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Application of Real-Time Tumor-Tracking and Gated Radiotherapy System for Unresectable Pancreatic Cancer

Yong Chan Ahn[1], Shinichi Shimizu[2], Hiroki Shirato[3], Takayuki Hashimoto[3], Yasuhiro Osaka[3], Xiao-Qing Zhang[3], Tatsuya Abe[2], Masao Hosokawa[2], and Kazuo Miyasaka[3]

[1]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea;
[2]Department of Surgery, Keiyukai Sapporo Hospital, Sapporo, Japan;
[3]Department of Radiology, Hokkaido University Hospital, Sapporo, Japan.

Herein is reported our experience of radiation therapy using a real-time tumor-tracking and gated radiotherapy (RTRT) system for inoperable pancreatic cancer. Three unresectable pancreatic cancer patients were treated with intraoperative electron beam radiation therapy, at the time of open biopsy, and postoperative external beam radiation therapy using an RTRT system with a 2.0 mm diameter gold ball implanted into the pancreas. The total BED's $_{\alpha/\beta=10}$ was intended to be equivalent to that of delivering 60 Gy by 2.0 Gy/fraction, while the actual dose schedules were individualized. The movement of the pancreas was analyzed based on the 3-dimensional marker positions during the RTRT. The side effects and tumor responses were evaluated. During the RTRT course, the average movement of markers in the x (left to right), y (cranial to caudal) and z (dorsal to ventral) directions were 3.0 mm (1.7 - 5.2 mm), 5.2 mm (3.5 - 6.8 mm) and 3.5 mm (2.7 - 5.1 mm), respectively. During and after the course of postoperative radiation therapy, no acute side effects of RTOG grade II or higher were detected. The objective tumor responses, as evaluated by CT scans 3 months after the treatment, were 2 partial responses and no response in one patient. Using the RTRT technique the margin of treatment planning and the possible errors in target localization were reduced, and the 3-dimensional movement of the internal marker implanted in the pancreas was able to be analyzed.

Key Words: Pancreas cancer, gated radiotherapy, organ movement

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Reprint address: requests to Dr. Yong Chan Ahn, Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong, Kangnam-gu, Seoul 135-710, Korea. Tel: 82-2-3410-2602, Fax: 82-2-3410-2619, E-mail: ycahn@smc.samsung.co.kr

INTRODUCTION

Pancreatic cancer is usually diagnosed at the late advanced stage when radical curative surgery cannot be performed and radiation therapy is usually considered with a mainly palliative intent. For patients with early stage pancreatic cancer who underwent curative surgical resection, postoperative radiation therapy is frequently indicated to reduce the risk of local and regional recurrence. Radiation therapy thus plays an increasingly important role in treating pancreatic cancer both in curative and palliative settings.

Involuntary respiratory movement of the upper abdominal organs inevitably leads to enlargement of the radiation therapy portals.[1-5] Efforts not to miss the target lesions requiring high dose irradiation, however, may cause acute and delayed unwanted reactions in the radiation sensitive normal organs adjacent to the radiation target. Furthermore, the instantaneous changes in the tissue density due to the respiratory movement increases the uncertainty and unpredictability of the radiation dose distribution within and around the radiation target volume.[6]

To overcome the difficulties of high dose radiation, a real-time tumor tracking and gated radiotherapy (RTRT) system was developed[7-10] and applied to the treatment of various types of cancer, such as lung, liver and prostate cancers. The results, such as the movement of these organs in response to RTRT and their clinical significance, are reported.[11-17] Here, the RTRT was applied to three patients with inoperable pancreas cancer,

and the movements of the pancreas during RTRT analyzed by the 3 dimensional coordinates of the metallic marker inserted in or near the pancreas and report our experiences.

MATERIALS AND METHODS

Three patients with inoperable pancreatic cancers were enrolled in this study (Table 1). All three patients were female, and the main tumor was in the head of the pancreas in two patients and in the body of the pancreas in the third. All patients were T4N1, with direct invasion into the surrounding structures of the portal vein, the duodenum and the aorta. As the lesions were inoperable, all patients underwent an open biopsy, gastro-jejunal bypass and received intraoperative radiation therapy (IORT) using 12 MeV electron beams. The IORT doses were 12 Gy in two patients and 15 Gy in the third. As the IORT dose was judged to be insufficient to achieve local control, postoperative external beam radiation therapy was planned to give an additional radiation dose. A 2.0 mm diameter metallic ball, made of gold, was implanted directly to the pancreas during the operation in one patient and through the drainage tube near the tumor in the other two after the operation. A multi-detector computed tomography scan was performed in the exhale position with the breath-hold technique for the treatment planning. After delineating the gross tumor volume, as well as the organs at risk, the 3-dimensional radiation therapy dose plan was made using the Focus® system (Version 3.0, CMS Inc., St. Louis, MO, USA). The margins of the clinical target volume (CTV) from the gross tumor volume (GTV) were either 3 or 5 mm, which were individually determined based on the geometry of each patient. The margin of the planning target volume (PTV) was 5 mm in all patients.

Three goals in the postoperative RT were established. It was intended to first, complete the postoperative RT in 8 fractions within 2 weeks; second, to limit the fractional dose to the duodenum below 2.5 Gy; and third, to apply a total biologically equivalent dose ($BED_{\alpha/\beta=10}$) as high as the total dose in the 2.0 Gy/fraction schedule.

Table 1. The Patient Characteristics

	Case #1	Case #2	Case #3
Age/Sex	60/Female	71/Female	58/Female
Location of tumor	Body	Head	Head
Tumor size	6.0 cm × 4.0 cm	3.2 cm × 2.0 cm	4.0 cm × 3.3 cm
Stage	T4N1	T4N1	T4N1
Organ(s) invaded	Portal vein	Duodenum, portal vein	Duodenum, aorta
Maker implantation	via drainage tube	via drainage tube	at operation
Margin for CTV	5 mm → 3 mm*	3 mm	5 mm
Margin for PTV	5 mm	5 mm	5 mm
Intraoperative RT dose	12 Gy	15 Gy	12 Gy
Postoperative RT dose & schedule	32 Gy 4 Gy × 8 fractions	24 Gy 3 Gy × 8 fractions	40 Gy 2.5 Gy × 16 fractions
Total dose in $BED_{\alpha/\beta=10}$	71.2 Gy	68.7 Gy	76.4 Gy
Total dose in $BED_{\alpha/\beta=3}$	134.67 Gy	138.0 Gy	133.33 Gy

CTV, clinical target volume; PTV, planning target volume.
$BED_{\alpha/\beta=10}$, biologically equivalent dose assuming the α/β is 10 in the tumor.
$BED_{\alpha/\beta=3}$, biologically equivalent dose assuming the α/β is 3 in late responding normal tissues.
*The margin for the CTV was reduced from 5 mm to 3 mm after the initial 3 fractions in patient #1.

These three goals were fulfilled in only one patient (Case #1) who received 8 fractions of 4 Gy/fraction within 2 weeks, with a total $BED_{\alpha/\beta=10}$ of 71.2 Gy. In the other two patients, with tumors invading the duodenum, the schedule was modified. In one patient (Case #2), the maximum fraction dose to the duodenum was 3.0 Gy, while the fractional dose to the most of the duodenum was at or under 2.5 Gy. The treatment was completed within 2 weeks, and the total $BED_{\alpha/\beta=10}$ was 68.7 Gy. In the other patient (Case #3), the treatment was completed in 4 weeks with 16 fractions. The fractional dose and total $BED_{\alpha/\beta=10}$ were 2.5 and 76.4 Gy, respectively. As a total $BED_{\alpha/\beta=10}$ of 60 Gy in 2.0 Gy/fraction is 72.0 Gy, the dose schedules of the three patients were equivalent to the local tumor control probability. After finishing the postoperative RT, all three patients received single agent, Gemcitabin (1000 mg/m^2 IV in 30 minutes) chemotherapy, weekly on an outpatient's basis.

The 3-dimensional coordinates of the marker in relation to the gravity center of the CTV (isocenter) was determined on the 3-D planning system, and the distance between these two points subsequently calculated. The RTRT system was applied only when the marker was within the predetermined permitted range of dislocation (3 mm was applied in this study) from the original position during X-ray fluoroscopy. The 3-dimensional coordinates of the marker during RTRT were calculated 30 times per second and stored into the RTRT system. The movement of the pancreas was measured by analyzing the 3-dimensional marker positions during the RTRT using MatLab® (Version 6.0, The MathWorks, Inc., Natick, MA, USA).

The local tumor response was evaluated by a follow-up CT scan taken in 3 months after surgery. Acute side effects and other events were monitored during and after the treatment course.

RESULTS

The average distances from the isocenter to the marker were 4.07 (-26.7 - 7.8) mm in x direction (left to right), 13.77 (9.6 - 16.3) mm in y direction (cranial to caudal) and 31.27 (18.3 - 57.2) mm in z direction (dorsal to ventral) (Table 2). The average ranges of the marker movement during the entire RTRT were 3.0 (1.7 - 5.2), 5.2 (3.5 - 6.8) and 3.5 (2.7 - 5.1) mm in x, y and z directions, respectively. The average ranges of the marker movement during the beam-on time were 1.9 (1.7 - 2.1), 2.5 (2.3 - 2.9) and 2.3 (2.2 - 2.4) mm in the x, y and z directions, respectively (Table 2). The projections of the 3 dimensional coordinates of the marker during RTRT in three patients are shown in Fig. 1. The marker position during the beam-on condition was restricted to the part of the total range of the marker movement during X-ray fluoroscopy in all three patients. This implies that the maximum movement was reduced in all three patients.

During and after the postoperative RTRT course, no acute side effects of RTOG grade II or higher were detected. The objective responses, as evaluated by CT scans in 3 months after surgery, were 2 partial responses and no response in the other patient. Subsequently, two patients developed carcinomatous peritoneal seeding and metastasis in the liver, and died of disease progression. One patient is still alive, but still with the disease (Table 3).

Table 2. The Position and the Movement Range of the Marker During RTRT

	X (left-right)				Y (cranio-caudal)				Z (dorso-ventral)			
	Case #1	Case #2	Case #3	Mean	Case #1	Case #2	Case #3	Mean	Case #1	Case #2	Case #3	Mean
Marker position from isocenter (mm)	7.8	-26.7	6.7	-4.07	15.4	16.3	9.6	13.77	57.2	18.3	18.3	31.27
Range of marker movement during entire RTRT (mm)	1.7	5.2	2.1	3.0	3.5	6.8	5.2	5.2	2.7	5.1	2.8	3.5
Range of marker movement during beam-on time (mm)	1.7	2.1	1.9	1.9	2.3	2.4	2.9	2.5	2.3	2.4	2.2	2.3

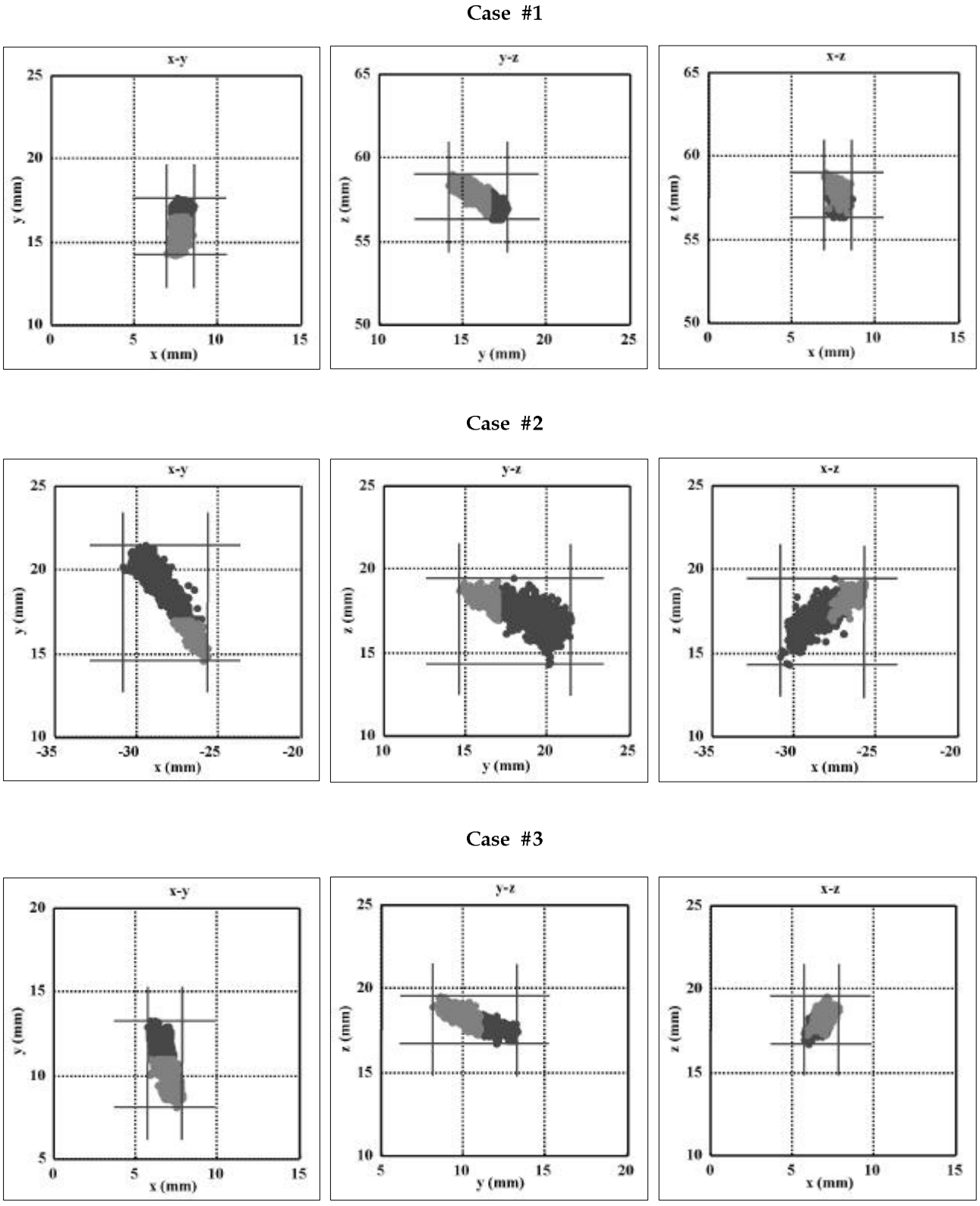

Fig. 1. The projection of the 3-dimensional coordinates of the maker during the real-time tumor-tracking and gated radiotherapy in three patients with unresectable pancreatic cancer. The gray and black dots represent the marker positions under the beam-on and the beam-off conditions, respectively.

Table 3. The Follow-up Status

	Response at 3 months	Progression	Survival status
Case #1	Partial response	Peritoneal seeding (7 months)	Dead (8 months)
Case #2	Partial response	None (5 months)	Alive (5 months)
Case #3	No response	Liver metastases + peritoneal seeding (10 months)	Dead (11 months)

DISCUSSION

Numerous studies have reported the magnitudes of the upper abdominal organ movement during respiration measured by ultrasonography, CT scan or MR imaging.[4,5,18-20] The shift of the organ position prompted by respiration was well known to be greater along the cranio-caudal direction than along the ventro-dorsal or lateral directions. For example, the normal pancreas moves approximately 2.0 cm in the cranio-caudal direction during normal respiration, while it can move more than 4.0 cm during forced respiration. The magnitude of the marker movement in this study, presumed to reflect the movement of the pancreas, was, as expected, greatest in the cranio-caudal direction. This magnitude, however, was much smaller than that previously reported. This difference might be explained by the followings: first, the movement of the malignant pancreas was measured, while others studied the normal pancreas; second, all our patients had inoperable tumors that had already invaded the surrounding normal organs; third, the measurements were started 3 to 4 weeks following the surgical procedure, when local inflammation as well as fibrosis may have already begun.

The position of the inserted gold marker was not at or very close to the center of the CTV. The marker was inserted near the tumor in all three patients. Inserting the marker within the CTV is not practical. Furthermore, such insertion is not advisable because the needle track for the placement of the marker may become the source of cancer spread. By assessing the marker position expressed in the 3-dimensional coordinates from the isocenter, the actual position of the isocenter was determined by re-calculating from the marker coordinates. Gating in our system depended solely on these marker coordinates, as identified by X-ray fluoroscopy. Our practice was to insert three or more markers in the treatment of lung cancer or liver cancer. However, in this study only one marker was able to be inserted due to the technical difficulty and the palliative nature of the current treatment. To put more markers invasively in these patients was considered too aggressive, and could not be ethically justified. Consequently, the possible error in the rotation of the patient set-up, the distortion of the tumor after obtaining the planning CT and the migration of the marker from its original position might not have been properly taken into account.[21] Observing that the range of marker movement in our patients was not big, the current RTRT for these patients was assumed to be technically successful. However, inserting more markers would be highly advisable whenever it is technically feasible.

The total BED's$_{\alpha/\beta=10}$ was applied to the level frequently employed in high dose schedules (total 60.0 Gy, 2.0 Gy/fraction). Objective responses comparable to high dose schedules were able to be achieved. Delivering 60 Gy in 2.0 Gy/fraction, the BED$_{\alpha/\beta=3}$ was 100 Gy. In our study, the total BED's$_{\alpha/\beta=3}$, combining IORT and postoperative RT, were apparently 30% higher than those of conventional dose schedules (Table 2). However, as the normal organs adjacent to tumors were retracted away from the IORT cone, in order to focus a high radiation dose to the grossly visible tumor, it may be more reasonable to ignore the contribution by IORT in the BED$_{\alpha/\beta=3}$ calculation. The fact that there was no incidence of acute or delayed side effects of RTOG grade 2 or higher in this study actually reflected that the BED$_{\alpha/\beta=3}$ by the postoperative RTRT component only was clinically relevant with respect to the development of radiation morbidity. Intestinal radiation damage is very difficult to manage.[22,23] For patients

with fistula or bleeding, total parenteral nutrition and systemic glucocorticoid treatment is required. Surgical intervention is usually reserved for patients with acute perforating peritonitis, occlusion, irreversible chronic obstruction or fistulae. Intestinal resection and anastomosis is the preferred procedure to internal by-pass when it is possible to perform such procedures without extreme risks or unacceptable sequelae. The situation may become much worse if the duodenum, lying in the retroperitoneal space and very close to the pancreas, becomes the victim of high dose radiation. In the management of patients with radiation-induced duodenal ulcer or bleeding, surgery may be needed when refractory to other conservative medical measures. Unlike other intraperitoneal small bowels, however, a very high surgical risk may have to be taken. The best policy is to prevent irreversible complications in advance. Limiting the total dose below the tolerance of the duodenum, however, may be inadequate for local tumor control. The technique of intensity modulated radiation therapy might be effective in deriving the dose plan that could deliver a higher radiation dose to the tumor, while not exceeding the tolerance limit of the duodenum; however, the respiratory movement might lead to increased uncertainty regarding the dose distribution. Gating the respiratory movement during RT is considered highly justifiable in this context. Four-dimensional radiotherapy that is able to detect the temporal changes of the anatomy during respiration as well as peristaltic bowel movement is required to improve the accuracy of radiation therapy.[8] By applying the RTRT technique, the margin of the PTV was able to be diminished. This, in turn, may decrease the risk of radiation-related bowel morbidity, especially if tumors have invaded the neighboring structure of the duodenum.

The uncertainty in the dose distribution in the PTV may stem largely from the uncertainty in the CTV delineation. As the anatomical structure surrounding the pancreas is complex, the CTV delineation becomes difficult if tumors have invaded the adjacent organs. Furthermore, the subclinical extension of the grossly enlarged tumors is often extensive in nature. These uncertainties may negate the expected advantages of RTRT in the reduction of the margin of the PTV. However, to avoid unacceptable complication, safety must be regarded as the most important goal in the control of local tumor radiation therapy for pancreatic cancer, particularly when the main aim is the palliation. The advantage of accurate target localization by RTRT is worthwhile to reduce the intestinal damage risk.

In summary, when applying the RTRT technique, the errors caused by organ movement as well as the margin of PTV were able to be reduced. Our data showed that RTRT is useful in the analysis of the 3-dimensional movement of an internal marker implanted around pancreatic tumors. In addition, our data suggest that the combination therapy of IORT and RTRT may be an alternative to conventional radiotherapy in the treatment of inoperable pancreatic cancer.

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