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PHYSICS CONTRIBUTION

THREE-DIMENSIONAL INTRAFRACTIONAL MOTION OF BREAST DURING TANGENTIAL BREAST IRRADIATION MONITORED WITH HIGH-SAMPLING FREQUENCY USING A REAL-TIME TUMOR-TRACKING RADIOTHERAPY SYSTEM

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Purpose: To evaluate the three-dimensional intrafraction motion of the breast during tangential breast irradiation using a real-time tracking radiotherapy (RT) system with a high-sampling frequency.
Methods and Materials: A total of 17 patients with breast cancer who had received breast conservation RT were included in this study. A 2.0-mm gold marker was placed on the skin near the nipple of the breast for RT. A fluoroscopic real-time tumor-tracking RT system was used to monitor the marker. The range of motion of each patient was calculated in three directions.
Results: The mean ± standard deviation of the range of respiratory motion was 1.0 ± 0.6 mm (median, 0.9; 95% confidence interval [CI] of the marker position, 0.4–2.6), 1.3 ± 0.5 mm (median, 1.1; 95% CI, 0.5–2.5), and 2.6 ± 1.4 (median, 2.3; 95% CI, 1.0–6.9) for the right–left, craniocaudal, and anteroposterior direction, respectively. No correlation was found between the range of motion and the body mass index or respiratory function. The mean ± standard deviation of the absolute value of the baseline shift in the right–left, craniocaudal, and anteroposterior direction was 0.2 ± 0.2 mm (range, 0.0–0.8 mm), 0.3 ± 0.2 mm (range, 0.0–0.7 mm), and 0.8 ± 0.7 mm (range, 0.1–1.8 mm), respectively.
Conclusion: Both the range of motion and the baseline shift were within a few millimeters in each direction. As long as the conventional wedge-pair technique and the proper immobilization are used, the intrafraction three-dimensional change in the breast surface did not much influence the dose distribution. © 2008 Elsevier Inc.

Breast cancer, Organ motion, Real-time tumor-tracking radiotherapy system, Intrafraction error.

INTRODUCTION

Breast conservation therapy, lumpectomy, and whole breast radiotherapy (RT) have been accepted as the standard treatment for early-stage breast carcinoma on the basis of trials comparing breast conservation therapy with mastectomy (1, 2). After breast conservation surgery, the breast is irradiated with lateral and medial tangential fields using the wedge-pair technique. Detailed observations of breast motion have been made during RT using two-dimensional (2D) portal imaging systems (3, 4). The portal image represents the relationship between the breast and radiation field but does not have sufficient information about the three-dimensional (3D) motion of the breast tissue. Recently, complicated treatment methods such as the dynamic wedge method, intensity-modulated RT, and partial breast RT have been introduced for breast RT (5–8). The 3D intrafraction motion of the breast has been given a lot of attention in response to the introduction of these technologies.

The purpose of this study was to evaluate the 3D intrafraction magnitudes of respiratory motion of the breast precisely with a high-sampling frequency. Our hope is that the results of this study will provide the basic data needed to calculate an appropriate internal margin in each direction for precise irradiation using a 3D treatment planning system.

METHODS AND MATERIALS

A total of 17 patients who received breast conservation treatment were included in this study. The median age was 58 years (range, 37–76). In 16 of 17 patients whose weight and height were available, the mean ± standard deviation (SD) of the body mass index [BMI] was 22.0 ± 2.6 kg/m^2. One of the women had malignant lymphoma

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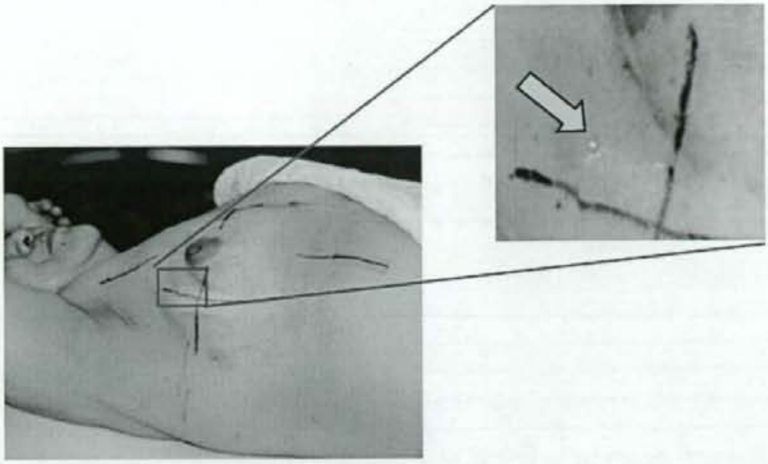

Fig. 1. Gold marker (2 mm) placed on skin near nipple (broad arrow) of right breast. Patient in supine position, with ipsilateral arm abducted and immobilized using Moldcare arm rest (Alcare, Tokyo, Japan). Patients were instructed to maintain light, easy breathing during radiotherapy.

and underwent biopsy only. The remainder underwent breast conservation surgery. Of the 17 patients, 12 had right-sided and 5 left-sided breast cancer. All patients provided written informed consent for the additional study using the real-time tracking radiotherapy system.

Each patient was placed in the supine position with the ipsilateral arm abducted and immobilized using a Moldcare arm rest (Alcare, Tokyo, Japan) (9). The Moldcare is a custom-made arm rest that comfortably immobilizes a patient's arm during RT. A 2.0-mm gold marker was placed near the nipple of the breast to be irradiated (Fig. 1). Treatment planning was performed using computed tomography images under normal breathing with a 3-mm slice thickness for the breast region and 7 mm for the rest of the region.

A fluoroscopic real-time tracking system was used to monitor the position of the gold marker. The details of the tracking system have been previously described (10–12). The system consists of four sets of a diagnostic fluoroscope, an image processor unit, a trigger control unit, and an image display unit, as well as a conventional linear accelerator with multileaf collimators. The system was developed to determine the 3D position of a metallic marker on the human body every 0.03 s using two sets of diagnostic fluoroscopy.

In this study, breast motion was evaluated using tracking data from the real-time tumor-tracking RT system. The software used was the same as that used in previous series for lung tumors and the digestive tract (13, 14). In brief, the marker coordinates were used to measure the range (maximum minus minimum) of the marker position. Fluoroscopic imaging of the breast motion was taken for 1 min. During the fluoroscopic examination, 95% of the marker position was within the border of the original marker position. The Wilcoxon signed rank test was used to compare the range of motion in each direction (right–left [R–L], craniocaudal [CC], and anteroposterior [AP]). A p value <0.05 was considered statistically significant. Regression analysis was performed between the range of motion in the AP direction and BMI (weight in kilograms divided by the height in square meters).

In 10 of 17 patients who underwent examination of respiratory function, regression analysis was performed between the range of motion in the AP and two parameters of respiratory function as follows:

$$\%VC = \text{actual VC}/\text{predicted VC} \times 100$$
$$FEV_1\% = FEV_1/FVC \text{ (forced VC)} \times 100$$

where %VC is the ratio of vital capacity, VC is the vital capacity, $FEV_1\%$ is the ratio of forced expiratory volume in 1 s, and FVC is the forced VC. We also calculated the baseline shift during 1 min using linear regression fitting of the breast motion data.

RESULTS

Respiratory motion range

The mean ± SD of the range of motion of the breast was 1.0 ± 0.6 mm (median, 0.9; 95% confidence interval [CI] of the marker position, 0.4–2.6), 1.3 ± 0.5 mm (median, 1.1; 95% CI, 0.5–2.5), and 2.6 ± 1.4 mm (median, 2.3; 95% CI 1.0–6.9) for the R–L, CC, and AP direction, respectively. The range of motion was the largest in the AP direction in all patients. The range of motion was the smallest in the R–L direction in 15 of 17 patients. Figure 2 shows the range of respiratory motion for each patient in the R–L, CC, and AP directions. The range of motion in the AP direction was statistically greater than that in the other directions (AP vs. R–L, $p = 0.0003$, and AP vs. CC, $p = 0.0003$, Wilcoxon signed rank test; Fig. 3). The mean ± SD of the range of motion of the right breast was 1.2 ± 0.6, 1.5 ± 0.5, and 3.1 ± 1.4 mm for the R–L, CC, and AP direction, respectively. The mean ± SD of the range of motion of the left breast was 0.7 ± 0.6, 0.9 ± 1.0, and 1.4 ± 1.2 mm for the R–L, CC, and AP directions, respectively.

Regression analysis

No correlation was apparent between the range of motion in the AP direction and the BMI. The body weight range was

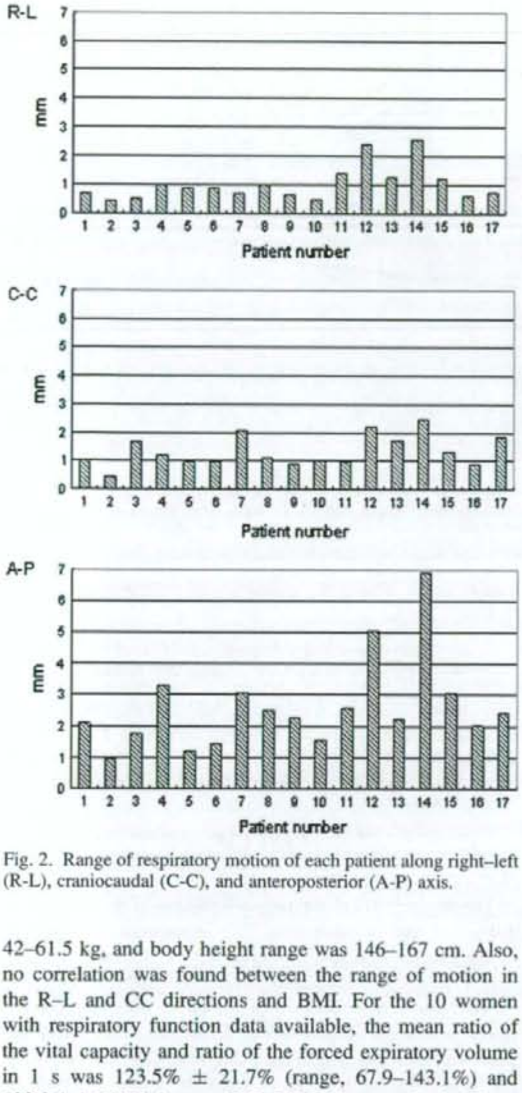

Fig. 2. Range of respiratory motion of each patient along right–left (R-L), craniocaudal (C-C), and anteroposterior (A-P) axis.

42–61.5 kg, and body height range was 146–167 cm. Also, no correlation was found between the range of motion in the R–L and CC directions and BMI. For the 10 women with respiratory function data available, the mean ratio of the vital capacity and ratio of the forced expiratory volume in 1 s was 123.5% ± 21.7% (range, 67.9–143.1%) and 120.3% ± 24.1% (range, 64.5–146.7%), respectively. These parameters did not correlate with the range of respiratory motion in the AP direction.

Baseline shift

No subject had >1 mm baseline shift in the R–L or CC directions; however, 4 patients had a >1 mm baseline shift in the AP direction (Fig. 4). Two patients had no apparent baseline shift in the R–L direction, and two had no apparent baseline shift in the AP direction. The mean ± SD of the absolute value of the baseline shift in the R–L, CC, and AP direction was 0.2 ± 0.2 mm (range, 0.0–0.8 mm), 0.3 ± 0.2 mm (range, 0.0–0.7 mm), and 0.8 ± 0.7 mm (range, 0.1–1.8 mm), respectively.

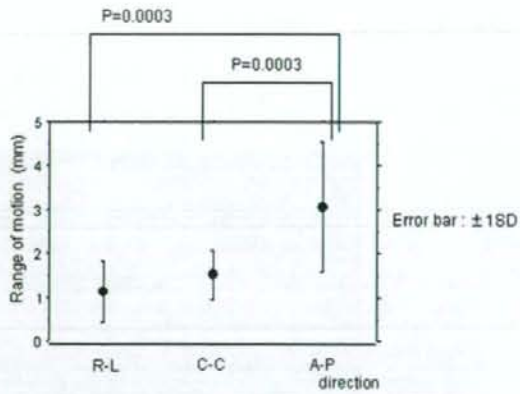

Fig. 3. Mean and standard deviation of range of respiratory motion along right–left (R-L), craniocaudal (C-C), and anteroposterior (A-P) axis.

DISCUSSION

Fein *et al.* (3) and Smith *et al.* (4) used an electronic on-line portal imaging system with a 2D beam's eye view. The beam's eye view represents the relationship between the breast and the radiation field; however, it is not suitable for investigating the 3D motion of the breast tissue. The present on-line portal imaging system can acquire 30–60 images/min. We monitored using a greater sampling frequency, 30 times/s, using a real-time tracking RT system, which potentially has more accuracy in detecting finite motion.

Fein *et al.* (3) have shown that 2D intrafraction movement of the breast resulted in CC motion (described as the interior central margin in their report) of 0.85 mm (range, 0.1–3.2 mm) and motion tangential to the beam axis (the central breast distance in their report) of 2.1 mm (range, 0.4–19 mm). The 2D data of their study were compatible with our 3D findings of a mean ± SD of 1.3 ± 0.5 mm (range, 0.5–2.5 mm), 2.6 ± 1.4 mm (range, 1.0–6.9 mm), and 1.0 ± 0.6 mm (range, 0.4–2.6 mm) in the CC, AP, and R–L direction, respectively. In our study, the motion of the breast in the AP direction was significantly greater than that in the R–L direction. Therefore, our results suggest that the relatively large intrafraction motion tangential to the beam axis in the

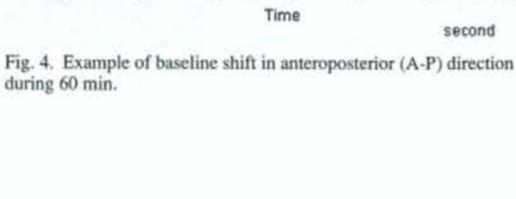

Fig. 4. Example of baseline shift in anteroposterior (A-P) direction during 60 min.

study by Fein *et al.* (3) mainly resulted from the motion of the breast in the AP direction rather than in the R–L direction.

We have speculated that obesity might be related to the amplitude of surface marker movement on the breast and measured the BMI. However, we found no predictive value between the range of motion of the breast and BMI, at least in our data from relatively thin Japanese women. No predictive value was found between the range of motion of surface markers on the breast and the respiratory function tests, ratio of vital capacity and ratio of forced expiratory volume in 1 s. This is consistent with our previous analysis of motion during RT for lung cancer, in which we did not find any significant correlation between respiratory function and the magnitude of marker movement in any direction (15).

We did not examine the interfraction uncertainty of tangential breast RT in this study, because we found that maintaining the gold marker on the chest wall during RT was no better than using a tattoo on the skin surface as a surrogate. Fein *et al.* (3) and Smith *et al.* (4) have shown that intrafractional changes of the irradiated lung area were much smaller than the interfraction changes of the lung area on electronic portal imaging during tangential field breast RT. We agree that the intrafractional changes on the breast surface are usually only a few millimeters and should not influence the dose distribution very much.

Seppenwoolde *et al.* (16) have already shown that a baseline shift often occurs in the position of the internal fiducial marker in lung cancer patients. They demonstrated that the direction of the shift was largest in the AP direction. We also found the baseline shift in the position of the surface marker on the skin to be mainly in the AP direction. The time trends could be attributed to patient relaxation throughout the treatment or to gravity acting on breast tissue shortly after the patient was placed in the supine position with one arm held overhead. When the conventional wedge-pair technique with the Moldcare arm rest was used, the baseline shift was <2 mm, and often <1 mm; therefore, we concluded that we did not need to be concerned about the baseline shift. Even in intensity-modulated RT or focused partial RT for breast cancer, gated RT or close observation during RT might not be beneficial in most patients in terms of the intrafractional movement. However, for intensity-modulated RT, with a longer treatment time, or for poor treatment positioning techniques without proper armrest equipment, the intrafractional movement and baseline shift have the potential to increase the intrafractional dislocation. Gated RT or close observation during RT, not fluoroscopic but optical, might be useful for these situations. Recent sophisticated methods such as 3D relocation of the breast using multiple surface markers and infrared optical beams might be useful for reducing the interfraction setup error (17).

Real-time tumor tracking RT systems inevitably use diagnostic X-rays for the observation during RT. For breast RT, optical observation of the skin surface is more appropriate because it foregoes excessive X-ray exposure. Real-time tracking RT is not used for breast RT in routine practice, but the lessons from this study should be useful for contouring the internal target volume in a hospital setting.

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Organ motion

Real-time tumor-tracking radiotherapy for adrenal tumors

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Abstract

***Purpose*: To investigate the three-dimensional movement of internal fiducial markers near the adrenal tumors using a real-time tumor-tracking radiotherapy (RTRT) system and to examine the feasibility of high-dose hypofractionated radiotherapy for the adrenal tumors.**

***Materials and methods*: The subjects considered in this study were 10 markers of the 9 patients treated with RTRT. A total of 72 days in the prone position and 61 treatment days in the supine position for nine of the 10 markers were analyzed. All but one patient were prescribed 48 Gy in eight fractions at the isocenter.**

***Results*: The average absolute amplitude of the marker movement in the prone position was 6.1 ± 4.4 mm (range 2.3–14.4), 11.1 ± 7.1 mm (3.5–25.2), and 7.0 ± 3.5 mm (3.9–12.5) in the left–right (LR), craniocaudal (CC), and anterior–posterior (AP) directions, respectively. The average absolute amplitude in the supine position was 3.4 ± 2.9 mm (0.6–9.1), 9.9 ± 9.8 mm (1.1–27.1), and 5.4 ± 5.2 mm (1.7–26.6) in the LR, CC, and AP directions, respectively. Of the eight markers, which were examined in both the prone and supine positions, there was no significant difference in the average absolute amplitude between the two positions. No symptomatic adverse effects were observed within the median follow-up period of 16 months (range 5–21 months). The actuarial freedom-from-local-progression rate was 100% at 12 months.**

***Conclusions*: Three-dimensional motion of a fiducial marker near the adrenal tumors was detected. Hypofractionated RTRT for adrenal tumors was feasible for patients with metastatic tumors.**

Keywords: Adrenal gland; Kidney; Organ motion; Radiotherapy

In the management of metastatic adrenal tumors, adrenalectomy is often performed with the intent to improve survival [5,9,11,12,14–17,19], even though its complication rates have been found to be 9–20% [5,9,11,12,14,15,19] and radiotherapy for adrenal metastases is usually chosen as a palliative option. Since the adrenal gland is located near organs such as the stomach, duodenum, kidney, and liver, it has been thought to be difficult to deliver sufficient doses to adrenal tumors. Rigorous accounting of organ motion may be necessary to ensure accurate radiotherapy of the adrenal gland so that an adequate dose for tumor control can be provided. Although several articles have been published regarding the measurement of renal mobility [1,2,4,29], to the best of our knowledge there are no data on organ motion in the adrenal/perirenal region. We have developed a method of inserting a fiducial marker near the adrenal gland and have used a real-time tumor-tracking radiotherapy (RTRT) system to investigate the three-dimensional movement of markers near the adrenal tumors in the supine and prone patient positions. The feasibility of high-dose hypofractionated radiotherapy for adrenal tumors was also clinically investigated.

Materials and methods

The RTRT system has already been described in detail in other literature [21–23]. In brief, the process for synchronizing the tracking of a marker with irradiation was as follows. Before treatment, a 2-mm gold marker was implanted near the tumor by means of image-guided procedures under local anesthesia, principally within 5 cm from the center of the gross tumor volume (GTV). Fig. 1 shows a representative case. After the insertion of the fiducial marker, multidetector-row CT with a slice thickness and an interval of 2 mm was performed in patient positions as the patient held his breath at the end of expiration, the point at which our previous research showed that gating efficiency was highest [20]. The fluoroscopic RTRT system

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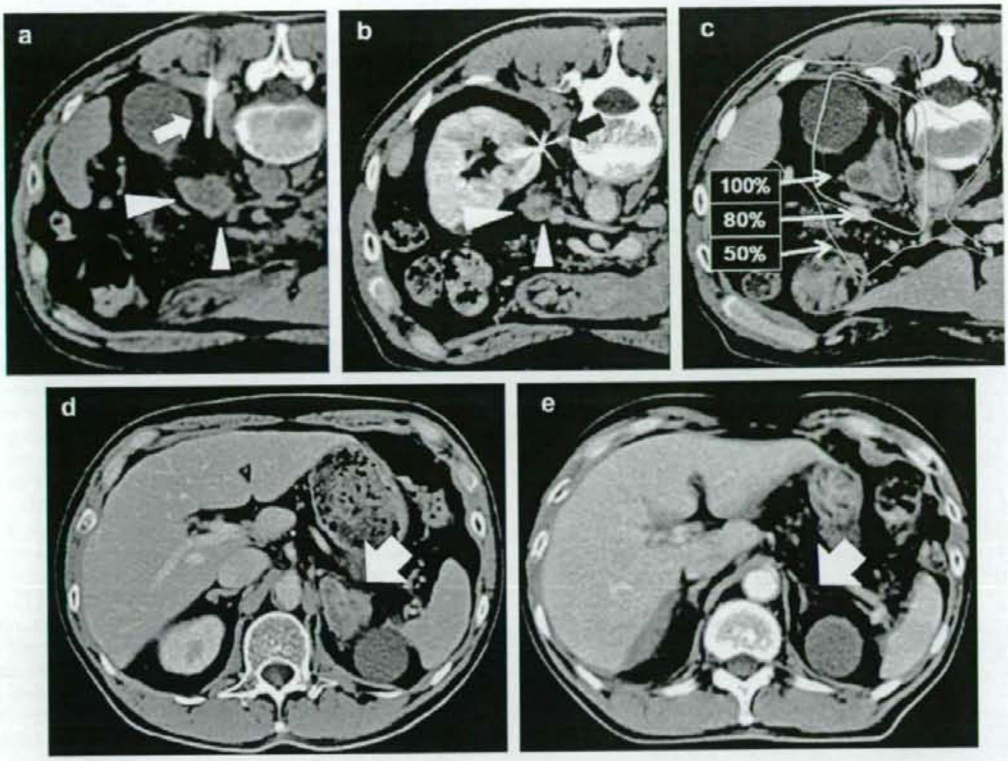

Fig. 1. Patient (No.8) with the left adrenal metastatic tumor treated with RTRT. There was an incidental left renal cyst near the tumor. (a) The fiducial gold marker was implanted near the left adrenal tumor (arrowhead) using a percutaneous approach. The 18-Gauge needle used for gold marker implantation (arrow) is visible in the CT image. (b) Implanted gold marker (arrow) was seen near the left adrenal tumor (arrowhead). (c) Radiation treatment plan. Red line showed 100% isodose line, aqua line 80%, and orange line 50%. (d) Tumor (arrowhead) as seen before RTRT. (e) Tumor had disappeared 12 months after RTRT with dose of 48 Gy in eight fractions.

consists of four sets of diagnostic fluoroscopic, image-processor units, a trigger-control unit, an image-display unit, and a conventional linear accelerator with multileaf collimators. Using two of the four fluoroscopy image-processor units, the system determines the three-dimensional position of the gold marker (2 mm in diameter) 30 times per second by using real-time pattern recognition and calibrated projection geometry. To avoid blocking the fluoroscopic images with the gantry of the linear accelerator, any two of the four X-ray systems can be selected. The linear accelerator is triggered to irradiate the tumor only when the gold marker is located within 2.0 mm of the planned coordinates relative to the isocenter in the lateral, craniocaudal, and anterior–posterior directions. The process of image acquisition and processing causes a small delay of 0.09 s between the marker recognition and the start of irradiation. A correction algorithm predicts the marker position from the speed of the marker movement, compensating for this delay.

Patients with metastatic adrenal tumors were candidates for RTRT if they were refractory to chemotherapy, or not eligible for surgery or chemotherapy. We included patients with perirenal metastatic lymphnodes as well as patients with adrenal tumors in this study. They were required to have a Karnofsky performance status of 70% or more and were excluded if their life expectancies were six months or less. Written informed consent was obtained from all patients before the treatment was initiated.

The subjects considered in this study were 9 male patients from October 2004 to September 2006. The median age was 66 years old (range 55–79 years old). Five of these patients had right-sided adrenal tumors, two had left-sided adrenal tumors, one patient had both-sided tumors, and one patient had a paraaortic node near the left adrenal gland, for a total of 10 tumors (Table 1). Each tumor had one fiducial marker, and so 10 markers in 9 patients were analyzed. All of the tumors were clinically diagnosed as metastatic tumors by computed tomography (CT) and/or positron emission tomography (PET). One patient with a left-sided adrenal tumor simultaneously had a renal tumor at the upper pole of the left kidney that was clinically diagnosed as renal cell carcinoma by CT. This patient was treated with RTRT for both tumors using a single fiducial marker at the perirenal region.

Table 1
Patient characteristics, the marker identifier, and clinical results of high-dose hypofractionated radiotherapy for adrenal tumors

Patient No.	Marker	Age	KPS	Tumor site	Primary cancer	Maximum diameter of GTV (cm)	Dose/fraction	Follow-up time (months)	Local tumor response	Status at the last follow-up
1	a	66	90	Left adrenal gland	Lung small cell carcionma	5.5	48 Gy/8 Fr	16	SD	Dead
2	b	74	80	Right adrenal gland	Lung adenocarcinoma	3.5	48 Gy/8 Fr	21	CR (right)	Dead
2	c	–	–	Left adrenal gland	–	4.0	48 Gy/8 Fr	17	CR (left)	
3	d	55	90	Paraaortic lymphnode near left adrenal gland	HCC	3.0	30 Gy/8 Fr	19	CR	Dead
4	e	64	80	Right adrenal gland	Prostate adenocarcinoma	7.1	48 Gy/8 Fr	18	PR	Dead
5	f	79	90	Left adrenal gland	Lung adenocarcinoma	2.9	48 Gy/8 Fr	12	SD (adrenal)	Alive
5	f	–	–	Upper pole of left kidney	RCC	2.2	48 Gy/8 Fr		PR (renal)	
6	g	72	90	Right adrenal gland	Lung adenocarcinoma	2.0	48 Gy/8 Fr	13	CR	Alive
7	h	55	90	Right adrenal gland	HCC	8.0	48 Gy/8 Fr	5	SD	Dead
8	i	67	90	Left adrenal gland	Lung adenocarcinoma	6.0	48 Gy/8 Fr	18	CR	Dead
9	j	78	70	Left adrenal gland	Lung adenocarcinoma	6.5	48 Gy/8 Fr	3	SD	Dead

Abbreviations: No., number; KPS, Karnofsky performance status; GTV, gross tumor volume; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; CR, complete response; PR, partial response; SD, stable disease; Fr, fraction.

Multidetector-row CT was performed in both the prone and supine patient positions in this study. We have adopted the prone position in our protocol to reduce the dose to the stomach and duodenum. Eight of the 9 patients tolerated the protocol, but 1 patient complained of shortness of breath and was treated in the supine position. Patients were required to refrain from food for 4 h or more before the CT scan and actual treatment to keep the stomach and duodenum in a similar condition. Computed tomography was taken every three treatment days during the 2-week treatment period before the actual irradiation due to the possibility of the migration of the marker.

In this study, we investigated the difference between prone position and supine position in the trajectory of the marker and in the distance from the surface of the tumor to the stomach and duodenum. The coordinates of the gold marker implanted in the perirenal region were tracked continuously and recorded automatically to a hard disc every 0.033 s during RTRT in the prone treatment position for 1–2 min. Subsequently, the patient was moved to the supine position, and the marker was tracked for 1–2 min so that movement data could be acquired while in this position. Patients were not immobilized in either position. Each patient was treated with eight fractions for their tumors. A total of 72 treatment days for nine of the 10 markers in the prone position and 61 treatment days for nine of the 10 markers in the supine position were properly recorded. The absolute amplitudes of marker movement were defined as the distance between the maximum and minimum coordinates along each of the axes (left–right, craniocaudal, and anterior–posterior direction) in each log file [24]. Variations in amplitude among patients and also among treatment days for the same patient were examined. The movements observed in the different positions were compared in eight markers and the amplitudes of these movements were examined in each position. The minimum distance between the surface of the tumor and the stomach and duodenum was measured using the axial images of planning CT scans performed both in the prone and in the supine positions. The difference was evaluated using a paired or an unpaired t test according to the subject. $P < 0.05$ was considered statistically significant.

Clinical target volume (CTV) was defined as the GTV on CT with a 3-mm margin three-dimensionally. Planning target volume (PTV) was defined as CTV plus a 5-mm margin three-dimensionally with optimal reduction near the stomach and duodenum.

In principle, a dose of 48 Gy in eight fractions in 2 weeks was prescribed at the isocenter with the dose in the PTV greater than 80% of the isocenter dose. This dose fractionation schedule had been commonly used in RTRT for liver tumors [27]. One patient (No. 3) was treated with 30 Gy in eight fractions because he had a history of abdominal irradiation with 30 Gy in 10 fractions adjacent to the PTV in the present study. The dose–volume constraint for the stomach and duodenum was that 1 ml or less would receive 35 Gy in eight fractions, which is equivalent to 52 Gy using a daily fraction of 2 Gy (52 Gy/2 Gy) assuming an α/β ratio of 3 for late injury. As long as the contralateral kidney had sufficient enhancement on the CT image with a normal serum creatinine level, half of the ipsilateral renal volume was allowed to be given 20 Gy in eight fractions, which is equivalent to 22 Gy/2 Gy assuming an α/β ratio of 3 for late injury.

The patients were seen and examined by one or two of the investigating physicians every 1–3 months. This evaluation included a physical examination, laboratory evaluation, and CT scan.

Disease progression was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST criteria) [28]. Local failure was defined as progression of the treated tumor. Adverse events were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. In 2 patients, one who had bilateral tumors and another who underwent surgical removal of the opposite adrenal gland aldosteronoma 14 years before RTRT, we examined the adrenal hormonal level at rest before the treatment and every three months. The Kaplan–Meier method was used to calculate the actuarial rates of overall survival (OS) and freedom from local progression (FFLP), from the first day of radiotherapy.

Results

In the procedure of marker insertion, there was no patient who experienced symptomatic complications. Positions of the 10 markers are shown in Figs. 2 and 3. No further adverse effects related to the inserted markers were observed. There was no apparent migration or dislocation of the markers between the planning CT image and the CT images taken during the treatment period.

The average absolute amplitude of the marker movement in the prone position was 6.1 ± 4.4 mm (range 2.3–14.4), 11.1 ± 7.1 mm (range 3.5–25.2), and 7.0 ± 3.5 mm (range 3.9–12.5) in the left–right (LR), craniocaudal (CC), and anterior–posterior (AP) directions, respectively (Table 2). The average absolute amplitude in the supine position was 3.4 ± 2.9 mm (range 0.6–9.1), 9.9 ± 9.8 mm (range 1.1–27.1), and 5.4 ± 5.2 mm (range 1.7–26.6) in the LR, CC, and AP directions, respectively (Table 2). The average absolute amplitude was found to be significantly smaller in the LR direction compared to the CC direction ($p = 0.0364$) and AP direction ($p = 0.0441$) in the supine position.

Relationships between the average absolute amplitude and patient position and marker location are shown in Table 3. There was no statistically significant difference in the average absolute amplitude between the supine and prone positions along the three axes. Irrespective of patient position, no statistically significant difference in the average absolute amplitude was found between the left and right perirenal regions.

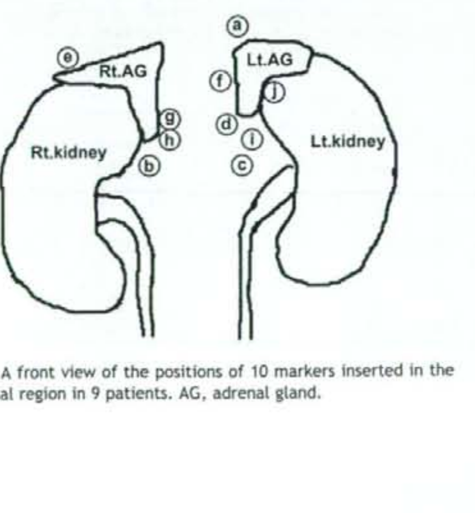

Fig. 2. A front view of the positions of 10 markers inserted in the perirenal region in 9 patients. AG, adrenal gland.

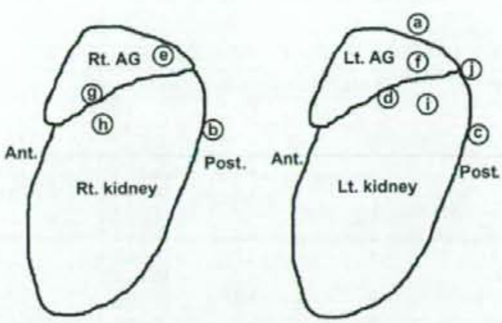

Fig. 3. A lateral view of the positions of 10 markers inserted in the perirenal region in 9 patients. AG, adrenal gland.

The minimum distances between the tumor and the stomach and duodenum are shown in Table 4. The averages of the minimum distances were 16.3 ± 21.5 mm and 17.6 ± 24.8 mm in the prone and supine positions, respectively. There were no significant differences in the mean minimum distances between the supine position and the prone position.

The volume of stomach and duodenum, which received 35 Gy or more, and the maximum dose at the stomach and duodenum are shown in Table 4. All the tumors were treated without violation in the dose constraint in the protocol except in one patient (No. 9) who had a left adrenal tumor attached to the gastric wall. His volume of the stomach and duodenum which received 35 Gy or more was larger than 1 ml. No patient complained of acute gastrointestinal adverse effects. In 2 patients, whose adrenal hormonal levels were examined at rest before the treatment and 7 and 11 months after the treatment, respectively, there was no decline in hormonal level. No other symptomatic adverse effects were observed within the median follow-up period of 16 months (range 5–21 months) in 9 patients. One patient (No. 9) who complained of tumor-related flank pain had experienced improvement of the pain after RTRT. All other patients without any tumor-related symptoms before RTRT showed no tumor-related symptoms after their treatment. By the time of the last follow-up, 7 patients had died. There were five tumors that showed a complete response, two with a partial response, and four with stable disease according to RECIST criteria (Table 1). The actuarial OS and FFLP rates at 12 months were 78% and 100%, respectively.

Discussion

Although there have been several articles regarding renal mobility [1,2,4,7,29] the three-dimensional movement of the adrenal gland or perirenal region has not yet been

Table 2
Average absolute amplitude of the marker for each patient

Marker	Average absolute amplitude ± SD (mm)							
	Prone position				Supine position			
	N[a]	LR	CC	AP	N[a]	LR	CC	AP
a	8	11.3 ± 9.6	25.2 ± 10.5	10.7 ± 13.0	8	9.1 ± 2.6	27.1 ± 12.1	14.2 ± 2.1
b	8	3.5 ± 1.9	4.2 ± 1.0	3.9 ± 1.3	3	1.3 ± 0.2	3.0 ± 0.9	1.8 ± 0.1
c	8	3.3 ± 1.1	13.0 ± 2.8	5.0 ± 1.4	8	3.5 ± 1.6	6.4 ± 3.1	2.2 ± 1.4
d	8	2.5 ± 1.5	3.5 ± 1.1	5.4 ± 2.7	8	0.6 ± 0.1	1.2 ± 0.1	0.7 ± 0.1
e	8	2.6 ± 0.7	17.9 ± 5.4	4.0 ± 0.7	8	3.5 ± 1.7	22.7 ± 4.7	6.6 ± 1.8
f	8	7.4 ± 4.3	10.2 ± 4.5	11.4 ± 8.6	8	6.4 ± 8.3	8.2 ± 4.2	12.5 ± 19.6
g	8	14.4 ± 5.7	10.1 ± 10.2	12.5 ± 8.7	8	4.3 ± 3.9	16.2 ± 3.1	7.9 ± 4.1
h	8	2.3 ± 1.1	4.2 ± 1.4	4.7 ± 1.1	8	1.4 ± 0.2	3.0 ± 0.5	2.2 ± 0.4
i	8	7.7 ± 4.5	11.2 ± 6.6	5.2 ± 1.2	—	—	—	—
j	—	—	—	—	2	0.7 ± 0.4	1.1 ± 1.1	0.7 ± 0.2
Total[b]	72	6.1 ± 4.4	11.1 ± 7.1	7.0 ± 3.5	61	3.4 ± 2.9	9.9 ± 9.8	5.4 ± 5.2

Abbreviations: SD, standard deviation; LR, left–right; CC, cranio-caudal; AP, antero-posterior.
[a] The value of *N* represents the number of treatment days which were properly recorded.
[b] The average at "Total" was calculated as (the sum of the average of each patient)/(number of patients). The standard deviation at "Total" was the standard deviation for the average of each patient.

Table 3
Relationships between the average absolute amplitude and patient position and marker location

	Average absolute amplitude ± SD (mm)			
	N[a]	LR	CC	AP
Patient position				
Prone	64	5.9 ± 4.7 (0.117)	11.0 ± 7.6 (0.962)	7.2 ± 3.7 (0.328)
Supine	59	3.8 ± 2.9	11.0 ± 9.8	6.0 ± 5.1
Marker location in prone position				
Right	32	5.7 ± 5.8 (0.815)	9.1 ± 6.5 (0.496)	6.3 ± 4.2 (0.619)
Left	40	6.5 ± 3.6	12.6 ± 7.9	7.5 ± 3.2
Marker location in supine position				
Right	27	2.6 ± 1.5 (0.484)	11.2 ± 9.9 (0.734)	4.6 ± 3.1 (0.712)
Left	34	4.1 ± 3.7	8.8 ± 10.7	6.1 ± 6.7

Abbreviations as in Table 2.
[a] The value of *N* represents the sum of the number of treatment days which were properly recorded for each condition. Data in parentheses are the *p* values for patient position; prone or spine and for marker location; right or left.

Table 4
The minimum distance between the surface of tumor and the stomach/duodenum, the volume of stomach/duodenum, which received 35 Gy or more, and the maximum dose at the stomach and duodenum

Patient No.	Minimum distance (mm)		Stomach and duodenum	
	Prone position	Supine position	Volume received 35 Gy or more (ml)	Maximum dose (cGy)
1	30	30	0.0	2936
2	7 (right)	8 (right)	0.1	3970
2	55 (left)	68 (left)	0.0	1624
3	18	15	0.0	2158
4	0	0	0.4	4119
5	50	53	0.1	4018
6	3	2	<0.1[a]	3626
7	0	0	<0.1[a]	3628
8	0	0	0.0	3416
9	0	0	4.6	4335

[a] Less than 0.1 ml

reported. As far as we could survey, this is the first report of the three-dimensional movement of the adrenal/perirenal region measured in the prone and supine positions using internal fiducial markers. The present study can be the basis for the determination of the PTV margin of adrenal gland tumors.

Contrary to our expectation, there was no statistically significant difference in the average absolute amplitude between the supine and prone positions along the three axes (LR, CC, and AP). Also, there were no statistically significant differences in the distance between the tumor and the stomach and that between the tumor and the duodenum regardless of whether the patients were in the prone or supine position. Thus, instead of the prone position, we now use the supine position, which is more comfortable for patients. In fact, there seems to be a tendency for reduced marker motion for patients in supine position in 5 of 8 patients as shown in Table 2. Although *t*-tests showed negative results on 2D motion in our series, there might be some difference in a larger study or in more detailed 3D analysis.

There have been only a few series of radiation therapy for metastatic adrenal tumors [10,25,31]. Zeng et al. reported that 22 patients with adrenal metastases from hepatocellular carcinoma were treated with palliative radiation therapy (median dose of 50 Gy/25 fractions), and 13 of 14 patients who had pain related to adrenal tumors had complete or marked pain relief [31]. In the present study, one patient experienced improvement of the pain and all other patients without any tumor-related symptoms before RTRT showed no tumor-related symptoms after their treatment. Since our treatment requires only a one-night stay in the hospital followed by a 2-week treatment as an out-patient in principle, patients would be more comfortable receiving our treatment than receiving 50 Gy in 25 fractions.

Several articles, with larger number of patients, on adrenalectomy for metastatic adrenal tumors reported that a few of patients survived more than 5 years [5,11,12,14–17,19]. In our series, the longest follow-up time was as short as 21 months. Therefore, surgery still has an advantage in terms of the possibility for the long-term survival until we would have longer follow-up and show the similar findings.

When compared with open adrenalectomy, laparoscopic adrenalectomy is associated with less intraoperative blood loss, lower analgesic requirement, decreased convalescence, superior cosmesis, and lower post-operative complication rates [3,13,18]. Laparoscopic adrenalectomy is currently considered to be the procedure of choice for benign adrenal masses. Several retrospective studies also showed the possible application of laparoscopic adrenalectomy for solitary adrenal metastasis [5,9,11,15,17,19]. However, the use of laparoscopic adrenalectomy for adrenal metastasis is controversial [8,30]. Even though laparoscopic surgery is a less invasive procedure, perioperative complications, such as diaphragm injury, inferior epigastric injury, pancreatic fistula, wound infection and bleeding, have been reported [5,9,11,15,17,19]. It was reported that complication rates ranged from 9% to 13% in laparoscopic surgical series [5,9,11,15,19]. Moreover, there have been several case reports about port site recurrence after laparoscopic adrenalectomy for adrenal metastatic tumors [6,26]. Our results showed no symptomatic complications, and no adrenal relapses were experienced in the treatment of 11 tumors. Although the number of patients was too small to draw definitive conclusions, the present study suggested that our procedure would be a feasible alternative to surgical adrenalectomy for treating adrenal metastasis.

The drawback to fluoroscopic imaging throughout treatment is the additional patient dose. However, we have found that the dose was negligible in most of occasions and can be included in treatment planning if necessary [22]. We still do not have any experience with RTRT for benign adrenal tumors, which would also be a challenging procedure in patients who, for medical reasons, have a high risk of surgical complication.

In conclusion, hypofractionated RTRT was feasible for patients with metastatic adrenal tumors. The motion of a fiducial marker near the tumor was demonstrated using the RTRT system. The minimum distances between the tumor and the stomach and duodenum were 16.3 ± 21.5 mm and 17.6 ± 24.8 mm in the prone and supine positions, respectively, with no significant difference between the two.

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