Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Respiratory motion of lymph node stations in pancreatic cancer: Analyses using contrast-enhanced four-dimensional computed tomography

Shigeo Takahashi *, Masahide Anada, Toshifumi Kinoshita, Toru Shibata

Department of Radiation Oncology, Kagawa University Hospital, Japan

A R T I C L E I N F O

Article history:
Received 22 November 2017
Received in revised form 3 May 2018
Accepted 6 May 2018
Available online xxxx

Keywords:
Respiratory motion
Lymph node
Pancreatic cancer
Four-dimensional computed tomography

A B S T R A C T

Background and purpose: Data regarding respiratory motion of lymph node (LN) stations in pancreatic cancer is limited. Therefore, we assessed their respiratory motion using contrast-enhanced four-dimensional-computed tomography (CE-4DCT).

Material and methods: We evaluated respiratory motion in 18 pancreatic cancer patients. We selected LN stations around major arteries which were visible on CE-4DCT images. This included the common hepatic, celiac, splenic, and superior mesenteric stations. Two radiation oncologists individually delineated the gross tumor volume (GTV) and the LN stations as observers 1 and 2.

Results: The respiratory motion of the celiac (median, 3.9 mm each for both observers) and superior mesenteric (median, 4.5 and 5.0 mm for observers 1 and 2, respectively) stations in the craniocaudal (CC) directions was significantly smaller than that of the GTV (median, 8.9 and 7.8 mm for observers 1 and 2, respectively). The respiratory motion of the common hepatic station (median, 3.8 and 3.6 mm for observers 1 and 2, respectively) in the anterior–posterior (AP) direction was significantly larger than that of the GTV (median, 2.8 and 2.2 mm for observers 1 and 2, respectively).

Conclusions: We observed significant differences in respiratory motion between the GTV and the LN stations in pancreatic cancer.

Radiation therapy (RT) is performed in patients with pancreatic cancer as part of neoadjuvant, definitive, adjuvant, or palliative therapy [1]. Respiratory motion of the pancreas and other abdominal organs can be an obstacle to delivering a sufficient radiation dose to the planning target volume and sparing organs at risk. Four-dimensional computed tomography (4DCT) is usually used in radiation treatment planning to measure respiratory motion. The respiratory motion of the gross tumor volume (GTV) in pancreatic cancer has been evaluated in a number of previous studies [2–8]. However, data on respiratory motion for lymph node (LN) stations in pancreatic cancer are lacking, despite the fact that some groups have aimed to treat not only the GTV but also its LN stations [9]. In neoadjuvant setting, local recurrence was reported in 13% [10] and 25% [11] of patients irradiated with or without elective LN stations, respectively. On the other hand, in definitive setting, local recurrence was reported in 36% [12] and 26% [13] of patients irradiated with or without elective LN stations, respectively. These studies often reported local recurrence and distant metastasis as treatment failures, and the data of the exact number of LN recurrence is limited: Murphy et al. [13] reported that four patients (5%) had peripancreatic LN failures including three within and one straddling the 80% isodose line and no patient had a regional LN failure outside the 80% isodose line in definitive setting without irradiating elective LN stations. Therefore, a conclusion has not been reached concerning whether irradiating elective LN stations. On the other hand, commonly involved regional LN stations except for around the pancreas were the common hepatic (10–15%), celiac (10%), splenic (36%), and superior mesenteric (10–16%) stations [14], and the delineation of elective LN stations was investigated based on the data [15]. In our institution, we irradiate elective LN stations depending on the case that patients have multiple LN metastases and marked extrapancreatic nerve plexus invasion based on diagnostic CT [16] in definitive setting, although we perform neoadjuvant RT without elective LN stations because it is decided by the protocol of a prospective study.

Therefore, we conducted the present study to assess the respiratory motion of not only the GTV but also the regional LN stations in pancreatic cancer using contrast-enhanced 4DCT (CE-4DCT), and evaluated the relationships between respiratory motion and clinical factors.

* Corresponding author at: Department of Radiation Oncology, Kagawa University Hospital, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan.
E-mail address: shigeot@med.kagawa-u.ac.jp (S. Takahashi).

https://doi.org/10.1016/j.radonc.2018.05.007
0167-8140/

Materials and methods

Patients

We evaluated respiratory motion in 18 adenocarcinoma patients who underwent radiation treatment planning for pancreatic cancer using CE-4DCT between September 2014 and December 2015. Patient and tumor characteristics are listed in Table 1. The tumors were located at the pancreatic head in 17 patients and at the pancreatic body in the remaining patient. Three patients had clinically positive LNs. Sixteen patients and two patients underwent radiation treatment planning in neoadjuvant and definitive settings, respectively. The institutional review board approved this retrospective study: the approved number was H28-066.

Data acquisition

Patients were positioned in the supine position with arms positioned above the head. CE-4DCT images were acquired under free breathing without breath coaching. The respiratory motion was monitored using a Real-time Position Management™ system (Varian Medical Systems, Palo Alto, CA, USA). The intravenous contrast medium was infused at an injection rate of 2 mL/s to scan arterial phase for the planning CT and venous phase for the CE-4DCT. The slice thickness of the CE-4DCT scan was 2 mm. The CE-4DCT images were binned into 10 respiratory phases, and all respiratory phases were imported to a radiation treatment planning system (Eclipse™ v11.0; Varian Medical Systems). Fiducial markers were not used.

Delineation of the tumor and lymph node stations

According to the Classification of Pancreatic Carcinoma by the Japan Pancreas Society [17], we selected the regional LN stations around major arteries which were visible on the CE-4DCT images: (1) common hepatic, (2) celiac, (3) splenic, and (4) superior mesenteric stations. Concerning about inter-observer variations, two radiation oncologists individually delineated the GTV and the LN stations as observers 1 (S.T.) and 2 (M.A.). The two observers delineated the arteries and the GTV including only the primary tumor on the CE-4DCT images at all respiratory phases without any propagated contours from different phases referring to diagnostic images of magnetic resonance imaging or positron emission tomography. Diagnostic images were not matched with the CE-4DCT. As for the three patients with positive LNs, the primary tumor was only used as the GTV for this study. Margins from the arteries to the LN stations were decided with reference to the Pancreas Atlas of the Radiation Therapy Oncology Group [18]. The contouring images of the respiratory motion of the GTV and the LN stations are shown in Fig. 1a–e. The common hepatic, celiac, and splenic arteries were delineated to the first branch and were expanded by 1 cm in all directions to define each of their LN stations. The superior mesenteric artery was delineated to 2.5 cm proximally and was expanded by 1 cm in all directions to obtain the LN station. In this study, additional margins for clinical target volumes were not used for the GTV and the LN stations because the aim of this study to assess the respiratory motion of the GTV and the regional LN stations. Abdominal aortic station was excluded because it was classified as distant metastasis and its respiratory motion was influenced by the celiac artery: the top of the abdominal aortic station was defined as the most cephalad contour of the celiac artery [18].

Table 1
Patient and tumor characteristics.

Characteristics			%
Sex	Male	7	39
	Female	11	61
Age (years)	Median	71	
	Range	41–81	
ECOG-PS	0	10	56
	1	8	44
Height (m)	Median	1.56	
	Range	1.37–1.74	
Body weight (kg)	Median	56	
	Range	38–68	
BMI	Median	21	
	Range	18–28	
Histology	Adenocarcinoma	18	100
Tumor location	Pancreatic head	17	94
	Pancreatic body	1	6
TNM Classification[a]	cT1N0M0	1	6
	cT2N0M0	1	6
	cT3N0M0	12	65
	cT3N1M0	2	11
	cT3N1M1LYM[b]	1	6
	cT4N0M0	1	6

Abbreviation: ECOG-PS; Eastern Cooperative Oncology Group Performance Status; BMI: body mass index.
[a] Seventh edition of the Union for International Cancer Control.
[b] The patient had an abdominal aortic lymph node metastasis classified as a distant metastasis.

Statistics

The respiratory motion was calculated from the movement of the center of the GTV and the LN stations in the left–right (LR), anterior–posterior (AP), and craniocaudal (CC) directions. The Wilcoxon signed-rank test was used to analyze differences in the respiratory motion between the GTV and the LN stations. The Wilcoxon rank-sum test was used to analyze the relationships between respiratory motion and clinical factors for sex, age, Eastern Cooperative Oncology Group Performance Status, height, body weight and body mass index. Medians were used as the cut-off values for continuous variables. Statistical significance was defined as $p < 0.05$. The software program JMP 11 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Differences in respiratory motion between gross tumor volume and lymph node stations

The respiratory motion values of the GTV and the LN stations are listed in Fig. 2 and Supplementary Table 1. The respiratory motion of the common hepatic station (median, 3.8 and 3.6 mm for observers 1 and 2, respectively) in the AP direction was significantly larger than that of the GTV (median, 2.8 and 2.2 mm for observers 1 and 2, respectively) for both observers: $p = 0.031$ and 0.001 for observers 1 and 2, respectively. The respiratory motion of the celiac (median, 3.9 mm each for both observers) and superior mesenteric (median, 4.5 and 5.0 mm for observers 1 and 2, respectively) stations in the CC directions was significantly smaller than that of the GTV (median, 8.9 and 7.8 mm for observers 1 and 2, respectively) for both observers: $p < 0.001$ each for both observers as for the celiac and superior mesenteric stations. No significant differences were observed in the LR direction for both observers.

Relationships between the respiratory motion and clinical factors

The significant relationships between respiratory motion and clinical factors for both observers are listed in Table 2. Patients aged ≤70 years had significantly larger respiratory motion of the common hepatic station (median, 4.7 and 4.2 mm for observers 1

Please cite this article in press as: Takahashi S et al. Respiratory motion of lymph node stations in pancreatic cancer: Analyses using contrast-enhanced four-dimensional computed tomography. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.05.007