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Comprehensive Clinical Study of Concurrent Chemotherapy Breathing IMRT Middle Part of Locally Advanced Esophageal Cancer*

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— Abstract —

The standard treatment of locally advanced type of mid-esophageal cancer is concurrent chemoradiation therapy (CRT). We evaluated the feasibility of chemotherapy with adding docetaxel to the classical basic regimens of cisplatin plus 5-fluorouracil (5-FU) and radiotherapy up to 70.2 Gy using dose escalations for esophageal cancer. It was possible to escalate radiation treatment dose up to 70.2 Gy by the respiratory-gated intensity-modulated radiotherapy (gated-IMRT) based on the 4DCT-simulation, with improving target coverage and normal tissue (ex., lung, heart, and spinal cord) sparing. This study suggested that the definitive chemo-radiotherapy with docetaxel, cisplatin, and 5-fluorouracil (i.e., DCF-R) and gating IMRT is tolerable and active in patients with locally advanced mid-esophageal cancer (AEC).

Key Words : Docetaxel, Gating IMRT, 4DCT-simulation, Esophageal cancer

I . INTRODUCTION

The overarching purpose of this study was to perform radiobiological determination of dose escalation and normal tissue toxicity in concurrent chemoradiation therapy (CRT) for a locally advanced type of mid-esophageal cancer based on the comprehensive analysis of the study's accumulated experiences and data for high difficulty radiotherapy of a locally advanced type of mid-esophageal cancer.

This study had two primary goals: 1) to estimate the level of dose escalation up to 70.2 Gy required for a

clinically significant increase in tumor control using radio-biological modeling across a group of representative patients, and to examine whether this dose could be safely delivered by calculating the normal tissue complication probability (NTCP) for heart and lungs; and 2) to evaluate the feasibility of chemotherapy with adding docetaxel to the classical basic regimens of cisplatin plus 5-fluorouracil (5-FU) and radiotherapy up to 70.2 Gy using dose escalation for esophageal cancer patients treated with definitive CRT by comparing results for individual patients.

There has been a growing body of research concerning

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radiotherapy techniques for esophageal carcinoma in recent years, including intensity-modulated radiotherapy (IMRT) which has emerged as the most actively implemented approach. The static gantry IMRT, helical tomotherapy (Accuracy Inc., Sunnyvale, CA) and rapid arc are especially complex technologically integrated therapeutic techniques being applied to IMRT, and the research to date reflects a high degree of conformity. This means that the potential exists to reduce the volume of normal organs that are exposed to the damaging effects of radiation therapy by using an appropriate radiation beam arrangement and optimizing its application. The current study is in the continuum of the aforementioned research, and conducted a static gantry IMRT in the most typical esophagus cancer patient population where any satisfactory results of the three-dimensional conformal radiation therapy (3D-CRT) were expected to be particularly difficult to derive.

The esophagus is located at the median of the mediastinum, and is described anatomically by specific names and parts, including cervical esophagus, upper thoracic esophagus, mid-thoracic esophagus and lower thoracic esophagus. Among these components, the middle and distal lower esophagus comprise the relatively unfixed esophagus and are capable of considerable respiratory diaphragmatic movement. Therefore, a four-dimensional computed tomography (4DCT) simulation and simulation of gated treatment was conducted in order to minimize the adverse effects of treatment from the motion of tumor induced by respiration, and to ensure the accuracy of the treatment, i.e., for precision targeting of radiation on the tumor site when conducting radiotherapy for esophageal cancer of the middle or distal lower portions which moves up and down. To date, our esophageal cancer center has performed accurate individualized identification of the moving esophageal tumor volume, and effective and precise clinical approaches in targeting the internal target volume (ITV) through 4DCT simulation for gated-IMRT of all advanced middle or distal lower esophageal cancers. The present study performed step and shoot IMRT of the middle esophageal tumor which is specifically visualized by 4DCT simulation and a gating image registration algorithm.

The respiratory-gated IMRT based on the 4DCT dataset in the radiotherapy of mid-esophageal cancer was used. A gating radiotherapy was attempted to overcome two problems, i.e., the uncertainty in tumor location caused by the respiration-induced tumor motion and the difficulty in delivering therapeutic radiation doses without increasing side effects to the normal surrounding tissues. In addition, the cutting-edge radiation therapeutic technologies used in the present study were the 4DCT simulation, the static gantry IMRT, and the gating radiotherapy. The application of these three technologies is presented in detail in the description of the study's methods and materials below.

At present, cisplatin and 5-fluorouracil remain the chemotherapy regimen of choice for treating esophageal cancer, and docetaxel acts as an excellent radiation sensitizer, arresting cells in G2/M, the most radiation-sensitive phase of the cell cycle. The chemotherapy was performed by adding docetaxel to the cisplatin and 5-fluorouracil using the methods and materials described below.

II. MATERIALS AND METHODS

1. Patient clinical features and case selection

During the period from February 2008 through January 2014, a total of 49 patients were enrolled in this study. There were seven females and 42 males with a median age of 62 (range 47-77 years). Patients with previously untreated, biopsy-confirmed esophageal carcinoma were eligible for participation in this study. Patients were considered eligible if they had clinically resectable, locoregionally advanced esophageal carcinoma (AEC; stage II, III, or IV with mediastinal lymph node metastases according to the American Joint Committee on Cancer, 6th edition); were aged ≥ 40 or ≤ 80 years; and had the Eastern Cooperative Oncology Group (ECOG) performance status of 2, adequate bone marrow reserve, serum creatinine level of < 1.5 mg/dL, serum bilirubin concentration level of < 1.5 mg/dL, and no history of

prior malignancy.

Patients were excluded if the primary tumor was located in the cervical esophagus (upper border <18 cm from the incisor teeth), if para-aortic lymph node involvement was evident, if tracheobronchial infiltration was present, or if laryngeal nerve palsy or evidence of distant metastasis was noted. To determine criteria for inclusion, meticulous pretreatment evaluation was performed. Pretreatment evaluations included a medical history review and detailed physical examination, assessments of ECOG performance status, complete differential blood cell counts, liver function testing, measurements of creatinine concentration, electrocardiography, thallium myocardial perfusion scanning or echocardiography, a pulmonary function test, chest radiography, esophagogastroduodenoscopy (EGD) with biopsy, endoscopic ultrasonography (US), CT of the chest and upper abdomen, and positron emission tomography (PET).

2. Image data sets of 4DCT simulation

All patients participating in the study had simulations including a 4DCT study to measure their total respiratory motion and determine the gating interval around end-exhalation, which limited motion to approximately 5 mm. Before IMRT planning, CT image data of the patient were obtained by 4DCT as follows: 1) The patient's respiration was monitored by tracking the vertical displacement of the abdomen. 2) Each of the patient's skin, at the carina level, was marked with three tattoos and was used as a criterion for making the target of the axis array in order to be consistent with the lasers in the treatment room for daily radiotherapy. 3) Ball bearings (BBs) were placed on the skin spots to make the spots' positions evident during each imaging period. 4) The scanning was done by the cine CT respiratory protocol and respiratory waveform files, as well as variant's real-time position management TM (RPM) system, were all concurrently recorded. 5) The image data obtained from the cine mode were materialized, classified, and stored into 4DCT data set by utilizing 4D software respiratory signal. It was possible to perform

a customized treatment plan and an effective radiotherapy treatment by analyzing the individualized respiratory patterns of each patient through such a method. 6) All patients were immobilized at the supine position in a vacuum bag (Vac-Loc) placed on a wing-board/T-bar (both from Med Tec, Orange City, IA), and were instructed to tightly hold the tee-bar with both hands after extending both arms over their heads. 7) All CT images were obtained at a 2-mm slice thickness on a PET-CT scanner (Discovery ST; GE Medical Systems, Waukesha, WI) with an 80-cm hole using feedback advice or instruction during normal resting breathing.

The 4DCT image data sets were imaged in multiple acquisitions of 1 or 2 cm length along the cranial-caudal direction. The external approach registers the image data according to an externally recorded respiratory signal generated by the RPM respiratory gating system (Varian Medical Systems, Palo Alto, CA). This system consists of an infrared camera that is mounted to foot of the CT couch and a marker block containing two reflections.

3. Contouring of target volumes for respiratory gating with IMRT

The primary objective of respiratory gating is to direct beam delivery in a patient's treatment for a small portion of the respiratory cycle only. Based on the tumor contours for each phase of multiple 4DCT data sets, with each representing the patient during normal respiration (100% duty cycle, no gating), it is possible to easily simulate respiratory-gated treatment by removing specific phases from the tumor contour sets. The 50% exhalation phase-specific images (50%ex images) were used to design IMRT plan for the respiratory gating system. To simulate a 50% duty cycle, the tumor contours from the five phases surrounding end inspiration (i.e., the 0% phase) were removed, leaving only the contours from the 30%, 40%, 50%, 60%, and 70% phases of the 4DCT data set (Figure 1).

The remaining gross tumor volumes from the 4DCT for 50% duty cycle gating IMRT planning were registered from their respective CT data sets to the free-breathing CT data set. The union of the GTVs of

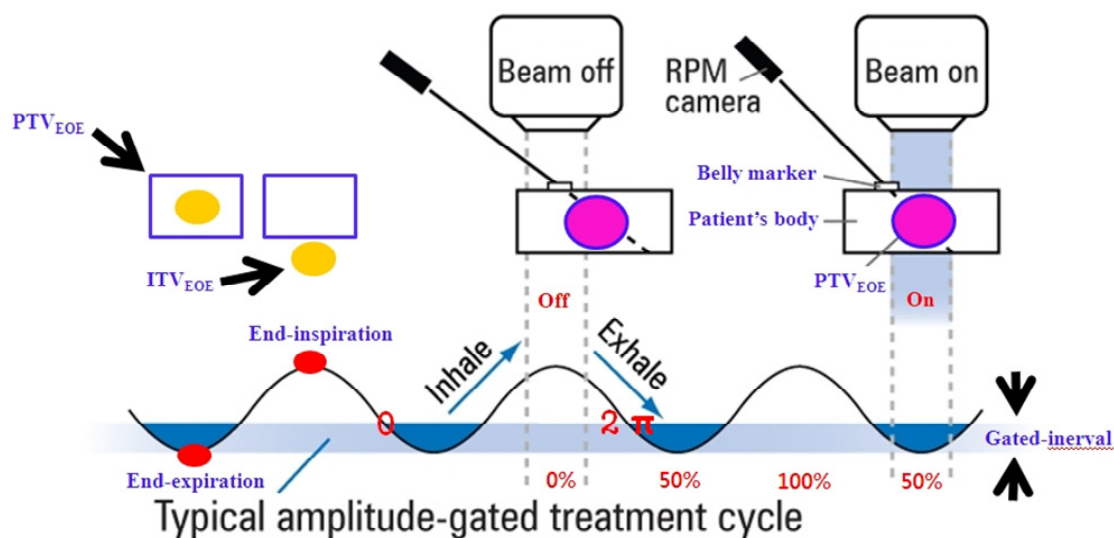


Figure 1 Concepts of respiratory-gated radiotherapy. In the respiratory-gated radiotherapy setting, treatment delivery is done in only gating window periods when the target position is pre-determined end-exhale phases. For simulating a 50% duty cycle, we used the tumor contours from the five phases surrounding end inspiration (i.e., the 0% phase) were removed, leaving only the contours from the 30%, 40%, 50%, 60%, and 70% phases of the 4DCT data set.

the five phases was denoted as GTV5. The GTV5 contour was expanded to generate the clinical target volume (CTV5) based on the following guidelines. The proximal border is a 3- to 4-cm margin above the proximal edge of the GTV5, or 1 cm above any grossly involved periesophageal nodes, whichever is more cephalad. This margin should be oriented along the esophageal mucosa instead of being a simple geometric expansion. For mid-esophageal tumors, the distal border is a 3- to 4-cm margin below the proximal edge of the GTV5, oriented along the esophageal mucosa. In general, the CTV5 should include the GTV5 (including any grossly involved nodes) with at least a 1-cm margin in all directions. A 1-cm radial margin from the outer esophageal wall was recommended to encompass the periesophageal lymph nodes (level 8 in the International Association for the Study of Lung Cancer [IASLC] system). Unless the GTV5 was located at the esophagus/heart interface, it was recommended that the GTV5 expansion be limited to 0.5 cm into cardiac tissue (including pericardium) based on the concern about excessive cardiac doses and the unlikelihood of microscopic extension into the myocardium in the

absence of gross invasion.

The planning target volume (PTV5) was made by expanding CTV5 by 3mm to account for inter-fractional uncertainty in tumor motion, and then by an additional 7 mm to account for patient setup uncertainties. The OARs were contoured on all 5 phase bins for the heart, spinal cord, esophagus, and both lungs. The heart was delineated from the infundibulum of the right ventricle to the lowest part distinguishable from the liver. The spinal cord was delineated or its total length was shown on the CT scan. The outer wall of the esophagus was contoured from the cricoid to the gastroesophageal junction; no attempts were made to exclude the esophagus from the PTV5. The lungs were automatically contoured using a Hounsfield unit threshold algorithm. The volume of both lungs excluding the PTV5 was used to calculate the lung evaluation parameters.

4. IMRT plan design

To minimize the effects of changing tumor size/shape/contouring uncertainties from week to week, the treatment planning system was used to identify

the center of volume of the GTV contour on the 50% phase of each 4DCT data set. Intensity-modulated radiation therapy plans were generated by using the step-and-shoot technique using the Pinnacle planning system (Phillips Medical Systems). Beam arrangements were optimized for each of the 49 patients with the goal of reducing both cardiac and pulmonary doses. Dose calculation was performed using the analytical anisotropic algorithm (AAA)¹⁾ using a grid of 2.5 mm. The implementation of IMRT was divided into course 1 and course 2. In course 1, 50.4 Gy/28 fxs was prescribed for PTV5. In course 2, 19.8 Gy/11 fxs was prescribed for the cone-down boost radiotherapy to GTV5. All IMRT plans were generated with the six radiation beams such as 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315° using 6-MV photons.

5. Radiobiological determination of dose escalation and normal tissue toxicity by calculating tumor control probability (TCP) and normal tissue complication probability (NTCP)

In order to determine the level of dose escalation to the GTV Radiobiological, modeling of TCP was carried out using the parameters from Geh et al.²⁾. Analysis was based on the protocol-prescribed doses of radiation therapy and chemotherapy (5-fluorouracil and cisplatin) to predict the TCP of pathologic complete remission (pCR) and included total dose, dose per fraction and duration among the fitting parameters. The values of the covariates and coefficients used were those listed in the original paper.

A clinically significant 20% increase in tumor local control requires ≥ 67 Gy. Stop-and-shoot IMRT was used as the radiotherapy. In course 1, 1.8 Gy/1 fx, 5fxs/wk, and a total up to 50.4 Gy/28 fxs were prescribed to PTV5 by using IMRT plan, whereas in course 2, 1.8 Gy/1 fx, 5fxs/wk and a total up to 19.8 Gy/11 fxs was prescribed to GTV5, respectively. Dose constraints of GTV5 and PTV5 were as follows: 1) GTV5 (70.2 Gy), 2) $V_{95\%}$ (66.69 Gy) $> 95\%$, 3) D_{\max} (0.1 cc) $< 107\%$ (75.11 Gy), 4) PTV5 (50.4 Gy), $V_{95\%}$ (47.88

Gy) $> 95\%$, 5) D_{\max} (0.1cc) $< 107\%$ (53.92 Gy). Dose limitations for the OARs were as follows: 1) Bilateral lungs, $V_{20} < 20\%$; 2) Mean lung dose, < 25 Gy; heart, $V_{30} < 40\%$; 3) Mean heart dose, < 25 Gy; 4) Esophagus, $V_{50} < 35\%$; 5) Mean esophagus dose, < 33 Gy; 6) Spinal cord, maximum dose < 45 Gy.

TCP calculations were performed using the equation suggested by the Geh et al.²⁾.

$$TCP(z) = \frac{\exp(z)}{1 + \exp(z)} \quad (1)$$

where

$$z = a_0 + a_1 \text{total RT dose} + a_2 \text{total RT dose} \times \text{dose per fraction} + a_3 \text{duration} + a_4 \text{age} + a_5 \text{5FU dose} + a_6 \text{cisplatin dose} + a_7 \text{docetaxel dose}$$

To calculate predicted risk of RP, an application of a combined heart and lung irradiation model was used where the dose to the hottest 19% of the heart volume (D_{10H}), and the mean lung dose (MLD) in Gy are used to calculate NTCP.

$$NTCP = \frac{1}{1 + \exp(-x)} \quad (2)$$

where

$$x = 0.0234 \times D_{10H} + 0.0649 \times MLD - 3.5$$

6. Chemotherapy

Patients were assigned to receive a 1-hour intravenous infusion of docetaxel (35 mg/m²) and a 2-hour intravenous infusion of cisplatin (40 mg/m²) with adequate hydration and antiemetic treatment on day 1 and a continuous intravenous infusion of 5-fluorouracil (400 mg/m²/24 hours) on day 1 to 5, every 2 weeks, plus concurrent radiation (Figure 2). Following definitive chemoradiation therapy (dCRT) with docetaxel, cisplatin, and 5-fluorouracil (DCF-R), patients received at least 2 cycles of monthly DC (docetaxel 40 mg/m² on day 1, cisplatin 60 mg/m² on day 1, and 5-fluorouracil 600 mg/m² on day 1 to 5, every 4 weeks).

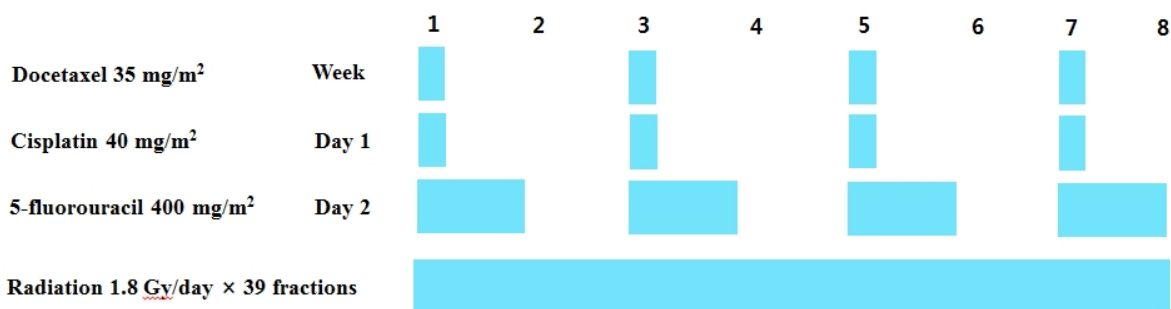


Figure 2 Treatments schema. Patients were assigned to receive a 1-hour intravenous infusion of docetaxel (35 mg/m²) and a 2-hour intravenous infusion of cisplatin (40 mg/m²) and a continuous intravenous infusion of 5-fluorouracil (400 mg/m²/24 hours) on days 1 to 5, every 2 weeks, plus concurrent radiation. The total radiation dose to GTV5 was 70.2 Gy/39 fxs including cone-down boost radiotherapy

7. Statistical analysis

The clinical primary endpoint of this research was the pCR rate; clinical secondary endpoints included the progression-free survival (PFS), and overall survival (OS). Overall survival was calculated from the date of randomization to the date of death from any cause. Progression-free survival was defined as the interval from the date of randomization to the date of first observation of progression, recurrence, or death from any cause. Survival was evaluated by the Kaplan-Meier method. The Cox proportional hazards regression model was used to identify prognostic factors in univariate and multivariate analyses. A two-sided p value <0.05 was considered to indicate statistical significance. All analyses were performed using SPSS 13.0 for Windows (SPSS, Chicago, IL).

III. RESULTS

1. Patient characteristics

Table 1 shows the clinical T and N stage distribution of the population according to the 7th edition of American Joint Committee on Cancer (AJCC) staging classification. Most patients (43 of 49 or 87.7%) had squamous cell carcinoma, whereas the remaining six patients (6 of 49 or 12.3%) had adenocarcinoma. The 17 patients (34.6%)

had T4a disease, while the 32 patients (65.3%) had T4b disease. Patient's characteristics are shown in Table 1. All patients had histologically confirmed squamous cell carcinoma or adenocarcinoma.

Table 1 Patients (*n*=49) characteristics

| Variables | Patients (average) |
|-----------------------------|--------------------|
| Median age (range) | 62 (47-77) |
| Sex | |
| Male | 42 (85.7) |
| Female | 7 (14.2) |
| ECOG performance status | |
| 0 | 16 (32.6) |
| 1 | 29 (59.1) |
| 2 | 4 (8.1) |
| Weight loss within 3 months | |
| ≥10% | 7 (14.2) |
| <10% | 6 (12.2) |
| No | 32 (65.3) |
| NA (not available) | 4 (8.1) |
| Tumor size | |
| <5cm | 7 (70) |
| ≥5cm, <10cm | 20 (40.8) |
| ≥10cm | 22 (44.8) |
| Pathologic subtypes | |
| Squamous cell carcinoma | 43 (87.7) |
| Adenocarcinoma | 6 (12.3) |
| AJCC 7th edition TNM stage | |
| T4aN1M0 | 5 (10.2) |
| T4aN2M0 | 4 (8.1) |
| T4aN3M0 | 8 (16.3) |
| T4bN1M0 | 9 (18.3) |
| T4bN2M0 | 10 (20.1) |
| T4bN3M0 | 13 (26.5) |

2. Analysis of the clinical endpoints of GTV5 and PTV5 using TCP and NTCP algorithm

The TCPs median of PTV5 (50.4 Gy) was 39%, and the TCPs median of GTV5 (70.2 Gy) was 63% by the Webb–Nahum model³⁾ with parameters from the Geh et al. model²⁾. The dose escalation up to 70.2 Gy increased the TCP by 24%, compared to the PTV5 (50.4 Gy). The Plan_{IMRTs} resulted in an increase on average of less than 3 Gy in mean dose to heart and pericardium, compared to the Plan_{3Ds}. The exposure of radiation to the heart was directly dependent on the overlap volumes of heart with the GTV5 (70.2 Gy) or PTV5 (50.4 Gy), and mean heart dose was exceeded when the boost dose was applied. The calculated heart NTCPs median of PTV5 (50.4 Gy) was 14.3%, and the heart NTCPs median of GTV5 (70.2 Gy) was 16.5% by the Gagliardi et al. model⁴⁾. Heart mortality predicted using the criteria by Gagliardi et al.⁴⁾ showed a statistically significant increase of 1.9% (on average) with increased dose to the GTV5 ($p < 0.001$).

The calculated lung NTCPs median of PTV5 (50.4 Gy) was 16.2%, and the lung NTCPs median of GTV5 (70.2 Gy) was 18.4% by the Huang et al model. The calculated lung NTCPs median of GTV5 (70.2 Gy) was 7.8%, and the lung NTCP median of PTV5 (50.4 Gy) was 9.5% by the Lyman–Kutcher–Murman (LKB) model^{5,6)}. Using the combined heart and lung irradiation model for radiation pneumonitis, the

predicted risks of RP are greater than for the lung only model, though the increase in predicted RP with dose escalation is on average $< 2.2\%$ (median NTCP: 16.2% [PTV5 (50.4 Gy)] versus 18.4% [GTV5 (70.2 Gy)] $p < 0.003$). The median mean dose of the lung was 13.7 Gy in the plan of PTV5 (50.4 Gy), and 14.4 Gy in the plan of GTV5 (70.2 Gy), respectively ($p < 0.001$). The median V_{10Gy} (%) and V_{20Gy} (%) of the lung was 42% and 13.7%, respectively, in the plan of PTV5 (50.4 Gy). The median V_{10Gy} (%) and V_{20Gy} (%) of the lung was 46.7% and 16.9%, respectively, in the plan of GTV5 (70.2 Gy). There were statistical differences in the variable values associated with the dosimetric factors of lung between PTV5 (50.4 Gy) and GTV5 (70.2 Gy). The median mean dose of the heart was 20.3Gy in the plan of PTV5 (50.4 Gy), and 21.7Gy in the plan of GTV5 (70.2 Gy), respectively ($p = 0.17$). The median V_{30Gy} (%) of the heart was 17.8% in the plan of PTV5 (50.4 Gy), and 19% in the plan of GTV5 (70.2 Gy), respectively ($p = 0.02$). Consequently, IMRT boost to GTV5 (70.2 Gy) had increased TCP within the safe range of NTCP of the heart or lung. The results indicate $\geq 97\%$ of the total patients had shown mild toxicity.

3. Efficacy of DCF-R

In this study, 29 of 49 patients had a complete clinical

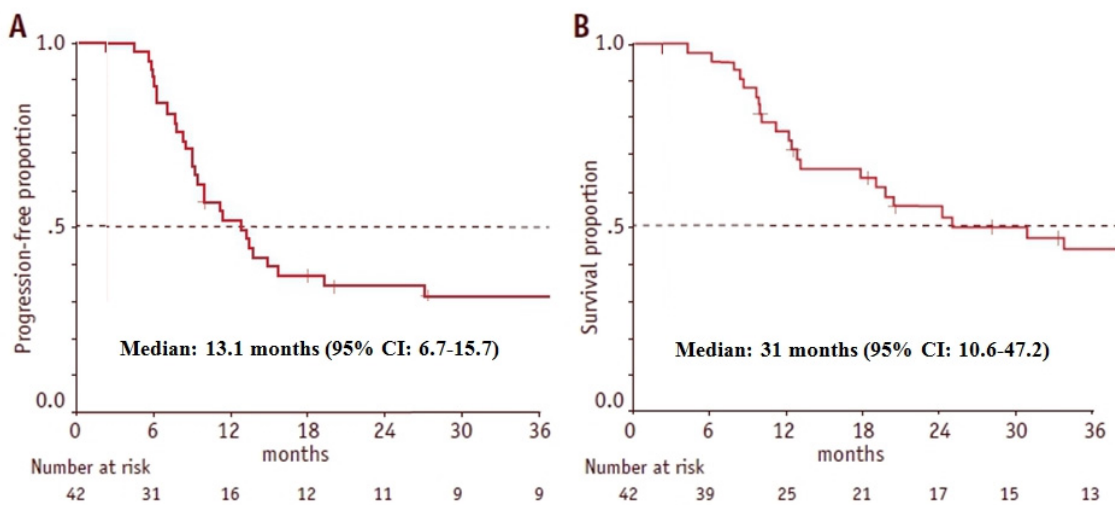


Figure 3 Survival and disease-specific outcomes A, progression-free survival, B, overall survival. The median PFS was 13.1 months (95% CI, 6.7–15.5 months), and the median survival time (MST) was 31 months (95% CI, 10.7–47.3 months), with a survival rate of 65.9% at 1 year and 44.1% at 3 years.

response (cCR), 17 had a partial response, and 3 had a stable disease. The cCR rate was 60% (95% confidence interval [CI], 37.3%-67.5%). As of May 30, 2015, the median follow-up for patients with censored data was 41.3 months (95% CI, 25.4-57 months). Disease progression was observed in 19 patients. The initial sites of disease progression were as follows: lymph nodes in 10 patients, lung in five, primary tumor in three, liver in one, bone in one (some overlap).

The median PFS was 13.1 months (95% CI, 6.7-15.5 months), and the median survival time (MST) was 31 months (95% CI, 10.7-47.3 months), with a survival rate of 65.9 % at 1 year and 44.1% at 3 years. Figure 3 shows the Kaplan-meier curves of progression-free survival and overall survival.

4. Univariate and multivariate analysis of prognostic factors in generation dataset

Table 2 shows the univariate and multivariate analyses for each prognostic factor. The left panel shows the crude hazard ratio (HR) for each variable based on univariate

analysis.

In univariate analysis, gender, performance status, N stage, histological grade, and ND were shown to be significant predictors of survival. The other variables showed no significant correlation with the mortality in the univariate analysis. In the final multiple regression model (the right panel of Table 2), gender, N stage, ND were independently and significantly associated with survival after controlling for other explanatory variables. Prognostic factors associated with overall survival are shown in Table 2.

IV. DISCUSSION AND CONCLUSION

A common concern associated with radiation therapy for esophageal tumors is the inter- and intra-fraction motions during the treatment delivery. The intra-fraction motion of the esophagus or esophageal tumor, caused primarily by respiration, cardiac motion, and esophageal peristalsis, leads to errors in imaging, planning, and delivery⁷⁾. Although this intra-fraction

Table 2 Univariate and multivariate analysis of prognostic factors in generation dataset

| | Pts (n) | Univariate analysis | | | Multivariate analysis | | |
|------------------------|---------|---------------------|------------|---------|-----------------------|-----------|---------|
| | | HR | 95% CI | P value | HR | 95% CI | P value |
| Age (y) | | | | | | | |
| <65 | 23 | (rf) | - | - | (rf) | - | - |
| ≥65 | 26 | 0.97 | 0.70-1.39 | 0.57 | | | |
| Gender | | | | | | | |
| male | 42 | (rf) | - | - | (rf) | - | - |
| female | 7 | 0.47 | 0.21-0.98 | 0.018 | 0.23 | 0.52-1.48 | 0.002 |
| PS | | | | | | | |
| 0-1 | 14 | (rf) | - | - | (rf) | - | - |
| 2-4 | 35 | 2.59 | 1.44-3.93 | 0.001 | 0.76 | 0.43-1.48 | 0.46 |
| N stage (7th) | | | | | | | |
| N1 | 31 | (rf) | - | - | (rf) | - | - |
| N2 | 11 | 5.64 | 2.64-8.70 | <0.001 | 1.98 | 1.06-3.25 | 0.038 |
| N3 | 7 | 8.39 | 3.21-17.84 | <0.001 | 2.41 | 0.94-8.15 | 0.089 |
| Histologic grade (7th) | | | | | | | |
| 1 | 8 | (rf) | - | - | (rf) | - | - |
| 2 | 21 | 2.47 | 1.34-4.53 | 0.0075 | 1.89 | 0.92-3.45 | 0.083 |
| 3 | 5 | 2.35 | 0.97-5.40 | 0.069 | 1.64 | 0.75-4.73 | 0.33 |
| X | 15 | 2.05 | 1.13-4.42 | 0.031 | 1.83 | 0.97-7.58 | 0.25 |
| ND | | | | | | | |
| 0 | 18 | (rf) | - | - | (rf) | - | - |
| 0-3 | 25 | 3.58 | 2.05-6.54 | <0.001 | 1.97 | 1.05-3.35 | 0.031 |
| >3 | 6 | 7.88 | 4.28-15.13 | <0.001 | 3.54 | 1.65-7.57 | 0.002 |

motion is generally smaller than the inter-fraction motion at this tumor site⁸⁾ and smaller than the intra-fraction motions observed in other tumor sites (e.g., lung, liver), it is always desirable to accurately account for the intra-fraction motion so that the treatment margin can be optimized. In particular, large margins (e.g., 5 cm above and below, 2.5 cm radial) are generally used in this tumor site, mainly for covering the subclinical disease and to account for inter- and intra-fraction motions.

As the exactness to decide microscopic disease extensions⁹⁾ and to explain the inter-fraction motion (due to the widely used image guided RT [IGRT]), the need to exactly account for the intra-fraction motion is becoming significant because there are many organs at risk situated close to the target (e.g., lungs, heart, spinal cord, liver, and kidneys). Any reformation in minimizing radiation exposure to these organs at risk would be helpful, particularly for the effort of dose escalation to have local control better¹⁰⁾. To account for intra-fraction motion, an ITV is introduced¹¹⁾. The PTV is then defined as the ITV plus a margin to give a detailed account for inter-fraction tumor position changes or differences. An accepted and favourite ITV assessment method is to use 4DCT¹²⁾, which is classified into different phase bins (usually 10 bins) of a respiratory cycle to invent phase images. By definition, ITV is the unification of GTVs defined on all phases of the 4DCT file. In practice, however, creating ITV needs delineation of a target on all phase images and is therefore repetitive skilled manual work demanding and time consuming. As a more efficient another choice, ITV may be produced based on the maximum intensity projection (MIP), which permits generating ITV based on a single image set¹³⁾.

The CRT is becoming accepted as a standard treatment for locally advanced esophageal cancer, as a neoadjuvant strategy for operable adenocarcinomas or as a radical treatment when there is a high risk of surgical morbidity and mortality¹⁴⁾. Long-term survival for operable squamous cell carcinomas treated with dCRT is comparable in clinical results to surgery alone¹⁵⁾. Although CRT is more effective than either radiation

therapy or chemotherapy alone¹⁶⁾, locoregional control rates with the standard radiation therapy dose of 50Gy are still low, and >75% of recurrences happen within the GTV¹⁷⁾. A clinical relationship between higher dose and better tumor control and survival was described by Zhang et al.¹⁸⁾ when patients were separated into low-dose (51 Gy) and high dose (>51 Gy) groups. Further proof of a radiation dose response has been found by a systematic analysis¹⁹⁾ which looked at rates of pCR in preoperative CRT. Fitting the data to a radiobiological model indicated that increasing the radiation dose prescription from the standard 50 Gy could result in significant advancement and betterment in TCP. Diagonally opposite, data from a phase 3 clinical trial, Radiation Therapy Oncology Group (RTOG) 9405, investigating the administration of higher radiation dose (64.8 Gy) versus standard dose (50.4 Gy), didn't find any improvement in survival or local control, and a relatively severe comorbidity in the high-dose arm²⁰⁾. The radiation therapy treatment technique at this time, though, was done by the use of 2D planning (using relatively large treatment fields) and a consecutive dose boost regimen. The several deaths in the high-dose arm before reaching 50.4 Gy has prevented additional investigation of dose escalation in spite of common comprehending of 2D planning in adequacies. The clinical position and function of radiation therapy dose escalation in improving outcomes for dCRT has been recently identified as one of the priorities for research in esophageal cancer in the United Kingdom²¹⁾. Nevertheless, the most desirable combination of radiation therapy and chemotherapy doses needs to be carefully made stable and firm in order to raise the locoregional control to a better quality or condition. Long-term toxicities, particularly to the cardiorespiratory system, have been described following CRT for esophageal cancer. Acute toxicity related to the part or structure of the heart has been studied specifically, for example, pericardial effusion (onset within 6 months)²²⁾. These studies suggest a higher mean pericardial dose is associated with increased risk of pericardial effusion. Left ventricular mean dose²³⁾ has also been found to be related to acute cardiac damage and destruction checked by MRI for

patients experiencing CRT for esophageal cancer.

As mentioned in the introduction, this study had two primary purposes: 1) to estimate the level of dose escalation up to 70.2 Gy required for a clinically significant increase in tumor control using radiobiological modeling across a group of representative patients, and to examine whether this dose could be safely transferred by computing NTCP for heart and lungs; and 2) to judge and determine the worth or quality of the practical possibility of chemotherapy with mixing docetaxel with the traditional or conventional basic regimens of cisplatin plus 5-FU and radiotherapy up to 70.2 Gy using dose escalation for esophageal cancer patients treated with dCRT by comparing results for individual patients. Radiobiological modeling in this study suggested that dose escalation to the GTV in esophageal cancer has the powerful ability to yield significant clinical advantages in tumor control with only a small increase in lung or heart toxicity for the large number of patients. The relationship between tumor response and normal tissue toxicity during dose escalation should be carefully proved to be valid in clinical trials.

Locally AEC is often resistant to current therapeutic approaches, resulting in impoverished clinical results²⁰. Patients with inoperable disease are usually treated with the dCRT. The standard regimen for chemoradiation therapy combines cisplatin plus 5-fluorouracil (CF) with radiation to gain optimal clinical outcomes and a radiation-sensitizing effect²⁴. In phase 2 studies of CRT with CF plus 60 Gy of radiation therapy in patients who had thoracic AEC with T4 tumors or M1 lymph node metastasis (M1 LYM), or both, the cCR rate was 15% to 33%, with a 3-year survival rate of 23%²⁵. To complete both local and distant control in patients with AEC, new regimens must be invented and newly made. Noticeable pursuit has focused on the use of taxanes for this purpose. Many studies have demonstrated that taxanes are effective in patients with local AEC²⁶. Taxanes help bring about or further the growth or establishment of the tubulin conjugation and stabilize microtubule formation, thereby repressing cancer cell division. Besides cytotoxic effect, taxanes are also outstanding radiosensitizers, capturing the cell cycle in the G2/ M phase²⁷.

The addition of taxanes to CF plus concurrent radiation therapy was thus supposed to improve treatment results in patients with AEC. In a previous phase 1 study, firm chemoradiation therapy with docetaxel, cisplatin, and 5-fluorouracil was endurable and sufferable in patients with AEC, and the active dose for phase 2 studies was recommended²⁸. Based on these findings, this study organized and managed a clinical study of DCF-R plus radiotherapy of 70.2 Gy in patients with thoracic AEC who had T4 tumors and N1-N3, to confirm the efficacy and toxicity of this regimen in AEC, and gained relatively satisfactory clinical results. The cCR rate was chosen as the primary point at which a titration is complete because it is a well-known alternative and representative endpoint for OS patients with esophageal cancer. The cCR rate of 54.9% is stimulating and inspiring compared with former data on the combination of 5-fluorouracil (5-FU) and cisplatin, showing CR rates from 15% to 30%²⁹. The increase in the cCR rate might be ascribed to the fact that the gated-IMRT based on 4DCT data set could distribute high doses to the GTV5, and decrease the radiation dose affected to the normal esophagus epithelium with milder esophagitis and more immediate refreshment of epithelium, making evaluation of a CR of the primary lesion easier and more accurate.

In mid-esophageal cancer, respiration is recognized as a critical cause of target movements. It is also one of the baddest uncertainties during the whole treatment period. A magnified target volume with a certain margin is commonly needed such that the optimized dose encirclement can be achieved. This access, though, may increase the dangers of treatment side effects to the normal tissues around target volume. The disturbance of the GTV centroid was found to be different from one direction to another. The largest tumor motion was revealed in the SI direction, since most of the patients had T4 disease. Images acquired from 4DCT are more likely to represent the true condition and state of patients as compared with 3DCT since the respiratory signals are integrated with the stereoscopic 3DCT imaging during the image obtainment and recreation process. Therefore, 4DCT images could be used to evaluate the scale of the GTV changes in the three dimensions in making a detailed

design or plan of radiotherapy.

Survival in patients with esophageal cancer is affected by the stage of the disease. Squamous cell carcinoma and adenocarcinoma, stage-by-stage, seem to have even survival rates. Lymph node or solid organ metastases affect low survival rates. In 2001–2007, the overall 5-year survival rate for esophageal cancer was 19%³⁰⁾. Patients without lymph node involvement have a significantly better prognosis and 5-year survival rate than patients with the metastases to lymph nodes. Stage IV lesions are associated with a 5-year survival rate of less than 5%. A report of 1,085 patients who had transhiatal esophagectomy for cancer showed that the operation was tied up with a 4% operative mortality rate and a 23% 5-year survival rate. A better 5-year survival rate (48%) was comprehended in a subgroup of patients who had a complete response (i.e., disappearance of the tumor) undergoing preoperative radiation and chemotherapy (i.e., neoadjuvant therapy)³¹⁾. Transhiatal and transthoracic esophagectomies have equivalent long-term survival rates³²⁾. Suzuki et al.³³⁾ revealed that a higher initial standardized uptake value on PET scanning is associated with poorer overall survival among patients with esophageal or gastroesophageal carcinoma receiving chemoradiation. The authors suggested that PET scanning may become useful for customized radiotherapy³³⁾. A study by Gillies et al.³⁴⁾ also found that PET-CT scanning can be used to forecast survival. In this study, the presence of fluorodeoxyglucose (FDG)-avid lymph nodes was a unique poor prognostic factor³³⁾. A study by Prins et al.³⁵⁾ of human epidermal growth factor 2 (HER-2) protein over-expression and HER-2 gene amplification in esophageal carcinomas discovered that HER-2 positivity and gene amplification are independently related to adverse survival. In their study, which involved 154 patients with esophageal adenocarcinoma, HER-2 positivity was showed in 12% of these patients and over-expression was appeared in 14% of them³⁵⁾.

In conclusion, this study suggested that the definitive chemo-radiotherapy with docetaxel, cisplatin, and 5-fluorouracil (i.e., DCF-R) and gating IMRT is tolerable and active in patients with locally AEC.

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•국문초록

국소진행성 중위부 식도암의 동시항암화학 호흡동조 세기변조방사선치료의 포괄적인 임상고찰

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본 논문은 상당히 진행된 중위 식도암의 동시항암화학 방사선치료에 대한 분석의 것이다. 사용한 항암제는 전통적으로 사용되어온 시스플라틴, 5-플루오로우라실, 도세탁실을 추가 시행하였다. 과거 식도암의 방사선 치료에서는 총 선량 50.4 Gy/28회를 처방하였다. 하지만 현대의 방사선치료기술의 비약적인 발전으로, 호흡동조치료와 세기변조방사선치료를 적용하여, 정상조직의 손상을 최대한 감소시키면서 총 선량을 50.4 Gy 이상으로 증가시키는 것이 가능하다. 이에 우리는, 도세탁실, 시스플라틴, 5-플루오로우라실 이라는 새로운 3제 병합요법(DCF-R)에 추가하여, 4DCT 모의시뮬레이션을 기반으로 한 호흡동조 세기변조방사선치료(gated-IGRT) 총 선량 70.2 Gy/39회를 동시에 시도하였으며, 치료기간 동안, 그리고 치료 종료 후 임상적으로 환자에게 위중한 합병증 및 부작용 발생은 관찰되지 않았다. 또한 생존율 향상을 이루어 냈다. 이를 바탕으로, 식도암의 새로운 치료방법을 제안한다.

중심 단어: 도세탁실, 호흡동조세기변조방사선치료, 4DCT 모의시뮬레이션, 식도암