accordance with the concept of 3-field LN dissections in curative surgery, ENI has been adopted for definitive CCRT at our institution, but the benefit of ENI in CCRT for thoracic esophageal cancer lacks consensus [9–13]. The purpose of this study was to retrospectively describe patterns of recurrence of ENI in CRT for thoracic esophageal cancer.

Patients and methods

Patients

The subjects considered were 126 consecutive esophageal SqCC patients treated with definitive and entirely 3D-CRT between 2000 and 2009. Final analysis was based on all of these 126 patients. Characteristics of the group are summarized in Table 1.

Patients were staged according to the American Joint Commission on Cancer (AJCC) 1997 Staging System. Initial staging consisted of a history and medical examination, routine blood tests, chest X-ray, upper endoscopy with Lugol's staining, chest CT with upper abdomen, barium contrast X-ray, and pulmonary function tests. Bone scan and CT or MRI of the brain was done only in case of clinical suspicion of metastases. All patients had positron emission tomography (PET) done for an initial staging. Only 20% of patients underwent endoscopic ultrasonography.

Patients deemed to have technically unresectable cancer, patients who refused to undergo surgery, or those considered medically unfit for surgery were eligible for definitive CRT.

Table 1
Patient and tumor characteristics.

Characteristic	No.	%
No. of patients	126	
Sex		
Male	111	88%
Female	15	12%
Age, year		
Range	42–85	
Median	67	
Histology		
Squamous cell carcinoma	126	100%
Adenocarcinoma	0	0%
Primary site		
Upper thoracic portion	29	23%
Middle thoracic portion	53	42%
Lower thoracic portion	44	35%
Tumor length, cm		
Range	3–18	
Median	7	
T stage		
T1	28	22%
T2	18	14%
T3	54	43%
T4	26	21%
N stage		
N0	50	40%
N1	76	60%
M stage		
M0	91	72%
M1a	5	4%
M1b	30	24%
Stage		
I	22	17%
II	31	25%
III	38	30%
IV	35	28%
Initial response & patterns of failure		
CR (complete response)	87	69%
Failure-free	47	37%
Any failure	40	31%
First site of failure		
Local alone	20	16%
Distant alone	12	10%
Both local + distant	8	6%
Elective node alone	0	0%
Non-CR	39	31%

Radiotherapy planning and target volume definition

All patients received extended ENI and were treated with 50–50.4 Gy delivered in 1.8–2 Gy per fraction over 5–5.6 weeks. Gross Tumor Volume (GTV) was defined for each subject as tumor volume was visualized on CT and endoscopic extension. All LNs with a diameter at least 1 cm in short axis in CT or positive by FDG-PET (excluding physiological accumulation) were included in the GTV. To sum up, GTV included primary cancer and metastatic lymph nodes. Clinical target volume (CTV) was defined as the whole thoracic esophagus (=from the supraclavicular fossae to the esophagogastric junction) including GTV plus 5 mm margin. CTV comprised up to M1a LNs as well as regional LNs including positive LNs. The definition of regional LNs by AJCC 1997 is mediastinal and perigastric LN excluding celiac LN. The definition of M1a region by AJCC 1997 is cervical LNs in the upper thoracic, none in the middle thoracic, and celiac LNs in the lower thoracic esophagus (Fig. 1). PTV was created by adding margins of 5–10 mm to the respective CTVs. Dose was specified to the ICRU point. Treatment was entirely 3D-planned, and dose homogeneity criteria within respective PTVs had to be within 95–107% of the prescribed dose even if the field-in-field technique was used. At least four fields were used (two anterior–posterior opposed fields, and two anterior–posterior oblique opposed fields to remove the spinal cord from the radiation fields) and one or two beams were added with the field-in-field technique if necessary. Mean lung dose had to be kept at or below 20 Gy and V20 (=the lung volume rate receiving over 20 Gy) < 20%. Spinal cord dose had to be kept at or below 45 Gy. Treatment was delivered by linear accelerators with 6–10 MV photons.

Chemotherapy regimen

All patients received chemotherapy concurrently with irradiation. The chemotherapy consisted of two cycles of 5-fluorouracil (800 mg/m^2/day, days 1–4 & days 29–32, continuous) combined with nedaplatin (80 mg/m^2, day 1 & day 29, bolus); standard techniques were used for hydration and alkalization. The chemotherapy started at the first day of irradiation. After concurrent CRT, in the adjuvant setting an additional one or two cycles of the same dose of chemotherapy were given for patients who still had sufficient bone-marrow function and performance status and who did not refuse additional chemotherapy.

Follow-up

Patients were followed on a regular basis, with visits at 1 month following treatment, and every 3 months thereafter during the first 2 years, and every 6 months thereafter. Chest X-rays were performed at every visit, CT of the chest every 6 months or more frequently at the suspicion of tumor progression.

Endpoints and statistical analysis

Local progression was scored as enlargement of initial (primary or nodal) abnormalities on CT (any abnormalities on chest X-ray were verified by CT). Kaplan–Meier method was used for estimation of overall survival and disease-free survival. The times for survival were calculated from the start of RT. Differences in patients' or tumor's characteristics were analyzed by the chi-square test or

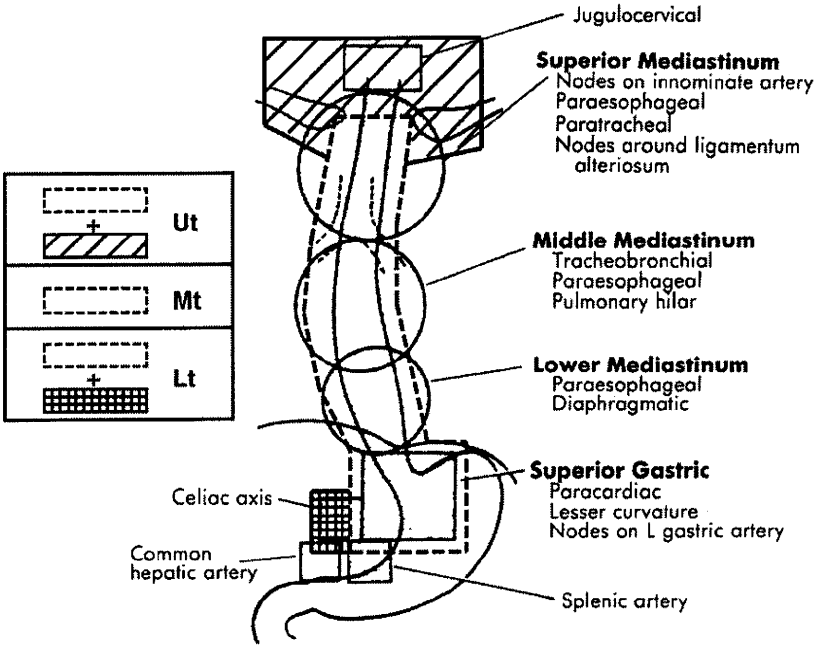

Fig. 1. A schema of each radiation field.

Fisher's exact test for 2 × 2 columns and unpaired *t*-test for a succession of numbers. Differences with values of $p < 0.05$ were considered statistically significant. Complete response (CR) for the primary tumor was defined by endoscopy when all visible tumors, including ulcerations, disappeared with a negative biopsy. CR for metastatic LNs was defined as the complete disappearance of all measurable and assessable disease for ⩾4 weeks and the persistence of small nodes (<1 cm) with no evidence of progression at ⩾3 months after the completion of treatment or without any uptake by FDG-PET.

Results

The characteristics of the 126 patients are listed in Table 1. The median age was 67 years, ranging from 42 to 75 years. The tumor histology was SqCC in all 126 patients. The sub-sites of the primary tumors included upper/middle/lower thoracic portions, with the following distribution: 29/53/44 (23%/42%/35%). Summary of TNM classification was as follows: T1/T2/T3/T4, 28/18/54/26 (22%/14%/43%/21%); N0/N1, 50/76 (40%/60%); M0/M1a/M1b, 91/5/30 (72%/4%/24%); Stage I/II/III/IV, 22/31/38/35 (17%/25%/30%/28%). The metastatic sites of 30 M1b patients were lower cervical, supra-clavicular or celiac LNs. After concurrent CRT, 53 patients (42%) who achieved CR included 16 and 38 patients who received a total of 3 and 4 cycles, respectively.

Mean follow-up for the living 63 patients was 28.3 (±22.8) months. The initial response after CCRT and the patterns of failure are shown in Table 1. Eighty-seven patients (69%) achieved CR without any residual tumor at least once after completion of CRT. Local progression and distant metastases after CR occurred in 20 (16%) and 20 (16%) patients, respectively, as any component of failure. Isolated nodal failure was not found in any patient.

The details of 20 local recurrence cases are shown in Table 2. The median age was 64 years, ranging from 48 to 75 years. The sub-sites of the primary tumors included upper/middle/lower thoracic portions, with the following distribution: 50%/25%/25%. Summary of TNM classification was as follows: T1/T2/T3/T4, 15%/15%/50%/20%; N0/N1, 35%/65%; M0/M1a/M1b, 75%/0%/25%; Stage I/II/III/IV, 15%/15%/45%/25%. The upper thoracic esophageal carcinoma showed more relapses (10/29 patients = 34%) to have a relapse at the local site than the middle (5/53 patients = 9%) or lower thoracic carcinomas (5/44 patients = 11%) (X^2, $p = 0.0073$). The summary characteristics of patients with the upper thoracic esophageal cancers were T1/T2/T3/T4, 24%/10%/28%/38%; N0/N1, 38%/62%; M0/M1a/M1b, 66%/17%/17%; Stage I/II/III/IV, 21%/17%/28%/34%; median age, 68 years (range, 42–75). There was no perceptible bias in the background of patients with the upper thoracic esophageal cancer. The median period to local recurrence was 6.9 months (range, 2.4–25.8 months).

The details of 20 distant recurrence cases are shown in Table 2. The median age was 64 years, ranging from 54 to 75 years. The sub-sites of the primary tumors included upper/middle/lower thoracic portions, with the following distribution: 16%/53%/31%. Summary of TNM classification was as follows: T1/T2/T3/T4, 16%/16%/42%/26%; N0/N1, 47%/53%; M0/M1a/M1b, 68%/0%/32%; Stage I/II/III/IV, 11%/37%/21%/31%. No risk factor that was likely to have a relapse at the distant site was found. Nine patients out of 19 distant recurrence cases (47%) were given 3–4 cycles of chemotherapy. The median period to distant recurrence was 9.0 months (range, 2.6–68.4 months). Thirty-six (92%) of the 39 relapses occurred within 26 months.

The 2-year and 3-year overall survival rates were 56% and 43%, respectively (Fig. 2). The median survival time (MST) was 28.5 ± 6.9 months. The 1-year, 2-year and 3-year disease-free survival rates were 46%, 38% and 33%, respectively (Fig. 2). The median disease-free survival time was 9.0 ± 1.1 months.

Adverse events observed after definitive CRT were shown in Table 3. During CRT, when hematological adverse events of grades 3 and 4 were studied in the acute phase of all 126 patients, leukopenia was seen in 62 (49%) and 30 patients (24%), anemia in 23 (18%) and 15 (12%) patients, and thorombocytopenia in 24 (19%) and 21 patients (17%). Eighty-nine (71%) and 29 patients (23%) were free from grade 4 and grades 3–4 of acute hematological adverse events, respectively. On the other hand, for non-hematological side effects, acute radiation esophagitis of grades 2, 3, and 4 was seen in 37 (29%), 29 (23%), and 3 patients (2%), respectively.

Table 2
Details of 20 local & 20 distant recurrent cases.

No.	Age, y	Sex	Location	Stage	TNM stage	CTx cycle	Recurrent site	Local	DFS (mo)	Salvage Tx	OS (mo)	State
Local recurrence												
7	60	M	Middle	I	T1N0M0	2	Primary		19.8	BSC	56.4	Dead
20	70	M	Upper	III	T3N1M0	2	Primary		4.7	BSC	20.9	Dead
29	60	M	Upper	III	T4N1M0	2	#108		5.4	CTx	13.2	Dead
38	71	M	Upper	I	T1N0M0	2	Primary		9.1	BSC	17.0	Dead
41	56	M	Middle	IVB	T3N0M1b	2	Primary		25.8	Surgery	41.2	Dead
44	63	M	Middle	IVB	T3N1M1b	2	#1		6.5	CTx	22.0	Dead
47	53	M	Upper	III	T4N1M0	2	#106rec R		6.4	CTx	20.5	Dead
48	78	M	Upper	III	T3N1M0	2	#107		7.3	BSC	23.5	Dead
49	48	F	Middle	III	T3N1M0	2	Primary		7.8	BSC	17.1	Dead
71	76	M	Lower	III	T3N1M0	2	#3		15.9	CTx	26.3	Alive
78	64	M	Lower	III	T3N1M0	4	Primary		5.2	CTx	9.6	Dead
81	67	M	Upper	MA	T2N0M0	4	Primary		15.5	Surgery	27.6	Alive
84	79	F	Upper	IVB	T4N1M1b	2	Primary		3.3	BSC	5.2	Dead
91	64	M	Upper	I	T1N0M0	4	Primary		8.7	Surgery	22.7	Alive
93	67	M	Lower	MA	T3N0M0	2	Primary		7.2	CTx	18.1	Dead
95	61	F	Lower	III	T3N1M0	2	Primary		8.6	Surgery	11.6	Dead
99	60	M	Middle	MA	T2N0M0	2	Primary		2.4	Surgery	18.7	Alive
103	55	M	Upper	IVB	T4N1M1b	4	Primary		4.4	Surgery	17.8	Alive
104	70	F	Upper	IVB	T2N1M1b	4	Primary		5.2	CTx	13.7	Dead
117	76	M	Lower	III	T3N1M0	4	Primary		5.3	ESD	11.1	Alive
Distant recurrence												
3	54	F	Middle	III	T4N0M0	4	PALN	Control	24.1	BSC	34.1	Dead
4	73	M	Middle	MA	T2N0M0	4	Liver	Control	57.4	BSC	60.1	Dead
6	59	F	Middle	MA	T2N0M0	2	Lung	Primary	12.3	BSC	14.9	Dead
9	64	M	Lower	MA	T3N0M0	3	Bone	Control	17.9	BSC	32.4	Dead
10	57	M	Middle	IVB	T3N1M1b	2	Bone	Control	3.1	Surgery	8.5	Dead
16	61	F	Lower	MA	T2N0M0	2	PALN	Control	68.4	CCRT	86.0	Alive
18	65	M	Middle	I	T1N0M0	2	Axial LN	Control	3.8	CCRT	38.1	Dead
19	63	M	Lower	IVB	T4N1M1b	2	Lung	Primary + LNs	9.3	BSC	13.7	Dead
22	61	M	Upper	MA	T3N0M0	2	Lung	Primary	13.5	BSC	17.2	Dead
30	58	M	Middle	III	T3N1M0	2	Brain	Control	9.0	Brain SRT	31.6	Dead
39	65	M	Middle	IVB	T4N1M1b	2	Lung	Primary	4.3	CTx	10.3	Dead
46	72	M	Lower	III	T3N1M0	2	Pleural	Primary	31.6	CTx	43.6	Dead
76	75	M	Middle	IVB	T3N1M1b	4	Liver	Primary	7.3	BSC	8.5	Dead
80	73	M	Upper	IVB	T3N1M1b	2	Lung	Control	2.6	BSC	8.4	Dead
90	55	M	Upper	IVB	T4N1M1b	4	Lung	Control	4.1	BSC	9.5	Dead
94	70	M	Middle	III	T4N1M0	3	Lung	Primary	9.8	Surgery	21.0	Alive
109	60	M	Middle	I	T1N0M0	4	Liver	LN	8.0	CTx	15.9	Alive
113	66	M	Lower	MA	T3N0M0	4	Adrenal	Control	6.9	CCRT	13.5	Alive
115	70	M	Lower	MB	T1N1M0	4	Lung + Liver	Control	8.4	BSC	12.5	Alive
121	68	M	Middle	IVB	T4N1M1b	4	Lung + Adrenal	Control	10.0	CTx	10.3	Alive

Abbreviations: LN = lymph node, Tx = treatment, M = male, F = female, CTx = chemotherapy, BSC = best supportive care, #108 = Middle paraesophageal LN, #1 = Right cardiac LN, #106rec R = Right recurrent nerve LN, #107 = Subcarinal LN, #3 = LN along the lesser curvature, DFS = disease-free survival, OS = overall survival, ESD = endoscopic submucosal dissection, yo = years old, PA = paraaortic, LN = lymph node, Tx = treatment, CCRT = concurrent chemoradiation, SRT = stereotactic radiotherapy.

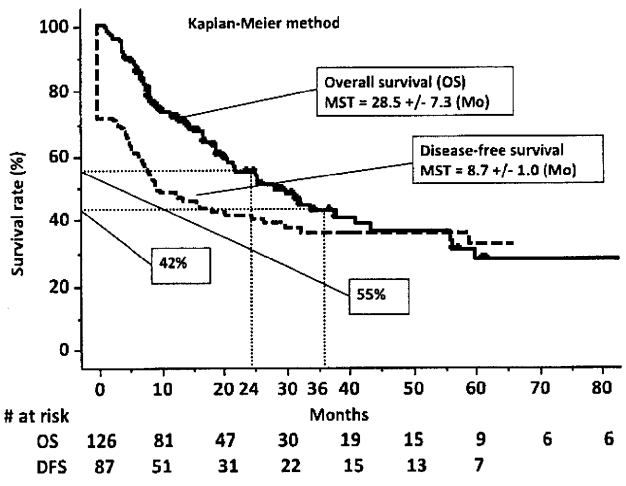

Fig. 2. Overall and disease-free (Kaplan–Meier) survival curves.

One patient suffered from treatment-related death (=grade 5) by esophageal bleeding at 2.1 months after starting definitive CRT. Diarrhea of grade 3 or 5FU-induced hyper-ammonemia was each seen in one patient. Severe bacterial pneumonia including sepsis was seen in 9 patients (7%), and 3 of these patients died of the side effect (=grade 5).

In the late phase of 87 patients achieving CR after CCRT, severe side effects ($\geq$grade 3) of the lung and heart were seen in two patients (radiation pneumonitis) and in one patient (cardiac tamponade), respectively. These three patients recovered from those side effects. No late side effect involving the esophagus, skin, or spinal cord was seen.

Discussion

A retrospective study was conducted of the efficacy of ENI in 126 consecutive patients with thoracic esophageal SqCC treated with definitive CRT that applied 50/50.4 Gy in 20/28 fractions from 2000 until 2009 in a single center. Concurrent and adjuvant chemotherapy consisted of 2–4 cycles of 5-FU/platinum repeated every four weeks. CTV included the whole thoracic esophagus and comprised regional lymph nodes and up to M1a lymph nodes. The mean follow up time was 28.3 months (±22.8) and the median overall survival time was 28.5 months (±6.9). The reason for the

Table 3
Severe acute and late adverse effects recorded.

Adverse effect	Grade 3		Grade 4		Grade 5	
	n	(%)	*n*	(%)	*n*	(%)
Acute phase						
Hematological toxicity						
Leukopenia	62	(49%)	30	(24%)	0	(0%)
Anemia	23	(18%)	15	(12%)	0	(0%)
Thorombocytopenia	24	(19%)	21	(17%)	0	(0%)
Non-hematological toxicity						
Radiation esophagitis	29	(23%)	3	(2%)	1	(1%)
Diarrhea	1	(1%)	0	(0%)	0	(0%)
Hyper-ammonemia	1	(1%)	0	(0%)	0	(0%)
Bacterial pneumonia	9	(7%)	0	(0%)	3	(2%)
Late phase						
Radiation pneumonitis	0	(0%)	2	(2%)	0	(0%)
Cardiac tamponade	1	(1%)	0	(0%)	0	(0%)
Esophagitis	0	(0%)	0	(0%)	0	(0%)
Dermatitis	0	(0%)	0	(0%)	0	(0%)
Myelitis	0	(0%)	0	(0%)	0	(0%)

large radiation fields used in our institution was the fundamental adherence to the first radiation field used in RTOG 85-01 [1] and to the operative procedure of 3-field LN dissections plus subtotal esophagectomy in curative surgery. Eighty-seven patients (69%) achieved CR at the time of completing treatment. Subsequently, 40 of the 87 (46%) patients had recurrences during follow-up. The first recurrence site was local-alone in 50% and distant (=outside radiation field) in 50%. Recently, Onozawa et al. [14] reported that after achieving CR, only one patient experienced elective nodal failure without any other site of recurrence. This result concurred with our results (no EN failures), although radiation dose of 50–50.4 Gy was less than the 60 Gy used by Onozawa et al. [14].

The upper thoracic esophageal carcinoma (34%) had more relapses at the local site than the middle (9%) or lower thoracic (11%) ($p = 0.0073$). Almost two-thirds of the recurrences occurred first at local or regional sites in cervical esophageal cancer [15,16]. In general, upper thoracic esophageal carcinoma as well as cervical may also be likely to have recurrence at the loco-regional region.

With respect to lymphatic drainage of thoracic esophageal cancer, the esophagus has an extensive and longitudinal interconnecting system of lymphatics. Lymphatic channels in the mucosa and submucosa communicate with the lymphatic channels throughout the muscle layers. Lymph can travel the entire length of the esophagus before draining into LNs [17], and thus the entire esophagus is at potential risk for lymphatic involvement. Up to 8 cm or more of "normal" tissue can exist between gross tumor and micro-metastatic "skip areas" secondary to this extensive lymphatic network [18]. Additionally, as much as 71% of frozen tissue sections scored as margin-negative by conventional histopathology showed lymphatic micro-metastases with immunohistochemistry [19].

There has been the trend towards treating locally advanced non-small cell lung cancer with involved field radiotherapy (IFRT) [20,21]. Regarding the radiation field (=target volume) of CRT for esophageal cancer, there is no global consensus on whether or not ENI should be performed. In the RTOG 85-01 trial [1], radiation was delivered at 30 Gy from the supra-clavicular fossae to the esophago-gastric junction as ENI, followed by cone down of 20 Gy to the primary tumor with 5 cm proximal and distal margins. On the other hand, in the INT0123 trial [22], ENI was omitted to improve the tolerance to treatment. In our institution, ENI has been used because the results of most surgical series in Japan have indicated a survival benefit of prophylactic 3-field LN dissection for SqCC in the thoracic esophagus [7,23]. In the current study, no patient with isolated elective nodal failure was identified. Recently, Zhao et al. [4] irradiated the primary tumor and positive LNs for 53 esophageal SqCC and of the 10 node metastases alone, regional node recurrences outside the CTV occurred in only three patients (8%).

According to recent randomized trials of esophageal cancer treated with CCRT, 2-year overall survival (OS) was 31–40%, 3-year OS was 21–32%, and the median survival time (MST) was 13.0–19.3 months [2,24–26]. In this study, 2-year OS was 55%, 3-year OS was 42%, and the MST was 28.5 months. Our survival results using ENI field were not inferior to those of the previous reports [2,24–26].

Aisner et al. [27] and LePrise et al. [28] suggested that high rates of local recurrence occur when either radiation therapy or surgery alone are used. In contemporary randomized trials, local failure rates with surgery alone range from 32% to 45% [2,29,30]. Data from recent randomized trials of esophageal cancer using "definitive" CRT suggest local failure is a major cause of overall failure, with approximately 50% of patients failing locally [2,24,25]. In this study, the rate of local residual tumor was 31% (=39/126 patients) immediately after completion of CRT. After achieving CR (=87 patients), 20 patients (16%) had a local recurrence. Altogether, 47% was local recurrence and/or residual tumor, 15% was distant failure, and only 38% of the others remained failure-free.

This result suggests that if the gross tumor is controlled with CRT, ENI may prevent elective nodal failure. This preventive activity may occur through control of micro-metastases. However, it is not clear whether ENI improves overall survival. The incidence of local/regional failure and the persistence of disease in the CRT arm of RTOG 85-01 [1], which used ENI, was lower than that in the standard dose arm of INT0123 [22], which omitted ENI (46% vs. 55%), but the MST and the 2-year OS rates were similar in both groups (14.1 months, 36% vs. 18.1 months, 40%).

There are, however, concerns about the adverse effects of ENI. We adopted the same treatment regimen as the INT0123 trial with the total dose of 50.4 Gy. As to the irradiation technique, the multiple-field was used to avoid excessive dosing to the surrounding normal tissues. Since the radiation field was large in the cranio-caudal direction and many thoracic vertebrae were included in the radiation field, the possibility was considered for myelo-suppression occurring more severely during treatment by chemotherapy. Thus, there may be fewer patients for a total cycle of chemotherapy. Since the volume of the esophageal wall irradiated with a high dose of more than 50 Gy is larger than IFRT, it may be very likely that radiation-induced esophagitis occurring during and/or immediately after treatment was more severe. There are some reports [31–33] indicating that the incidence of radiation esophagitis depends on the esopha-

geal volume irradiated with a higher radiation dose. Morota et al. [34] using extended field of up to 40 Gy plus a boost of 20 Gy reported that acute esophagitis of grade 2 or greater was seen in 13 patients (19%). This incidence was much less than ours (55%), the reason for which is unclear. Moreover, Morota et al. [34] reported that late lung or heart toxicities of grade 3 or greater were seen in five patients (7%). This incidence was similar with ours (3.4%). Wei et al. [35], respectively, reviewed 101 patients using RTOG 94-05 protocol and found a 28% incidence of radiation-induced pericardial effusion, despite the fact that the 95% PTV received only 45–50.4 Gy.

The data obtained in this study suggest that ENI was effective for preventing regional nodal failure in CRT for esophageal SqCC and that more local recurrences were detected in the upper than in the middle and lower thoracic carcinomas.

A conflict of interest statement

There is no conflict of interest.

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ORIGINAL ARTICLE

Patient setup error and day-to-day esophageal motion error analyzed by cone-beam computed tomography in radiation therapy

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Abstract

Little has been reported on the errors of setup and daily organ motion that occur during radiation therapy (RT) for esophageal cancer. The purpose of this paper was to determine the margins of esophageal motion during RT. *Methods and materials.* The shift of the esophagus was analyzed in 20 consecutive patients treated with RT for esophageal cancer from November 2007. CT images for RT planning were used as the primary image series. Computed tomography (CT) images were acquired using an Elekta Synergy System, equipped with a kilovoltage-based cone-beam CT (CBCT) unit. The subsequent CBCT image series used for daily RT setup were compared with the primary image series to analyze esophageal motion. CBCT was performed before treatment sessions a total of 10 times in each patient twice a week. The outer esophageal wall was contoured on the CBCT images of all 200 sets. *Results.* In the 200 sets of CBCT images, the mean (absolute) ± standard deviation (SD) of setup errors were 2 +/– 2 mm (max, 8 mm) in the lateral direction, 4 +/– 3 mm (max, 11 mm) in the longitudinal direction, and 4 +/– 3 mm (max, 13 mm) in the vertical direction. Additionally, the mean ± SD values of daily esophageal motion comparing the CBCT with RT planning CT were 5 +/– 3 mm (max, 15 mm) in the lateral direction and 5 +/– 3 mm (max, 15 mm) in the vertical direction. *Conclusions.* Our data support the use of target margins (between the clinical target volume and planning target volume) of 9 mm for day-to-day esophageal motion and 8 mm for patient setup in all directions, respectively.

Inter-fraction and intra-fraction motion of critical structures is a significant concern when patients undergo intensity modulated radiation therapy (IMRT). Improper dose modulation can be a result of anatomical motion among other factors. Overdosage to normal tissues can cause toxicity, while underdosage can lead to tumor progression. Image guided radiation therapy (IGRT) has been used in an attempt to minimize the impact of this motion.

Esophageal motion can be attributed to peristalsis, respiratory action, and cardiac action [1]. However, it was not addressed in reviews on inter-fraction and intra-fraction organ motions during RT [2]. Only the limited amount of data is available on the esophageal movement in patients undergoing RT planning [1,3]. The majority of patients with esophageal cancers are treated during free respiration. Thus, cone-beam computed tomography (CBCT) scans acquired during free respiration could provide relevant data on respiration-induced motion. Dieleman et al. [4] performed four-dimensional CT analysis of esophageal mobility during normal respiration and concluded that the distal esophagus showed more mobility than other parts. Thus, they derived margins of mobility for use in treatment planning that can encompass all movement. The present study analyzed the patient setup error and day-to-day esophageal motion during IGRT. The 20 consecutive patients in this study represent the largest analysis heretofore conducted of daily inter-fraction esophageal movement during free respiration.

Materials and methods

Subjects

In this study, both patient setup error and inter-fraction daily shifts of the esophagus were analyzed in 20

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consecutive patients with stage I-IVB esophageal cancer treated with chemoradiation with curative intent between November 2007 and May 2008 in University of Tokyo Hospital, Tokyo, Japan. The entire thoracic esophagus in all 20 cases was included within the radiation field. Ten sets of computed tomography (CT) images from each patient were acquired using an Elekta Synergy System (Elekta Ltd, Crawley, UK), equipped with a kilovoltage (kV)-based CBCT unit [5].

The clinical and demographic data of the 20 patients are shown in Table I. The 6th edition of the American Joint Committee on Cancer TNM staging system [6] was used. For each patient, the CT images for RT planning (slice thickness of 5 mm, index of 1 mm, helical pitch of 15, and beam pitch of 15/16) acquired in free respiration by a large-bore CT system (Aquilion/LB, Toshiba, Tokyo, Japan) without any contrast media one or two days before treatment were used as the primary image series. The subsequent CBCT image series (slice thickness of 5 mm) used for daily RT setup were then compared to the primary image series to analyze inter-fraction esophageal motion. CBCT was performed before treatment sessions a total 10 times in each patient: one set of images was acquired twice a week during an overall RT duration of five weeks. The patient setup for RT treatment was carried out daily without referring to the previous data on setup error generated by CBCT and only the automatic bony landmark matching was carried out each time. However, because the CBCT imaging performed after this bone-matching registration (i.e. after correcting for the setup error) was used in the comparison, only day-to-day esophageal motion was taken into account. Automatic matching of anatomic bony landmarks was carried out and part of the image set for the matching was removed (e.g. shoulders, which are easily moved). A bony co-registration based on a window around the vertebral column was used for esophageal treatment since the esophagus is a posterior structure in close proximity to the vertebral column. Only an arm support was used as an immobilization device.

CBCT imaging

To generate a set of CBCT images, the typical patient dose was 15.1 mGy (120 kV, 40 mA, 40 ms, 640 frames, 360°data collection), based on the weighted CT dose index ($CTDI_W$), and this radiation dose was expected to have almost no effect on the total dose in the treatment. The outer esophageal wall was contoured on the CBCT images of all 200 sets from the esophageal orifice to the esophago-gastric junction under the mediastinal window setting (window width, 350 HU; window level, 40 HU). Only one radiation oncologist (HY), who was experienced with the RT planning system and had utilized it for routine planning, was involved in the contouring process.

Measurements method

After bone-matching registration, the primary and pre-treatment CT image series were fused and compared

Table I. Patient and tumor characteristics.

Case No.	Gender	Age (y)	Primary Site	Clinical Tumor Stage	Clinical Nodal Stage	Clinical Metastasis Stage	AJCC Stage
1	M	78	Lt	3	1	0	III
2	M	81	Mt	1	0	0	I
3	F	70	Lt	3	1	1b	IVB
4	M	64	Ut	1	0	0	I
5	M	73	Lt	3	1	1b	IVB
6	M	67	Ut	2	0	0	IIA
7	M	53	Lt	2	0	0	IIA
8	M	72	Ut	3	1	0	III
9	F	79	Ut	3	1	0	III
10	M	80	Lt	3	1	0	III
11	M	90	Lt	3	1	0	III
12	M	78	Mt	4	1	1b	IVB
13	M	73	Ut	1	1	0	IIB
14	M	74	Mt	4	1	0	III
15	F	62	Mt	1	0	0	I
16	M	68	Lt	2	0	0	IIA
17	M	55	Ut	4	1	1a	IVA
18	M	73	Mt	1	0	0	I
19	M	64	Ut	1	0	0	I
20	M	67	Lt	3	1	1b	IVB

Abberviations: AJCC=American Joint Committee on Cancer; F=female; Lt=lower thoracic; M=male; Mt=middle thoracic; Ut=upper thoracic; y=years.

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using a Pinnacle[3] treatment-planning workstation (Philips Healthcare, Andover, MA, USA; ADAC, Milpitas, CA, USA). A case with the outer esophageal wall contoured on the CBCT image is shown in Figure 1. Inter-fraction motion was measured using approximately 50 axial CT images of 5-mm slices from the esophageal inlet to the esophago-gastric junction. The measurements were done in the anterior-posterior and right-left (lateral) directions on all slices and then the maximum deviation between esophageal walls delineated in the each CBCT after the bone matching registration and the planning CT images across all scans were used. Therefore, all values of the inter-fraction motion were positive.

The formalism of Stroom et al. for margin derivation [7] ($= 2.0\Sigma + 0.7\sigma$) and van Herk et al. [8] ($= 2.5\Sigma + 0.7\sigma$) were used to evaluate the values as margin for setup error and daily esophageal motion error. However, another new optimization algorithm for the determination of treatment margins around moving and deformable targets like esophagus in radiotherapy proposed by Redpath & Muren [9] was not used this time.

Results

Setup errors

In the 200 sets of CBCT images, the mean and SD values of the patient setup errors were 0 +/– 2 mm in the lateral direction, 0 +/– 3 mm in the longitudinal direction, and 0 +/– 4 mm in the vertical direction.

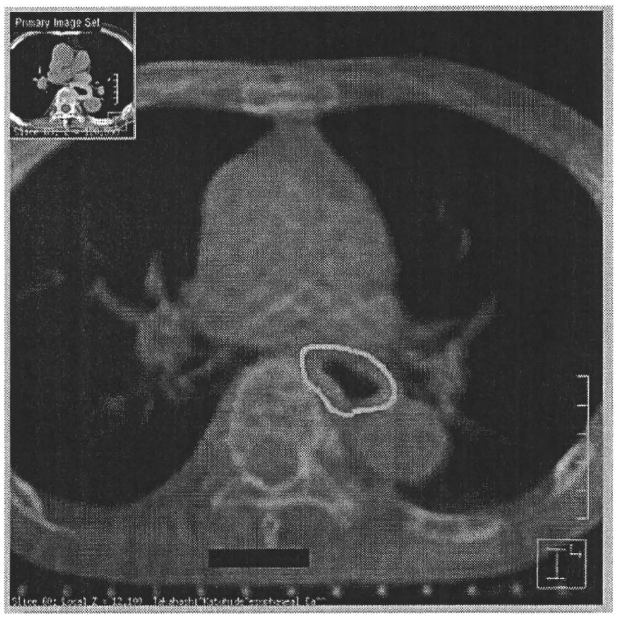

Figure 1. CBCT image of the middle thoracic region, scanned under free respiration and processed after transferring data onto a Pinnacle[3] workstation for planning of RT. A case with the outer esophageal wall contoured on the CBCT images (sky-blue contour).

The composite (all) SD was defined simply as the average of the individual SDs in each direction. The value of SD ($=\Sigma$) of the absolute value of the setup error in all 200 data was 2 mm (lateral), 3 mm (longitudinal), and 3 mm (vertical), respectively. The mean of the absolute value of the setup error in all 200 data was 2 mm (max, 8 mm) in the lateral direction, 4 mm (max, 11 mm) in the longitudinal direction, and 4 mm (max, 13 mm) in the vertical direction (Table II). Based on the setup error for each patient, the maximum of SD was 4 mm in the lateral direction (case no. 14), 6 mm in the longitudinal direction (case no. 7), and 6 mm in the vertical direction (cases 5 and 18). The frequencies of setup errors >2 mm on the lateral, longitudinal, and vertical axes were 48%, 60%, and 73%, respectively, and the frequencies of errors >5 mm were 11%, 31%, and 30%, respectively. The patient setup error was corrected only by parallel translation, so the lag of rotation was not considered. According to the formalism of Stroom for margin derivation, the evaluation value as margin for setup error was 4 mm of right-left direction, 6 mm of dorsal-ventral direction, and 6 mm of cranio-caudal direction, and additionally, according to van Herk 5 mm, 8 mm, and 8 mm (Table II).

Esophageal motion errors

Additionally, the means±SD's of daily esophageal motion comparing the CBCT with RT planning CT were 5 +/– 3 mm (max, 15 mm) in the lateral direction and 5 +/– 3 mm (max, 15 mm) in the vertical direction (Table III). A maximum shift in the lateral direction was found at the upper thoracic site in 79 sets (39.5%), at the middle thoracic site in 63 sets (31.5%), and at the lower thoracic site in 58 sets (29.0%). Moreover, there were shifts on the left side in 136 sets (68.0%) and on the right side in 64 sets (32.0%). A maximum shift in the vertical direction was found at the upper thoracic site in 49 sets (24.5%), at the middle thoracic in 80 sets (40%), and at the lower thoracic in 71 sets (35.5%). The motion was the same in the upper or the lower esophagus. Also, shifts were noted to the anterior direction in 88 sets (44.0%) and to the posterior direction in 112 sets (56%). Based on each patient's daily esophageal motion, the maximum SD was 4 mm in both vertical

Table II. Setup error in three dimension.

Direction	Right-left	Dorsal-ventral	Cranio-caudal
Mean (Absolute)	2 mm	4 mm	4 mm
Σ (systematic error)	2 mm	3 mm	3 mm
Max	8 mm	11 mm	13 mm
δ (random error)	0 mm	1 mm	1 mm
Stroom [30]	4 mm	6 mm	6 mm
van Herk [31]	5 mm	8 mm	8 mm

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Table III. Organ motion error.

Direction	Right-left	Dorsal-ventral
mean	5 mm	5 mm
SD	3 mm	3 mm
max	15 mm	15 mm
95%*	10 mm	11 mm
σ	1 mm	2 mm
Stroom [30]	7 mm	7 mm
van Herk [31]	8 mm	9 mm

*Margin value covering 95% of data.

(cases 6 and 11) and lateral directions (case 3). According to Stroom, the evaluation value as margin for daily organ motion error was 7 mm of right-left direction and 7 mm of dorsal-ventral direction, and additionally, according to van Herk, 8 mm and 9 mm (Table III).

Clinical results

Though the median follow up time has been only nine months, six patients (30%) have died of esophageal cancer and two patients (10%) who are still alive have loco-regional and/or distant recurrences of esophageal cancer. To date, there has been no non-hematological toxicity of grade 3 and acute or sub-acute esophagitis or pneumonitis.

Discussion

Brief summary of main points

In this study patient setup error and inter-fraction motion of the esophagus were examined during RT in 20 patients. To our knowledge, this is the first report of the study of inter-fraction esophageal motion during day-to-day RT in patients with esophageal cancer. In fact, corrections for the setup errors have already been made in our method using CBCT and thus the setup errors are pertinent for our patients. The interesting aspect of our data is the remaining internal organ motion of the esophagus. In this study, the inter-fraction error was defined as the difference between day-to-day esophageal positions after eliminating daily setup error. This inter-fraction error included tumor motion due to the patient's random movement, cardiac motion, peristaltic motion and respiratory motion (i.e. intra-fraction motion).

Main findings in relation to other studies

The kV CBCT was used for determining setup error in this study. The different interaction mechanisms of kV photons with tissues and image transducers offer improved imaging compared with megavoltage (MV) photons. This capability enhances the localization of target volumes and adjacent organs at risk during treatment compared with MV electronic portal imaging. The scatter component should not have as much an impact with MV CBCT compared with kV CBCT. The use of MV photos for imaging is a departure from the general preference for kV beams in imaging. The visibility of large low-contrast objects in tomographic images depends on the contrast-to-noise ratio. Contrast is determined by the differential attenuation of the beam through different bodily tissues. Most importantly, the image sequence from rotation fluoroscopy can be used in filtered back-projection to reconstruct an x-ray volumetric image. Recently, Xu et al. [10] utilized CBCT measurements before and after treatment in the same day in order to detect intra-fraction tumor position errors (including 19 head and neck, 25 thoracic and 10 abdominal-pelvic tumors). Guckenberger et al. [11] used CBCT scanning for the evaluation of setup errors and demonstrated the feasibility of its use in day-to-day clinical practice.

Esophageal movement was not addressed in an earlier review on inter-fraction and intra-fraction organ motion during RT [2]. In our study, the daily esophageal motion were 5 +/– 3 mm (max, 15 mm) in the left-right direction and 5 +/– 3 mm (max, 15 mm) in the anterio-posterior direction. These values were almost similar to those of the following previous reports. Measurements of lower esophageal sphincter pressure during quiet respiration revealed lateral esophageal motion of 6 +/– 2 mm in the abdominal portion and 4 +/– 1 mm in the thoracic region [12]. Cine-fluoroscopic barium swallow images of the esophagus in 51 patients undergoing catheter ablation for atrial fibrillation indicated that lateral shifts of more than 20 mm occurred in a majority of patients [13]. Daily online CT images in a study of six IGRT-treated patients were reported to show maximal motion in the distal esophagus, and indicated that margins of 2 ~ 5 mm could account for all motion [14]. A study of esophageal positions at the extreme phases of respiration in six patients suggested that a margin of 5 – 6 mm was sufficient to account for variations in organ position [15]. Hashimoto et al. [1] analyzed the motion during quiet respiration in 13 patients with implanted fiducial markers inserted into the esophageal wall and it was 4 +/– 2 mm, 8 +/– 4 mm, and 4 +/– 3 mm for the medio-lateral, cranio-caudal, and antero-posterior directions, respectively. According to Dieleman et al. [4], margins that would have incorporated all esophageal movement in the medio-lateral and dorso-ventral (anterior-posterior) directions were 5 mm proximally, 7 mm and 6 mm in the mid-esophagus, and 9 mm and 8 mm in the distal esophagus, as determined by 4D-CT. According to Guerrero et al. [16], the displacement of the esophageal tumors,

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which estimated from breath-hold CT imaging using the 3-D optical flow method, was non-uniform and up to 14 mm.

Limitations of this study

The possible sources of methodological errors in assessing inter-fraction esophageal motion in this study could involve (a) inaccurate contouring of the outer esophageal wall on CBCT and/or planning CT images (i.e. human error), (b) mistakes in fusing CBCT images after correcting setup errors on the planning CT image on the Pinnacle^3 workstation because the form or relative position of the chest wall and/or vertebral bone might be different, (c) correcting the setup error only by parallel translation, and not considering the lag of rotation and the longitudinal displacement could not be evaluated with our method, and, therefore, the error in the longitudinal direction was also detected as the error in the left-right or anterior-posterior directions, (d) the difference in the speed at which free breathing scans were acquired with the conventional CT and the CBCT, and (e) the CBCT is a slow scan over approximately 2 minutes and it therefore blurs the intra-fraction motion which is predominantly respiratory motion with a period of about 4 seconds. The probability of the first error (a) was minimized by having only a single experienced radiation oncologist (i.e. not multiple clinicians) contouring the outer esophageal wall and by expanding the image significantly. The other potential errors (b and c) were not formally evaluated in this study; however, images displayed on the Pinnacle^3 workstation were checked to make sure they were not significantly out of position after they were fused (Figure 1). The slow scan blurs the esophageal outline and makes accurate delineation more difficult (e). So in this study, only the intra-fraction esophageal motion during treatment could not be extracted.

In this study, the margin recipes of Stroom [7] and van Herk [8] were used in order to evaluate errors of setup and daily esophageal motion. In addition, Redpath & Muren [9] proposed a new optimization algorithm for the determination of treatment margins around moving and deformable targets like bladder or esophagus in radiotherapy. The algorithm is completely empirical and is based on an iterative method of determining margins around the planning clinical target volume (CTV) to provide the optimum coverage of the envelope of CTV positions observed during treatment. The major advantage with this approach is that it can be used on non-solid organs, circumventing any assumptions on the nature of the geometrical uncertainties. In this study, this empirical approach was not used. Therefore, our chosen method may be the limitation to detect the structure of the esophageal wall and this may not be the ideal approach. We are currently planning to introduce this empirical algorithm for determining margin of CTV.

Impact of the findings for future work

In our study, the motion was the same in the upper or the lower esophagus but this is contrary to the findings of other authors such as Dieleman et al. [4]. The reason may be that the whole thoracic esophagus was analyzed which was difficult to identify the esophageal tumor on the CBCT. It may be necessary to determine whether the movement of the tumor bearing part of the esophagus was the same as the parts without gross tumor involvement. This is a problem for future study.

The present study is the first study to evaluate inter-fraction esophageal motion with patients in the supine position on the linear accelerator bed during RT and under free respiration. It cannot be concluded from this study who requires CBCT or whether every patient needs CBCT imaging. The change in mean esophageal position arising from twice-weekly imaging of individual patients was very small. This finding could be interpreted to mean that target volume coverage was fully adequate and that therefore costly daily imaging is not required.

In the present study, the patient setup error was not small, and therefore using twice-weekly CBCT might not be enough to reach the levels of target margin confidence. In the era of modern IGRT systems, the daily registration performed using CBCT was assumed to be necessary in order to minimize the setup error. The use of IGRT with CBCT will most likely benefit treatments such as IMRT for head and neck cancer, prostate cancer [17,18], or breast cancer; stereotactic RT for lung cancer or brain tumor; and patients with tumors commonly associated with organ motion, such as gastric cancer or urinary bladder cancers.

Conclusions

Both the patient setup error and day-to-day esophageal movements were detected in every patient in this study. The highest amounts of motion were distributed across various sites in the esophagus. However, the amount of motion did not appear to be clinically significant provided an appropriate internal target volume was considered. Our data support the use of target margins of 9 mm for day-to-day esophageal motion and 8 mm for patient setup error of motions in all directions. Also, when using daily kV CBCT during RT in order to minimize the setup error, only

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day-to-day motion of esophagus should be considered since it was found to be so small that the radiation field for esophageal cancer can be reduced.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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PHYSICS CONTRIBUTION

FOUR-DIMENSIONAL MEASUREMENT OF THE DISPLACEMENT OF INTERNAL FIDUCIAL MARKERS DURING 320-MULTISLICE COMPUTED TOMOGRAPHY SCANNING OF THORACIC ESOPHAGEAL CANCER

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Purpose: To investigate the three-dimensional movement of internal fiducial markers placed near esophageal cancers using 320-multislice CT.

Methods and Materials: This study examined 22 metal markers in the esophageal wall near the primary tumors of 12 patients treated with external-beam photon radiotherapy. Motion assessment was analyzed in 41 respiratory phases during 20 s of cine CT in the radiotherapy position.

Results: Motion in the cranial–caudal (CC) direction showed a strong correlation ($R^2 > 0.4$) with the respiratory curve in most markers (73%). The average absolute amplitude of the marker movement was 1.5 ± 1.6 mm, 1.6 ± 1.7 mm, and 3.3 ± 3.3 mm in the left–right (LR), anterior–posterior (AP), and CC directions, respectively. The average marker displacements in the CC direction between peak exhalation and inhalation for the 22 clips were 1.1 mm (maximum, 5.5 mm), 3.0 mm (14.5 mm), and 5.1 mm (16.3 mm) for the upper, middle, and lower thoracic esophagus, respectively.

Conclusions: Motion in primary esophagus tumor was evaluated with 320-multislice CT. According to this study, 4.3 mm CC, 1.5 mm AP, and 2.0 mm LR in the upper, 7.4 mm CC, 3.0 mm AP, and 2.4 mm LR in the middle, and 13.8 mm CC, 6.6 mm AP, and 6.8 mm LR in the lower thoracic esophagus provided coverage of tumor motion in 95% of the cases in our study population. © 2011 Elsevier Inc.

Intrafraction motion, Computed tomography, Esophageal cancer, Internal margin.

INTRODUCTION

Interfraction and intrafraction motion of critical structures is a significant concern when patients undergo intensity-modulated radiotherapy. Improper dose modulation can be a result of anatomical motion. Overdosage to normal tissues can result in toxicity, whereas underdosage can lead to tumor progression. Image-guided radiotherapy has been used in an attempt to minimize the impact of anatomic motion.

The thoracic esophagus is more mobile than the proximal (cervical) esophagus because it passes through the less-confining space of the mediastinum. This is especially true in the region of the diaphragm, where the relatively unconstrained esophagus can be subjected to considerable respiratory diaphragmatic motion. Although esophageal motion can be attributed to peristalsis, respiratory action, and cardiac action (1), it was not addressed in reviews on interfraction and intrafraction organ motions during radiotherapy (2). Information on esophageal motion is scarce because of the limited amount of data available on this organ's movement in patients undergoing radiotherapy planning (1, 3). The majority of patients with esophageal cancers are treated during free respiration. Thus, the 320-multislice CT (320MSCT) acquired during free respiration could provide relevant data on respiration-induced motion. Dieleman *et al.* (4) performed four-dimensional (4D) CT analysis of esophageal mobility during normal respiration and concluded that the distal esophagus showed more mobility than other parts. Moreover, they derived margins of mobility for use in treatment planning that can encompass all movements.

Recently, 4D-CT simulation has enabled CT data acquisition to be gated to the respiratory cycle (5–7). This approach enables esophageal motion to be tracked over the entire length of the organ and at all phases within the respiratory cycle. The present study analyzed the three-dimensional movement of internal fiducial markers near esophageal cancers using 320MSCT. The 12 patients in this study represent the largest analysis heretofore conducted of intrafraction esophageal movement during free respiration.

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METHODS AND MATERIALS

320-Multislice CT scanner

A 320-slice columetric CT scanner (320-slice Aquilion ONE; Toshiba Medical Systems, Otawara, Tokyo) was used to scan the esophageal metal clips for 20 s (8–10). Images were collected on a clinical multidetector CT scanner. Images were acquired in volume mode (16 cm z coverage per rotation). Images were reconstructed at slice thicknesses of 1 mm (with 1-mm slice intervals). The 320MSCT has 512 × 512 (transverse) × 320 (cranial–caudal [CC]) elements, each approximately 0.5 mm × 0.5 mm at the center of rotation. The 160-mm total beam width allows the continuous use of several collimation sets. Superior to inferior (SI) coverage is 160 mm per rotation. The detector element consists of a Gd_2O_2S ceramic scintillator and a single-crystal silicon photodiode, as used for MSCT.

Instructions for quiet free breathing were reviewed by a physician. All scans were performed under free-breathing conditions. After several minutes' rest, volumetric cine scanning was started without the patient being informed to avoid any psychosomatic effect on breathing. Scan conditions were 120 kV, 50 mA, 0.5 s per rotation, 160 mm × 0.5 mm slice collimation, and 20.0 s acquisition time. Continuous scan mode was used. Field of view size was set LL (= 500 mm). When these protocols were used, CT dose index volume was 110 mGy, dose length product was 1770 mGy · cm, and effective dose (dose length product × 0.017) was 30 mSv. In other words, a three-dimensional image 16 cm in length was acquired every 0.5 s.

Patients

Intrafraction motions of the esophagus were analyzed in 12 patients with thoracic esophageal cancer treated with radiotherapy between July and November 2009 at University of Tokyo Hospital, Tokyo, Japan.

The clinical and demographic data of the 12 patients (11 male, 1 female) are shown in Table 1. All of the tumors were pathologically diagnosed as esophageal squamous cell carcinoma. The median age was 72 years (range, 56–86 years). The sixth edition of the American Joint Committee on Cancer TNM staging system (11) was used. The 320MSCT was performed after placement of a metal clip (EZ endoclip, HX-610-090; Olympus, Tokyo, Japan) in the normal esophageal wall near the primary tumor for one time in each patient. The clip is cylindrically structured after closing the wings. The length is approximately 10 mm, and the diameter is approximately 2 mm. The primary site in the esophagus was upper thoracic for 3 patients, middle for 5 patients, and lower for 4 patients (Table 1). Each tumor had one or two fiducial markers, and 22 markers in 12 patients were analyzed. The flat board (CABMO21A) was used in place of a body mat, to flatten the superior surface of the patient table. In this way, patients were placed in the same position as for radiotherapy.

Table 1. Patient characteristics

Patient no.	Sex	Age (y)	Primary tumor location	Location Clip 1 from incisor tooth		Location Clip 2 from incisor tooth	
				cm	Ut/Mt/Lt	cm	Ut/Mt/Lt
1	M	67	Mt	27	Mt	35	Lt
2	M	66	Ut	19	Ut	29	Mt
3	F	79	Ut	20	Ut	21	Ut
4	M	68	Ut	22	Ut	25	Mt
5	M	82	Mt	26	Mt	30	Mt
6	M	74	Lt	32	Mt	40	Lt
7	M	70	Lt	34	Lt	36	Lt
8	M	79	Lt	37	Lt	40	Lt
9	M	56	Mt	18	Ut	—	—
10	M	81	Mt	29	Mt	31	Mt
11	M	86	Mt	30	Mt	32	Mt
12	M	57	Lt	43	Lt	—	—

Abbreviations: Ut = upper thoracic; Mt = middle thoracic; Lt = lower thoracic; M = male; F = female.

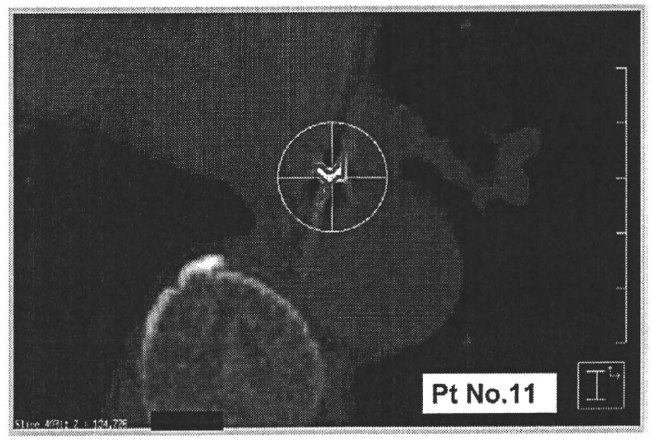

Fig. 1. Contouring of metal clip and center of gravity of each metal clip, performed on a Pinnacle[3] workstation.

Written informed consent was obtained from all patients before the treatment was initiated. This study was approved by the institutional review board of Tokyo University (no. 2613).

Metal clip and lung delineation

One or two metal clips and bilateral lung delineation was performed for each timing and each patient (total 41 sets each metal clip) on a Pinnacle[3] treatment-planning workstation (Philips Healthcare, Andover, MA; ADAC, Milpitas, CA). The delineation was performed semiautomatically. The lower auto-contour threshold

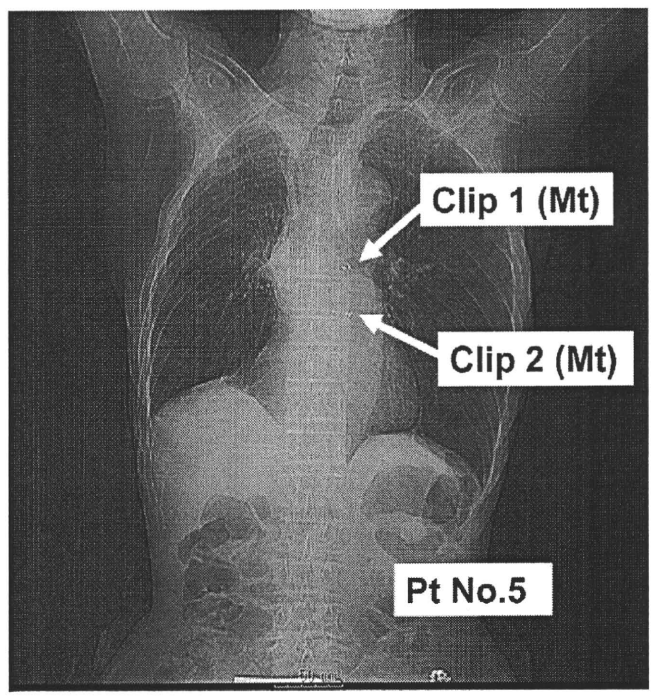

Fig. 2. Position of metal clips (Patient 5).

Table 2. Relationship between marker position and respiratory curve for each patient

Patient no.	R^2 of Clip 1 with lung volume			R^2 of Clip 2 with lung volume			Respiration frequency during 20 s
	x (RL)	y (AP)	z (CC)	x (RL)	y (AP)	z (SI)	
1	0.31	<0.2	0.77	0.34	0.71	0.76	5.0 (regular)
2	<0.2	<0.2	0.36	<0.2	<0.2	0.47	7.0 (regular)
3	<0.2	0.45	0.47	<0.2	0.79	0.82	5.0 (regular)
4	<0.2	0.6	0.48	<0.2	<0.2	0.48	6.5 (irregular)
5	0.31	0.36	0.71	0.570	0.86	0.61	8.0 (regular)
6	0.67	0.8	0.93	0.68	0.7	0.97	6.5 (regular)
7	<0.2	<0.2	0.31	<0.2	<0.2	0.31	6.5 (irregular)
8	<0.2	<0.2	0.76	0.4	0.52	0.78	8.5 (regular)
9	<0.2	<0.2	<0.2	—	—	—	7.0 (irregular)
10	<0.2	<0.2	0.36	<0.2	<0.2	0.33	9.5 (regular)
11	0.38	0.88	0.61	0.26	0.81	0.66	6.0 (irregular)
12	0.81	0.9	0.97	—	—	—	5.5 (regular)

Abbreviations: RL = right–left; AP = anterior–posterior; CC = crano-caudal.

was set at 1400 Hounsfield units for the metal clips (Fig. 1) and 800 Hounsfield units for the lung. The coordinates (x, y, and z) of the center of gravity of each metal clip were calculated automatically on a Pinnacle^3 workstation (Fig. 1). Positive directions were right to left on the x-axis, from posterior to anterior on the y-axis, and from superior to inferior on the z-axis.

Statistical methods

Using a Wilcoxon signed ranked test, with a level of significance of $\alpha = 0.05$, we compared the measured changes in right and left lung volumes and in average CT intensity due to respiration. We also calculated R^2 values (decision coefficient, i.e., the square of correlation coefficient) to assess the possible correlation between metal clip displacements and bilateral lung volume only within the scan range of 16 cm in the CC direction, not the full length of the lung. Histograms and cumulative distribution curves were generated for the entire set of calculated slice-by-slice centroid displacements, in each of the x (right–left [RL]), y (anterior–posterior [AP]), and z (SI) directions. From these displacement data the 95th percentile displacements were determined in all x, y, and z directions.

RESULTS

In the procedure of marker insertion, no patient experienced symptomatic complications. Positions of the 22 metal markers are shown in Table 1. Upper, middle, and lower thoracic positions had 5, 10, and 7 clips, respectively (Fig. 2). There was no apparent migration or dislocation of the markers until after the 320MSCT was performed.

Motion in the CC direction (z-axis) showed a strong correlation ($R^2 > 0.4$) with the respiratory curve for most markers (16 of 22 markers, 73%) (Table 2). Especially in 9 clips (41%), a very strong correlation ($R^2 > 0.7$) was shown with the respiratory curve (Fig. 3). For the LR (x-axis) and AP (y-axis) directions, 5 clips (23%) and 11 clips (50%), respectively, also showed a strong correlation ($R^2 > 0.4$) with the respiratory curve (Table 2). In the CC direction, 5 of 7 clips (71%) showed a strong correlation ($R^2 > 0.4$) with the respiratory curve in the lower, 8 of 10 clips (80%) in the middle, and 3 of 5 clips (60%) in the upper thoracic esophagus.

The respiratory curve for 20 s, which was obtained using bilateral lung volume within the scan range per 0.5-s image-set per each patient, showed a regular sine curve in 8 patients and an irregular one in the other 4 patients (Fig. 4 and Table 2). There was no relationship between age and regular (average, 73.1 years; median, 76.5 years) or irregular (average, 70 years; median, 69 years) respiratory curves. The respiration frequency during 20 s ranged from 5.0 cycles (4 s per cycle) to 9.5 cycles (2.1 s per cycle), with median values of 6.5 cycles and 3.1 s per cycle (Table 2).

The average amplitudes of the marker from the minimum values, which were the most right, posterior, and caudal position in the LR, AP, and CC directions per each clip, respectively, for each patient are shown in Table 3. The average ± SD amplitude from the minimum of the marker movements was 1.5 ± 1.6 mm (maximum, 11.7 mm), 1.6 ± 1.7 mm (maximum, 10.8 mm), and 3.3 ± 3.3 mm (maximum, 16.3 mm) in the LR, AP, and CC directions,

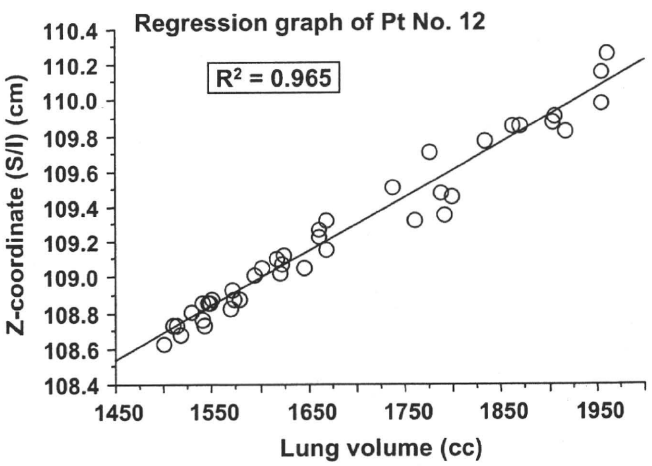

Fig. 3. Correlation of metal clip motion with respiratory curve (Patient 12).

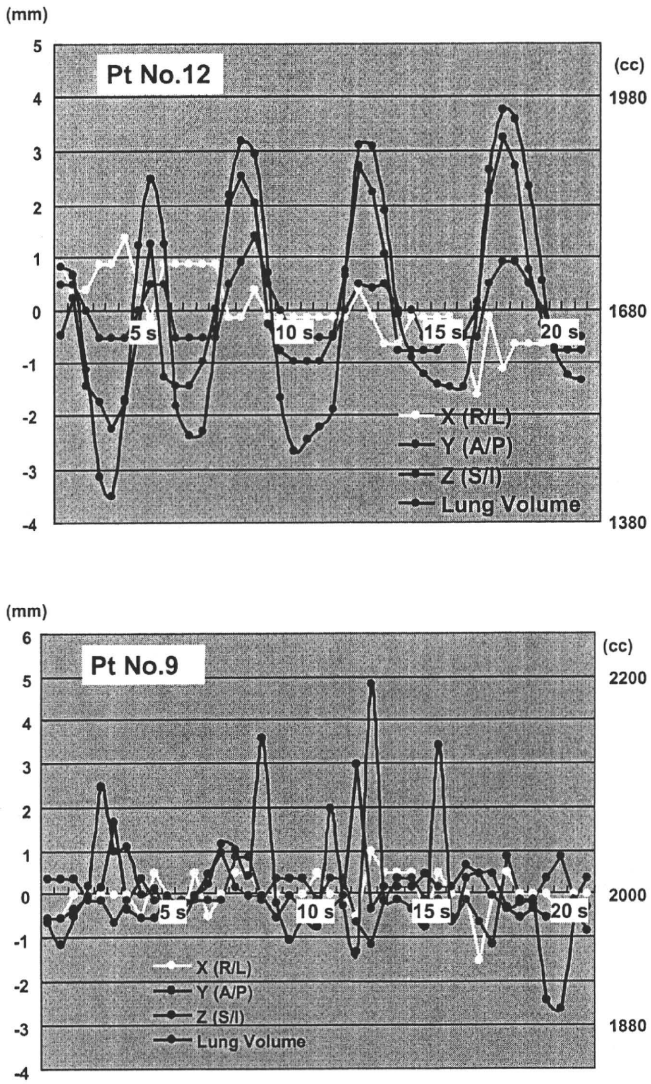

Fig. 4. Metal clips' centroid trajectories in all 41 phases for 20 s of the four-dimensional CT scans. (A) Patient 12. (B) Patient 9. R/L = right–left; A/P = anterior–posterior; S/I = superior–inferior.

respectively (Tables 3 and 4). The average amplitude from the minimum in the CC direction was found to be significantly larger in the lower thoracic compared with the middle ($p < 0.0001$) and upper ($p < 0.0001$) by the Wilcoxon test.

The average marker displacements in the CC direction between peak exhalation and inhalation were 3.2 mm (range, 0.7–5.5 mm), 6.4 mm (range, 1.5–14.5 mm), and 10.3 mm (range, 4.0–16.3 mm) for the upper, middle, and lower thoracic esophagus, respectively (Fig. 5 and Tables 2 and 4).

The 95th percentile values from the cumulative distributions (Fig. 6) were used to define minimum margins to account for gross tumor volume motion during treatment planning. The values of the CC direction were 4.3 mm, 7.4 mm, and 13.8 mm in the upper, middle, and lower thoracic esophagus, respectively (Table 5). For the axial margin, the values were 2.0 mm, 3.0 mm, and 6.8 mm in the upper, middle, and lower thoracic esophagus, respectively. According to Stroom *et al.* (12), the evaluation values as margin for esophageal motion error in the CC direction were 2.68 mm, 5.69 mm, and 9.10 mm in the upper, middle, and lower thoracic esophagus, respectively. Additionally, evaluation values of 3.28 mm, 6.99 mm, and 11.20 mm (Table 5) were reported by van Herk *et al.* (13). As for the axial margin, the values were 1.54 mm, 2.21 mm, and 4.55 mm by Stroom's formula and 1.89 mm, 2.71 mm, and 5.60 mm by van Herk's formula in the upper, middle, and lower thoracic esophagus, respectively.

DISCUSSION

The literature describing esophageal tumor motion is limited. Lorchel *et al.* (14) reported measurements of esophageal tumor motion acquired by CT scans during inspiratory and expiratory breath-hold for a series of 8 patients. Dieleman *et al.* (4) analyzed healthy esophageal motion using normal-breathing 4D-CT in 29 patients with non-esophageal thoracic malignancies. In two recently published

Table 3. Average amplitudes of marker from minimum values for each patient

		Clip 1 (mm)									Clip 2 (mm)								
		LR			AP			CC			LR			AP			CC		
Patient no.	*n*	Mean	SD	Max	Mean	SD	Max	Mean	SD	Max	Mean	SD	Max	Mean	SD	Max	Mean	SD	Max
1	41	0.2	0.2	0.4	0.9	0.4	1.5	4.8	1.6	6.7	1.2	0.4	2.0	1.2	0.8	3.5	8.0	2.8	10.8
2	41	0.6	0.3	1.0	0.2	0.2	0.5	0.2	0.2	0.7	0.4	0.4	1	0.5	0.1	0.5	0.8	0.4	1.5
3	41	0.9	0.3	1.4	0.5	0.4	0.9	1.9	1.3	4.8	1.60	0.6	3.0	0.5	0.5	1.9	2.3	1.4	5.5
4	41	0.0	0.0	0.0	0.1	0.3	1.5	0.4	0.3	1.0	0.1	0.3	1.0	0.0	0.0	0.0	1.0	0.6	1.8
5	41	0.9	0.3	1.0	0.7	0.4	1.9	3.5	1.2	4.0	0.7	0.4	1.0	0.5	0.6	2.0	3.5	1.2	4.7
6	41	1.7	0.8	3.7	1.6	1.0	4.0	3.8	2.3	8.6	3.8	1.6	6.9	3.1	2.0	7.2	4.6	2.9	10.2
7	41	1.1	0.8	3.9	3.0	1.3	5.8	1.7	1.3	4.0	2.4	1.2	5.9	2.6	1.1	5.8	2.1	1.7	5.2
8	41	4.0	2.0	7.3	3.8	1.9	8.8	3.7	2.7	10.0	5.5	2.1	11.7	4.6	2.5	10.8	5.7	4.1	15.3
9	41	1.5	0.4	2.5	1.2	0.5	2.0	0.8	0.7	3.8	—	—	—	—	—	—	—	—	—
10	41	1.5	0.6	2.9	2.4	0.6	3.0	2.7	1.2	4.5	1.4	0.9	2.9	1.2	0.6	2.9	2.6	1.3	4.8
11	41	1.2	0.6	2.3	0.9	1	3.4	3.5	4.1	12.5	0.7	0.5	2.0	1.4	1.6	5.3	3.9	4.6	14.5
12	41	1.5	0.8	2.5	2.7	1.8	6.8	10.2	4.6	16.3	—	—	—	—	—	—	—	—	—
Total	492	1.5	1.6	11.7	1.6	1.7	10.8	3.3	3.3	16.3									

Abbreviations: CC = cranial–caudal; Max = maximum. Other abbreviations as in Table 2.
"Total" is the SD for all 12 patients.

Table 4. Relationships between average amplitude and primary tumor location

		LR (mm)				AP (mm)				CC (mm)			
Parameter	*n*	Mean	Max	Σ	σ	Mean	Max	Σ	σ	Mean	Max	Σ	σ
Total	902	1.5	11.7	1.6	1.9	1.6	10.8	1.7	2.4	3.3	16.3	3.3	5.0
Ut	205	0.9	3.0	0.7	0.2	0.6	2.0	0.5	0.2	1.1	5.5	1.2	0.4
Mt	410	0.9	3.7	0.7	0.2	1.0	5.3	1.0	0.3	3.0	14.5	2.6	0.7
Lt	287	2.8	11.7	2.1	0.5	3.0	10.8	2.0	0.6	5.1	16.3	4.2	1.0

Abbreviations: Σ, systematic error; σ, random error. Other abbreviations as in Tables 1–3.

studies by Zhao *et al.* (15) and Yaremko *et al.* (16), normal-breathing 4D-CT was used to characterize the motion of tumors at the gastroesophageal junction in 25 and 31 patients, respectively. Patel *et al.* (17) evaluated the motion of malignancies in the upper ($n = 1$), mid- ($n = 4$), and lower ($n = 25$) esophagus of 30 patients using normal-breathing 4D-CT. Moreover, they measured the motion of pathologically enlarged or positron emission tomography–positive celiac region lymph nodes. As far as could be determined, this is the first report of the three-dimensional movement of the esophageal wall measured in the radiotherapy positions using internal fiducial markers, except for one report by Hashimoto *et al.* (1), which had only a single marker. In the previous reports that evaluated esophageal tumor motions using 4D-CT (14–17), a radiation oncologist contoured the volume of the primary tumor and/or lymph nodes as shown on several respiratory-phase CT images, and its motions were analyzed. However, in this study, because the motions of 22 metal clips were analyzed and the contouring was performed semi-automatically using the threshold CT value, the human error of contouring is less than in the previous reports, and the same position coordinate is provided whoever performs the contouring. Moreover, in this study, because the continuous cine-mode shooting for 20 s under free breathing was performed over 16 cm in the CC direction using the 320MSCT, no respiratory monitoring system like the Real-Time Positional Management (RPM) (Varian Medical Systems, Palo Alto, CA) or the AZ-733V system (Anzai Medical, Tokyo, Japan) was used, and the respiratory curves were made using the change of lung volume for each respiratory phase. Although Patel *et al.* (17) analyzed the motion of upper ($n = 1$) and middle ($n = 4$) thoracic esophageal tumors

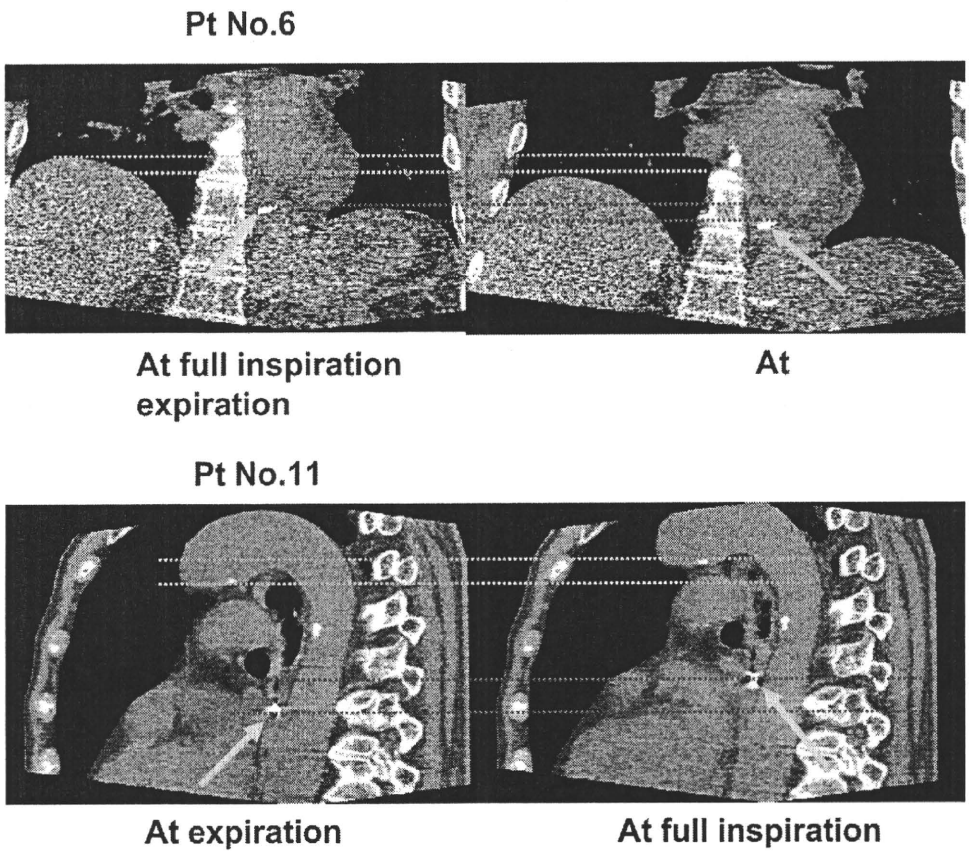

Fig. 5. Four-dimensional CT images of end-expiration and end-inspiration taken during normal breathing. (A) Coronal of Patient 6. (B) Sagittal of Patient 11.

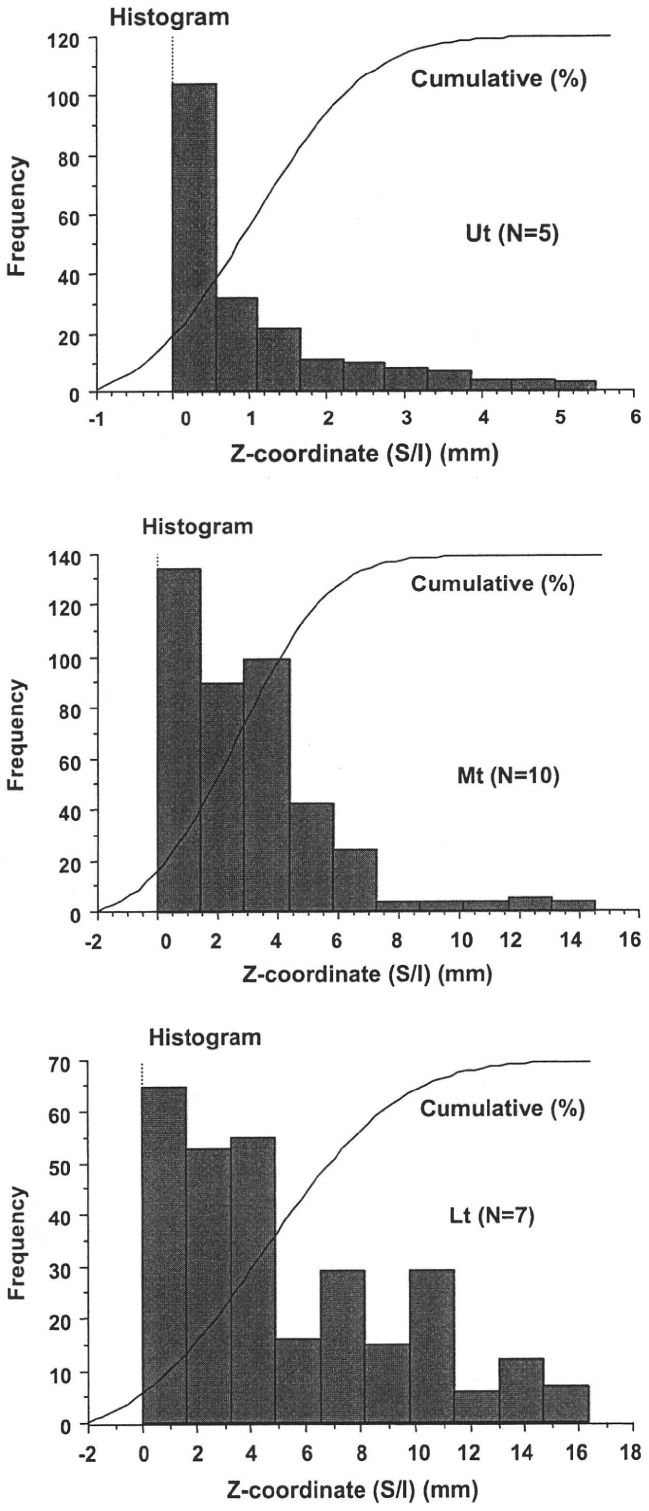

Fig. 6. Cumulative distribution of metal clips in the cranial–caudal direction. (A) Upper thoracic, (B) middle thoracic, (C), lower thoracic. S/I = superior–inferior.

in addition to the lower for the first time, our study evaluated more cases with upper (5 clips) and middle (10 clips) thoracic esophageal cancer. The present study can serve as the basis for the determination of the internal margins of thoracic esophageal cancers.

Measurements of lower esophageal sphincter pressure during quiet respiration revealed lateral esophageal motions of 6.0 ± 2.0 mm in the abdominal portion and 4.0 ± 1.0 mm in the thoracic region (18). Cine-fluoroscopic barium-swallow images of the esophagus in 51 patients undergoing catheter ablation for atrial fibrillation indicated that lateral shifts of more than 20 mm occurred in a majority of patients (19). Daily online CT images in a study of 6 patients treated with image-guided radiotherapy showed maximal motion in the distal esophagus and indicated that margins of 2.0–5.0 mm could account for all motion (20). A study of esophageal positions at the extreme phases of respiration in 6 patients suggested that a margin of 5.0–6.0 mm was sufficient to account for variations in organ position (21). Motion during quiet respiration for thoracic and abdominal tumors was analyzed in 13 patients with implanted fiducial markers, and the predominant source of motion was found to be respiration, whereas motion resulting from cardiac action was of far smaller magnitude (1). The means ± SD of motion of fiducial markers inserted into the esophageal wall using a fluoroscopic real-time tumor tracking system were 3.5 ± 1.8 mm, 8.3 ± 3.8 mm, and 4.0 ± 2.6 mm for the LR, CC, and AP directions, respectively (1). Lorchel *et al.* (14) proposed an internal target volume (ITV) margin of 10 mm, because 95% of CTV movements were <10 mm on the basis of the measurements of tumor motion in the various locations. Zhao *et al.* (15) reported measurements of mean peak-to-peak gross tumor volume centroid motion of 3.9 ± 2.7 mm in the LR, 3.8 ± 2.3 mm in the AP, and 8.7 ± 4.7 mm in the CC directions, based on scans of 25 patients. Asymmetric margins were recommended because of variations in tumor boundaries and deformation: 10 mm left, 8 mm right, 11 mm anterior, 6 mm posterior, 10 mm superior, and 16 mm inferior. Yaremko *et al.* (16) measured the following values for mean (SE) tumor motion among 31 patients: CC 7.1 (0.2) mm, AP 2.3 (0.1) mm, and LR 1.3 (0.06) mm; and they concluded that a radial margin of 8 mm and an axial margin of ±18 mm would provide distal esophageal tumor motion coverage for 95% of the cases. Patel *et al.* (17) concluded that the minimum radiation field margins required to cover the ITV of 95% of the primary tumors were 15 mm, 7.5 mm, and 7.5 mm in the CC, AP, and LR dimensions, respectively. Similarly, ITV coverage of 100% of celiac-region lymph nodes could be achieved with CC, AP, and LR margins of 22.5 mm, 10 mm, and 7.5 mm, respectively. According to Dieleman *et al.* (4), margins that would have incorporated all esophageal movement in the LR and AP directions were 5.0 mm proximally, 7.0 mm and 6.0 mm in the middle esophagus, and 9.0 mm and 8.0 mm in the lower esophagus, as determined by 4D-CT. A comparable lateral motion of 6.8 mm and a maximum CC motion of 14 mm have been reported in patients with primary esophageal tumors (1, 22, 23). This latter value is also comparable to our maximum values, which were 16.3 mm in the CC direction and 11.7 mm and 10.8 mm in the LR and AP direction, respectively.

In our study, the CC motion was significantly larger in the lower than in the upper or middle esophagus, and this is

Table 5. Intrafractional esophageal motion error

	95th percentile			$2.0\Sigma + 0.7\sigma$ (Stroom *et al.* [12])			$2.5\Sigma + 0.7\sigma$ (van Herk *et al.* [13])		
Direction	Ut	Mt	Lt	Ut	Mt	Lt	Ut	Mt	Lt
LR (mm)	2.0	2.4	6.8	1.54	1.54	4.55	1.89	1.89	5.60
AP (mm)	1.5	3.0	6.6	1.14	2.21	4.42	1.39	2.71	5.42
CC (mm)	4.3	7.4	13.8	2.68	5.69	9.10	3.28	6.99	11.20

Abbreviations as in Tables 1, 2, and 4.

consistent with the findings of other authors, such as Dieleman *et al.* (4). In addition to the lower thoracic, even the middle or upper thoracic esophagus also showed a strong correlation ($R^2 > 0.4$) with the respiratory curve at a high rate in this study.

We are aware of the concern that may be raised about radiation exposure to patients during the continuous cine-mode shooting for 20 s using the 320MSCT procedure. The continuous shooting for 20 s may be too long for patients with a regular respiratory cycle. Actually, however, there were some patients with an irregular respiratory cycle, and for these patients the continuous shooting for 20 s was considered necessary to obtain sufficient data about respiratory motion. With our protocol, the dose of radiation exposure from 320MSCT for 20 s was approximately 40–50 mGy at the skin surface, which is approximately 1% of the total isocenter dose of radiotherapy for esophageal cancer. Because all 12 patients in this study were given radiotherapy for curative intent, the radiation exposure by 320MSCT was considered to be within the allowable range. A secondary concern in this study is the blurring for 0.5 s that occurs in imaging because the time response remains at 0.5 s. As for a very quick movement of <0.5 s, the error may occur in the evaluation of the motion. Because the typical breathing period of a patient is approximately 3–5 s, the data are acquired for roughly every 10% of the respiratory cycle in this study, which is comparable to what typical 4D-CTs acquire using RPM or the Anzai belt. Finally, there might be a problem regarding the resolution of the reading system. Because the resolution is 512 × 512 segments in the transverse, there is a limit to the resolution of reading power. Therefore, although the motion can be traced in a patient with a broad movement to a certain extent, the data will show a poor resolution in a patient with only a small movement. The small sample size of 12 patients and 22 metal clips limits our ability to make firm recommendations regarding adequate ITV margin expansions, although prior studies of esophageal tumor motion had similar sample sizes. Additionally, we recognize that the measurements of organ motion based on 4D-CT taken on the day of simulation may not accurately represent the magnitude of motion occurring during the subsequent daily radiation treatments. Practical considerations make it difficult to obtain multiple 4D scans during the treatment course.

Strengths of our study relative to other published work include the use of normal-breathing 4D-CT scans rather than breath-holding techniques, inclusion of tumors in all esophageal locations, and the comparison with a respiratory curve. Our study provides reasonable guidelines for margins to account for respiratory motion of primary esophageal tumors.

CONCLUSIONS

In conclusion, 320MSCT significantly improves the observation of tumor displacement and overcomes some of the limitations of present CT methods. Moreover, owing to its accurate determination of the margin, volumetric cine scan is a useful complement to current irradiation methods.

We have shown that primary esophageal tumors can move substantially with respiration and that the magnitude of motion can vary significantly from patient to patient. The lower primary tumors seem to have greater respiratory motion than upper- or middle-esophageal tumors, and the motion is greatest in the CC direction. The following margin expansions were proposed to allow for >95% motion of primary esophageal tumors (removing the 5% outlier values): 4.3 mm CC, 1.5 mm AP, and 2.0 mm LR in the upper, 7.4 mm CC, 3.0 mm AP, and 2.4 LR in the middle, and 13.8 mm CC, 6.6 mm AP, and 6.8 mm LR in the lower thoracic esophagus.

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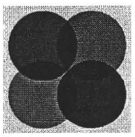

RADIATION ONCOLOGY

RESEARCH **Open Access**

Prescreening based on the presence of CT-scan abnormalities and biomarkers (KL-6 and SP-D) may reduce severe radiation pneumonitis after stereotactic radiotherapy

Hideomi Yamashita*, Shino Kobayashi-Shibata, Atsuro Terahara, Kae Okuma, Akihiro Haga, Reiko Wakui, Kuni Ohtomo and Keiichi Nakagawa

Abstract

Purpose: To determine the risk factors of severe radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT) for primary or secondary lung tumors.

Materials and methods: From January 2003 to March 2009, SBRT was performed on 117 patients (32 patients before 2005 and 85 patients after 2006) with lung tumors (primary = 74 patients and metastatic/recurrent = 43 patients) in our institution. In the current study, the results on cases with severe RP (grades 4-5) were evaluated. Serum Krebs von den Lungen-6 (KL-6) and serum Surfactant protein-D (SP-D) were used to predict the incidence of RP. A shadow of interstitial pneumonitis (IP) on the CT image before performing SBRT was also used as an indicator for RP. Since 2006, patients have been prescreened for biological markers (KL-6 & SP-D) as well as checking for an IP-shadow in CT.

Results: Grades 4-5 RP was observed in nine patients (7.7%) after SBRT and seven of these cases (6.0%) were grade 5 in our institution. A correlation was found between the incidence of RP and higher serum KL-6 & SP-D levels. IP-shadow in patient's CT was also found to correlate well with the severe RP. Severe RP was reduced from 18.8% before 2005 to 3.5% after 2006 ($p = 0.042$). There was no correlation between the dose volume histogram parameters and these severe RP patients.

Conclusion: Patients presenting with an IP shadow in the CT and a high value of the serum KL-6 & SP-D before SBRT treatment developed severe radiation pneumonitis at a high rate. The reduction of RP incidence in patients treated after 2006 may have been attributed to prescreening of the patients. Therefore, pre-screening before SBRT for an IP shadow in CT and serum KL-6 & SP-D is recommended in the management and treatment of patients with primary or secondary lung tumors.

Introduction

Stereotactic body radiation therapy (SBRT) has been widely used as a safe and effective treatment method for primary or metastatic lung tumors [1]. According to the protocol of Japan Clinical Oncology Group (JCOG) 0403 study [2,3], the absolute contraindication to SBRT was pregnancy. Relative contraindications consisted of (a) a history of irradiation to the concerned site, (b) severe interstitial pneumonitis or pulmonary fibrosis, (c) severe diabetes or connective tissue disease, and (d) common use of steroids. However, these complications preclude other treatment methods in some cases and radiation therapy becomes the only available treatment. Favorable initial clinical results, and local control rates around 90% have been reported [4-10].

Although the mechanisms are not completely understood, it is critical to review the biologic factors involved in radiation lung damage. Current evidence suggests that many factors and various lung parenchymal cells contribute to the pathogenesis of radiation lung damage [11].

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