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TECHNICAL NOTE

# Synchronous monitoring of external/internal respiratory motion: validity of respiration-gated radiotherapy for liver tumors

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**Abstract**
*Purpose.* Four-dimensional (4D) radiotherapy, in particular respiration gating for the treatment of lung tumors, is gaining popularity. Its utility for other sites, however, has not been investigated fully. The purpose of this study was to see whether 4D therapy is feasible for liver tumors.
*Material and methods.* Six patients (five with hepatomas and one with metastatic liver tumor) had a fiducial, gold marker 1.5 mm in diameter implanted in the vicinity of their liver tumors. The inner and external (i.e., upper abdominal wall) respiratory movements were simultaneously recorded using a real-time tumor-tracking radiotherapy system and respiration monitor equipment applied to the mid to upper abdomen.
*Results.* The fluctuations from the baseline position of liver tumors were small; the mean absolute value was 3.92 ± 1.94 mm. The mean right–left, anteroposterior, and craniocaudal total movements were 4.19 ± 2.46, 7.23 ± 2.96, and 15.98 ± 6.02 mm, respectively. The phase shift was negligible.
*Conclusion.* Liver tumors may be suitable for respiration-gated radiotherapy, and they may become curable with 4D radiotherapy.

**Key words** Gated radiotherapy · Exhale fluctuation · Liver cancer · Respiration · Radiotherapy

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## Introduction

We previously reported a pitfall of respiration-gated radiotherapy of lung tumors.[1] In brief, in our system radiation beams are turned on when a respiratory monitor detects an end-exhale signal from the external anatomy, the mid to upper abdomen. However, the position of a tumor can vary among end-exhales, depending on the tumor site, patient's condition, and the treatment session.[1] Variation may cause an underdose to the tumor or an overdose to the surrounding lung tissues.[1] The implications from that study were that we should watch the end-exhale positions of external respiratory waves carefully on a monitor; and if an unexpected large shift is observed on end-exhale positions, we should interrupt the treatment session and seek the reason for the shift. Reasons include an influence of coexisting lung disease, lung segment volume inflation varying among respiration cycles, unexpected movements depending on tumor sites (i.e., tumors near the heart), or more problematically, patients suddenly falling into a deep sleep. The latter condition requires us to awaken patients and ask them to achieve stable breathing. The former conditions could require replanning, taking the shift into consideration for the planning target volume (PTV) determination. In the present study, to clarify respiratory liver tumor motion for four-dimensional radiotherapy, we used the same synchronous dual internal/external monitoring system as we did for the lung. The system enabled us to produce the position wave of a fiducial implanted in the liver and to correlate it with the respiratory wave of the mid to upper abdomen.

## Materials and methods

The real-time tumor-tracking radiotherapy (RTRT) system developed by Mitsubishi Co. and Shirato and colleagues,[2,3] was used to detect fiducials implanted into the liver. Six patients (five with hepatomas and one with metastatic liver tumor) had a fiducial, gold marker 1.5 mm in diameter implanted in the vicinity of their liver tumors under ultrasound (US) guidance. Informed consent was obtained from all patients, and the study was approved by the institutional ethics committee.

All of the patients were male, and their age ranged from 58 to 68 years (mean 62 years). The fiducial locations were in the right lobe of the liver in all six patients. A respiratory gating system (Anzai Medical, Tokyo, Japan) was applied on the mid to upper abdomen to detect respiratory motion (i.e., amplitude and phase).

The details of our dual synchronous internal/external monitoring were described previously.[1] Six to eight stereotactic conformal beams were used to treat the patients with a typical dose-fractional schedule of 40 Gy in four fractions. A 4-MV linac machine designed specifically for the RTRT system was used for the treatment. Patients were treated during free breathing, and the therapy was carried out using the RTRT system; that is, the respiration gating in this study was imaginary, and it was solely for the purpose of testing the validity of respiration gating for the liver. At the time of computed tomography (CT) examination and with the patient on the treatment couch, the patient was first asked by the medical staff to perform shallow, stable breathing. The CT examination and treatment started only after the patient's breathing waves became regular and small, which was confirmed by the radiation oncologist in charge. This process was usually finished within a few minutes. This treatment preparation was the same for both the lung and the liver.

For the respiration-gating window, we used 30% amplitude from the baseline, a line connecting at least 50 end-exhale points of the external wave. The major concern in the present study was whether the baseline was stable because it is crucial for respiration-gated radiotherapy, as mentioned above. The respiratory wave was correlated to the position of the fiducial recorded by the RTRT system; thereby, we could obtain (1) the degree of baseline fluctuation of the external wave (translated into fiducial fluctuation in millimeters), (2) the total movement of fiducials, and (3) the phase difference between the fiducial wave and the external waves. With regard to the baseline fluctuation and phase shift, the data for 24 lung fiducials were used for comparison. Student's *t*-test was used to compare the means of the two groups

## Results

### Degree of baseline fluctuation

The baseline fluctuation was surprisingly small for all six patients (Fig. 1). The mean absolute value was 3.92 ± 1.94 mm for liver tumors. Figure 1 suggests that the end-exhale respiratory wave positions of the liver were stable and correlated well with the end-exhale positions of the fiducial waves recorded by the RTRT system. For comparison with the lung, we show the baseline fluctuations of 24 fiducials implanted in 18 patients. The mean absolute value was 6.82 ± 2.21 mm (statistically not significant).

### Total movement of fiducials

The mean right–left, anteroposterior, and craniocaudal total movements were 4.19 ± 2.46, 7.23 ± 2.96, and 15.98 ± 6.02 mm, respectively. As expected, the movement was largest in the craniocaudal direction. In the imaginary respiration-gated radiotherapy, the position of the fiducials fell within 30% amplitude of their total movements in half of the patients. For the reminder of the patients,

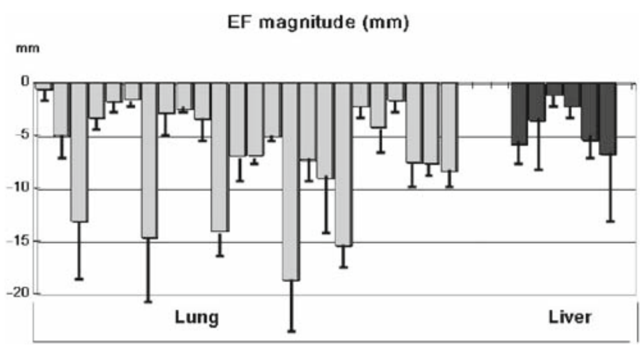


**Fig. 1.** Degree of exhale fluctuation of fiducials for the lung and the liver. The *bars* indicate standard deviations. The fluctuation was mostly downward for the lung, whereas it was slightly upward for the liver. The mean (SD) absolute values for fluctuations were 6.82 ± 2.21 mm for the lung and 3.92 ± 1.94 mm for the liver. Although a larger value was observed for lung patients, the difference was not statistically significant

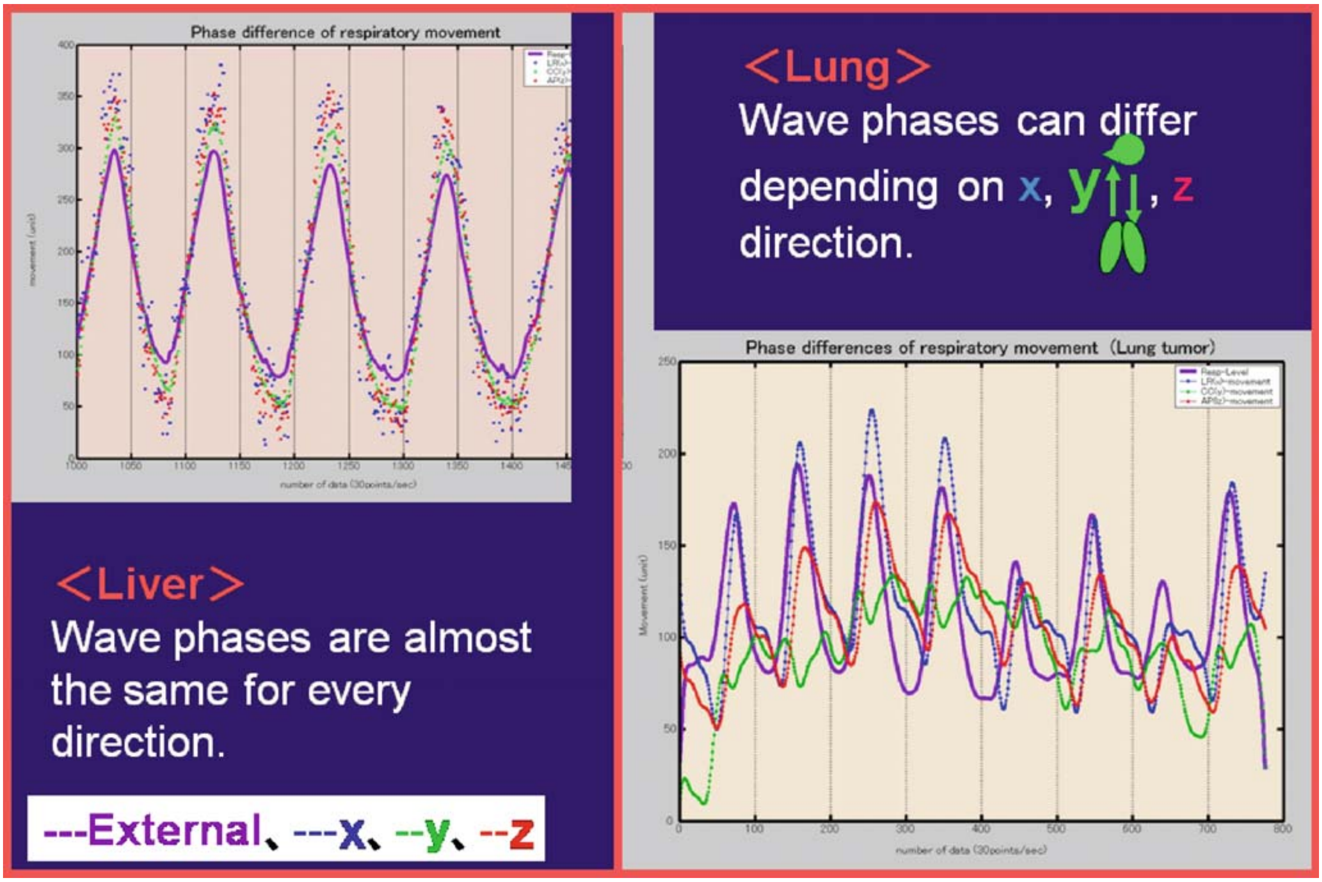


**Fig. 2.** Representative respiratory phase shift between internal (fiducial) and external (mid to upper abdomen) waves. The *dots* (*left*) or *dotted line* (*right*) indicates fiducials (*blue*, right–left; *green*, craniocaudal; *red*, anteroposterior direction). The *solid purple line* shows the external wave for both the liver and the lung. Note that there is almost no phase shift in each direction for the liver, whereas the phases of the craniocaudal (*green*) and anteroposterior (*red*) directions are shifted to a certain degree for the lung. The absolute shift values are shown in Fig. 3

the end-exhale position of the fiducial was not within 30% gating threshold set previously during simulation. These results suggest that in some patients internal/external waves were well correlated, whereas in others the correlations were not excellent, except for their baseline, as discussed below.

### Phase shift between fiducial and mid to upper abdomen waves

In Fig. 2, we show each wave (i.e., internal/external) superimposed in the same frame. This graph is representative of the wave recordings of six patients. The phase shift was defined as the phase difference between central lines crossing each wave peak of the fiducial and external waves, and it was expressed in terms of $\pi$. A total of 4680 wave-phase data from 78 beams of six patients, were evaluated. For practical reasons, the first and last treatment beams for each session were analyzed. The mean phase shift was 0.09 $\pi$ in the right–left direction, 0.03 $\pi$ in the anteroposterior direction, and 0.03 $\pi$ in the craniocaudal direction. For lung tumors, a total 5820 waves of 24 fiducials were analyzed. The respective mean phase shifts were 0.18 2 $\pi$ ($P = 0.0027$), 0.09 $\pi$ ($P = 0.001$), and 0.09 $\pi$ ($P = 0.0043$) (Fig. 3).

### Outcome

Table 1 shows the patients' characteristics and treatment outcomes. Four of the six patients achieved local control during a follow-up period ranging from 16 to 59 months.

## Discussion

Four-dimensional CT planning and radiotherapy are used increasingly for moving tumors. Some groups use phase-adjusted high-resolution CT for radiation planning and treat moving tumors accordingly. Such treatment requires some type of synchronous (i.e., between simulation CT and X-ray therapy) equipment. Currently, the most widely used method is respiration gating. Ideally, moving tumors can be irradiated as if they were in a static condition. However, this kind of therapy is based on the assumption that respiration gating is completely synchronized between CT simulation and irradiation.

Obviously, to verify such synchronization, we need sophisticated measures. Cone-beam CT mounted on a linear accelerator together with a respiration monitor is one such measure. Chang and colleagues carried out an excellent study in which they meticulously evaluated lung tumor delineation with and without respiration-gated cone-beam CT.[4] They showed a significant improvement in tumor volume determination with respiration-gated CT. The tumor centroid also became much closer to the one simulated on four-dimensional (4D) planning CT. Another way to verify tumor position is to use a real-time electronic portal imaging device (EPID). Spoelstra and coworkers used time-integrated electronic portal images (TI-EPIs) and verified lung tumor position during irradiation sessions.[5] They showed that lung tumor positions during radiotherapy sessions were displaced from their planned position by approxi-

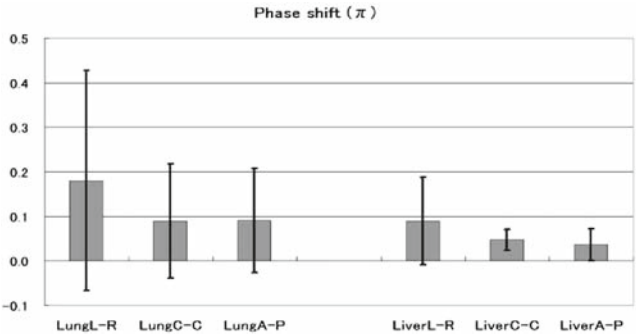


**Fig. 3.** Absolute mean phase-shift values—left–right (*LR*), craniocaudal (*CC*), anteroposterior (*AP*)—are shown for the liver and the lung. A small but statistically significant difference was observed in each direction

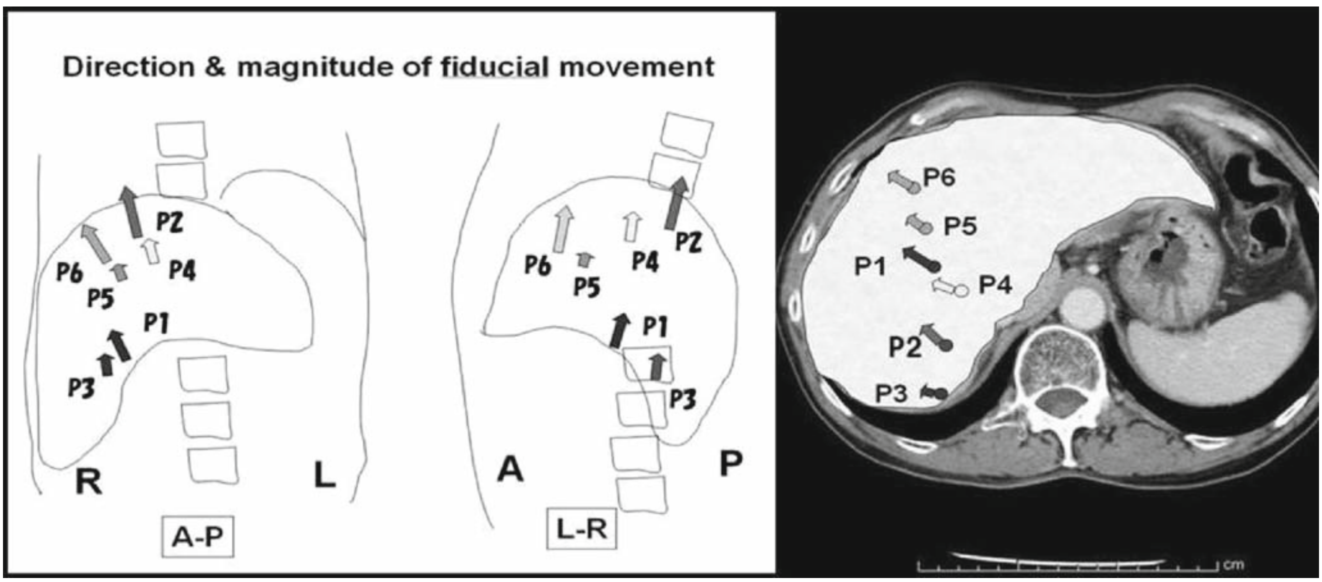


**Fig. 4.** Movements of fiducials (*P1–P6*). Note that all fiducials moved in the same direction. Our previous study showed that fiducials implanted in the lung moved in different directions depending on the location (data not shown). *R*, right; *L*, left; *A*, anterior; *P*, posterior

**Table 1.** Patients' characteristics and treatment outcomes

| Patient no. | Histology | Age (years)/sex | Site | Child | Dose (Gy/fractions) | Follow-up (months) | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | HCC | 66/M | S6 | A | 48/8 | 16 | Controlled |
| 2 | HCC | 63/M | S7 | A | 48/8 | 20 | Residual |
| 3 | HCC | 57/M | S8 | D | 45/15 | 17 | Controlled |
| 4 | Solitary metastasis | 56/M | S6 | A | 40/4 | 17 | Regrowth |
| 5 | HCC | 62/M | S6 | D | 40/4 | 41 | Controlled |
| 6 | HCC | 56/M | S4 | A | 52/8 | 59 | Controlled |

HCC, hepatocellular carcinoma; S, segment mately 5 mm. Respiration-gated CT was used for their simulation. With regard to liver tumors, Krishnan and colleagues recently published a pilot study.[6] One patient had a fiducial implanted in her liver, and the isocenter displacement from its original position on 4D CT simulation was evaluated. EPID allowed them to detect a radius of around 2.5 mm displacement.

Our approach was different from the methods mentioned above in the sense that fiducial positions were evaluated in a three-dimensional coordinate using the RTRT system, and external anatomy (the mid to upper abdomen) positions were correlated with the fiducial position (Figs. 4, 5). Furthermore, the imaging frequency was 30 Hz, meaning that ours is really "real-time" object tracking. Thus, data obtained from our system are quite reliable. The TI-EPIs approach is excellent, but only a single plane image can be obtained. Their image sampling was very good; a total of 243 TI-EPIs were acquired over 288 fractions.

In the previous lung study, we reported that a "baseline shift" can occur at inter- and intrafractional levels.[1] These results prompted us to do a similar study on the liver. The most surprising finding was that the baseline shifts for liver tumors were small, on the order of a few millimeters. Although statistically not significant, Fig. 1 shows that end-exhale positions of fiducials were stable compared to those of the lung. Phase shifts of respiration motion waves were almost negligible. We also found that the total fiducial movement was <2.5 cm. These findings suggest that 4D radiotherapy is feasible for liver tumors. One can argue that it is natural to think that the phase shift is smaller for the liver because the monitor is placed on the abdomen. However, to the best of our knowledge, there is no report showing that. This article seems to be the first to show the exact values. It is surprising that fiducial movements were within 2.5 cm. This is counterintuitive; we usually think that respiratory liver movements are large, probably 4–6 cm, in the craniocaudal direction. Part of the reason why the value was so small might have been our pretreatment preparation; the medical staff asked patients for shallow, stable breathing. Normal lung function of liver patients may also explain the smaller baseline shift, total tumor movements, and phase shifts.

The number of patients was too small to draw a definitive conclusion, although we found a trend that liver tumors move in a smoother fashion than lung tumors. Four-dimensional stereotactic radiotherapy for lung tumors is gaining popularity,[7,8] but the current results suggest that liver tumors may be much more suitable for such therapy. Respiration gating may be a powerful tool to ensure precise high-dose delivery to liver tumors and may lead to a higher rate of local control of the tumors.

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## References

1. Nishioka S, Nishioka T, Kawahara M, Tanaka S, Hiromura T, Tomita K, et al. Exhale fluctuation in respiratory-gated radiotherapy of the lung: a pitfall of respiratory gating shown in a synchronized internal/external marker recording study. Radiother Oncol 2008;86:69–76.
2. Shirato H, Shimizu S, Shimizu T, Nishioka T, Miyasaka K. Real-time tumour-tracking radiotherapy, Lancet 1999;353:1331–2.
3. Shirato H, Oita M, Fujita K, Watanabe Y, Miyasaka K. Feasibility of synchronization of real-time tumor-tracking radiotherapy and intensity-modulated radiotherapy from viewpoint of excessive dose from fluoroscopy. Int J Radiat Oncol Biol Phys 2004;60:335–41.
4. Chang J, Mageras G, Yorke E, De Arruda F, Sillanpaa J, Rosenzeig KE, et al. Observation of interfractional variations in lung tumor position using respiratory gated and ungated megavoltage cone-beam computed tomography. Int J Radiat Oncol Biol Phys 2007;67:1548–58.
5. Spoelstra FO, van Sörnsen de Koste JR, Cuijpers JP, Lagerwaard FJ, Stotman BJ, Senan S. Analysis of reproducibility of respiration-triggered gated radiotherapy for lung tumors. Radiother Oncol 2008;87:59–64.
6. Krishnan S, Briere TM, Dong L, Murthy R, Ng C, Balter P, et al. Daily targeting of liver tumors: screening patients with a mock treatment and using a combination of internal and external fiducials for image-guided respiratory-gated radiotherapy. Med Phys 2007;34:4591–3.
7. Ng A, Tung S, Wong VY. Hypofractionated stereotactic radiotherapy for medically inoperable stage I non-small cell lung cancer: report on clinical outcome and dose to critical organs. Radiother Oncol 2008;87:24–8.
8. Guckenberger M, Meyer J, Wilbert J, Richter A, Baier K, Mueller G, et al. Intra-fractional uncertainties in cone-beam CT based image-guided radiotherapy (IGRT) of pulmonary tumors: intra-fractional uncertainties in cone-beam CT based image-guided radiotherapy (IGRT) of pulmonary tumors. Radiother Oncol 2007;83:57–64.