Dummy Run for a Phase II Multi-institute Trial of Chemoradiotherapy for Unresectable Pancreatic Cancer: Inter-observer Variance in Contour Delineation

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Abstract. *The aim of this study was to examine the inter-observer variance in delineating the contour of unresectable pancreatic cancer for chemoradiotherapy. Patients and Methods: CT images of two cases of unresectable pancreatic tumors (head and body cancer) were sent to eight radiation therapy facilities in a CD-ROM. Gross tumor volume (GTV) and planning target volume (PTV) were delineated using the radiotherapy treatment planning system (RTP) of the respective facilities. The mean and variance of the GTV and PTV of 11 plans by the eight facilities were analyzed. Results: The respective mean volumes of the GTV of pancreatic head and body cancer cases were 34.8 cm^3 (SD, 30.4; median, 31.8; range, 13.5-122 cm^3) and 73.4 cm^3 (SD, 28.1; median, 67.9; range, 46.3-152 cm^3). The ratios of the largest to the smallest contoured GTV were 9 and 3, respectively. The corresponding average volumes of PTV were 148 cm^3 (SD, 84.3; median, 129; range, 69.6-363 cm^3) and 240 cm^3 (SD, 79.8; median, 227; range, 148-420 cm^3). The ratios of the largest to the smallest contoured volume were 5 and 2.8 for PTV delineation, respectively. Conclusion: Dummy run using CD-ROM is possible on a multi-institute scale but also disclosed inter-observer variance. Unified protocol interpretation to reduce inter-observer variance is therefore essential for successful multi-institute clinical trials.*

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Pancreatic cancer is an ominous disease with a high fatality rate and with similar rates of prevalence and morbidity. While operation is the only curative treatment, the number of operable cases is no more than 30%. Radiotherapy combined with fluorouracil (5-FU) is regarded in Western countries as the standard treatment for inoperable pancreatic cancer based on the findings of several trials (GITSG) (1). In Japan, however, institutions use their own therapeutic approach without consensus regarding treatment and with rather few institutes using radiotherapy for unresectable pancreatic cancer. Recently, gemcitabine (GEM) replaced 5-FU as the first-line single chemotherapeutic agent. Since it has a strong radiosensitizing effect, various clinical trials of GEM have combined it with radiation therapy (2). As GEM simulates radiosensitivity not only for tumor cells but also for normal tissue, the dosage of GEM or intensity of radiotherapy is usually reduced to minimize toxicity. Many institutes have tried chemoradiotherapy concurrently with reduced dosage of GEM (3), but our trial at the Osaka Medical Center for Cancer and Cardiovascular Diseases used the standard dose

of GEM with limited radiation fields (4). Since the phase I trial was completed safely, we were able to raise the radiation dose from 30 Gy in 15 fractions to 50 Gy in 25 fractions without any severe adverse reaction even though used concurrently with full-dose GEM (three administrations of 1 g/m^2 GEM once a week followed by one week rest for a cycle of four weeks) (4). We then ran this protocol (50 Gy/25 fraction RT + 1 g/m^2 GEM) without any severe toxicity (5) and had the opportunity to perform this protocol as a multi-institution collaborative effort. In view of the ominous character of pancreatic cancer and the potential risk of lethal adverse reactions associated with this protocol, a dummy run was performed to analyze inter-observer variance in delineating gross tumor volume (GTV) and planning target volume (PTV). We also examined the feasibility of radiation RTP acquiring the data from CD-ROM and making a treatment plan according to a given protocol.

Patients and Methods

A CD-ROM containing the CT images of two cases of unresectable pancreatic cancer formatted with the digital imaging and communications in medicine (DICOM; Rosslyn, VA, USA) software was dispatched to eight institutes (Case 1: pancreatic head cancer, cT4N0M0; Case 2: pancreatic body cancer, cT4N1M0) (UICC 2002 version). CT images were acquired with an Aquilion 16 (Toshiba Medical Systems, Tokyo, Japan) with CT slice thickness of 5 mm (initial level and window of images were 60 HU and 300 HU, respectively). To use these images outside the hospital, we obtained additional written informed consent from the two patients and approval from the Ethical Review Board chairperson. The protocol to be used involves concurrent external radiotherapy (50 Gy / 25 fractions - 50.4 Gy / 28 fractions) and administration of GEM 1 g/m^2 (once a week for three weeks followed by one week rest: 3 times in 4 weeks) for unresectable pancreatic tumor (cT3-4, N0-1M0, PS =0-1). GEM administration was planned as a 30-minute infusion weekly for 3 consecutive weeks every 4 weeks. When compliance allowed, GEM alone would be continued thereafter depending on the response and toxicity.

Radiation fields were determined with following procedure. The primary tumor was defined as a low density area detected by contrast enhanced CT before treatment since a tumor shadow shows a different pattern of enhancement than the circumference of normal tissue. Whenever possible, images of ultrasonography and/or MRI were recommended for reference. A minor axis >1 cm on CT images was defined as a metastasis lymph node. For concomitant use with 1 g/m^2 of GEM, the radiation field was confined to GTV (clinical target volume: CTV = GTV) not including the prophylactic lymph node area. PTV was determined by adding a margin of 1-1.5 cm to GTV because of the set-up margin and internal margin. The radiation treatment field was determined by the addition of a leaf margin of 0.5-1.0 cm to the PTV. Radiation therapy was to be delivered through four portals (anterior, posterior, right and left) to five (210, 300, 0, 60 and 120 degree portals) fields for a single course of 50 Gy in 25 fractions, or 50.4 Gy in 28 fractions, and using 6 or more megavoltage photons. At each institute, images on the CD-ROM were transferred to RTP to create an RTP for four or five portals. The prescribed dose was determined at the intersection of each four or five beams with equally loaded portals. Uniformity of dose distribution was assessed in terms of the minimum and maximum prescribed dose for PTV. Organs at risk were identified as the liver, kidneys and spinal cord, and it was decided that 75% of the whole kidney should be irradiated with less than 18 Gy, 50% of the liver with less than 30 Gy, and the spinal cord with less than 40 Gy. Since dose calculation was done without correction for electronic density in the various RTP, the result was considered to be a reference dose. All physicians taking part in this study were required to submit data for GTV, PTV and a dose volume histogram (DVH) (prescribed dose of organ at risk, maximum and minimum dose for PTV).

Table I. *Variation of volume of GTV, PTV and prescribed dose in PTV.*

	GTV (cm^3) (n=11)	PTV (cm^3) (n=11)	PTVmin 4-portal (n=9)	PTVmin 5-portal (n=5)	PTVmax 4-portal (n=9)	PTVmax 5-portal (n=5)
Case 1: Pancreatic head tumor						
Average	34.8	148	0.77	0.86	1.02	1.02
Median	31.8	129	0.83	0.86	1.02	1.01
Max	122	362	0.94	0.89	1.05	1.03
Minimum	13.5	69.6	0.19	0.81	1.01	1.01
SD	30.4	84.3	0.21	0.03	0.01	0.01
Case 2: Pancreatic body tumor						
Average	73.4	240	0.83	0.87	1.02	1.03
Median	67.9	227	0.82	0.88	1.01	1.03
Max	152	419	0.94	0.91	1.07	1.04
Minimum	46.3	148	0.71	0.80	1.02	1.02
SD	28.1	79.8	0.08	0.04	0.02	0.01

PTVmin, minimal dose in PTV divided by prescribed dose; PTVmax, maximal dose in PTV divided by prescribed dose; SD, standard deviation.

Results

The GTVs and PTVs were submitted by 11 radiation oncologists from eight institutions. Although capturing images from the CD-ROM and incorporating them into RTP was possible, several institutions reported difficulties with the reverse rotation phenomenon, where images were upside down and left and right are reversed. These problems need to be fixed by changing several default

Table II. *Variation of field size.*

	4-portal (n=8)				5-portal (n=4)				
(cm)	1 Anterior	2 Posterior	3 Left	4 Right	1 210 degree	2 300 degree	3 0 degree	4 60 degree	5 120 degree
Case 1: Pancreatic head tumor									
Average	7.6x7.5	7.6x7.5	7.0x7.5	7.2x7.5	7.8x9.2	7.4x9.2	8.2x9.2	7.3x9.2	8.3x9.2
Median	7.5x7.4	7.5x7.3	7.0x7.4	7.2x7.3	7.4x9.4	7.3x9.4	7.8x9.4	7.2x9.5	7.7x9.4
Max	8.9x9.6	8.9x9.6	8.1x9.7	8.2x9.7	9.8x11.0	8.6x11.2	10.5x11.0	8.4x10.9	10.8x11.1
Minimum	6.6x5.9	6.6x5.9	6x5.9	6.2x5.9	7.5x9.3	7.3x9.3	7.7x9.3	7.1x9.4	7.7x9.4
SD	0.7x1.1	0.8x1.1	0.8x1.1	0.7x1.1	1.4x1.5	0.8x1.5	1.6x1.6	0.9x1.5	1.8x1.5
Case 2: Pancreatic body tumor									
Average	9.5x8.6	9.5x8.6	8.7x8.6	8.7x8.5	9.7x9.2	9.9x8.8	9.5x9.5	9.4x9.4	9.4x9.4
Median	9.6x8.7	9.6x8.5	8.5x8.6	8.6x8.6	9.7x9.0	10.1x8.7	9.6x9.3	9.1x9.0	9.45x9.0
Max	10.7x10.2	10.7x10.2	9.9x10.2	9.9x10.2	10.7x10.2	11.1x9.4	9.8x11	11.1x11.1	10.1x11.2
Minimum	8.3x7.4	8.3x7.4	7.6x7.4	7.6x7.4	8.6x8.6	8.5x8.3	8.8x8.7	8.3x8.6	8.8x8.6
SD	0.7x0.9	0.8x1.0	0.9x0.9	0.8x0.9	0.9x0.7	1.1x0.5	0.4x1.1	1.2x1.1	0.6x1.2

Several plans used diffirent ang;les of portals in 5-portal plan to avoid the spinal cord; SD: Standard deviation.

setting of each RTP. Three of the RTP used Xio (CMS Japan, Tokyo, Japan) and five used Eclipse (Varian ME Medical Systems K.K., Tokyo, Japan). Because three physicians made plans using both four and five portals, altogether 14 treatment plans were submitted. GTV and PTV were analyzed in 11 examples. Maximal and minimal doses for PTV and field size in the 14 plans were analyzed.

Case 1.

Pancreatic head tumor; cT4N0M0 with celiac axis involvement. The mean GTV of the pancreatic head cancer was 34.8 cm^3 (SD, 30.4 cm^3; median, 31.8 cm^3; range, 13.5-122 cm^3) (Table I), and the ratio of the largest to the smallest contoured volume was 9 (Figures 1a and 2). The average PTV was 148 cm^3 (SD, 84.3 cm^3; median, 129 cm^3; range, 69.6-363 cm^3), and the ratio of the largest to the smallest contoured volume was 5.

In four field plans, the ratio of minimum and maximum dose for PTV to the prescribed dose ranged from 0.19 to 0.94 (median, 0.83; mean, 0.77; SD, 0.02) and from 1.01 to 1.03 (median, 1.01; mean, 1.02; SD, 0.01), respectively. In five field plans, the corresponding ratio ranged from 0.81 to 0.89 (median, 0.86; mean, 0.86; SD, 0.03) and from 1.01 to 1.03 (median, 1.01; mean, 1.02; SD, 0.01), respectively. The anterior field size of four-portal plans was 7.6x7.1 cm (range, 6.6x5.9-8.9x9.6 cm) and was 8.2x9.2 cm for five-portal plans (range, 7.7x9.3-10.5x11.0 cm) (Table II).

The dose for organs at risk was examined in 11 cases. The prescribed dose for the spinal cord was 43 Gy in one case which exceeded the determined dose, and below 34 Gy in the other 10 cases. As for the kidneys, 75% of the doses were less than 5 Gy except for one case with 16.5 Gy, and the dose for 50% of the liver was less than 10 Gy in all cases. In other words, none of the plans exceeded the determined dose for the kidney and liver.

Case 2.

Pancreatic body tumor with celiac axis and SMA invasion and lymph node metastasis. The mean volume of GTV was 73.4 cm^3 (SD, 28.1 cm^3; median, 67.9 cm^3; range 46.3-152 cm^3) (Table I), and the ratio of the largest to the smallest contoured volume was 3.3 (Figures 1b and 2).

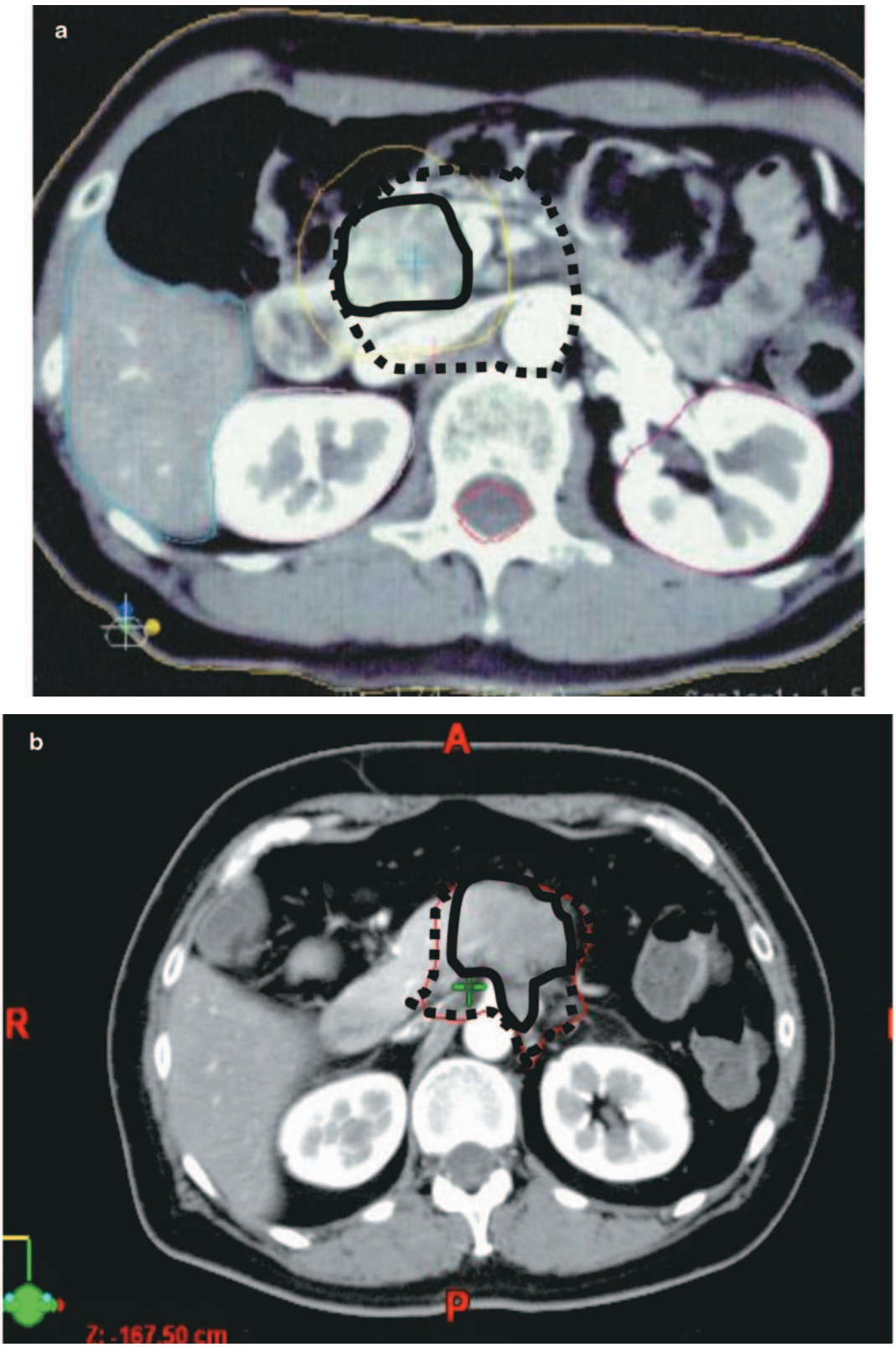

Figure 1. *a) Case 1. A pancreatic head tumor: cT4N0M0, celiac axis involvement. Solid line depicts small GTV (32 cm^3) and dotted line depict large GTV (122 cm^3) delineations. b) Case 2. A pancreatic body tumor: CT4N1M0, celiac axis, SMA invasion and lymph node metastasis (1 cm diameter) located by common hepatic artery adjacent to primary tumor. Solid line depicts small GTV (56 cm^3) and dotted line depicts large GTV (152 cm^3) delineations.*

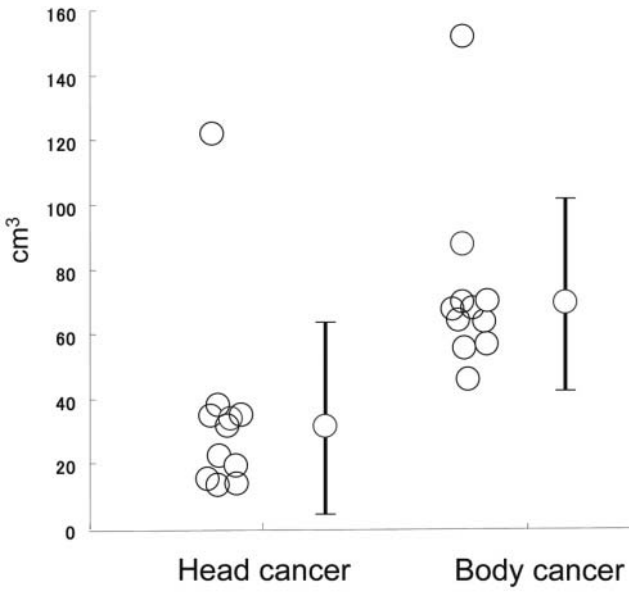

Figure 2. *GTV variation in two cases of unresectable pancreatic cancer.*

The average volume of PTV was 240 cm^3 (SD, 79.8 cm^3; median, 227 cm^3; range, 148-420 cm^3), and the ratio of the largest to the smallest contoured volume was 2.8.

The average of the smallest prescribed dose divided by the prescribed dose in PTV (four-portal plans) was 0.83 (SD, 0.08; median, 0.82; range, 0.71-0.94) and the mean maximum dose was 1.02 (SD, 0.02; median, 1.01; range, 1.01-1.07). The average minimal prescribed dose % in the PTV for five-portal plans was 0.87 (SD, 0.04; median, 0.88; range, 0.80-0.91) and the mean maximum dose was 1.03 (SD, 0.01; median, 1.03; range, 1.02-1.04).

The average anterior portal of four-portal plans was 9.5x8.6 cm (range, 8.3x7.4-10.7x10.2 cm) (Table II) and in five-portal plans the mean anterior portal size was 9.5x9.5 cm (range, 8.8x8.7-9.8x11.0 cm).

The prescribed dose for organs at risk was assessed in 11 cases. For the spinal cord, it was less than 34 Gy in 10 cases and 41.75 G in only one case. For the kidneys, 75% of the doses were less than 5 Gy and 16 Gy in one case, while the dose for 50% dose of the liver was less than 10 Gy in all cases. As in case 1, none of the plans exceeded the determined dose for the kidney and liver.

To compare different RTP, the same physician made an RTP with both Xio and Eclipse for reference. GTV of the head cancer was 19.2 cm^3 for Xio and 19.1 cm^3 for Eclipse, and the PTV was 88 cm^3 and 82.3 cm^3, while the corresponding volumes for the body cancer were 54 cm^3 and 58 cm3, and 175 cm^3 and 172 cm^3.

Discussion

Observer variation is a well-known problem in medical practice. Gandevia and Stradling (6) first reported on this issue in the 1950s, and it became a subject for discussion in the radiotherapeutic community in the 1970's (7). In the 1990's, many articles were published about observer variation for a various types of cancer: prostate cancer (8), a brain tumor (9), breast cancer (10, 11), head and neck cancer (12, 13), and lung cancer (14-16). However, we have been unable to find any paper which examines observer variation in radiotherapy for pancreatic cancer, thus making ours, to the best of our knowledge, the first such report.

As the increasingly permeating nature of pancreatic cancer is generally accompanied by fibrosis, it is difficult to locate the disease on CT images. Enhanced CT examination, low attenuation and delayed enhancement detected on early and late scans may help locate the disease, but indirect CT findings such as pancreatic duct dilatation or disruption may be the only signs of the disease. Tumor progression outside the pancreas is an important factor for GTV delineation, but can sometimes be difficult because the pancreas does not have a thick fibrous capsule, so that tumor extension may result in only slight density elevation in surrounding fat tissue and/or a strand-shaped shadow. Sometimes tumor invasion outside the pancreas must be deduced only from the subtle finding that there is no layer between the tumor and surrounding fat tissue. We have also found it difficult to identify lymph node metastasis without a swelling or to exclude the possibility of inflammatory lymphadenopathy. Although modern imaging techniques, such as MRI, endoscopic ultrasound, and PET could add useful information, not all institutes can utilize these new imaging modalities in routine clinical situations, so that their applicability is still being investigated.

Quantitative comparison of inter-clinician variability in defining target volume has been used for many diseases. In the case of non-small cell lung cancer, for example, Steenbakkers *et al.* (14) reported that the size of GTV ranged from 36 cm^3 to 129 cm^3 (ratio, 3.6; average, 69 cm^3), while van Sornsen de Koste *et al.* (15) found that the average GTV for the main tumor of a cT2N2M0 lung cancer was 13.6 cm^3 (SD, 5.2 cm^3; median, 12.3 cm^3; range, 8.3-26.9 cm^3) as determined by 16 radiation oncologists. The ratio of the largest to the smallest contoured volume was 3.3. The most pronounced difference was observed in right hilar CTV delineation; in fact, deviation by a factor of 23 was found in a case of swollen mediastinal lymph node. The average CTV was 33.7 cm^3 (SD, 1.2 cm^3; median, 1.7 cm^3; range, 4.8-109.9 cm^3). Van Sornsen de Koste *et al.* recommend the use of a delineation protocol (guidelines for Level/Window) and delineation software

(double window with lung and mediastinum Level/Window setting at the same time), with enforced use of coronal and sagittal views and of FDG-PET information (for lymph node delineation and the exclusion of atelectasis). Furthermore, Horan *et al.* recommended participation of a diagnostic radiologist in contouring GTV (17). Although many radiation oncologists in Japan have also received training in diagnostic radiology, it is impossible to go along with the modern imaging procedure throughout whole body. These recommendations may therefore be also applicable even in Japan.

Many reports have cited the importance of the normal anatomical structure surrounding the tumor for delineating tumor contour. Seki *et al.* (16) examined inter-observer variance in delineating T1N0 non-small cell lung cancer in Japan and found that the standard deviation tended to increase if the tumor was located around the bronchus and/or large blood vessel. Their analysis of two cases of cancer showed an average GTV of 7.0 cm^3 (SD, 0.7 cm^3; range, 5.8-7.6 cm^3) and 12.1 cm^3 (SD, 1.7 cm^3; range, 9.5-14.1 cm^3). The ratio of the largest to the smallest contoured volume was 1.5.

3D CRT makes it possible to deliver a higher dose to the target lesion without increasing the risk for the surrounding tissue. However, observer variation in contour delineation has been identified and needs to be solved. We found variations by a factor of more than 9 in GTV delineation, and in one instance the prescribed dose for the spinal cord was exceeded. These results underline the importance of QA assessment especially for a multi-institute study. One institute submitted a relatively large GTV, which included a low density area surrounding the major tumor (122 cm^3 for the head tumor and 152 cm^3 for the body tumor). If this highest value of GTV is excluded, the ratios of the largest to the smallest contoured GTV can be reduced to 2.8 for the head tumor and 1.9 for the body tumor. Although we made it clear that, as mentioned earlier, GTV=CTV in the protocol, delineation of pancreatic cancer is so difficult that it is hard to decide which planning is not appropriate in a routine clinical situation. For a multi-institute trial, however, consensus should be attained by the participants to avoid uncertainty; definitions of major violations should be provided and followed up with training of the participants. Initial individual review at the time of case registration will be fruitful if enough human and financial resources are available for a multi-institute joint protocol.

Conclusion

A dummy run using a CD-ROM is possible on a multi-institute scale but also disclosed inter-observer variance. Unified protocol interpretation to reduce inter-observer variance is therefore essential for successful multi-institute clinical trials.

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