

Scientific Article

A Pilot Study of Synchronization of Respiration-Induced Motions in the Duodenum and Stomach for the Primary Tumor in Radiation Therapy for Pancreatic Cancer Using 4-Dimensional Computed Tomography



Rei Umezawa, MD, PhD,^{a,b,*} Akihisa Wakita, MSc,^a Yoshiyuki Katsuta, PhD,^b Yoshinori Ito, MD, PhD,^{a,c} Satoshi Nakamura, MSc,^a Hiroyuki Okamoto, PhD,^a Noriyuki Kadoya, PhD,^b Kana Takahashi, MD, PhD,^a Koji Inaba, MD, PhD,^a Naoya Murakami, MD, PhD,^a Hiroshi Igaki, MD, PhD,^a Keiichi Jingu, MD, PhD,^b and Jun Itami, MD, PhD^a

^aDepartment of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan; ^bDepartment of Radiation Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan; ^cDepartment of Radiation Oncology, Showa University School of Medicine, Tokyo, Japan

Received December 22, 2020; revised April 7, 2021; accepted May 18, 2021

Abstract

Purpose: We investigated the synchronization of respiration-induced motions at the primary tumor and organs at risk at radiation planning for pancreatic cancer.

Methods and Materials: Four-dimensional computed tomography images were acquired under the condition of shallow free breathing in patients with pancreatic cancer. The gross tumor volume (GTV), duodenum (DU), and stomach (ST) were contoured. The center of mass was computed for each 4-dimensional volume of interest. The respiration dependence of coordinates for the center of each volume of interest was computed relative to its location at the 50% (maximum exhalation) phase. Based on the shift of the GTV, we investigated the synchronization of respiration-induced motions between each contouring target. We examined the differences in the volume averaged dose to the ST and DU in each respiratory phase.

Results: Nine patients with pancreatic cancer were analyzed in this study. The mean maximum 3-dimensional excursions at the GTV, DU, and ST were 9.6, 9.8, and 11.4 mm, respectively. At phase 0% and 90% (inhale phases), mean distance changes in the positional relationship with the GTV were 0.3 and 0.7 mm respectively for the DU and -2.5 and -2.4 mm respectively for the ST. There was no significant respiration associated change (RAC) between each respiratory phase in the DU ($P = .568$), and there was a significant RAC in the ST ($P < .001$). There was a significant RAC of the volume averaged dose to the ST ($P = .023$).

Presented at the Annual Meeting of the American Society of Radiation Oncology (ASTRO), San Antonio, TX, October 2018.

Sources of support: This work had no specific funding.

Disclosures: none.

Data Sharing Statement: Research data are not available at this time.

*Corresponding author: Rei Umezawa, MD, PhD; E-mail: reirei513@hotmail.com

<https://doi.org/10.1016/j.adro.2021.100730>

2452-1094© 2021 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Conclusions: Our results indicate that the DU but not the ST might move synchronously with GTV due to respiration.

© 2021 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Radiation therapy (RT) is one of the treatment options for pancreatic cancer. RT for the primary tumor plays an important role in local control. However, local control in conventionally fractionated RT for pancreatic cancer has been poor.¹ Recently, results of studies on the effects of dose escalation for intensity modulated radiation therapy (IMRT) and stereotactic radiation therapy (SRT) on pancreatic cancer have been reported.¹⁻⁴ By using those high-precision RT modalities for pancreatic cancer, more local control can be expected. However, RT for pancreatic cancer is susceptible to respiratory movement of the primary tumor and it is necessary to consider the variation of this movement in high-precision RT for pancreatic cancer.

A method for the reconstruction of 4-dimensional computed tomography (4DCT) images acquired during free breathing has been reported.⁵ There have been many reports about movement of the primary tumor determined by using 4DCT in RT for pancreatic cancer, and movement of the primary tumor in the craniocaudal directions has been shown to be more variable than that in other directions.⁶⁻⁸ Thus, respiratory movement of the primary tumor in pancreatic cancer can be understood to some extent, but there have been few reports on respiratory movements of normal organs close to the primary tumor. Moreover, there is a possibility that organs at risk (OARs) may move without interlocking with the primary tumor due to breathing. In that case, evaluation of the dose distribution at RT planning may not be precisely reflected. There is a possibility that the actual dose to the stomach (ST) and duodenum (DU) is higher than the calculated dose. High-dose irradiation of the DU and ST may cause serious gastrointestinal toxicity.⁹⁻¹¹ We should be more careful in performing high-precision RT. Therefore, we hypothesized that the dose distribution of RT planning for pancreatic cancer could be more reliably calculated by evaluating the relations of respiratory movement between the primary tumor and OARs. The primary purpose of this study was to investigate the synchronization of respiration-induced motions at OARs for the primary tumor using 4DCT as a pilot study.

Methods and Materials

Patients

Patients with pancreatic cancer who underwent 4DCT at RT planning for 3-dimensional conformal RT (3DCRT),

IMRT, or SRT between January 2015 and March 2016 was analyzed retrospectively. This study was approved by the local institutional review board (2016-058).

CT simulator

Patients were immobilized in the supine position with both arms above their head. Intravenous contrast medium was administered after each patient had fasted for at least 3 hours. The slice thickness of the CT scan was 2 mm. No fiducial markers were placed in the primary tumor. External abdominal compression was not delivered.

Two phases at the inhale and exhale phases in 3-dimensional CT images and 10 phases in 4DCT images using a 16-slice CT machine (Aquilion LB, Canon Medical Systems Corporation) and a real-time positioning management system (Varian Medical Systems, Palo Alto, CA) were acquired under the condition of shallow free breathing.

Contouring

RT planning was performed by ECLIPSE (Varian Medical Systems, Palo Alto, CA). The gross tumor volume (GTV) and the DU and ST were contoured in images at the 3D exhale phase. Then contouring of those images was adapted to 4D images of each phase using deformable image registration by MIM Maestro software (version 6, MIM software, OH). Those adapted images were confirmed by one radiation oncologist and one medical physicist.

GTV was defined as the primary tumor identified on CT. The clinical target volume (CTV) was defined as GTV plus 5 mm. Basically, the planning target volume (PTV) was defined as CTV plus 10-mm margins in 3DCRT. The PTV was defined as CTV plus 5 mm in IMRT or SRT. Contouring of the DU and ST was based on the report by Jabbour et al.¹² The ST, separated into cardia, fundus, body, antrum and pylorus, was contoured as one organ. The DU was contoured as one organ from the first portion to the fourth portion.

Evaluation of movement in the contouring target

The center of mass was computed for each 4D volume of interest. The respiration dependence of the x (left-right), y (anterior-posterior), and z (craniocaudal) coordinates for the center of each volume of interest was

computed relative to its location at the 50% (maximum exhalation) phase. Based on those distances, the 3D excursions of each contouring target were calculated.

Next, we examined the synchronization of respiration-induced motions. To investigate the synchronization of respiration-induced motions of other contouring targets for the GTV, we evaluated the changes in distances of the DU and ST in their positional relationships with the GTV for each respiratory phase. The difference between the synchronization of each contouring target in each respiratory phase was analyzed by the Kruskal-Wallis test. We defined no significant difference in this test as synchronization of respiratory movement between each target. To determine the reliability of this synchronization, the respiration associated change (RAC) in the cohort mean of the volume averaged doses to the ST and DU was evaluated. The cohort means of percentage changes in each respiratory phase were investigated on the basis of 50% phase. The differences between each respiratory phase in the volume averaged doses to the ST and DU were also analyzed by the Kruskal-Wallis test. Moreover, provisional treatment plans without gating (0%-90%) and with gating (30%-70% and 50%) were made. We evaluated the differences of the volume averaged doses to the ST (ST0%-90%, ST30%-70%, and ST50%) and DU (DU0%-90%, DU30%-70%, and DU50%) between treatment plans with and without gating. As a planning method, 3DCRT was delivered with a total dose of 50.4 Gy in 28 fractions. The internal target volume was provided by superimposing GTV at each respiratory phase, and the PTV was defined as internal target volume plus 5-mm margins. Four field techniques with photon beams of 10 MV using a linear accelerator were delivered, and the reference point for the prescribed dose was put at the center of the PTV. RT planning was performed by ECLIPSE (Varian Medical Systems, Palo Alto, CA) with an analytical anisotropic algorithm. Similarly, the stomach contouring and duodenum contouring were superposed at each respiratory phase.

Continuous variables are presented as mean values \pm standard deviation (SD). Statistical significance was set at the level of $P < .05$. Statistical analysis was performed using JMP@10 (SAS Institute Inc, Cary, NC).

Results

Patient characteristics

Nine patients with pancreatic cancer were analyzed in this study. All patients had unresectable locally advanced pancreatic cancer. Patient characteristics are shown in Table 1. Six patients had pancreas head/uncus cancer and 3 patients had body/tail cancer. The mean \pm SD of GTV volume was 24.50 ± 8.75 mL. The mean \pm SD of PTV volume was 167.9 ± 67.8 mL.

Correlations between respiratory movements of the GTV and other contouring targets

The distances for respiratory movements in the contouring targets are shown in Figure 1. The means \pm SD of maximum excursions at the GTV were 2.0 ± 0.9 , 3.2 ± 1.3 , and 9.0 ± 2.8 mm in the x-axis, y-axis, and z-axis directions, respectively. The means \pm SD of maximum 3D excursions at the GTV, DU, and ST were 9.6 ± 3.3 , 9.8 ± 4.6 , and 11.4 ± 3.8 mm, respectively. The respiratory movements between contouring targets are shown in Table 2.

Synchronization of respiration-induced motions between the GTV and other contouring targets

The results for synchronization of respiratory motions are shown in Figure 2. At 0% and 90% phases (inhale phases), means \pm SD of distance changes in the positional relationship with the GTV were 0.3 ± 1.9 and 0.7 ± 2.0 mm, respectively, for the DU and -2.5 ± 1.7 and -2.4 ± 2.0 mm, respectively, for the ST. At 20% and 70% phases, those with the GTV were 0.5 ± 0.7 and 0.2 ± 1.3 mm, respectively, for the DU and -0.9 ± 0.8 and -0.3 ± 1.4 mm, respectively for the ST. There was no

Table 1 Patient characteristics

Patient	Age	Sex	Tumor location	GTV volume (mL)	PTV volume (mL)	Treatment technique
1	58	Male	Uncus	20.1	176.8	3DCRT
2	59	Female	Head	28.77	289.7	3DCRT
3	70	Male	Uncus	16.33	181.4	3DCRT
4	56	Male	Uncus	29.86	222.7	3DCRT
5	65	Female	Body	9.79	88.9	3DCRT
6	64	Male	Body	35.79	188.9	3DCRT
7	64	Female	Head	24.93	161	3DCRT
8	69	Male	Body	35.16	139.2	SRT
9	59	Male	Head	19.84	62.2	IMRT

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; GTV = gross tumor volume; IMRT = intensity modulated radiation therapy; PTV = planning target volume; SRT = stereotactic radiation therapy.

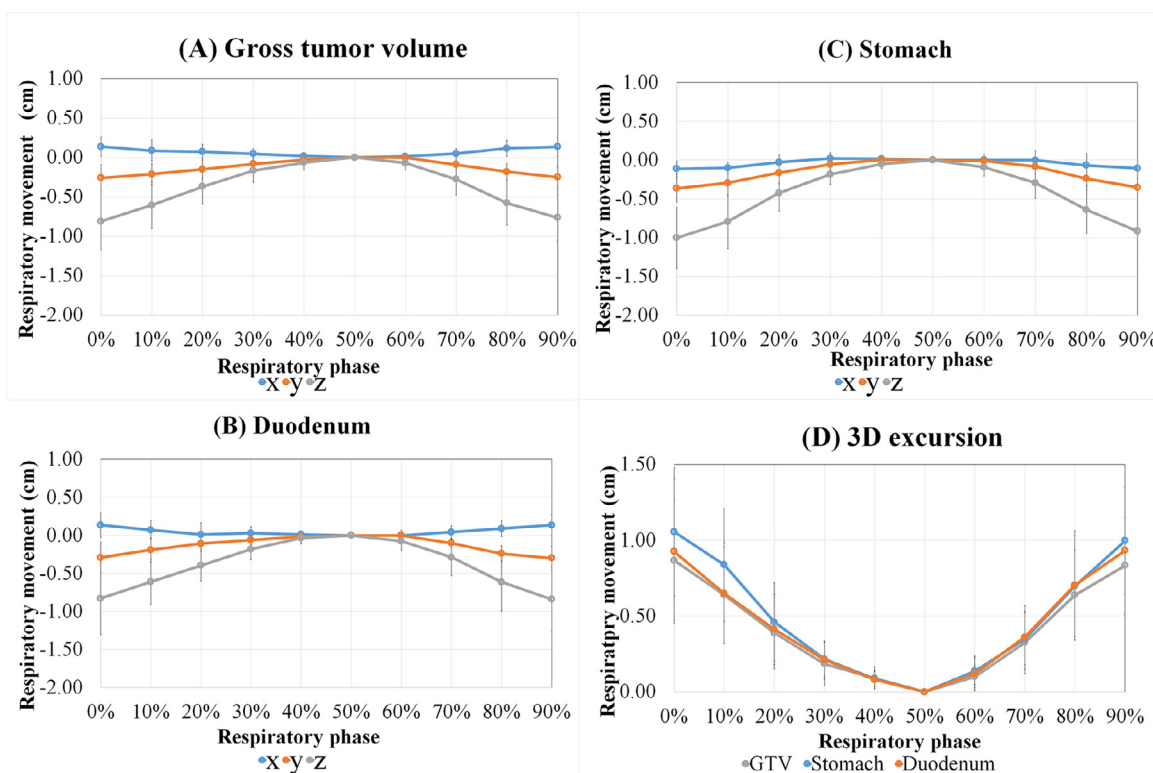


Fig. 1 Results for movement distance at each respiratory phase in each target volume: A, gross tumor volume, B, duodenum, C, stomach, and D, 3-dimensional excursion. *Abbreviations:* 3D = 3-dimensional; GTV = gross tumor volume.

Table 2 Results for maximum respiratory movement in each contouring target

	3D excursion (mm)	X-axis(mm)	Y-axis(mm)	Z-axis(mm)
GTV	9.6 ± 3.3	2.0 ± 0.9	3.2 ± 1.4	9.0 ± 3.0
DU	9.8 ± 4.6	2.5 ± 1.4	3.5 ± 1.6	9.2 ± 4.4
ST	11.4 ± 3.8	2.8 ± 1.3	4.6 ± 1.3	1.07 ± 3.8

Abbreviations: 3D = 3-dimensional; DU = duodenum; GTV = gross tumor volume; ST = stomach.

significant RAC in the DU ($P = .568$) for GTV. The distance between the ST and GTV at the inhale phase was significantly shorter ($P < .001$). An example case is shown in [Figure E1](#). There was a tendency for the results of this synchronization in the pancreas head/uncus (DU: $P = .823$, ST: $P = .002$) but not in the pancreas body/tail (DU: $P = .051$, ST: $P = .078$).

The results for RAC of the volume averaged doses and maximum doses of the ST and DU in each respiratory phase are shown in [Figure 3](#). The cohort mean of the volume averaged doses to the ST and DU at the 50% phase were 12.80 ± 8.30 and 25.57 ± 14.81 Gy, respectively. The cohort mean of maximum doses at the 50% phase in the ST and DU were 47.79 ± 6.90 and 47.68 ± 10.77 Gy, respectively. At 0% and 90% phases, cohort means of percentage changes in the volume averaged dose to the DU were $-12.7 \pm 23.7\%$ and $-11.9 \pm 21.0\%$, respectively, and those to the ST were $38.9 \pm 55.9\%$ and $33.8 \pm 51.7\%$,

respectively. At 20% and 70% phases, cohort means of percentage changes in maximum dose to the DU were -5.3 ± 11.1 and -3.1 ± 9.1 , respectively, and those to the ST were 20.5 ± 28.1 and $13.2 \pm 22.1\%$, respectively. The cohort mean of the volume averaged dose to the ST changed significantly with respiration ($P = .023$), but it did not change significantly for the DU ($P = .933$). The results for the volume averaged doses to the DU and ST at treatment planning with and without gating are shown in [Figure 4](#). The cohort means of DU0%-90%, DU30%-70% and DU50% were 25.6 ± 9.75 Gy, 22.4 ± 9.62 Gy, and 20.1 ± 8.64 Gy, respectively. The cohort means of ST0%-90%, ST30%-70%, and ST50% was 14.3 ± 6.23 Gy, 12.5 ± 5.47 Gy, and 11.0 ± 5.33 Gy, respectively. There were no significant differences in the volume averaged doses to DU and ST between treatment plans with and without gating (DU30%-70%: $P = .402$, DU50%: $P = .354$; ST30%-70%: $P = .508$, ST50%: $P = .310$).

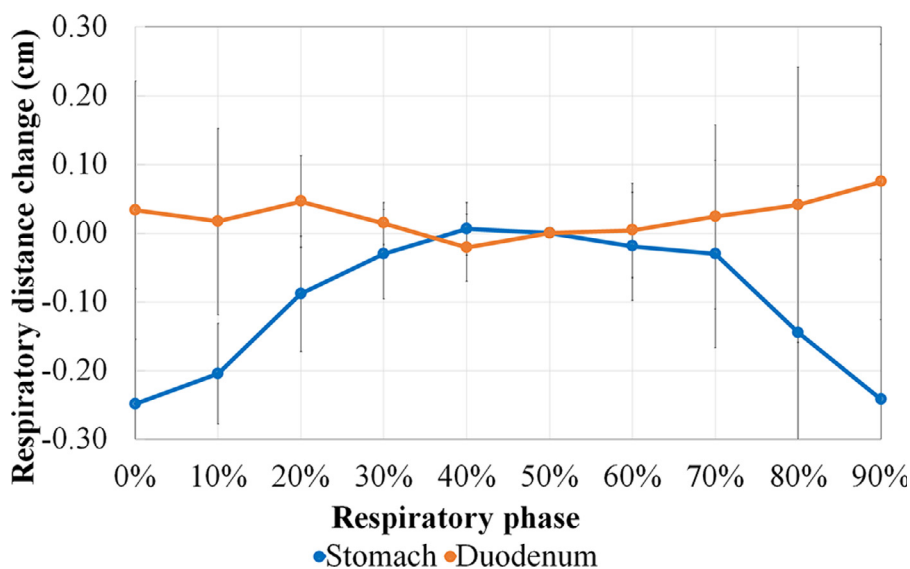


Fig. 2 Results for synchronization by respiration-induced motion with organs at risk for the gross tumor volume.

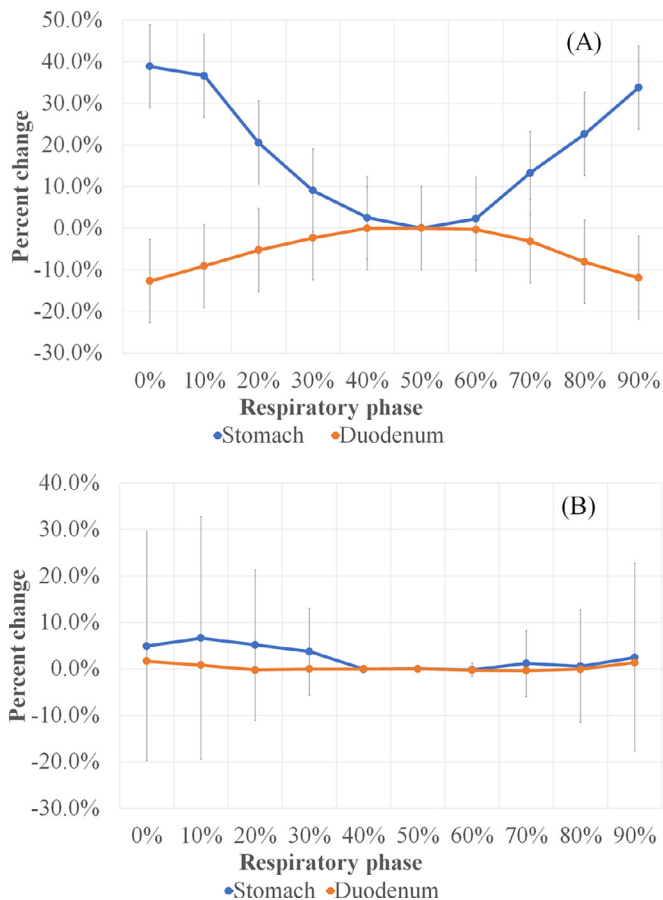


Fig. 3 Results for differences in the A, volume averaged doses and B, maximum doses to the stomach and duodenum in each respiratory phase.

Discussion

IMRT and SRT have been used for pancreatic cancer in clinical practice. SRT has the merit of treatment being

completed in a short period of time. SRT was shown to be superior to conventionally fractioned RT for local control.¹ However, late gastrointestinal toxicity of the stomach and duodenum must be considered. In fact, severe

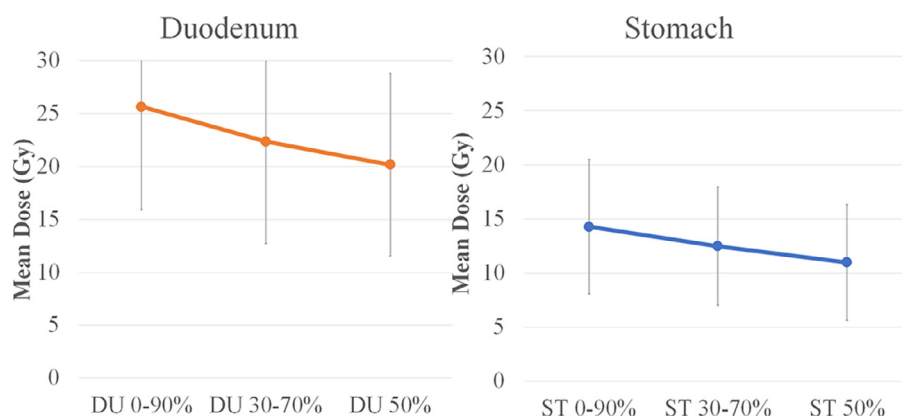


Fig. 4 The volume averaged doses to the stomach (ST0%-90%, ST30%-70%, and ST50%) and duodenum (DU0%-90%, DU30%-70%, and DU50%) at treatment planning without gating (0%-90%) and with gating (30%-70% and 50%).

late toxicities after SRT have been reported.¹³ Therefore, we have reported the relationships between the primary tumor and OARs due to respiratory movement in RT for pancreatic cancer. To the best of our knowledge, this is the first detailed report about the synchronization of respiratory movements. In the present study, we examined the absolute value of respiratory movement in the primary tumor itself, and our results are similar to previously reported results for 4DCT.⁶⁻⁸ In previous studies, the distances of the x-axis, y-axis, and z-axis in respiratory movement were 0.7 to 4.9 mm, 2.0 to 6.5 mm, and 5.2 to 13.4 mm, respectively. Therefore, we think that the results for synchronization of respiratory movement in our study are reliable. We believe that an understanding of this synchronization would make it easier for radiation oncologists to set RT doses and fields in pancreatic cancer.

Although there are a few previous reports on respiratory movements of the stomach and duodenum, our results are similar to the results of those previous studies.¹⁴⁻¹⁷ Watanabe et al reported that intrafractional gastric motions were 11.7 ± 8.3 , 11.0 ± 7.1 , 6.5 ± 6.5 , 3.4 ± 2.3 , 7.1 ± 8.2 , and 6.6 ± 5.8 mm for the superior, inferior, right, left, ventral and dorsal points, respectively.¹⁶ Uchinami et al reported that the average respiratory amplitudes of the stomach were 4.1 ± 1.4 , 2.9 ± 1.3 , and 10.1 ± 4.5 mm in the anterior-posterior, left-right, and superior-inferior directions, respectively.¹⁷ These results suggest that respiratory changes in the stomach and duodenum are as large as those in the primary lesion. The movements of the stomach and duodenum in the craniocaudal direction were conspicuous as expected. Therefore, it seems necessary to consider the synchronization between GTV and the stomach/duodenum.

Regarding the synchronization of respiratory movements, it was found that there was no difference in the positional relationship between the duodenum and the primary tumor in each respiratory phase, but the distance between the stomach and primary tumor at the inspiratory phase was shortened. The mean dose to the ST clearly increased in the expiratory phase. As a result, it was found that the duodenum, but not

the stomach, moved synchronously with the primary tumor and breathing. Taniguchi et al reported how the respiratory phase effects doses to normal organs during SRT for pancreatic cancer,¹⁸ and they demonstrated that the dose to the duodenum was higher in the inspiratory phase than in the expiratory phase and that there was a significant overlap of the PTV with the duodenum. The results for the duodenum were different in their study and our study. Although there were differences in the number of cases, irradiation method, and PTV volume, the reason for the difference in the results is not clear. However, it is thought that the doses to the stomach and duodenum would be likely to change under the condition of free breathing. Changes in doses to the stomach and duodenum due to respiratory changes also occurred in SRT for hepatic cell carcinoma.¹⁹ Therefore, a strict approach for respiratory movement may be required at dose escalation by SRT or IMRT. Irradiation using gating can be considered as one of the measures to reduce respiratory movement. Huguet et al reported that gating around end-exhalation reduced pancreatic tumor motion by 46% to 60%.⁸ Campbell et al also demonstrated that respiratory gating is an effective strategy for reducing motion in pancreatic SRT.²⁰ They reported that average target motions in left-right/anterior-posterior/superior-inferior directions with abdominal compression were 5.2, 5.3, and 8.5 mm, respectively, and that those with respiratory gating were 3.2, 3.9, and 5.5 mm, respectively. They also reported that target coverage was improved by respiratory gating. Although there was no significant difference in the present study, gating led to a reduction in the volume averaged doses to the stomach and duodenum. Application of gating also has the advantage of reducing the PTV volume. Taniguchi et al reported that a large PTV volume produced more overlapping volume of the duodenum and stomach,¹⁸ and the PTV volume was shown to be significantly correlated with the development of acute intestinal toxicity.²¹ Therefore, those methods for respiratory movement would be necessary in the case of large PTV volume.

There were some limitations in the present study. First, the number of cases in this study was small.

Second, the distance between each target was from the center of the target in the present study, and evaluation of the target edge was not performed. However, we consider that this point would be supplemented by the cohort mean of the volume averaged doses to the stomach and duodenum due to respiratory movement. Third, the RAC at maximum exhale or inhale phase in the present study was not always the greatest. Fourth, only 4DCT in RT planning was used in the analysis in our study, and variations of the intrafraction and interfraction during RT were not considered. Akimoto et al showed that there was a change in the position of the pancreatic tumor during interfraction and intrafraction,²² and some studies have shown that 4DCT alone does not adequately reflect respiratory movement of pancreatic cancer during daily treatment.^{23,24} Moreover, large deformation and displacement of the stomach and duodenum on CT images taken on separate days have also been reported.^{25,26} Furthermore, there has been a report showing dose changes in the stomach and duodenum during interfraction.²⁷ Therefore, it seems that not only the technique for considering respiratory movement but also the setting of the planning organ at risk volume (PRV) margins for the duodenum and stomach is important. In fact, PRV has been established to determine dose constraints of the stomach and duodenum in guidelines of SRT for pancreatic cancer.²⁸ In those guidelines, it is stated that minimum PRV expansion should be 3 mm. However, the appropriate PRV margin for the stomach and duodenum remains unclear. Magallon-Baro reported that daily center of mass displacements in the stomach and duodenum were 11 mm and 8 mm.²⁷ Larger PRV margins may need to be considered depending on the case. A more reproducible treatment plan must be made when performing high-dose irradiation for pancreatic cancer.

Conclusions

Our results showed a tendency for respiration-induced motions of the DU and ST for the GTV. The DU may shift synchronously with the GTV due to respiratory movement. The distance change of the ST in its positional relationship with the GTV was reduced in the inhale phase. There is a possibility that OARs are incidentally irradiated more than expected in RT for pancreatic cancer in a free breathing condition.

Acknowledgments

The authors thank all of the patients who participated in the present study and all of the staff of the Department of Radiation Oncology in National Cancer Center Hospital for support of the present study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.adro.2021.100730>.

References

1. Pollom EL, Alagappan M, von Eyben R, et al. Single versus multifraction stereotactic body radiation therapy for pancreatic adenocarcinoma: Outcomes and toxicity. *Int J Radiat Oncol Biol Phys*. 2014;90:918–925.
2. Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. *Int J Radiat Oncol Biol Phys*. 2011;81:615–622.
3. Krishnan S, Chadha AS, Suh Y, et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. *Int J Radiat Oncol Biol Phys*. 2016;94:755–765.
4. Ben-Josef E, Schipper M, Francis JR, et al. A phase I/II trial of intensity modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2012;84:1166–1171.
5. Low DA, Nystrom M, Kalinin E, et al. A method for the reconstruction of four-dimensional synchronized CT scans acquired during free breathing. *Med Phys*. 2003;30:1254–1263.
6. Tai A, Liang Z, Erickson B, et al. Management of respiration-induced motion with 4-dimensional computed tomography (4DCT) for pancreas irradiation. *Int J Radiat Oncol Biol Phys*. 2013;86:908–913.
7. Goldstein SD, Ford EC, Duhon M, et al. Use of respiratory-correlated four-dimensional computed tomography to determine acceptable treatment margins for locally advanced pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2010;76:597–602.
8. Huguet F, Yorke ED, Davidson M, et al. Modeling pancreatic tumor motion using 4-dimensional computed tomography and surrogate markers. *Int J Radiat Oncol Biol Phys*. 2015;91:579–587.
9. Nakamura A, Shibuya K, Matsuo Y, et al. Analysis of dosimetric parameters associated with acute gastrointestinal toxicity and upper gastrointestinal bleeding in locally advanced pancreatic cancer patients treated with gemcitabine-based concurrent chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;84:369–375.
10. Cattaneo GM, Passoni P, Longobardi B, et al. Dosimetric and clinical predictors of toxicity following combined chemotherapy and moderately hypofractionated rotational radiotherapy of locally advanced pancreatic adenocarcinoma. *Radiother Oncol*. 2013;108:66–71.
11. Bae SH, Kim MS, Cho CK, et al. Predictor of severe gastroduodenal toxicity after stereotactic body radiotherapy for abdominopelvic malignancies. *Int J Radiat Oncol Biol Phys*. 2012;84:469–474.
12. Jabbour SK, Hashem SA, Bosch W, et al. Upper abdominal normal organ contouring guidelines and atlas: A Radiation Therapy Oncology Group consensus. *Pract Radiat Oncol*. 2014;4:82–89.
13. Petrelli F, Comito T, Ghidini A, et al. Stereotactic body radiation therapy for locally advanced pancreatic cancer: A systematic review and pooled analysis of 19 trials. *Int J Radiat Oncol Biol Phys*. 2017;97:313–322.
14. Hallman JL, Mori S, Sharp GC, et al. A four-dimensional computed tomography analysis of multiorgan abdominal motion. *Int J Radiat Oncol Biol Phys*. 2012;83:435–441.
15. Heinzerling JH, Bland R, Mansour JC, et al. Dosimetric and motion analysis of margin-intensive therapy by stereotactic ablative radiotherapy for resectable pancreatic cancer. *Radiat Oncol*. 2011;6:146.
16. Watanabe M, Isobe K, Takisima H, et al. Intrafractional gastric motion and interfractional stomach deformity during radiation therapy. *Radiother Oncol*. 2008;87:425–431.

17. Uchinami Y, Suzuki R, Katoh N, et al. Impact of organ motion on volumetric and dosimetric parameters in stomach lymphomas treated with intensity-modulated radiotherapy. *J Appl Clin Med Phys*. 2019;20:78–86.
18. Taniguchi CM, Murphy JD, Eclon N, et al. Dosimetric analysis of organs at risk during expiratory gating in stereotactic body radiation therapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2013;85:1090–1095.
19. Jung SH, Yoon SM, Park SH, et al. Four-dimensional dose evaluation using deformable image registration in radiotherapy for liver cancer. *Med Phys*. 2013;40: 011706.
20. Campbell WG, Jones BL, Scheffer T, et al. An evaluation of motion mitigation techniques for pancreatic SBRT. *Radiother Oncol*. 2017;124:168–173.
21. Ito Y, Okusaka T, Kagami Y, et al. Evaluation of acute intestinal toxicity in relation to the volume of irradiated small bowel in patients treated with concurrent weekly gemcitabine and radiotherapy for locally advanced pancreatic cancer. *Anticancer Res*. 2006; 26:3755–3759.
22. Akimoto M, Nakamura M, Nakamura A, et al. Inter- and intrafractional variation in the 3-dimensional positions of pancreatic tumors due to respiration under real-time monitoring. *Int J Radiat Oncol Biol Phys*. 2017;98:1204–1211.
23. Lens E, van der Horst A, Kroon PS, et al. Differences in respiratory-induced pancreatic tumor motion between 4D treatment planning CT and daily cone beam CT, measured using intratumoral fiducials. *Acta Oncol*. 2014;53:1257–1264.
24. Ge J, Santanam L, Noel C, Parikh PJ. Planning 4-dimensional computed tomography (4DCT) cannot adequately represent daily intrafractional motion of abdominal tumors. *Int J Radiat Oncol Biol Phys*. 2013;85:999–1005.
25. Nakamura A, Shibuya K, Nakamura M, et al. Interfractional dose variations in the stomach and the bowels during breathhold intensity-modulated radiotherapy for pancreatic cancer: Implications for a dose-escalation strategy. *Med Phys*. 2013;40: 021701.
26. Liu F, Erickson B, Peng C, et al. Characterization and management of interfractional anatomic changes for pancreatic cancer radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;83:423–429.
27. Magallon-Baro A, Loi M, Milder MTW, et al. Modeling daily changes in organ-at-risk anatomy in a cohort of pancreatic cancer patients. *Radiother Oncol*. 2019;134:127–134.
28. Oar A, Lee M, Le H, et al. Australasian Gastrointestinal Trials Group (AGITG) and Trans-Tasman Radiation Oncology Group (TROG) guidelines for pancreatic stereotactic body radiation therapy (SBRT). *Pract Radiat Oncol*. 2020;10:136–146.