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Original Article

Novel simulation for dosimetry impact of diaphragm respiratory motion in four-dimensional volumetric modulated arc therapy for esophageal cancer ☆

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ABSTRACT

Background and purpose: The diaphragm respiratory motion (RM) could impact the target dose robustness in the lower esophageal cancer (EC). We aimed to develop a framework evaluating the impact of different RM patterns quantitatively in one patient, by creating virtual four-dimensional computed-tomography (v4DCT) images, which could lead to tailored treatment for the breathing pattern. We validated virtual 4D radiotherapy (v4DRT) along with exploring the acceptability of free-breathing volumetric modulated arc therapy (FB-VMAT).

Methods and Materials: We assessed 10 patients with superficial EC through their real 4DCT (r4DCT) scans. v4DCT images were derived from the end-inhalation computed tomography (CT) image (reference CT) and the v4DRT dose was accumulated dose over all phases. r4DRT diaphragm shifts were applied with magnitudes derived from r4DCT scans; clinical target volume (CTV) dose of v4DRT was compared with that of r4DRT to validate v4DRT. CTV dosage modifications and planning organ at risk volume (PRV) margins of the spinal cord were examined with the diaphragm movement. The percentage dose differences (ΔDx) were determined between the v4DRT and the dose calculated on the reference CT image.

Results: The CTV ΔDx between the r4DRT and v4DRT were within 1% in cases with RM ≦ 15 mm. The average $\Delta D_{100\%}$ and ΔD_{mean} of the CTV ranging from 5 to 15 mm of diaphragm motion was 0.3% to 1.7% and 0.1% to 0.4%, respectively. All CTV index changes were within 3% and ΔD_{1cc} and ΔD_{2cc} of Cord PRV were within 1%.

Conclusion: We postulate a novel method for evaluating the CTV robustness, comparable to the conventional r4DCT method under the diaphragm RM ≦ 15 mm permitting an impact of within 3% in FB-VMAT for EC on the CTV dose distribution.

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Esophageal cancer (EC), one of the most common cancers [1], is often locally advanced or distantly metastasized at diagnosis.

Radiotherapy is less invasive than surgery and beneficial for organ preservation. However, cardiac radiation exposure is associated with complications like such as pericarditis and coronary artery disease [2–4]. The overall incidence rates of cardiac toxicity are reportedly as high as 9.3–20.8% [5–8]. Radiation therapy for lower EC is challenging due to the proximity of surrounding organs at risk (OAR).

In recent years, intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) technique has enabled OAR dose sparing while maintaining target dose coverage [9,10]. Compared to three-dimensional conformal radiotherapy techniques, above-mentioned techniques potentially reduce the dose to heart [11–14]. However, concerns regarding respiratory motion (RM) disrupting the dose distribution to the patient persist [15]. RM management techniques such as breath-hold technique and tumor-tracking system may resolve this [16], but are time intensive.

☆ EC: esophageal cancer, v4DCT: virtual four-dimensional computed-tomography, v4DRT: virtual 4D radiotherapy, FB-VMAT: free-breathing volumetric modulated arc therapy, r4DCT: real 4DCT, CTV: clinical target volume, PRV: planning organ at risk volume, CT: computed tomography, ΔDx: percentage dose differences, OAR: organs at risk, IMRT: intensity modulated radiation therapy, TPS: treatment planning system, DIR: Deformable Image Registration, GTV: gross tumor volume, PTV: planning target volume, AP: anterior-posterior, LR: left–right.

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Free breathing VMAT (FB-VMAT) allows less treatment time and has the potential to treat many patients with a single machine. Its implementation for EC requires studying how the action of breathing, particularly the diaphragm RM impacts the dose distribution through the widely used four-dimensional computed tomography (4DCT) [17–19]. However, performing multiple 4DCT scans on a single patient for simulating many different amplitude patterns is not pragmatic given the radiation exposure.

Recently, an optimization tool in commercial treatment planning system (TPS) RayStation version 10.0.1 (RaySearchMedical Laboratories AB, Stockholm, Sweden) has facilitated generating large numbers of virtual 4DCT (v4DCT) images from existing original planning CT images, to simulate the diaphragm motion, based on user-defined organ motion. Previously, the dose distribution of multiple setup error scenarios through shifting the isocenter in version 6.2.0, enabled robust evaluation [20]. The current version allows deformation of the specific organ by Deformable Image Registration (DIR) [21].

We aimed to establish a novel framework to evaluate the impact of the diaphragm RM quantitatively by creating v4DCT images and validating virtual four-dimensional radiation therapy (v4DRT), along with measuring the effect of RM on the dose distribution at certain amplitudes and assessing the acceptability of FB-VMAT for EC.

Materials and methods

Patients

This study was approved by the Institutional Review Board of Hiroshima University (E-1656–4). Inclusion criteria was as follows: i) Superficial cancer. Patients with early T stage (T1a - T1b) EC were included in the study, using the 8th edition International Union Against Cancer Tumor-Node-Metastasis staging system [22]. ii) Tumor locations medial to the esophagogastric junction (EGJ). Upper esophagus, unaffected by the diaphragm motion, was excluded. iii) Marked with for identification before CT scans. Consequently, ten patients (A–J) EC, were included in this study (Table 1). All tumors were squamous cell carcinoma, and tumor depths were identified as mucosal (T1a) in one case and submucosal (T1b) in nine cases. The tumor locations were middle esophagus and the EGJ in one case, and lower esophagus in eight cases.

Preparation of this study

Equipment and instruments used

In all patients, free-breathing three-dimensional planning CT scans from the mediastinum to the upper abdominal region were performed with 2.5 mm slice thickness, followed by real 4DCT scans (r4DCT) on Lightspeed RT16 CT simulator (GE Medical Systems, Milwaukee, WI, USA). The respiratory signal was recorded with the Varian Real-time Position Management Respiratory Gating system (Varian Medical Systems, Palo Alto, CA). These images were sorted into 10 respiratory phases to reconstruct r4DCT images, with 0% and 50% phases corresponding to end-inhalation and end-exhalation, respectively. VMAT plan was optimized and calculated on the RayStation TPS commissioned through a TrueBeam (Varian Medical Systems, Palo Alto, CA) linear accelerator.

Contouring

Targets and OAR, delineated on the end-inhalation phase image, were regarded as "reference CT image." The gross tumor volume (GTV), identified with metallic fiducial markers was the total volume of the primary lesion. The clinical target volume (CTV) was defined as the GTV with a 30 mm margin longitudinally along the esophagus and a 10 mm margin around the GTV, where bone, air, and blood vessels without tumor invasion were excluded. The planning target volume (PTV) was contoured by expanding 7 mm margin in the anterior-posterior (AP) and left–right (LR) direction, and a 15 mm margin in the SI direction around CTV, considering set-up errors and respiratory movements. The lung, spinal cord, heart, and left ventricle were delineated as OAR. A margin of 3 mm was added to the spinal cord for planning organ at risk volume (PRV). The vertebral body and the diaphragm were also contoured for v4DCT image creation.

VMAT treatment plan

VMAT plans consisted of double arcs which rotated 360°, with two 90° lateral avoidance sectors (Fig. 1). Collimator angles were either 10° or 350° depending on the shape of the PTV. The prescribed dose was set at the mean PTV dose of 50.4 Gy in 28 fractions. Dose constraints of the PTV and OAR, including the lung, spinal cord PRV, heart, and left ventricle under our clinical protocol were given in Supplementary Materials Table S1. Dose calculated on the reference CT image was used as "the reference does evaluation".

r4DRT creation

The r4DRT was constituted to validate v4DCT images and v4DRT. Each r4DCT image dose was recalculated by the reference dose evaluation. Recalculated dose distributions were mapped onto the reference CT image after DIR, and subsequently accumulated. The weight of 0.1 as dose accumulation of each respiratory phase was used, since the probability of existence was identical. In this method, the influence of interplay effects was excluded.

Creation of v4DCT images and validation of v4DRT

The following steps were taken to develop a new framework to assess the impact of the diaphragm RM on the 4D dose distribution using v4DCT images (Fig. 2, Step (a) - (c)). v4DCT image creation and validation were included here.

Table 1
Patients' characteristics of superficial esophageal cancer.

Patient	Age	Location	T stage	GTV (cc)	CTV (cc)
A	82	EGJ	T1b	22.7	82.3
B	79	Lower	T1b	16.3	75.3
C	71	Lower	T1b	14.2	69.9
D	67	Lower	T1b	18.3	72.6
E	63	Lower	T1b	10.5	50.4
F	77	Lower	T1b	23.8	78.3
G	77	Lower	T1b	13.0	97.6
H	72	Lower	T1a	12.6	54.6
I	86	Lower	T1b	28.6	264.2
J	73	Middle	T1b	8.5	44.2

GTV: gross tumor volume, CTV: clinical target volume, EGJ: esophagogastric junction.

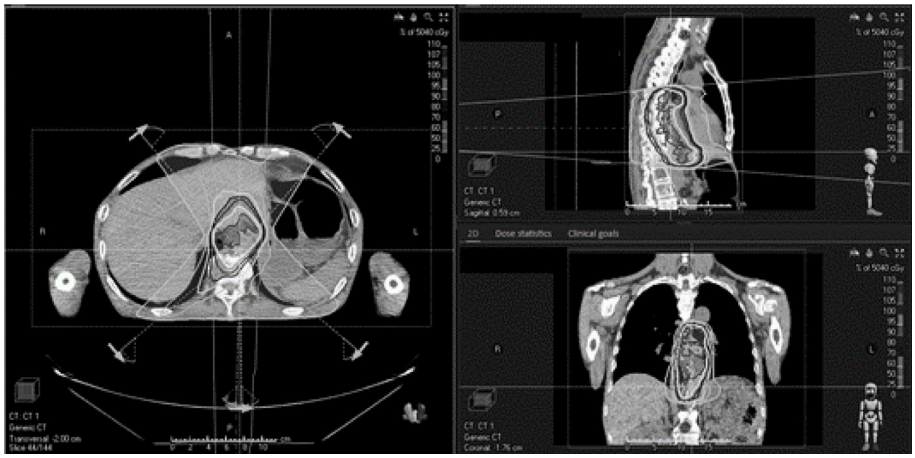

Fig. 1. An example of beam angles of the volumetric modulated arc therapy plan. They were consisted of partial double arcs including two 90° lateral avoidance sectors.

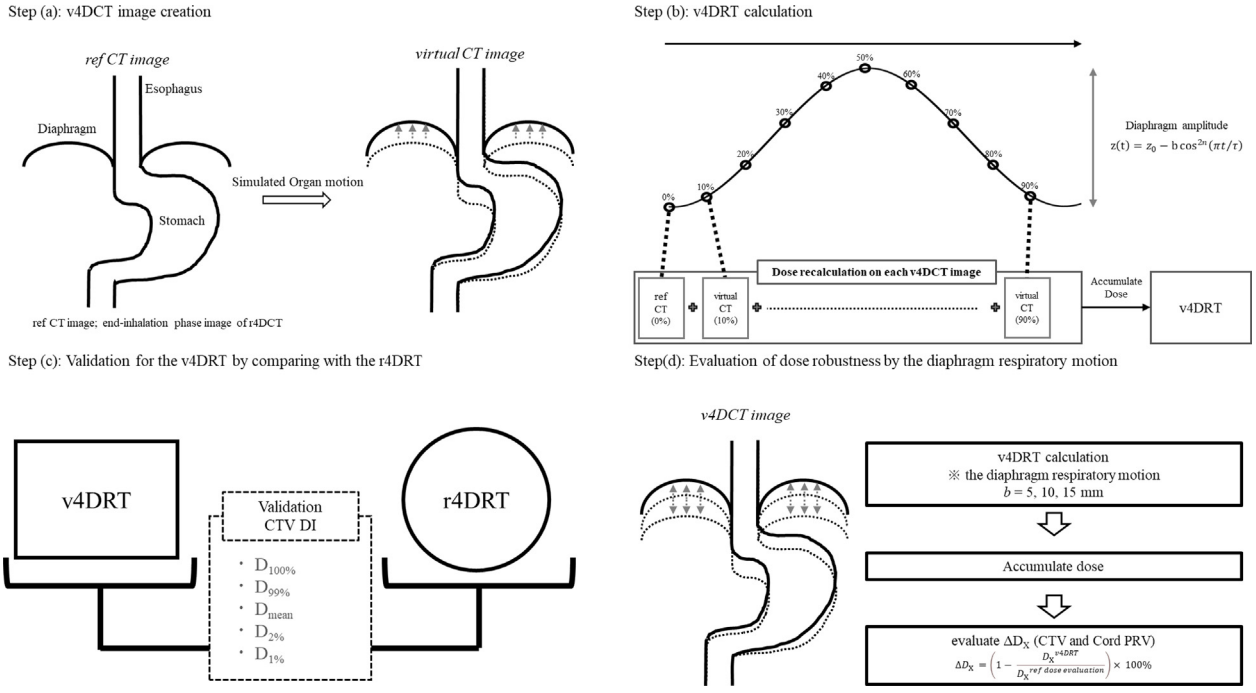

Fig. 2. Illustration of the process of this study. Details are shown in Materials and Methods section. *Abbreviations*. . .v4DCT: virtual four-dimensional computed tomography, r4DCT: real four-dimensional computed tomography, ref CT image: reference computed tomography image, VMAT: volumetric modulated arc therapy, DI: dose index CTV: clinical target volume, PRV: planning organ at risk volume.

Step (a): v4DCT image creation

The reference CT images were deformed into v4DCT images through the simulated-organ motion (SOM) mode on the RayStation [21], with the diaphragm deformed in the superior direction with vertebrae fixation. Created v4DCT images comprised of ten respiratory phases in total, whose amplitude was calculated by the mathematical equation proposed by Lujan *et al.* [23]: $z(t) = z\_0 - bcos^2n(\pi t/\tau)$, with z_0 as the exhale coordinate, b as respiratory amplitude, τ as respiratory period and n as a fitting parameter showing asymmetry of the breathing pattern. The subsequent analyses were performed for n = 1, assuming a symmetrical respiratory cycle. The value of z-axis was also determined for each as $z\_0 = b$, and the amplitude of each phase was calculated as t = 0.1 τ, 0.2 τ, . . ., 1.0 τ.

Step (b): v4DRT creation

v4DCT image doses were recalculated based on the reference does evaluation, which were then deformed onto the reference CT images and merged to calculate the v4DRT [18]. As previously reported by Rosu et al. [24], the dose accumulation was done using coefficients derived from the respiratory movement model [23], considering the probability of existence of each phase for n = 1.

Step (c): Validation for the v4DRT by comparing with the r4DRT

The validation for the accumulated CTV dose in the v4DRT was performed by comparing it with the r4DRT. The diaphragm amplitudes in r4DCT images were applied to v4DCT images. The amplitude in r4DCT image was evaluated as follows: DIR was done between the end-inhale (0%) and end-exhale (50%) phase. The diaphragm deformation vector field representing each voxel displace-

ment was quantified through an in-house program, and v4DRT was calculated corresponding to the magnitude of the diaphragm amplitude obtained through the process similar to step (a) and (b).

Then, accuracy of accumulated CTV dose indexes ($D_{100\%}$, $D_{99\%}$, D_{mean}, $D_{2\%}$ and $D_{1\%}$) between the v4DRT and r4DRT was evaluated as follows:

$$v4DRT\ accuracy\ \text{in}\ D_X\ (\%) = \left(D_X^{v4DRT} / D_X^{r4DRT} \right) \times\ 100\%$$

D_x% was the largest dose level percentage covering x% volume of the CTV and D_{mean} indicated mean dose of the CTV. Setting a large amplitude in v4DRT could cause the deformed CTV to deviate from the PTV margin. Therefore, we divided the patients into those with the real diaphragm amplitudes ≦ 15 mm or > 15 mm, and calculated the v4DRT accuracy in each group.

Step (d): Evaluation of dose robustness by RM

In this investigation (Fig. 2, Step (d)), the CTV robustness and the Cord PRV dose was evaluated for the moving diaphragm, 5 to 15 mm superiorly. The v4DCT images and v4DRT were generated at the amplitude b = 5, 10, 15 mm like step (a) and (b). The accumulated dose was evaluated through the dose indexes of the CTV ($D_{100\%}$, $D_{99\%}$, D_{mean}, $D_{2\%}$ and $D_{1\%}$) and the Cord PRV (D_{1cc} and D_{2cc}). D_{xcc} was the largest dose level percentage covering × cc volume of the Cord PRV. Furthermore, the percentage changes (ΔD_x) between v4DRT and the reference does evaluation was calculated as follows;

$$\Delta D\_X(\%) = \left(1 - D_X{}^{v4DRT} / D_X{}^{thereferencedoese\,valuation}\right) \times 100\%$$

As reference data, the ΔD_x of the CTV between r4DRT and the reference does evaluation was determined. In addition, the amount of GTV motion in the SI direction between the 0% and 50% phase of r4DCT was also obtained using the in-house program.

Results

Table 2 shows the diaphragm amplitude on r4DCT images. The diaphragm motion ranged from 12–38 mm at maximum. Fig. 3 showed the accuracy between the two dose evaluations for accumulated CTV dose indexes ($D_{100\%}$, $D_{99\%}$, D_{mean}, $D_{2\%,}$ and $D_{1\%}$). For amplitudes ≦ 15 mm, all dose indices were close to 100% and matched well within ± 1% accuracy from it in all patients [Patient A, E, H, J]. However, at amplitudes > 15 mm, 5 of 6 patients [Patient B, C, D, F, I] showed errors of > 3% at $D_{100\%}$. Only Patient G (amplitude = 20 mm) showed all dose indices were close to 100%.

ΔD_x of the CTV and the Cord PRV were shown in Fig. 4. The average of $\Delta D_{100\%}$ at 5 mm diaphragm motion was 0.3% (interquartile range (IQR): 0.0–0.6), and at 10 and 15 mm was 1.0% (IQR: 0.6–1.5), and 1.7% (IQR: 1.8–2.1), respectively. Likewise, the average of $\Delta D_{99\%}$, ΔD_{mean}, $\Delta D_{2\%}$ and $\Delta D_{1\%}$ with the diaphragm motion from 5 to 15 mm were 0.2%—1.3%, 0.1%—0.4%, 0.1%—0.3%, and 0.1%—0.3%, respectively. For the diaphragm amplitude up to 10 mm, all CTV index changes were within 2%, and within 3% at 15 mm. The largest difference of $\Delta D_{100\%}$ was 2.8% at 15 mm amplitude.

ΔDx of CTV between r4DRT and the reference does evaluation was shown in Supplementary Materials Figure S1: all CTV index changes were within 3% for the RM ≦ 15 mm. Even if > 15 mm, 5 of 6 patients had a change of within 4% (Patient D showed slightly high 3.3% change in $\Delta D_{100\%}$). Patient I showed significant changes with a $\Delta D_{100\%}$ of 18.9%; the CTV deviated from the PTV margin at some phases in r4DCT owing to the large GTV motion of 21 mm (Table 2).

Considering the Cord PRV, the average ΔD_{1cc} at 5 mm diaphragm motion was 0% (IQR: 0.0–0.0), and at 10 and 15 mm was 0.1% (IQR: 0.0–0.2) and 0.2% (IQR: 0.0–0.4), respectively. Similarly, the average ΔD_{2cc} at 5 mm diaphragm motion was 0% (IQR: 0.0–0.1), and at 10 and 15 mm was 0.1% (IQR: 0.0–0.2) and 0.2% (IQR: 0.1–0.5), respectively. For the diaphragm amplitude up to 15 mm, ΔD_{1cc} and ΔD_{2cc} of the Cord PRV were within 1%.

Discussion

Here, we develop a novel framework to evaluate the impact of RM quantitatively by creating v4DCT images and validating a v4DRT. For the diaphragm RM ≦ 15 mm, the accumulated CTV dose differences between the v4DRT and r4DRT were all within ± 1%, and that v4DCT images may be an alternative to the r4DCT images. Furthermore, we examined the dose robustness by RM and found that the CTV and Cord PRV dosimetry impact was within 3% and 1%, respectively.

This system has a few advantages over conventional methods using r4DCT. First, v4DCT method enables employing many different amplitude patterns on the same patient and RT plan without radiation exposure. Therefore, it may facilitate evaluating the robustness of dose distributions according to the arbitrary RM quantitatively. Moreover, r4DCT scanning, known to produce artefacts, such as blurring, due to patient breathing disturbance, made it challenging to perform accurate 4D dose assessment. [25]. However, the v4DCT method was able to generate CT images without artefacts. Sarrut *et al.* also simulated dynamic respiratory CT scans noninvasively without increasing irradiated dose by the DIR method [26]. We further evaluated the CTV and Cord PRV robustness due to RM based on the new framework.

In the condition of the diaphragm RM ≦15 mm, this study demonstrated that v4DCT images could be generated with high reproducibility comparable to the r4DCT images. One of the reasons for the limited conditions was that the esophagus SI-directional motion could not be completely reproduced when large diaphragm RM was simulated. Only one targeted organ was allowed to be deformed through the SOM function and the deformations of esophagus were performed in a way that followed the adjacent diaphragm deformation. When the diaphragm RM > 15 mm was set, there were some cases of deformed GTV deviation from the superior margin of the PTV (Supplementary Materials Figure S2), which were due to unintentional movement of the esophagus to the same degree as the diaphragm, and could result in poor accuracy between v4DRT and r4DRT in condition of > 15 mm.

Table 2
The diaphragm and GTV motion of patients measured by the in-house program.

Patient	diaphragm motion (mm)	GTV motion (mm)	Patient	diaphragm motion (mm)	GTV motion (mm)
A	15	8	F	43	9
B	26	10	G	20	7
C	23	9	H	15	11
D	30	10	I	38	21
E	15	4	J	12	5

GTV: gross tumor volume.

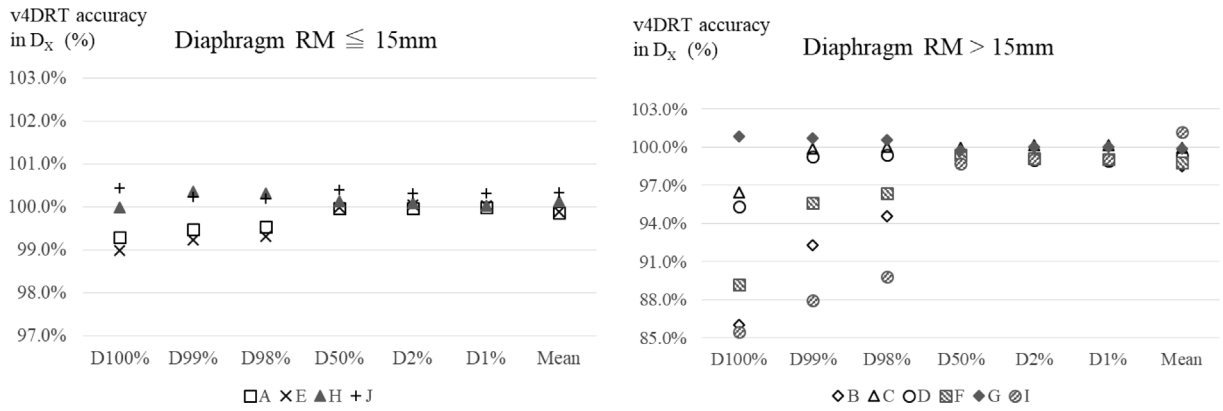

Fig. 3. v4DRT accuracy between virtual four-dimensional radiotherapy (v4DRT) and real 4DRT (r4DRT) in accumulated clinical target volume (CTV) dose indexes ($D_{100\%}$, $D_{99\%}$, D_{mean}, $D_{2\%}$ and $D_{1\%}$) for cases the diaphragm respiratory motion (RM) ≦ 15 mm [Patient A, E, H, J], and > 15 mm [Patient B, C, D, F, I, G].

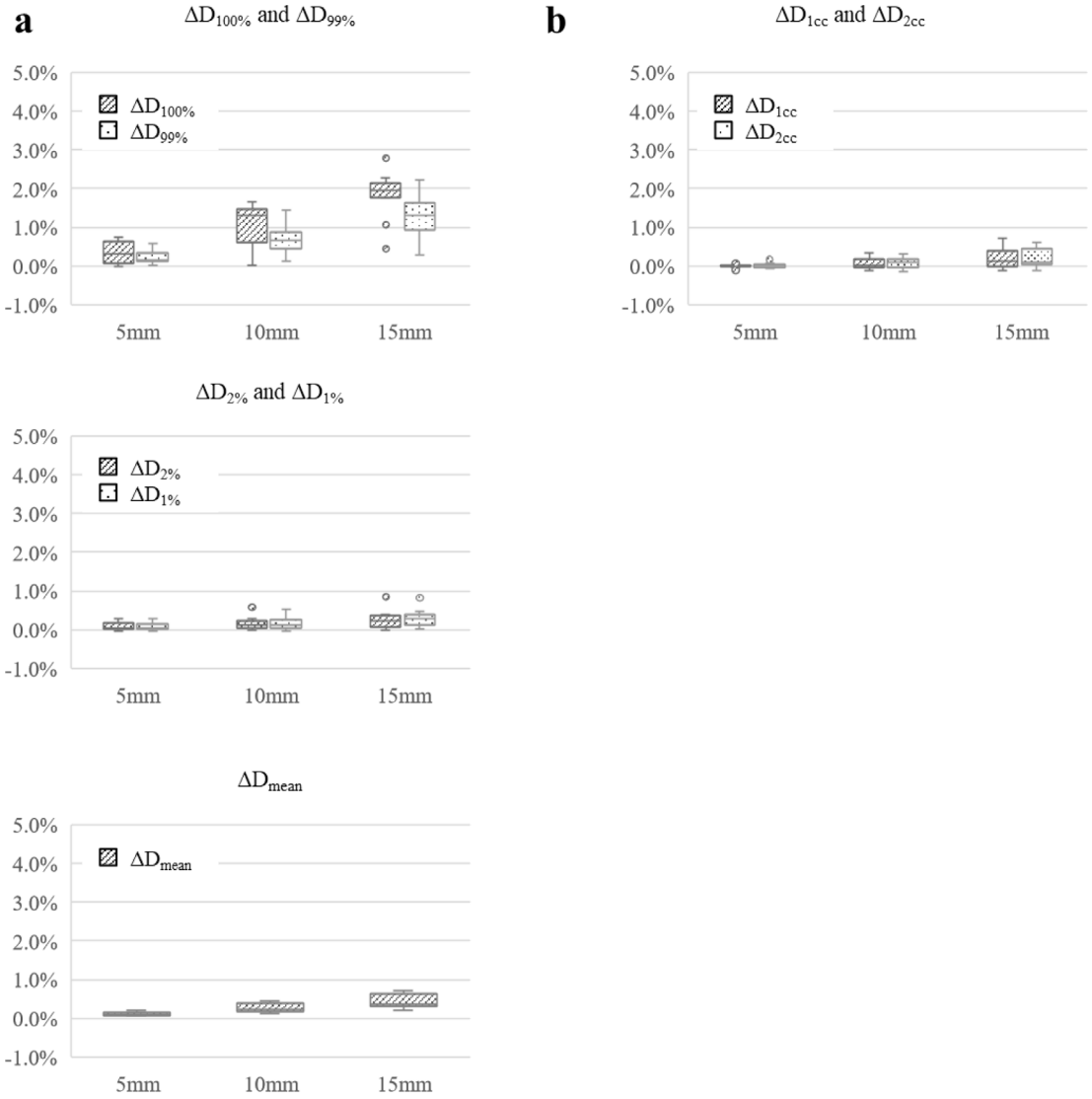

Fig. 4. The percentage change (ΔD_X) of the accumulated dose for clinical target volume (CTV) [a] and Cord planning organ at risk volume (PRV) [b] between virtual four-dimensional radiotherapy (v4DRT) and the dose evaluation on the reference CT image.

In FB-VMAT for EC, the RM of the esophagus as well as the diaphragm can affect dose robustness. Scarsbrook reported SI motions of the esophagus at a maximum of 10 mm [27], although some cases reported greater values [28,29]. In the present study, as seen in Table 2, most cases were approximately 10 mm; however, as high as 21 mm of motion was observed in one patient, resulting in a large reduction in CTV $D_{100\%}$ in r4DRT. Therefore, it is impor-

tant to place a fiducial marker near the tumor in advance, to monitor its movement in clinical practice.

Since this study has not evaluated the CTV robustness using the v4DCT method in cases of the diaphragm RM > 15 mm, breath-hold or respiratory-suppression technique should be recommended. However, even for the larger diaphragm amplitudes, Supplementary Materials Fig. 1 showed that $\Delta D_X(\%)$ of the CTV between r4DRT and the reference dose evaluation was within < 3% in many cases, indicating the possibility of further application of FB-VMAT. In the future, we would like to develop the v4DCT method further to accommodate larger amplitudes.

In high-precision radiotherapy like IMRT and intensity-modulated proton therapy (IMPT), target and surrounding anatomical position changes may also affect the dose distribution. Especially, for treating EC in the lower and EGJ, the diaphragm daily position shifts could cause target and OAR ambiguity in dose distribution. [30–32] Nyeng et al. reported that daily diaphragm position shifts were the most frequent cause for decrease in the volume receiving 95% of the prescribed dose ($V_{95\%}$) coverage of CTV and PTV and the need for replanning in static IMRT [31]. Additionally, the lateral beam passing through the diaphragm considerably affects the target coverage [33]. Our study showed that the effect of the diaphragm RM was within 3%, possibly because our VMAT plan encompassed partial arcs avoiding irradiation from lateral side to decrease lung dose, and the beam angles could have reduced dose uncertainty through the diaphragm.

Assessing the robustness of target for high-precision irradiation is crucial. Conventionally, PTV base planning has been performed, but there have been reported some situations where the dose uncertainties to the CTV could be an issue [33,34]. For limitations of the PTV concept, robust and probabilistic evaluation methods have been developed to directly incorporate motion and uncertainty into treatment planning optimization [15,35]. Previously, the robustness evaluation focused at range and setup issues. Recently, additional strategies have become available within commercial TPS [21]. We were able to evaluate the CTV and Cord PRV robustness in FB-VMAT for EC by SOM mode on the RayStation. Prospectively, this framework could be applied for the evaluation of other organs that are likely to suffer due to RM.

The interplay effect must be mentioned while considering the RM effect. This effect is due to the lack of synchronization between dynamic multi-leaf collimator (MLC) and tumor motion. Missing targets may result from the high conformal field, the numerous MLC positions needed for IMRT, and the tumor's intra-fractional motion. Since our study was conducted under free-breathing conditions, very small effect could occur, based on previous reports. Uchinami *et al.* showed that the maximum CTV dose variation was < 1% for the assessment of the interplay effect in abdominal irradiation assuming the RM ≦ 15 mm [36]. Some reports have also demonstrated that the interplay effect became smaller as the number of fractions was increased [37,38], indicating that the tolerance of the RM considering the robustness of the dose distribution according to the RM and interplay effect was 15 mm.

There were some limitations in this study. One is that it was limited to early EC. In addition, several studies reported that respiratory-induced esophageal movements occur not only in the SI direction but also in the AP direction. [30,39] However, the current study evaluated only the motion effects in the SI direction since it was not possible to set esophageal motion arbitrarily. Despite this, the v4DRT showed a dose difference of < 1% from the r4DRT, and previous reports showed that the movement of the esophagus other than in the SI direction was < 5 mm [30,32], therefore, the dose evaluation using this framework was considered valid.

Conclusion

This study proposed a novel approach to evaluate the robust by generating v4DCT images. Under the conditions of the diaphragm RM ≤ 15 mm, the accumulated CTV dose differences between the v4DRT and r4DRT were all within 1%, and the v4DCT method was comparable to the conventional r4DCT method. In FB-VMAT for EC case near the diaphragm, if the diaphragm motion was within 15 mm, rendering that the impact on CTV dose distribution could be performed within 3%.

CRediT authorship contribution statement

Tsuyoshi Katsuta: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization, Project administration. **Yuji Murakami:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision, Project administration. **Daisuke Kawahara:** Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Writing – review & editing. **Shota Miyoshi:** Writing – review & editing. **Nobuki Imano:** Validation, Writing – review & editing. **Junichi Hirokawa:** Validation, Writing – review & editing. **Ikuno Nishibuchi:** Validation, Writing – review & editing. **Yasushi Nagata:** Validation, Writing – review & editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109849.

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