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Scientific Article

Neoadjuvant twice daily chemoradiotherapy for esophageal cancer: Treatment-related mortality and long-term outcomes

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Abstract

Objective: Because of the short potential doubling time of esophageal cancer, there is a theoretical benefit to using an accelerated radiation treatment schedule. This study evaluates outcomes and treatment-related mortality and morbidity of patients treated with neoadjuvant hyperfractionated accelerated chemoradiation for resectable esophageal cancer.

Methods and materials: Outcomes from 250 consecutive patients with resectable esophageal cancer treated with preoperative hyperfractionated accelerated chemoradiotherapy (45 Gy in 30 twice-daily fractions over 3 weeks) followed by planned transhiatal esophagectomy were analyzed. Grade 3 or greater treatment related toxicity, surgical complications, and treatment-related mortality were determined. Additionally, available surgical specimens were graded for pathological response to chemoradiation. Overall survival (OS) and locoregional control were calculated using the Kaplan-Meier method. The log rank test was used to determine statistical significance.

Results: Median follow-up was 59 months for surviving patients; 87% of patients had adenocarcinoma and 13% had squamous cell carcinoma. Eleven percent of patients did not have surgery because of the development of metastases, declining performance status, or refusal. Twenty-seven patients were found to have unresectable and/or metastatic disease at the time of surgery. Overall, 10 of 223 operated patients died within 3 months, resulting in a perioperative mortality rate of 4%. Median OS was 28.4 months (95% confidence interval, 22.3-35.6 months) for

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all patients and 35.1 months (95% confidence interval, 27.4-47 months) for patients who underwent esophagectomy. There were 32 isolated locoregional failures with a 3-year locoregional control rate of 83%. Of 129 patients who had independent pathology review, 29% had complete response to treatment. This group had a median OS of 98.9 months and 3-year OS of 74%.
Conclusion: Neoadjuvant twice-daily chemoradiation for esophageal cancer is a safe and effective alternative to daily fractionation with low treatment-related mortality and long-term outcomes similar to standard fractionation courses.

Introduction

Despite advances in technology and our increased understanding of tumor biology, esophageal cancer remains one of the most difficult cancers to cure, with a 5-year overall survival (OS) of approximately 30% to 40% for patients with localized disease. Esophagectomy, either via a transhiatal or transthoracic approach, remains the treatment of choice for resectable patients. A recently reported randomized trial shows that the addition of preoperative chemoradiation improves esophageal cancer patients' outcomes without significantly increasing their postoperative mortality risk.[1] Trimodality therapy is currently considered standard of care for resectable patients with clinical stage T2 or greater or node positive esophageal cancer.

Because of the commonly seen poorly differentiated histology and the aggressive nature of esophageal cancer, there is a theoretical benefit of delivering hyperfractionated radiation (1.5 Gy twice a day for 3 weeks) to take advantage of the large differences in alpha/beta ratios of the tumor (approximately 10 Gy) and normal tissue (approximately 3 Gy) and counteract tumor repopulation that occurs in between radiation treatments. This regimen also has an overall treatment time that is 2 weeks less than daily treatment fractionation schedules, making it potentially more convenient for patients who require lodging during radiation.

A limited number of small studies investigating the role of twice-daily radiation for esophageal cancer have been previously reported. French investigators published a 32-patient series of neoadjuvant chemoradiation with cisplatin, fluorouracil, and L-folinic acid and twice-daily radiation (45 Gy in 1.5-Gy fractions) over 3 weeks,[2] and the University of Texas Southwestern published its experience with 45 patients who received either daily or twice-daily treatment.[3] Given the poor outcomes of patients treated with conventional fractionated radiation, we decided to analyze our substantial experience with hyperfractionated accelerated radiation therapy for esophageal cancer. The primary aim of this study is to determine the treatment-related mortality and acute toxicities related to hypofractionated radiation therapy with concurrent chemotherapy. Additionally, we sought to determine the pathological response rate to hyperfractionated accelerated chemoradiation and the effect of response on patient outcomes.

Methods

Patient population

Under an institutional review board–approved protocol, we performed a retrospective analysis of 250 consecutive patients with resectable esophageal cancer treated from 1999 through 2010 with preoperative hyperfractionated accelerated chemoradiotherapy with planned transhiatal esophagectomy. Patients eligible for the analysis were those with a new diagnosis of localized esophageal or gastroesophageal junction cancer with no evidence of distant metastatic disease who were determined to be candidates for esophagectomy. Patient characteristics, including age, sex, stage, nodal status, chemotherapy regimen, tumor histology, and tumor grade, were collected for all patients.

Staging

Patients typically underwent staging with an upper endoscopy and biopsy and a barium swallow. Computed tomography scans of the chest and abdomen were performed to assess the primary site and regional lymph nodes and to rule out distant metastases. Before 2004, it was not routine to perform endoscopic ultrasound staging on all patients at our institution. After 2004, endoscopic ultrasound was performed on most patients. Only patients who underwent endoscopic ultrasound had their clinical stage reported.

Treatment

Patients were treated with 3-dimensional conformal radiation therapy using low-density foam cradles or

thorax boards for immobilization. The gross tumor volume was defined by computed tomography and positron emission tomography as well as barium swallow and upper endoscopy. The treatment volumes were created in most cases by expanding the gross tumor volume by 4 to 5 cm superiorly and inferiorly and 1.5 cm longitudinally. Periesophageal, gastrohepatic, and supraclavicular lymph nodes were treated as clinically indicated based on the location and stage of the cancer. The spinal cord dose was limited to 36 Gy and dosimetric constraints were placed on critical structures including lung, heart, and bowel. Four field plans were typically delivered fields using 6- or 16-MV photons. Patients were treated twice daily Monday through Friday for 3 weeks for a total of 30 fractions. The minimum interfraction time was 6 hours. Concurrent chemotherapy regimens evolved over the period of the study as previously described.[4-7]

Pathologic analysis

Postsurgical specimens were evaluated for complete response and pathologic downstaging after concurrent radiation and chemotherapy. Additionally, available specimens were independently reevaluated by a surgical pathologist (JBH) for treatment response based on the Becker criteria, which uses the presence of residual cancer, fibrosis, and inflammation at the primary site of the esophagectomy specimen.[8] Scores between 0 and 3 were used to determine the extent of residual disease: 0 for complete response, 1 for near complete response, 2 for partial response with >50% reduction in tumor with extensive fibrosis and inflammation, and 3 for <50% reduction in tumor burden with minimal fibrosis and inflammation.

Statistical analysis

The primary objectives of our study were to determine perioperative mortality, treatment-related toxicity, and perioperative complications in addition to OS in patients receiving neoadjuvant twice-daily chemoradiation therapy for esophageal cancer. In addition, we determined progression free survival (PFS) and locoregional recurrence. OS, PFS, and locoregional recurrence were calculated using the Kaplan-Meier method. The log-rank test was used to determine statistical significance. P values $< .05$ were considered statistically significant. Perioperative mortality was defined as death within 1 and 3 months of surgery. Toxicity was assessed using Common Terminology Criteria for Adverse Events, version 4.0. A grade 3 event was a severe or medically significant event that typically required hospitalization and/or major intervention. Additionally, treatment response to neoadjuvant therapy was assessed and evaluated for prognostic significance. Prognostic factors were evaluated using univariate and multivariate Cox proportional hazards regression models. Factors selected for the analysis were selected for their prognostic and clinical implications and included age, chemotherapy regimen, sex, clinical stage, pathological stage, histological grade, and operation status.

Table 1 Patient demographics and clinical characteristics

Characteristic	No. (%)
Age, y	
Median	61 (range, 39-76)
Male	221 (88)
Clinical stage[a]	
I	12 (6)
II	58 (29)
III	128 (65)
Nodal status[b]	
Negative	61 (25)
Positive	184 (75)
Histology	
Squamous cell carcinoma	33 (13.2)
Adenocarcinoma	217 (86.8)
Chemotherapy	
Cisplatin-based	216 (86.4)
Other	34 (13.6)
Grade[c]	
Well-differentiated	10 (8)
Moderately differentiated	41 (32)
Poorly differentiated	76 (60)
Resection	
Yes	223
No	27

[a] Clinical staging was available for 198 patients.
[b] Nodal status was available for 245 patients.
[c] Histological grade was available for 127 patients.

Results

Patient characteristics

The baseline characteristics for the 250 patients analyzed in this study are shown in Table 1. Clinical staging was available for 198 of the 250 patients. Most of our patients were male (88%) with stage III disease (65%) and lymph node metastases (75%). Regarding histological factors, 65% had poorly differentiated tumors and 87% had adenocarcinoma. The majority of patients received cisplatin-based concurrent chemotherapy (86%), the most common regimen being cisplatin with paclitaxel. Eighty-nine percent of the patients completed preoperative therapy and had an esophagectomy, whereas 11% did not. Reasons for not having surgery included the discovery of metastases (n = 15), declining performance status (n = 7), or patient refusal (n = 5). Patients were treated with a transhiatal esophagectomy approximately 1 month

Table 2 Toxicity and complications

Grade 3+ treatment-related toxicity	N	Percentage
Esophagitis/dehydration/dysphagia	28	11.2
Infection	12	4.8
Pneumonitis	2	0.8
Other	3	1.2
Perioperative complications		
Cervical anastomotic leak	17	7.3
Wound Infection	6	2.6
Arrhythmia	22	9.4
Bowel obstruction/perforation	4	1.7
Myocardial infarction	3	1.3
Pulmonary embolism	17	7.3
Postoperative bleed	6	2.6
Chyle leak	3	1.3

(median, 33 days; interquartile range, 26-44 days) after completing neoadjuvant therapy.

Toxicity and complications

In the 223 patients who had resection, 2 died within 1 month and 10 died within 3 months of treatment. Thirty- and 90-day treatment-related mortality rates were 0.5% and 4%, respectively. There were a total of 45 grade 3 or greater toxicities related to treatment in the 250 patients on study. The most common toxicity was dysphagia leading to hospitalization in 11.2% of patients. Other serious treatment-related toxicities included infection in 4.8% of patients and pneumonitis in 0.8% of patients (Table 2). The most common perioperative complications included cervical anastomotic leak in 7.3% of patients, cardiac arrhythmia in 9.4%, wound infection in 2.6%, pulmonary embolism in 7.3%, and postoperative bleed in 2.6%. Other perioperative complications occurring in less than 2% of patients included bowel obstruction, myocardial infarction, and chyle leak (Table 2).

Pathologic response to neoadjuvant treatment

Independent pathologic reevaluation was performed on the available 129 specimens (55% of the patients included in the study) to determine response to treatment using the Becker criteria.[8] Of the 129 specimens reviewed, 29% had a complete response (category 0), 36% had a near complete response (category 1), 28% had a partial response (category 2), and 7% had minimal response (category 3). Because of the small number of patients with a category 3 response (n = 9), this subgroup was not analyzed individually. For the patients with category 0 response, the median and 3-year OS was 98.9 months and 74% (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.14-0.49); for a category 1 response, the median and 3-year overall survival was 60.8 months and 60.5% (HR, 0.46; 95% CI, 0.25-0.85); and for a category 2 response, the median and 3-year OS was 16 months and 32.4%. Kaplan-Meier analysis revealed significant differences in OS (Fig 1A), PFS (Fig 1B), and metastasis-free survival (Fig 1D). The association between a complete pathological response and locoregional control was not statistically significant ($P = .060$; HR, 0.28; 95% CI, 0.06-1.26). Response categories 1 and 2 had a similar rate of local failure (Fig 1C).

Prognostic factors

On univariate analysis, pretreatment factors found to be significant variables associated with survival included histologic grade 3, node-positive disease, and nonsurgical candidacy (Table 3). Conversely, pathologic downstaging was associated with improved OS. Factors that did not significantly affect survival included age, sex, chemotherapy, histological subtype, and disease location (Table 3). On multivariate analysis, variables associated with OS included partial and complete responses to treatment, resection, stage IIIC, and histologic grade 3 disease (Table 4). On multivariate analysis of patients who underwent definitive surgery and had their pathology reviewed for treatment response using the Becker criteria (n = 129),[8] the only variables independently associated with OS were treatment response category ($P < 0.0010$; HR, 4.1; 95% CI, 2.1-7.7) and clinical node positivity ($P = 0.020$; HR, 4.0; 95% CI, 1.2-13.7). Factors included in the analysis but not found to be significant were age, chemotherapy regimen, and sex.

Survival

The Kaplan-Meier method was used to calculate overall survival with a 95% CI (Fig 2). The median follow-up for surviving patients was 59 months. For the entire group, the median OS was 28.4 months (95% CI, 22.3-35.6 months) and 3-year OS was 44%. For patients who did and did not undergo esophagectomy, the median survival was 35.1 months (95% CI, 27.4-47 months) and 6 months (95% CI, 4.1-7.8 months), respectively. Median PFS for the entire cohort was 21.5 months (95% CI, 15.3-28.5 months) and 3-year PFS was 39%. For the 223 patients who underwent resection, the median PFS was 28.3 months (95% CI, 19.6-35.5 months) and 3-year PFS was 43%. There were 32 isolated locoregional failures for a 3-year locoregional control rate of 83%.

Discussion

To our knowledge, this report is the largest published experience of patients treated with neoadjuvant twice-daily chemoradiation for localized esophageal cancer. In

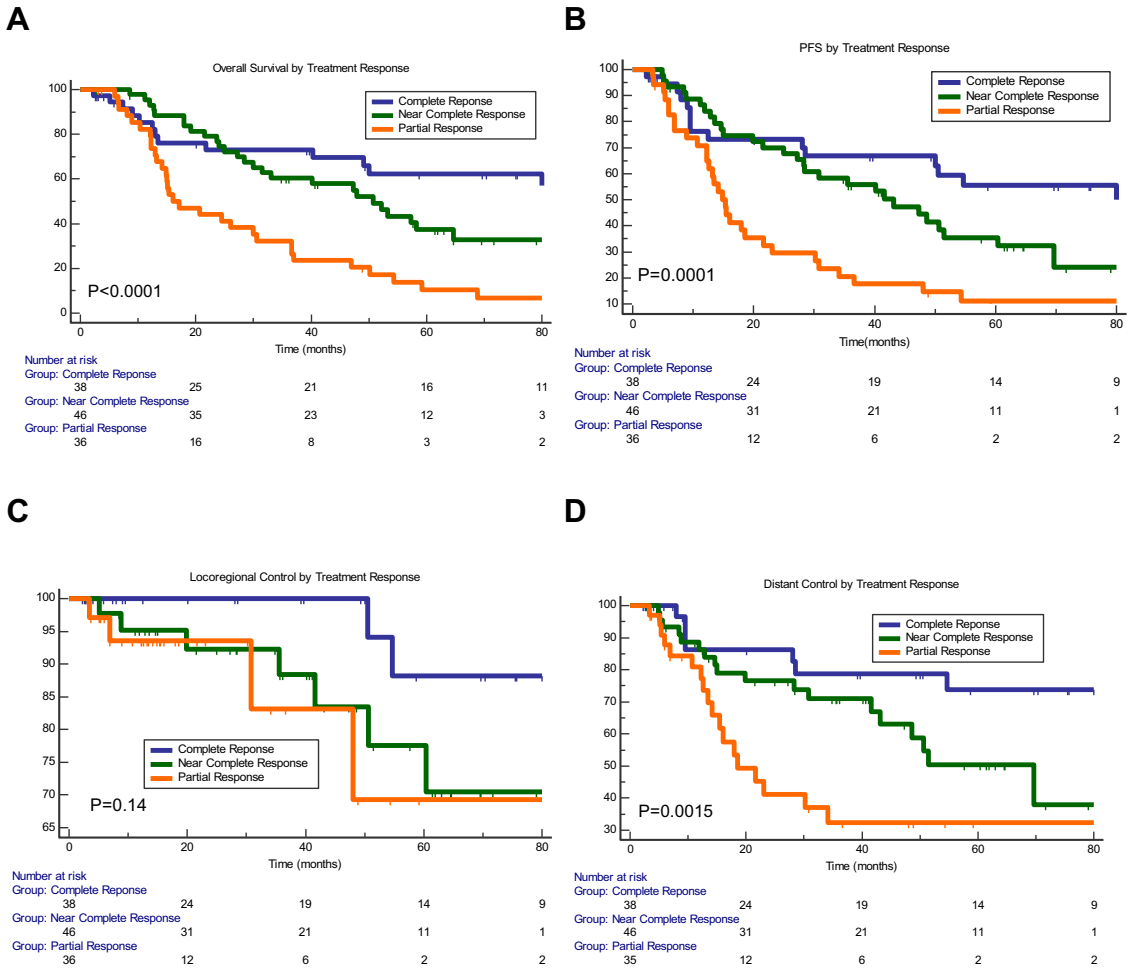

Figure 1 Kaplan-Meier curves for evaluable patients with a complete response, near complete response, and partial response according to the Becker criteria[8] following neoadjuvant twice-daily chemoradiation for esophageal cancer. All pathological specimens were reviewed and graded by a single pathologist. Figures for (A) overall survival, (B) progression-free survival (PFS), (C) locoregional control, and (D) distant control are shown.

our study, the median overall survival of the entire cohort was 28 months and the 3-year overall survival was 44%. For patients who completed trimodality treatment with transhiatal esophagectomy, the median survival was 35 months. These outcomes appear favorable to aggregated outcomes of randomized trials that have shown a survival advantage of neoadjuvant chemoradiation over surgery alone.[9,10] For example, the 3-year OS of patients receiving neoadjuvant therapy was 32% in the Irish trial[11] and 58% in the ChemoRadiotherapy for Oesophageal

Table 3 Univariable analysis with Kaplan-Meier estimate for OS

Factor	Median OS with factor, mo	Median OS without factor, mo	Significance (*P* value)
Resection	35.1	6.0	<.0001
Cisplatin-based chemotherapy	28.9	22.3	.52
cN positive	28.4	40.2	.089
Histologic G3	19.9	47.3	.029
pN positive	20.9	50.0	.0001

OS, overall survival.

Table 4 Cox proportional regression HR with stepwise method for overall survival

Covariate	*P* value	HR	95% confidence interval
Partial response	.0083	0.602	0.414-0.876
Complete response	.0002	0.181	0.075-0.437
Grade 3 (high)	.0045	1.707	1.182-2.465
No resection	<.0001	6.400	2.990-13.685
Clinical stage IIIC	.0409	2.516	1.043-6.066

Factors included in the analysis but not found to be significant were age, chemotherapy regimen, sex, and clinical nodal stage.
HR, hazard ratio.

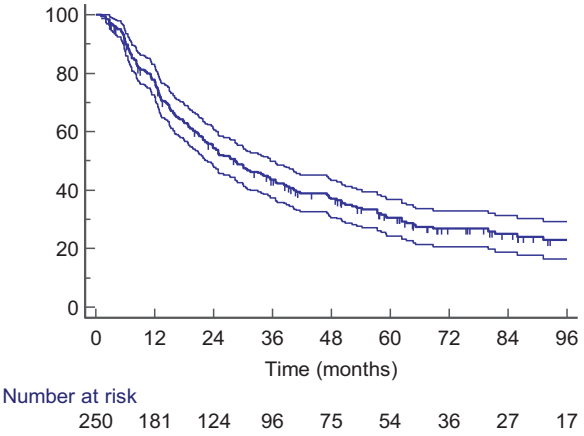

Figure 2 Kaplan-Meier curve with 95% confidence interval for overall survival (OS) in patients with esophageal cancer undergoing neoadjuvant twice-daily chemoradiation therapy. The median follow-up for surviving patients was 59 months. For the entire group, the median OS was 28 months and 3-year OS was 44%.

cancer followed by Surgery Study (CROSS) trial.[1] Our survival outcomes of unselected sequentially treated patients are especially impressive in light of the higher numbers of patients with adenocarcinomas (86% vs 75%) and node-positive disease (75% vs 64%) compared with patients in the CROSS trial. We have previously reported the results from a series of prospective studies from our institution investigating neoadjuvant twice-daily radiation consisting of 1.5 Gy twice daily to a total dose of 45 Gy.[4,5] In a randomized study using this treatment regimen versus surgery alone, there was a trend toward an OS benefit in the neoadjuvant therapy arm compared with the surgery alone arm at 3 years (16% vs 30%, respectively). A follow-up study was performed to investigate whether a change in the concurrent chemotherapy regimen to cisplatin and paclitaxel could improve

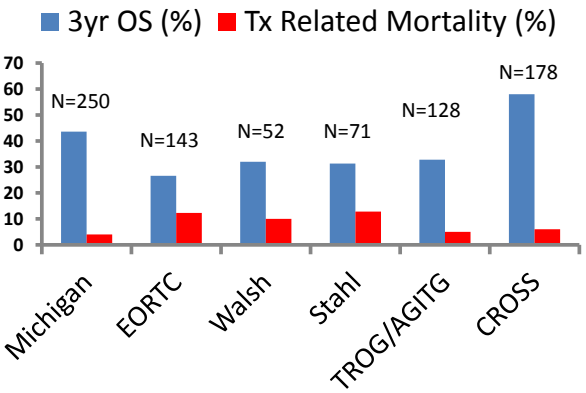

Figure 3 Comparison of overall survival and treatment related mortality for esophageal cancer. Shown are the reported outcomes from our series compared to outcomes from the studies performed by EORTC[14], Walsh et al.[11], Stahl et al.[13], TROG[15], and the CROSS Trial[1].

outcomes. The results of this phase 2 trial demonstrated a 13% rate of grade 3 or 4 toxicity with a 17% rate of feeding tube placement.[6]

A concern with using twice-daily radiation regimens is the possibility of increasing the rate of surgical complications and postoperative mortality. Our population had a 4% rate of perioperative mortality defined as death within 3 months from treatment. This compares favorably with the neoadjuvant arms of several trials including Cancer and Leukemia Group B 9781 (4%),[12] Walsh et al (10%),[11] Stahl et al (13%),[13] and CROSS (6%) (Fig 3).[1] All patients in our report, however, underwent a transhiatal, rather than a transthoracic, esophagectomy, which likely contributes to this finding. Additionally, patients from our cohort were treated using modern radiation planning techniques including 3-dimensional conformal radiation and image guidance. Grade 3 or greater toxicity rates were also similar to reported studies using conventional fractionation. In the CROSS trial,[1] chemoradiation was associated with an 8% hematological and 11% nonhematological toxicity rate. In the current study, there was a 17% rate of grade 3 or greater toxicity.

A secondary aim of our study was to examine pathologic response to hyperaccelerated chemoradiation. Several studies have demonstrated improved outcomes in patients with complete pathologic response to neoadjuvant treatment.[16-19] In our study, a pathologic complete response or near-complete response using the Becker criteria[8] was associated with improved overall, progression-free, and metastasis-free survival compared with a partial response. On multivariate analysis, treatment response and nodal status were the only variables independently associated with OS and PFS. Others series have reported pathologic complete response rates between 25% and 35%.[1,11,13,14] In our study, the pathologic complete response rate was 29% and the near-pathologic complete response rate was 36% despite a shorter interval to surgery, which has been negatively correlated with pathologic complete response rates.[20]

Limited data from the United States or Europe directly compare daily with twice-daily neoadjuvant radiation for esophageal cancer. French investigators published a 32-patient series of neoadjuvant chemoradiation with cisplatin, fluorouracil, and L-folinic acid and twice-daily radiation (45 Gy in 1.5-Gy fractions) over 3 weeks and found a high toxicity rate with half of the patients experiencing grade 3 toxicity. They also found a high complete response rate (56%) and encouraging survival rate (52% at 3 years), however.[2] Researchers at the University of Texas Southwestern have published their experience with 45 patients who received either daily or twice-daily treatment. This study found no difference in outcomes or toxicity in patients receiving daily radiation compared with patients receiving twice-daily treatment.[3] The use of accelerated radiation courses is more common in Asia, and several trials have been performed to compare

fractionation schemes. A study from Shanghai Medical University randomized 85 patients with locally advanced esophageal cancer to a standard fractionated radiation course versus an accelerated course that used twice-daily fractionation for the final third of the treatment course. This study found improved survival and local control with the accelerated radiation schedule.[21] More recently, a meta-analysis of 29 trials with 3187 patients treated at medical centers in Asia suggested improved survival and local control using accelerated radiation fractionation schedules.[22] Of note, the studies in the analysis mainly included patients receiving definitive radiation or chemoradiation without surgery and had higher rates of squamous cell carcinoma than in modern North American and European series.

There are potential advantages to using an accelerated course in esophageal cancer. In studies examining both squamous cell and adenocarcinoma of the esophagus, the potential doubling time for this disease is estimated to be approximately 5 days,[23,24] which is similar to head and neck and cervical cancers. An accelerated course has the potential to counteract tumor cell repopulation, which may be accelerated in patients undergoing radiation therapy.[25] Additionally, total treatment time has been shown to impact local control[26] in patients undergoing definitive radiation therapy for esophageal cancer. In addition to the potential radiobiological advantages, accelerated courses may be more convenient for patients who require lodging during treatment. The results from our study suggest that twice-daily chemoradiation given before transhiatal resection is associated with low treatment-related mortality and outcomes similar to those of standard fractionated schedules.

In summary, our study confirms the use of twice-daily radiation concurrent with chemotherapy for the preoperative treatment of esophageal cancer is effective and associated with low treatment-related mortality and acceptable toxicity. Additionally, our study validates the prognostic role of pathologic treatment response to neoadjuvant therapy at the time of surgery. Future studies optimizing preoperative chemoradiation regimens will be important for this disease.

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