivariate statistical analysis for these patients.

METHODS

Patient Population

We retrospectively reviewed records of 843 consecutive patients with primary esophageal cancer who underwent radiation therapy at The University of Texas M. D. Anderson Cancer Center between January 1985 and December 2003. Seven hundred fifty-six patients who received radiation therapy with definitive intent either as the sole treatment or as a component of multimodality therapy were included in this analysis. Patients with metastatic disease and those treated with palliative intent (radiation dose <30 Gy) have been excluded. Patients were grouped by 5-year intervals chosen because of major shifts in the standard of radiotherapy care for esophageal cancer. January 1985, when computed tomography (CT) became the routine diagnostic evaluation was chosen as the beginning of the first interval so stage migration could be minimized. Assignment to interval was made by date of diagnosis. This retrospective chart review study was approved by the institutional review board and informed consent was waived. The study was compliant with the HIPPA regulations.

Staging and Modality

Patients were staged using technology available at the time and physician preference. Cancer stage was retrospectively classified according to the American Joint Committee on Cancer 1997 staging manual.⁸ Endoscopy was not routinely performed until 2000 when endoscopic ultrasonography became commonplace. When 2-fluoro-2-deoxy-D-glucose-PET became available around 2000, it was performed at the treating physician's determination.

Radiation Treatment

Treatment options have traditionally been based on disease histology, tumor site, and stage of disease. Since 1985, more and more patients have been undergoing chemotherapy simultaneously with radiotherapy, and use of radiation as a method of down-staging disease before surgery has expanded.

Until 1999 all patients were treated with two-dimensional radiation therapy; using high-energy photons with cobalt-60 to 18-MV photons with accelerated (3 Gy per fraction once a day to 30 Gy) or conventional (1.8–2.0 Gy per fraction once a day to at least 45 Gy) fractionation. We used same doses of radiation for definitive and neoadjuvant treatments. The initial target volume encompassed the primary tumor with a minimal 5-cm margin in the cephalad and caudal directions and a 2-cm margin radially. If conventional fractionation was used, the subclinical disease was treated to at least 45 Gy before the field size was

reduced. Radiation dose was determined by the treating physician according to the accepted practice at the time of treatment. Individual and total doses were not corrected for inhomogeneity of the irradiated tissue. The dose prescriptions point before 1999 was usually to isocenter.

Beginning in 1999, three-dimensional conformal radiation became the standard of care, and radiation dose came to be prescribed to the isodose volume that covered the target of interest. Starting in 2001, patients also underwent intensity-modulated radiation. All patients treated in 1999 and subsequently have had a three-dimensional treatment plan before initiation of radiation therapy. All patients underwent CT simulation. Patients were immobilized with a customized vacuum-locked cradle. The gross tumor volume was defined as any visible tumor on the image, clinical target volume was defined as the gross tumor volume plus a 2- to 5-cm margin superior to the highest extension of the tumor and a 4- to 5-cm margin inferior to the lowest extension with a 2-cm radial margin, planning target volume was defined as the clinical target volume plus a 5-mm margin. Individual and total doses were corrected for the heterogeneity of irradiated tissue when three-dimensional or intensity-modulated radiation technique was used.

Chemotherapy

Chemotherapy included primarily 5-fluorouracil (5-FU), platinum, and taxanes, given as neoadjuvant, concurrent, or adjuvant modality. CPT-11 was used in recent years as well. Concurrent chemotherapy was usually platinum- or 5-FU-based and started on day 1 with radiation therapy. Cisplatin was administered at a dose of 20 mg/m² on days 1 to 5. In all, 5-FU was administered at a dose of 300 mg/m²/d as a continuous infusion, 5 days per week, using a portable electronic pump from Monday to Friday during radiotherapy. Patients did not receive chemotherapy on weekends.

Surgery

Decision on surgery was made in a multidisciplinary esophageal cancer tumor board. All patients who were considered a candidate for surgery were recommended to have esophagectomy. Patients whose tumor was not resectable, who had significant comorbidities, or who refused surgery were not operated on, and they were offered other definitive treatment such as chemoradiation instead. In patients who underwent surgery, esophagectomy was performed 6 to 8 weeks after the completion of concurrent chemotherapy and radiation therapy. Surgical procedure selection was at the discretion of the operating surgeon and included total thoracic esophagectomy ($n = 11$), transthoracic esophagectomy ($n = 225$), transhiatal esophagectomy ($n = 48$), and radical en bloc esophagectomy ($n = 12$). Sixty-eight cases had other or unknown surgical procedures.

Follow-Up

Follow-up evaluations were performed every 3 to 4 months after treatment until a patient's death. Follow-up evaluations included a clinical examination, barium swal-

low, and chest radiography. CT scans, esophagogastroduodenoscopy, and biopsies were performed when indicated. Disease recurrence was documented as it occurred, but only the first site of failure was noted in this study. The treatment implemented for recurrence was at the discretion of the treating physician and consisted of any modality deemed appropriate for the situation. All patients were followed by direct evaluation or phone interview until death or up to the current study.

Statistical Analysis

Multivariable analysis was used to identify factors associated with long-term survival. The nonparametric Cuzick Trend Test was used in contingency tables to provide a test of trend across three or more ordered groups.⁹ The survival function was analyzed using time to event Kaplan-Meier estimation of the survival function.^{10,11} The log-rank test for trend was carried out for the Kaplan-Meier survival analysis to assess the equality of the survivor function across cohort groups.¹² The equality of means for continuous variables was assessed using Linear regression to test means across groups (e.g., mean age across cohorts).¹³ A value of 0.05 or less was considered to be statistically significant. All tests were two-sided. Survival time was calculated from the diagnosis date to the first occurrence of the considered event (local-regional disease progression, distant metastasis, or death). Overall survival was defined as the time between date of diagnosis and date of death from any cause. Local-regional progression free survival was defined as the time between date of diagnosis and the time at which during or after treatment that locoregional recurrence or disease progression was detected. Distant metastasis-free survival was defined as the time between date of diagnosis to the date during or after treatment that the distant metastasis was first detected. Progression-free survival was defined as the time between date of diagnosis and the date during or after treatment when disease, either locoregional disease or distant metastasis, was detected.

Cox's proportional hazard model¹² was used for multivariate analysis to assess the effect of patient characteristics and other prognostic factors of significance on the end points. All variables with a significance level of 0.25 or less on univariate analysis were entered into the model, and backward elimination was carried out. The final model consisted of variables with a significance value of less than or equal to 0.05 or of biologic significance to the model. Interaction variables were assessed. The estimated hazard is reported. The Wald test was used to assess the role of covariates in the model.¹⁴ All statistical analyses were carried out using Stata/SE 10.0 for Windows.¹³

RESULTS

Patient and Disease Characteristics

From 1985 to 2003 in the populations studied, increases were observed in the male-to-female ratio, in the proportion of cases with kps score >90%, <5% weight loss, and no symptom of dysphagia, and in the proportion of cases that were adenocarcinoma, and in the proportion of cases with

primary tumor located in the lower esophagus and gastroesophageal junction (Table 1). The median age remained stable. Adenocarcinoma became the predominant histology in the third interval (1995–1999), when adenocarcinomas were located most commonly at the lower esophagus and esophageal-gastric junction, and it remained dominant in the last interval.

Preclinical Evaluation

Ninety-five percent or more of the patients had a CT scan as part of their staging work-up in every interval, except the earliest, when only 76.5% of patients had a CT scan of the chest for staging. There was a significant increase in staging by endoscopic ultrasonography, and its use increased to 80.3% in the most recent interval in comparison with 10.4% or less in the first 2 study intervals. PET was used as a pretreatment evaluation in 54.8% of patients in the last study interval when it became available. There was a significant decrease in the use of barium swallow as a pretreatment evaluation modality (Table 1).

Treatment

Significant changes to treatment included increases in the use of chemotherapy, particularly its concurrent use with radiotherapy (Table 2). The median dose of radiation therapy remained relatively stable—from 45 to 50 Gy—except for the 1990–1994 interval, when 30 Gy at 3-Gy per fraction given in 10 daily fractions was used as standard definitive radiation therapy dose. Concurrent chemotherapy and radiation therapy, induction chemotherapy plus concurrent chemoradiation, and use of taxanes, have increased dramatically over time. The proportion of patients undergoing esophagectomy also increased slightly over the study period, ranging from 33.0 to 45.9% ($p = 0.015$).

Outcomes

The median follow-up time for the entire study population was 16.4 months (range, 0.5–238.3 months), the median follow-up time for the surviving patients was 61.4 (range, 0.6–238.3) months, and the median follow-up time for each cohort was 12.7, 11.1, 19.7, and 19.7 months, respectively. At time of analysis, 134 of the 756 patients (17.7%) are alive. The Kaplan-Meier median overall survival (OS) estimate for the entire population was 17.4 months. Three-year overall survival for the entire population was 27.1%, and 5-year overall survival was 19.1% (Figure 1A). The rates of 3-year Kaplan-Meier survival was significantly different between cohorts, with the last 2 groups having significantly higher survival rates (1995–1999, 32.7%; 2000–2003, 35.2%) than the first (1985–1989, 16.7%) (Figure 1B), which was nonetheless better than the rate for 1990–1994 (11.8%) (Table 3). The interval with the lowest overall survival rate was that in which the dose of radiation therapy was lowest (1990–1994). Similarly, rates for progression-free survival and locoregional progression free survival were lowest during this same period (Table 3).

Univariate analysis of factors that significantly affected survival is summarized in Table 4. Patient- and

TABLE 1. Patient and Disease Characteristics by Cohort

Characteristic	1985–1989		1990–1994		1995–1999		2000–2003		Cuzrick Trend Test <i>p</i>
Patients number	115		144		218		279		
Ethnic group									0.001
Caucasian	83	72.2%	109	75.7%	184	84.4%	236	84.6%	
Non-Caucasian	32	27.8%	35	24.3%	34	15.6%	43	15.4%	
Gender									0.005
Male	86	74.8%	106	73.6%	177	81.2%	235	84.2%	
Female	29	25.2%	38	26.4%	41	18.8%	44	15.8%	
Median age in years (range)	64	(33–86)	62	(24–88)	63.5	(32–87)	63	(33–87)	0.6374 ^a
≥90	26	22.6%	84	58.3%	126	57.8%	141	50.5%	KPS<0.001
<90	89	77.4%	60	41.7%	92	42.2%	138	49.5%	
Weight loss									<0.001
<5%	42	36.5%	46	31.9%	92	42.2%	154	55.2%	
≥5%	73	63.5%	98	68.1%	126	57.8%	125	44.8%	
Dysphagia									<0.001
Yes	106	92.2%	133	92.4%	191	87.6%	215	77.1%	
No	9	7.8%	11	7.6%	17	12.4%	64	22.9%	
Staging tests									
Barium swallow									0.012
Yes	104	90.4%	117	81.3%	196	89.9%	218	78.1%	
No	11	9.6%	27	18.8%	22	10.1%	61	21.9%	
CT chest									<0.001
Yes	88	76.5%	137	95.1%	211	96.8%	267	95.7%	
No	27	23.5%	7	4.9%	7	3.2%	12	4.3%	
Endoscopic ultrasonography									<0.001
Yes	1	0.9%	15	10.4%	78	35.8%	224	80.3%	
No	114	99.1%	129	89.6%	140	64.2%	55	19.7%	
PET									<0.001
Yes	0	0.0%	0	0.0%	1	0.5%	153	54.8%	
No	115	100.0%	144	100.0%	127	99.5%	126	45.2%	
Disease									
Barretts esophagus									0.231
Yes	12	10.4%	15	10.4%	54	24.8%	37	13.3%	
No	103	89.6%	129	89.6%	164	75.2%	242	86.7%	
Histology									<0.001
ADC	50	43.5%	65	45.1%	143	65.6%	201	72.0%	
SCC	65	56.5%	79	54.9%	75	34.4%	78	28.0%	
Tumor location									0.036
Lower/EGJ	96	83.5%	117	81.2%	193	88.5%	248	88.9%	
Mid/Upper	19	16.5%	27	18.8%	25	11.5%	31	11.1%	
Stage									0.772
I	4	3.5%	2	1.4%	12	5.5%	4	1.4%	
II	53	46.1%	29	20.1%	92	42.2%	91	32.6%	
III	23	20.0%	65	45.1%	69	31.7%	114	40.9%	
IV	32	27.8%	45	31.3%	40	18.3%	61	21.9%	
Unknown	3	2.6%	3	2.1%	5	2.3%	9	3.2%	

^a Cuzick Trend Test was utilized for all analyses on this table except for age parameter where Linear Regression was used. ADC, adenocarcinoma; SCC, squamous cell carcinoma; EGJ, esophagogastric junction; PET, positron emission tomography.

disease-related factors that favorably affected overall survival and that were associated with a reduced average relative risk (RR) were good Karnofsky performance status and not having dysphagia. Undergoing endoscopic ultrasonography or PET—tests that are used in more than half of patients now but were used in less than 1% in the first cohort—has been

associated with reduced risk (RR = 0.53 [CI = 0.45–0.62], $p < 0.0001$; and RR = 0.72 [CI = 0.58–0.88], $p = 0.002$; for EUS and PET, respectively) with univariate analysis, but they were no longer associated with significant reductions with multivariate analysis. A separate analysis was performed to assess the effect of PET on

TABLE 2. Treatment Characteristics by Cohort

Characteristic	1985–1989		1990–1994		1995–1999		2000–2003		Cuzick Trend Test <i>p</i>
Patients (Total)	115		144		218		279		
Radiotherapy dose (Gy) ^a									<0.001 ^a
Median (range)	45	(30–70)	30	(30–66)	45	(30–66)	50.4	(30–67)	
Any chemotherapy									<0.001
Yes	78	67.8%	107	74.3%	205	94.0%	265	95.0%	
No	37	32.2%	37	25.7%	13	6.0%	14	5.0%	
Paclitaxel chemo									<0.001
Yes	0	0.0%	10	6.9%	69	31.7%	145	52.0%	
No	115	100.0%	134	93.1%	149	68.3%	134	48.0%	
Concurrent CRT									<0.001
Concurrent CRT	36	31.3%	67	46.5%	121	55.5%	148	53.0%	
Induction chemo + concurrent CRT	24	20.9%	28	19.5%	76	34.9%	102	36.6%	
No concurrent CRT	55	47.8%	49	34.0%	21	9.6%	29	10.4%	
Adjuvant therapy									<0.001
Yes	15	13.0%	15	10.4%	16	7.3%	8	2.9%	
No	100	87.0%	129	89.6%	202	92.7%	271	97.1%	
Surgery									0.015
Yes	38	33.0%	57	39.6%	100	45.9%	128	45.9%	
No	77	67.0%	87	60.4%	118	54.1%	151	54.1%	

^a Cuzick Trend Test was utilized for all analyses on this table except for radiation dose parameter where Linear Regression was used.

Chemo, chemotherapy, CRT, chemoradiation.

survival for the last cohort. The result showed no difference, in the rates of 3 year OS were 37.7% and 32.1% ($p = 0.48$) in patients who had and who did not have PET as a pretreatment evaluation, respectively, suggesting that stage migration believed to be caused by the use of PET had minimal influence on OS.

Adversely affecting overall survival and associated with a higher than average RR were weight loss (RR = 1.03 [CI = 1.02–1.04], $p < 0.001$) and Barrett esophagus (RR = 1.29 [CI = 1.03–1.62], $p = 0.02$), not being white (RR = 1.41 [CI = 1.16–1.72], $p = 0.001$), squamous histology and, having disease of clinical stage III or IV disease.

Treatment factors associated with a reduced RR for overall survival by univariate Cox regression analysis included undergoing treatment after 1995, undergoing surgery (Figure 2A), undergoing concurrent chemoradiation, undergoing induction chemotherapy plus concurrent chemotherapy (Figure 2B), undergoing paclitaxel chemotherapy (Figure 2C), and undergoing three-dimensional radiotherapy (Table 4). Since paclitaxel was only used for the last two cohorts of patients, a separate analysis was performed to assess the effect of this drug on survival for patients treated during these two cohorts only. The rates for 3-year survival were 43.4% and 29.9%, and median survival times were 24.4 (range, 36.6–50.1) and 18.8 (range, 21.8–32.3) months in patients who were treated with and without paclitaxel, respectively ($p < 0.0001$), confirming the favorable effect on OS of paclitaxel.

Outcome factors adversely affecting overall survival were having residual tumor after surgery, or not having a complete response after treatments.

Multivariate Cox regression analysis confirmed that having lower stage disease at diagnosis, having a good Karnofsky performance score, being treated in the last cohort, and having received induction chemotherapy plus concurrent chemoradiotherapy significantly reduced risk in these patients and that having clinical stage III or IV disease or not having complete response after treatments significantly adversely affected overall survival (Table 5).

DISCUSSION

In this review of radiotherapy used to treat esophageal cancer at The University of Texas M. D. Anderson Cancer Center between 1985 and 2003, trends noted nationally are observed locally. These include increasing numbers of cases, an increasing proportion of cases with adenocarcinoma, an increasing proportion of cases with disease in the distal third of the esophagus, and an increasing use of drugs in therapy. The clinical stage of the cases has varied over time with the 2000–2003 cohort having twice the percentage of stage III and considerably fewer stage II cases compared with the 1985–1989 cohort. This shift in clinical stage may have been the result of more extensive pretreatment evaluation, especially the common clinical use of functional image. These also echo findings from a study of esophageal cancer by the Commission on Cancer of the American College of Surgeons.² The commission's data was collected in 1994 and encompassed 46% of the patients diagnosed that year. Investigators noted that rates of adenocarcinoma had been rising, the location of tumors had shifted to the lower third of the esophagus, and an association to Barrett esophagus was more commonly made.²

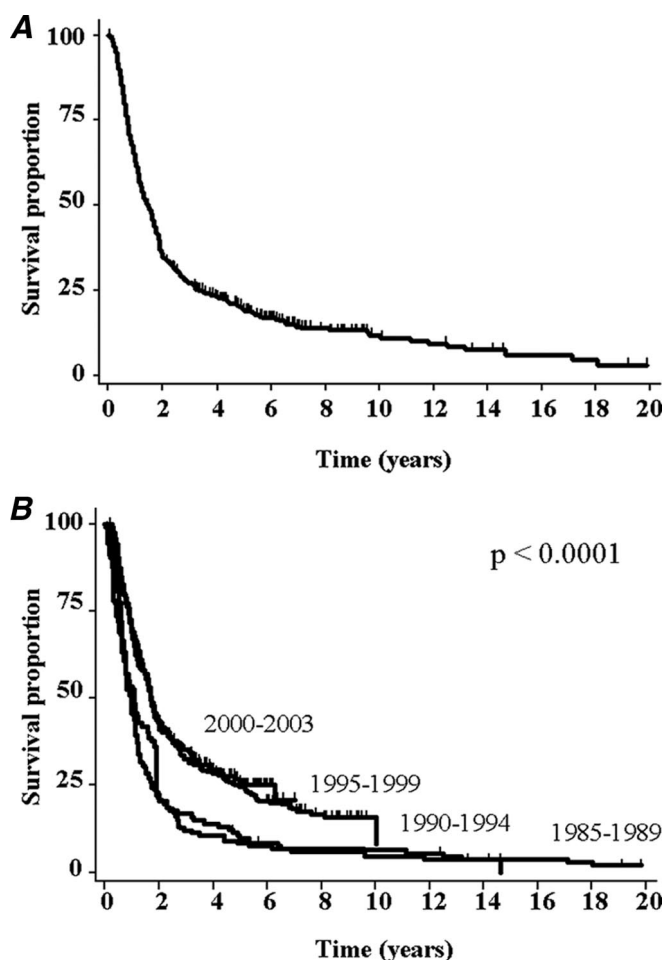


FIGURE 1. A, Overall survival for all patients. 3-year overall survival was 27.1%, and 5-year overall survival was 19.1%. B, Overall survival of the cohorts. Kaplan-Meier survival was statistically significant between the cohorts with the last two cohorts (1995–1999, 35.2%; 2000–2003, 35.2%) having higher 3-year rates than the first 2 (1985–1989, 16.7%; 1990–1994, 11.8%) (log-rank test of trend p value <0.001).

One noteworthy finding of this study was nonwhite race was associated with higher risk of death from esophageal cancer, regardless of treatment received. Members of the nonwhite population encompass racial and ethnic minorities,

including those who do not speak the dominant language, those with problems accessing and successfully navigating the health care system, and those likely to be socioeconomically disadvantaged and be less well educated than whites. These differences and the resulting marginalization can have dramatic negative effects, as evidenced in the increased RR in this population.

In our series, 3-year overall survival rates improved from 16.7% (1985–1989) to 35.2% (2000–2003), and the overall survival rates were similar for the last two cohorts. Parallel to this moderate improvement in survival was a number of significant advancement in diagnostic and treatment modalities in the management of esophageal cancer during the study period. First, a trend of more rigorous staging using endoscopic ultrasonography and functional image of PET was observed during these times, which could cause stage migration. However, there was no significant change in stage distribution throughout the studied period. Separate analysis of the effect of PET on survival of last cohort showed no difference, suggesting that the survival effect of stage migration would be minimal. Second, more dramatic reductions in risk were associated with being treated with recent therapies, including concurrent chemoradiation, paclitaxel-containing chemotherapy, and three-dimensional radiotherapy that has enabled us to increase radiation dose to 50.4 Gy with concurrent chemotherapy without increasing toxicity.¹⁵ Improving rates further will depend on overcoming the challenges of achieving control of locoregional disease, residual disease postsurgery, and metastasis. Overall, our data is supported by a national series using 5-year relative survival rates, with significant improvements also reported.¹

Evidence has indicated that combined radiation and chemotherapy promote better survival rates over radiotherapy alone.^{16,17} but results from phase III studies of preoperative chemoradiation followed by surgery compared with surgery alone have resulted in mixed findings.^{18–20} Of these, the one that found clear advantage to multimodal therapy in overall survival enrolled fewer than 60 patients in each arm²⁰ and another enrolling 43 found none.¹⁹ However, another with 282 patients evaluated found preoperative chemotherapy could prolong disease-free survival and survival free of locoregional disease but not overall survival.¹⁸

In the current study, undergoing surgery after concurrent chemoradiation was associated with higher survival. However, this improvement of outcome was probably the

TABLE 3. Three-year Survival of the Four Cohorts (1985–2003)

End Points	1985–1989 (95% CI)	1990–1994 (95% CI)	1995–1999 (95% CI)	2000–2003 (95% CI)	Log Rank Test of Trend p
Median survival (month)	12.9	11.1	20.1	20.4	
Overall survival (%)	16.7 (10.5–24.1)	11.8 (7.2–17.7)	32.7 (26.5–39.1)	35.2 (29.5–41.0)	<0.001
Progression-free survival (%)	49.5 (36.0–61.6)	16.0 (10.2–23.0)	34.5 (27.8–41.4)	28.7 (21.3–36.5)	<0.001
Distant metastasis-free survival (%)	67.3 (52.3–78.6)	39.5 (28.4–50.4)	51.0 (43.2–58.2)	36.4 (27.7–45.1)	0.0006
Locoregional progression free survival (%)	70.9 (57.4–80.8)	30.4 (22.1–39.1)	54.4 (46.3–61.7)	57.6 (47.6–66.3)	<0.001

CI, confidence interval.

TABLE 4. Univariate Cox Regression Analysis of Factors Affecting Overall Survival

Factors	Relative Risk	95% Confidence Interval	<i>p</i> > Z	Comparison Group
Patient characteristics				
Age	1.01	1.01–1.02	<0.001	Continuous
Non-white	1.41	1.16–1.72	<0.001	White
No alcoholism	0.84	0.71–0.99	0.04	Alcoholism
No dysphagia	0.59	0.46–0.74	<0.001	Dysphagia
Karnofsky performance score (kps)	0.58	0.50–0.68	<0.001	kps < 90
Weight loss	1.03	1.02–1.04	<0.001	Continuous
Staging tests				
Barium swallow	0.83	0.67–1.02	0.08	No barium swallow
CT chest	0.81	0.60–1.11	0.19	No CT chest
Endoscopic ultrasonography	0.53	0.45–0.62	<0.001	No endoscopic ultrasonography
PET study	0.28	0.33–0.50	<0.001	No PET
Disease characteristics				
Barrett esophagus	1.29	1.03–1.62	0.02	No Barrett esophagus
Squamous histology	1.36	1.16–1.60	<0.001	Adenocarcinoma
Mid/lower/GEJ tumor	0.87	0.69–1.09	0.23	Cervical/upper esophagus
Clinical stage III	1.35	1.12–1.63	0.002	Stage I/II
Clinical stage IV	2.76	2.23–3.42	<0.001	Stage I/II
Treatment characteristics				
1990–1994	1.09	0.85–1.40	0.51	1985–1989
1995–1999	0.62	0.48–0.78	<0.001	
2000–2003	0.57	0.45–0.73	<0.001	
Surgery	0.46	0.39–0.54	<0.001	No surgery
Induction chemo plus concurrent CRT ^a	0.64	0.53–0.77	<0.001	Concurrent CRT
Concurrent CRT	0.39	0.33–0.46	<0.001	No concurrent CRT
Taxanes chemotherapy ^b	0.56	0.47–0.67	<0.001	No taxanes
Three-dimensional (3D) radiotherapy	0.71	0.60–0.84	<0.001	No 3D conformal
Total radiation dose	0.97	0.97–0.99	<0.001	Continuous
Outcome characteristics				
Residual tumor after surgery	2.12	1.48–3.12	<0.001	No residual disease
No complete response to treatments ^c	3.56	2.99–4.24	<0.001	Complete response to all treatment

^a Only patients (*n* = 602, 230 who received induction plus concurrent, 372 concurrent CRT) who received concurrent CRT were included in the analysis.

^b The results from a separate comparative analysis including patients who were treated during last two cohorts was consistent with the result from the above analysis, which included patients from all 4 cohorts.

^c Completer response to treatment indicates that patient had complete response after non-surgical treatment, or R0 resection after surgery. Chemo, chemotherapy; CRT, chemoradiation; CT, computed tomography.

combined result of patient selection, disease resectability, and surgical boost of the primary tumor. In univariate analysis, failing to achieve tumor control at surgery was associated in our study with increased risk (RR = 2.29 [CI = 1.59–3.30], *p* < 0.001), and presurgical therapy is an attempt to circumvent residual disease postsurgery. In Germany, Stahl et al.²¹ undertook a randomized trial to assess the effect of surgery on overall survival of 172 patients with locally advanced squamous cell esophageal cancer (T3 or T4) who underwent chemotherapy and radiotherapy. With a median follow-up of 6 years, investigators found local progression-free survival was better in the surgery with chemoradiotherapy group than in the group undergoing chemoradiotherapy alone (RR, 2.1; 95% CI, 1.3–3.5). The surgery group also had significantly higher treatment-related mortality compared with the group treated without surgery (12.8% versus 3.5%, respectively; *p* = 0.03). Though overall survival was determined to be equivalent between the two treatment arms, the single independent factor

that predicted overall survival was clinical response to induction chemotherapy (RR, 0.30; 95% CI, 19–0.47; *p* < 0.0001). Therefore, investigators concluded that locoregional control in advanced squamous cell esophageal carcinoma could be improved by adding surgery to chemoradiotherapy but that such a change did not favorably affect overall survival when measured at a median of 6 years' follow-up (range, 1.4–9.3 years) and was associated with a treatment-related mortality rate significantly higher than that observed in the nonsurgical group. Three recent meta-analyses have examined the value of combining therapies to treat esophageal cancer with inconsistent conclusions in respect of survival benefit adding surgery to chemoradiation for esophageal cancer patients.^{22–24} Additional randomized trials are required to resolve these differences.

One important observation of the current study is that the outcome of patients treated in the 1990–1994 interval, when the standard radiation dose was 30 Gy in 10 fractions,

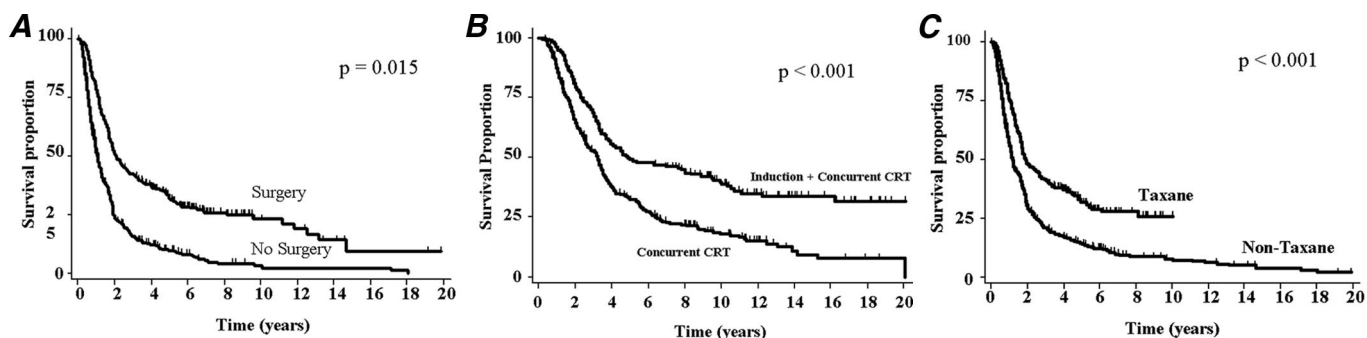


FIGURE 2. A, Overall survival by surgical treatment status. Undergoing surgery was associated with reduced risk (RR = 0.46 [CI = 0.39–0.54], $p < 0.001$); B, Induction chemotherapy plus concurrent chemotherapy. Undergoing induction chemotherapy plus concurrent chemoradiation was associated with reduced relative risk (RR = 0.64 [CI = 0.53–0.77], $p < 0.001$); C, Taxane (paclitaxel) therapy. Undergoing paclitaxel chemotherapy reduced relative risk (RR = 0.56 [CI = 0.47–0.67], $p < 0.001$).

TABLE 5. Multivariate Cox Regression Analysis of Factors Affecting Overall Survival

Factors	Relative Risk	95% Confidence Interval	$p > Z$
Patient characteristics			
Karnofsky performance score	0.68	0.56–0.83	<0.001
Disease characteristics			
Clinical stage III	1.53	1.22–1.93	<0.001
Clinical stage IV	2.36	1.79–3.11	<0.001
Treatment characteristics			
1990–1994	1.01	0.70–1.45	0.97
1995–1999	0.79	0.57–1.10	0.16
2000–2003	0.63	0.44–0.88	0.007
Induction chemo plus concurrent CRT	0.68	0.56–0.84	<0.001
Outcome characteristics			
No complete response to treatments	2.65	2.13–3.29	<0.001

CRT, chemoradiation.

had the poorest survival measured by all end points used. In a meta-analysis, investigators found that the probability of complete response increased with the dose of radiotherapy,²⁴ therefore, the poor outcome 1990–1994 might be associated with the low total radiation dose (30 Gy in 10 fractions) used during this period, confirming a previous report by Zhang et al.²⁵ It is noteworthy that 30 Gy of total radiation given with rapid fractionation was, at one time, the definitive treatment chosen in our institution for prospective clinical trials. It was estimated that a 30-Gy total dose of radiation given in 10 fractions was considered radiobiologically equivalent to a standard 4.5-week (45 Gy in 25 fractions) program with a shortened overall treatment time.^{26,27} However, the Radiation Therapy Oncology Group trial 94–05²⁸ that investigated the possibility of intensification of the radiation dose failed to show any benefit in survival in the high-dose (64.8 Gy) arm. In fact, there were no differences between the high-dose and the standard-dose (50.4 Gy) arms in the median survival time (13.0 versus 18.1 months), 2-year survival rate (31% versus 40%), and rate of local-regional failure or local-regional

disease persistence (52% versus 56%). Taking together, we could conclude that, for esophageal cancer and when chemotherapy is given concurrently with radiation, at least 50 Gy is needed to achieve reasonable local control, and surgical resection after chemoradiation could remove the residual disease, hence increase local control of the cancer. Another observation from the current study was that during 1985–1989, the best rates of progression free survival, distant metastasis free survival, and the local regional progression free survival were reported. The overall survival, however, was moderate. With the limitation of a retrospective review, one could only speculate that follow-up tests for disease progression was not as rigorous as the cohorts treated during the later periods and the event of disease progression might have been under reported.

Limitations of this study include (a) its retrospective nature; (b) the tendency of stage to be revised over time because of differences in diagnostic evaluation technology, reductions in tumor because of presurgical therapy, and restaging at surgery; and the (c) short follow-up for the last interval. In particular, because the stage of the patients' disease could not be as reliably measured as other factors (for example, age), stage of disease is less reliable as a data point. Poorer diagnostic technology in the early cohorts meant that clinical stage was more likely to be revised in the earlier cohorts than in the later ones. Likewise, differences in pre-surgical or postsurgical therapy might have affected outcome statistics.

These findings demonstrate that the changes in esophageal cancer epidemiology noted nationally are observed locally, that the improved survival rates coincided with more rigorous pretreatment staging, increased use of combined modality and new drugs and technology in treatment. Furthermore, improved and more aggressive salvage therapies may also contributed to the improved outcomes of patients who were treated in the more recent years. Achieving further improvements in survival rates will depend on conducting well-planned, sufficiently powered randomized controlled trials using the most promising radiation and chemotherapeutic tools. The benefits of these tools, including promising molecular targeted agents, new and more effective chemothera-

peutic drugs and three-dimensional radiation therapy, are only beginning to be recognized and managed to produce the best results. Building on the therapies that are producing improved survival rates will also require controlling postoperative complications and reducing toxicities associated with combination therapy. This will also continue to increase in importance as more and more of these patients live longer posttherapy and additional efforts to minimize normal tissue toxicity must be undertaken to avoid negative effects on quality of life²⁹ and to improve posttherapy quality of life.³⁰

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