Original Article

Image-guided Radiotherapy Of Esophageal Cancer By Helical Tomotherapy: Acute Toxicity And Preliminary Clinical Outcome

Yi-Jen Chen, MD, PhD, Kemp H. Kernstine, MD, PhD, Stephen Shibata, MD, Dean Lim, MD, David D. Smith, PhD, Martin Tang, An Liu, PhD, Richard D. Pezner, MD, and Jeffrey Y. C. Wong, MD

From Divisions of Radiation Oncology (Drs Chen, Liu, Pezner, and Wong, and Martin Tang), Thoracic Surgery (Dr Kernstine), Medical Oncology (Drs Shibata and Lim), Biostatistics (Dr Smith), City of Hope Medical Center, Duarte, CA, USA

ABSTRACT

Background: Helical tomotherapy is a novel intensity-modulated radiotherapy modality with a helical 360° radiation delivery system and CT imaging ability. The purpose of this report is to review our initial experiences and to assess the toxicity and efficacy of helical tomotherapy for esophageal cancer.

Methods: Twenty patients with locally advanced esophageal cancer (T3-4 and/or N+ and/or M1a/b) were treated with helical tomotherapy. Radiotherapy included simultaneous 50 Gy to gross tumorous areas and 45 Gy to areas of suspected subclinical disease. All received combination chemotherapy. Ten patients underwent surgical resection after completion of chemoradiation. Ten patients were ineligible for surgery.

Results: The treatment was well-tolerated. There were no treatment-related deaths or Grade 4 toxicity. Grade 3 toxicities were noted in 9 of 20 patients (45%). Down-staging was noted in 7 of 10 patients (70%) who underwent surgery. The median follow-up time was 24.5 months. Eight patients, including 3 with surgery and 5 without surgery, have died. The 1-year overall survival rates for the entire group, patients with and without surgical resection are 80.0%, 100.0% and 60.0% respectively (log-rank p = 0.244, surgery versus no surgery).

Conclusions: The regimen of combined chemoradiation by helical tomotherapy for locally advanced esophageal cancer is well-tolerated. The toxicity profile compares favorably with that of protocols based on conventional approach and the preliminary indications of efficacy are encouraging.

KeyWords: Esophageal cancer; radiotherapy; Image-guided radiotherapy; helical tomotherapy.

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Introduction

Radiotherapy (RT) plays a major role in multimodality treatment for patients with esophageal cancer. The standard therapy for patients with localized carcinoma of the esophagus selected for nonsurgical treatment is combined chemoradiation up to 50 Gy (1,2). Delivering higher radiation doses did not increase survival or local/regional control (3,4). Adding surgery to chemoradiation significantly increased local tumor control and reduced chances of death from cancer (5). However, the results were achieved at the cost of an in-hospital mortality rate of 11.3% in patients who underwent surgery. Therefore, studies focusing on improving quality of treatment and reducing treatment-related complications are essential.

Delivery of adequate radiation doses by the conventional approach to the esophageal tumorous areas is limited by radiation-sensitive normal structures in the thoracic cavity including lungs, heart, and spinal cord. Helical tomotherapy is a novel RT modality (6). It is a form of intensity-modulated RT (IMRT) that uses a helical 360° radiation delivery system. It delivers image-guided RT through comparison of daily pretreatment megavoltage CT (MVCT) scans with CT scans performed at the time of simulation for treatment planning. By rapid opening and closing of leaves in a collimator rotating around the patient, tomotherapy provides the ability to sculpt radiation doses to complex shaped tumor regions while limiting dose to normal organs (7,8). Compared to conventional IMRT techniques, tomotherapy may provide sharper dose gradients around the target, which will lead to superior sparing of surrounding normal structures and possibly less radiation-related side effects (9-11). Since October 2004, we have implemented tomotherapy in the treatment of patients with locally advanced, operable and non-operable, esophageal cancer. The regimen includes upfront chemoradiation

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Corresponding author: Dr Yi-Jen Chen, MD, PhD, Division of Radiation Oncology, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010, USA. Tel: 626-301-8247; Fax: 626-930-5334. Email:yichen@coh.org

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up to definitive dose, 50 Gy (1,2). The patients would then be evaluated. For operable cases, including initially non-operablecases who become operable after chemoradiation, surgical resection would be offered. This report primarily evaluates the toxicity of this regimen and provides preliminary efficacy data. To our knowledge, this is the first study addressing the clinical efficacy using helical tomotherapy for patients with locally advanced esophageal cancer.

Patients and Methods

Patient population

Between October 2004 and January 2007, twenty consecutive patients with locally advanced esophageal cancer treated with chemoradiation using helical tomotherapy were identified. The clinical data were collected and reviewed. This study was approved by the Institutional Review Board of City of Hope Medical Center. All cases had a minimum follow-up time from histological diagnosis of 12 months. Workup prior to treatment included esophagogastroduodenoscopy (EGD), CT scan of chest and abdomen, endoscopic ultrasound (EUS) with fine needle aspiration (FNA) if indicated, and PET scan. Twelve patients were considered not surgical candidates initially because of T4/M1a/b disease (10 cases) or severe co-morbidities (2 cases). After completion of chemoradiation, the 5 cases with T4N1M0 disease were offered surgical intervention. Among these 5 cases, 3 went on to undergo surgical resection and 2 patients refused the suggestion. Patients with metastatic disease (M1a or M1b, 5 cases) and patients with severe co-morbidities (2 cases) were not offered surgery after chemoradiation. There were 8 initially operable cases and 1 did not undergo surgery after chemoradiation because of patient refusal. In summary, 10 patients completed upfront chemoradiation followed by surgical resection and another 10 patients had chemoradiation alone. Patient characteristics are shown in Table 1.

Chemotherapy

During radiation treatment, 15 patients received 2 cycles of chemotherapy consisting of cisplatin 75 mg/m2 IV bolus on day 1 and 5-FU 1,000 mg/m2/24 hours infusion on days 1 through 4 of a 28-day-cycle chemotherapy. Two patients received continuous 5-FU without cisplatin because of renal insufficiency. Two patients with severe co-morbidities received oral capecitabine 1,600 mg/m2 daily in two divided doses during RT. One patient received carbo platin and paclitaxel. After completion of chemoradiation and/or surgery, 10 patients received additional chemotherapy at the discretion of treating physicians.

RT

Details of radiation treatment planning were described

Table 1 Patient characteristics

Characteristics	CRT + Op	CRT alone
Patients number	10	10
Age		
Mean Age	51	74
Range	29 - 71	55 - 86
Sex		
Male	9	5
Female	1	5
Histology		
Adenocarcinoma	8	8
Squamous carcinoma	2	2
Location		
Upper Thoracic	0	0
Mid Thoracic	1	1
Lower Thoracic	9	9
TNM Stage		
$T_2N_1M_0$	0	1
$T_3N_1M_0$	7	2
$T_3N_1M_{1a}$	0	2
$T_4N_1M_0$	3	2
$T_4N_1M_{1a}$	0	2
$T_4N_1M_{1b}$	0	1

CRT = chemoradiation therapy
Op = operation

Table 2 Acute treatment-related toxicity and weight change in 20 patients with esophageal cancer treated with helical tomotherapy combined with chemotherapy.

Toxicity	Grade 0 (%)	Grade I (%)	Grade II (%)	Grade III (%)
Nausea/Vomiting	2 (10)	10 (50)	6 (30)	2 (10)
Dysphagia	4 (20)	5 (25)	6 (30)	5 (25)
Hematologic	8 (40)	3 (15)	5 (25)	4 (20)
Weight	Loss (>3%)	Stable (+/- 3%)	Gain (>3%)	
	8 (40%)	12 (60%)	0 (0%)	

previously (11). Briefly, prior to RT, a treatment-planning CT scan was obtained. Based on diagnostic imaging, including EGD, EUS, CT/PET scans, 2 target volumes were delineated. Gross tumor volume (GTV) consisted of areas with gross tumor. Clinical target volume (CTV) consisted of areas with suspected subclinical disease adjacent to GTV (an extension of 5 cm in the superior and inferior directions and 2 cm in the transversal direction) and celiac nodal area for patients with lower thoracic esophageal carcinoma. Margins were added to GTV and CTV to account for organ motion and setup variations. An inverse IMRT plan was performed using Tomotherapy Hi-Art system, version 2.0 (TomoTherapy, Madison, WI). The prescribed dose was 50 Gy to GTV and 45 Gy to CTV in 25 fractions, which means both targets would be treated simultaneously with daily doses of 2.0 and 1.8 Gy respectively. The following inverse planning constraints were used: 95% coverage of the targets to the prescribed dose, volume of lung receiving more than 10, 15 and 20 Gy (V10, V15 and V20) less than 40, 30 and 20% respectively, volume of heart receiving more than 30 Gy (V30) less than 30% and maximal dose to the spinal cord less than 45 Gy.

Surgery

Before surgery, patients were evaluated to ensure medical operability. Resection of the esophagus and the proximal stomach was performed by a robotic-assisted minimally invasive approach (12,13). Resection included excision of the paraesophageal, paracardial, left gastric, celiac and bilateral cervical lymph nodes. The resected esophagus was replaced by the stomach with a cervical esophagogastric anastomosis.

Toxicity Assessment During Treatment and Follow-up

Patients were evaluated on a weekly basis during chemoradiation. Toxicity was scored using the National Cancer Institute's Common Toxicity Criteria, version 2.0. Patients were evaluated within 28 days after completion of all therapy. Follow-up assessments were performed every 3 months for 2 years, every 6 months for 2 years, then yearly. For patients without surgery, imaging studies including CT scan, PET scan and EGD were done 3 months after completion of chemoradiation to evaluate response.

Statistical Methods

Survival and disease control parameters were calculated using Kaplan-Meier analysis. Overall survival (OS) was defined as the time from pathologic diagnosis until death or the last date of contact. Progression free survival (PFS) was defined as the time from pathologic diagnosis until the date of disease recurrence or death. We excluded patients with persistent disease from the PFS analysis. No patients were lost to follow-up.

Results

Acute Toxicity during chemoradiation

Treatment was well tolerated. Acute toxicity and weight change are summarized in Table 2. There were no treatment-related deaths or Grade 4 toxicity. Grade 3 toxicities were noted in 9 of 20 patients (45%). Twelve patients (60%) maintained stable weight (+/- 3% of initial weight) and among these, 3 actually gained 0.9, 1.0 and 1.2% of their initial weights respectively by the end of chemoradiation. No patients required extra nutritional support, such as enteral feeding or total parenteral nutrition.

Results for Patients Without Surgery

Among the 10 patients without surgery, studies at 3 months after chemoradiation confirmed 6 patients with complete response including 1 case by FNA from a celiac node showing atypical cells. Four patients were found to have partial response with persistent disease.

Results at Surgery

Of the 10 patients who underwent surgery there were 9 R0 and 1 R1 resection. The mean number of examined lymph nodes was 21.7 (range, 10 to 39). Down-staging was found in 7 patients (70%) by final pathology. No viable tumor was present in 2 specimens (20%). Four specimens (40%) showed microscopic residual disease. Four patients were found to have persistent gross disease including 1 patient with positive distant lymph nodes. Post-operative morbidity was seen in 6 cases (60%) including 5 anastomotic leakages, 2 pneumonitis, 1 chylous effusion and 1 acute cholecystitis. No post-operative mortality was noted.

Table 3 Overall and progression-free survival for entire group, patients with and without surgery.

	1 year (%)	2 year (%)	Log-rank p
Overall survival			
Entire group	80.0	64.3	
Surgery	100.0	78.8	0.2440
No Surgery	60.0	50.0	
Progression-free survival			
Entire group	75.0	43.7	
Surgery	70.0	36.0	0.4279
No surgery	83.3	62.5	

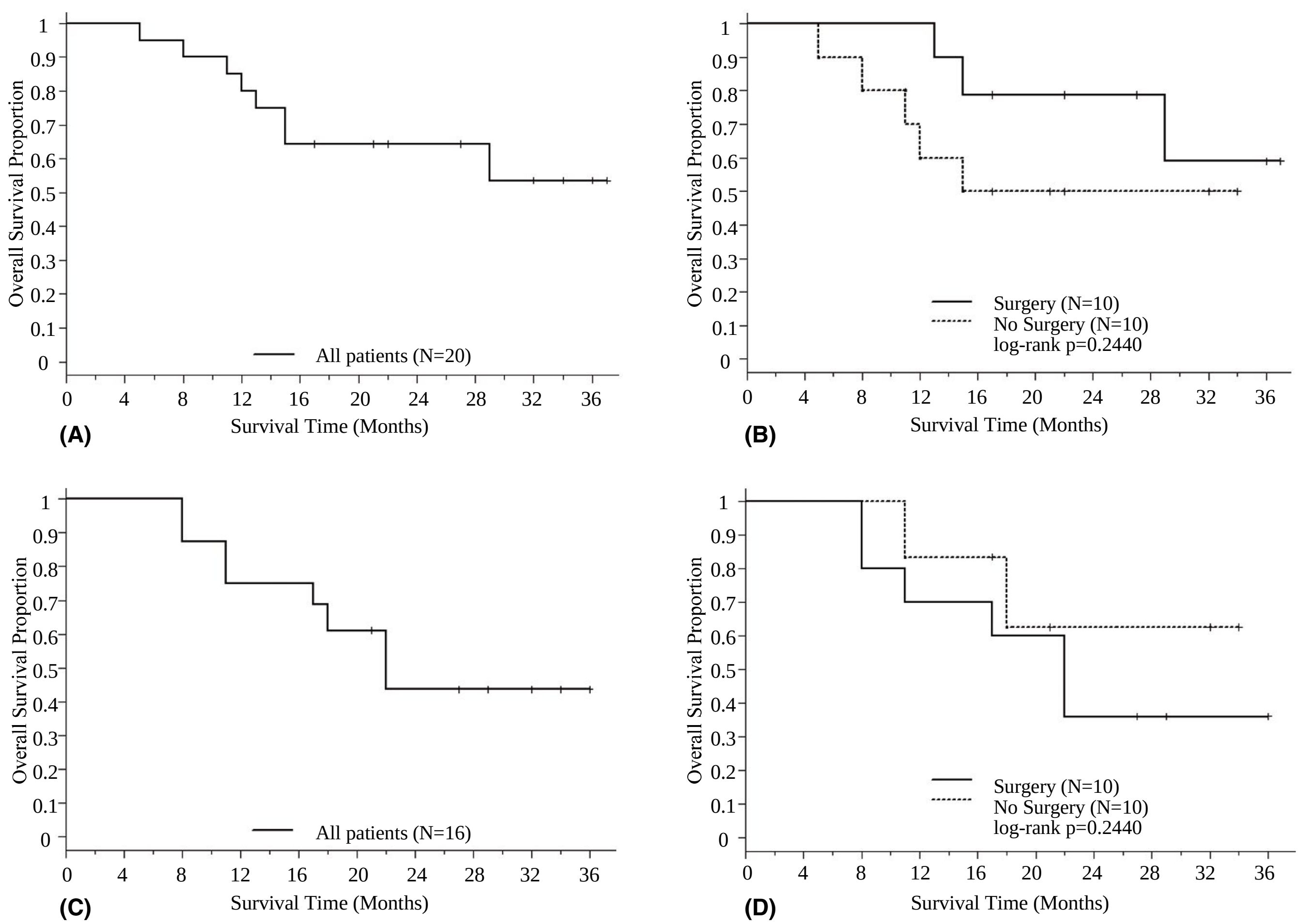

Fig. 1 Kaplan–Meier plots showing (A) overall survival of all patients, (B) overall survival for patients with and without surgery (log–rank p = 0.2440) (C) progression–free survival of all patients and (D) progression–free survival for patients with and without surgery (log–rank p = 0.4279).

Survival

At the date of evaluation (February, 2008), 8 patients, including 3 with surgery and 5 without surgery, have died. The median follow-up time was 24.5 months. The 1-year OS rates for the entire group, patients with and without surgery were 80.0%, 100.0% and 60.0% respectively (log-rank p = 0.2440, surgery versus no surgery). The 2-year OS rates for the entire group, patients with and without surgery were 64.3%, 78.8% and 50.0% respectively. Excluding 4 patients with persistent disease by the end of treatment in the chemoradiation only group, the 1-year PFS rates for the entire group, patients with and without surgery were 75.0%, 70.0% and 83.3% respectively (log-rank p = 0.4279, surgery versus no surgery). The 2-year PFS rates for the entire group, patients with and without surgery were 43.7%, 36.0% and 62.5% respectively (Table 3 and Fig. 1). Of note, we acknowledge that comparing results between patients with or without surgery after chemoradiation is meaningless because of inhomogeneous population of patients and obvious patient selection bias between the 2 groups.

Discussion

Definitive chemoradiation or chemoradiation followed by surgery are two well-established curative treatments for patients with locally advanced esophageal cancer (1,2,4,5,14-16). For operable cases, compared to surgery alone, neoadjuvant chemoradiation and surgery usually improves overall survival and shows better local-regional cancer control (15,16). It is noted that neoadjuvant chemoradiation also results in significant post-operative morbidity and mortality (15,17). Therefore, to reduce post-operative complications, the radiation dose in neoadjuvant chemoradiation regimens has been as low as 35 to 45 Gy (5,17-20). Unfortunately, oftentimes planned surgery is not done for various reasons. A study by Stahl et al. has showed up to 34% of patients not proceeding to surgery after neoadjuvant chemoradiation (5). Although these patients can receive additional chemoradiation later, the pause between two courses of radiation would cause repopulation of tumorous cells and hence inferior results (21). Therefore, better results might be expected if upfront treatment up to 50 Gy could be delivered. However, higher postoperative complication rates could become an issue if surgery is going to be followed.

It is proven that lung sparing could be improved by IMRT compared to three-dimensional conformal RT (3DCRT) in treating esophageal cancers (22,23). Since the target volume of esophageal cancer is approximately cylindrical and located at the center of the body, the 360-degree freedom of beam projection of tomotherapy is expected to provide more benefit in terms of treating esophageal cancer. Indeed, compared to step-and-shoot IMRT, we have found that tomotherapy can provide a preferred plan with better conformal target coverage, more homogeneous target dose distribution and better heart and lung sparing for patients with esophageal cancer (11). In addition, with its image guidance ability by using daily MVCT scan before each fraction of RT, setup errors could be detected and corrected and thereby extra margins to account for setup errors for target coverage could be reduced (24). Therefore, significant less amount of lung and heart will be covered in radiation treatment volume, which would likely reduce treatment-related toxicities. This report summarizes our initial experiences of using tomotherapy for patients with esophageal cancer. We were able to deliver definitive/upfront RT dose up to 50 Gy without causing too much toxicity. As shown in Table 2, the low toxicity profile of chemoradiation by tomotherapy (45% grade 3 and no grades 4 or 5 toxicities) compares favorably with that of conventional approach, 66 to 76% grade 3 or higher toxicities (1,4).

Studying patients undergoing neoadjuvant chemoradiation followed by surgery, Lee et al. have shown that the threshold for lung irradiation for patients to be given multimodality therapy may be lower than previously expected (25). By a multivariate analysis, a lung V10 of 40% or more was the only factor that was associated with occurrence of pulmonary complications. Using tomotherapy, there is no postoperative mortality in our series. However, among the 10 patients treated by combined chemoradiation followed by surgery, 60% developed one or more severe complications, including 2 pneumonitis and 5 anastomotic leakages. Reviewing the treatment planning for the two cases who developed pneumonitis a lung V10 of 65% (in a patient with a long segment of disease) and 40% were identified respectively, indicating the importance of minimizing the lung V10 as low as possible, perhaps <40%. The 50% anastomotic leakage rate in our series is higher than reported by others. It is likely due to the fact that the greater curvature of the gastric cardia used for cervical esophagogastrostomy anastomosis was always covered by a moderate dose of RT by the nature of tomotherapy. To improve the results, we are conducting a project with the surgeon to define the area of future anastomosis as an avoidance structure in tomotherapy planning.

Locally advanced esophageal cancer is still a deadly disease. With definitive chemoradiation up to 50 Gy, the RTOG 85-01 and INT 0123 studies reported 50% and 68% 1-year survival rate respectively (1,4). With combined chemoradiation followed by surgery, trials by EORTC and University of Michigan reported 67% and 72% 1-year survival rates respectively (17,19). It is noted that the EORTC study included only stages I and II squamous cell cancer and the study by University of Michigan included only potentially resectable cases. The 80.0% 1-year survival rate by our regimen compares favorably to conventional approaches with or without surgery. Since this is not a randomized study and because of selection bias, we acknowledge that comparing survival between patients with or without surgery after chemoradiation is meaningless although results showed slightly better survival for the group of patients with surgery. It is not the intension of this paper to discuss the role of surgery after chemoradiation. However, in fact, recently, the role of surgery after chemoradiation for responders has been questioned. Study by Bedenne et al. has suggested that in patients with locally advanced esophageal cancer, especially squamous cell carcinoma, responding to initial chemoradiation, there is no benefit for the addition of surgery compared with continuation of additional chemoradiation (26). However, available clinical prognostic factors do not help in choosing patients between responders and non-responders and therefore studies are still needed to search for new predictive factors and evaluate new tools to detect early responders. Nevertheless, for operable locally advanced esophageal cancer including initially operable or cases becoming operable after chemoradiation treatment, routinely at our institution we offer surgery following chemoradiation for feasible cases.

In conclusion, this is the first study evaluating patients with esophageal cancer treated with tomotherapy. The toxicity profile compares favorably with that of protocols based on conventional

RT approaches. The preliminary indications of efficacy are encouraging.

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