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Original article

Phase I study of integrating PET/CT and dose-escalated intensity modulated radiation therapy using a simultaneous integrated boost technique for thoracic esophageal cancer

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Background: Esophageal cancer has a poor prognosis because most patients have locally advanced disease upon presentation, and are therefore not suitable for upfront surgery. Modern radiation therapy techniques using intensity modulated radiation therapy (IMRT) combined with a novel imaging technique using integrated positron emission tomography and computed tomography (PET/CT) may help radiation oncologists increase radiation dose to the tumor and may improve tumor response.

Objective: The primary aim was to analyze the toxicity of dose-escalated IMRT using a simultaneous integrated boost (SIB) technique and concurrent chemotherapy in esophageal cancer patients using PET/CT as a guide for target delineation. Secondary endpoints were to evaluate response rate, overall survival, and event-free survival rates.

Method: Seventeen consecutive patients with locally advanced carcinoma of the esophagus were treated with preoperative concurrent chemoradiation that consisted of IMRT 64 Gy in 30 fractions (SIB technique), together with two cycles of cisplatin (80 mg/m^2, day 1 and 29) and 5-fluorouracil (1000 mg/m^2/d, days 1–4 and 29–32). Baseline PET/CT was used for staging and target delineation. After complete chemoradiation for 3 months, PET/CT was repeated and the patients were evaluated for esophagectomy. Treatment toxicities were collected. Baseline and 3-month postchemoradiation PET/CT imaging were analyzed and correlated with the pathological findings.

Result: The median follow-up time was 12 months. All 17 patients had squamous cell carcinoma of thoracic esophageal cancer and were treated with chemoradiation. The most common acute ≥grade 3 adverse effects were leucopenia (58.8) and vomiting (23.5%), respectively. Acute ≥grade 3 cardiotoxicities and pulmonary toxicities were observed in 5.9% and 11.7% of the patients, respectively. One patient (5.9%) died from an esophagopericardial fistula. Seven patients underwent esophagectomy after chemoradiation. A pathologic complete remission was achieved in 4 patients (57.1% of the surgical group or 23.5% of the entire group). The overall 1-year survival and event free survival rates for the entire group of patients were 87% and 59%, respectively. There was a statistically significant difference in the overall 1-year survival between surgical and nonsurgical groups (overall 1-year survival, 100% versus 74%, respectively, $p = 0.037$). In contrast, there was no significant difference in 1-year event-free survival between groups (1-year event-free survival, 72% versus 56%, $p = 0.085$). Applying the average absolute reduction and percentage reduction of SUV_{max} in these patients, PET/CT could not predict the pathologic response.

Conclusion: Integrating PET/CT for dose-escalated IMRT in esophageal cancer patients showed acceptable toxicities and promising overall survival, especially when followed by surgery.

Keywords: Chemoradiation, esophageal cancer, intensity modulated radiation therapy (IMRT), positron emission tomography/computed tomography (PET/CT), simultaneous integrated boost, target delineation

Esophageal cancer has a poor prognosis because most patients have locally advanced disease upon presentation. Although esophagectomy remains the curative treatment, only 30% to 40% of patients have a potentially resectable disease. The remainder require neoadjuvant chemoradiotherapy to convert to resectable disease [1, 2] or need definitive chemoradiation [3]. The role of imaging has evolved from only providing anatomical information to providing biological information. Positron Emission Tomography/Computed Tomography (PET/CT), a combination of anatomical and functional tools, has emerged as an essential part of cancer treatment [4, 5]. Positron emission tomography using fluorine-18 fluorodeoxyglucose (FDG-PET) has a higher accuracy, sensitivity, and specificity for the diagnosis of primary tumors and pathological lymph nodes than conventional techniques. Thus, PET/CT has been increasingly used for delineation of the tumor volume, assessment of treatment response, detection of occult metastatic disease, as well as follow-up of the patients [6-8].

In parallel with the advancement in biological imaging, there has been a tremendous improvement of radiotherapy techniques such as 3-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiotherapy (IMRT). To increase the therapeutic ratio of radiation treatment, one must try to precisely locate the target volumes, in particular using FDG-PET, and use IMRT to administer patients the maximum dose while keeping dose to the surrounding organs at a minimum. Recent studies confirmed the use of FDG-PET to estimate the length of gross tumor as compared with resected specimens, both sources of information support the standard uptake value (SUV) cutoff of 2.5 [9, 10]. Furthermore, dosimetric studies showed that IMRT improved dosimetry—at least to the target volumes, lungs [11], and heart [12-15]. Nevertheless, its effects on clinical outcomes are less well documented [13, 16, 17]. By using PET/CT as a tool to delineate tumor extent and utilizing IMRT to conform the maximum dose to target volumes, we hypothesized a better tumor response. Furthermore, if PET/CT could predict pathologic complete remission, patients might not need esophagectomy.

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Materials and methods

Between August 2009 and July 2010, 17 consecutive patients (mean age 58 years; range 43–71 years) with potentially curable, locally advanced esophageal cancer were recruited into this prospective phase I trial. All patients were treated with chemotherapy concurrently with IMRT at the Division of Therapeutic Radiation and Oncology, King Chulalongkorn Memorial Hospital (KCMH). The primary aim was to analyze the toxicities of dose-escalated intensity modulated radiation therapy (IMRT), by using PET/CT as a guide for target delineation. Secondary endpoints were to evaluate response rate, overall survival, event-free survival rates, and to evaluate the role of PET/CT to predict pathologic response and survival outcomes.

All patients had histologically confirmed primary squamous cell carcinoma of the esophagus and did not receive any prior treatment. Other eligibility criteria were as follows: clinical stages I to IVa disease according to the American Joint Committee on Cancer (AJCC) TNM classification of Carcinoma of the Esophagus, 2002 [18]; age 15–75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; adequate bone marrow reserve (absolute neutrophil count of ≥1500 cell/μL; hemoglobin count of ≥10 g%, and platelet count of ≥150,000 cell/μL), normal renal function (serum creatinine level of ≤1.5 mg/dl). Patients with documented distant metastases were excluded. All patients underwent a routine systemic work-up and disease evaluation, which included history and physical examination, routine laboratory studies, computed tomography (CT) imaging of the chest and abdomen, PET/CT imaging, and esophagogastroduodenoscopy (EGD) with biopsy. This study was conducted under the review and approval of the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand. All Patients gave informed consent and patients' anonymity has been preserved.

The patients were treated with concurrent chemoradiotherapy that consisted of intensity modulated radiotherapy to the primary tumor site and pathologic lymph nodes to a planned 64 Gy in 30 fractions using a simultaneous integrated boost (SIB) technique (5 days/week), together with chemotherapy consisting of a combination of cisplatin (80 mg/m^2 via

iv injections) on days 1 and 29, and 5-fluorouracil (1000 mg/m^2/day via continuous intravenous infusions) on days 1–4 and 29–32.

The patients underwent an initial CT acquisition with no administration of oral or intravenous contrast agents, followed by PET scan and intravenous CT scan, for simulation and IMRT planning respectively. Imaging was performed while the patient was breathing normally during both parts of the procedure. The patient's arms were positioned above the head throughout the acquisition period. All images were taken with a hybrid PET/CT system [Siemens-Biograph 16] with a flat table and immobilizing device. The gross tumor volume (GTV) was delineated by using all information from EGD reports, PET, and CT with contrast images. EGD reports were used as a starting point for GTV delineation, i.e. the cranial and caudal margin of GTV (called GTV-primary). An SUV of 2.5 was considered malignant both in primary tumor and lymph node. This SUV was used to delineate the cranial and caudal extent of the GTV-primary[9]. A lateral margin of 1 cm and a longitudinal margin of 3 cm for the GTV-primary were applied to obtain the planning target volume-high risk (PTV HR-primary), while a uniform margin of 1 cm was used for pathological lymph nodes (PTV-lymph node). The lateral margin and longitudinal margin were extended to 1.5 cm and 5 cm from GTV to create the planning target volume—low risk (PTV-LR). All PTVs should be at least 0.7 cm away from the spinal cord. Dose–volume constraints used for IMRT planning are indicated in **Table 1**. PTV-HR and PTV-LR were treated simultaneously to 64 Gy and 54 Gy, respectively, in 30 fractions. The IMRT plan was calculated using an Eclipse treatment planning system (Eclipse version 7.2.34, Varian, PA). Lung homogeneity corrections were used. The treatment was delivered by Varian linear accelerator with a dynamic 80-Leaf MLC (Varian 21EX) or a 120-Leaf MLC (Varian 23EX).

After completion of treatment, the patients underwent a physical examination with complete blood count and chemistry examination every 3 months for 3 years, every 6 months for 2 years, and then annually. At 3 months after completion of chemoradiotherapy, the patients were re-evaluated with PET/CT to assess the therapeutic response, and if feasible, followed by esophagectomy within 1 month interval. CT of the chest and abdomen was performed every 6 months. The other imaging was performed when it was clinically indicated. All acute and late adverse effects were scored according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) [19].

The tumors were classified as responding or nonresponding using Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) [20]. We modified this classification system by using the maximum standard uptake value (SUV_{max}) instead of standardized uptake value using lean body mass (SUL) for PERCIST criteria. All pathologic specimens were reviewed by pathologists who were blinded to the results of the PET/CT. Pathologic response was scored in 3 categories: complete response was defined by the absence of any residual viable tumor cells on histological examination of the esophagectomy specimen; microscopic residual disease was defined as residual tumor less than 10 percent; and, macroscopic residual disease was defined as residual disease more than 10 percent. Correlation between pathologic response and pre-/post-chemoradiation FDG-PET SUV_{max} [21, 22] was evaluated.

Statistical analysis

The survival rates were calculated using the Kaplan–Meier method for analysis of censored data. The significance of differences in survival rates were analyzed using a log–rank test. Event-free survival was determined from the date of commencing radiation to the date of the locoregional, systemic esophageal cancer recurrence or second primary cancer. In patients who did not receive surgery, event was determined at time to tumor progression or metastases. Overall survival was determined from the date of commencing radiation until the date of death from any cause. Statistical software (STATA/MP version 10.0; STATA) was used for analysis. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics and treatment compliance

The characteristics of the patients are shown in **Table 2**. The median length of follow-up was 12 months (range 4–25.8 months). Sixteen patients were male (94.1%). The most common initial stage was stage IV in 9 patients (52.9%), followed by stage III in 7 patients (41.2%). All patients except one received 2 cycles of chemotherapy. Six patients required dose reduction in the second cycle of the concurrent

chemotherapy, mainly because of hematologic toxicities. The average dose to 95% (D95) of PTV-HR and PTV-LR volume were 61.5 Gy and 53.6 Gy in 30 fractions, respectively (**Table 1**). Some patients needed radiation dose reduction to the tumor because of overdose to the surrounding organs, particularly the lungs. The percentage of normal lung volume receiving a total dose of 20 Gy and 10 Gy (V20 and V10) was 26.3% and 48.4%, respectively. The average maximum dose to the spinal cord was 40.6 Gy. Median dose to the heart (D50) was 30.8 Gy.

Table 1. Dose-volume constraints used for IMRT planning and their compliance

Target volume	Simultaneous Integrated Boost			Average dose in patients (Gy) (n = 17)
	Goal dose (Gy)	Fractions	Dose/fraction (Gy)	
PTV-LR	54	30	1.8	D95* = 53.6
PTV-HR	64	30	2.13	D95* = 61.5
Organs at risk	**Dmax (Gy)**	**Dose volume constraints**		
		Dose (Gy)	Max Volume (%)	
Spinal cord	45			Dmax = 40.6 Gy
Lung		10	40	V10 = 48.4%
Lung		20	20	V20 = 26.3%
Heart		30	50	Median dose = 30.8Gy

*D95 = dose encompass 95% of PTV volume; Dmax = maximum dose; V10 = percentage of lung volume received 10 Gy; V20 = percentage of lung volume received 20 Gy

Table 2. Patient Characteristics

Patient Characteristics	All Patients (n = 17)
Age (y)	
Mean	58.29
Range	43–71
Gender	
Male	16 (94.1%)
Female	1 (5.9%)
Histology	
Squamous cell carcinoma	17 (100%)
Tumor location	
Upper thoracic	3 (17.6%)
Mid thoracic	6 (35.3%)
Lower thoracic	8 (47.1%)
Tumor status	
T3	10 (58.8%)
T4	7 (41.2%)
Lymph node status	
N0	3 (17.7%)
N1	14 (82.3%)
Stage grouping	
II	1 (5.9%)
III	7 (41.2%)
IV	9 (52.9%)
Surgery	
Resectable	7 (41.2%)
Unresectable	6 (35.2%)
Refused surgery	3 (17.7%)
Death before surgery	1 (5.9%)

Treatment toxicities

The most common acute ≥grade 3 adverse effects were leucopenia (58.8) and vomiting (23.5%) respectively (**Table 3**). Acute ≥grade 3 cardiotoxicities and pulmonary toxicities were observed in 5.9% and 11.7% of the patients, respectively. One of these patients (5.9%) died from an esophagopericardial fistula at 186 days after first day of radiation. No patient had febrile neutropenia. Two patients (11.8%) had grade 3 weight loss.

Response rates

Seventeen patients completed chemoradiation, 7 of them underwent surgical resection. Among patients in this surgical group, a pathologic complete response (pCR) was achieved in 4 patients (57.1%); microscopic residual disease in 2 patients (28.6%); and macroscopic residual in 1 patient (14.3%). Ten remaining patients did not receive surgery; 6 of them had unresectable disease; 3 refused surgery; and 1 died before undergoing the second PET/CT imaging from an unknown cause.

Overall survival

The 1-year survival rate was 87% for the 17 eligible patients. The overall 1-year survival rate was higher in patients who underwent esophagectomy versus who did not at 100% and 74%, respectively (P = 0.0366) (**Figure 1**). Median survival time was not reached for the entire group or in the surgical group. However, it was 14 months in the nonsurgical group.

Event-free survival

The median event-free survival time was 15.5 months, whereas the 1-year event-free survival rate was 59%. One-year event-free survival rates were 72% in surgical group and 56% in nonsurgical group (P = 0.0849) (**Figure 2**).

Table 3. Treatment toxicities (number of patients)

Toxicities	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	14	3	0	0	0
White blood cell decrease	1	6	6	4	0
Platelet decrease	13	4	0	0	0
Dysphagia	3	12	2	0	0
Cardiovascular, general	16	0	0	0	1
Lung, general	15	0	2	0	0
Weight loss	11	4	2	0	0
Vomiting	3	10	4	0	0

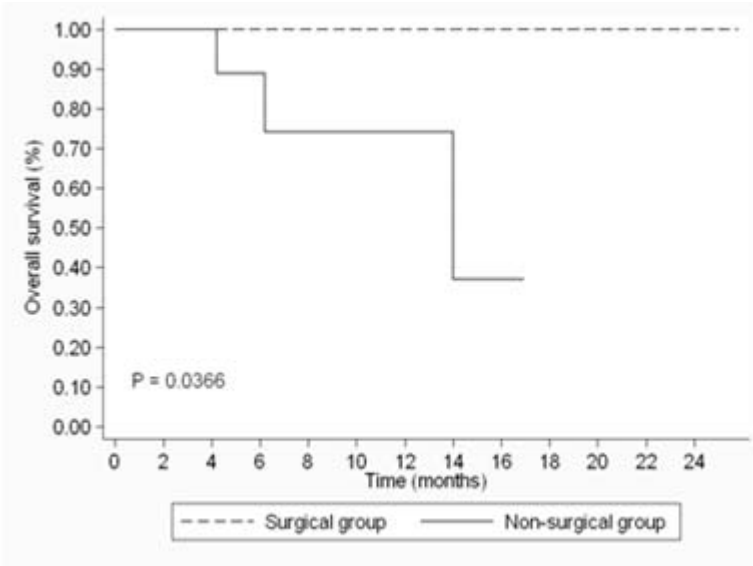

Figure 1. Kaplan–Meier analysis of the overall survival of esophageal carcinoma patients according to their surgical status.

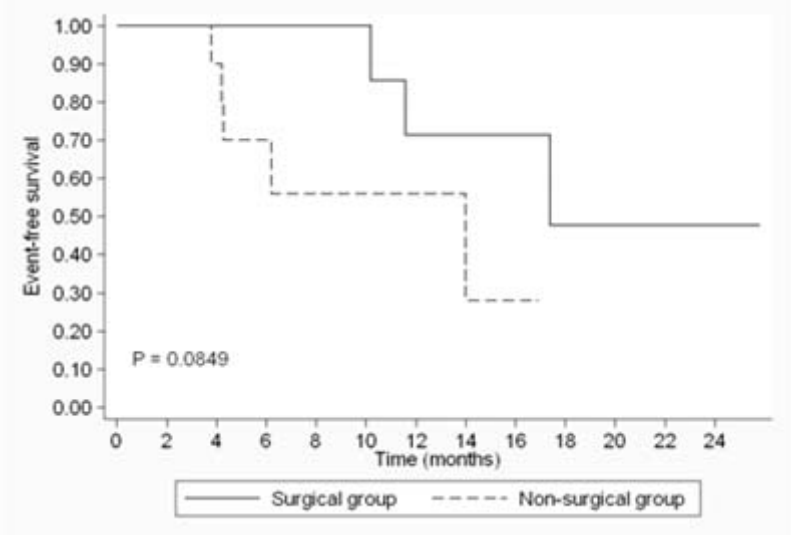

Figure 2. Kaplan–Meier analysis of the event-free survival of esophageal carcinoma patients according to their surgical status

Using metabolic change to predict for pathologic response

Excluding one patient who died before receiving second PET/CT imaging and one who had a misregistration between CT and PET, resulting from uncontrollable movement of the patient during the second PET/CT imaging that may have caused imprecise metabolic and anatomical localization, fifteen patients remained for interpretation of metabolic response. The median time to second PET/CT was 84 days (range 34–126) after concurrent chemoradiation. Of the 15 patients who completed PET/CT studies, the average SUV_{max} of the pre- and postchemoradiation images were 13.2 (range 5.2–19.6) and 4.9 (range 2.3–7.2), respectively. Using PERCIST criteria to evaluate the therapeutic response, all patients had a partial response to therapy with a mean percent SUV_{max} reduction of 61.7% (range 36.5–82.3).

In the 7 resectable patients who had definite pathologic reports, the average reduction in SUV_{max} for patients who had pCR was 5.9. The corresponding figures for patients who had microscopic and macroscopic residual tumor were 8.8 and 1.9, respectively. The average percentage reductions in FDG uptake were 52% in patients with pCR, 64.6% in microscopic residual tumor and 36.6% in macroscopic residual tumor. The average absolute reduction and percentage reduction of SUV_{max} in resectable patients was 6.2 and 53.5%, respectively. By applying these values for classification of pathologic response, no significant difference was observed between the groups. The percentage reduction in FDG uptake for the patients who did not have surgery was 68.7%.

Patterns of failure

One patient experienced regional failure and was treated with palliative chemotherapy. Four patients developed distant metastases; sites of failure were the liver (n = 1), lung (n = 1), nonregional lymph node (n = 1), and multiple distant metastases (n = 1). All of these 4 patients received two cycles of concurrent chemotherapies, and had at least 80% of planned dose. Five patients are alive with persistent disease; all of them refused surgery or had unresectable disease. Four patients are alive without any documented disease progression. Three patients died; one from disease progression; one from treatment-related complication; and, the other from an unknown cause.

Discussion

This prospective analysis reports the toxicities, response rate, overall survival, and event-free survival rates of integrating PET/CT to escalated dose IMRT using an SIB technique for thoracic esophageal carcinoma. We hypothesized that by giving higher than a conventional dose of radiation to the exact tumor location, better local control would be expected. However, treatment toxicity was our concern. RTOG 85-01 [3, 23], a landmark trial for concurrent chemoradiation in esophageal cancer, reported an

overall survival benefit of concurrent chemoradiation over radiation alone. The 1-year survival rate improved from 34% to 52% when adding chemotherapy to 50 Gy of radiation treatment. Severe hematological side effects were reported in 29 out of 60 patients (48.3%) who received combined therapy. Our study revealed severe leucopenia in 58.8%. Since then, concurrent chemoradiation has become the standard treatment in locally advanced esophageal cancer. In an attempt to improve the outcome by giving a higher dose instead of the standard dose of radiation, RTOG 94-05 [24] attempted to escalate the radiation dose from 50.4 to 64.8 Gy combined with concurrent cisplatin and 5FU. Unfortunately, there was no significant difference in median survival. The 2-year survival rates in standard dose and higher dose RT were 40% and 31%, respectively. Eleven patients (10%) in the higher RT dose arm succumbed from treatment-related complications. This might reflect the poor RT technique at that time. Our study revealed a 1-year OS of 87%, which was superior to the historic data and there was only 1 treatment-related death from an esophagopericardial fistula (5.9%). Esophagopericardial fistulas might be the result of higher than conventional fractionation in our study.

Other than radiation dose escalation, there was an attempt to give multimodal treatment to improve treatment outcomes. Chemoradiation followed by surgery, as tested in the FFCD trial 9102, reported by Bedenne et al. [25] involved 444 patients. Only 259 of these patients who had a clinical response to induction chemoradiation were randomized between surgery or further chemoradiation to a total dose of 66 Gy, which is higher than standard practice. Median overall survival for trimodality group (i.e. conventional dose chemoradiation followed by surgery) was 18 months compared with 19 months in higher dose chemoradiation groups. The corresponding estimated overall 1-year survival from the survival curve was 64% and 67%, respectively. The pCR was 24.2% in 149 patients who underwent surgery. While the pCR in our study was 57.1%, only 7 patients were resected. Bedenne et al. concluded that patients with operable locally advanced thoracic esophageal cancer had no benefit from addition of surgery after initial response to concurrent chemoradiation. Stahl et al. [26] included 172 patients with locally advanced upper- and midesophageal cancer randomized between induction chemotherapy followed by chemoradiation 40 Gy and surgery (arm A) versus chemoradiation alone (arm B) using high dose RT (60–65 Gy). Again, there was no difference in overall survival between the groups (16 months in the trimodality arm versus 15 months in the higher chemoradiation arm). The estimated overall 1-year survival was 60% and 65% in the trimodality and high-dose chemoradiation groups, respectively. The overall treatment-related mortality was 12.8% in arm A and 3.5% in arm B. Many other studies [1, 2, 23-32] detailed in **Table 4**, utilized trimodal treatment and produced an overall 1-year survival between 52% to 78%, and a median survival time between 9 months and 4.5 years. By using high-dose radiation concurrently with chemotherapy, our results showed 1-year OS rates of 74% and this increased to 100% when followed by surgery, which is better than the survival in the previously mentioned studies [1, 2, 23-27, 29, 30]. Furthermore, this is also proof of principle that high-dose radiation when delivered with IMRT, with or without esophagectomy, is feasible and tolerable. There was only one treatment-related death (5.9%) in our study compared with 9% in the FFCD study [25] and 13% in the study by Stahl et al. [26] using trimodal treatment. This might be the result of the IMRT technique used in our study that can improve the toxicity profile.

Nutting et al. [15] included 5 patients with esophageal carcinoma comparing conformal radiotherapy (CRT) plan with the IMRT plan. Radiation dose was planned to 55 Gy. The investigators concluded that the IMRT plan offered comparable PTV dose homogeneity, but had a significant improvement in lung sparing. The mean lung dose decreased from 11 Gy using CRT to 9.5 Gy using IMRT, and V18 (percentage volume received 18 Gy) from 18.8% to 14.1 %. A dosimetric study by Wu et al. [14], evaluated 15 midthoracic esophageal cancer patients with radiation dose of 60 Gy. Again, IMRT could reduce lung V25 significantly, while delivered a similar spinal cord dose as in the CRT plan. Recently, Welsh et al. [33] described an analysis of 10 patients with distal esophageal cancer comparing different radiation techniques: two-dimensional conformal radiotherapy (2D-CRT), IMRT to 50.4 Gy, and SIB-IMRT to 64.8 Gy, all in 28 fractions. The SIB-IMRT to 64.8 Gy reduced the significant dose to normal structures and significantly escalated the dose to the GTV by 28% as compared with the 50.4 Gy IMRT. Of note, the V10 and V20 of the lung in this study (22% and 11%, respectively) are lower than in our study (48.4% and 26.3%, respectively) because

Table 4. Treatment outcomes in randomized control trials between trimodality treatment versus surgery alone or chemoradiation alone

First author, year	Randomized	N	RT dose (Gy)		Chemotherapy	Survival		
			Total dose	Daily dose		3-yr OS (%)	1-yr OS (%)	MST (months)
Urba [1], 2001	CRT+SS	50	45	1.5 bid	CDDP/5FU/VB	30	70*	16.9
		50				16	60*	17.6
Bosset [2], 1997	CRT+SS	151	37	3.7	CDDP	36	74*	18.6
		146				34	70*	18.6
FFCD 9102 [25], 2007	CRT+SCRT	129	46 or 30	2 or 3	CDDP/5FU	33.6†	64*	17.7
		130	66 or 45	2 or 3	Same	39.8†	67*	19.3
Stahl [26], 2005	CRT+SCRT	86	40	2	Induction : FLEP	39.9†	67*	16
		86	At least 65	2	Concurrent : PE Same	35.4†	64*	15
Walsh [27], 1996	CRT+SS	58	40	2.67	CDDP/5FU	32	52	16‡
		55				6	44	11
CALGB 9781 [28], 2006	CRT+SS	30	50.4	1.8	CDDP/5FU	39§	NR	4.5 y‡
		26				16§	NR	1.8 y
Burmeister [29], 2005	CRT+SS	128	35	2.33	CDDP/5FU	33	78*	22.2
		128				27	60*	19.3
Le Prise [30], 1994	CRT+SS	41	20	2	CDDP/5FU	NR	47	10
		45				NR	47	10
Nygaard [31], 1992	CRT+SS	53	35	1.75	CDDP/BLM	17	NR	9
		50				10	NR	8.4
Apinop [32], 1994	CRT+SS	35	40	2	CDDP/5FU	NR	NR	10
		34				NR	NR	10
Our study 2010	CRT+SCRT	7	64	2.13	CDDP/5FU	NR	100	Not reach
		10	64	2.13	Same	NR	74	14

*Estimated from survival curve §5-year overall survival †2-year overall survival ‡$P < 0.05$; CDDP = Cisplatin; CRT = Chemoradiation; FLEP = 5FU/leucovorin/etoposide/cisplatin; MST = Median survival time; NR = Not reported; OS = Overall survival; PE = Cisplatin/etoposide; S = Surgery; VB = Vinblastine

all cases were adenocarcinoma of the distal esophagus. Shi et al. reported the incidence of severe acute radiation pneumonitis in the patients who kept V10 ≤50% as approximately 6% [34]. In our study, only 2 patients (11.8%) experienced grade 3 lung toxicity. This means that when strictly applying dose–volume constraints (Table 1), we can prevent treatment-related complications and mortality, particularly our results revealed no perioperative death.

La et al. [13] reported a cohort of 30 noncervical esophageal cancer patients treated with the IMRT technique, 18 of them received definitive chemoradiation, while the remainder were treated with preoperative chemoradiation. The median radiation dose was 50.4 Gy. The investigators observed a 2-year disease-free rate of 38% and the overall survival rate of 56%. Patients treated in the preoperative group had a favorable, but nonsignificant difference in 2-year locoregional control as compared with those who received definitive chemoradiation (83% versus 51%, $P = 0.32$). There were 7%, 6.7% and 0% with acute grade 3 hemotoxicity, cardiotoxicity, and pulmonary toxicity, respectively. No acute grade ≥Gr 4 hematotoxicity was seen, while both acute grade ≥Gr 4 cardiotoxicity and pulmonary toxicity was 3%. The incidence of acute toxicity was lower compared with our results, which can be explained by the lower radiation dose compared with our study.

Weber et al. [6] studied 40 patients with locally advanced adenocarcinoma of the esophagogastric junction using ^{18}F-FDG-PET imaging prior to receiving

neoadjuvant cisplatin-based polychemotherapy and 14 days after chemotherapy. The investigators observed that PET imaging may differentiate responding and nonresponding tumors early in the course of therapy. The reduction of tumor FDG uptake after therapy was significantly correlated with treatment response. A cutoff value of 35% reduction of initial FDG uptake was associated with an improved response and survival, with sensitivity and specificity of 93% and 95%, respectively. Flamen et al. [35] described an analysis of 36 patients with locally advanced esophageal cancer who underwent ^{18}F-FDG-PET imaging before and 1 month after chemoradiation. A reduction in the tumor-to-liver uptake ratio between post-treatment ^{18}F-FDG-PET imaging of 80% or greater was a predictive factor for clinical response and improvement of overall survival with a sensitivity of 71% and specificity of 82%. Swisher et al. [22] reported a study including 83 patients with carcinoma of the esophagus who underwent baseline and postchemoradiation ^{18}F-FDG-PET imaging. They reported that postchemoradiation FDG-PET SUV of 4 or less showed a strong correlation with 2-year survival rate, but post-CRT FDG-PET failed to discriminate complete response and microscopic residual disease. By contrast with a previous study, Levine et al. [21] described an analysis of 64 patients with T3-4 N0M0 or T1-T4 N1 M0 esophageal cancer who underwent baseline ^{18}F-FDG-PET imaging and repeated this imaging 4–6 weeks after therapy. The authors observed a strong correlation between the patient survival and pretreatment $SUV_{max\ 1\ hour}$ of 15 or more, but the reason for this result remains unknown. A decrease in $SUV_{max1\ hour}$ of 10 or more was also correlated with treatment responses.

Because of the small number of patients included in our study, especially patients who could undergo esophagectomy, we cannot draw any conclusion regarding the suitable SUV to predict pathologic response. Moreover, the interval between the first and second PET/CT was different compared with previous studies. However, at present there is no widely accepted protocol using PET/CT to predict for pathologic response, we suggested that surgery should remain the therapeutic option after chemoradiation in patients for whom this is feasible. Our results confirmed an overall survival benefit in the surgical groups. However, more patients and a long-term follow-up are needed to determine whether PET/CT can be used to categorize which patients can avoid surgery.

Conclusion

SIB dose-escalated IMRT concurrent with chemotherapy is feasible and tolerable in treatment of thoracic esophageal cancer patients.

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